Dairy Product, Saturated Fatty Acid, and Calcium Intake and Prostate Cancer in a Prospective Cohort of Japanese Men

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Abstract

Many epidemiologic studies have reported a positive association between dairy products and prostate cancer. Calcium or saturated fatty acid in dairy products has been suspected as the causative agent. To investigate the association between dairy products, calcium, and saturated fatty acid and prostate cancer in Japan, where both the intake of these items and the incidence of prostate cancer are low, we conducted a population-based prospective study in 43,435 Japanese men ages 45 to 74 years. Participants responded to a validated questionnaire that included 138 food items. During 7.5 years of follow-up, 329 men were newly diagnosed with prostate cancer. Dairy products were associated with a dose-dependent increase in the risk of prostate cancer. The relative risks (95% confidence intervals) comparing the highest with the lowest quartiles of total dairy products, milk, and yogurt were 1.63 (1.14-2.32), 1.53 (1.07-2.19), and 1.52 (1.10-2.12), respectively. A statistically significant increase in risk was observed for both calcium and saturated fatty acid, but the associations for these were attenuated after controlling for potential confounding factors. Some specific saturated fatty acids increased the risk of prostate cancer in a dose-dependent manner. Relative risks (95% confidence intervals) on comparison of the highest with the lowest quartiles of myristic acid and palmitic acid were 1.62 (1.15-2.29) and 1.53 (1.07-2.20), respectively. In conclusion, our results suggest that the intake of dairy products may be associated with an increased risk of prostate cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(4):930–7)

Introduction

Although the incidence of prostate cancer in Japan is much lower than in western populations (1), latent prostate cancer appears to be equally distributed across areas with high and low incidence of prostate cancer (2). Further, prostate cancer incidence increases in men migrating from areas of low incidence to areas of higher incidence (3, 4). These results support the view that the development of prostate cancer may be impacted by environmental factors, including diet.

In the years since World War II, the Japanese diet has changed to a more westernized diet. Ecologic studies have shown an association between westernized dietary habits and the mortality of cancers that are more common in western countries. In particular, milk intake shows a strong positive association with prostate cancer (5). Given that the incidence of prostate cancer in Japan has increased (6), as has the consumption of dairy foods (7), increased dairy consumption might increase the risk of prostate cancer in Japanese men. However, previous epidemiologic studies regarding dairy product intake and prostate cancer in Japanese are few, and the results are equivocal (8-10).

High dairy product intake in western populations has been associated with an increased risk of prostate cancer in case-control as well as cohort studies. A meta-analysis of prospective studies estimated that the excess risk of prostate cancer in men with higher intakes of dairy products compared with those with lower intakes was 11% (11). Moreover, a recent meta-analysis of case-control studies showed a combined odds ratio of 1.68 for the highest versus lowest category of milk consumption (12).

Dairy products contain both fat and calcium. A comprehensive review concluded that dietary fat may be related to prostate cancer risk but that the specific fat components responsible are not yet clear (13). On the contrary, a recent meta-analysis of prospective studies reported that men with the highest intake of calcium had a 39% higher risk of prostate cancer than those with the lowest intake (11). Average calcium intake in Japanese is lower than in western populations, however, at <600 mg/d in men (7), whereas positive associations with prostate cancer in previous studies were limited to those with high intakes over 1,000 mg/d (14-18). In Japan, dairy products are the main source of not only calcium but also saturated fatty acid (19). In a population based case-control study, moreover, Whittemore et al. reported (20) that saturated fat intake was associated with a higher risk of prostate cancer for Asian Americans than for Blacks and Whites.

These results suggest that the effects of dairy products and nutrients in dairy products, such as saturated fatty

Received 10/9/07; revised 1/10/08; accepted 1/17/08.

Grant support: Ministry of Health, Labour and Welfare of Japan grants-in-aid for Cancer Research (19shi-2), Third Term Comprehensive 10-Year Strategy for Cancer Control (H18-sanjigan-ippan-001), and Research on Risk of Chemical Substances (H17-kagaku-ippan-014) and Ministry of Education, Culture, Sports, Science and Technology grants-in-aid for Scientific Research on Priority Areas (17015049).

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doi:10.1158/1055-9965.EPI-07-2681

acid and calcium, on prostate cancer might differ between Japanese and western populations.

Here, we investigated the association between the intake of dairy products, saturated fatty acid, and calcium and the risk of prostate cancer in a prospective study in Japanese.

Materials and Methods

Study Population and Food Frequency Questionnaire. The Japan Public Health Center–Based Prospective Study was launched in 1990 for cohort I and in 1993 for cohort II, involving 11 prefectural public health center areas. Details of the study design have been described previously (21). The study was approved by the institutional review board of the National Cancer Center (Tokyo, Japan). In the present analysis, subjects registered at one public health center area were excluded because data on cancer incidence were not available. The study population was defined as all Japanese residents ages 40 to 69 years at each baseline survey, who had registered their addresses in 10 public health centers. The initial cohort consisted of 65,801 men.

At baseline, participants completed a self-administered questionnaire that assessed information on various lifestyle factors and medical history. Simultaneously, a food frequency questionnaire (FFQ) in the baseline survey had 44 food items for cohort I and 52 food items for cohort II, with 4 (cohort I) or 5 (cohort II) frequency categories but without standard portions/units. In contrast, the 5-year follow-up survey included a self-administered FFQ, which included lifestyle factors, medical history, and 138 food and beverage items with standard portions/units and 9 frequency categories. Owing to this greater detail, the present study therefore used the 5-year follow-up survey as baseline and followed the subjects from 1995 for cohort I and from 1998 for cohort II until 2004. At the 5-year follow-up survey, a population-based cohort of 58,541 men was established. After the 5-year follow-up survey, 128 subjects were found to be ineligible and were excluded because of non-Japanese nationality (n = 28), late report of emigration occurring before the start of the follow-up period (n = 97), incorrect birth data (n = 1), and duplicate registration (n = 2), leaving 58,413 men eligible for participation. Among eligible subjects, 46,036 men (79%) returned valid responses to the 5-year follow-up FFQ.

The FFQ asked about the usual consumption of 138 foods and beverages during the previous year. Dairy product consumption was assessed as the frequency of consumption and portion size of the following food items: ''milk,'' ''cheese,'' ''yogurt,'' ''lactic acid drink,'' ''milk in black tea,'' and ''milk in coffee.'' Milk is not fortified with vitamin D in Japan. The frequency of milk, cheese, and yogurt consumption was divided into nine categories (almost never, 1-3 times monthly, 1-2 times weekly, 3-4 times weekly, 5-6 times weekly, once daily, 2-3 times daily, 4-6 times daily, ≥7 times daily). Portion sizes were specified, and the amounts were provided in three categories (less than half, same, >1.5 times). Ten frequency categories were used for lactic acid drinks (almost never, 1-3 times monthly, 1-2 times weekly, 3-4 times weekly, 5-6 times weekly, 1 glass/d, 2-3 glasses/d, 4-6 glasses/d, 7-9 glasses/d, >9 glasses/d). Similarly, the frequency of black tea and coffee consumption was assessed using the 10 categories, and the amount of milk added to the black tea or coffee was provided in five categories (0, 0.5, 1, 2, ≥3 teaspoons). The total consumption of dairy products (g/d) or each food (g/d) was calculated by multiplying the frequency by the relative portion for each food item in the FFQ. The daily intake of calcium was calculated using the fifth revised edition of the *Standard Tables of Food Composition in Japan* (22), whereas that of saturated fatty acids and specific saturated fatty acids (myristic acid, palmitic acid, and stearic acid) was calculated using a fatty acid composition table of Japanese foods (23).

Validity among subsamples (102 men) was assessed using 14- or 28-day dietary records. Spearman's correlation coefficient between the energy-adjusted intake of dairy products from the questionnaire and from dietary records was 0.52 for cohort I and 0.69 for cohort II, respectively, whereas that for energy-adjusted intake of calcium and saturated fatty acid was 0.43 and 0.61 for cohort I and 0.65 and 0.62 for cohort II, respectively. With regard to the reproducibility of estimations between two questionnaires administered 1 year apart, respective correlation coefficients for the energy-adjusted intake of dairy products, calcium, and saturated fatty acid were 0.48, 0.49, and 0.53 for cohort I and 0.69, 0.70, and 0.61 for cohort II (24-28).

Among the 46,036 men who responded to the questionnaire, those with a history of prostate cancer (n = 65) and those who reported extreme total energy intake (<800 or >4,000 kcal; n = 2,536) were excluded, leaving 43,435 men for analysis.

Follow-up and Identification of Cancer Cases. We followed all registered cohort subjects from the 5-year follow-up survey until December 31, 2004. Changes in residence status, including survival, were identified annually through the residential registry in each area or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Among questionnaire respondents to the 5-year follow-up FFQ, 1,603 (3.5%) moved out of the study area and 129 (0.3%) were lost to follow-up during the study period. Incidence data for prostate cancer were identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries. Death certificate information was used as a supplementary information source. Cases were coded using the *International Classification of Diseases for Oncology, Third Edition* (29).

The proportion of cases of prostate cancer first notified by death certificate was 0.9%. The proportion of case patients with prostate cancer ascertained by death certificate only was 0.6%. These ratios were considered satisfactory for the present study. A total of 329 newly diagnosed prostate cancer cases were identified by December 31, 2004. Regarding detection, 38.3% were detected by screening, 32.2% by subjective symptoms, and 14.0% incidentally during attendance at hospital for another condition, whereas no information on detection available for 15.5%. Advanced cases were defined by a diagnosis of extraprostatic or metastatic cancer involving lymph nodes or other organs. If this information was not available, advanced cases were defined as those with a high Gleason score (8-10) or poor differentiation. These criteria were selected to allow the identification of advanced cases with a high likelihood of poor prognosis. The remaining cases were organ localized. In this study, there were 90 advanced cases, 227 localized cases, and 12 (4% of total) cases of undetermined stage.

Statistical Analysis. Person-years of follow-up were calculated for each man from the date of completion of the 5-year follow-up questionnaire survey to the date of prostate cancer diagnosis, date of emigration from the study area, date of death, or end of the study period (December 31, 2004), whichever occurred first. For men who were lost to follow-up, the last confirmed date of presence in the study area was used as the date of censor.

The relative risks (RR) of prostate cancer were calculated by quartile for the categories of consumption of dairy products, milk, cheese, yogurt, calcium intake, and saturated fatty acid intake, with the lowest consumption category as the reference. RRs and 95% confidence intervals (95% CI) were calculated by the Cox proportional hazards model, adjusting for age at 5-year follow-up survey and study area (10 public health centers) according to the SAS PHREG procedure (version 9.1; SAS Institute). For further adjustment, additional possible confounders were incorporated into the model: smoking status (never, former, current), alcohol intake (almost never, <3-4, >5 days/wk), marital status (yes, no), and consumption of green tea (0, ≤6 times weekly, 1 cup/d, 2−3cups/d, ≥4 cups/d) and genistein (mg/d) in the analysis of the association between dairy products and prostate cancer. These variables are either known or suspected risk factors for cancer or have been found previously to be associated with the risk of prostate cancer (30, 31).

Trends were assessed by assignment of the median value in each category. All P values were two sided, and statistical significance was determined at the <0.05 level.

Results

During 323,648 person-years of follow-up (average follow-up, 7.5 years) for 43,435 men, a total of 329 cases of prostate cancer were newly diagnosed and included in the analyses.

Table 1 shows subject characteristics at baseline according to category of dairy product consumption. Participants with higher dairy product consumption tended to be older, smoke less, and drink less alcohol. The proportion of men who drank green tea daily and that of men who lived with their wives was low in the lowest category. The consumption of genistein increased with the consumption of dairy products from the first to third categories, although this consumption decreased in the highest categories. Naturally, consumption of milk, cheese, and yogurt increased as dairy product consumption increased. As expected, intake of saturated fatty acid calcium increased as dairy product consumption increased.

In Table 2, we observed a strong positive association between energy-adjusted intake of dairy products and total prostate cancer risk. The multivariate RRs of total prostate cancer across increasing quartiles of total dairy products were 1.00, 1.34, 1.29, and 1.63 (95% CI, 1.14-2.32; $P_{\text{trend}} < 0.01$). Similar findings were observed when we analyzed the association between milk and yogurt and total prostate cancer. Multivariable RRs for the highest versus lowest quartile of milk and yogurt consumption were 1.53 (95% CI, 1.07-2.19; $P_{\text{trend}} = 0.01$) and 1.52 (95% CI, 1.10-2.12; $P_{\text{trend}} < 0.01$), respectively. Intake of cheese was not clearly associated with total prostate cancer. Multivariable RR for the highest versus lowest quartile of cheese was 1.32 (95% CI, 0.93-1.89; $P_{\text{trend}} = 0.30$).

Table 3 shows the RRs for the intake of energy-adjusted calcium and whole and specific saturated fatty acid in relation to total prostate cancer risk. On adjustment for age and study area, intake of calcium and whole and specific saturated fatty acid increased the risk of total prostate cancer in a statistically significant manner. Age-area adjusted RRs for the highest versus lowest quartile of calcium and saturated fatty acid intake were 1.43 (95% CI, 1.03-1.97; $P_{\text{trend}} = 0.01$) and 1.53 (95% CI, 1.12-2.08; $P_{\text{trend}} = 0.01$), respectively. However, when we adjusted for further potential confounding factors, the associations were attenuated and became statistically nonsignificant, with multivariate RRs for the highest

Table 1. Characteristics of study subjects according to dairy products intake

	Dairy products intake			
	Lowest	Second	Third	Highest
Age (y) ± SD	56.5 ± 7.9	55.6 ± 7.7	56.8 ± 7.7	58.1 ± 7.9
Body mass index ± SD (kg/m^2)	23.5 ± 3.0	23.6 ± 2.9	23.6 ± 2.8	23.5 ± 2.8
Current smoker, %	51.1	47.9	41.4	34.3
Alcohol intake (>5 days/wk), %	57.0	49.8	49.5	35.9
Green tea intake (daily), %	50.5	55.0	59.4	55.7
Men who live with their wife, %	79.2	83.4	85.9	83.6
Milk ± SD (g/d)	4.5 ± 8.3	44.3 ± 43.0	143.2 ± 70.0	328.3 ± 309.8
Cheese ± SD (g/d)	1.0 ± 2.7	2.0 ± 4.7	2.5 ± 6.8	2.5 ± 7.1
Yogurt ± SD (g/d)	0.9 ± 3.1	7.4 ± 16.2	16.7 ± 31.4	34.5 ± 82.9
Meat ± SD (g/d)	66.2 ± 60.7	70.9 ± 57.0	69.9 ± 52.0	50.6 ± 38.3
Protein ± SD (g/d)	66.9 ± 28.8	72.8 ± 29.6	79.3 ± 27.2	72.1 ± 26.9
Genistein ± SD (mg/d)	23.2 ± 24.2	25.5 ± 23.6	28.2 ± 21.4	24.6 ± 19.9
Saturated fatty acid ± SD (g/d)	12.9 ± 8.2	15.4 ± 8.3	17.9 ± 7.9	19.3 ± 10.0
Calcium ± SD (mg/d)	325.3 ± 164.8	409.9 ± 193.2	555.0 ± 207.1	721.9 ± 410.6

NOTE: Values are reported as means with standard deviations.

Table 2. RRs and 95% CIs for total prostate cancer according to quartile of energy-adjusted intake of dairy products

	Intake by quartile (median)				P_{trend}
	Lowest (12.8 g/d)	Second (66.1 g/d)	Third (165.2 g/d)	Highest (339.8 g/d)	
Total dairy products					
No. cases	60	71	83	115	
Person-years of follow-up	80,805	81,640	82,137	79,066	
Age-area adjusted RR (95% CI)	1.00	1.26 (0.90-1.78)	1.28 (0.92-1.79)	1.73 (1.26-2.37)	<0.01
Multivariate RR (95% CI)	1.00	1.34 (0.92-1.95)	1.29 (0.90-1.86)	1.63 (1.14-2.32)	0.01
	Lowest (2.3 g/d)	Second (32.4 g/d)	Third (125.8 g/d)	Highest (290.5 g/d)	
Milk					
No. cases	62	69	92	106	
Person-years of follow-up	79,972	81,201	82,827	79,648	
Age-area adjusted RR (95% CI)	1.00	1.26 (0.89-1.78)	1.39 (1.00-1.92)	1.54 (1.12-2.11)	< 0.01
Multivariate RR (95% CI)	1.00	1.41 (0.97-2.05)	1.49 (1.04-2.14)	1.53 (1.07-2.19)	0.01
	Lowest (1.9 g/d)	Second (2.2 g/d)	Third (3.0 g/d)	Highest (6.2 g/d)	
Cheese					
No. cases	74	98	85	73	
Person-years of follow-up	83,006	77,857	81,744	81,040	
Age-area adjusted RR (95% CI)	1.00	1.30 (0.96-1.77)	1.40 (1.02-1.91)	1.29 (0.93-1.79)	0.26
Multivariate RR (95% CI)	1.00	1.40 (1.00-1.96)	1.49 (1.06-2.09)	1.32 (0.93-1.89)	0.30
	Lowest (1.9 g/d)	Second (2.1 g/d)	Third (5.2 g/d)	Highest (31.5 g/d)	
Yogurt					
No. cases	73	66	85	105	
Person-years of follow-up	84,974	80,313	79,925	78,436	
Age-area adjusted RR (95% CI)	1.00	0.90 (0.64-1.25)	1.13 (0.82-1.55)	1.55 (1.14-2.09)	<0.01
Multivariate RR (95% CI)	1.00	0.93 (0.65-1.33)	1.15 (0.81-1.62)	1.52 (1.10-2.12)	<0.01

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, and intake of green tea and genistein.

versus lowest quartile of calcium of 1.24 (95% CI, 0.85-1.81; P_{trend} = 0.16) and 1.37 (95% CI, 0.97-1.95; P_{trend} = 0.11), respectively. Intake of some specific saturated fatty acids dose-dependently increased the risk of total prostate cancer. Multivariable RRs for the highest versus lowest quartiles of myristic acid and palmitic acid were 1.62 (95% CI, 1.15-2.29; P_{trend} < 0.01) and 1.53 (95% CI, 1.07-2.20; P_{trend} = 0.04), respectively. Multivariate RRs of stearic acid were attenuated when we controlled for potential confounding factors. However, this fatty acid did tend to increase the risk of total prostate cancer, albeit without statistically significance (highest versus lowest: multivariate RR, 1.35; 95% CI, 0.94-1.94; P_{trend} = 0.14).

We also analyzed the energy-adjusted intake of dairy products, calcium, and saturated fatty acid in relation to prostate cancer according to local staging (Table 4). Analysis of energy-adjusted intake of total dairy products and saturated fatty acid showed stronger associations for localized than for total prostate cancer. The multivariate RR for total dairy products was 1.69 (95% CI, 1.10-2.59; P_{trend} = 0.02) in the highest compared with the lowest category. Saturated fatty acid intake tended to increase the risk of localized prostate cancer, but without statistical significance (highest versus lowest: multivariate RR, 1.51; 95% CI; 0.98-2.31; P_{trend} = 0.08). No association was observed between calcium intake and localized prostate cancer (highest versus lowest: multivariate RR, 1.25; 95% CI, 0.80-1.97; P_{trend} = 0.21). Similarly, increased RR estimates for total dairy products were also seen for advanced prostate cancer but did not show statistical significance because of the limited number of advanced cases. Multivariate RR for the highest versus lowest category was 1.41 (95% CI, 0.73-2.73) for total dairy products. Intake of saturated fatty acid showed no association with advanced prostate cancer (highest versus lowest; multivariate RR, 1.21; 95% CI, 0.62-2.35). Results for calcium intake in advanced cancer were not substantially different to those in localized cancer (highest versus lowest: multivariate RR, 1.14; 95% CI, 0.54-2.41). To weaken the influence of prostate cancer detected by prostate-specific antigen (PSA) screening, we also analyzed the association between prostate cancer and the three items after excluding screening-detected tumors, notwithstanding that screening information was not available for 15% of cases.

Results for both localized and advanced prostate cancer were similar to those in Table 4 when screening-detected prostate cancer was included, although statistical significance was lost due to the small numbers. Multivariable RRs for the highest versus lowest quartile were 1.81 (95% CI, 0.88-3.71) for dairy products, 1.47 (95% CI, 0.71-3.05) for saturated fatty acid, and 1.15 (95% CI, 0.56-2.35) for calcium in localized prostate cancer and 1.13 (95% CI, 0.50-2.54) for dairy products, 1.12 (95% CI, 0.45-2.83) for saturated fatty acid, and 1.15 (95% CI, 0.42-3.15) for calcium in advanced prostate cancer (data not shown).

Discussion

We found a dose-dependent increase in the risk of prostate cancer with intake of dairy products in Japanese men. For specific saturated fatty acids, myristic acid and palmitic acid increased the risk of prostate cancer in a dose-dependent manner. To our knowledge, this is the first prospective study to investigate the association between the intake of dairy products, saturated fatty acid, and calcium and prostate cancer in an Asian population.

An association between dairy products and prostate cancer has been reported in many previous papers. Recently, two meta-analyses showed an 11% and 68% increase in the risk of prostate cancer in the highest category of dairy products (11) and milk consumption (12), respectively. Our present findings support the results of these meta-analyses. The mechanism of this increased risk has been proposed to owe to the calcium and fat content of dairy products. One mechanism is the effect of calcium in suppressing circulating levels of the active form of vitamin D (1,25-hydroxyvitamin D), or increasing those of insulin-like growth factor-I, which have been shown to be related to the risk of prostate cancer (32-34). A recent meta-analysis of prospective studies estimated that men with a higher intake of calcium had an increased risk of prostate cancer compared with those with a lower intake (RR, 1.39; 95% CI, 1.09-1.77; ref. 11). Another mechanism is that increased fat intake might lead to increased testosterone levels (35), and this might lead to increased cell division, activation of proto-oncogenes, and inactivation of tumor suppressor genes (36) and that high testosterone levels may therefore influence prostate cancer risk (37). Findings from previous epidemiologic studies examining the intake of saturated fatty acid in relation to prostate

Table 3. RRs and 95% CIs for prostate cancer according to quartile of energy-adjusted calcium and saturated fatty acid

	Intake by quartile (median)				P_{trend}
	Lowest (282.8 mg/d)	Second (403.6 mg/d)	Third (521.9 mg/d)	Highest (725.1 mg/d)	
Calcium					
No. cases	56	68	98	107	
Person-years of follow-up	80,438	81,652	82,005	79,554	
Age-area adjusted RR (95% CI)	1.00	1.09 (0.76-1.55)	1.40 (1.00-1.95)	1.43 (1.03-1.97)	0.01
Multivariate RR (95% CI)	1.00	1.03 (0.70-1.51)	1.32 (0.92-1.90)	1.24 (0.85-1.81)	0.16
	Lowest (9.7 g/d)	Second (13.8 g/d)	Third (17.3 g/d)	Highest (22.9 g/d)	
Saturated fatty acid					
No. cases	70	77	75	107	
Person-years of follow-up	82,409	81,945	80,180	79,114	
Age-area adjusted RR (95% CI)	1.00	1.13 (0.82-1.56)	1.10 (0.80-1.53)	1.53 (1.12-2.08)	0.01
Multivariate RR (95% CI)	1.00	1.09 (0.77-1.55)	0.99 (0.69-1.42)	1.37 (0.97-1.95)	0.11
	Lowest (0.6 g/d)	Second (1.0 g/d)	Third (1.4 g/d)	Highest (2.0 g/d)	
Myristic acid (14:0)					
No. cases	68	68	81	112	
Person-years of follow-up	82,223	81,990	81,325	78,110	
Age-area adjusted RR (95% CI)	1.00	1.08 (0.77-1.51)	1.27 (0.92-1.75)	1.82 (1.34-2.47)	< 0.01
Multivariate RR (95% CI)	1.00	1.10 (0.77-1.58)	1.24 (0.87-1.75)	1.62 (1.15-2.29)	< 0.01
	Lowest (6.0 g/d)	Second (8.1 g/d)	Third (10.0 g/d)	Highest (12.9 g/d)	
Palmitic acid (16:0)					
No. cases	63	82	76	108	
Person-years of follow-up	82,455	81,801	79,954	79,438	
Age-area adjusted RR (95% CI)	1.00	1.32 (0.95-1.84)	1.22 (0.87-1.70)	1.65 (1.20-2.28)	<0.01
Multivariate RR (95% CI)	1.00	1.27 (0.89-1.82)	1.09 (0.75-1.58)	1.53 (1.07-2.20)	0.04
	Lowest (2.1 g/d)	Second (3.1 g/d)	Third (4.0 g/d)	Highest (5.5 g/d)	
Stearic acid (18:0)					
No. cases	65	84	82	98	
Person-years of follow-up	82,497	81,801	79,858	79,491	
Age-area adjusted RR (95% CI)	1.00	1.31 (0.94-1.81)	1.31 (0.94-1.82)	1.46 (1.05-2.02)	0.03
Multivariate RR (95% CI)	1.00	1.23 (0.87-1.74)	1.15 (0.80-1.65)	1.35 (0.94-1.94)	0.14

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, and intake of green tea and genistein.

Table 4. RRs and 95% CIs for prostate cancer according to quartile of energy-adjusted intake of dairy products, calcium, and saturated fatty acid by local staging

	Intake in quartile				P_{trend}
	Lowest	Second	Third	Highest	
Localized prostate cancer					
Total dairy products					
No. cases	40	46	60	81	
Multivariate RR (95% CI)	1.00	1.32 (0.84-2.09)	1.37 (0.88-2.12)	1.69 (1.10-2.59)	0.02
Calcium					
No. cases	39	47	70	71	
Multivariate RR (95% CI)	1.00	1.03 (0.65-1.62)	1.36 (0.88-2.10)	1.25 (0.80-1.97)	0.21
Saturated fatty acid					
No. cases	45	55	55	72	
Multivariate RR (95% CI)	1.00	1.21 (0.79-1.84)	1.15 (0.75-1.78)	1.51 (0.98-2.31)	0.08
Advanced prostate cancer					
Total dairy products					
No. cases	19	22	22	27	
Multivariate RR (95% CI)	1.00	1.30 (0.66-2.56)	1.17 (0.59-2.32)	1.41 (0.73-2.73)	0.37
Calcium					
No. cases	15	20	26	29	
Multivariate RR (95% CI)	1.00	1.13 (0.55-2.34)	1.27 (0.62-2.61)	1.14 (0.54-2.41)	0.72
Saturated fatty acid					
No. cases	22	20	20	28	
Multivariate RR (95% CI)	1.00	0.95 (0.49-1.83)	0.84 (0.42-1.68)	1.21 (0.62-2.35)	0.74

NOTE: Multivariate RRs were adjusted for age, area, smoking status, drinking frequency, marital status, and intake of green tea and genistein.

cancer are inconsistent, although dietary fat may be related to prostate cancer risk (13). Only one prospective and four case-control studies have reported that the intake of saturated fatty acid increased the risk of prostate cancer (20, 38-41).

In Japanese men, dairy products are the main source of not only calcium but also saturated fatty acid, with data from a validation study in this cohort showing a mean intake and cumulative percent of 120.2 mg/d and 19.3% for calcium and 2.6 g/d and 16.0% for saturated fatty acid, respectively (19). In a previous study, a stronger association between saturated fat intake and prostate cancer risk was reported among Japanese Americans and Chinese Americans than among Blacks and Whites (20). These findings may explain our result that saturated fatty acid seemed to increase the risk of localized prostate cancer. In contrast, although calcium intake is reported to have increased the risk of prostate cancer in many epidemiologic studies, our lack of an association between calcium and prostate cancer may be due to the low intake of calcium in this study: the positive associations in several previous studies were limited to men with high intakes of >1,000 mg/d (14-18), whereas average intake here was only 500 mg/d, and only 3.5% consumed >1,000 mg/d. These results suggest that saturated fatty acid may play a relatively more important role than calcium in the incidence of prostate cancer in Japanese, to some extent at least. Owing to the relatively high correlation between dairy products, calcium, and saturated fatty acid shown in this study, however, we were unable to clarify what component of dairy is relevant to prostate cancer. Spearman's correlation coefficient between the energy-adjusted intake of dairy products and saturated fatty acid was 0.51, that of dairy products and calcium was 0.79, and that of calcium and saturated fatty acid was 0.48. These high correlations made it difficult to separate their effect on prostate cancer.

With regard to specific saturated fatty acids, our results showed that myristic acid and palmitic acid were associated with a dose-dependent increase in risk even after controlling for potential confounding factors. The main saturated fatty acids in dairy products are palmitic acid, myristic acid, and stearic acid, with palmitic acid levels more than twice those of the others (42). Our study accordingly showed a higher intake of palmitic acid than myristic acid, and we expected that palmitic acid would have the strongest relation with prostate cancer but instead found the greatest risk with myristic acid. Our results are supported by a nested case-control study, which found that high serum myristic acid levels were associated with a 2-fold increase in risk over low levels (41). In contrast, a second prospective study showed no association between dietary palmitic and stearic acid and prostate cancer risk, albeit without describing risk for myristic acid (43). In this study, Spearman's correlation coefficients between the energy-adjusted intake of dairy products and myristic acid, palmitic acid, and stearic acid were 0.76, 0.41, and 0.35, respectively. Thus, myristic acid may well reflect the intake of dairy products. Regarding specific saturated fatty acids, epidemiologic and laboratory data are sparse, and further studies on the effects of specific saturated fatty acids are required.

It has also been suggested that a high consumption of dairy products increases the risk of prostate cancer, especially advanced disease (11). However, our results for dairy products in advanced cancer were not substantially different from those in localized cancer, although RRs for them in advanced prostate cancer were smaller than those in localized cancer. The difference with some previous studies may be due to the difference in the proportion of PSA-detected cancers. PSA-based detection is less common in Japanese (38% in this study) than in western populations (e.g., ~80% in the United States; ref. 44). Giovannucci et al. (44) reported that the association between several risk factors and prostate cancer in the pre-PSA era differed from these associations in the PSA era, that is, because these cancers may have been largely diluted by the high prevalence of PSA-detected cancers.

Given that our results were not changed after the exclusion of screening-detected cancers, however, PSA screening in this study may have had less effect on the association between dairy products, calcium, and saturated fatty acid and prostate cancer than in other studies. Overall, moreover, the total prostate cancers in this study may have been more aggressive than those in western populations due to the lower PSA screening. On this basis, the results of total prostate cancers in this study may be similar to those for advanced cancer in western populations. An additional reason might be the small number of advanced cases; if so, a larger sample size may have detected positive effects of dairy products on advanced prostate cancer with greater precision.

The major strengths of our study were its prospective design that diminished the probability of recall bias, which is inherent to case-control studies. Because the study subjects were selected from the general population, the response rate was high (~80%), and the proportion of loss to follow-up was negligible (0.3%), the findings can be generalized to middle-aged and elderly Japanese men. Further, dietary information was ascertained using a validated FFQ.

Several limitations also warrant mention. First, misclassification of exposure due to changes in dairy product consumption during the study period might have occurred because information on consumption was obtained at one point only. If present, however, such misclassification would probably be nondifferential and may underestimate the true RR. Second, we could not distinguish between regular and low-fat milk intake, because the FFQ unfortunately did not enquire about the kind of milk. In Japan, regular milk accounts for nearly 90% of total milk consumption (45). Although our results showed that intake of milk and that of a specific saturated fatty acid increased the risk of prostate cancer, we could not clarify the association between low-fat milk and prostate cancer in Japanese men, notwithstanding several previous studies that it did indeed increase risk (46, 47). Finally, we did not consider the effect of calcium from supplements on prostate cancer. However, the proportion of calcium supplement users in this study was markedly low (0.2% of total subjects), and our results were not substantially changed after the exclusion of subjects who used calcium supplements (data not shown).

In summary, we found that the intake of dairy products was associated with an increased risk of prostate cancer. Given other findings that increased intake of dairy products may be protective for bone health, hypertension and colorectal cancer (48), further research is required to clarify the potential benefits and risks of a high intake of dairy foods.

Appendix A

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Acknowledgments

We thank all the staff members in each study area and in the central offices for cooperation and technical assistance and the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa Cancer Registries for provision of incidence data.

References

1. Parkin DM, Whelan SL, Ferlay J, Thomas DB. Cancer incidence in five continents. Vol. 8. Lyon: IARC; 2002.

2. Yatani R, Kusano I, Shiraishi T, Hayashi T, Stemmermann GN. Latent prostatic carcinoma: pathological and epidemiological aspects. Jpn J Clin Oncol 1989;19:319 – 26.
3. Tsugane S, de Souza JM, Costa ML, Jr., et al. Cancer incidence rates among Japanese immigrants in the city of Sao Paulo, Brazil, 1969-78. Cancer Causes Control 1990;1:189 – 93.
4. Shimizu H, Ross RK, Bernstein L, Yatani R, Henderson BE, Mack TM. Cancers of the prostate and breast among Japanese and white immigrants in Los Angeles County. Br J Cancer 1991;63:963 – 6.
5. Tominaga S, Kuroishi T. An ecological study on diet/nutrition and cancer in Japan. Int J Cancer 1997;Suppl 10:2 – 6.
6. Center for Cancer Control and Information Services. Japan: National Cancer Center; 2007.
7. The National Health and Nutrition Survey in Japan, Ministry of Health, Labour and Welfare of Japan; 2004.
8. Mishina T, Watanabe H, Araki H, Nakao M. Epidemiological study of prostatic cancer by matched-pair analysis. Prostate 1985;6:423 – 36.
9. Allen NE, Sauvaget C, Roddam AW, et al. A prospective study of diet and prostate cancer in Japanese men. Cancer Causes Control 2004;15:911 – 20.
10. Sonoda T, Nagata Y, Mori M, et al. A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. Cancer Sci 2004;95:238 – 42.
11. Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. J Natl Cancer Inst 2005;97:1768 – 77.
12. Qin LQ, Xu JY, Wang PY, Kaneko T, Hoshi K, Sato A. Milk consumption is a risk factor for prostate cancer: meta-analysis of case-control studies. Nutr Cancer 2004;48:22 – 7.
13. Kolonel LN, Nomura AM, Cooney RV. Dietary fat and prostate cancer: current status. J Natl Cancer Inst 1999;91:414 – 28.
14. Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 1998;58: 442 – 7.
15. Chan JM, Giovannucci E, Andersson SO, Yuen J, Adami HO, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). Cancer Causes Control 1998;9:559 – 66.
16. Rodriguez C, McCullough ML, Mondul AM, et al. Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. Cancer Epidemiol Biomarkers Prev 2003;12: 597 – 603.
17. Giovannucci E, Liu Y, Stampfer MJ, Willett WC. A prospective study of calcium intake and incident and fatal prostate cancer. Cancer Epidemiol Biomarkers Prev 2006;15:203 – 10.
18. Mitrou PN, Albanes D, Weinstein SJ, et al. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). Int J Cancer 2007;120:2466 – 73.
19. Sasaki S, Takahashi T, Iitoi Y, et al. Food and nutrient intakes assessed with dietary records for the validation study of a self-administered food frequency questionnaire in JPHC Study Cohort I. J Epidemiol 2003;13:S23 – 50.
20. Whittemore AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity, and body size in Blacks, Whites, and Asians in the United States and Canada. J Natl Cancer Inst 1995; 87:652 – 61..
21. Tsugane S, Sobue T. Baseline survey of JPHC study-design and participation rate. Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001;11: S24 – 9.
22. Science and Technology Agency, editors. Standard tables of food composition in Japan. The fifth revised edition [in Japanese]. Tokyo: Printing Bureau, Ministry of Finance; 2000.
23. Science and Technology Agency, editors. Fatty acids, cholesterol, vitamin E composition table of Japanese foods [in Japanese]. Tokyo: Ishiyaku Shuppan Publishers; 1990.
24. Tsugane S, Kobayashi M, Sasaki S; JPHC. Validity of the self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for main nutrients. J Epidemiol 2003;13:S51 – 6.
25. Sasaki S, Kobayashi M, Tsugane S; JPHC. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I: comparison with dietary records for food groups. J Epidemiol 2003;13:S57 – 63.
26. Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Tsugane S; JPHC. Validity of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess fatty acid intake: comparison with dietary records and serum phospholipid level. J Epidemiol 2003;13:S64 – 81.
27. Sasaki S, Ishihara J, Tsugane S; JPHC. Reproducibility of a self-administered food frequency questionnaire used in the 5-year follow-up survey of the JPHC Study Cohort I to assess food and nutrient intake. J Epidemiol 2003;13:S115 – 24.
28. Ishihara J, Sobue T, Yamamoto S, et al. Validity and reproducibility of a self-administered food frequency questionnaire in the JPHC Study Cohort II: study design, participant profile and results in comparison with Cohort I. J Epidemiol 2003;13:S134 – 47.
29. WHO. International classification of diseases for oncology. 3rd ed. Geneva (Switzerland): WHO; 2000.
30. Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S. Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol Biomarkers Prev 2007;16: 538 – 45.
31. Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, Tsugane S. Green tea consumption and prostate cancer risk in Japanese men: a prospective study. Am J Epidemiol 2008;167:71 – 7.
32. Giovannucci E. Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control 1998;9:567 – 82.
33. Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentrations. Cancer Epidemiol Biomarkers Prev 2002;11:852 – 61.
34. Gunnell D, Oliver SE, Peters TJ, et al. Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. Br J Cancer 2003;88:1682 – 6.
35. Dorgan JF, Judd JT, Longcope C, et al. Effects of dietary fat and fiber on plasma and urine androgens and estrogens in men: a controlled feeding study. Am J Clin Nutr 1996;64:850 – 5.
36. Ross RK, Henderson BE. Do diet and androgens alter prostate cancer risk via a common etiologic pathway? J Natl Cancer Inst 1994;86: 252 – 4.
37. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118 – 26.
38. Heshmat MY, Kaul L, Kovi J, et al. Nutrition and prostate cancer: a case-control study. Prostate 1985;6:7 – 17.
39. West DW, Slattery ML, Robison LM, French TK, Mahoney AW. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. Cancer Causes Control 1991;2:85 – 94.
40. Bairati I, Meyer F, Fradet Y, Moore L. Dietary fat and advanced prostate cancer. J Urol 1998;159:1271 – 5.
41. Mannisto S, Pietinen P, Virtanen MJ, et al. Fatty acids and risk of prostate cancer in a nested case-control study in male smokers. Cancer Epidemiol Biomarkers Prev 2003;12:1422 – 8.
42. Science and Technology Agency, editors. Standard tables of food composition in Japan. The fifth revised and enlarged edition, fatty acids section [in Japanese]. Tokyo: Printing Bureau, Ministry of Finance; 2005.
43. Schuurman AG, van den Brandt PA, Dorant E, Brants HA, Goldbohm RA. Association of energy and fat intake with prostate carcinoma risk: results from The Netherlands Cohort Study. Cancer 1999;86:1019 – 27.
44. Giovannucci E, Liu Y, Platz EA, Stampfer MJ, Willett WC. Risk factors for prostate cancer incidence and progression in the Health Professionals Follow-up Study. Int J Cancer 2007;121:1571 – 8.
45. Statistics of Agriculture, Forestry and Fisheries. Statistic on milk and dairy products. Ministry of Agriculture, Forestry and Fisheries; 2007.
46. Tseng M, Breslow RA, Graubard BI, Ziegler RG. Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. Am J Clin Nutr 2005;81:1147 – 54.
47. Torniainen S, Hedelin M, Autio V, et al. Lactase persistence, dietary intake of milk, and the risk for prostate cancer in Sweden and Finland. Cancer Epidemiol Biomarkers Prev 2007;16:956 – 61.
48. Alvarez-Leon EE, Roman-Vinas B, Serra-Majem L. Dairy products and health: a review of the epidemiological evidence. Br J Nutr 2006; 96:S94 – 9.