Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study[1–3]

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ABSTRACT

Background: High calcium intake has been associated with an increased risk of advanced-stage and high-grade prostate cancer. Several studies have found a positive association between phosphorus intake and prostate cancer risk.

Objective: We investigated the joint association between calcium and phosphorus and risk of prostate cancer in the Health Professionals Follow-Up Study, with a focus on lethal and high-grade disease.

Design: In total, 47,885 men in the cohort reported diet data in 1986 and every 4 y thereafter. From 1986 to 2010, 5861 cases of prostate cancer were identified, including 789 lethal cancers (fatal or metastatic). We used Cox proportional hazards models to assess the association between calcium and phosphorus intake and prostate cancer, with adjustment for potential confounding.

Results: Calcium intakes >2000 mg/d were associated with greater risk of total prostate cancer and lethal and high-grade cancers. These associations were attenuated and no longer statistically significant when phosphorus intake was adjusted for. Phosphorus intake was associated with greater risk of total, lethal, and high-grade cancers, independent of calcium and intakes of red meat, white meat, dairy, and fish. In latency analysis, calcium and phosphorus had independent effects for different time periods between exposure and diagnosis. Calcium intake was associated with an increased risk of advanced-stage and high-grade disease 12–16 y after exposure, whereas high phosphorus was associated with increased risk of advanced-stage and high-grade disease 0–8 y after exposure.

Conclusions: Phosphorus is independently associated with risk of lethal and high-grade prostate cancer. Calcium may not have a strong independent effect on prostate cancer risk except with long latency periods. *Am J Clin Nutr* 2015;101:173–83.

Keywords calcium, epidemiology, phosphorus, prostate cancer, fatal prostate cancer, high-grade prostate cancer, diet, nutritional epidemiology

INTRODUCTION

Dairy foods have generally been associated with an increased risk of prostate cancer, with a 2005 meta-analysis reporting a summary relative risk of 1.11 (95% CI: 1.03, 1.19) for the highest compared with the lowest total dairy intakes (1). Some but not all studies published since this meta-analysis have tended to support an association between higher milk or dairy consumption and prostate cancer risk (2–5).

Dairy foods represent a major dietary source of calcium and are also rich in other nutrients. Trying to disentangle the independent effects of various components of dairy foods on prostate cancer risk is challenging because of the high correlations between these components. However, cohort studies that have tried to separate effects generally suggest that calcium may be the predominant player underlying positive associations with prostate cancer. The 2005 meta-analysis found a relative risk of 1.39 (95% CI: 1.09, 1.77) for extreme categories of calcium intake (1). In the Health Professionals Follow-Up Study (HPFS),[4] with 16 y of follow-up and 3544 prostate cancer cases, we previously found that calcium intakes >1500 mg/d were associated with a higher risk of advanced-stage and fatal prostate cancers as well as cancer defined by higher tumor grade (Gleason score ≥7) (6, 7).

Phosphorus is another mineral found in dairy foods, although it is more widely distributed in the diet than is calcium. Fewer studies have examined phosphorus intake and prostate cancer risk. We previously reported that higher phosphorus intake was associated with an increased risk of high-grade disease in the HPFS, independent of calcium intake (6). Three other cohort studies have looked at phosphorus and prostate cancer; 2 found an increased risk with higher intakes, whereas another found a suggestion of a positive association (8–10). Whether the association for phosphorus is independent of calcium intake has not been fully investigated.

In this article, we update our analysis of calcium and phosphorus intake with 24 y of follow-up and 5861 cases of prostate cancer. With additional cases and follow-up time, we were better able to separate the effects of calcium and phosphorus, examine lethal and high-grade (Gleason scores 8–10) prostate cancer, and

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[4] Abbreviations used: CaSR, calcium-sensing receptor; FFQ, food-frequency questionnaire; HPFS, Health Professionals Follow-Up Study; PSA, prostate-specific antigen.

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study different latency periods between exposure and cancer diagnosis.

SUBJECTS AND METHODS

Study population

The HPFS started in 1986 when 51,529 male health professionals aged 40–75 y completed a mailed questionnaire on personal and lifestyle characteristics and disease history. New medical diagnoses and lifestyle factors are updated with new questionnaires every 2 y, and diet information is collected every 4 y. Men who adequately completed the baseline food-frequency questionnaire (FFQ) in 1986 form the study population for this analysis. After excluding men who reported a diagnosis of cancer (except nonmelanoma skin cancer) before baseline, a total of 47,885 men were followed prospectively for cancer incidence, metastases, and mortality until 2010. The HPFS is approved by the Human Subjects Committee at the Harvard School of Public Health.

Assessment of dietary intakes

Semiquantitative FFQs with more than 130 food items were administered in 1986 and every 4 y thereafter, through 2006. The FFQ specifies a portion size and asks the participant how often, on average, he has consumed each item over the past year, with 9 possible frequency responses. Supplement use, including the dose and frequency of specific brands of multivitamins and calcium supplements, is also assessed. Nutrient intakes are calculated by multiplying the frequency of consumption of each food by the serving size and the nutrient content of the food. Dairy intake is calculated as the sum of servings per day of the following foods: skim or 1% fat milk, whole milk, cream, sour cream, ice cream and sherbet, yogurt, cottage cheese, cream cheese, and other cheese. (Butter is not included in dairy intake.) Processed meat is the sum of servings per day of sausage/salami/bologna, hot dogs, and bacon. A validation study comparing 2 wk of diet records with the FFQ found a correlation of 0.61 for total calcium, 0.60 for calcium without supplements, and 0.63 for phosphorus, adjusting for energy intake (11).

Identification and follow-up of prostate cancer cases

Prostate cancer diagnoses were initially identified by self-reports from the participants or their next of kin on the biennial questionnaires and then confirmed by review of medical records and pathology reports. Deaths in the cohort were ascertained through reports from family members and searches of the National Death Index. Underlying cause of death was assigned by an endpoints committee based on all available data, including medical history, medical records, registry information, and death certificates. We followed men with prostate cancer starting in 2000 with a biennial prostate cancer–specific questionnaire, separate from the regular HPFS questionnaire, to ascertain disease progression and diagnosis of metastases.

We studied total prostate cancer incidence excluding stage T1a cancers, which are discovered incidentally during treatment of benign prostatic hypertrophy. Because of the considerable heterogeneity in the biological potential of prostate cancer, we also examined the data for men with advanced-stage, lethal, or localized cancers separately to distinguish those patients in whom the cancer was likely to progress clinically. Advanced-stage cancers were those that had spread beyond the prostate, including to the seminal vesicle, lymph nodes, or bone. This category included men with stage T3b, T4, N1, or M1 prostate cancer at diagnosis; men who developed lymph node or distant metastases during follow-up; and men who died of prostate cancer before the end of follow-up. Lethal cancers, a subset of advanced-stage cancers, were those that caused death or distant metastases before the end of follow-up. Localized cancers were stage T1 or T2 and N0 and M0 at diagnosis and did not progress to the lymph node or distant metastases or death during the follow-up period. Cancers were also categorized as high grade (Gleason scores 8–10), grade 7, or low grade (Gleason scores 2–6) at diagnosis based on prostatectomy or biopsy pathology reports.

Statistical analysis

Each participant contributed person-time from the date on which he returned the baseline questionnaire in 1986 until prostate cancer diagnosis, death, or the end of the study period, 31 January 2010. Participants' data were divided according to energy-adjusted mineral intake, and relative risks of prostate cancer were calculated as the incidence rate in a given category of intake divided by the rate in the lowest category.

We used the cumulative average intake as our primary measure of exposure to best represent long-term dietary intake. That is, the intake in 1986 was used as the exposure for the 1986–1990 follow-up period, the average of the intakes reported in 1986 and 1990 was used for the 1990–1994 follow-up period, the average of the intakes reported in 1986, 1990, and 1994 was used for the 1994–1998 follow-up period, and so on. In addition, we used our repeated measures to analyze the effect of latency time (time from exposure to cancer diagnosis) by relating each measure of mineral intake to prostate cancer incidence during specific time periods: 0–4, 4–8, 8–12, and 12–16 y after exposure.

We used Cox proportional hazards regression to adjust for potential confounding by prostate cancer risk factors previously identified in this cohort and in other studies. Age-adjusted models were adjusted for age in months and calendar year. Multivariable models were also adjusted for race (Caucasian, African American, Asian American, or other); height (quartiles); BMI (in kg/m^2) at age 21 y (<20, 20 to <22.5, 22.5 to <25, or ≥ 25); current BMI (<21, 21 to <23, 23 to <25, 25 to <27.5, 27.5 to <30, or ≥ 30); vigorous physical activity (quintiles, metabolic equivalents-hours/wk); smoking (never, former quit >10 y ago, former quit ≤ 10 y ago, or current); diabetes (type I or II, yes or no); family history of prostate cancer in father or brother (yes or no); multivitamin use (yes or no); history of prostate-specific antigen (PSA) testing (yes or no, lagged by 1 period to avoid counting diagnostic PSA tests as screening; collected from 1994 onward); intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol (all quintiles); and energy intake (continuous). Some models were also adjusted for quintiles of animal protein intake or dairy, red meat, white meat, and fish intake. All covariates except race, height, and BMI at age 21 y were updated in each questionnaire cycle. Dietary data from the previous questionnaire were carried forward for missing questionnaires. Other missing covariates were handled by using missing indicator variables. To test for a linear trend across categories of intake, we modeled nutrient intake as a continuous variable by using the median intake for each category.

All P values were 2-sided, with a P value <0.05 considered statistically significant. Analyses were performed by using SAS version 9.2 (SAS Institute).

RESULTS

From 1986 to January 2010, we documented 5861 incident prostate cancer cases (excluding T1a cases) during 941,471 person-years. Age-adjusted characteristics of the study population according to intakes of calcium and phosphorus are shown in **Table 1**. Men consuming higher levels of total calcium were slightly more likely to be Caucasian, were less likely to smoke, engaged in more vigorous physical activity, and used more dietary supplements than did men consuming lower levels. In addition, they reported more intensive PSA testing. Higher total calcium intakes were associated with higher intakes of phosphorus, supplemental vitamin E, and animal protein and lower intakes of alcohol and coffee.

Men consuming higher levels of total phosphorus were also more likely to be Caucasian, were less likely to smoke, engaged in more vigorous physical activity, and reported more intensive PSA testing than did men consuming lower levels. Higher intakes were associated with somewhat greater supplement use, although to a lesser extent than was calcium. Men consuming the most phosphorus also consumed higher levels of calcium, supplemental vitamin E, and animal protein and lower intakes of alcohol and coffee. Men with the highest intakes of phosphorus were also more likely to be diabetic.

In 2002, the contributors to total calcium intake were dairy foods (milk, cheese including on pizza, yogurt, and ice cream;

TABLE 1
Age-adjusted characteristics of the study population in 1986 by category of intake[1]

	Category of total calcium			Quintile of total phosphorus		
	<750 mg	1000–1249 mg	≥1500 mg	1	3	5
N	21,486	6480	3869	9546	9640	9601
Age, y	53.9 ± 9.6[2]	54.7 ± 9.8	56.3 ± 9.7	54.5 ± 9.8	54.3 ± 9.7	55.2 ± 9.8
BMI, kg/m^2	25.6 ± 3.4	25.4 ± 3.3	25.4 ± 3.3	25.3 ± 3.3	25.6 ± 3.3	25.6 ± 3.5
BMI at age 21 y, kg/m^2	22.9 ± 3.1	23.0 ± 2.9	23.3 ± 3.0	22.6 ± 3.0	23.1 ± 3.0	23.3 ± 3.1
Height, inches	70.0 ± 2.9	70.2 ± 2.7	70.3 ± 2.8	70.0 ± 2.9	70.1 ± 2.8	70.2 ± 2.9
% Caucasian	94	97	97	94	96	97
% Never smokers	41	47	49	39	45	49
% Current smokers	11	9	8	15	9	7
Vigorous activity, % top quintile	14	16	19	12	15	18
Has diabetes, %	3	4	4	1	3	6
Family history of PCa, %	12	12	12	11	13	12
PSA test in previous 2 y, 1994, %	35	40	36	31	40	40
PSA test in previous 2 y, 2006, %	54	69	63	57	68	64
No. of periods with PSA test, 1994–2006[3]	3.7 ± 2.4	4.6 ± 2.2	4.4 ± 2.3	3.8 ± 2.5	4.5 ± 2.2	4.4 ± 2.3
Daily dietary intakes						
Calcium, mg	586 ± 106	1117 ± 72	1942 ± 467	617 ± 269	828 ± 287	1344 ± 499
Dietary calcium, mg	580 ± 108	997 ± 202	1240 ± 502	543 ± 124	743 ± 158	1174 ± 359
Phosphorus, mg	1240 ± 171	1526 ± 193	1752 ± 347	1079 ± 90	1365 ± 33	1783 ± 195
Energy, kcal	1977 ± 625	2105 ± 616	1869 ± 586	1983 ± 632	1981 ± 614	1982 ± 611
Alcohol, g	13.8 ± 17.5	9.8 ± 14.0	7.6 ± 11.9	18.4 ± 21.6	10.4 ± 13.3	6.5 ± 9.6
α-Linolenic acid, g	1.1 ± 0.4	1.1 ± 0.3	1.0 ± 0.4	1.1 ± 0.4	1.1 ± 0.3	1.0 ± 0.3
Supplemental vitamin E, mg	23.8 ± 67.8	45.4 ± 89.3	101 ± 128	28.4 ± 74.7	36.6 ± 82.5	50.4 ± 97.2
Animal protein, g	65.4 ± 18.1	69.7 ± 16.8	74.2 ± 19.1	54.7 ± 13.3	68.2 ± 15.1	79.6 ± 19.0
Dairy, servings	1.2 ± 0.9	2.8 ± 1.4	3.2 ± 2.2	1.2 ± 1.0	1.7 ± 1.1	3.1 ± 1.8
Milk, servings	0.3 ± 0.3	1.6 ± 1.0	2.1 ± 1.8	0.3 ± 0.3	0.7 ± 0.6	2.0 ± 1.4
Cheese, servings	0.3 ± 0.3	0.5 ± 0.6	0.5 ± 0.7	0.3 ± 0.3	0.4 ± 0.4	0.4 ± 0.6
Red meat, servings	1.1 ± 0.8	1.0 ± 0.7	0.7 ± 0.6	1.1 ± 0.8	1.0 ± 0.7	0.8 ± 0.6
Beef, servings	0.5 ± 0.4	0.4 ± 0.3	0.3 ± 0.3	0.4 ± 0.3	0.4 ± 0.4	0.4 ± 0.3
Processed meat, servings	0.4 ± 0.5	0.4 ± 0.4	0.2 ± 0.3	0.5 ± 0.5	0.4 ± 0.4	0.3 ± 0.3
White meat, servings	0.4 ± 0.3	0.3 ± 0.3	0.3 ± 0.2	0.3 ± 0.2	0.4 ± 0.3	0.4 ± 0.4
Fish, servings	0.4 ± 0.3	0.4 ± 0.3	0.4 ± 0.3	0.3 ± 0.2	0.4 ± 0.3	0.5 ± 0.4
Nuts, servings	0.5 ± 0.7	0.5 ± 0.7	0.4 ± 0.6	0.4 ± 0.5	0.5 ± 0.7	0.5 ± 0.7
Tomato sauce, servings/wk	0.97 ± 1.25	0.94 ± 1.18	0.82 ± 1.07	0.94 ± 1.30	0.97 ± 1.23	0.85 ± 1.06
Bread, servings	1.4 ± 1.2	1.6 ± 1.3	1.3 ± 1.2	1.5 ± 1.4	1.4 ± 1.2	1.4 ± 1.2
Cereal, servings	0.3 ± 0.4	0.5 ± 0.5	0.4 ± 0.5	0.2 ± 0.4	0.4 ± 0.4	0.6 ± 0.6
Coffee, servings	2.0 ± 1.8	1.9 ± 1.8	1.6 ± 1.8	2.1 ± 1.8	2.0 ± 1.8	1.7 ± 1.8
Multivitamin supplement use, %	32	50	66	35	41	49
Calcium supplement use, %	2	26	64	13	15	21
Zinc supplement use, %	6	16	37	8	11	17

[1]Values are standardized to the age distribution of the study population (except for age). PCa, prostate cancer; PSA, prostate-specific antigen.
[2]Mean ± SD (all such values).
[3]Number of 2-y questionnaire periods in which participant reported having a PSA test in the previous 2 y, 1994–2008. Maximum is 8.

38%), supplements (multivitamins and calcium pills; 20%), grains (cereal, breads, pasta, rice, and crackers; 9%), vegetables (8%), juice and fruit (including calcium-fortified orange juice; 9%), meat/fish/eggs (4%), and other foods (12%). The contributors to total phosphorus intake were dairy (26%), meat/fish/eggs (23%), grains (16%), vegetables (9%), juice and fruit (4%), baked goods (4%), potatoes (4%), nuts (4%), supplements (multivitamins; 2%), and other foods (8%). The correlation was 0.68 between total calcium and total phosphorus and 0.75 between dietary calcium and dietary phosphorus. The correlation with dairy was 0.59 for total calcium and 0.48 for total phosphorus. Of the dairy foods, skim milk was most correlated with mineral intakes (0.57 for calcium, 0.59 for phosphorus), whereas whole milk was not strongly correlated with either (0.01 for calcium, −0.07 for phosphorus). Both calcium and phosphorus were positively correlated with intakes of yogurt and cottage cheese ($r \sim 0.2$), and calcium was positively correlated with other cheese intake ($r = 0.16$). The correlation with animal protein was 0.17 for total calcium, 0.20 for dietary calcium, and 0.50 for total phosphorus. Phosphorus intake was positively correlated with fish and white meat intake ($r = 0.20, 0.15$) and negatively correlated with red and processed meats ($r = -0.18, -0.19$).

The highest intakes of total calcium were associated with higher risk of prostate cancer (adjusted relative risk, RR, for ≥2000 mg/d compared with 500–749 mg/d = 1.24; 95% CI: 1.02, 1.51; *P* value for linear trend across categories = 0.02) (**Table 2**). Risk of lethal and advanced-stage cancers was significantly increased in the highest category of intake, although *P* values for linear trends across categories were not significant (*P*-trend = 0.06 for lethal, 0.07 for advanced). Calcium intake was not associated with the risk of localized cancers. Intakes of 2000 mg/d or more were also associated with high-grade and grade 7 cancers. Calcium intake was not associated with low-grade cancers. Age-adjusted results were very similar to the fully adjusted results and are not shown.

The associations between calcium intake of 2000 mg/d or more and total, advanced-stage, and higher grade cancers were attenuated and no longer statistically significant when phosphorus intake was also included in the models, except for grade 7 cancers, which remained statistically significant in the top category, although the *P* value for trend was no longer statistically significant (*P*-trend = 0.15) (Table 2). Adjustment for quintile of dairy intake, with (Table 2) or without (data not shown) phosphorus in the models, had no important effect.

We examined separately calcium from dietary and supplementary sources (**Table 3**) and found that the highest quintiles of dietary calcium were associated with increased risk of total, lethal, advanced-stage, high-grade, and grade 7 prostate cancers. Again, these associations were attenuated and no longer statistically significant when phosphorus intake was also included in the model. Supplementary calcium intake of >400 mg/d was not associated with prostate cancer risk (Table 3). Supplemental calcium intake of >800 mg/d was also not associated with risk of total, lethal, advanced-stage, or grade 7 cancers, but it was associated with significantly higher risk of high-grade disease (adjusted RR: 1.53; 95% CI: 1.00, 2.34); this association was attenuated and no longer statistically significant when phosphorus was also adjusted for. (Other results for supplemental calcium >800 mg/d are not shown.)

Higher quintiles of phosphorus intake were associated with greater risk of prostate cancer (adjusted RR for quintile 5 compared with quintile 1: 1.12; 95% CI: 1.03, 1.23; *P*-trend = 0.003) (**Table 4**). In particular, higher intakes were associated with greater risk of lethal, advanced-stage, high-grade, and grade 7 cancers. Phosphorus intake was not associated with the risk of localized or low-grade cancer. Again, age-adjusted results were very similar to the fully adjusted results and are not shown.

The associations between the highest quintile of phosphorus intake and risk of lethal, advanced-stage, and high-grade cancer remained when category of total calcium intake was also included in the models; however, the *P* values for linear trend across quintiles remained significant only for high-grade cancer (*P*-trend = 0.006 for high grade, 0.22 for lethal, and 0.06 for advanced stage). Adjustment for quintile of dairy or animal protein intake had not effect on the associations (Table 4); adjustment for quintiles of red meat, white meat, and fish intake also had no effects (data not shown).

We used the repeated measures of diet over time to study the effect of latency time by relating each measure of intake to prostate cancer incidence during specific time intervals after exposure. Calcium intake was associated with significantly increased risk of advanced-stage and grade 7–10 cancers 12–16 y after exposure but not for shorter latency periods (**Table 5**). These associations were independent of phosphorus intake. Phosphorus intake, on the other hand, was more strongly associated with advanced and grade 7–10 cancers for shorter time lags, 0–4 and 4–8 y after exposure (**Table 6**). These associations were independent of calcium intake. Neither calcium nor phosphorus was associated with localized or low-grade disease for any latency period.

DISCUSSION

In this cohort, we previously reported that high intakes of calcium were associated with fatal and high-grade prostate cancer but not with localized or low-grade cancers (6). In that study, phosphorus intake was associated with high-grade prostate cancer independent of calcium intake but not with fatal or advanced-stage cancers.

With additional diet assessments and follow-up time, we again found that very high calcium intakes, >2000 mg/d, were associated with the risk of lethal, advanced-stage, high-grade, and grade 7 prostate cancer; however, these associations were attenuated and no longer statistically significant when phosphorus was also adjusted for. In addition, we found that the positive associations between phosphorus intake and lethal, advanced-stage, high-grade, and grade 7 cancers persisted when calcium was also adjusted for. The calcium and phosphorus associations were both independent of dairy and other animal food or animal protein intake.

Given the high correlation between calcium and phosphorus intake, because dairy is the major contributor of both minerals in this population, it is difficult to truly separate their effects. When we looked separately at dietary and supplemental calcium intakes, the increased risk was associated with higher quintiles of dietary intake but not with higher supplemental intake. This is in contrast to our previous results with 16 y of follow-up, in which we found increased risks for both dietary and supplemental calcium (6). The current results suggest that the observed association for dietary calcium may, in fact, be due to confounding by phosphorus intake, because dietary calcium and phosphorus are correlated, but supplemental calcium is not strongly associated with phosphorus intake. Indeed, when phosphorus was

TABLE 2
RRs (95% CIs) of prostate cancer by category of total calcium intake, 1986–2010[1]

	Category of calcium intake							
	<500 mg	500 to <750 mg	750 to <1000 mg	1000 to <1250 mg	1250 to <1500 mg	1500 to <2000 mg	≥2000 mg	*P*-trend
All cancer, *n*	245	1604	1898	1079	551	365	119	
Fully adjusted RR	1.02 (0.89–1.17)	1.00	1.10 (1.02–1.17)	1.06 (0.98–1.15)	1.05 (0.95–1.17)	1.13 (1.00–1.27)	1.24 (1.02–1.51)	0.02
With adjustment for P	1.03 (0.90, 1.19)	1.00	1.06 (0.99, 1.15)	1.01 (0.92, 1.11)	0.99 (0.88, 1.11)	1.06 (0.93, 1.21)	1.17 (0.95, 1.43)	0.49
Also with dairy	1.04 (0.90, 1.20)	1.00	1.05 (0.97, 1.13)	1.00 (0.91, 1.10)	0.99 (0.88, 1.12)	1.06 (0.92, 1.22)	1.17 (0.95, 1.43)	0.44
Also with animal protein	1.04 (0.90, 1.19)	1.00	1.06 (0.99, 1.14)	1.01 (0.92, 1.10)	0.99 (0.88, 1.11)	1.06 (0.92, 1.21)	1.16 (0.95, 1.43)	0.52
Lethal cancer[2]	46	228	225	134	69	59	28	
Fully adjusted RR	1.13 (0.81, 1.56)	1.00	1.00 (0.82, 1.20)	1.03 (0.82, 1.29)	0.96 (0.73, 1.28)	1.26 (0.93, 1.71)	1.66 (1.09, 2.53)	0.06
With adjustment for P	1.18 (0.85, 1.66)	1.00	0.94 (0.76, 1.15)	0.91 (0.70, 1.17)	0.82 (0.60, 1.14)	1.07 (0.76, 1.52)	1.41 (0.89, 2.21)	0.39
Also with dairy	1.20 (0.85, 1.70)	1.00	0.93 (0.75, 1.15)	0.90 (0.68, 1.18)	0.81 (0.58, 1.14)	1.05 (0.73, 1.52)	1.39 (0.87, 2.21)	0.35
Also with animal protein	1.19 (0.85, 1.67)	1.00	0.93 (0.76, 1.14)	0.90 (0.70, 1.17)	0.82 (0.59, 1.51)	1.07 (0.76, 1.51)	1.40 (0.89, 2.21)	0.42
Advanced-stage cancer[2]	59	290	297	183	86	75	31	
Fully adjusted RR	1.13 (0.84, 1.50)	1.00	1.03 (0.87, 1.21)	1.11 (0.91, 1.34)	0.95 (0.74, 1.23)	1.26 (0.97, 1.65)	1.49 (1.01, 2.20)	0.07
With adjustment for P	1.18 (0.87, 1.58)	1.00	0.97 (0.81, 1.16)	0.97 (0.78, 1.21)	0.80 (0.60, 1.07)	1.05 (0.77, 1.43)	1.23 (0.81, 1.88)	0.71
Also with dairy	1.17 (0.87, 1.59)	1.00	0.98 (0.81, 1.18)	0.99 (0.78, 1.25)	0.82 (0.60, 1.10)	1.07 (0.78, 1.47)	1.25 (0.82, 1.92)	0.52
Also with animal protein	1.18 (0.88, 1.59)	1.00	0.96 (0.80, 1.15)	0.96 (0.77, 1.20)	0.79 (0.59, 1.06)	1.04 (0.77, 1.42)	1.23 (0.80, 1.86)	0.75
Localized cancer[2]	141	1060	1350	746	388	228	63	
Fully adjusted RR	0.98 (0.82, 1.17)	1.00	1.15 (1.06, 1.25)	1.07 (0.97, 1.18)	1.10 (0.98, 1.25)	1.06 (0.92, 1.24)	1.07 (0.82, 1.39)	0.34
With adjustment for P	0.97 (0.81, 1.17)	1.00	1.12 (1.03, 1.23)	1.02 (0.91, 1.15)	1.06 (0.92, 1.22)	1.02 (0.86, 1.20)	1.03 (0.78, 1.35)	0.88
Also with dairy	0.96 (0.80, 1.16)	1.00	1.11 (1.01, 1.22)	1.01 (0.90, 1.14)	1.05 (0.91, 1.22)	1.02 (0.85, 1.21)	1.02 (0.78, 1.35)	0.84
Also with animal protein	0.97 (0.81, 1.17)	1.00	1.13 (1.03, 1.23)	1.03 (0.92, 1.15)	1.06 (0.92, 1.22)	1.02 (0.86, 1.21)	1.03 (0.78, 1.36)	0.92
High-grade cancer[3]	28	181	215	156	70	43	18	
Fully adjusted RR	1.06 (0.71, 1.60)	1.00	1.17 (0.95, 1.43)	1.41 (1.13, 1.77)	1.21 (0.91, 1.61)	1.21 (0.86, 1.72)	1.88 (1.13, 3.12)	0.01
With adjustment for P	1.16 (0.76, 1.76)	1.00	1.05 (0.84, 1.30)	1.19 (0.91, 1.54)	0.98 (0.70, 1.37)	0.98 (0.66, 1.46)	1.51 (0.88, 2.60)	0.62
Also with dairy	1.08 (0.70, 1.65)	1.00	1.09 (0.86, 1.36)	1.22 (0.92, 1.61)	1.01 (0.71, 1.43)	1.00 (0.66, 1.51)	1.54 (0.89, 2.67)	0.51
Also with animal protein	1.16 (0.76, 1.77)	1.00	1.05 (0.84, 1.30)	1.19 (0.91, 1.55)	0.98 (0.70, 1.38)	0.98 (0.66, 1.45)	1.51 (0.88, 2.59)	0.63
Grade 7 cancer	69	472	596	325	167	114	40	
Fully adjusted RR	1.02 (0.79, 1.33)	1.00	1.15 (1.02, 1.30)	1.07 (0.92, 1.23)	1.09 (0.91, 1.32)	1.25 (1.01, 1.55)	1.64 (1.17, 2.30)	0.01
With adjustment for P	1.03 (0.79, 1.34)	1.00	1.11 (0.97, 1.27)	1.00 (0.84, 1.18)	1.01 (0.82, 1.25)	1.15 (0.90, 1.46)	1.51 (1.06, 2.15)	0.15
Also with dairy	1.00 (0.77, 1.31)	1.00	1.11 (0.97, 1.28)	1.00 (0.83, 1.19)	1.02 (0.81, 1.27)	1.16 (0.90, 1.49)	1.52 (1.05, 2.18)	0.12
Also with animal protein	1.04 (0.79, 1.35)	1.00	1.10 (0.96, 1.26)	0.98 (0.83, 1.17)	1.00 (0.80, 1.23)	1.13 (0.8, 1.45)	1.49 (1.04, 2.13)	0.18
Low-grade cancer[3]	103	686	823	444	231	149	32	
Fully adjusted RR	1.06 (0.85, 1.31)	1.00	1.08 (0.97, 1.20)	0.98 (0.87, 1.11)	1.02 (0.87, 1.19)	1.05 (0.87, 1.27)	0.79 (0.55, 1.14)	0.45
With adjustment for P	1.06 (0.85, 1.32)	1.00	1.06 (0.95, 1.19)	0.94 (0.82, 1.09)	0.97 (0.81, 1.16)	1.00 (0.81, 1.23)	0.75 (0.51, 1.09)	0.18
Also with dairy	1.09 (0.90, 1.36)	1.00	1.04 (0.92, 1.17)	0.93 (0.80, 1.09)	0.97 (0.80, 1.18)	1.01 (0.81, 1.25)	0.75 (0.51, 1.10)	0.22
Also with animal protein	1.06 (0.85, 1.31)	1.00	1.07 (0.95, 1.20)	0.95 (0.82, 1.10)	0.98 (0.82, 1.17)	1.01 (0.82, 1.24)	0.76 (0.52, 1.11)	0.22

[1]Models were adjusted for age (mo); calendar time; race; height (quartiles); BMI at age 21 y (4 categories); current BMI (6 categories); vigorous physical activity (quintiles); smoking (never, former quit >10 y ago, former quit ≤10 y ago, or current); diabetes; family history of prostate cancer; intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol (all quintiles); energy intake (continuous); multivitamin use (yes/no); and history of prostate-specific antigen testing (yes/no, lagged by one questionnaire cycle). Model with adjustment for P also includes phosphorus intake (quintiles). Model also with dairy includes terms from fully adjusted model, phosphorus, and also quintiles of dairy intake. Model also with animal protein includes terms from fully adjusted model, phosphorus, and also quintiles of animal protein intake (it does not include dairy).

[2]Lethal prostate cancer: prostate cancer death or distant metastases. Advanced: lethal or stage T3b or T4 or N1 or M1 at diagnosis or during follow-up. Localized: T1, T2, T3, or T3a, and N0, M0 without progression during follow-up.

[3]High-grade prostate cancer: Gleason scores 8–10. Low-grade prostate cancer: Gleason scores 2–6.

TABLE 3
RRs (95% CIs) of prostate cancer by calcium intake from dietary and supplementary sources, 1986–2010[1]

	Quintile of calcium intake from foods						Supplemental calcium intake			
	1	2	3	4	5 (high)	*P*-trend	0 mg/d	1–400 mg/d	>400 mg/d	*P*-trend
Mean intake, mg/d	508	650	761	903	1239		0	120	709	
All cancer, *n*	1039	1115	1229	1257	1221		2607	2666	588	
Fully adjusted RR	1.00	1.00 (0.92, 1.09)	1.09 (1.00, 1.19)	1.11 (1.02, 1.20)	1.10 (1.01, 1.20)	0.008	1.00	1.00 (0.94, 1.08)	1.04 (0.94, 1.16)	0.38
With adjustment for P	1.00	0.99 (0.90, 1.08)	1.07 (0.97, 1.17)	1.07 (0.96, 1.18)	1.04 (0.92, 1.17)	0.44	1.00	1.00 (0.93, 1.07)	1.04 (0.93, 1.15)	0.45
Lethal cancer[2]	133	152	144	177	183		434	270	85	
Fully adjusted RR	1.00	1.16 (0.91, 1.47)	1.06 (0.83, 1.35)	1.30 (1.03, 1.64)	1.28 (1.01, 1.62)	0.03	1.00	0.88 (0.73, 1.07)	0.93 (0.71, 1.21)	0.76
With adjustment for P	1.00	1.15 (0.90, 1.48)	1.05 (0.80, 1.37)	1.26 (0.95, 1.67)	1.16 (0.84, 1.60)	0.36	1.00	0.88 (0.73, 1.06)	0.91 (0.70, 1.19)	0.70
Advanced-stage cancer[2]	178	193	188	228	234		543	370	108	
Fully adjusted RR	1.00	1.09 (0.89, 1.34)	1.04 (0.84, 1.29)	1.25 (1.02, 1.53)	1.26 (1.02, 1.54)	0.01	1.00	0.95 (0.81, 1.12)	0.96 (0.76, 1.22)	0.84
With adjustment for P	1.00	1.08 (0.87, 1.35)	1.03 (0.94, 1.30)	1.21 (0.94, 1.54)	1.12 (0.84, 1.49)	0.41	1.00	0.95 (0.80, 1.12)	0.94 (0.74, 1.20)	0.75
Localized cancer[2]	692	767	864	845	808		1642	1965	369	
Fully adjusted RR	1.00	1.00 (0.90, 1.10)	1.11 (1.00, 1.23)	1.09 (0.98, 1.20)	1.08 (0.97, 1.20)	0.10	1.00	1.04 (0.95, 1.13)	1.00 (0.87, 1.14)	0.77
With adjustment for P	1.00	0.99 (0.89, 1.11)	1.09 (0.97, 1.22)	1.04 (0.92, 1.18)	1.02 (0.88, 1.19)	0.74	1.00	1.04 (0.95, 1.13)	0.99 (0.87, 1.13)	0.71
High-grade cancer[3]	120	130	142	152	167		336	300	75	
Fully adjusted RR	1.00	1.02 (0.79, 1.32)	1.15 (0.90, 1.48)	1.22 (0.95, 1.56)	1.33 (1.04, 1.70)	0.009	1.00	0.87 (0.71, 1.06)	0.97 (0.73, 1.31)	0.86
With adjustment for P	1.00	0.93 (0.71, 1.22)	0.98 (0.74, 1.30)	0.96 (0.71, 1.30)	0.97 (0.68, 1.36)	0.86	1.00	0.86 (0.70, 1.05)	0.94 (0.70, 1.26)	0.97
Grade 7 cancer	306	333	373	400	371		750	844	189	
Fully adjusted RR	1.00	1.01 (0.86, 1.18)	1.13 (0.97, 1.32)	1.21 (1.03, 1.41)	1.17 (0.99, 1.36)	0.02	1.00	1.04 (0.91, 1.18)	1.19 (0.99, 1.44)	0.06
With adjustment for P	1.00	1.01 (0.86, 1.19)	1.13 (0.95, 1.34)	1.19 (0.98, 1.43)	1.11 (0.89, 1.39)	0.27	1.00	1.04 (0.91, 1.18)	1.19 (0.98, 1.43)	0.07
Low-grade cancer[3]	464	476	530	510	488		1040	1208	220	
Fully adjusted RR	1.00	0.92 (0.81, 1.05)	1.00 (0.88, 1.14)	0.96 (0.85, 1.10)	0.96 (0.84, 1.09)	0.78	1.00	1.07 (0.96, 1.19)	0.96 (0.81, 1.13)	0.38
With adjustment for P	1.00	0.91 (0.79, 1.04)	0.97 (0.84, 1.12)	0.91 (0.78, 1.07)	0.88 (0.73, 1.06)	0.27	1.00	1.06 (0.96, 1.18)	0.95 (0.80, 1.12)	0.33

[1]Models adjusted for age in months; calendar time; race; height (quartiles); BMI at age 21 y (4 categories); current BMI (6 categories); vigorous physical activity (quintiles); smoking (never, former quit >10 y ago, former quit ≤10 y ago, or current); diabetes; family history of prostate cancer; intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol (all quintiles); energy intake (continuous); multivitamin use (yes/no); and history of prostate-specific antigen testing (yes/no, lagged by one questionnaire cycle). Model with adjustment for P also includes phosphorus intake (quintiles). Calcium from foods (quintiles) and supplements (categories) was included in the same model.

[2]Lethal prostate cancer: prostate cancer death or distant metastases. Advanced: lethal or stage T3b or T4 or N1 or M1 at diagnosis or during follow-up. Localized: T1, T2, T3, or T3a, and N0, M0 without progression during follow-up.

[3]High-grade prostate cancer: Gleason scores 8–10. Low-grade prostate cancer: Gleason scores 2–6.

TABLE 4
RRs (95% CIs) of prostate cancer by quintile of phosphorus intake, 1986–2010[1]

	Quintile of phosphorus intake, mean intake/d					
	1 (1079 mg)	2 (1248 mg)	3 (1365 mg)	4 (1499 mg)	5 (1783 mg)	*P*-trend
All cancer, *n*	1039	1125	1193	1255	1249	
Fully adjusted RR	1.00	1.04 (0.95, 1.13)	1.06 (0.97, 1.16)	1.12 (1.03, 1.22)	1.12 (1.03, 1.23)	0.003
With adjustment for Ca	1.00	1.03 (0.94, 1.12)	1.04 (0.95, 1.15)	1.10 (1.00, 1.22)	1.11 (1.00, 1.24)	0.04
Also with dairy	1.00	1.03 (0.94, 1.12)	1.04 (0.95, 1.14)	1.10 (0.99, 1.21)	1.11 (0.99, 1.24)	0.04
Also with animal protein	1.00	1.03 (0.94, 1.13)	1.05 (0.95, 1.16)	1.11 (1.00, 1.24)	1.13 (1.00, 1.27)	0.04
Lethal cancer[2]	138	148	149	163	191	
Fully adjusted RR	1.00	1.08 (0.85, 1.38)	1.04 (0.82, 1.33)	1.15 (0.90, 1.46)	1.28 (1.01, 1.62)	0.04
With adjustment for Ca	1.00	1.13 (0.88, 1.45)	1.11 (0.86, 1.45)	1.25 (0.95, 1.64)	1.36 (1.01, 1.84)	0.22
Also with dairy	1.00	1.13 (0.88, 1.45)	1.11 (0.86, 1.45)	1.24 (0.94, 1.64)	1.34 (0.99, 1.83)	0.20
Also with animal protein	1.00	1.16 (0.90, 1.49)	1.15 (0.87, 1.51)	1.30 (0.96, 1.74)	1.43 (1.02, 1.99)	0.22
Advanced-stage cancer[2]	180	197	185	211	248	
Fully adjusted RR	1.00	1.11 (0.90, 1.37)	1.01 (0.81, 1.24)	1.16 (0.94, 1.43)	1.31 (1.06, 1.61)	0.01
With adjustment for Ca	1.00	1.15 (0.93, 1.42)	1.05 (0.84, 1.33)	1.23 (0.97, 1.57)	1.39 (1.07, 1.81)	0.06
Also with dairy	1.00	1.15 (0.93, 1.42)	1.06 (0.84, 1.33)	1.24 (0.97, 1.58)	1.40 (1.08, 1.83)	0.04
Also with animal protein	1.00	1.16 (0.93, 1.45)	1.07 (0.84, 1.37)	1.27 (0.98, 1.64)	1.45 (1.08, 1.94)	0.06
Localized cancer[2]	706	748	834	875	813	
Fully adjusted RR	1.00	0.98 (0.89, 1.09)	1.06 (0.95, 1.17)	1.11 (1.00, 1.23)	1.07 (0.96, 1.19)	0.06
With adjustment for Ca	1.00	0.96 (0.86, 1.07)	1.01 (0.90, 1.13)	1.07 (0.95, 1.20)	1.04 (0.91, 1.19)	0.10
Also with dairy	1.00	0.96 (0.86, 1.07)	1.01 (0.90, 1.13)	1.06 (0.94, 1.19)	1.04 (0.90, 1.20)	0.13
Also with animal protein	1.00	0.95 (0.85, 1.06)	1.00 (0.89, 1.12)	1.05 (0.92, 1.19)	1.02 (0.88, 1.19)	0.20
High-grade cancer[3]	109	124	151	157	170	
Fully adjusted RR	1.00	1.17 (0.90, 1.52)	1.33 (1.03, 1.72)	1.44 (1.11, 1.86)	1.56 (1.20, 2.02)	0.0002
With adjustment for Ca	1.00	1.17 (0.89, 1.54)	1.32 (1.00, 1.74)	1.39 (1.03, 1.87)	1.50 (1.09, 2.08)	0.006
Also with dairy	1.00	1.19 (0.90, 1.56)	1.34 (1.01, 1.77)	1.43 (1.06, 1.92)	1.54 (1.10, 2.14)	0.005
Also with animal protein	1.00	1.17 (0.89, 1.55)	1.32 (0.98, 1.77)	1.40 (1.02, 1.92)	1.51 (1.06, 2.17)	0.01
Grade 7 cancer	316	331	374	379	383	
Fully adjusted RR	1.00	0.98 (0.84, 1.15)	1.09 (0.93, 1.27)	1.11 (0.95, 1.30)	1.17 (0.99, 1.37)	0.02
With adjustment for Ca	1.00	0.97 (0.82, 1.14)	1.05 (0.89, 1.24)	1.08 (0.90, 1.29)	1.12 (0.92, 1.37)	0.27
Also with dairy	1.00	0.97 (0.82, 1.14)	1.05 (0.89, 1.25)	1.08 (0.90, 1.30)	1.13 (0.92, 1.38)	0.23
Also with animal protein	1.00	0.98 (0.83, 1.16)	1.08 (0.91, 1.30)	1.13 (0.93, 1.37)	1.19 (0.95, 1.48)	0.14
Low-grade cancer[3]	444	483	507	529	505	
Fully adjusted RR	1.00	1.00 (0.88, 1.14)	1.01 (0.88, 1.15)	1.05 (0.92, 1.20)	1.03 (0.90, 1.18)	0.54
With adjustment for Ca	1.00	1.00 (0.87, 1.15)	1.01 (0.87, 1.16)	1.06 (0.91, 1.24)	1.08 (0.91, 1.28)	0.20
Also with dairy	1.00	1.00 (0.87, 1.14)	1.00 (0.86, 1.15)	1.05 (0.90, 1.23)	1.8 (0.91, 1.28)	0.21
Also with animal protein	1.00	0.98 (0.85, 1.13)	0.98 (0.84, 1.13)	1.02 (0.87, 1.21)	1.03 (0.85, 1.24)	0.50

[1]Models adjusted for age in months; calendar time; race; height (quartiles); BMI at age 21 y (4 categories); current BMI (6 categories); vigorous physical activity (quintiles); smoking (never, former quit >10 y ago, former quit ≤10 y ago, or current); diabetes; family history of prostate cancer; intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol (all quintiles); energy intake (continuous); multivitamin use (yes/no); and history of prostate-specific antigen testing (yes/no, lagged by one questionnaire cycle). Model with adjustment for Ca also includes calcium intake (categories). Model also with dairy includes terms from fully adjusted model, calcium, and also quintiles of dairy intake. Model also with animal protein includes terms from fully adjusted model, calcium, and also quintiles of animal protein intake (it does not include dairy).

[2]Lethal prostate cancer: prostate cancer death or distant metastases. Advanced: lethal or stage T3b or T4 or N1 or M1 at diagnosis or during follow-up. Localized: T1, T2, T3, or T3a, and N0, M0 without progression during follow-up.

[3]High-grade prostate cancer: Gleason scores 8–10. Low-grade prostate cancer: Gleason scores 2–6.

adjusted for along with dietary calcium, the association with dietary calcium disappeared.

However, the results from the latency analysis suggest that phosphorus and calcium may each have an independent effect on advanced-stage and high-grade prostate cancer in different time periods. Calcium intake was associated with increased risk 12–16 y later, whereas phosphorus intake was associated with increased risk more immediately, between 0 and 8 y after exposure. This would indicate that calcium intake has an impact early in the development of prostate cancer, whereas phosphorus intake has much later effects, not showing an association until several years before diagnosis.

Ten prospective studies have looked at calcium intake and prostate cancer since our earlier publication; however, most did not examine or adjust for phosphorus intake, making it difficult to directly compare our results. Four studies found some suggestion of an increased risk of prostate cancer with higher calcium intakes, although the associations by grade and stage were somewhat inconsistent (2, 4, 8, 9). Five studies found no associations for total calcium intake, and one found a significantly decreased risk of high-grade cancer and a significantly increased risk of low-grade cancer with higher total calcium intake (3, 4, 12–15). Total calcium intakes varied widely across study populations; the highest category of intake was <1000 mg/d in 3 studies, whereas the highest category was >2000 mg/d in 3 other studies (3, 4, 9, 12–14).

The finding from the European Prospective Investigation into Cancer and Nutrition (EPIC) study that dairy calcium, but not

TABLE 5
RRs (95% CIs) of prostate cancer by category of calcium intake for various latency periods between exposure and cancer diagnosis[1]

	Total prostate cancer			Advanced prostate cancer[2]			Grades 7–10 prostate cancer		
	n	Adjusted RR	With adjustment for P	*n*	Adjusted RR	With adjustment for P	*n*	Adjusted RR	With adjustment for P
0- to 4-y lag									
<500 mg	316	0.92 (0.81, 1.04)	0.92 (0.81, 1.04)	68	0.92 (0.70, 1.21)	0.96 (0.73, 1.27)	128	0.93 (0.77, 1.13)	0.95 (0.78, 1.16)
500 to <750 mg	1493	1.00	1.00	293	1.00	1.00	609	1.00	1.00
750 to <1000 mg	1649	1.09 (1.01, 1.17)	1.07 (0.99, 1.15)	258	0.95 (0.80, 1.12)	0.89 (0.75, 1.07)	673	1.09 (0.98, 1.22)	1.04 (0.93, 1.17)
1000 to <1250 mg	939	1.01 (0.93, 1.10)	0.98 (0.89, 1.07)	161	1.00 (0.82, 1.22)	0.90 (0.72, 1.12)	455	1.20 (1.06, 1.36)	1.10 (0.95, 1.26)
1250 to <1500 mg	629	1.09 (0.99, 1.20)	1.05 (0.94, 1.16)	110	1.18 (0.94, 1.48)	1.04 (0.81, 1.35)	259	1.10 (0.95, 1.28)	0.99 (0.84, 1.17)
1500 to <2000 mg	537	1.05 (0.94, 1.16)	1.00 (0.89, 1.12)	79	0.97 (0.74, 1.25)	0.85 (0.64, 1.14)	230	1.09 (0.92, 1.27)	0.97 (0.81, 1.16)
≥2000 mg	298	1.09 (0.96, 1.24)	1.05 (0.91, 1.20)	52	1.22 (0.89, 1.67)	1.07 (0.76, 1.51)	140	1.27 (1.05, 1.54)	1.14 (0.92, 1.40)
P-trend		0.11	0.70		0.15	0.84		0.01	0.59
4- to 8-y lag									
<500 mg	382	0.99 (0.88, 1.11)	1.01 (0.90, 1.14)	61	0.87 (0.65, 1.16)	0.91 (0.68, 1.22)	163	1.01 (0.85, 1.20)	1.08 (0.90, 1.29)
500 to <750 mg	1586	1.00	1.00	263	1.00	1.00	667	1.00	1.00
750 to <1000 mg	1511	1.05 (0.98, 1.13)	1.02 (0.95, 1.10)	217	0.97 (0.80, 1.16)	0.92 (0.75, 1.11)	657	1.09 (0.97, 1.21)	1.00 (0.89, 1.12)
1000 to <1250 mg	841	1.00 (0.92, 1.09)	0.98 (0.89, 1.07)	141	1.09 (0.89, 1.35)	1.02 (0.81, 1.29)	379	1.07 (0.94, 1.21)	0.96 (0.83, 1.10)
1250 to <1500 mg	547	1.10 (0.99, 1.21)	1.08 (0.96, 1.21)	88	1.14 (0.89, 1.46)	1.07 (0.80, 1.41)	238	1.14 (0.98, 1.33)	1.04 (0.87, 1.23)
1500 to <2000 mg	403	0.97 (0.87, 1.09)	0.96 (0.85, 1.09)	43	0.67 (0.48, 0.93)	0.63 (0.44, 0.90)	163	0.91 (0.76, 1.09)	0.83 (0.68, 1.01)
≥2000 mg	212	1.06 (0.92, 1.24)	1.05 (0.90, 1.23)	39	1.31 (0.92, 1.87)	1.23 (0.84, 1.81)	106	1.28 (1.03, 1.59)	1.17 (0.93, 1.48)
P-trend		0.51	0.95		0.51	0.93		0.20	0.71
8- to 12-y lag									
<500 mg	358	1.08 (0.96, 1.21)	1.11 (0.98, 1.26)	51	1.18 (0.86, 1.63)	1.19 (0.85, 1.66)	161	1.13 (0.94, 1.34)	1.14 (0.95, 1.37)
500 to <750 mg	1350	1.00	1.00	162	1.00	1.00	574	1.00	1.00
750 to <1000 mg	1213	1.07 (0.99, 1.16)	1.05 (0.96, 1.14)	146	1.08 (0.86, 1.35)	1.05 (0.83, 1.34)	548	1.14 (1.01, 1.28)	1.12 (0.99, 1.27)
1000 to <1250 mg	644	1.06 (0.97, 1.17)	1.05 (0.94, 1.17)	88	1.18 (0.90, 1.54)	1.15 (0.85, 1.55)	317	1.23 (1.07, 1.41)	1.22 (1.04, 1.43)
1250 to <1500 mg	398	1.14 (1.02, 1.28)	1.14 (1.00, 1.30)	47	1.07 (0.77, 1.50)	1.07 (0.73, 1.57)	176	1.18 (0.99, 1.41)	1.20 (0.99, 1.46)
1500 to <2000 mg	295	1.11 (0.98, 1.27)	1.11 (0.96, 1.29)	36	1.05 (0.72, 1.52)	1.05 (0.69, 1.59)	132	1.19 (0.98, 1.44)	1.21 (0.97, 1.50)
≥2000 mg	118	1.00 (0.82, 1.21)	1.00 (0.81, 1.22)	16	1.07 (0.63, 1.83)	1.08 (0.61, 1.90)	54	1.10 (0.83, 1.47)	1.12 (0.83, 1.52)
P-trend		0.26	0.75		0.85	0.99		0.09	0.28
12- to 16-y lag									
<500 mg	285	1.12 (0.98, 1.28)	1.14 (0.99, 1.31)	27	1.25 (0.81, 1.94)	1.24 (0.79, 1.96)	133	1.20 (0.98, 1.46)	1.19 (0.97, 1.45)
500 to <750 mg	1040	1.00	1.00	91	1.00	1.00	450	1.00	1.00
750 to <1000 mg	936	1.12 (1.03, 1.23)	1.11 (1.01, 1.22)	93	1.30 (0.97, 1.75)	1.31 (0.95, 1.80)	433	1.21 (1.06, 1.39)	1.20 (1.04, 1.39)
1000 to <1250 mg	455	1.06 (0.95, 1.19)	1.04 (0.91, 1.18)	57	1.46 (1.04, 2.05)	1.50 (1.02, 2.20)	213	1.15 (0.97, 1.35)	1.10 (0.91, 1.33)
1250 to <1500 mg	286	1.19 (1.04, 1.36)	1.15 (0.99, 1.34)	32	1.52 (1.00, 2.31)	1.59 (0.99, 2.54)	132	1.31 (1.07, 1.59)	1.21 (0.97, 1.53)
1500 to <2000 mg	172	1.05 (0.89, 1.24)	1.02 (0.85, 1.22)	24	1.62 (1.01, 2.59)	1.69 (1.00, 2.84)	77	1.14 (0.89, 1.46)	1.06 (0.81, 1.39)
≥2000 mg	81	1.17 (0.93, 1.48)	1.14 (0.89, 1.45)	13	1.85 (1.00, 3.42)	1.93 (1.00, 3.73)	45	1.63 (1.18, 2.24)	1.51 (1.08, 2.12)
P-trend		0.18	0.66		0.008	0.03		0.009	0.12

[1] Multivariable model adjusted for age; calendar time; race; height (quartiles); BMI at age 21 y (4 categories); current BMI (6 categories); vigorous physical activity (quintiles); smoking (never, former quit >10 y ago, former quit ≤10 y ago, or current); diabetes; family history of prostate cancer; intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol (all quintiles); energy intake (continuous); multivitamin use (yes/no); and history of prostate-specific antigen testing (yes/no, lagged by one questionnaire cycle). Model with adjustment for P also includes phosphorus intake (quintiles).

[2] Advanced: lethal or stage T3b, T4, N1, or M1 at diagnosis or during follow-up.

TABLE 6
RRs (95% CIs) of prostate cancer by quintiles of phosphorus intake for various latency periods between exposure and cancer diagnosis[1]

	Total prostate cancer			Advanced prostate cancer[2]			Grades 7–10 prostate cancer		
	n	Adjusted RR	With adjustment for Ca	*n*	Adjusted RR	With adjustment for Ca	*n*	Adjusted RR	With adjustment for Ca
0- to 4-y lag									
Q1 (low)	1069	1.00	1.00	177	1.00	1.00	429	1.00	1.00
Q2	1106	1.01 (0.92, 1.10)	0.98 (0.90, 1.07)	207	1.21 (0.98, 1.48)	1.23 (0.99, 1.52)	451	1.02 (0.89, 1.17)	1.01 (0.88, 1.16)
Q3	1142	1.01 (0.92, 1.10)	0.98 (0.89, 1.07)	165	0.93 (0.75, 1.16)	0.96 (0.76, 1.22)	491	1.09 (0.95, 1.24)	1.06 (0.92, 1.22)
Q4	1274	1.10 (1.01, 1.20)	1.07 (0.97, 1.17)	234	1.29 (1.05, 1.59)	1.35 (1.07, 1.70)	558	1.22 (1.07, 1.39)	1.18 (1.02, 1.36)
Q5 (high)	1270	1.09 (1.00, 1.18)	1.06 (0.95, 1.17)	238	1.27 (1.03, 1.56)	1.30 (1.01, 1.68)	565	1.25 (1.09, 1.42)	1.21 (1.03, 1.42)
P-trend		0.01	0.05		0.02	0.06		<0.0001	0.001
4- to 8-y lag									
Q1 (low)	989	1.00	1.00	153	1.00	1.00	396	1.00	1.00
Q2	1058	1.03 (0.95, 1.13)	1.03 (0.94, 1.13)	158	1.07 (0.85, 1.34)	1.06 (0.84, 1.34)	434	1.07 (0.93, 1.22)	1.08 (0.94, 1.25)
Q3	1128	1.08 (0.99, 1.18)	1.08 (0.98, 1.19)	170	1.14 (0.91, 1.43)	1.14 (0.90, 1.45)	509	1.24 (1.08, 1.42)	1.27 (1.10, 1.47)
Q4	1187	1.13 (1.03, 1.23)	1.13 (1.02, 1.24)	186	1.23 (0.98, 1.53)	1.23 (0.95, 1.58)	543	1.32 (1.16, 1.51)	1.36 (1.17, 1.59)
Q5 (high)	1120	1.05 (0.96, 1.15)	1.04 (0.93, 1.16)	185	1.14 (0.91, 1.43)	1.16 (0.87, 1.53)	491	1.19 (1.03, 1.36)	1.23 (1.04, 1.46)
P-trend		0.18	0.24		0.17	0.23		0.003	0.007
8- to 12-y lag									
Q1 (low)	791	1.00	1.00	108	1.00	1.00	360	1.00	1.00
Q2	862	1.05 (0.95, 1.16)	1.07 (0.96, 1.18)	99	0.94 (0.71, 1.24)	0.96 (0.72, 1.28)	382	1.02 (0.88, 1.18)	1.02 (0.88, 1.19)
Q3	923	1.12 (1.01, 1.23)	1.12 (1.01, 1.25)	109	1.02 (0.77, 1.34)	1.04 (0.77, 1.40)	401	1.07 (0.92, 1.24)	1.04 (0.89, 1.22)
Q4	913	1.11 (1.00, 1.22)	1.10 (0.98, 1.23)	118	1.09 (0.83, 1.43)	1.09 (0.79, 1.49)	423	1.15 (0.99, 1.33)	1.08 (0.92, 1.28)
Q5 (high)	887	1.08 (0.98, 1.20)	1.05 (0.93, 1.19)	112	0.99 (0.75, 1.31)	0.98 (0.69, 1.39)	396	1.08 (0.93, 1.25)	0.98 (0.81, 1.18)
P-trend		0.11	0.25		0.75	0.80		0.15	0.54
12- to 16-y lag									
Q1 (low)	595	1.00	1.00	60	1.00	1.00	276	1.00	1.00
Q2	653	1.04 (0.93, 1.16)	1.05 (0.93, 1.18)	59	0.96 (0.66, 1.38)	0.93 (0.64, 1.37)	291	1.00 (0.84, 1.18)	1.00 (0.84, 1.19)
Q3	664	1.05 (0.94, 1.18)	1.04 (0.92, 1.18)	71	1.14 (0.80, 1.62)	1.05 (0.71, 1.55)	284	0.96 (0.81, 1.14)	0.94 (0.78, 1.13)
Q4	668	1.06 (0.95, 1.19)	1.04 (0.91, 1.19)	69	1.11 (0.78, 1.59)	0.94 (0.62, 1.42)	305	1.06 (0.90, 1.26)	1.01 (0.83, 1.23)
Q5 (high)	675	1.11 (0.99, 1.24)	1.08 (0.93, 1.25)	78	1.24 (0.87, 1.77)	0.93 (0.59, 1.44)	327	1.19 (1.00, 1.41)	1.11 (0.89, 1.37)
P-trend		0.08	0.23		0.15	0.99		0.02	0.28

[1]Multivariable model adjusted for age; calendar time; race; height (quartiles); BMI at age 21 y (4 categories); current BMI (6 categories); vigorous physical activity (quintiles); smoking (never, former quit >10 y ago, former quit ≤10 y ago, or current); diabetes; family history of prostate cancer; intakes of tomato sauce, α-linolenic acid, supplemental vitamin E, and alcohol (all quintiles); energy intake (continuous); multivitamin use (yes/no); and history of prostate-specific antigen testing (yes/no, lagged by one questionnaire cycle). Model with adjustment for Ca also includes calcium intake (categories). Mean intakes of phosphorus (in mg/d) by quintile, from Q1 to Q5, are as follows: 0- to 4-y lag: 1164, 1311, 1408, 1515, and 1727; 4- to 8-y lag: 1154, 1304, 1404, 1515, and 1734; 8- to 12-y lag: 1144, 1297, 1400, 1515, and 1743; and 12- to 16-y lag: 1131, 1288, 1395, 1513, and 1754. Q, quintile.

[2]Advanced: lethal or stage T3b, T4, N1, or M1 at diagnosis or during follow-up.

nondairy calcium, was associated with total and high-grade prostate cancer risk is consistent with our finding that phosphorus, but not calcium, was independently associated with risk (2). Phosphorus intake was not examined in that EPIC study.

Three studies have looked at both calcium and phosphorus intakes. All 3 of these studies found suggestions that both calcium and phosphorus intake increased prostate cancer risk; however, the independent effects of these nutrients were not fully investigated. In the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) trial cohort, calcium was associated with a statistically significantly increased risk of total prostate cancer (RR: 1.63; 95% CI: 1.27, 2.10 for ≥2000 mg/d compared with <1000 mg/d) and non–advanced-stage cancer, with similar but nonsignificant point estimates for advanced-stage, high-grade, and low-grade disease (9). These results were unchanged when calcium-adjusted phosphorus intake was included in the models; however, because this phosphorus intake variable was adjusted for calcium intake by using the residual method, the variable should be uncorrelated with calcium intake and would be unlikely to affect the calcium estimates. This study found a suggestion of increased risk with higher phosphorus intakes (RR: 1.17; 95% CI: 0.97, 1.40 for extreme quintiles for total prostate cancer), with similar associations by stage and grade. These results were unchanged when adjusted for phosphorus-adjusted calcium intake.

In the SUpplementation en VItamines et Minéraux AntioXydants (SU.VI.MAX) trial cohort, both total calcium and phosphorus intake were associated with an increased risk of total prostate cancer (RR: 2.43; 95% CI: 1.05, 5.62; *P*-trend = 0.04 for highest compared with lowest quartile of calcium; RR: 1.83; 95% CI: 0.89, 3.73; *P*-trend = 0.04 for phosphorus) (8). There were only 69 cases overall, so analysis by stage or grade was not possible. The association for calcium was not affected by adjustment for phosphorus intake. The effect of calcium adjustment on the phosphorus association was not reported.

Tseng et al. (10) found a significantly increased risk of total prostate cancer with higher calcium and phosphorus intakes in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (RR: 2.2; 95% CI: 1.4, 3.5; *P*-trend = 0.001 for highest compared with lowest tertile of calcium; RR:

1.5; 95% CI: 1.0, 2.4; *P*-trend = 0.08 for phosphorus). Phosphorus was no longer associated with risk when calcium was adjusted for (RR: 0.9; 95% CI: 0.5, 1.6). The effect of adjusting for phosphorus on the calcium association was not given. This study had 131 total prostate cancer cases, so analysis by stage or grade was not possible.

One possible mechanism linking calcium intake and prostate cancer is the action of calcium on the calcium-sensing receptor (CaSR) in prostate cells. We previously found a significant association between genetic variation across *CaSR* and lethal prostate cancer risk in Caucasian men in this cohort, suggesting a role for CaSR in lethal disease (16). In the prostate cancer cell line, PC-3, stimulation of CaSR by its agonists caused secretion of parathyroid-related protein, a protein that promotes invasion and the development of bone metastases (17). Interestingly, in colon cancer, in which dietary calcium is protective, activation of CaSR decreases proliferation and increases differentiation, whereas in prostate cancer, overexpression of CaSR is associated with increased cell proliferation and bone metastasis (18–24).

High phosphorus intake may affect prostate cancer progression through its effects on bone turnover. High phosphorus intake increases parathyroid hormone, which promotes bone remodeling (25). Prostate cancer preferentially metastasizes to bone and is more likely to spread to bone with higher remodeling activity (26, 27). Mice treated with parathyroid hormone show a 3-fold increase in metastases to bone (27). An effect of phosphorus intake on the bone, later in prostate cancer progression, would be consistent with the short latency period that we observed between phosphorus intake and cancer diagnosis.

Strengths of our study include the prospective design, collection of multiple FFQs over time, high follow-up rates, and large case numbers, which allow us to look at prostate cancer endpoints by stage and grade. We also have extensive and updated information on possible confounders. The updated questionnaire information also has the effect of reducing some of the measurement error inherent to the FFQ (28). The major limitation of this study is likely measurement error in phosphorus intake. Phosphorus content of processed and restaurant foods is high, because phosphate additives are used to improve appearance, shelf life, and cooking properties of these foods (29). Intake of phosphorus has increased over time in the United States, attributable largely to the increased use of processed foods (29). It has been found that nutrient composition databases do not measure these sources of dietary phosphorus well, and phosphorus intake is probably substantially estimated in this and other studies (30). As such, the observed associations for phosphorus are likely underestimated. In addition, our results by Gleason score are somewhat limited due to our reliance on pathology reports. Gleason scoring has shifted over time, and having slides regraded at a single point in time by a single pathology team has been shown to greatly improve the predictive ability of the Gleason score (31). The measurement error in our Gleason data is likely unrelated to calcium and phosphorus intakes, which suggests that the true association between calcium, phosphorus, and high-grade cancer may be greater than estimated here.

In conclusion, we found that phosphorus intake is associated with increased risk of poorly differentiated and clinically advanced-stage prostate cancer, independent of calcium intake. Calcium intake was associated with these prostate cancers but only at very high intakes and not independently of phosphorus intake. From our latency analysis, calcium may affect advanced-stage and high-grade tumors early in their development, ≥12 y before diagnosis, whereas phosphorus may affect tumors at later stages, 0–8 y before diagnosis. Given the high correlation between calcium and phosphorus intake, as well as their correlation with dairy and meat (for phosphorus) intake, our findings should be interpreted cautiously. However, future studies should thoroughly examine both calcium and phosphorus with respect to prostate cancer. In addition, efforts to improve the measurement of phosphorus intake and the accuracy of nutrient composition databases should be made.

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The authors' responsibilities were as follows—KMW, LAM, and EG: designed the study; KMW and IMS: analyzed data; KMW, IMS, LAM, and EG: wrote the manuscript; and EG: had primary responsibility for final content. All authors read and approved the final manuscript. The authors reported no conflicts of interest related to this study.

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