Research Article

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Milk and Dairy Consumption among Men with Prostate Cancer and Risk of Metastases and Prostate Cancer Death

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Abstract

Background: Whether milk and dairy intake after a prostate cancer diagnosis is associated with a poorer prognosis is unknown. We investigated postdiagnostic milk and dairy intake in relation to risk of lethal prostate cancer (metastases and prostate cancer death) among participants in the Health Professionals Follow-Up Study.

Methods: The cohort consisted of 3,918 men diagnosed with apparently localized prostate cancer between 1986 and 2006, and followed to 2008. Data on milk and dairy intake were available from repeated questionnaires. We used Cox proportional hazards models to calculate HRs and 95% CIs of the association between postdiagnostic milk and dairy intake and prostate cancer outcomes.

Results: We ascertained 229 prostate cancer deaths and an additional 69 metastases during follow-up. In multivariate analysis, total milk and dairy intakes after diagnosis were not associated with a greater risk of lethal prostate cancer. Men with the highest versus lowest intake of whole milk were at an increased risk of progression (HR = 2.15, 95% CI: 1.28–3.60; $P_{trend} < 0.01$). Men in the highest versus lowest quintile of low-fat dairy intake were at a decreased risk of progression (HR = 0.62; 95% CI: 0.40–0.95; $P_{trend} = 0.07$).

Conclusions: With the exception of whole milk, our results suggest that milk and dairy intake after a prostate cancer diagnosis is not associated with an increased risk of lethal prostate cancer.

Impact: This is the first larger prospective study investigating the relation between postdiagnostic milk and dairy intake and risk of lethal prostate cancer. *Cancer Epidemiol Biomarkers Prev; 21(3); 428–36. ©2012 AACR.*

Introduction

Millions of men globally are living with a diagnosis of prostate cancer. Beyond medical treatment decisions, many patients wonder what dietary and lifestyle changes they can make to alter their clinical course and improve cancer outcomes. In several observational studies, a significantly increased risk of prostate cancer among men has been seen with high compared with low intake of milk or other dairy products (1–23), although only a suggestive positive association (24, 25), or no association has been seen in others (26–41). In some studies, stronger associations have been observed for high stage, high grade, and/or fatal disease with high intake of milk or other dairy products (4, 8, 15, 23), suggesting that milk and dairy intake may influence progression. However, other studies have not confirmed findings for more aggressive cancers (1, 5, 9, 13, 30, 32, 34–36). In addition, per capita consumption of milk correlates positively with both prostate cancer incidence and mortality (42, 43).

High milk and dairy intake may increase prostate cancer progression via several mechanisms. The calcium in dairy products could potentially increase disease progression by suppressing circulating levels of 1,25-dihydroxyvitamin D, the active form of vitamin D, which can induce differentiation and apoptosis and exert other anticancer effects in experimental studies (44, 45). Also, high intake of dairy products, particularly milk, elevates circulating levels of insulin-like growth factor 1, a potent mitogenic and antiapoptotic hormone implicated in prostate carcinogenesis (46, 47). Furthermore, high intake of saturated fat from dairy products and other foods may increase prostate cancer progression (48).

Whether dairy intake after a prostate cancer diagnosis increases risk of progression has been minimally investigated. We previously reported a modest increased risk of progression, primarily in the form of biochemical recurrence, among men with the highest compared with the lowest postdiagnostic milk intake (multivariate HR = 1.30, 95% CI: 0.93–1.83) among 1,202 men diagnosed with

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prostate cancer between 1986 and 1996 in the Health Professionals Follow-Up Study (HPFS; ref. 49). In the current extended study, our primary aim was to investigate whether milk and dairy intake after a prostate cancer diagnosis is associated with increased risk of lethal outcomes.

Material and Methods

Study population

The HPFS started in 1986 when 51,529 U.S. male health professionals aged 40 to 75 years completed a detailed questionnaire about their medical history, lifestyle, and dietary habits. Follow-up questionnaires on medical history and lifestyle habits are mailed to the participants every 2 years and dietary questionnaires every 4 years. Follow-up of the cohort is >95% complete. Deaths in the cohort are identified through information from next of kin or the National Death Index (ascertainment rate >98%), and cause of death is assigned following a centralized review of medical records and death certificates by study physicians. The study was approved by the Institutional Review Board of the Harvard School of Public Health.

Exposure information

Participants were asked to complete a semiquantitative food frequency questionnaire (FFQ) in 1986, 1990, 1994, 1998, and 2002. The 1986 FFQ contained a list of 131 dietary items. Participants were asked how often, in 9 predefined frequency categories ranging from <1 per month to ≥6 per day, they consumed a specified unit of each item on average over the past year. The FFQ has changed minimally since 1986. The validity of the food intake measurements by the FFQ was evaluated in a sample of 127 HPFS participants (50). Correlations for dairy foods ranged from 0.34 for cottage/ricotta cheese to 0.72 for skim and low-fat milk, comparing the questionnaire measurements with measurements from two 1-week diet records. The correlation was 0.58 for whole milk.

We examined the following postdiagnosis dietary factors as exposure of interest: skim and low-fat milk (skim milk, low-fat milk, and 1% and 2% milk), whole milk, total milk, low-fat dairy products (skim and low-fat milk, sherbert, yogurt, cottage/ricotta cheese, and other low-fat cheeses), full fat dairy products (whole milk, cream, sour cream, ice cream, cream cheese, butter, and other cheeses specified as regular, nonlow fat, or not specified as low fat), and total dairy products.

Identification of men with prostate cancer and definition of endpoints

Eligible to be included in the study were men diagnosed with prostate cancer between 1986 and 2006, and the men were followed for cancer-specific endpoints to 2008. After a report of prostate cancer, we ask participants for permission to review relevant medical records and pathology reports (response rate 89%). Since 2000, participants with prostate cancer were sent an additional biennial questionnaire about their clinical course, and we asked for permission to contact their treating physicians to collect additional clinical information. Through these sources, we obtain data on date of prostate cancer diagnosis, tumor-node-metastasis (TNM) stage, Gleason score, prostate-specific antigen (PSA) level at diagnosis, primary treatment received, and date of any biochemical recurrence or metastases. Prostate cancer was determined to be the cause of death when there was evidence of extensive metastatic disease and no other more plausible cause of death. Biochemical recurrence was defined from medical records and physician questionnaires based on the primary treatment: for radical prostatectomy (51, 52), PSA >0.2 ng/mL postsurgery, sustained over 2 measures; for external beam radiation (53), a rise of ≥2 ng/mL above the nadir PSA; for brachytherapy (54), hormones or other treatments, a rise of ≥1 ng/mL above nadir, sustained over 2 measures; for active surveillance, a postdiagnosis PSA increase of ≥1 ng/mL, sustained over 2 measures. Date of biochemical recurrence was the date of first rise. When information was lacking from physician reports and medical charts, we used patient-reported PSA rise from participants' questionnaires: this data comprised 38% of all PSA rises.

We considered 4 distinct endpoints: (i) lethal prostate cancer, defined as metastases to distant organs and prostate cancer death; (ii) biochemical recurrence and clinical progression, defined as biochemical recurrence, local spread to lymph nodes, metastases to distant organs, and prostate cancer death; (iii) biochemical recurrence alone; and (iv) all cause mortality. Date of the first event within each respective endpoint category was considered the date of an endpoint.

Statistical analysis

We included in the analysis participants who completed the 1986 questionnaire, were free of any cancer (except for nonmelanoma skin cancer) in 1986 and were diagnosed with prostate cancer before 2006 ($N = 5{,}333$). We further restricted the study population to men with localized or locally advanced disease (≤T3a/N0/M0; $N = 4{,}238$) under the hypothesis that dietary factors have more influence on these tumors compared with more advanced tumors, and because most prostate cancers diagnosed after the introduction of PSA screening are clinically localized at the time of diagnosis (97% of men diagnosed with prostate cancer after 1992 in the HPFS have ≤T3a/N0/M0 tumors). We excluded 305 men with unknown dairy intake during follow-up and 15 men who had experienced metastases or died of prostate cancer before start of follow-up (see below). After these exclusions, 3,918 men remained.

We used Cox proportional hazards regression models to calculate HRs and 95% CIs for the association between postdiagnostic dairy intake and the endpoints of interest. The underlying timescale was months since diagnosis. Dietary data were updated every 4 years and lifestyle data every 2 years. Information from the questionnaire

immediately preceding the diagnosis was considered exposure data at the time of diagnosis (Spearman correlation coefficients comparing dairy intake reported on the questionnaire immediately preceding the diagnosis to intake reported on the first postdiagnostic questionnaire were >0.6 for all time periods for each dairy item, except for whole milk; for whole milk, the correlations ranged from 0.40 to 0.56 for different time periods). We used cumulative average (see below) intake to best represent long-term effects of diet. To minimize bias from reverse causation (the potential for the disease to affect diet), we added 2 calendar years between return of questionnaire and calendar time of follow-up. For example, for a man diagnosed with prostate cancer in 1991, follow-up started in 1992 (i.e., 2 calendar years after the return of his 1990 questionnaire) and the 1990 dietary information was used for the period 1992 to 1996, the average of the 1990 and 1994 (i.e., the cumulative average) for the period 1996 to 2000, and so forth. The men were followed until they experienced an endpoint or were censored at death due to other causes or end of follow-up (January 2008). As a sensitivity analysis, we used the same analytic approach described above but considered only information from questionnaires returned after the prostate cancer diagnosis as exposure data.

Total, low-fat, and full fat dairy intake were divided into quintiles of servings per day. Servings of total milk and skim/low-fat milk intake were divided into 4 categories (0–3/mo, >3/mo-4/wk, >4/wk-1/d, >1/d), whereas whole milk intake was divided into 3 categories (0–3/mo, >3/mo-4/wk, and >4/wk) because of the small number of high consumers. We constructed 3 different models. Model 1 was adjusted for age at diagnosis (continuous) and total caloric intake (quintiles). Model 2 was additionally adjusted for BMI (<25, 25–29.9, and 30+ kg/m^2), current smoking status (yes and no), total physical activity (quintiles of metabolic equivalent task, h/wk; MET, h/wk), tomato sauce intake (<1 serving/wk, 1–1.99 servings/wk, and ≥2 servings/wk), and α-linolenic acid intake (quintiles). To address the extent to which milk could influence progression beyond any associations with disease stage or grade, model 3 was additionally adjusted for clinical TNM-stage (T1, T2, and T3a), biopsy Gleason score (<7, 7, >7, and unknown), and PSA (<10, 10–20, >20 ng/mL, and unknown) at diagnosis. Gleason score was unknown for 12.8% of the men, and PSA at diagnosis was unknown for 8.6% of the men. Additional adjustment for ethnicity, family history of prostate cancer, height, past smoking history, consumption of total coffee, red meat, processed meat, egg, and poultry with skin showed limited confounding, and these variables were not retained in the final model. All models were stratified for time since diagnosis (months), and calendar period (2-year periods). We also ran exploratory analyses stratified by Gleason score (<7 and ≥7) at diagnosis and median age at diagnosis (69 years).

To assess confounding by PSA screening behavior, we conducted a sensitivity analysis among men diagnosed after 1994 ($N = 2{,}808$). We created a PSA screening history variable indicating if a man ever, or never, had reported a negative PSA screen before his cancer diagnosis. We also created a PSA screening intensity variable indicating if a man had reported a PSA screen on < or ≥50% of the questionnaires returned before his cancer diagnosis.

In secondary analyses, we first considered biochemical recurrence and clinical progression as a combined endpoint. The analysis was restricted to men who had completed the postdiagnostic biennial questionnaire about the clinical course of their disease ($N = 3{,}255$) and included all variables in model 3. We also examined these models stratified by Gleason score and median age at diagnosis. In a separate analysis, biochemical recurrence alone was considered the endpoint. In a final analysis, death from any cause was considered the endpoint ($N = 3{,}918$). This analysis included all variables in model 3, and we ran analyses stratified by median age at diagnosis.

The median or midpoint value of each dairy item category was modeled as a continuous variable to test for evidence of linear trends and was multiplied with other relevant factors (Gleason score and/or median age at diagnosis) to create interaction terms. We tested the proportional hazard assumption by creating interaction terms between the exposures of interest and time since diagnosis divided into 2 periods (≤5 years and >5 years) and used Wald tests to assess their statistical significance. We found no significant interactions in the primary analysis or when all cause mortality was considered the endpoint. When biochemical recurrence and clinical progression was considered the endpoint, we found a significant interaction ($P = 0.05$) between full fat dairy intake and time since diagnosis. We retained the interaction terms between full fat dairy intake and time since diagnosis to calculate HRs for the period ≤5 years since diagnosis and >5 years since diagnosis separately.

SAS (version 9.2) was used for all analyses and 2-sided $P < 0.05$ was considered statistically significant.

Results

Among the 3,918 men diagnosed with prostate cancer between 1986 and 2006, the median age at diagnosis was 69 years, and 8% of the men had Gleason 8–10 tumors. With follow-up to 2008, the median time of follow-up was 7.6 years with 229 prostate cancer deaths, and 69 distant metastases.

Table 1 lists age-adjusted characteristics at the start of follow-up by quintiles 1, 3, and 5 of total dairy, low-fat dairy, and full fat dairy intake. Men with the highest intake of both low-fat dairy and full fat dairy included a higher proportion of Caucasians and men who exercised more. Men with greater intake of low-fat dairy were more likely to have Gleason score 8–10 tumors at diagnosis, whereas men with greater intake of full fat dairy products were more often current smokers and had higher BMI.

Table 2 shows HRs of lethal prostate cancer by milk and dairy intake for simple and multivariate models. Results

Table 1. Age-adjusted[a] means and proportions among 3,918 men with prostate cancer by the 1st, 3rd, and 5th quintile of total dairy, low-fat dairy, and full fat dairy intake[b] at start of follow-up

	Total dairy intake			Low-fat dairy intake			Full fat dairy		
Characteristic	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**	**Q1**	**Q3**	**Q5**
Median intake, serving/d	0.6	1.7	3.9	0.1	1.1	3.0	0.1	0.9	2.6
Age at diagnosis, y	68.3	69.1	69.8	68.7	68.6	69.8	69.4	69.2	69.3
Caucasian, %	93.9	97.2	98.0	94.0	96.4	98.4	94.6	96.6	97.3
Family history of prostate cancer, %	9.9	10.1	11.0	9.6	11.3	10.4	10.6	10.6	11.7
TNM stage, %									
T1	54.9	58.1	56.6	55.0	56.0	56.9	55.9	54.8	55.1
T2	40.9	37.0	39.3	41.1	39.1	38.8	39.5	41.5	41.1
T3a	4.3	4.9	4.2	3.9	4.8	4.2	4.6	3.7	3.8
Gleason score, %									
2–6	64.9	67.5	63.9	65.6	66.8	63.3	66.1	65.8	67.4
7	27.1	24.7	26.2	26.2	24.1	27.1	25.6	25.2	24.7
8–10	8.0	7.8	9.9	8.2	9.1	9.6	8.4	9.0	7.8
PSA at diagnosis, %									
<10	71.8	72.5	68.7	69.6	71.3	70.1	71.8	71.2	67.7
10–20	19.8	18.8	21.5	20.6	18.8	19.7	19.0	20.2	22.7
>20	8.5	8.7	9.8	9.7	9.8	10.2	9.2	8.6	9.6
Treatment, %									
Radical prostatectomy	48.3	51.6	49.3	46.4	50.1	50.0	49.9	48.8	48.5
Radiation therapy	36.7	33.1	36.0	37.4	35.8	36.1	35.1	38.0	35.4
Hormonal treatment	5.2	5.5	6.2	5.7	5.3	5.5	5.7	5.1	5.8
Active surveillance	7.2	8.1	7.0	8.0	7.4	7.0	7.8	6.3	8.3
Other	2.7	1.7	1.4	2.5	1.4	1.5	1.6	1.8	2.0
BMI, kg/m[b]	25.6	25.7	26.0	25.9	25.6	25.8	25.2	25.8	26.2
Current smokers, %	4.7	4.0	6.1	5.6	4.2	4.7	3.0	5.4	5.6
Physical activity, MET-h/wk	34.8	33.9	37.3	33.5	34.7	36.3	36.2	34.8	36.5
Tomato sauce intake, servings/wk	1.0	1.1	1.0	1.0	1.1	1.0	1.0	1.1	1.1
α-linolenic acid intake, g/d	1.2	1.2	1.1	1.2	1.1	1.1	1.1	1.1	1.2
PSA screening, v%[c]	95.1	94.4	95.5	93.1	96.8	95.9	97.3	94.1	94.9

[a]Adjusted for age at prostate cancer diagnosis (<60, 60–64, 65–69, 70–74, and 75+).
[b]Quintiles of servings per day.
[c]Ever had a PSA test for routine screening; restricted to men diagnosed after 1992.

from the simple and multivariate models were qualitatively similar and below are summarized the results from the multivariate models. We found a suggestion of an inverse association between total dairy intake after diagnosis and risk of lethal prostate cancer. This association seemed to be driven primarily by intake of low-fat dairy products; the HR among men with the highest versus lowest intake of low-fat dairy products was 0.62 (95% CI: 0.40–0.95; $P_{trend} = 0.07$) and for full fat dairy products the HR was 1.30 (95% CI: 0.82–2.07; $P_{trend} = 0.95$). We observed no significant associations between total milk intake, or skim/low-fat milk intake, and risk of lethal disease. For whole milk intake, on the contrary, the HR of lethal prostate cancer was 2.15 (95% CI: 1.28–3.60; $P_{trend} < 0.01$) among men with highest (>4 servings/wk) versus lowest (0–3 servings/mo) intake. In sensitivity analyses, in which we considered only information from questionnaires returned after the prostate cancer diagnosis as exposure data, results were largely similar. The HR among men with the highest versus lowest intake of low-fat dairy products was 0.62 (95% CI: 0.36–1.08; $P_{trend} = 0.21$), and for whole milk intake, the HR was 2.52 (95% CI: 1.22–5.22; $P_{trend} = 0.01$) among men with highest versus lowest intake.

When we restricted the analysis to men diagnosed after 1994 (133 lethal events), additional adjustment for PSA screening behavior did not materially change the risk estimates. For example, the HRs for men with the highest versus lowest intake of whole milk was 3.52 (95% CI: 1.60–7.77; $P_{trend} < 0.01$) before adjustment and 3.50 (95% CI: 1.58–7.73; $P_{trend} < 0.01$) after adjustment for history of PSA screening. Similar results were seen when we instead adjusted for PSA screening intensity (data not shown).

Table 2. Dairy intake and HRs and 95% CIs of lethal prostate cancer ($N = 298$) among 3,918 men with prostate cancer

Dairy product intake	No.	Model 1[a]	Model 2[b]	Model 3[c]
Total milk, servings		HR (95% CI)	HR (95% CI)	HR (95% CI)
0–3/mo	44	1.00	1.00	1.00
>3/mo to 4/wk	57	0.87 (0.57–1.32)	0.90 (0.59–1.37)	1.01 (0.65–1.56)
>4/wk to 1/d	119	1.09 (0.76–1.58)	1.10 (0.75–1.59)	1.14 (0.77–1.69)
>1/d	78	0.96 (0.64–1.44)	0.95 (0.63–1.43)	0.89 (0.58–1.37)
P_{trend}		0.92	0.77	0.33
Skim to 2% fat milk, servings				
0–3/mo	66	1.00	1.00	1.00
>3/mo to 4/wk	57	0.77 (0.53–1.12)	0.78 (0.54–1.15)	0.85 (0.57–1.27)
>4/wk to 1/d	104	0.86 (0.62–1.20)	0.84 (0.60–1.18)	0.86 (0.61–1.23)
>1/d	71	0.82 (0.57–1.19)	0.81 (0.56–1.18)	0.73 (0.49–1.09)
P_{trend}		0.62	0.57	0.17
Whole milk, servings				
0–3/mo	264	1.00	1.00	1.00
>3/mo to 4/wk	13	0.87 (0.48–1.58)	0.83 (0.45–1.53)	0.89 (0.47–1.67)
>4/wk	21	2.07 (1.26–3.40)	2.09 (1.27–3.44)	2.15 (1.28–3.60)
P_{trend}		<0.01	<0.01	<0.01
Total dairy, quintiles[d], servings				
1 (0 to 0.9/d)	60	1.00	1.00	1.00
2 (>0.9 to 1.3/d)	58	0.82 (0.56–1.21)	0.83 (0.56–1.23)	0.83 (0.55–1.25)
3 (>1.3 to 1.8/d)	58	0.80 (0.54–1.19)	0.80 (0.53–1.19)	0.96 (0.63–1.46)
4 (>1.8 to 2.9/d)	64	0.80 (0.54–1.19)	0.80 (0.53–1.20)	0.83 (0.54–1.27)
5 (>2.9/d)	58	0.71 (0.47–1.08)	0.70 (0.46–1.07)	0.68 (0.43–1.05)
P_{trend}		0.15	0.13	0.09
Low-fat dairy, quintiles[d], servings				
1 (0 to 0.1/d)	65	1.00	1.00	1.00
2 (>0.1 to 0.6/d)	52	0.68 (0.46–1.01)	0.72 (0.49–1.07)	0.76 (0.50–1.14)
3 (>0.6 to 1.0/d)	60	0.80 (0.55–1.16)	0.81 (0.55–1.18)	0.83 (0.56–1.23)
4 (>1.0 to 1.4/d)	67	0.86 (0.59–1.24)	0.86 (0.59–1.26)	0.95 (0.64–1.41)
5 (>1.4/d)	54	0.67 (0.45–1.00)	0.68 (0.46–1.02)	0.62 (0.40–0.95)
P_{trend}		0.17	0.16	0.07
Full fat dairy, quintiles[d], servings				
1 (0 to 0.2/d)	46	1.00	1.00	1.00
2 (>0.2 to 0.6/d)	72	1.58 (1.06–2.35)	1.57 (1.05–2.34)	1.50 (0.99–2.27)
3 (>0.6 to 1.0/d)	63	1.38 (0.92–2.08)	1.37 (0.90–2.07)	1.33 (0.86–2.06)
4 (>1.0 to 1.7/d)	55	1.07 (0.70–1.63)	1.06 (0.69–1.63)	1.04 (0.66–1.62)
5 (>1.7/d)	62	1.34 (0.87–2.06)	1.30 (0.83–2.04)	1.30 (0.82–2.07)
P_{trend}		0.91	0.95	0.95

[a]Adjusted for age at diagnosis (continuous) and total caloric intake (quintiles).

[b]Adjusted for variables in model 1 + smoking status (nonsmoker and smoker), BMI (<25, 25–29.9, and 30+), exercise in MET-h/wk (quintiles), tomato sauce intake (<1 serving/wk, 1–1.99 servings/wk, and 2- servings/wk), and α-linolenic acid intake (quintiles).

[c]Adjusted for variables in model 1 + 2 + TNM stage (T1, T2, and T3a), Gleason score (<7, 7, >7, and unknown), and PSA at diagnosis (<10, 10–20, >20, and unknown).

[d]Cut points for quintiles of servings per day refer to the cut points for the baseline year, 1986. The cut points for the quintiles vary over time.

When we considered biochemical recurrence and clinical progression as the endpoint (741 events), men with the highest versus lowest whole milk intake were at a 51% (HR = 1.51, 95% CI: 1.03–2.20; $P_{trend} = 0.03$) increased risk of progression (Table 3). Intake of no other milk or dairy product category was associated with progression in this analysis (Table 3). Also, as we found a significant interaction ($P = 0.05$) between full fat dairy intake and time since diagnosis in this analysis, we ran analysis stratified by time since diagnosis; the HR for biochemical

Table 3. Dairy intake and multivariate HRs and 95% CIs of biochemical and clinical recurrence ($N = 741$) among 3,255 men with prostate cancer

Dairy product intake	No.	All men[a]
Total milk, servings		HR (95% CI)
0–3/mo	128	1.00
>3/mo to 4/wk	154	0.98 (0.76–1.27)
>4/wk to 1/d	257	0.97 (0.76–1.22)
>1/d	202	1.08 (0.84–1.39)
P_{trend}		0.34
Skim to 2% fat milk, servings		
0–3/mo	164	1.00
>3/mo to 4/wk	154	1.00 (0.79–1.28)
>4/wk to 1/d	239	0.92 (0.73–1.14)
>1/d	184	1.01 (0.79–1.28)
P_{trend}		0.77
Whole milk, servings		
0–3/mo	670	1.00
>3/mo to 4/wk	34	1.19 (0.80–1.78)
>4/wk	37	1.51 (1.03–2.20)
P_{trend}		0.03
Total dairy, quintiles[b], servings		
1 (0 to 0.9/d)	146	1.00
2 (>0.9 to 1.3/d)	149	0.99 (0.77–1.28)
3 (>1.3 to 1.8/d)	140	0.92 (0.71–1.19)
4 (>1.8 to 2.9/d)	139	0.96 (0.73–1.25)
5 (>2.9/d)	167	0.99 (0.76–1.29)
P_{trend}		0.93
Low-fat dairy, quintiles[b], servings		
1 (0 to 0.1/d)	133	1.00
2 (>0.1 to 0.6/d)	144	1.22 (0.94–1.58)
3 (>0.6 to 1.0/d)	156	1.16 (0.90–1.50)
4 (>1.0 to 1.4/d)	149	1.23 (0.95–1.59)
5 (>1.4/d)	159	1.11 (0.86–1.45)
P_{trend}		0.81
Full fat dairy, quintiles[b], servings		
1 (0 to 0.2/d)	153	1.00
2 (>0.2 to 0.6/d)	153	1.07 (0.83–1.37)
3 (>0.6 to 1.0/d)	147	0.92 (0.72–1.19)
4 (>1.0 to 1.7/d)	124	0.70 (0.54–0.92)
5 (>1.7/d)	164	1.02 (0.79–1.32)
P_{trend}		0.66

[a]Adjusted for age at diagnosis (continuous), total caloric intake (quintiles), smoking status (nonsmoker and smoker), BMI (<25, 25–29.9, and 30+), exercise in MET-h/wk (quintiles), tomato sauce intake (<1 serving/wk, 1–1.99 servings/wk, and 2- servings/wk), α-linolenic acid intake (quintiles), TNM stage (T1, T2, and T3a), Gleason score (<7, 7, >7, unknown), and PSA at diagnosis (<10, 10–20, >20, and unknown).

[b]Cut points for quintiles of servings per day refer to the cut points for the baseline year, 1986. The cut points for the quintiles vary over time.

recurrence and clinical progression among men with the highest versus lowest full fat dairy intake was 1.11 (95% CI: 0.82–1.49; $P_{trend} = 0.54$) ≤5 years since diagnosis and 0.81 (95% CI: 0.51–1.31; $P_{trend} = 0.06$) thereafter. In another secondary analysis, we considered only biochemical recurrence as the endpoint (696 events). The HR for men with the highest versus lowest whole milk intake was 1.27 (95% CI: 0.84–1.92; $P_{trend} = 0.24$) in this analysis, and all other associations between milk and dairy intake and risk of biochemical recurrence alone were null (data not shown).

The association between milk and dairy intake and risk of lethal prostate cancer did not differ significantly by median age at diagnosis (Supplementary Table S1). When we considered the biochemical recurrence and clinical progression endpoint, there was a significant interaction between full fat dairy intake, but not intake of other dairy products, and median age at diagnosis ($P_{interaction} = 0.04$). The HR among men with highest versus lowest intake was 0.81 (95% CI: 0.54–1.20; $P_{trend} = 0.12$) among men aged less than 70 at diagnosis and 1.47 (95% CI: 1.00–2.16; $P_{trend} = 0.09$) among men aged 70 years or more at diagnosis. There was some evidence of positive associations between intake of skim and low-fat milk and total milk and risk of lethal prostate cancer, as well as with risk of biochemical and clinical recurrence, among men with Gleason <7 tumors, and suggestive inverse associations among men with Gleason ≥7 tumors (Supplementary Table S2A and S2B).

We found no significant associations among men with the highest versus lowest milk and dairy intake and all cause mortality, or any significant trends (897 events; data not shown). There was a significant interaction between total milk intake and median age at diagnosis when all cause mortality was considered the endpoint ($P_{interaction} = 0.03$); men aged <70 at diagnosis with the highest versus lowest intake of total milk had an HR of 1.18 (95% CI: 0.75–1.84; $P_{trend} = 0.25$), whereas men aged ≥70 at diagnosis had an HR of 0.92 (95% CI: 0.65–1.29; $P_{trend} = 0.08$). Also, high intake of whole milk was associated with an increased risk of all cause mortality among men aged <70 at diagnosis (HR = 2.05; 95% CI: 1.16–3.63; $P_{trend} = 0.01$), but not among older men (HR = 1.02; 95% CI: 0.62–1.66; $P_{trend} = 0.99$; $P_{interaction} = 0.20$).

Discussion

Contrary to expectation based on studies examining prediagnostic intakes, our results suggest that among prostate cancer patients, overall intakes of milk and dairy products are not associated with a greater risk of lethal prostate cancer. We observed decreased risk of lethal disease among men with higher intakes of postdiagnostic low-fat dairy intake, and increased risk of lethal prostate cancer among men with higher intakes of whole milk.

Evidence linking milk and dairy intake with risk of total prostate cancer incidence are inconclusive, but some data support a link with incidence of high stage, high grade,

and/or fatal prostate cancer (4, 8, 15, 23). Furthermore, some studies support a link between low-fat milk intake and risk of total prostate cancer, whereas other studies support an association for whole milk. Secondary data analysis from randomized clinical trials, and prior analyses from this cohort, have suggested that calcium intake is related to lower risk of PSA screening detected low-grade prostate cancer, but positively related to risk of advanced disease (41, 55). In light of this, our finding of an inverse association between low-fat dairy intake and risk of lethal prostate cancer should be interpreted with caution. Moreover, there was no apparent trend when considering the individual HRs of the different quintiles of low-fat dairy intake (Table 2). In addition, even though biochemical recurrence is an imprecise predictor of prostate cancer death (56, 57), we found no inverse association between milk and dairy intake and risk of progression when biochemical and clinical recurrence was considered the endpoint. Although we were able to control for several known or suspected risk factors for prostate cancer progression, high intake of low-fat dairy products may be a marker for some other lifestyle factor which in turn has a protective effect on lethal prostate cancer. There could also be residual confounding due to measurement error of some factors we were able to control for. It is also possible, however, that high intake of low-fat dairy products after a prostate cancer diagnosis has a true protective effect on risk of lethal disease. Factors or mechanisms that act after diagnosis and treatment are likely different from those that act early in prostate carcinogenesis. Rather than exerting effects on the primary tumor cells, factors operating after diagnosis and treatment presumably have effects on circulating tumors cells or micrometastases, or on their target organs such as the bones. For instance, high postdiagnostic calcium and vitamin D intake from milk and other dairy foods could potentially decrease, rather than increase, metastatic growth by suppressing the levels of parathyroid hormone (PTH) and lowering the rate of bone resorption (58, 59), factors that may influence skeletal metastases and progression in prostate cancer (60, 61).

We found an increased risk of lethal prostate cancer among men with the highest versus lowest whole milk intake. A factor abundant in whole milk that may increase prostate cancer progression is saturated fat. High saturated fat intake has been associated with an increased risk of prostate cancer and a higher risk of biochemical recurrence after prostatectomy (48). However, we found no positive association between intake of total high fat dairy products and risk of lethal prostate cancer or biochemical recurrence and clinical progression. In addition, on average, less than 10% of the total amount of dairy fat consumed by the men in this cohort came from whole milk. Taken together, these findings suggest that some component in whole milk other than saturated fat may be associated with an increased risk of progression. It is also possible that the positive association between whole milk intake and risk of progression in our study is explained by residual confounding due to measurements error of potential confounding factors or unmeasured potential confounding factors, or by chance.

As exploratory analyses, we investigated whether the association between milk and dairy intake and prostate cancer endpoints differed by Gleason score or median age at diagnosis. There was some evidence of an increased risk of lethal prostate cancer, as well as biochemical recurrence and clinical progression, among men with high skim and low-fat milk intake and total milk intake and Gleason score <7 tumors, and at the same time a decreased risk among men with Gleason score $\geq$7 tumors. It is unclear what mechanism or factor would create such a pattern, and this interaction needs to be confirmed in other studies as it may have been due to chance. Also, we found no strong evidence in favor of an interaction between milk and dairy intake and median age at diagnosis.

In our previous study among 1,202 men diagnosed with prostate cancer between 1986 and 1996, we found a suggestion of a 30% increased risk of progression (HR = 1.30, 95% CI: 0.93–1.83), defined primarily by biochemical recurrence, among men with the highest versus lowest postdiagnostic total milk intake (49). With additional follow-up, we did not find that total milk intake is associated with an increased risk of prostate cancer progression; the HR in the current study was 0.89 (95% CI: 0.58–1.37) for lethal prostate cancer, and 1.08 (95% CI: 0.84–1.39) for biochemical recurrence and clinical progression (i.e., the endpoint in the current study comparable to the endpoint used in the previous study). Part of these discrepancies in the point estimates may be explained by biochemical recurrence being an imprecise proxy for lethal prostate cancer. Moreover, the previous study included men diagnosed with local or regional disease, whereas our current analysis included only men with apparently localized disease at diagnosis. Thus, the previous and the current study are not fully comparable in terms of inclusion criteria, cohort size, number of endpoints, or time period of follow-up. The new cases included in the present analysis were mainly PSA detected and therefore diagnosed at an earlier stage in the natural history of prostate cancer, which could explain some of the difference in the current findings. It should be noted, however, that in the previous study we did not examine low fat/skim milk and whole milk separately; this distinction seemed to be important in our current analyses.

There are several strengths and limitations to consider in interpreting our findings. To define stage at cancer diagnosis, we relied on medical records and to some extent on self-report (<6%). This could have led to inclusion of some men with extraprostatic disease at diagnosis. However, any misclassification of stage is likely unrelated to dairy intake and thus it is unlikely that such bias should have any effect on the risk estimates. Another limitation of this study is that we were unable to investigate finer categories, in terms of fat content, of milk intake in relation to risk of prostate cancer progression because of the phrasing of the questions in the FFQs. We were for example unable to separate intake of 2% fat milk from

intake of other skim and low-fat milk products. This precluded us from identifying potentially informative associations in finer categories of milk intake. In addition, the participants were predominately Caucasian, and therefore our findings may not be generalizable to other ethnic groups. Strengths of this study include the prospective design, complete long follow-up (up to 20 years), validated repeated follow-up questionnaires, and large number of lethal endpoints. We used repeated measurements of intake of milk and other dairy foods, which allowed us to evaluate potential changes in dairy (as well as adjust for measurement error).

In summary, with the exception of whole milk, our results suggest that overall milk and dairy intakes after diagnosis are not associated with a greater risk of distant metastases and prostate cancer death.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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