

## Calcium Intake Increases Risk of Prostate Cancer among Singapore Chinese

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### Abstract

Consumption of dairy products, the primary source of calcium in Western diets, has been found to be positively associated with prostate cancer. In an Asian diet, nondairy foods are the major contributors of calcium. Thus, a study of dietary calcium and prostate cancer in Asians can better inform on whether calcium, as opposed to other dairy components, is responsible for the dairy foods–prostate cancer association. We examined calcium intake and prostate cancer risk among 27,293 men in the Singapore Chinese Health Study that was established between 1993 and 1998. As of December 31, 2007, 298 incident prostate cancer cases had been diagnosed among the cohort members. Diet was assessed at baseline with a validated 165-item food-frequency questionnaire. It is hypothesized that there is greater net absorption of calcium in smaller individuals. Therefore, the calcium–prostate cancer association was also assessed in stratified analyses by median body mass index. Vegetables were the largest contributor of daily calcium intake in the study population. Overall, we observed a modest, statistically nonsignificant 25% increase in prostate cancer risk for the 4th (median = 659 mg/d) versus 1st (median = 211 mg/d) quartiles of calcium intake after adjustment for potential confounders. The association became considerably stronger and achieved statistical significance (hazard ratio, 2.03; 95% confidence interval, 1.23–3.34; *P* for trend = 0.01) for men with a below median body mass index (22.9 kg/m<sup>2</sup>). Dietary calcium might be a risk factor for prostate cancer even at relatively low intake. *Cancer Res*; 70(12); 4941–8.

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### Introduction

Dairy product consumption has consistently been found to increase the risk of prostate cancer in prospective epidemiologic studies (1–3). Dairy products are the major food source of calcium in Western populations, where nearly all of the previous studies were conducted. Although the underlying mechanism is unknown, there are several nutrients that might contribute to the observed association between dairy products and prostate cancer, such as calcium, saturated fatty acids, protein, and phosphorus. The focus of this article is on the role of calcium in prostate cancer risk.

There is a biological plausibility for the role for calcium in prostate carcinogenesis. Intracellular calcium pools have been shown to control prostate cancer cell growth and susceptibility to apoptosis (4). Although tightly maintained, small alterations in calcium homeostasis could result in

increased proliferation, differentiation, and apoptosis in prostate cancer cells (5, 6). Calcium homeostasis is maintained in part by the calcium-sensing receptor (7), a G protein-coupled cell surface glycoprotein that is expressed in PC-3 cells (8) and may play a role in malignant progression of prostate tumors (9).

In addition to the experimental evidence, prospective epidemiologic studies of calcium and prostate cancer also support a positive association (1, 2), particularly for high levels of intake (>2,000 mg/d; ref. 10). High levels of calcium intake are typical in Western populations, where dairy product intake is high (≈14% consume three or more servings per day; ref. 11) and calcium supplementation is common (≈48%; ref. 12). The strong correlation between dairy and calcium intake in previously studied populations made it difficult to evaluate the effects of calcium, independent of residual confounding from dairy intake or supplement use, or sociodemographic factors related to dairy intake and/or supplement use (13).

In Asian diets, dairy products are rarely consumed and thus are a minor source of dietary calcium. Instead, the major sources of dietary calcium in Asian diets are from soyfoods and green vegetables. Compared with dairy products, tofu and low-oxalate vegetables, such as kale, broccoli, and bok choy, provide similar volumetric amounts of bioavailable calcium (14). Utilizing the database of a prospective cohort of Singapore Chinese in whom dairy intake is low and calcium supplementation is rare, we will be able to assess the association between dietary calcium and prostate cancer with a lower likelihood of residual confounding by dairy intake and

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supplement use compared with previous studies. The present study population also allowed us to examine the effect of calcium from nondairy sources, and thus avoid the potential confounding effect of other components in the dairy products on the calcium–prostate cancer risk association.

## Materials and Methods

### Study population

The design of the Singapore Chinese Health Study has been previously described in detail (15). Briefly, the cohort consisted of 27,959 men and 35,298 women recruited between April 1993 and December 1998, from permanent residents or citizens of Singapore ages 45 to 74 years, and who resided in government-built housing estates (86% of the Singapore population resided in such facilities). We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore: the Hokkiens and the Cantonese. For these analyses, we used data from the 27,293 men who did not have a history of cancer diagnosis at baseline, based on self-report and computer-assisted record linkage analysis with the Singapore Cancer Registry. The Institutional Review Boards at the National University of Singapore and the University of Minnesota approved this study.

Identification of incident prostate cancer cases and deaths among cohort members was accomplished by record linkage of the cohort database with respective databases from the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases (16). As of April 2008, only 27 cases were known to be lost to follow-up due to migration out of Singapore. As of December 31, 2007 (an average of 11.0 years of follow-up), 298 cohort participants developed invasive prostate cancer. Staging was determined through comprehensive chart reviews by a single urology oncologist (A.S. Wong). Cases that had radical prostatectomy were staged according to pathologic criteria, as defined by The American Joint Committee on Cancer (17). The remaining cases were staged according to clinical criteria by D'Amico risk group categories (18). Early disease included cases with pathologically staged organ-confined disease (T1–T2), or clinically staged organ-confined disease and with either D'Amico good or intermediate risk. Locally advanced disease included cases with pathologically staged extracapsular (T3–T4) or nodal involvement (N1), clinically staged extraprostatic extension or regional nodal disease, or clinically organ-confined disease with D'Amico high risk. Metastatic disease was defined as disease with evidence of distant metastases, based on clinical information. In summary, 124 (41.6%) cases had early disease, 99 (33.2%) had locally advanced disease, and 63 (21.1%) had metastatic disease at diagnosis. The remaining 12 (4.0%) cases did not have sufficient information for the determination of disease stage.

### Exposure assessment

Enrollment in the cohort entailed completing a baseline in-person interview in the participant's home. The question-

naire elicited information on smoking, diet, demographics, current physical activity, occupational exposure, and medical history. We used a 165-item quantitative food-frequency questionnaire, developed for and validated in this population, to assess usual diet over the past year (19). Average daily intake of roughly 100 nutrient and nonnutrient compounds, including calcium, was computed for each study subject based on the Singapore Food Composition Database (19).

Our calculation of the food sources as percentages of dietary calcium in the study population was based on a series of 24-hour dietary recall interviews. Specifically, as part of the food-frequency questionnaire validation study, 24-hour diet recall data were collected from 1,022 (425 men and 597 women) randomly chosen cohort subjects (19). The percentage of contribution of calcium from a specified food item or food group was calculated as the ratio of  $A_i/B$ , where  $A_i$  = dietary calcium from a single food ( $i$ ) summed across all subjects who consumed that food, and  $B$  = total dietary calcium summed across the 1,022 subjects.

### Statistical methods

Person-years of follow-up were counted from the date of recruitment to the date of diagnosis of prostate cancer, death, migration, or December 31, 2007, whichever occurred first. Proportional hazards regression methods were used to examine the associations between calcium intake in quartile level (per 1,000 kcal) and prostate cancer risk, measured by hazard ratios (HR) and their corresponding 95% confidence intervals (CI; ref. 20). We considered whether calcium intake was associated with local and advanced disease (locally advanced and metastatic disease combined) separately, to infer whether calcium was related to earlier versus later stages of prostate carcinogenesis.

The linear trend tests for calcium–prostate cancer associations were based on ordinal values of the quartile levels of calcium intake (0, 1, 2, and 3). In all analyses, we adjusted for the following potential confounders: age at baseline interview (years), year of interview (1993–1995, 1996–1998), dialect group (Cantonese, Hokkien), level of education (no formal education/primary school, secondary school/or higher), and any weekly supplement use (yes, no), based on a 10% or greater change in the  $\beta$  estimate for fourth versus first quartile of total calcium intake and prostate cancer risk. Additional inclusion of the following variables did not materially change any of the study results: body mass index (BMI), weekly physical activity, alcohol consumption, green tea intake, family history of prostate cancer, and dietary intake of total fat, lycopene, phosphorus, vitamin D, and total soy isoflavones.

Based on previous analyses of our data and reports from the literature, we examined whether the association between calcium and prostate cancer risk varied by the following factors: age at baseline (below or above median), weekly physical activity (yes, no), dietary vitamin D (below or above median), and phosphorus (below or above median), by assessing the fitness of interaction terms in adjusted models. We also evaluated whether the calcium–prostate cancer risk association varied by BMI level (below or above median,

**Table 1.** Distribution of study population characteristics by quartiles of total calcium intake

	Calcium intake by quartiles*			
	<266 mg/d	266–371 mg/d	372–521 mg/d	≥523 mg/d
<i>N</i>	6,800	6,857	6,829	6,807
Median age (IQR), y	58 (13)	56 (13)	55 (13)	56 (13)
No or primary education only (%)	72.2	64.6	58.6	52.4
Any weekly physical activity (%)	33.5	41.9	46.3	51.5
Median BMI (IQR), kg/m <sup>2</sup>	22.9 (3.3)	22.9 (3.5)	22.9 (3.7)	23.0 (3.7)
At least weekly green tea (%)	25.9	33.7	38.2	40.8
Any weekly supplement use (%) <sup>†</sup>	1.3	3.0	5.0	10.0
Weekly calcium supplement use (%)	0.2	0.6	1.9	5.8
Median (IQR) daily energy intake (kcal)	1,213 (451)	1,552 (505)	1,834 (616)	2,196 (866)
Median (IQR) daily intake <sup>‡</sup>				
Calcium from food only (mg)	211 (66.6)	317 (52.1)	433 (73.7)	651 (205)
Calcium from food+supplements (mg)	211 (66.5)	317 (51.8)	435 (72.7)	659 (211)
Saturated fat (g)	9.7 (5.2)	14.2 (6.5)	18.0 (8.5)	23.0 (13.0)
Vitamin D (IU)	46.6 (39.4)	75.5 (48.4)	109 (59.9)	175 (90.1)
Lycopene (μg)	416 (702)	783 (1,042)	995 (1,221)	1,320 (1,994)
Red meat (g)	21.1 (19.5)	29.2 (24.6)	35.0 (31.0)	40.2 (40.8)
Total vegetables (g)	64.0 (40.3)	92.1 (50.4)	116 (67.4)	144 (99.6)
Dairy products (g)	3.4 (13.8)	15.4 (27.1)	32.1 (44.5)	134 (226)
Soyfoods (g)	47.3 (44.4)	83.4 (65.5)	117 (93.6)	165 (160)
Total soy isoflavones (mg)	7.4 (7.5)	13.1 (11.2)	19.0 (15.5)	26.7 (27.3)

Abbreviation: IQR, interquartile range.

\*Calcium intake from combined food and supplement sources.

<sup>†</sup>Supplement use was defined by responses (yes, no) to the question, "Did you take any vitamins or minerals at least once each week during the last year?"

<sup>‡</sup>Intake was based on food sources only, unless otherwise noted.

22.9 kg/m<sup>2</sup>) because it is hypothesized that there is greater net absorption of calcium in thinner individuals (21, 22). Statistical computing was conducted using SAS version 9.1 (SAS Institute Inc.). All *P* values were two-sided and considered statistically significant if less than 0.05.

## Results

Increasing quartiles of calcium intake were associated with less education, more frequent physical activity, higher frequency of green tea intake, and any supplement use (Table 1). Less than 5% of the cohort (*n* = 1,311) reported any weekly supplement use and 2.1% of the cohort reported use of calcium supplements on a weekly basis. Although there was no difference by median age, supplement users reported somewhat more frequent physical activity and intake of tea, regardless of type, as well as calcium (from food only; data not shown). In our cohort, consumption of dairy products was low, with a median daily intake of 19.3 g [interquartile range (IQR) = 51.6 g]. Although milk was the most commonly consumed dairy product, only 24% of the cohort reported drinking a glass of milk (250 mL) at least once a week. The major food sources of calcium (percentage of contribution to total calcium) in our study population were vegetables

(19.3%), dairy (17.3%), grain products (14.7%), soyfoods (11.8%), fruit (7.3%), and fish (6.2%; Table 2). Intake from any of these food groups was not individually associated with prostate cancer risk, regardless of whether calcium intake was in the model (data not shown).

Table 3 shows the association between calcium intake and prostate cancer risk in total subjects and among non-supplement users. There was a modest, statistically non-significant positive association between calcium intake, whether based on food sources only or food and supplement sources combined, and prostate cancer risk. Risk was elevated roughly 20% for subjects in the highest versus the lowest quartiles of intake, regardless of supplement use (Table 3). The association was not markedly different for local disease (HR, 1.43; 95% CI, 0.81–2.52; *P* for trend = 0.13) or for advanced disease (HR, 1.18; 95% CI, 0.75–1.87; *P* for trend = 0.6), comparing the highest versus lowest quartiles of total calcium intake among all subjects.

We further evaluated the calcium–prostate cancer association stratified by the median value of BMI (22.9 kg/m<sup>2</sup>) among all men in our cohort. There was a statistically significant, dose-dependent positive association between total calcium intake and prostate cancer risk in men with below median BMI (Table 4). Although the association for highest

versus lowest calcium intake seemed to be stronger for local disease (HR, 2.42; 95% CI, 1.11–5.28;  $P$  for trend = 0.02) compared with advanced disease (HR, 1.70; 95% CI, 0.86–3.35;  $P$  for trend = 0.2), the two sets of HRs were not statistically different from each other ( $P = 0.4$ ). No association with calcium intake was noted among men with greater than median BMI ( $P$  for interaction = 0.02; Table 4). Table 5 shows the association between total calcium intake and prostate cancer risk among men with below median BMI, stratified by duration of follow-up. Although the association seemed stronger among subjects with a longer duration of follow-up, the two sets of HRs were not statistically different from each other ( $P = 0.7$ ).

There was no evidence of effect modification by age or physical activity (data not shown). Vitamin D and phosphorus are determinants of calcium absorptive efficiency (23, 24). Among men with greater than median (92.9 IU/d) vitamin D, the point estimate for highest versus lowest calcium was stronger (HR, 1.85; 95% CI, 0.92–3.73;  $P$  for trend = 0.5) than their counterparts with less than median vitamin D intake (HR, 1.21; 95% CI, 0.71–2.04;  $P$  for trend = 0.5). There was no difference in the association between calcium and prostate cancer by median phosphorus intake (863 mg/d; data not shown).

## Discussion

We report a 25% increase in prostate cancer risk comparing 4th (median = 659 mg/d) versus 1st (median = 211 mg/d) quartiles of total calcium intake, using data from a prospective cohort of Singapore Chinese. Among men with less than median BMI, and thus thought to have greater net calcium absorption, we observed a statistically significant, dose-dependent positive association that yielded a 2-fold increased risk between subjects in the highest versus the

lowest quartiles of intake. Thus, our results support the notion that calcium plays a risk-enhancing role in prostate cancer development.

Our overall finding supports the modest positive association reported from a pooled analysis of prospective epidemiologic studies for calcium intake and prostate cancer risk (1). With one exception (25), all previous prospective studies were conducted among Western populations with diets relatively high in calcium and from primarily dairy food sources. The calcium intake levels in the referent group of all previous prospective studies were higher than among Singapore Chinese (e.g., <266 mg/d). Thus, our study is the first to report a positive association between calcium and prostate cancer risk at such a low calcium level.

Ecologic analyses show a strong correlation between milk intake, the major contributor of calcium intake in Western populations, and prostate cancer incidence (Fig. 1; ref. 26), yet several prospective cohorts from the United States recently reported no association between calcium intake and prostate cancer risk (27–31). In addition to the methodologic reasons for discrepant results between ecologic and analytic analyses, it is also possible that a nonlinear relationship exists between calcium intake and prostate cancer risk, in which a very wide range of intake would be needed at the higher end of intake to be able to observe even a small difference in prostate cancer risk. A similar hypothesis has been used to explain the discrepancy between ecologic and analytic analyses for dietary fat and breast cancer risk (32). Our results suggest that evaluating calcium and prostate cancer risk might be more informative among a population with relatively low calcium intake, given the notion of diminishing returns at higher intake.

Calcium intake accounts for only ~26% of interindividual variation in calcium absorption (33), so even at relatively

**Table 2.** Daily intake, calcium concentration, and percentage of contribution to total calcium for selected food groups

Food item/group	Median daily intake (g)*	Average mg of calcium per gram food group*	Contribution of each food group to total calcium intake (%)†
Total vegetables	98.2	3.7	19.3
Green vegetables	58.8	6.2	16.3
Cruciferous vegetables	37.6	9.7	9.3
Dairy products	19.3	16.8	17.3
All grain products	555.7	0.6	14.7
Noodles	47.9	7.8	4.7
Rice	441.4	0.8	3.0
All soyfoods	91.0	4.0	11.8
Total fruit	174.1	2.2	7.3
Citrus fruit	39.1	9.9	4.4
All fish and shellfish	54.2	7.0	6.2

\*These values were derived from intake among all male cohort subjects.

†The percentage of contribution to total calcium intake was calculated using 24-h dietary recalls among a randomly selected subset of cohort subjects (see Materials and Methods).

**Table 3.** HRs and 95% CI for quartiles (Q) of calcium intake and prostate cancer risk

	Median intake (mg/d)	Total cases (n)	Adjusted HR*	95% CI
Total calcium: food + supplement				
Q1	211	60	1.0	—
Q3	317	75	1.20	0.85–1.69
Q3	435	71	1.10	0.78–1.55
Q4	659	92	1.25	0.89–1.74
<i>P</i> for trend			0.3	
Dietary calcium: food only				
Q1	210	59	1.0	—
Q3	315	78	1.27	0.90–1.78
Q3	432	75	1.18	0.84–1.67
Q4	651	86	1.23	0.88–1.72
<i>P</i> for trend			0.4	
Among non-supplement users				
Dietary calcium: food only				
Q1	210	56	1.0	—
Q3	315	71	1.23	0.88–1.78
Q3	431	66	1.15	0.80–1.64
Q4	648	76	1.28	0.90–1.81
<i>P</i> for trend			0.3	

\*Adjusted models included variables for age at interview (year), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), education (no formal education/primary school, secondary school/or higher), and any weekly supplement use (yes, no).

high intake, achieving an internal minimum dose necessary to observe an adverse effect may not be possible without efficient calcium absorption. There is evidence for greater calcium absorption efficiency among Chinese (34, 35), compared with whites (36), and among thinner individuals compared with heavier individuals (21, 22). Our Singapore Chinese men were relatively thin, especially compared with Western populations. For example, the prevalence of overweight or obese (BMI > 25.0 kg/m<sup>2</sup>) men from the United States at 40 to 59 years of age was 78% (37), compared with 22% among men in the Singapore Chinese cohort.

A strong association and dose-dependent trend were revealed for calcium intake and prostate cancer risk only after we restricted our analyses to men with below median BMI (22.9 kg/m<sup>2</sup>). Although individuals with larger body size, and thus, larger gut mass (or intestinal surface area; ref. 38) have greater intestinal absorption of exogenous (e.g., dietary) calcium (39), they also have greater endogenous loss of calcium from the proximal and distal intestine, compared with individuals with smaller body size (21, 22). This hypothesized inverse correlation between body size and calcium absorption efficiency implies that studies conducted in Singapore

**Table 4.** HRs and 95% CI for quartiles (Q) of total daily calcium intake and prostate cancer risk by median BMI

Total calcium intake	BMI <median (22.9 kg/m <sup>2</sup> )		BMI ≥median (22.9 kg/m <sup>2</sup> )	
	Total cases (n)	HR (95% CI)*	Total cases (n)	HR (95% CI)*
All cases				
Q1 (lowest)	23	1.0 (reference)	37	1.0 (reference)
Q2	37	1.58 (0.94–2.67)	38	0.95 (0.60–1.50)
Q3	34	1.44 (0.85–2.44)	37	0.87 (0.55–1.38)
Q4 (highest)	56	2.03 (1.23–3.34)	36	0.77 (0.48–1.23)
<i>P</i> for trend		0.01		0.2

\*Models included variables for age at interview (year), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), education (no formal education/primary school, secondary school/higher), and any weekly supplement use (yes, no).

**Table 5.** HRs and 95% CI for quartiles (Q) of daily total calcium intake and prostate cancer risk by duration of follow-up, among men with <median BMI, 22.9 kg/m<sup>2</sup>

Total calcium intake	<10 y		≥10 y	
	Cases, N n = 101	HR (95% CI)*	Cases, N n = 49	HR (95% CI)*
Q1 (lowest)	17	1.0 (reference)	6	1.0 (reference)
Q2	24	1.41 (0.76–2.64)	13	2.07 (0.79–5.46)
Q3	22	1.27 (0.67–2.39)	12	1.95 (0.73–5.20)
Q4 (highest)	38	1.70 (0.94–3.08) <sup>†</sup>	18	3.03 (1.19–7.68) <sup>†</sup>
P for trend		0.1		0.03

\*Models included variables for age at interview (year), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), education (no formal education/primary school, secondary school/or higher), and any weekly supplement use (yes, no).

<sup>†</sup>P for difference in relative risk for <10 y vs. ≥10 y of follow-up among subjects with below median BMI = 0.7.

Chinese might be more likely to reveal the underlying association between calcium and prostate cancer risk, if it exists, compared with studies conducted among their heavier Western counterparts.

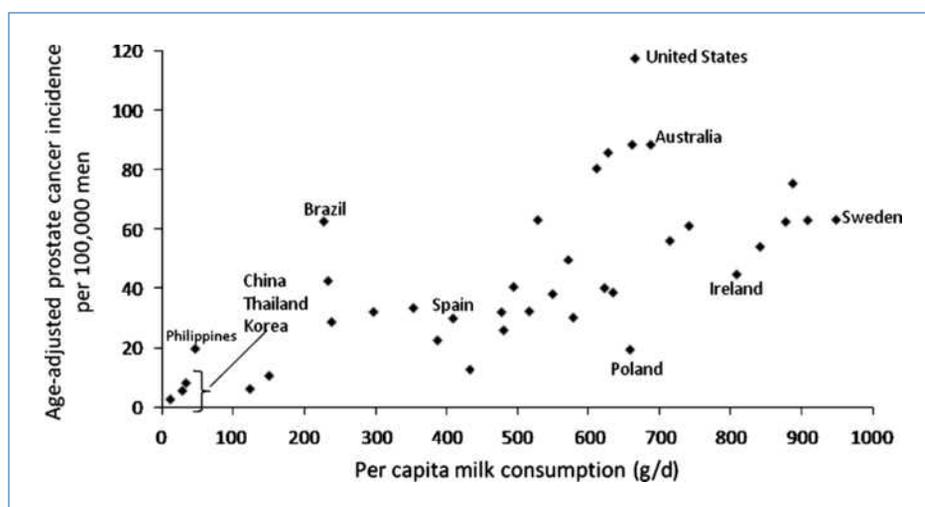
Calcium may play a role in prostate carcinogenesis through its effects on the insulin-like growth factor (IGF) system (40). IGF-I has mitogenic and antiapoptotic effects on normal and transformed prostate epithelial cells (41). A recent meta-analysis reported a 20% increase in prostate cancer risk per SD increase in IGF-I peptide levels (42).

In a subset of the Singapore Chinese cohort ( $n = 312$  men, 326 women), we previously evaluated determinants of serum IGF-I and reported statistically significant positive associations with dietary calcium ( $\beta = 0.044$ ,  $P = 0.007$ ; ref. 43). Although prior studies reported similar associations (40, 44), it was not clear whether the associations were due to the strong correlation with dairy products (45), or whether calcium alone was associated with increased IGF-I levels. Our finding for calcium and IGF-I was not due to correlations with dairy because dairy intake was low and vegetables were

the largest contributor of calcium intake among Singapore Chinese.

There is experimental evidence that an important player in the malignant progression of prostate tumors are factors contributing to the maintenance of calcium homeostasis, or the balanced release of parathyroid hormone and 1,25-dihydroxyvitamin D to maintain extracellular calcium within a tight physiologic range (5, 6, 9). The calcium-sensing receptor is also responsible for maintaining calcium homeostasis by sensing extracellular calcium concentrations and by mediating alterations in parathyroid hormone secretion and renal calcium reabsorption (46, 47). Calcium-sensing receptor expression in prostate cancer cells was correlated with the proliferative effect of elevated extracellular calcium and the cellular metastatic behavior, suggesting that the calcium-sensing receptor is a mediator of extracellular calcium-initiated effects on prostate cancer cells (48).

Results from prospective epidemiologic studies are inconclusive on the question of whether stage of disease has an influence on the strength of the calcium–prostate cancer



**Figure 1.** Prostate cancer incidence rates versus per capita milk intake among 38 countries [adapted from Zhang and Kesteloot (26)].

association (28, 49). There is no evidence from the present study that the observed calcium–prostate cancer association varied by stage of disease. However, it should also be noted that our modest study sample size does not allow for a meaningful analysis of this modification effect. In addition, there were likely to be few indolent cases among our study population given that population-wide prostate cancer screening is not recommended in Singapore (50).

The prospective nature of our study design reduced the opportunity for differential misclassification of self-reported diet to bias our findings. The major food sources, or those that contributed >10% of total daily calcium in our study population were diverse, and included vegetables, dairy, grain products, and soyfoods. Thus, our observed positive association between calcium and prostate cancer risk is unlikely to be driven by any one major food group.

In summary, we reported a positive association with prostate cancer risk for 659 mg/d median calcium intake among a prospective cohort of Singapore Chinese compared with 211 mg/d median intake. When we restricted analyses to men with below median BMI, we observed a dose-dependent trend with increasing calcium intake and prostate cancer risk that reached a 2-fold increase, comparing highest to lowest intake. These data suggest a positive association with calcium at relatively low levels and from primarily nondairy food

sources. In conclusion, our findings warrant further experimental exploration into the possible roles of calcium, as opposed to other dairy product components, in prostate carcinogenesis.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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