Dairy products and the risk of developing prostate cancer: A large-scale cohort study (JACC Study) in Japan

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Abstract
Dairy products have been indicated as a risk factor for prostate cancer. However, only a few epidemiological studies have reported dairy products as being a risk factor for prostate cancer in Japan, reporting contradictory results. We therefore investigated the association between the intake of dairy products and the occurrence of prostate cancer through a large-scale cohort study. The Japan Collaborative Cohort study analyzed approximately 110,000 residents from various Japanese districts who participated in our questionnaire survey during 1988–1990. The subjects of the present study were 26,464 men (age range: 40–79 years) from 24 districts wherein cancer incidence was reported. Their clinical course was followed up until 2009. Hazard ratios (HRs) were calculated using Cox’s proportional hazards model, adjusted for age, survey area, family history of prostate cancer, body mass index, and total energy intake. For diet, we calculated the HRs associated with intermediate and high consumption of dairy products and compared them with those associated with low consumption. There were 412 cases of prostate cancer in the survey population. As dairy products, milk, yogurt, cheese, and butter were evaluated. Among them, milk consumption was associated with a significant risk (HR = 1.37, \( p = 0.009 \)) and a dose-dependent response (\( p \) for trend = 0.009) adjusted for age and family history of prostate cancer, stratified...
Welfare, Health and Labor Sciences research grants, Japan (Comprehensive Research on Cardiovascular Disease and Life-Style Related Diseases: H20–Junkankitou [Seishuu]–Ippan–013; H23–Junkankitou [Seishuu]–Ippan–005); an Intramural Research Fund (22-4-5) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center; Comprehensive Research on Cardiovascular Diseases and Life-Style Related Diseases (H26–Junkankitou [Seisaku]–Ippan–001) and H29–Junkankitou [Seishuu]–Ippan–003 and 20FA1002.

1 | INTRODUCTION

Although the incidence of prostate cancer in Western countries has always been high, this was in contrast to that in Japan in the past. However, the incidence of prostate cancer in Japan has increased rapidly. Recently, prostate cancer has become one of the most common cancers in men. While many epidemiological studies, including cohort studies, have conducted investigations on this cancer in the Western world, only relatively few studies have been reported from Japan.1–7

Prostate cancer is one of the androgen-dependent cancers. Age, family history of prostate cancer, and race are well-known risk factors. In addition, total energy intake and obesity have been reported as risk factors. Intake of dairy products has also been indicated as a risk factor.8–10 Although several case–control and cohort studies have reported a positive correlation between the occurrence of prostate cancer and dairy product consumption, the results have been contradictory. In approximately 50% of these studies, the intake of dairy products was found to be a significant risk factor.8–10 Recent meta-analyses showed positive associations between dairy product consumption and prostate cancer development,11,12 and many studies showed significant relationships between the intake of dairy products and occurrence of advanced prostate cancer.13,14

In Japan, dairy products are not part of the traditional diet. However, the intake of dairy products has increased recently. According to The National Health and Nutrition Survey in Japan, intake of dairy products per day for each person increased rapidly from 103.5 g in 1975 to 122.2 g in 1988 and increased gradually to 125.1 g in 2009.15 Several decades ago, some Japanese studies investigated the association between the intake of dairy products and occurrence of prostate cancer.1,2 A case–control study reported a positive but nonsignificant risk associated with milk consumption through a semi-quantitative food frequency questionnaire.6 A cohort study showed a significant positive risk associated with dairy product consumption and a dose–response relationship.7 Therefore, we investigated the relationship between the risk of developing prostate cancer and consuming dairy products in a large-scale cohort study in Japan.

2 | SUBJECTS AND METHODS

The Japan Collaborative Cohort (JACC) study was conducted based on a subsidy for scientific research from the Ministry of Education, Culture, Sports, Science, and Technology.16,17 The cohort comprised 110,585 residents (46,395 men and 64,190 women, aged 40–79 years) from various districts in Japan who participated in our questionnaire survey during 1988–1990. The survey was conducted across 45 districts in 19 prefectures. The subjects of the present study were 26,464 men residing in the 24 districts wherein cancer incidence was reported. A follow-up survey on the incidence and mortality rates in various cancers was conducted until the end of 2009. However, some study areas stopped the follow-up survey of cancer incidence before 2009. Follow-up was terminated in 1994, 1999, 2000, 2002, and 2003 in one study area each; it was terminated in 1997, 2006, and 2008 in two areas each.

We initially investigated survival rates using resident registration books in the municipalities for death due to prostate cancer, and the cause of death was confirmed from death certificates. We judged prostate cancer from the code C61 in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

The questionnaire covered medical history, family history, health status, health habits, dietary habits, favorites, alcohol consumption, smoking, occupation, height, body weight, residential area, education level, stress, marital status, and child-bearing (delivery and pregnancy). Thirty-two dietary items were covered in the questionnaire.
Among dairy products, milk, cheese, butter, and yogurt were included. The frequency of eating these items was classified into five categories; “seldom,” “once or twice a month,” “once or twice a week,” “three or four times a week,” and “almost every day.” We reclassified these five categories into three groups (low, intermediate, and high consumption), calculated the risks of intermediate and high consumption, and compared the data with those of low consumption. In milk and yogurt, “seldom to twice a week” was classified as low, “three to four times a week” was classified as intermediate, and “almost every day” was classified as high consumption. In cheese and butter, “seldom” was classified as low, “once a month to two times a week” was classified as intermediate, and “over three times a week” was classified as high consumption.

We analyzed hazard ratios (HRs) and 95% confidence intervals (CIs) related to age, family history of prostate cancer, and dietary intake using Cox’s proportional hazard model, stratified by survey area. Regarding dairy products, the HRs of intermediate and high consumption were calculated in comparison to those of low consumption, adjusted according to age and family history of prostate cancer, stratified by survey area. BMI, total energy intake, and education were optionally added to the adjustment factors. The dose–response relationship of each HR (p for trend) was calculated by a linear function using quintile numbers. The PHREG procedure in the Statistical Analysis System (SAS) package was used for statistical calculations.

### 3 | RESULTS

Table 1 shows age, BMI, family history of prostate cancer, and total energy intake of the subjects according to the frequency of dairy product intake. Although family history of prostate cancer showed no association with consumption of any dairy product, BMI and total energy intake showed a positive association with consumption of all dairy products.

During the 697,777 person-years of follow-up, there were 412 cases of prostate cancer. The risk of prostate cancer increased with age, with an HR of 1.10 per 1-year increase (95% CI: 1.09, 1.11). A family history of prostate cancer tended to be a risk factor, with an age-adjusted HR of 3.90 (95% CI: 1.45, 10.47). Medians of time to diagnosis were 16.5, 16.7, 16.3, 14.3, and 9.8 years for the age at the time of recruitment of under 45 years, 45–49 years, 50–54 years, 55–59 years, and ≥60 years, respectively.

Milk consumption showed a positive association with the risk of developing prostate cancer adjusted for age and family history of prostate cancer, stratified by area. The HR for high consumption was 1.37 (95% CI: 1.08, 1.73), and a dose–response relationship was detected (p for trend = 0.009). Yogurt and cheese consumption showed positive correlations or dose–response relationships with prostate cancer, without any statistically significant difference (Table 2). Butter consumption alone showed a significant dose–response relationship (p for trend = 0.048).

After adjusting for BMI, milk consumption continued to show a significant positive risk (HR = 1.32 for intermediate consumption and 1.37 for high consumption) and a dose–response relationship (p for trend = 0.011). Butter consumption was also associated with a tendency for positive risk and showed a significant dose–response relationship (p for trend = 0.048).

After the addition of both BMI and total energy intake to the adjustment factors, the consumption of milk and yogurt was still associated with a significant positive risk. The HR of high milk consumption was 1.48 (95% CI: 1.11, 1.97) and that of high yogurt consumption was 1.68 (95% CI: 1.02, 2.80). Both milk and yogurt showed a significant dose–response relationship (p for trend: milk, 0.008; yogurt, 0.041).

When the HR was additionally adjusted for education, the HR for high milk consumption (1.43, p = 0.036) and the dose–response (p = 0.039) were still significant. However, the HR for high yogurt consumption and the dose–response became nonsignificant. As Westernized lifestyle such as high intake of dairy products is thought to be associated with high education level in Japan, this adjustment may underestimate the risk of dairy products.

### 4 | DISCUSSION

In Japan, only a few epidemiological studies have investigated the incidence of prostate cancer,1,7 and Hirayama conducted a cohort study a long time ago.1 With regard to dairy products, that study showed that high milk intake did not increase the risk of prostate cancer. However, some case–control studies reported that consumption of dairy products, especially milk, is a positive risk factor for the development of prostate cancer.1,2

In the last 10 years, many epidemiological studies have been conducted,5,7,20,32 including ours.7,29–32 Dietary habits,6,7,23–28,32 especially the intake of dairy products,6 were investigated. A case–control study that used a semi-quantitative food frequency questionnaire reported a positive but non-significant risk with milk consumption.5 The
TABLE 1  Characteristics of the subjects in the baseline survey (1988–1990) of the Japan Collaborative Cohort Study according to the frequency of dairy product consumption

### Milk

| Age (years) | Low level\(^a\) | Middle level\(^b\) | High level\(^c\) | Total | \(p\) \(^b\) |
|-------------|-----------------|-------------------|-----------------|-------|----------|
|             | No. | %   | No. | %   | No. | %   | Total |       |
| Mean±SD     | mean | SD  | mean | SD  | mean | SD  |       |       |
| Age (years) | 56.7 | 10.2 | 56.2 | 10.3 | 58.8 | 10.2 |       |       |
| Family history of prostate cancer | 23378 | 0.164 |
| No | 9940 | 42.5 | 2949 | 12.6 | 10489 | 44.9 |
| Yes | 28 | 41.2 | 4 | 5.9 | 36 | 52.9 |
| Unknown | 2874 |       |       |       |       |       |
| Body mass index (kg/m\(^2\)) | 1274 | < 0.05 |
| < 18.5 | 566 | 44.4 | 124 | 9.7 | 584 | 45.8 |
| 18.5–24.9 | 7457 | 42.3 | 2250 | 12.8 | 7938 | 45.0 |
| ≥ 25.0 | 1925 | 45.3 | 540 | 12.7 | 1782 | 42.0 |
| Unknown | 3154 |       |       |       |       |       |
| Total energy intake (kcal) | 17645 |       |
| 393–1380 | 2123 | 51.5 | 442 | 10.7 | 1555 | 37.7 |
| 1381–1685 | 1805 | 43.7 | 509 | 12.3 | 1819 | 44.0 |
| 1686–2026 | 1721 | 41.5 | 534 | 12.9 | 1891 | 45.6 |
| 2027–4262 | 1651 | 39.9 | 605 | 14.6 | 1878 | 45.4 |
| Unknown | 9787 |       |       |       |       |       |

### Yogurt

| Age (years) | Low level\(^a\) | Middle level\(^b\) | High level\(^c\) | Total | \(p\) |
|-------------|-----------------|-------------------|-----------------|-------|-------|
|             | No. | %   | No. | %   | No. | %   | Total |       |
| Mean±SD     | mean | SD  | mean | SD  | mean | SD  |       |       |
| Age (years) | 56.5 | 10.1 | 58.4 | 10.5 | 60.1 | 10.1 |       |       |
| Family history of prostate cancer | 19688 | 0.570 |
| No | 17934 | 91.1 | 772 | 3.9 | 982 | 5.0 |
| Yes | 58 | 87.9 | 3 | 4.5 | 5 | 7.6 |
| Unknown | 6566 |       |       |       |       |       |
| Body mass index (kg/m\(^2\)) | 1080 | < 0.05 |
| < 18.5 | 959 | 88.8 | 38 | 3.5 | 83 | 7.7 |
| 18.5–24.9 | 13777 | 91.3 | 592 | 3.9 | 721 | 4.8 |
| ≥ 25.0 | 3266 | 91.8 | 134 | 3.8 | 159 | 4.5 |
| Unknown | 6591 |       |       |       |       |       |
| Total energy intake (kcal) | 15090 |       |
| 393–1380 | 3635 | 93.0 | 120 | 3.1 | 152 | 3.9 |
| 1381–1685 | 3541 | 92.1 | 128 | 3.3 | 176 | 4.6 |
| 1686–2026 | 3561 | 92.5 | 120 | 3.1 | 169 | 4.4 |
| 2027–4262 | 3442 | 90.9 | 167 | 4.4 | 176 | 4.6 |
| Unknown | 10933 |       |       |       |       |       |

(Continues)
| Age (years) |  | Low level<sup>d</sup> |  | Middle level<sup>e</sup> |  | High level<sup>f</sup> |  | Total |  | p  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | No. | % | No. | % | No. | % | | | | |
| Mean±SD | 57.6 | 10.1 | 55.3 | 10.1 | 58.6 | 10.0 |
| Mean±SD | 54.3 | 10.1 | 58.5 | 10.0 | 58.6 | 10.0 |
| Mean±SD | 55.3 | 10.1 | 58.5 | 10.0 | 58.6 | 10.0 |
| Family history of prostate cancer |  |  |  |  |  |  |  |  |  |  |
| No | 10078 | 49.6 | 8789 | 43.2 | 1470 | 7.2 | 20337 | 0.499 |
| Yes | 31 | 44.3 | 36 | 51.4 | 3 | 4.3 | 70 |  |  |
| Unknown |  |  |  |  |  |  | 5913 |  |  |
| Body mass index (kg/m²) |  |  |  |  |  |  |  |  |  |  |
| < 18.5 | 531 | 51.6 | 406 | 39.5 | 92 | 8.9 | 1029 | < 0.05 |
| 18.5–24.9 | 7321 | 49.1 | 6495 | 43.6 | 1085 | 7.3 | 14901 |  |  |
| ≥ 25.0 | 1817 | 49.5 | 1627 | 44.3 | 229 | 6.2 | 3673 |  |  |
| Unknown |  |  |  |  |  |  | 6717 |  |  |
| Total energy intake (kcal) |  |  |  |  |  |  |  |  |  |  |
| 393–1380 | 2583 | 63.2 | 1362 | 33.3 | 144 | 3.5 | 4089 | < 0.05 |
| 1381–1685 | 2075 | 50.5 | 1819 | 44.3 | 213 | 5.2 | 4107 |  |  |
| 1686–2026 | 1963 | 47.8 | 1863 | 45.4 | 281 | 6.8 | 4107 |  |  |
| 2027–4262 | 1743 | 42.3 | 1963 | 47.7 | 410 | 10.0 | 4116 |  |  |
| Unknown |  |  |  |  |  |  | 9901 |  |  |

| Age (years) |  | Low level<sup>d</sup> |  | Middle level<sup>e</sup> |  | High level<sup>f</sup> |  | Total |  | p  |
|---|---|---|---|---|---|---|---|---|---|---|
|  | No. | % | No. | % | No. | % | | | | |
| Mean±SD | 57.2 | 10.1 | 55.4 | 10.1 | 58.7 | 10.6 |
| Mean±SD | 54.3 | 10.1 | 58.5 | 10.0 | 58.6 | 10.0 |
| Mean±SD | 55.3 | 10.1 | 58.5 | 10.0 | 58.6 | 10.0 |
| Family history of prostate cancer |  |  |  |  |  |  |  |  |  |  |
| No | 10484 | 52.2 | 7892 | 39.3 | 1718 | 8.5 | 20094 | 0.488 |
| Yes | 32 | 47.8 | 31 | 46.3 | 4 | 6.0 | 67 |  |  |
| Unknown |  |  |  |  |  |  | 6159 |  |  |
| Body mass index (kg/m²) |  |  |  |  |  |  |  |  |  |  |
| < 18.5 | 523 | 51.7 | 362 | 35.8 | 127 | 12.5 | 1012 | < 0.05 |
| 18.5–24.9 | 7649 | 52.0 | 5836 | 39.6 | 1238 | 8.4 | 14723 |  |  |
| ≥ 25.0 | 1890 | 51.9 | 1465 | 40.2 | 289 | 7.9 | 3644 |  |  |
| Unknown |  |  |  |  |  |  | 6941 |  |  |
| Total energy intake (kcal) |  |  |  |  |  |  |  |  |  |  |
| 393–1380 | 2566 | 63.5 | 1268 | 31.4 | 206 | 5.1 | 4040 | < 0.05 |
| 1381–1685 | 2220 | 54.5 | 1578 | 38.7 | 275 | 6.8 | 4073 |  |  |
| 1686–2026 | 2112 | 52.0 | 1629 | 40.1 | 320 | 7.9 | 4061 |  |  |
| 2027–4262 | 1825 | 44.6 | 1809 | 44.2 | 460 | 11.2 | 4094 |  |  |
| Unknown |  |  |  |  |  |  | 10052 |  |  |

<sup>a</sup>Seldom to twice/week.
<sup>b</sup>Three to four times/week.
<sup>c</sup>Almost everyday.
<sup>d</sup>Seldom.
<sup>e</sup>Once/month to twice/week.
<sup>f</sup>Three times/week.
<sup>g</sup>Standard deviation.
<sup>h</sup>Pearson’s chi-square test.
Japan Public Health Center–Based Prospective Study showed significant positive risk and dose–response relationships for the consumption of dairy products. However, recent studies reported that each kind of fatty acids, monounsaturated fatty acids, or polyunsaturated fatty acids and overall prostate cancer development and also “advanced/high-grade” prostate cancer development. However, recent studies reported that each kind of fatty acids may have heterogeneous effects, which might explain the contradictory results of the role of dietary fat regarding prostate cancer development. In our results, the HR of milk intake was slightly decreased after adjusting for BMI. The risk associated with the intake of dairy products may thus be influenced by total energy intake.

Calcium and vitamin D in dairy products are suggested to play important roles in the pathogenesis of prostate cancer. It is hypothesized that the intake of high amounts of calcium inhibits the synthesis of 1,25(OH)2 vitamin D, thus increasing the risk of developing prostate cancer. Epidemiologically, the Health Professional Follow-up Study reported that calcium was a risk factor for prostate cancer incidence independent of fat intake, especially for advanced and metastatic cancer (RR = 1.6 in advanced cases, RR = 1.8 in metastatic cases). In the Cancer Prevention Study II Nutrition Cohort, total calcium intake including supplements other than the intake through diet was examined, and the relationship with prostate cancer was investigated. However, another study similarly examining calcium intake concluded that moderate intake of calcium did not markedly increase prostate cancer risk. A positive relationship of total calcium and dairy calcium intakes, but not nondairy calcium or supplemental calcium intakes, with total prostate cancer risk was reported. Additional intake of calcium from food supplements was associated with an increased risk of fatal prostate cancer. In Japan, as in the Western world, milk and dairy products are major dietary sources of calcium intake. Calcium and vitamin D, in concurrence with saturated fat in dairy products, favor the development of prostate cancer.

Insulin-like growth factor-1 (IGF-1) was suggested to be positively associated with the risk of prostate cancer in meta-analyses. High-energy intake and milk consumption may increase plasma IGF-1 levels. One study suggested a link between fat intake and prostate cancer involving IGF-1, insulin, or leptin. Moreover, another study showed that vitamin D levels increased circulating IGF-1 levels.

In our previous study, unfortunately, we could not show a correlation between serum IGF-1 levels and prostate cancer incidence. The largest pooled analysis, including our previous study, investigating the association between circulating concentrations of IGFs (IGF-I, IGF-II, IGFBP-1, IGFBP-2, and IGFBP-3) and prostate cancer risk, provided strong evidence that IGF-I is highly likely to be involved in prostate cancer development.
Based on PSA levels, but no area surveyed in our study was included.

Moreover, our study did not collect detailed clinical information on cancer cases, such as information on serum PSA levels, tumor-lymph node-metastasis (TNM) stage, or pathological grade, because we obtained information about cancer incidence not from local hospitals but from local cancer registries. Thus, we could not investigate the risk adjusted for the characteristics of prostate cancer. The participants who visited a hospital regularly for some chronic disease might have had a higher probability of undergoing PSA testing. In our study, the opportunities to take a PSA test were not recorded. We tried to assess the risk of dairy products adjusted for diseases (diabetes mellitus, hypertension, and gastric ulcer) under treatment at the time of the baseline survey, but the results did not change (data not shown).

In summary, despite such limitations, our cohort study suggests that the intake of dairy products is an important risk factor for prostate cancer development in Japan. In particular, the data may provide further clues regarding the effects of high intake of fat, calcium, and IGFs. Further studies are needed to clarify which components of dairy products contribute to this increased risk. The consumption of dairy products is worthy of consideration when comparing Japanese and Western diets regarding the risk of developing prostate cancer.

**ACKNOWLEDGMENTS**

The authors express their sincere gratitude to Dr. Kunio Aoki, Professor Emeritus, Nagoya University School of Medicine, and the former chairman of the JACC Study Group. The authors also offer special thanks to Dr. Haruo Sugano, the former Director of the Cancer Institute of the Japanese Foundation for Cancer Research, who greatly contributed to the initiation of the study. For this study, we appreciate Dr. Fumio Sakauchi and Dr. Masakazu

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**TABLE 2** Hazard ratios (HRs) of the incidence of prostate cancer with 95% confidence intervals (CIs) for the consumption of dairy products

|                | Person-years | No. of cases | HR1a  | 95% CI  | p    | p for trend | HR2b  | 95% CI  | p    | p for trend | HR3c  | 95% CI  | p    | p for trend | HR4d  | 95% CI  | p    |
|----------------|--------------|--------------|--------|---------|------|-------------|--------|---------|------|-------------|--------|---------|------|-------------|--------|---------|------|
| **Milk (n = 24,220)** |              |              |        |         |      |             |        |         |      |             |        |         |      |             |        |         |      |
| Low level⁵     | 165,980      | 126          | Ref.   |         |      |             |        | Ref.    |      |             |        |         |      |             |        |         |      |
| Middle level⁶  | 50,275       | 50           | 1.29   | 0.93    | 1.80 | 0.127       | 0.127  | 0.009** | 1.32 | 0.94        | 1.85   | 0.114   |      |             |        |         |      |
| High level⁷    | 170,219      | 196          | 1.37   | 1.08    | 1.73 | 0.009**     | 1.37   | 1.08    | 1.74 | 0.010**     |        |         |      |             |        |         |      |
| **Yogurt (n = 20,518)** |            |              |        |         |      |             |        |         |      |             |        |         |      |             |        |         |      |
| Low level⁵     | 302,638      | 222          | Ref.   |         |      |             |        | Ref.    |      |             |        |         |      |             |        |         |      |
| Middle level⁶  | 12,498       | 16           | 1.45   | 0.87    | 2.41 | 0.153       | 0.153  | 0.092*  | 1.47 | 0.87        | 2.49   | 0.150   |      |             |        |         |      |
| High level⁷    | 15,251       | 22           | 1.35   | 0.87    | 2.11 | 0.184       | 1.28   | 0.81    | 2.04 | 0.292       |        |         |      |             |        |         |      |
| **Cheese (n = 20,407)** |          |              |        |         |      |             |        |         |      |             |        |         |      |             |        |         |      |
| Low level⁵     | 160,112      | 137          | Ref.   |         |      |             |        | Ref.    |      |             |        |         |      |             |        |         |      |
| Middle level⁶  | 146,927      | 146          | 1.23   | 0.97    | 1.56 | 0.090*      | 0.259  | 1.26    | 0.99 | 1.60        | 0.065* |         |      |             |        |         |      |
| High level⁷    | 23,710       | 26           | 1.04   | 0.68    | 1.58 | 0.874       | 0.99   | 0.63    | 1.55 | 0.964       |        |         |      |             |        |         |      |
| **Butter (n = 20,161)** |            |              |        |         |      |             |        |         |      |             |        |         |      |             |        |         |      |
| Low level⁵     | 254,905      | 223          | Ref.   |         |      |             |        | Ref.    |      |             |        |         |      |             |        |         |      |
| Middle level⁶  | 46,085       | 53           | 1.26   | 0.94    | 1.71 | 0.128       | 0.128  | 0.048** | 1.29 | 0.95        | 1.75   | 0.099*  |      |             |        |         |      |
| High level⁷    | 25,950       | 34           | 1.34   | 0.93    | 1.93 | 0.114       | 1.37   | 0.95    | 1.98 | 0.096*      |        |         |      |             |        |         |      |

†Adjusted for age and family history of prostate cancer (FHPCa), and stratified by area.
‡Adjusted for age, FHPCa and body mass index (BMI), and stratified by area.
§Adjusted for age, FHPCa, BMI and total energy intake, and stratified by area.
¶Adjusted for age, FHPCa, BMI, total energy intake and education level, and stratified by area.
*Seldom to twice/week.
†Three to four times/week.
‡Almost everyday.
§Seldom.
¶Once/ month to twice/week.
†Three times/week.
*p < 0.1; **p < 0.05.
Washio for their contributions to the data collection and discussion.

CONFLICT OF INTEREST
All authors declared no conflicts of interest on this study.

AUTHORS CONTRIBUTIONS
All authors contributed to the conceptualization and methodology of the present study and took part in data collection. Akiko Tamakoshi performed the administration of the whole project of the JACC Study. Data analysis was performed by Kazuya Mikami and Kotaro Ozasa. Tsuneharu Miki, Yoshiyuki Watanabe, Mitsuru Mori, Koji Suzuki, and Kenji Wakai supervised and provided advice from the viewpoint of their expertise in urology and epidemiology. The first draft of the manuscript was prepared by Kazuya Mikami, and all authors edited, reviewed, and approved it.

ETHICAL APPROVAL STATEMENT
This study was approved by the ethics committees of Hokkaido University, Hokkaido, Japan, and Osaka University, Osaka, Japan. number/ID 14285-6.

DATA AVAILABILITY STATEMENT
The data analyzed in this study are available from the corresponding author upon reasonable request.

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How to cite this article: Mikami K, Ozasa K, Miki T, et al. Dairy products and the risk of developing prostate cancer: A large-scale cohort study (JACC Study) in Japan. *Cancer Med*. 2021;10:7298–7307. [https://doi.org/10.1002/cam4.4233](https://doi.org/10.1002/cam4.4233)