Whole Milk Intake Is Associated with Prostate Cancer-Specific Mortality among U.S. Male Physicians[1–4]

Yan Song,[5,6] Jorge E. Chavarro,[8,10,11] Yin Cao,[8,11] Weiliang Qiu,[8] Lorelei Mucci,[8,11] Howard D. Sesso,[9,11] Meir J. Stampfer,[8,10,11] Edward Giovannucci,[8,10,11] Michael Pollak,[12] Simin Liu,[5–7] and Jing Ma[8,11]*

[5]Department of Epidemiology and Program on Genomics and Nutrition, Fielding School of Public Health, [6]Center for Metabolic Disease Prevention, and [7]Departments of Medicine and Obstetrics and Gynecology, David Geffen School of Medicine, University of California, Los Angeles, CA; [8]Channing Division of Network Medicine, and [9]Divisions of Preventive Medicine and Aging, Brigham and Women's Hospital and Harvard Medical School; Boston, MA; [10]Department of Nutrition, and [11]Department of Epidemiology, Harvard School of Public Health, Boston, MA; and [12]Cancer Prevention Research Unit, Departments of Medicine and Oncology, Lady Davis Research Institute of the Jewish General Hospital and McGill University, Montreal, Quebec, Canada

Abstract

Previous studies have associated higher milk intake with greater prostate cancer (PCa) incidence, but little data are available concerning milk types and the relation between milk intake and risk of fatal PCa. We investigated the association between intake of dairy products and the incidence and survival of PCa during a 28-y follow-up. We conducted a cohort study in the Physicians' Health Study (n = 21,660) and a survival analysis among the incident PCa cases (n = 2806). Information on dairy product consumption was collected at baseline. PCa cases and deaths (n = 305) were confirmed during follow-up. The intake of total dairy products was associated with increased PCa incidence [HR = 1.12 (95% CI: 0.93, 1.35); >2.5 servings/d vs. ≤0.5 servings/d]. Skim/low-fat milk intake was positively associated with risk of low-grade, early stage, and screen-detected cancers, whereas whole milk intake was associated only with fatal PCa [HR = 1.49 (95% CI: 0.97, 2.28); ≥237 mL/d (1 serving/d) vs. rarely consumed]. In the survival analysis, whole milk intake remained associated with risk of progression to fatal disease after diagnosis [HR = 2.17 (95% CI: 1.34, 3.51)]. In this prospective cohort, higher intake of skim/low-fat milk was associated with a greater risk of nonaggressive PCa. Most importantly, only whole milk was consistently associated with higher incidence of fatal PCa in the entire cohort and higher PCa-specific mortality among cases. These findings add further evidence to suggest the potential role of dairy products in the development and prognosis of PCa.

Introduction

Prostate cancer (PCa)[13] is one of the most common cancers among elderly men (1,2). Dairy product intake has been associated with higher risk of PCa in many (3–9) but not all (10–12) studies. In the Physicians' Health Study (PHS), we previously reported that higher intake of dairy products and dairy-derived calcium were associated with a greater risk of developing incident PCa, based on 11 y of follow-up (9). Compared with men consuming ≤0.5 servings/d of dairy products, those consuming >2.5 servings/d had a 34% increase in risk of developing PCa (95% CI: 4%, 71%). In 2 meta-analyses of the relation between dairy product intake and PCa incidence, one showed a significant positive association (13), whereas the other reported an overall null association (14). Part of the reason for this inconsistency could be that most cohort studies (including our previous report in the PHS) and the 2 meta-analyses did not separately evaluate whole milk and skim/low-fat milk. In addition, most studies did not consider advanced disease or PCa-specific death as a major outcome, partly due to the variable duration of follow-up.

In the present study, we assessed the relation between intakes of types of dairy products and PCa risk, with a special emphasis on cases that were high grade and in advanced stages at diagnosis as well as the occurrence of fatal PCa during a 28-y follow-up.

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[3] Parts of this study were presented in abstract form at the 2012 UICC World Cancer Congress on August 28, 2012 in Montreal, Canada.

[4] This trial was registered at www.clinicaltrials.gov as NCT00000500.

[13] Abbreviations used: FDR, false-discovery rate; PCa, prostate cancer; PHS, Physicians' Health Study; PSA, prostate-specific antigen.

* To whom correspondence should be addressed. E-mail: jing.ma@channing.harvard.edu.

Participants and Methods

Study population. The PHS was a randomized, blinded, and placebo-controlled trial of aspirin and β-carotene in the prevention of heart disease and cancer among 22,071 U.S. male physicians aged 40–84 y in 1982 (15,16). At enrollment, participants provided information in the enrollment questionnaires on medical history and several lifestyle factors. All the physicians who were eligible and willing to participate were enrolled in a run-in phase. After 18 wk, participants were sent a questionnaire asking about their health status, side effects of treatment, compliance, and willingness to continue in the trial. Follow-up questionnaires were mailed at 6 and 12 mo after randomization and annually thereafter. Participants were asked to report newly diagnosed diseases, including PCa. For this study, we limited the study population to men who returned the run-in questionnaires with relevant abbreviated dietary information. To reduce the potential for undiagnosed PCa to influence diet and to utilize the dietary data collected on the 12-mo questionnaire, we excluded PCa cases diagnosed during the first year in the study, men with BMI <18.5 kg/m^2 at baseline, and men without baseline BMI information. These exclusions resulted in a study population of 21,660 men for analysis. The study design and methods used in this investigation were reviewed and approved by the Institutional Review Board of Partners Healthcare.

Dietary assessment. The run-in and 12-mo questionnaires in the PHS included abbreviated FFQs. The run-in questionnaire asked about the consumption of whole milk, skim/low-fat milk, and cold breakfast cereal (categories: ≥2 servings/d, daily, 5–6 servings/wk, 2–4 servings/wk, 1 serving/wk, 1–3 servings/mo, rarely/never) in the past year. The 12-mo questionnaire asked about the intake during the previous year of hard cheese (e.g., American, Cheddar) and ice cream. We considered these 5 foods to be the main contributors to dairy product intake and combined those responses by servings to estimate total daily dairy product intake (9). Because the potential effects of dairy calcium on PCa risk were of interest, we also calculated total dairy calcium intake from each dairy product. Calcium content was obtained from the nutrient composition database of the USDA (17). The calcium content per serving (as weights in the total calcium consumption) is as follows: whole milk (1 serving = 237 mL), 276 mg; skim/low-fat milk (1 serving = 237 mL), 299 mg; ice cream (1 serving = 214 g, as in vanilla savor), 169 mg; and hard cheese (1 serving = 28 g, as an average of American cheese and Cheddar cheese), 173 mg. Two questions about red meat intake were also included in the 12-mo questionnaire, which asked about the intake of beef, pork or lamb as a sandwich or mixed dish (hamburger, stew, casserole, lasagna, etc.) and those as a main dish (steak, roast, ham, etc.). Daily intake of red meat was calculated as the sum of the servings (1 serving = 227 g) for each of these 2 items.

Ascertainment of PCa outcomes. For the PCa incidence analyses, men were followed from the date when the 12-mo questionnaire was returned until the date of PCa diagnosis, date of death, or the end of follow-up (March 9, 2010), whichever came first. For the PCa-specific analyses, men were followed from the date of PCa diagnosis until the date of death from PCa, date of death from other causes, or March 9, 2010, whichever came first. We learned of deaths in the cohort through notification by family members and postal authorities and through periodic systematic searches of the National Death Index. Cause of death was determined by an endpoint committee of 3 physicians based on all available information, including medical records and death certificates. Follow-up for mortality was at least 97.7% complete and for morbidity, 95.3% (18).

Whenever a participant reported a new diagnosis of PCa, we requested hospital records and pathology reports to confirm the diagnosis and determine tumor stage, grade, and other clinical characteristics at diagnosis. Histological grade was recorded following the Gleason scoring system from the pathology reports. Low-grade tumors were defined as Gleason ≤7 and high-grade was defined as Gleason >7. Clinical stage was determined using the TNM staging system. Tumors of stage T3 or higher (T3/T4/N1/M1) were categorized as advanced-stage tumors and tumors of stage T1 or T2 were defined as early-stage tumors. Cases without pathologic staging were classified as undetermined stage unless there was clinical evidence of distant metastases. Because prostate-specific antigen (PSA) screening has dramatically changed the clinical presentation of the cancer, we also categorized the cases into 3 groups: pre-PSA era cases (diagnosed before 1990), post-PSA era cases (diagnosed 1990 or thereafter) who presented with prostatic or metastatic symptoms, and post-PSA era cases detected by PSA or digital rectal examination screening.

Statistical analyses. To examine the association of dairy products and calcium consumption with PCa risk, we used Cox proportional hazards regression models to calculate the HR and 95% CI, with the lowest intake category as the reference group. We categorized the intake of each dairy food into 4 groups (rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d). Calcium intake from dairy products was categorized into 5 groups by quintiles. Tests for linear trend were performed using the median intake values in each category as a continuous variable. Beyond age-adjusted models, multivariable models additionally included terms for baseline (time when 12-mo questionnaire was returned) cigarette smoking (never, past, or current smoker), vigorous exercise (exercise vigorously to sweat more than twice per week or not), alcohol intake (drink alcoholic beverages every day or not), race (Caucasian or non-Caucasian), BMI (<25.0, 25.0–29.9, or ≥30.0 kg/m^2), diabetes status (yes or no), red meat consumption (servings/week), and assignment in the original trial (active treatment or placebo for aspirin and β-carotene). In addition, the models for whole milk and skim/low-fat milk were mutually adjusted for each other.

The abbreviated FFQs in the PHS were not comprehensive; thus, we were unable to calculate and adjust for total energy intake directly. To minimize the potential confounding due to total energy intake, we calculated total energy intake using only the food items that were recorded in the run-in and 12-mo questionnaires. These food items included 13 types of fruits and vegetables, 5 types of dairy foods investigated in this study, eggs, chicken, beef, 4 types of fish and seafood, cookies, chips, nuts, and fried foods. Under similar situations, previous studies used food scores by summing up servings of all recorded food items (9,19). In this study, we weighted the servings of recorded food items with total calorie per serving of each individual item to better emulate total energy intake calculated from comprehensive FFQs.

Separate multivariable models for PCa incidence were fit for subgroups of cancer according to Gleason grade, clinical stage, and disease presentation at diagnosis, and disease fatality during follow-up. We then modeled the relation between dairy product and PCa-specific mortality among cases using the Cox proportional hazard regression model. Besides the age- and multivariable-adjusted model [including the same set of covariates as in the incidence model and stage of tumor (T3/T4/N1/M1 or T1/T2) and Gleason score (>7 or ≤7)], we further stratified the analyses by disease presentation at diagnosis (pre-PSA era presented, post-PSA era presented by symptom, and post-PSA era presented by screening). To account for potential false positives due to multiple comparisons, we calculated the false-discovery rate (FDR) by incorporating all P values from multiple tests performed for the linear trends. The FDR statistics were obtained for each P value, and FDR statistics with $q < 0.05$ were considered significant (20). All analyses were performed in SAS version 9.3 (SAS Institute). All P values are 2-sided.

Results

We confirmed 2806 incident cases of PCa diagnosed among 21,660 men in 470,612 person-years through 2010. The baseline characteristics of the study population by categories of dairy product intake are presented in **Table 1**. Men who consumed more dairy products tended to be older, smoked less, drank less alcohol, exercised more, and were more likely to be Caucasian and diabetic. When stratified by type of milk, the data showed that men who consumed more skim/low-fat milk tended to smoke less, drink less alcohol, and exercise more and were more likely to be Caucasian, whereas men who consumed more

TABLE 1 Baseline characteristics by category of baseline dairy product intake in the PHS (n = 21,660)[1]

	Dairy product intake,[2] servings						Whole milk, servings			Skim/low-fat milk, servings		
	≤0.5/d (n =3446)	>0.5–1.0/d (n = 3878)	>1.0–1.5/d (n = 4527)	>1.5–2.5/d (n = 6390)	>2.5/d (n = 3302)	P	≤1/wk (n = 16,618)	≥2/wk (n = 4207)	P	≤1/wk (n = 11,834)	≥2/wk (n = 9186)	P
Age, *y*	52.3 ± 8.8	52.7 ± 9.0	53.4 ± 9.4	54.3 ± 9.7	55.1 ± 10.0	<0.001	53.0 ± 9.1	55.5 ± 10.2	<0.001	53.4 ± 9.4	53.6 ± 9.4	0.12
BMI, *%*						<0.001			0.08			0.004
Normal weight	56	55	56	60	61		58	56		57	59	
Overweight	40	41	40	36	35		38	39		39	37	
Obese	4	4	4	4	4		4	4		4	4	
Caucasian, *%*	85	91	93	95	96	<0.001	93	89	<0.001	90	95	<0.001
Diabetes, *%*	1.6	1.4	1.5	2.4	2.6	<0.001	1.7	2.6	<0.001	1.6	2.3	<0.001
Smoking, *%*						<0.001			<0.001			<0.001
Never	46	47	49	53	56		51	48		48	54	
Former	41	41	40	39	35		40	37		41	37	
Current	13	12	11	8	9		9	15		12	8	
Frequent drinker,[3] *%*	29	25	24	24	20	<0.001	24	24	0.97	26	21	<0.001
Vigorous exercise,[4] *%*	48	52	54	56	59	<0.001	55	50	<0.001	51	58	<0.001
Red meat intake,[5] *servings/wk*	0.6 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.4	0.8 ± 0.5	<0.001	0.7 ± 0.4	0.8 ± 0.5	<0.001	0.7 ± 0.5	0.7 ± 0.4	<0.001

[1] Values are percentage or mean ± SE. PHS, Physicians' Health Study.
[2] Based on the consumption of 5 major dairy foods (whole milk, skim/low-fat milk, hard cheese, ice cream, and cold breakfast cereal) assessed from 1982 to 1984. One serving of whole milk, skim/low-fat milk, or cold breakfast cereal = 237 mL; 1 serving of ice cream = 214 g; 1 serving of hard cheese = 28 g.
[3] Frequent drinker was defined as someone who drinks alcoholic beverages every day.
[4] Vigorous exercise was defined as to exercise vigorously to a sweat more than twice per week.
[5] 1 serving of red meat = 227 g.

whole milk tended to be current smokers, exercise less, and less likely to be Caucasian.

Total dairy food intake was marginally associated with overall PCa risk. In multivariable-adjusted analyses, men in the highest category of total dairy foods had a 12% (95% CI: −7%, 35%) higher risk to develop PCa than men in the lowest intake category (P-trend = 0.06) (**Table 2**). For individual dairy foods, skim/low-fat milk had the strongest association with PCa incidence: the multivariable-adjusted HR was 1.19 (95% CI: 1.06, 1.33; P-trend = 0.001), comparing the highest [≥237 mL/d (1 serving/d)] with the lowest (rarely consumed) intake category. In contrast, whole milk, hard cheese, ice cream, and cold breakfast cereal intakes were not significantly associated with overall risk of PCa incidence. Calcium from dairy foods was marginally associated with PCa incidence (P-trend = 0.07).

We next examined the association of total dairy products, whole milk, and skim/low-fat milk with special attention to cancer subtypes and the timing of diagnosis (i.e., 1982–1989, pre-PSA era vs. 1990–2010, post-PSA era) (**Table 3**). We found that higher intake of skim/low-fat milk was mainly associated with a higher risk of low-grade, early-stage, and screen-detected disease; comparing the highest with the lowest intake category, the HR were 1.20 for low-grade cases (95% CI: 1.06, 1.37), 1.19 for early-stage cases (95% CI: 1.04, 1.35), and 1.21 for post-PSA era cases detected by screening (95% CI: 1.02, 1.43) (P-trend ≤ 0.01 for all the subgroup analyses). In contrast, for risk of fatal PCa, whole milk was the only dairy food that had a positive association [HR = 1.49 (95% CI: 0.97, 2.28); P-trend = 0.01]. This association was independent of age, cigarette smoking status, BMI, alcohol intake, vigorous physical activity, diabetes status, red meat consumption, and total energy intake from recorded food items.

Finally, among all the PCa cases, we conducted a survival analysis to evaluate the associations of prediagnostic dairy food intake with risk of progression to fatal PCa after initial diagnosis and found that whole milk was the only dairy food that was significantly associated with an increased risk of PCa-specific mortality (**Table 4**). Compared with nondrinkers of whole milk, the multivariable-adjusted HR was 2.17 (95% CI: 1.34, 3.51; P-trend < 0.001) for those who consumed ≥237 mL/d (1 serving/d). A stratified analysis on age at diagnosis showed that high intake of whole milk was significantly associated with risk of progression to fatal PCa in both old and young age groups, except that there tended to be a J-shaped relation in the older group (data not shown). In a stratified analysis on the presentation of disease, we found that, among post-PSA era cases presented by screening, whole milk intake was associated with PCa deaths, although the q value was not significant [HR = 1.82 (95% CI: 0.69, 4.84); P-trend = 0.07]. The associations with skim/low-fat milk, however, were not significant in any of the substrata by PSA era and screening.

Discussion

In this study, we confirmed and extended our previous findings that total dairy product intake and calcium from dairy foods were positively associated with overall risk of PCa. Admittedly, the dairy variables in our study did not capture all dairy product intake (did not include information on intakes of yogurt, cream, butter, etc.). However, according to data from the NHANES, milk and cheese intakes can account for ~98% of total dairy product intake (21). Thus, our data on available dairy food items sufficiently represented the total dairy product intake in our population. The magnitude of the overall association between total dairy product intake and the risk of incident PCa [HR = 1.12 (95% CI: 0.93, 1.35)] in this study, however, was weaker than in our previous report [RR = 1.34 (95% CI: 1.04, 1.71)]. Because the current analysis had a much larger sample size (2806 cases vs. 1012 cases) and an additional 15 y of follow-up, these allowed us to specifically evaluate subtypes of dairy products and by subtypes of PCa, cancer diagnosed before vs. in the PSA era, mode of diagnosis, and cancer-specific mortality (9). We found that skim/low-fat milk intake were

TABLE 2 HR estimates for PCa by intake of dairy product and dairy calcium in the PHS (n = 21,660)[1]

	Category 1	Category 2	Category 3	Category 4	Category 5	P-trend[2]
All dairy food[3]						
Cases/person-years	388/76,216	446/86,740	586/98,871	910/137,667	458/69,738	
Age-adjusted	1.00	1.00 (0.88, 1.15)	1.11 (0.98, 1.26)	1.19 (1.06, 1.34)	1.15 (1.00, 1.31)	0.003[4]
Multivariable-adjusted[5]	1.00	0.96 (0.83, 1.11)	1.07 (0.93, 1.23)	1.15 (0.99, 1.32)	1.12 (0.93, 1.35)	0.06
Whole milk[6]						
Cases/person-years	1674/279,675	504/86,554	273/47,723	244/39,924		
Age-adjusted	1.00	0.97 (0.88, 1.08)	0.89 (0.78, 1.01)	0.89 (0.78, 1.02)		0.04
Multivariable-adjusted[5]	1.00	1.02 (0.92, 1.13)	0.93 (0.81, 1.07)	0.95 (0.81, 1.10)		0.32
Skim/low-fat milk[6]						
Cases/person-years	895/160,367	531/98,250	579/94,591	724/104,959		
Age-adjusted	1.00	1.05 (0.94, 1.17)	1.17 (1.05, 1.29)	1.21 (1.10, 1.34)		<0.001[4]
Multivariable-adjusted[5]	1.00	1.02 (0.91, 1.14)	1.12 (1.00, 1.25)	1.19 (1.06, 1.33)		0.001[4]
Hard cheese[6]						
Cases/person-years	197/35,560	1207/208,462	1175/190,531	178/28,270		
Age-adjusted	1.00	1.05 (0.90, 1.22)	1.12 (0.96, 1.30)	1.10 (0.90, 1.35)		0.14
Multivariable-adjusted[5]	1.00	1.01 (0.87, 1.18)	1.07 (0.91, 1.25)	1.05 (0.85, 1.30)		0.32
Ice cream[6]						
Cases/person-years	455/75,120	1415/251,406	805/124,783	84/12,177		
Age-adjusted	1.00	0.96 (0.86, 1.06)	1.06 (0.95, 1.19)	1.05 (0.83, 1.32)		0.06
Multivariable-adjusted[5]	1.00	0.95 (0.85, 1.06)	1.02 (0.90, 1.15)	1.03 (0.80, 1.32)		0.26
Cold breakfast cereal[6]						
Cases/person-years	743/131,310	654/120,759	678/112,540	679/98,469		
Age-adjusted	1.00	0.96 (0.86, 1.06)	1.02 (0.92, 1.13)	1.11 (1.00, 1.23)		0.01[4]
Multivariable-adjusted[5]	1.00	0.95 (0.85, 1.06)	1.00 (0.88, 1.12)	1.06 (0.93, 1.22)		0.17
Calcium from dairy food[7]						
Cases/person-years	487/95,147	516/95,489	578/93,334	598/92,688	609/91,575	
Age-adjusted	1.00	1.04 (0.92, 1.18)	1.15 (1.02, 1.30)	1.16 (1.03, 1.31)	1.17 (1.03, 1.31)	0.004[4]
Multivariable-adjusted[5]	1.00	1.01 (0.89, 1.15)	1.12 (0.98, 1.28)	1.12 (0.97, 1.30)	1.14 (0.97, 1.34)	0.07

[1] Values are HR (95% CI). FDR, false-discovery rate; PCa, prostate cancer; PHS, Physicians' Health Study.
[2] Calculated in a separate regression model with the median intake levels in each category as a continuous variable.
[3] Based on the consumption of 5 major dairy foods (whole milk, skim/low-fat milk, hard cheese, ice cream, and cold breakfast cereal) assessed from 1982 to 1984. The 5 intake level groups are: ≤0.5 servings/d, >0.5–1.0 serving/d, >1.0–1.5 servings/d, >1.5–2.5 servings/d, and >2.5 servings/d. One serving of whole milk, skim/low-fat milk, or cold breakfast cereal = 237 mL; 1 serving of ice cream = 214 g; 1 serving of hard cheese = 28 g.
[4] FDR < 0.05.
[5] Adjusted for baseline measures of age (y), cigarette smoking (never, past, current), vigorous exercise (exercise vigorously to a sweat more than twice per week or not), alcohol intake (drink alcoholic beverages every day or not), race (Caucasian, non-Caucasian), BMI (normal weight, overweight, obese), baseline diabetes status (yes, no), red meat consumption (servings/wk), total energy intake from recorded food items (kcal), assignment in the original aspirin trial (treatment, placebo), and assignment in the original β-carotene trial (treatment, placebo). In addition, the models for whole milk and skim/low-fat milk were mutually adjusted for each other (rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d).
[6] The 4 intake level groups were: rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d.
[7] The 5 intake level groups were categorized according to quintiles.

related to a higher risk of nonaggressive disease (low-grade, early-stage, and screen-detected cases), whereas whole milk intake was associated with a higher risk of fatal PCa and, among all the cases, with a higher risk of progression to fatal PCa.

The positive association between dairy product intake and PCa has been reported in several studies, including the European Prospective Investigation into Cancer and Nutrition (22) and studies from Canada (23) and Japan (4). These data raised concerns regarding whether dairy should be recommended as part of a healthy diet for aging men (24,25). However, the results of 2 meta-analyses of the relation between dairy product intake and PCa provided conflicting conclusions: one showed a significant positive association (13) and the other (supported by the National Dairy Council) showed an overall null association (14). Part of the reason for this inconsistency could be a lack of detailed data for the effect of whole compared with skim/low-fat milk and their impact on high-risk disease or PCa-specific death.

Our finding that the strongest association with total dairy products was in the pre-PSA era was consistent with findings of Rodriguez et al. (26). We observed a significant positive association of skim/low-fat milk with overall PCa risk. These results are consistent with previous studies (6,27). Few studies specifically evaluated high-risk PCa. Park et al. (28) observed that skim milk, but not other dairy foods, was associated with a nonsignificantly increased risk of advanced PCa. The null effect of whole milk on overall PCa risk is likely due to the fact that the whole milk drinkers accounted for only a small portion of all milk drinkers. Thus, the associations of whole milk with the nonfatal cases, if any, were not large enough to be detected with a limited number of cases, which may have driven the overall effect.

The commonly accepted risk factors for incident PCa are older age, a family history of PCa, and being African American (29). However, there is no consensus about risk factors for fatal PCa beyond clinical characteristics such as PSA at diagnosis, Gleason grade, and clinical stage. Identifying modifiable risk

TABLE 3 Multivariable-adjusted HR estimates for categories of PCa cases by intake of dairy product in the PHS (n = 21,660)[1,2]

Selected case[3]	Category 1	Category 2	Category 3	Category 4	Category 5	P-trend[4]
Dairy product[5]						
High grade	1.00	1.04 (0.69, 1.58)	0.77 (0.50, 1.20)	1.09 (0.71, 1.68)	1.04 (0.60, 1.80)	0.64
Low grade	1.00	0.95 (0.81, 1.12)	1.11 (0.95, 1.30)	1.13 (0.95, 1.33)	1.13 (0.91, 1.39)	0.12
Advanced	1.00	0.92 (0.59, 1.46)	0.79 (0.50, 1.27)	0.92 (0.57, 1.48)	0.68 (0.36, 1.27)	0.35
Localized	1.00	0.94 (0.80, 1.11)	1.09 (0.93, 1.29)	1.11 (0.94, 1.32)	1.13 (0.91, 1.39)	0.13
Fatal	1.00	1.19 (0.68, 2.06)	1.81 (1.08, 3.02)	2.14 (1.26, 3.64)	1.73 (0.90, 3.35)	0.05
Pre-PSA	1.00	1.70 (0.95, 3.05)	1.77 (1.00, 3.13)	1.82 (1.01, 3.27)	2.12 (1.07, 4.19)	0.10
Post-PSA (symptom)	1.00	1.44 (0.78, 2.68)	1.25 (0.66, 2.34)	1.83 (0.99, 3.40)	1.61 (0.76, 3.40)	0.19
Post-PSA (screening)	1.00	0.83 (0.67, 1.03)	1.10 (0.90, 1.34)	1.04 (0.84, 1.28)	0.99 (0.75, 1.30)	0.64
Whole milk[6]						
High grade	1.00	0.69 (0.48, 1.00)	1.29 (0.91, 1.84)	0.78 (0.49, 1.25)		0.81
Low grade	1.00	1.09 (0.97, 1.23)	0.86 (0.73, 1.01)	0.91 (0.76, 1.10)		0.10
Advanced	1.00	0.89 (0.61, 1.29)	1.04 (0.68, 1.61)	0.83 (0.49, 1.41)		0.63
Localized	1.00	1.06 (0.94, 1.19)	0.87 (0.74, 1.03)	0.89 (0.74, 1.07)		0.08
Fatal	1.00	0.89 (0.60, 1.31)	1.77 (1.23, 2.54)	1.49 (0.97, 2.28)		0.01[7]
Pre-PSA	1.00	1.29 (0.89, 1.86)	1.51 (1.00, 2.27)	1.35 (0.85, 2.15)		0.15
Post-PSA (symptom)	1.00	1.22 (0.80, 1.86)	1.19 (0.71, 1.99)	1.29 (0.76, 2.21)		0.38
Post-PSA (screening)	1.00	1.00 (0.86, 1.17)	0.74 (0.59, 0.93)	0.73 (0.57, 0.94)		0.002[7]
Skim/low-fat milk[6]						
High grade	1.00	1.11 (0.79, 1.56)	1.07 (0.76, 1.51)	1.19 (0.85, 1.67)		0.39
Low grade	1.00	0.99 (0.87, 1.13)	1.18 (1.04, 1.35)	1.20 (1.06, 1.37)		0.001[7]
Advanced	1.00	0.94 (0.64, 1.38)	1.02 (0.69, 1.49)	0.99 (0.67, 1.45)		0.96
Localized	1.00	0.99 (0.86, 1.13)	1.18 (1.04, 1.35)	1.19 (1.04, 1.35)		0.004[7]
Fatal	1.00	1.04 (0.72, 1.51)	1.01 (0.69, 1.47)	1.04 (0.71, 1.51)		0.91
Pre-PSA	1.00	1.38 (0.92, 2.07)	1.69 (1.15, 2.48)	1.43 (0.97, 2.12)		0.11
Post-PSA (symptom)	1.00	0.84 (0.52, 1.35)	1.02 (0.64, 1.62)	1.22 (0.79, 1.88)		0.23
Post-PSA (screening)	1.00	0.98 (0.83, 1.17)	1.20 (1.01, 1.42)	1.21 (1.02, 1.43)		0.01[7]

[1] Values are HR (95% CI). FDR, false-discovery rate; PCa, prostate cancer; PHS, Physicians' Health Study; PSA, prostate-specific antigen.
[2] Adjusted for baseline measures of age (y), cigarette smoking (never, past, current), vigorous exercise (exercise vigorously to a sweat more than twice per week or not), alcohol intake (drink alcoholic beverages every day or not), race (Caucasian, non-Caucasian), BMI (normal weight, overweight, obese), baseline diabetes status (yes, no), and red meat consumption (servings/wk), total energy intake from recorded food items (kcal), assignment in the original aspirin trial (treatment, placebo), and assignment in the original β-carotene trial (treatment, placebo). In addition, the models for whole milk and skim/low-fat milk were mutually adjusted for each other (rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d).
[3] High grade (n = 317): Gleason >7; low grade (n = 2105): Gleason ≤7; advanced (n = 272): T3/T4/N1/M1; localized (n = 2016): T1/T2; fatal (n = 305): died of PCa; pre-PSA era (n = 274): diagnosed before 1990; post-PSA era: diagnosed after 1990; presented by symptom (n = 192): presented by prostate-related symptoms or metastases; presented by screening (n = 1233): presented by PSA test screening or digital rectal examination;
[4] Calculated in a separate regression model with the median intake in each category as a continuous variable.
[5] Based on baseline consumption of 5 major dairy foods (whole milk, skim/low-fat milk, hard cheese, ice cream, and cold breakfast cereal). The 5 intake level groups are: ≤0.5 servings/d, >0.5–1.0 serving/d, >1.0–1.5 servings/d, >1.5–2.5 servings/d, and >2.5 servings/d. One serving of whole milk, skim/low-fat milk, or cold breakfast cereal = 237 mL; 1 serving of ice cream = 214 g; 1 serving of hard cheese = 28 g.
[6] The 4 intake level groups were: rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d.
[7] FDR < 0.05.

factors for fatal PCa is critical, because widespread PSA testing in the US is likely to detect and overtreat a large number of men with indolent cancer (30). A major challenge in PCa research is distinguishing risk factors for aggressive PCa from indolent disease to reduce overtreatment. Our results showed that higher intakes of whole-fat milk predispose men to a higher risk of developing fatal PCa and, once they had the cancer, a higher risk of progression to fatal disease. This association was unlikely confounded by skim/low-fat milk according to our analysis.

Given that dairy product intakes were assessed years before cancer diagnosis, our findings need to be further confirmed by cohorts with more detailed dietary information, especially dietary intakes at or around the time of the cancer diagnosis. In the Health Professionals Follow-up Study cohort, Chan et al. (31) found that men in the highest compared with the lowest quartile of milk consumption after diagnosis had a nonsignificantly elevated risk of fatal PCa [HR = 1.30 (95% CI: 0.93, 1.83)], but this study did not examine specific types of dairy food. Another explanation of the association between whole milk intake and fatal PCa risk is also possible: it is likely that men who drink more whole milk are less likely to be screened and therefore are diagnosed at a later stage and are at a higher risk for fatal disease. In the survival analysis, we adjusted for Gleason score and stage of tumor at diagnoses. The association remained significant after the adjustment, which supports that the association was not due to confounding by screening. However, further data on PSA screening intensity are needed to justify or refute this explanation.

In our study, the average interval between dairy product intake assessment and PCa diagnosis was 14 y, yielding possible exposure misclassification. This is of particular concern for the analysis of PCa survival, because patients may have changed

TABLE 4 HR estimates of PCa death by prediagnostic intake of dairy product and dairy calcium in PCa cases in the PHS (n = 2806)[1]

	Category 1	Category 2	Category 3	Category 4	Category 5	P-trend[2]
All dairy food[3]						
Deaths/person-years	27/3601	45/4012	74/5222	115/8503	43/4416	
Age-adjusted	1.00	1.50 (0.93, 2.41)	1.83 (1.18, 2.85)	1.73 (1.14, 2.63)	1.22 (0.75, 1.97)	0.75
Multivariable-adjusted[4,5]	1.00	0.97 (0.53, 1.78)	2.23 (1.26, 3.92)	1.87 (1.04, 3.37)	1.71 (0.82, 3.58)	0.16
Pre-PSA	1.00	1.16 (0.33, 4.05)	2.20 (0.66, 7.29)	1.02 (0.29, 3.51)	2.15 (0.53, 8.79)	0.76
Post-PSA (screening)	1.00	0.74 (0.27, 2.03)	1.09 (0.45, 2.64)	1.24 (0.50, 3.06)	0.93 (0.26, 3.36)	0.80
Whole milk[6]						
Deaths/person-years	161/15,350	43/4860	49/2504	43/2092		
Age-adjusted	1.00	0.85 (0.60, 1.18)	1.81 (1.32, 2.49)	1.85 (1.32, 2.59)		<0.001[7]
Multivariable-adjusted[4,5]	1.00	0.73 (0.47, 1.13)	1.79 (1.15, 2.79)	2.17 (1.34, 3.51)		<0.001[7]
Pre-PSA	1.00	0.77 (0.36, 1.63)	0.68 (0.23, 1.98)	1.21 (0.45, 3.24)		0.67
Post-PSA (screening)	1.00	0.84 (0.40, 1.79)	2.26 (1.07, 4.78)	1.82 (0.69, 4.84)		0.07
Skim/low-fat milk[6]						
Deaths/person-years	115/8106	58/4856	53/5493	68/6789		
Age-adjusted	1.00	0.89 (0.65, 1.22)	0.71 (0.51, 0.98)	0.70 (0.52, 0.94)		0.02[7]
Multivariable-adjusted[4,5]	1.00	1.01 (0.67, 1.52)	0.87 (0.56, 1.36)	1.02 (0.67, 1.56)		0.98
Pre-PSA	1.00	1.18 (0.53, 2.59)	0.61 (0.24, 1.56)	0.77 (0.34, 1.76)		0.38
Post-PSA (screening)	1.00	1.48 (0.71, 3.11)	1.34 (0.66, 2.73)	1.22 (0.54, 2.73)		0.79
Calcium from dairy food[8]						
Deaths/person-years	41/4412	52/4755	73/5174	74/5535	64/5879	
Age-adjusted	1.00	1.18 (0.79, 1.78)	1.45 (0.99, 2.13)	1.36 (0.93, 1.99)	1.11 (0.75, 1.64)	0.75
Multivariable-adjusted[4,5]	1.00	1.06 (0.63, 1.79)	1.70 (1.00, 2.89)	1.64 (0.94, 2.89)	1.71 (0.91, 3.21)	0.09
Pre-PSA	1.00	0.83 (0.33, 2.08)	1.30 (0.49, 3.48)	0.63 (0.23, 1.77)	1.30 (0.41, 4.19)	0.99
Post-PSA (screening)	1.00	1.09 (0.44, 2.69)	1.08 (0.45, 2.62)	1.63 (0.65, 4.10)	1.22 (0.41, 3.65)	0.59

[1] Values are HR (95% CI). FDR, false-discovery rate; PCa, prostate cancer; PHS, Physicians' Health Study; PSA, prostate-specific antigen.
[2] Calculated in a separate regression model with the median intake levels in each category as a continuous variable.
[3] Based on the consumption of 5 major dairy foods (whole milk, skim/low-fat milk, hard cheese, ice cream, and cold breakfast cereal) assessed from 1982 to 1984. The 5 intake level groups are: ≤0.5 servings/d, >0.5–1.0 serving/d, >1.0–1.5 servings/d, >1.5–2.5 servings/d, and >2.5 servings/d. One serving of whole milk, skim/low-fat milk, or cold breakfast cereal = 237 mL; 1 serving of ice cream = 214 g; 1 serving of hard cheese = 28 g.
[4] Adjusted for baseline measures of age at diagnosis (y), cigarette smoking (never, past, current), vigorous exercise (exercise vigorously to a sweat more than twice per week or not), alcohol intake (drink alcoholic beverages every day or not), race (Caucasian, non-Caucasian), BMI (normal weight, overweight, obese), baseline diabetes status (yes, no), red meat consumption (servings/wk), Gleason score (>7, ≥7), stage of tumor (T3/T4/N1/M1, T1/T2), total energy intake from recorded food items (kcal), assignment in the original aspirin trial (treatment, placebo), and assignment in the original β-carotene trial (treatment, placebo). In addition, the models for whole milk and skim/low-fat milk were mutually adjusted for each other (rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d).
[5] Pre-PSA era (n = 274): diagnosed before 1990; post-PSA era: diagnosed after 1990; presented by symptom (n = 192): presented by prostate-related symptoms or metastases (results not presented because of very low statistical power); presented by screening (n = 1233): presented by PSA test screening or digital rectal examination.
[6] The 4 intake level groups were: rarely, ≤1 serving/wk, 2–6 servings/wk, and ≥1 serving/d.
[7] FDR < 0.05.
[8] The 5 intake level groups were categorized according to quintiles.

their diet after diagnosis. We evaluated correlations among nutrients between the 2000 and 2004 FFQs, comparing men diagnosed with PCa in that interval with those who remained free of PCa. We found that the correlations ranged between 0.5 and 0.7 for all nutrients assessed, including dairy products. There were no obvious trends in the absolute levels of intake between cases and non-cases. These observations suggest that men tended to keep their dietary habits after PCa diagnosis. One advantage of using prediagnostic dietary information is to avoid confounding by recall bias, change of diet due to disease severity or treatments, or other reasons. Recently, Pettersson et al. (32) found that in the Health Professionals Follow-up Study, post-diagnostic milk and dairy product intake was not significantly associated with increased risk of fatal PCa, whereas Torfadottir et al. (33) found that milk intake during adolescence, rather than in midlife or currently, was associated with advanced PCa. One possibility is that dairy product intake in earlier life may be more relevant to the progression and mortality of PCa in later life.

Several potential mechanisms could explain the observed associations of dairy food (primarily skim/low-fat milk) with overall PCa risk. First, skim/low-fat milk is the major source of dairy calcium and higher intake might lower intra-cellular 1,25-dihydroxycholecalciferol concentrations and induce prostate carcinogenesis (8,34–36). Second, the association could be mediated via phytanic acid, which may upregulate expression of α-methylacyl-CoA racemase (37,38). The involvement of α-methylacyl-CoA racemase in PCa is implicated by a recent observation (39). Third, the relation could be through the effect of phosphate. Newmark et al. (40) suggested that the high dietary phosphate content of dairy products might explain the risk of PCa induced by dairy products, because the plasma phosphate concentration can appreciably influence 1,25-dihydroxycholecalciferol concentrations. Fourth, the ability of dairy products to raise concentrations of insulin-like growth factor 1 have also been suggested as a possible explanation for the association (41–43). The association of whole milk with fatal PCa and

PCa-specific mortality may be via the effects of dairy fat (primarily saturated fat) or other factors (including obesity and hyperinsulinemia). Whole milk has an ~40 times higher content of saturated fat compared with skim milk and the difference of the saturated fat content between 237 mL of whole milk and skim milk is ~20% of its average daily intake (17). High-fat dairy has been positively correlated with higher C-peptide concentrations, which were positively related to risk of aggressive PCa (44).

In summary, the results from the present study confirm a potential role of dairy products in PCa risk and survival. Skim/low-fat milk dairy products have been suggested as being beneficial for several disease outcomes, including colorectal cancer; so future research is warranted to investigate the optimal intake of skim/low-fat dairy products. However, our results add further evidence to suggest that the intake of whole-fat dairy products is associated with the risk of developing advanced or fatal PCa in elderly men and worse survival in PCa cases. Thus, minimal intake of whole-fat dairy products may be beneficial for elderly men, particularly PCa survivors. However, these results still need to be confirmed in other male populations.

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