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Dairy intake after prostate cancer diagnosis in relation to disease-specific and total mortality

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Abstract

Information regarding post-diagnostic dairy intake and prostate cancer survival is limited. We evaluated intake of total, high-fat and low-fat dairy after prostate cancer diagnosis in relation to disease-specific and total mortality. We included 926 men from the Physicians' Health Study diagnosed with non-metastatic prostate cancer between 1982 and 2000 who completed a diet questionnaire a median of 5 years after diagnosis and were followed thereafter for a median of 10 years to assess mortality. Cox proportional hazards regression was used to estimate associations between dairy intake and prostate cancer specific and all-cause mortality. During 8,903 person-years of follow-up, 333 men died, 56 due to prostate cancer. Men consuming 3 servings/day of total dairy products had a 76% higher risk of total mortality and a 141% higher risk of prostate cancer-specific mortality compared to men who consumed less than 1 dairy product/ day (relative risk (RR) = 1.76, 95% confidence interval (CI): 1.21, 2.55, $P_{trend} < 0.001$ for total mortality; RR = 2.41, 95%CI: 0.96, 6.02, $P_{trend} = 0.04$ for prostate cancer specific mortality). The association between high-fat dairy and mortality risk appeared to be stronger than that of low-fat dairy, but the difference between them was not statistically significant (P for difference = 0.57 for prostate cancer-specific mortality and 0.56 for total mortality). Among men without metastases when diagnosed, higher intake of dairy foods after prostate cancer diagnosis may be associated with increased prostate cancer-specific and all-cause mortality.

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Keywords

dairy products; prostate cancer; all-cause mortality; Physicians' Health Study

INTRODUCTION

It is estimated that 220,800 men will be diagnosed and 27,540 men will die of prostate cancer in 2015, making it the most commonly diagnosed malignancy and the 2nd leading cause of cancer death in men in the United States (U.S.).[1] Dietary factors appear to play a role in prostate cancer development,[2-5] particularly dairy intake, given the hypothesized mechanisms involving calcium, vitamin D, saturated fatty acids, and insulin-like growth factors.[6-18] Many epidemiological studies have related dairy intake with higher prostate cancer risk,[19-29] particularly with clinically aggressive disease,[19-22, 26] although findings are inconsistent.[30-32] However, few studies have evaluated whether dairy intake after diagnosis affects prostate cancer progression and survival. To date, this relation has only been examined in the Health Professionals Follow-up Study (HPFS).[33, 34] The initial report from that cohort found an elevated risk of disease progression, defined primarily by biochemical recurrence, with higher milk intake.[33] In an updated analysis with longer follow-up and lethal endpoints, intake of whole milk, but not other dairy foods, was associated with increased risk of lethal prostate cancer.[34] To further evaluate the impact of post-diagnostic dairy intake on prostate cancer progression, we prospectively examined the association of dairy intake after diagnosis with prostate cancer-specific and all-cause mortality among men initially diagnosed with non-metastatic prostate cancer.

MATERIALS AND METHODS

Study population

The Physicians' Health Study (PHS) I was a randomized trial of aspirin and β-carotene for the primary prevention of cardiovascular disease and cancer among 22,071 U.S. male physicians aged 40-84 years in 1982.[35, 36] The aspirin and β-carotene arms were terminated in 1988 and 1995, respectively. The PHS II, initiated in 1997, was a randomized trial of vitamin E, vitamin C, and a multivitamin supplement for the primary prevention of cardiovascular disease, cancer, and age-related eye disease among 14,641 male U.S. physicians, 7,641 of whom had participated in PHS I. The vitamin C and E arms ended in 2007 and the multivitamin arm ended in 2011.[37, 38] Men who participated in both trials continue to be followed with mailed annual questionnaires to update risk factors and ascertain study endpoints. One food frequency questionnaire (FFQ) was sent to all PHS I & II participants to collect diet information between 1999 and 2002. Follow-up for mortality in PHS is over 98% complete. The Institutional Review Board of Partners HealthCare approved this study.

Assessment of dairy intake

Dairy consumption was assessed using a 127-item FFQ, which was modeled after the one used in the HPFS and validated previously.[39] Participants were asked how often they consumed a specified unit of each food item on average during the past year, ranging from

never or less than once per month to more than 6 per day. Dairy foods were categorized into low-fat dairy products (skim or low fat milk (8 oz. glass per serving), cottage or ricotta cheese (1/2 cup per serving), and yogurt (1 cup per serving)) and high-fat dairy products (whole milk (8 oz. glass per serving), other cheese such as American and Cheddar (1 slice or 1 oz. per serving), butter added to food or bread (1 pat per serving) and ice cream (1/2 cup per serving)). Total dairy intake was estimated by combining daily servings of low-fat dairy and high-fat dairy products. In a related cohort, the correlations for dairy foods comparing the FFQ estimates to two 1-week diet records ranged from 0.34 for cottage/ricotta cheese to 0.72 for skim and low-fat milk.[39]

Prostate cancer confirmation

Yearly follow-up questionnaires asked participants if they had been diagnosed with prostate cancer in the previous year. After a report of prostate cancer, medical records and pathology reports were requested to confirm the diagnosis and abstract information on date of diagnosis, tumor-node-metastasis (TNM) stage, Gleason score, prostate specific antigen (PSA) levels, initial treatments, and clinical presentation (i.e., PSA screening, abnormal digital rectal examination, clinical symptoms or other). Among the 1002 men diagnosed with prostate cancer who had complete post-diagnostic diet information, we excluded men with metastatic disease at diagnosis (T4/N1/M1; n=23) or missing data on clinical stage (n=53), leaving 926 men with confirmed non-metastatic prostate cancer at diagnosis available for analysis.

Death ascertainment

Participant deaths were determined by reports from family members and postal authorities or through systematic searches of the National Death Index. Deaths were confirmed through extensive review of death certificates and medical records to determine cause of death, which was assigned by the End Points Committee of three physicians. A death was attributed to prostate cancer if there was evidence of prostate cancer metastases and no other more plausible cause of death could be identified.

Statistical analysis

Descriptive statistics were calculated for demographic characteristics, clinical presentation and dietary intake. χ^2 test and analysis of variance were used to test for the significance of associations across categories of dairy intake. For analyses of prostate cancer-specific and all-cause mortality, person-years of follow-up were counted from the date of FFQ completion until death or end of follow-up (January 1, 2009 or return of the last available questionnaire if after January 1, 2009), whichever came first. In the analysis for prostate cancer mortality, deaths from other causes were censored.

Men with prostate cancer were categorized according to four groups of total dairy intake (less than 1 serving/day, 1 to less than 2 servings/day, 2 to less than 3 servings/day, and 3 or more servings per day). Intake distributions of individual dairy products were narrow thus we were unable to examine individual dairy intake in relation to endpoints. Cox proportional hazards regression models were employed to examine post-diagnostic total dairy consumption in relation to prostate cancer-specific and total mortality, using the lowest

intake category as the reference. P-values for trend were calculated by the Wald test of a score variable that used the median values of intake categories. Cox model was also used to assess continuous high-fat and low-fat dairy intake in relation to the fatal outcomes. Initial models were adjusted for age at diagnosis and total energy intake. Multivariable-adjusted models included additional terms for body mass index (BMI; <25, 25 to < 30, 30kg/m²), smoking status (never, past, current), vigorous exercise (yes, no), time interval between diagnosis and FFQ completion (years), Gleason score (6, 7, 8), clinical T stage (T1/T2, T3), PSA levels at diagnosis (<4, 4-9.9, 10-19.9, 20 ng/ml), initial treatment (radiation, prostatectomy, others, unspecified or missing), family history of prostate cancer (yes, no), and data-derived dietary patterns (excluding all dairy components) to account for the possibility of residual confounding by other dietary factors and overall food choices. Dietary patterns were derived using principal component analysis (PROC FACTOR), and indicators for prudent and western patterns were included in the Cox model. Adjustment for comorbidity scores using modified Charlson comorbidity index [40, 41], aspirin use, cholesterol medication, and personal history of diabetes did not change the results, and therefore, these variables were not included in the main analysis. Models examining low-fat dairy were adjusted for high-fat dairy intake, and vice versa. We also utilized multivariable competing-risk regression model proposed by Fine and Gray [42] to obtain sub-distribution estimates, taking into account prostate cancer-specific mortality and other-cause mortality as competing risks.

We evaluated whether the association between low-fat dairy and mortality differed from the association between high-fat dairy and mortality by including linear terms for both food groupings in the same Cox model and testing the null hypothesis that there was no difference between these terms. We conducted a sensitivity analysis excluding men who died within two years of completing the FFQ to examine the possibility of reverse causation (i.e., dairy consumption being a consequence rather than the cause of disease progression) (n=35 total deaths). To test the robustness of our results, we also performed sensitivity analyses excluding men with prostate cancer death classified without available medical records at the time of death (n=6) and men who developed distant metastases between diagnosis and completion of the diet questionnaire (n=9). P-values for trend were calculated by the Wald statistics of a score variable that contained median values of each category of total dairy intake. The proportional hazards assumption was assessed by including an interaction term of dairy intake and follow-up time divided into 2 periods (5 years and >5 years), and no major violation was observed. Effect modification by age at diagnosis and BMI was evaluated by adding cross-product terms to the multivariable model. All the statistical analyses were two-sided and carried out using SAS v. 9.2 and p-values < 0.05 were considered statistically significant.

RESULTS

We documented 333 deaths, 56 due to prostate cancer, during 8,093 person-years of follow-up among 926 men initially diagnosed with non-metastatic prostate cancer. The median time [25th, 75th percentile] between diagnosis and FFQ completion was 5.1 [2.4, 8.3] years and between FFQ completion and end of follow-up, 9.9 [7.9, 10.7] years.

Men with higher total dairy consumption were more likely to be diagnosed with prostate cancer at an older age (**Table 1**). Compared to men who consumed dairy less often, they were also more likely to consume less vegetable fat, and more animal fat, calcium and vitamin D. Dairy food intake was not related to clinical stage, Gleason score, PSA levels at diagnosis or initial treatment. The median dairy intake after prostate cancer diagnosis was 1.7 servings/day for all dairy foods combined, 0.64 servings/day for high-fat dairy, and 1 serving/day for low-fat dairy (**Table 2**). The most commonly consumed dairy foods (median [range]) were skim or low-fat milk (0.79 [0 - 6.0] servings/day) and American or Cheddar cheese (0.43 [0 - 2.5] servings/day), while the least commonly consumed were yogurt (0 [0 - 4.5] servings/day) and whole milk (0 [0 - 4.5] servings /day) (**Table 2**).

Total dairy food intake after diagnosis was associated with higher risks of prostate cancer-specific and all-cause mortality among men diagnosed with non-metastatic prostate cancer after adjusting for potential confounders (**Table 3**). The multivariable hazard ratios (HR) for men consuming 3 or more servings/day of dairy products were 1.76 (95% confidence interval [CI], 1.21, 2.55; P_{trend}<0.001) for all-cause mortality and 2.41 (95%CI: 0.96, 6.02; P_{trend}=0.04) for prostate cancer-specific mortality, compared with men who consumed less than 1 serving of dairy products per day (Table **3**). Total dairy intake was also significantly associated with higher mortality from other causes (HR$_{Quartile 4 vs Quartile 1}$= 1.62, 95% CI=1.07, 2.45, P$_{trend}$ =0.004), which was mainly driven by cardiovascular disease death (HR$_{Quartile 4 vs Quartile 1}$= 3.15, 95% CI=1.41, 7.06, P$_{trend}$ =0.002).

High-fat dairy consumption appeared to be associated with higher risk of fatal outcomes than low-fat dairy intake (Table **4**). Specifically, 1 serving increase of high-fat dairy was associated with 22% higher risk of total mortality and 30% increased risk of prostate cancer-specific mortality; and 1 serving increase of low-fat dairy was associated with 17% and 16% increased risks of these two outcomes. These associations were not significantly different from each other, however (P for difference =0.56 for all-cause mortality and 0.57 for prostate cancer-specific mortality). Analyses using competing-risk regression models demonstrated similar results (Supplementary Table **1**). In the-fully adjusted models, men consuming 3 or more servings of total dairy per day had a 136% increased risk of prostate cancer-specific mortality than those consuming less than 1 serving.

A sensitivity analysis was conducted by excluding deaths that took place within two years of diet assessment (35 deaths; 8 due to prostate cancer). The result with total dairy intake remained similar for total mortality (HR $_{3 times/day vs <1 time/day}$ =1.70; 95%CI: 1.15, 2.52). The relation between total dairy and prostate cancer-specific mortality remained positive, but was attenuated (HR $_{3 times/day vs <1 time/day}$= 1.50; 95%CI: 0.57, 3.98). However, with only 48 cases in this sensitivity analyses, our statistical power was limited. Excluding cases without medical records or men who reported distant metastases between diagnosis and diet assessment did not considerably alter the results. In addition, the observed associations were not modified by age at diagnosis (<65y vs. 65y) or BMI (<25 kg/m^2 vs. 25 kg/m^2).

DISCUSSION

In a cohort of men initially diagnosed with non-metastatic prostate cancer, we found that total dairy intake after diagnosis was associated with higher risks of prostate cancer-specific and all-cause mortality. The association of high-fat dairy with mortality appeared to be stronger than that of low-fat dairy but these apparent differences were not statistically significant.

Dairy foods have been positively associated with prostate cancer incidence,[19-29] although not in all studies.[30-32] Most of the existing literature suggests a positive association between dairy intake and risk of high stage, high grade and/or fatal prostate cancer.[19-22, 26] Of note, in a previous report from this cohort, dairy food intake in healthy men was related to a higher risk of total prostate cancer and higher risk of fatal prostate cancer.[26] In addition, an increased risk of progression to fatal disease after diagnosis was observed among patients with greater whole milk intake prior to diagnosis (HR $_{2.5 \text{ servings/d vs } 0.5 \text{ servings/d}}$: 1.49; 95% CI: 0.97, 2.28).[26]

Despite the wealth of literature on the relation between dairy and prostate cancer incidence, only two analyses in the same cohort have evaluated the impact of dairy intake after prostate cancer diagnosis on disease survival.[33, 34] In the HPFS cohort, Chan *et al.*[33] found that total milk intake after diagnosis was related to a non-statistically significant elevation in the risk of prostate cancer progression (defined primarily by biochemical recurrence; HR$_{\text{Quartile4 vs Quartile1}}$: 1.30, 95% CI: 0.93, 1.83) among 1,021 men diagnosed with local or regional prostate cancer between 1986 and 1996 and followed through 2000. The relation of total dairy intake or intake of other dairy foods was not reported, however. In a subsequent analysis of this cohort (3,918 men diagnosed with localized prostate cancer between 1986 and 2006 and followed through 2008), Pettersson *et al.*[34] observed no association between total milk and dairy intakes after diagnosis with lethal prostate cancer, but reported a 115% increased risk of lethal disease (95%CI: 28%, 260%) among men with the highest intake of whole milk (>4 servings/week) relative to those with the lowest intake (3 servings/month). In contrast, we found that total dairy food intake was associated with higher disease-specific mortality regardless of fat content. The reasons for the apparently discrepant findings between these studies are unclear but perhaps may be attributable to differences in follow-up time after diagnosis (a median 7.6 years in HPFS vs. a median of 13.8 years in this report), calendar year of disease diagnosis (diagnosis date of 1986 to 2006 in HPFS vs diagnosis date of 1982 to 2000 in PHS), and lower statistical power in the current study (particularly to identify differences between low-fat and high-fat dairy) relative to the previous report.

Mechanisms linking nutrients in dairy foods to prostate cancer progression have been proposed for calcium,[6-11] phosphate,[43] insulin-like growth factors,[12-15] estrogenic hormones,[44, 45] and saturated fat.[16-18] Circulating 1,25-dihydroxycholecalciferol, the active form of vitamin D, has been reported to exert pro-differentiating, anti-proliferative, and anti-metastatic effects on prostatic cells.[6, 7] Dairy calcium may suppress plasma 1,25-dihydroxycholecalciferol concentration, perhaps stimulating parathyroid hormone secretion and bone resorption, accelerating the progression of metastatic disease.[8-11] Phosphate content from dairy could also reduce serum 1,25-dihydroxycholecalciferol concentrations

and subsequently promote disease progression.[43] In addition, the relation may be mediated via raised insulin-like growth factor 1, a potent mitogenic and anti-apoptotic hormone implicated in prostate cancer pathogenesis.[12-15] Higher intake of saturated fat after diagnosis has also been associated with greater risk of prostate cancer progression.[16-18]

The small number of prostate cancer deaths is a critical limitation of this study. This limited our statistical power to evaluate whether low-fat and high-fat dairy and individual dairy products have differing associations with mortality risk. A single measure of post-diagnostic diet and lack of data on pre-diagnostic diet are also important limitations. However, studies where both pre- and post-diagnostic diet was assessed have found that adjustment for pre-diagnostic diet has little influence on post-diagnostic diet effect estimates.[46] Nonetheless, we cannot rule out the possibility that the association for the post-diagnosis diet is simply a reflection of the effect of pre-diagnostic intake. In addition, as is the case of all observational studies, we cannot rule out residual confounding as an explanation for our findings. Nevertheless, we adjusted for known potential confounders in our models, thus minimizing this possibility. Strengths of the study include our ability to adjust for overall dietary patterns, which decreases the likelihood that low-fat and high-fat dairy intakes are merely serving as proxies for overall healthy and unhealthy dietary choices, respectively. Other noteworthy advantages of our study were the long follow-up time (~14 years), use of mortality rather than surrogate outcomes such as disease recurrence, high follow-up rate, the use of a previously validated diet questionnaire, and relatively complete clinical information.

To summarize, in a cohort of men initially diagnosed with non-metastatic prostate cancer, greater post-diagnostic intake of dairy products was associated with higher risk of prostate cancer-specific and all-cause mortality. Positive associations were observed for both low-fat and high-fat dairy. These results contribute to the emerging literature linking post-diagnostic lifestyle factors with disease prognosis among men living with prostate cancer. Given the paucity of data on this area, these results merit replication in other cohorts to evaluate their utility in informing the long-term management of prostate cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENT

Abbreviations used

CI   confidence interval

FFQ   food frequency questionnaire

HR   hazard ratios

HPFS	Health Professionals Follow-up Study
PHS	Physicians' Health Study
TNM	tumor-node-metastasis
PSA	prostate specific antigen

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Table 1

Demographic and dietary characteristics according to post-diagnostic total dairy intake among men diagnosed with non-metastatic prostate cancer in the Physicians' Health Study (n=926)

| | Frequency of total dairy intake (1 serving) | | | | |
	<1 time/day	1 to <2 times/day	2 to <3 times/day	3 times/day	P value[a]
Subject characteristics					
n	187	363	170	206	
Age at diagnosis, mean (SD), y	68.1 (7.1)	68.4 (6.8)	68.5 (6.8)	69.4 (6.7)	0.06
Caucasian, %	93.1	96.7	96.5	95.6	0.23
BMI, kg/m^2, %					0.84
<25	46.0	47.1	44.1	48.5	
25 to < 30	48.1	47.7	50.0	43.7	
30	5.9	5.2	5.9	7.8	
Smoking status, %					0.27
Never	44.9	49.9	39.4	50.5	
Past	53.5	47.7	57.7	46.6	
Current	1.6	2.5	2.9	2.9	
Vigorous exercise, %	56.2	64.7	66.5	67.0	0.10
Family history of prostate cancer, %[b]	16.0	15.4	18.2	18.9	0.69
Clinical T-Stage, %					0.48
T1/T2	95.2	95.6	96.5	93.2	
T3	4.8	4.4	3.5	6.8	
Gleason score, %					0.66
6	67.4	68.9	74.7	66.5	
7	23.5	22.6	15.9	22.3	
8	5.9	6.6	7.7	7.8	
Missing	3.2	1.9	1.8	3.4	
PSA at diagnosis, ng/ml, %					0.66
<4	10.2	9.4	12.9	10.7	
4-9.9	47.1	49.0	42.9	42.2	
10-19.9	16.0	20.1	21.8	20.4	
20+	14.4	9.1	9.4	11.7	
Missing	12.3	12.4	12.9	15.1	
Initial treatment, %[c]					0.64
Radiation	9.6	11.0	7.7	12.1	
Prostatectomy	47.6	44.1	43.5	39.8	
Others	10.2	8.5	7.1	10.2	
Unspecified or missing	32.6	36.4	41.8	37.9	
Daily dietary intake					
Prudent dietary pattern[d]	−0.13 (1.02)	−0.08 (0.95)	0.21 (0.93)	0.09 (1.10)	0.001
Western Dietary pattern[d]	−0.20 (1.03)	−0.11 (0.87)	0.07 (0.96)	0.31 (1.13)	<0.001

	Frequency of total dairy intake (1 serving)				
	<1 time/day	1 to <2 times/day	2 to <3 times/day	3 times/day	P value[a]
Fat, mean (SD), g[e]	48.9 (12.4)	50.1 (11.4)	49.6 (11.5)	53.4 (12.1)	<0.001
Vegetable fat, mean (SD), g[e]	21.3 (7.8)	21.0 (7.6)	19.6 (6.6)	18.3 (6.5)	<0.001
Animal fat, mean (SD), g[e]	27.6 (13.1)	29.1 (10.4)	30.0 (10.2)	35.1 (12.0)	<0.001
Calcium, mean (SD), mg[e]	792 (634)	870 (463)	1139 (594)	1253 (476)	<0.001
Vitamin D, mean (SD), IU[e]	318 (324)	361 (274)	412 (273)	439 (251)	<0.001

[a]Chi-square test was used for categorical variables; Analysis of Variance was used for continuous variables. All statistical tests were two-sided. y = years; BMI = body mass index; PSA = prostate-specific antigen; IU = international unit.

[b]If a patient reported he had a brother or father was ever diagnosed with prostate cancer without including half siblings.

[c]Others include chemo or hormone therapy, orchiectomy, watchful waiting, and other treatments.

[d]Dietary patterns were extracted from food groups (excluding dairy foods) using principle component analysis. Two patterns were identified: a Prudent pattern, characterized by higher intake of vegetables, fruits, fish, legumes, and whole grains; and a Western pattern, characterized by higher intake of processed and red meats, potatoes, high-fat dairy and refined grains. Higher factors indicated higher correlation of Western dietary pattern.

[e]Dietary factors were energy-adjusted.

Table 2

Intake of dairy after diagnosis among men initially diagnosed with non-metastatic prostate cancer between 1982-2002 in Physicians' Health Study (n=926)

Dairy intake	Mean	Median	25th	75th	Range
			Servings per day		
Total dairy	2.06	1.71	1.07	2.71	0.00 - 10.5
High-fat dairy[a]	0.90	0.64	0.29	1.14	0.00 - 6.07
Low-fat dairy[b]	1.15	1.00	0.43	1.43	0.00 - 7.43
Milk	0.94	0.79	0.14	1.00	0.00 - 7.00
Whole milk	0.06	0.00	0.00	0.00	0.00 - 4.50
Skim/low fat milk	0.88	0.79	0.07	1.00	0.00 - 6.00
Cheese	0.47	0.43	0.14	0.57	0.00 - 6.14
Cottage/ricotta cheese	0.12	0.07	0.00	0.14	0.00 - 6.00
Other cheese	0.35	0.43	0.07	0.43	0.00 - 2.50
Ice cream	0.21	0.07	0.00	0.43	0.00 - 2.50
Butter	0.29	0.07	0.00	0.43	0.00 - 4.50
Yogurt	0.15	0.00	0.00	0.14	0.00 - 4.50

[a]High-fat dairy products included whole milk, cheese such as American and Cheddar, butter added to food or bread and ice cream.

[b]Low-fat dairy products included skim or low fat milk, cottage or ricotta cheese, and yogurt.

Table 3

Relative risk of prostate cancer-specific and all-cause mortality according to post-diagnostic intakes of total dairy among men diagnosed with non-metastatic prostate cancer in the Physicians' Health Study (n=926)

	Frequency of total dairy intake (1 serving)					Per serving increase	
	<1 time/day	1 to <2 times/day	2 to <3 times/day	3 times/day	P_{trend}[a]	HR (95% CI)	P-value
Dairy intake, serving/d	0 - 0.9	1.0 - 1.9	2.0 - 2.9	3.0 - 10.5			
Follow-up time, py	1666	3243	1503	1682			
Total mortality							
No. of cases	58	115	65	95		333	
Model1 HR(95%CI)[b]	1.00	1.00 (0.73, 1.38)	1.17 (0.81, 1.68)	1.60 (1.13, 2.29)	0.002	1.15 (1.07, 1.23)	<0.001
Model2 HR(95%CI)[c]	1.00	1.00 (0.73, 1.39)	1.18 (0.81, 1.73)	1.76 (1.21, 2.55)	<0.001	1.19 (1.09, 1.29)	<0.001
Prostate cancer-specific mortality							
No. of cases	9	20	7	20		56	
Model1 HR(95%CI)[b]	1.00	1.16 (0.52, 2.56)	0.91 (0.33, 2.50)	2.42 (1.03, 5.69)	0.02	1.21 (1.01, 1.44)	0.03
Model2 HR(95%CI)[c]	1.00	1.19 (0.53, 2.64)	0.98 (0.34, 2.81)	2.41 (0.96, 6.02)	0.04	1.22 (0.99, 1.50)	0.06

py = person years; HR = hazard ratio; CI = confidence interval.

[a] P_{trend} calculated by modeling the median of each category as a continuous term. All statistical tests were two-sided.

[b] Cox proportional hazards regression model adjusted for age at diagnosis (years, continuous) and total energy intake (kcal, continuous).

[c] Cox proportional hazards regression model adjusted for variables in Model 1 plus body mass index (kg/m², <25, 25 to < 30, 30), smoking status (never, past, current), vigorous exercise (yes, no), Gleason score (<7, 7, >7), clinical stage (T1/T2, T3), prostate-specific antigen level (ng/ml, <4, 4-9.9, 10-19.9, 20), time interval between diagnosis and FFQ completion (years, continuous), initial treatment after diagnosis (radiation, prostatectomy, others, unspecified or missing), family history of prostate cancer (yes, no), and indicators for prudent dietary pattern and western dietary pattern after excluding dairy products (continuous).

Table 4

Relative risk of prostate cancer-specific and all-cause mortality according to post-diagnostic intakes of high-fat and low-fat dairy among men diagnosed with non-metastatic prostate cancer in the Physicians' Health Study (n=926)

Total mortality	HR (95%CI)[a]	P value	P for difference[b]
High-fat dairy (per serving/day)	1.22 (1.08, 1.38)	0.002	0.56
Low-fat dairy (per serving/day)	1.17 (1.05, 1.29)	0.003	
Prostate cancer-specific mortality	**HR (95 %CI)[a]**	**P value**	**P for difference[b]**
High-fat dairy (per serving/day)	1.30 (0.97, 1.73)	0.08	0.57
Low-fat dairy (per serving/day)	1.16 (0.88, 1.53)	0.28	

HR = hazard ratio; CI = confidence interval.

[a] Hazard ratios were per-serving increase of dairy intake. Cox proportional hazards regression model adjusted for age at diagnosis (years, continuous), total energy intake (kcal, continuous), body mass index (kg/m^2, <25, 25 to < 30, 30), smoking status (never, past, current), vigorous exercise (yes, no), Gleason score (<7, 7, >7), clinical stage (T1/T2, T3), prostate-specific antigen level (ng/ml, <4, 4-9.9, 10-19.9, 20), time interval between diagnosis and FFQ completion (years, continuous), initial treatment after diagnosis (radiation, prostatectomy, others, unspecified or missing), family history of prostate cancer (yes, no) and indicators for prudent dietary pattern and western dietary pattern after excluding dairy products (continuous). High-fat dairy and low-fat dairy intakes were mutually adjusted.

[b] P for difference was calculated by including linear terms for both food groupings in the same Cox model and testing the null hypothesis that there was no difference between these terms.