Prospective Studies of Dairy Product and Calcium Intakes and Prostate Cancer Risk: A Meta-Analysis

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Background: **The *Dietary Guidelines for Americans 2005* recommends that Americans increase their intake of dairy products. However, some studies have reported that increasing dairy product intake is associated with an increased risk of prostate cancer. We conducted a meta-analysis to examine associations between intakes of calcium and dairy products and the risk of prostate cancer. *Methods:* We searched Medline for prospective studies published in English-language journals from 1966 through May 2005. We identified 12 publications that used total, advanced, or fatal prostate cancer as end points and reported associations as relative risks (RRs) with 95% confidence intervals (CIs) by category of dairy product or calcium intake. Data were extracted using standardized data forms. Random-effects models were used to pool study results and to assess dose–response relationships between dairy product or calcium intakes and the risk of prostate cancer. We conducted sensitivity analyses by changing criteria for inclusion of studies or by using fixed-effects models. All statistical tests were two-sided. *Results:* Men with the highest intake of dairy products (RR =1.11 [95% CI = 1.00 to 1.22], *P* = .047) and calcium (RR = 1.39 [95% CI = 1.09 to 1.77], *P* = .018) were more likely to develop prostate cancer than men with the lowest intake. Dose–response analyses suggested that dairy product and calcium intakes were each positively associated with the risk of prostate cancer (P_{trend} = .029 and .014, respectively). Sensitivity analyses generally supported these associations, although the statistical significance was attenuated. The pooled relative risks of advanced prostate cancer were 1.33 (95% CI = 1.00 to 1.78; *P* = .055) for the highest versus lowest intake categories of dairy products and 1.46 (95% CI = 0.65 to 3.25; *P*>.2) for the highest versus lowest intake categories of calcium. *Conclusions:* High intake of dairy products and calcium may be associated with an increased risk of prostate cancer, although the increase appears to be small. [J Natl Cancer Inst 2005;97:1768–77]**

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer mortality among men in the United States *(1)*, accounting for 33% of all newly diagnosed malignancies *(2)*. On the basis of laboratory and clinical evidence, it has been hypothesized that high intakes of calcium and dairy products may increase the risk of prostate cancer by suppressing the production of 1,25-dihydroxyvitamin D_3, the active form of vitamin D_3 *(3)*, which binds to vitamin D receptors and inhibits proliferation of normal and malignant prostate cells *(4)*. However, epidemiologic studies that have examined the effects of dairy product or calcium intakes on the risk of prostate cancer have yielded inconsistent findings *(5–14)*.

The inverse associations between dairy product and calcium intakes and the risks of some chronic diseases have been well documented. Intake of dairy products has been associated with reduced risks of osteoporosis *(15–17)* and, possibly, of insulin resistance syndrome *(18)*. These effects are thought to be due mainly to the high calcium content of dairy foods. On the basis of these observations, the *Dietary Guidelines for Americans 2005* recommends that all Americans increase their daily intakes of nonfat or low-fat milk and milk products *(19)*.

It is important to weigh potential benefits of such a recommendation against the potential risks. For example, results of a recent meta-analysis of case–control studies suggested that men with the highest milk consumption have a 68% higher risk of prostate cancer than men with the lowest intakes *(20)*. However, case–control studies are prone to recall and selection bias, which may have resulted in an overestimation of the association. We hypothesized that high intakes of dairy foods and calcium are associated with an increased risk of prostate cancer and examined this hypothesis by performing a meta-analysis of prospective studies.

Methods

Study Selection

We used guidelines established for including nonrandomized studies in Cochrane reviews *(21)* to select the publications to be included in this meta-analysis and to extract data. We conducted a comprehensive search of Medline (PubMed and OVID) English-language literature published from 1966 through May 2005, using the following search algorithm: (dairy OR milk OR calcium) AND (prostate cancer OR prostatic neoplasm). We also manually searched the reference lists of relevant publications to identify additional studies. To be included in our meta-analysis, studies had to 1) be conducted in adult men, 2) use an observational prospective study design, 3) present data on incident cases of prostate cancer or advanced prostate cancer or on mortality from prostate cancer, and 4) report associations in the form of relative risks (RRs) or odds ratios by categories of dairy product or calcium intake. We identified 13 publications that reported results from prospective studies: 10 publications *(8,9,14,22–28)* were identified by searching Medline and three publications were identified by the manual search *(10,29,30)*. One publication *(30)* was excluded from the meta-analysis because milk intake had been treated as a continuous variable, not discrete categories.

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See "Notes" following "References."

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The remaining 12 publications *(8–10,14,22–29)* were included in the meta-analysis. Two publications *(8,27)* examined associations among participants in the Health Professionals Follow-up Study, and two publications *(22,29)* examined associations among California members of the Seventh-day Adventist Church. The two publications from each study population examined different exposures (i.e., dairy and calcium intake) or outcomes (i.e., total and advanced prostate cancer). We therefore used one of each set of publications in separate analyses of different exposures and outcomes. We also identified a randomized clinical trial that examined prostate cancer risk after 10.3 years of follow up among men who were randomly assigned to receive calcium supplementation (1,200 mg/d) or placebo *(31)*. Although this study did not meet the inclusion criteria for the meta-analysis, we included it in the sensitivity analyses.

Data Extraction

We used a standardized protocol and reporting form to abstract the following data from each publication: the first author's name, the year of publication, the country in which the study was performed, the study design, the sample size, the mean age or age range of study subjects, the duration of follow-up, the method of assessment of dairy product or calcium intake, the categories of dairy product or calcium intake, whether prostate cancer was the primary end point, the covariates for adjustments in multivariable models, and the relative risks and 95% confidence intervals (CIs) for prostate cancer associated with dairy product or calcium intake.

Statistical Analysis

We used the reported relative risk as the measure of the association between dairy product or calcium intake and the risk of prostate cancer. We used the reported relative risks for total dairy product intake when they were provided. Two publications *(24,26)* reported separate relative risks for several dairy items (e.g., for milk or for cheese). In this situation, we pooled the relative risk estimates for the different dairy items, weighted by inverse of the variance, within each study. We used the reported relative risks for total prostate cancer, when they were provided, to examine the association between dairy product or calcium intake and the risk of prostate cancer. When the relative risks for total prostate cancer were not provided, we used the reported relative risks for clinical (stage 2–4) *(9)* or fatal *(10)* prostate cancer in our analyses. When both crude and adjusted relative risks were provided, we used the most fully adjusted relative risks for all studies except for the study by Michaud et al. *(27)*; for that study, we used the reported relative risk without calcium adjustment in our main analysis to avoid overadjustment. Reported relative risks were transformed to their natural logarithms to normalize the distributions. Standard errors (SEs) were calculated from the following equation *(32)*:

$$\mathrm{SE} = \ln(\text{upper 95\% CI}/\text{lower 95\% CI})/(2 \times 1.96).$$

The inverse of the variance (i.e., the square of the SE) was used to weight each relative risk estimate for calculations of the pooled relative risks.

To examine associations between the risk of prostate cancer and dairy product or calcium intake, we pooled the relative risk estimates for the highest intake category versus the lowest intake category from each study, weighted by the inverse of their variances. Random-effects models were used for the primary analysis of the association between prostate cancer risk and dairy product or calcium intake, and fixed-effects models were used for the sensitivity analysis. Because the two models produced identical results, we present only the results from the random-effects models, which consider both within- and between-study variation *(33)*. We used the meta-regression method *(34,35)* to examine associations between study characteristics, including the subjects' ages (≥60 years versus <60 years) at baseline (i.e., at enrollment or at first exposure assessment), the duration of follow-up (≥10 years versus <10 years), the location of study (United States versus elsewhere), and publication year (after 1998 versus before), on the pooled relative risks. We selected 1998 as a cutoff point because studies published after that year began to examine calcium and vitamin D hypotheses in relation to prostate cancer; 60 years of age and 10 years of follow up were selected as cutoff points because they were the approximate median values. Location was used to differentiate exposure to vitamin D–fortified liquid milk; vitamin D is added in the United States, but not generally in Europe *(36)*.

We examined dose–response relationships for dairy product and calcium intake and the risk of prostate cancer. Because the studies included in our meta-analysis used different units to report dairy product intake (e.g., servings, grams, grams of dry weight, frequencies, and glasses), we transformed all reported dairy intakes into servings per day. On the basis of the U.S. Food Guide Pyramid, we assumed that one serving of milk or yogurt was equivalent to 244 g, cheese to 43 g, ice cream to 132 g, and butter to 5 g *(37)*. We assumed that 1 glass of milk, as reported, was 1 serving. On the basis of the average dairy intake distribution in the United States *(38)*, we calculated the following intake ratios for milk, cheese, yogurt, ice cream, and butter as 7.5 : 1.0 : 0.4 : 1.0 : 0.1 for regular weight and 4.0 : 3.1 : 0.2 : 2.0 : 0.7 for dry weight, respectively. For studies that reported grams of total dairy item weight *(9,26)* or grams of dry weight *(27)*, we distributed the total grams to this set of dairy items, based on these intake ratios. We converted dry weight to regular weight based on the water content of each food, obtained from the Nutrient Data System, version 4.06 (NDS, University of Minnesota, Minneapolis, MN). We then converted regular weight (g) to number of servings for each dairy item separately.

Because the most recent dietary guidelines recommend increased intakes of milk, cheese, and yogurt, we used intake servings of these dairy items per day in our dose–response analysis *(19)*. However, the specific dairy items reported varied by study. Some studies *(25,29)* reported only milk intake, whereas other studies *(10,14,27,28)* included butter or ice cream in their total dairy intakes. Tseng et al. *(23)* provided separate data on the servings of milk, cheese, and yogurt. For the remaining studies, we assumed intake proportions (by servings) of milk, cheese, yogurt, ice cream, and butter as 0.32 : 0.24 : 0.02 : 0.08 : 0.34, based on average dairy intake proportions in the United States *(38)*. We then computed the number of intake servings of milk, cheese, and yogurt based on the dairy items that were reported by each study and on the intake ratio. For example, if a study reported only total intake from all of these five foods, we obtained milk, cheese, and yogurt intake servings by multiplying the total servings by 0.58 (the sum of 0.32, 0.24, and 0.02).

When median intakes per category were not presented in the publications, we estimated the mean intake of dairy item (milk, cheese, and yogurt) and calcium in each category by calculating

the midpoint of the upper and lower boundaries. When the upper boundary of the highest intake category was not reported, we assumed that it had the same amplitude of intake as the preceding intake category *(39,40)*. For example, if the highest calcium intake category was reported as greater than 2000 mg/d and the preceding category was reported as 1500–2000 mg/d, we would assign the average intake of the highest calcium intake category a value of 2250 mg/d. When studies in dose–response analyses are combined, the reference group must be comparable across studies *(39,40)*. Therefore, we eliminated from the dose–response analyses two studies *(9,10)* in which the reference groups (lowest intake category) for dairy intake had considerably higher intakes than those in the other studies. For the same reason, we excluded one study *(9)* that had a high calcium intake in the reference group. Another study *(14)* was excluded from the dose–response analysis of calcium intake and prostate cancer risk because it did not report total calcium intake. Thus, eight studies *(14,23–29)* were included in our dose–response analysis of intake of dairy products (i.e., milk, cheese, and yogurt) and prostate cancer risk, and four studies *(8,23,26,28)* were included in our dose–response analysis of calcium intake and risk of prostate cancer. However, we also performed sensitivity analyses in which all studies were included.

To examine dose–response relationships, we performed weighted regression analyses by regressing the natural log of the relative risk of prostate cancer for intakes of dairy products (milk, cheese, and yogurt) or calcium. All regression models were fit with no intercept term because all data points were derived from comparisons with reference groups *(32,39,41)*. However, for completeness, we repeated the analyses with inclusion of intercept terms. We used the PROC MIXED procedure in SAS software with a repeated statement to allow estimates of log relative risks from the same study to be correlated. Random-effects models were used because they consider both within- and between-study variation. Because the relationships between dairy and calcium intakes and risk of prostate cancer may not be linear, we introduced quadratic terms and the natural logs of intakes (dairy or calcium) into the models. Because quadratic and natural log terms were not statistically significant ($P>.05$ for all), we used simpler models with original scales for dairy product or calcium intakes in our analyses.

We conducted sensitivity analyses for pooled estimates by the stepwise introduction of stricter criteria for inclusion of studies. We first limited the analysis to studies that had used validated food frequency questionnaires, and we computed the pooled relative risks for dairy products and for calcium intake separately for these studies. Only four of the 10 studies that examined dairy product intake and four of the six studies that examined calcium intake met this criterion. We then computed the pooled relative risks after excluding studies that had not adjusted for total energy intake. We also performed a sensitivity analysis for calcium intake by including the study by Baron et al. *(31)*. We conducted sensitivity analyses for dose–response relationships between dairy product intake and risk of prostate cancer. We repeated each of the simpler dose–response analyses, described above, by including ice cream in total dairy intake. We also repeated these analyses by including only the studies that were conducted in the United States *(14,23–25,27–29)*.

We used the Q, H, and I^2 statistics *(42)* to examine heterogeneity among the studies included in this meta-analysis. For the Q statistic, a P value of less than .1 indicated statistically significant heterogeneity, an H statistic of less than 1.2 suggested no heterogeneity among studies, and I^2 was the proportion of total variation contributed by between-study variation *(42)*. Publication bias was examined with the use of funnel plots and with the Begg and Egger tests *(43–45)*. Relative risks of prostate cancer for men in the highest versus the lowest calcium or dairy product intake categories were used to examine publication bias. For the Begg and Egger tests, statistical significances were set at $P<.1$. Statistical analyses were performed with SAS statistical software (version 8.2, SAS, Inc., Cary, NC). All statistical tests were two-sided.

Results

The 10 studies included in this meta-analysis were conducted in Western countries: eight were conducted in the United States and two were conducted in Europe (Table 1). The first article reporting data from these studies was published in 1984 *(22)*. Sample sizes ranged from 3612 men *(23)* to 65 321 men *(28)*, and the number of incident prostate cancer cases ranged from 99 *(22)* to 3811 *(28)*. All of the included studies used food frequency questionnaires to collect dietary intake data, but only five studies *(8,9,26–28)* used validated questionnaires.

Eight of the 10 publications that examined the association between dairy intake and risk of prostate cancer reported a positive relationship (Fig. 1), and, in one publication *(23)*, the association was statistically significant. There was no statistically significant heterogeneity among the relative risks reported by the included studies (Q test: $P>.2$; $H = 1.12$; $I^2 = 0.28$). The overall pooled relative risk of prostate cancer was 1.11 (95% CI = 1.00 to 1.22, $P = .047$) for subjects in the highest dairy intake category compared with those in the lowest category. The midpoints of the lowest and highest categories of dairy product intake ranged from 0 *(25,29)* to 1.5 *(9)* servings/day of milk, cheese, and yogurt and from 2.0 *(27)* to 6.3 *(10)* servings/d of milk, cheese, and yogurt, respectively. When the analysis was limited to the studies that used a validated food frequency questionnaire *(9,26–28)*, the pooled relative risk of prostate cancer decreased slightly to 1.08 (95% CI = 0.92 to 1.28) and was no longer statistically significant ($P = .22$). Further limiting the analysis to studies that had adjusted for energy intake *(9,27,28)* did not change the pooled relative risk of prostate cancer greatly (RR = 1.09, 95% CI = 0.89 to 1.44).

All six publications *(8,9,14,23,26,28)* that examined associations between calcium intake and prostate cancer risk reported a positive relationship, and in three publications *(8,14,23)* the association was statistically significant (Fig. 2). The pooled relative risk of prostate cancer for subjects in the highest relative to lowest calcium intake category was 1.39 (95% CI = 1.09 to 1.77, $P = .018$). There was no statistically significant heterogeneity among those studies (Q test: $P = .107$; $H = 1.35$; $I^2 = 0.45$). The midpoints of the lowest and highest total calcium intake categories ranged from 228 *(23)* to 802 *(9)* mg/d and from 1329 *(26)* to 2250 *(8,28)* mg/d, respectively. Including the trial by Baron et al. *(31)* in the analysis did not substantially change the pooled relative risk estimate (RR = 1.32, 95%CI = 1.03 to 1.70, $P = .034$). The pooled relative risk of prostate cancer for the four studies that used validated food frequency questionnaires and adjusted for energy *(8,9,26,28)* was 1.30 (95% CI = 0.97 to 1.66; $P = .089$).

Eight publications *(14,23–29)* reported relative risks of total prostate cancer, and five publications *(10,14,22,27,28)* reported relative risks of advanced prostate cancer (i.e., stage C or D or fatal) for men in the highest relative to lowest dairy product intake

Table 1. Characteristics of 12 publications included in meta-analysis of dairy product and calcium intake and risk of prostate cancer*

First author (reference), year of publication	Study participants	Exposure assessment	Years of follow-up	Outcome	No. of cases	Dairy source: highest vs. lowest intake categories	RR (95% CI) for dairy†	RR (95% CI) for calcium, highest versus lowest intake categories	Controlled or matched variables
Snowdon *(22)*, 1984	6763 white male Adventists aged 60–99 y in California, United States	FFQ	21	Fatal prostate cancer by death certificate	99	Milk: ≥3 vs. <1 glass/d Cheese: ≥3 vs. <1 servings/wk	2.4 (1.3 to 4.3) 1.5 (0.9 to 2.6)	NA	Age
Mills *(29)*, 1989	14 000 white male Adventists aged ≥25 y in California, United States	FFQ	6	Prostate cancer by medical records and the Tumor Registry	180	Whole milk: ≥1 serving/d v. none	0.8 (0.54 to 1.19)	NA	Age
Severson *(24)*, 1989	7999 men of Japanese ancestry aged 46–68 y in Hawaii, United States	FFQ	17.5	Prostate cancer by the Tumor Registry	174	Butter, margarine, and cheese: ≥5 vs. ≤1 servings/wk Milk: ≥5 vs. ≤1 servings/wk	1.47 (0.97 to 2.25) 1.0 (0.73 to 1.38)	NA	Age
Hsing *(10)*, 1990	17 633 white men aged ≥35 y in upper Midwest and northeastern United States	FFQ	20	Fatal prostate cancer by death certificate	149	Milk and ice cream: 86–189 vs. <26 servings/mo	1.0 (0.6 to 1.7)	NA	Age and smoking status at baseline
Le Marchand *(25)*, 1994	20 316 men aged ≥45 y in Hawaii, United States	FFQ	21	Prostate cancer by the Tumor Registry	198	Milk: >1 glass/d vs. none	1.4 (1.0 to 2.1)	NA	Age, ethnicity, and income
Giovannucci *(8)*, 1998	47 781 male health professionals aged 40–75 y in the United States	Validated FFQ	7.4	Non–stage A1 and advanced prostate cancer by 1) self-report, verified by medical records, 2) family member report, and 3) the National Death Index	1369	NA	NA	1.71 (1.19 to 2.46) for total prostate cancer; 2.97 (1.61 to 5.5) for advanced prostate cancer, ≥2000 vs. <500 mg/d	Age, BMI at age 21, energy, and fat, fructose, phosphorus, vitamin D, vitamin E, and lycopene intakes
Schuurman *(26)*, 1999	58 279 men aged 55–69 y in The Netherlands	Validated FFQ	6.3	Prostate cancer by the Cancer Registry and the national data base of pathology reports	642	Milk and milk products: 566 vs. 72 g/d Cheese: 43 vs. 2 g/d	1.12 (0.81 to 1.56) 1.21 (0.87 to 1.7)	1.09 (0.79 to 1.5) for total prostate cancer; 0.83 (0.52 to 1.34) for advanced prostate cancer, 1329 vs. 602 mg/d	For milk and milk products, adjusted for age, family history of prostate cancer, and SES; for calcium, additional adjustment for energy and protein intake
Chan *(9)*, 2000	27 062 men aged 50–69 y in Finland	Validated FFQ	5–8	Stage 2–4 prostate cancer by the Cancer Registry and the Register of Causes of Death	184	Dairy: 919 vs. 275 g/d	1.1 (0.7 to 1.7)	1.6 (0.8 to 3.0), 1841 vs. 802 mg/d	For dairy, adjusted for energy and supplement use, education, age, BMI, and number of years as a smoker; for calcium, additional adjustment for phosphorus intake

(Table continues)

Table 1 (continued).

First author (reference), year of publication	Study participants	Exposure assessment	Years of follow-up	Outcome	No. of cases	Dairy source: highest vs. lowest intake categories	RR (95% CI) for dairy†	RR (95% CI) for calcium, highest versus lowest intake categories	Controlled or matched variables
Michaud *(27)*, 2001	47780 male health professionals aged 40–75 y in the United States	Validated FFQ	10	Non–stage A1 prostate cancer by 1) self-report, verified by medical records, 2) family member report, and 3) the National Death Index	1897	Milk, cream, sour cream, sherbet or ice milk, ice cream, yogurt, cottage or ricotta cheese, cream cheese, other cheese, and butter: >69 vs. <19 g (dry weight)/d	Age- and period-adjusted model: 1.04 (0.89 to 1.3) for non–stage A1 prostate cancer; 1.38 (1.04 to 1.8) for advanced prostate cancer Fully adjusted model: 1.07 (0.88 to 1.3) for non–stage A1 prostate cancer; 1.13 (0.77 to 1.7) for advanced prostate cancer	NA	Age, energy, calcium, smoking, tomato sauce, saturated fat and α-linolenic fat intakes, and vigorous exercise
Chan *(14)*, 2001	20885 male physicians aged 40–84 y in the United States	FFQ	11	Prostate cancer by self-report, verified by medical records	1012	Milk, cold breakfast cereal, cheese, and ice cream: >2.5 vs. ≤0.5 servings/d	1.27 (0.97 to1.66) for total prostate cancer; 1.38 (0.95 to 2.01) for advanced prostate cancer	1.29 (1.04 to 1.62) for total prostate cancer; 1.30 (0.94 to 1.78) for advanced prostate cancer, >600 vs. ≤150 mg/d dairy calcium	Age, smoking status, vigorous exercise, BMI, assigned treatment, and food score
Rodriguez *(28)*, 2003	65321 men aged 50–74 y in the United States	Validated FFQ	6.2	Prostate cancer by self-report, verified by medical records or the Cancer Registry	3811	Milk, cheese, yogurt, and ice cream: ≥4 servings/d vs. <3 servings/wk	1.1 (0.9 to 1.3) for total prostate cancer; 0.9 (0.5 to 1.4) for advanced prostate cancer	1.2 (1.0 to 1.6) for total prostate cancer; 1.6 (0.9 to 3.0) for advanced prostate cancer, ≥2000 vs. <700 mg/d	Age, ethnicity, family history of prostate cancer, energy, total fat intake, education, and phosphorus and vitamin D intake
Tseng *(23)*, 2005	3612 men with mean age of 57.8 y in the United States	FFQ	7.7	Prostate cancer by interview report, medical records, or death certificate	136	Milk, cheese or cheese dishes, yogurt, cream or sour cream, cottage cheese, and ice cream: 21 vs. 5 servings/wk	2.2 (1.2 to 3.9)	2.2 (1.4 to 3.5), 920.3 vs. 455.4 mg/d	Age, race, energy, design variables, U.S. region, rural/urban/ suburban residence, education, recreational sun exposure, recreational and usual level of physical activity, smoking status, and current alcohol intake

*RR = relative risk; CI = confidence interval; FFQ = food frequency questionnaire; BMI = body mass index; SES = socioeconomic status; NA = not applicable.
†Highest versus lowest intake category.

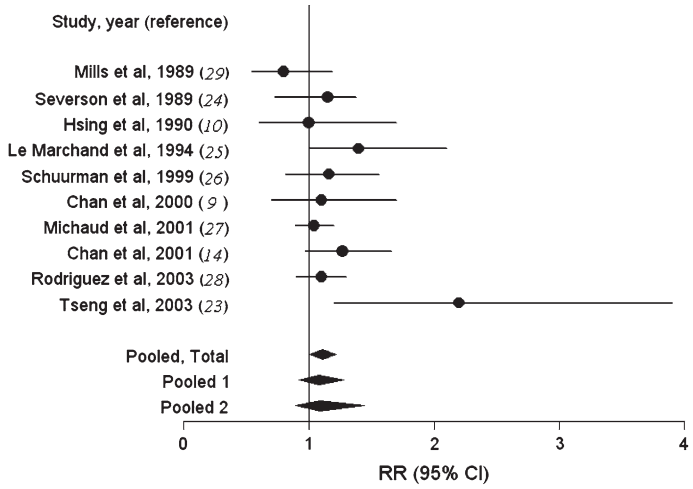

Fig. 1. Relative risks of prostate cancer comparing the highest with the lowest dairy product intake categories. **Pooled, Total** = pooled relative risks for all 10 studies. **Pooled 1** = pooled relative risk for studies with validated food frequency questionnaires (n = 4) *(9,26–28)*. **Pooled 2** = pooled relative risk for studies with validated food frequency questionnaires and energy adjustment (n = 3) *(9,27,28)*. **Dots** indicate point estimates for relative risks (RR); **error bars** indicate 95% confidence intervals (CIs); **diamonds** indicate RRs and 95% CIs from pooled analyses.

category (Table 2). High versus low dairy product intake was associated with a 12% increase in risk for total prostate cancer (RR = 1.12; 95% CI = 1.0 to 1.2) and a 33% increase in risk for advanced prostate cancer (RR = 1.33; 95% CI = 1.0 to 1.8). For high versus low calcium intake, the pooled relative risks for total *(8,14,23,26,28)* and advanced *(8,14,26,28)* prostate cancer were 1.38 (95% CI = 1.0 to 1.8) and 1.46 (95% CI = 0.7 to 3.3), respectively. There was statistically significant heterogeneity among the calcium studies (Q test: P for total and advanced prostate cancer = .07 and .013, respectively), but not among the dairy product studies (Q test: P>.1 for total and advanced prostate cancer). None of the study characteristics, including the mean age of subjects at baseline, the duration of follow-up, the location of the study, or the year the study was published, had statistically significant effects on the pooled relative risks for prostate cancer associated with dairy product or calcium intake (P>.05 for all).

The risk of prostate cancer increased with increasing intake of dairy foods and of calcium (P_{trend} = .029 and .014, respectively) (Table 3). When an intercept term was introduced into the analyses, however, the coefficient for dairy intake and prostate cancer decreased (from 0.068 to 0.055; P_{trend} = .11). Although the coefficient for calcium intake and prostate cancer increased (from 0.01 to 0.013 for each 100 mg of intake), the standard error also increased (from 0.002 to 0.007), and statistical significance was lost (P_{trend} = .159). In both analyses, the intercepts (0.03 for dairy products and −0.03 for calcium) were not statistically significant (P>.4 for both). When all studies were included in the dose–response analyses, the coefficient for dairy products in relation to prostate cancer decreased slightly (from 0.068 to 0.049) but remained statistically significant (P_{trend} = .027), whereas the coefficient for calcium increased (from 0.01 to 0.016 for each 100 mg of intake) and statistical significance did not change from the initial results (P_{trend} = .013). The association between dairy intake and the risk of prostate cancer decreased slightly when we added ice cream intake to total dairy foods (coefficient = 0.059, P_{trend} = .029) and when we included only studies performed in the United States (coefficient = 0.053, P_{trend} = .185).

There was no strong evidence of publication bias. A funnel plot of the log relative risk of prostate cancer versus the inverse of variance showed no clear asymmetry for studies of dairy intake (Fig. 3, A). For calcium intake, the funnel plot showed some asymmetry (Fig. 3, B), reflecting the relative absence of studies with both small numbers and small or null effects. However, P values obtained from the Begg and Egger tests were greater than .2 for studies that used either dairy products or calcium as an independent variable.

Discussion

Results of this meta-analysis of published studies support an association between greater dairy product and calcium intakes and an increased risk of prostate cancer. Men with higher intakes of dairy products or calcium were 11% or 39% more likely to develop prostate cancer, respectively, than men with lower intakes. Our findings are consistent with results from several ecologic studies *(46–48)* that found associations between milk consumption, especially consumption of nonfat milk, and prostate cancer incidence and mortality.

In a recent meta-analysis of case–control studies, Qin et al. *(20)* reported a combined odds ratio of prostate cancer of 1.68 for men in the highest milk intake category versus men in the lowest intake category, which is greater than the pooled relative risk of prostate cancer (1.11) for subjects in the highest dairy intake category compared with those in the lowest category that we report here. This difference in risk estimates may, in part, reflect recall bias, a common problem in case–control studies that can lead to an overestimation of the association between a dietary variable and the risk of cancer *(49)*. Furthermore, eight of the 11 studies in the meta-analysis by Qin et al. *(20)* used hospital-based control subjects; case–control studies that use hospital-based control subjects have been shown to report greater odds ratios than either case–control studies using population-based control subjects or prospective studies *(50,51)*. Another possible reason for the difference in risk estimates is that the prospective and case–control studies had different exposure levels for the highest intake categories.

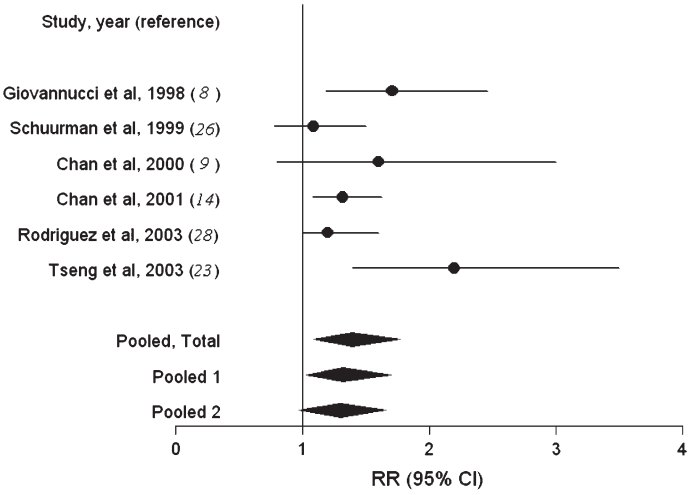

Fig. 2. Relative risks of prostate cancer comparing the highest with the lowest calcium intake categories. **Pooled, Total** = pooled relative risks for all six studies. **Pooled 1** = pooled relative risk including the study by Baron et al. *(31)*. **Pooled 2** = pooled relative risk for studies with validated food frequency questionnaires and energy adjustment (n = 4) *(8,9,26,28)*. **Dots** indicate point estimates for relative risks (RR); **error bars** indicate 95% confidence intervals (CIs); **diamonds** indicate RRs and 95% CIs from pooled analyses.

Table 2. Overall relative risks of total and advanced prostate cancer comparing the highest with the lowest intake categories for dairy products and calcium*

Type of intake	No. of studies	References	RR (95% CI)	P‡	Heterogeneity test†		
					H	I^2	*P*
Dairy product intake							
Total prostate cancer	8	*14*, *23–29*	1.12 (1.02 to 1.24)	.029	1.26	0.37	.133
Advanced prostate cancer	5	*10*, *14*, *22*, *27*, *28*	1.33 (1.00 to 1.78)	.055	1	0	>.2
Calcium intake							
Total prostate cancer	5	*8*, *14*, *23*, *26*, *28*	1.38 (1.04 to 1.83)	.036	1.48	0.54	.068
Advanced prostate cancer	4	*8*, *14*, *26*, *28*	1.46 (0.65 to 3.25)	>.2	1.89	0.72	.013

*RR = relative risk; CI = confidence interval.

†H<1.2 suggests no heterogeneity among studies; I^2 is interpreted as the proportion of total variation contributed by between-study variation; P<.1 was considered statistically significant for Q statistics.

‡Random-effects models were used, weighted by the inverse of variance. All statistical tests are two-sided.

The recently released *Dietary Guidelines for Americans 2005* recommends that Americans increase their intake of milk and milk products *(19)*. The new goal for people who require 6.72 MJ/d (1600 kcal/d) or more (including all adult men and women) is 3 servings/d of low-fat or fat-free milk or milk products. Given the recent release of these new dietary guidelines and the prevalence of prostate cancer among adult men in the United States, our findings are timely and have important public health implications. The United States has the highest prostate cancer incidence in the world *(46)*. Prostate cancer is the most common cancer among men in the United States (177 cases per 100 000 persons) *(1)*, and the number of incident cases is expected to increase substantially as the population ages *(2)*. Specifically, there were approximately 220 900 incident cases of prostate cancer in the United States in 2003 *(52),* and this number is projected to increase to 452 000 by 2045 *(1)*. Prostate cancer currently ranks sixth among all specific causes of death in the United States *(1)*. Dose–response analyses suggested that, among male adults, intakes of 3 servings/d of dairy products were associated with an approximately 9% greater risk of prostate cancer, compared with the current average intake of 1.8 servings/d *(53)* (RR with and without intercept term = 1.1 and 1.09, respectively). In the United States, this would be associated with approximately 20 000 more incident cases per year. Approximately 35 000 and 99 000 Americans are projected to die of prostate cancer in 2005 and 2045, respectively *(1)*.

There are several limitations that should be considered when interpreting our results. First, only four of the 10 studies used validated food frequency questionnaires to assess exposures. Misclassification of exposure may have occurred due to inaccurate dietary assessment in studies using unvalidated questionnaires. In addition, because total energy intake is associated with both dairy and calcium intakes as well as with risk of prostate cancer *(12)*, it may be a confounder of these associations. Adjustment for total energy intake was done in only three studies that analyzed dairy product intakes and in only four studies that analyzed calcium intakes. However, results of our sensitivity analysis showed that excluding studies that had not adjusted for energy or that had not used a validated food frequency questionnaire did not greatly change the pooled relative risk. These results suggest that our findings are not substantially confounded by a lack of energy adjustment or the lack of validated food frequency questionnaires. Although we cannot distinguish between the effects of calcium from food sources and calcium from supplements on the risk of prostate cancer from the information provided by the articles, Giovannucci et al. *(8)* showed that dietary and supplemental calcium intakes were each associated with an increased risk of prostate cancer.

A second limitation of these analyses is that all studies assessed dietary intake based on responses to a single questionnaire that was administered only once. Thus, misclassification of exposures may have been introduced, which could lead to an underestimation of the risk of prostate cancer. Several studies have examined the stability of dietary intakes over time. Correlations generally showed good stability of reported dairy intake (r = .45 over 6–10 years) *(54)*, of whole milk intake (r = .58 over 15–25 years) *(55)*, and of calcium intake (r = .63 over 3 years) over time *(56)*.

A third limitation is that heterogeneity may be introduced by methodologic differences among studies, including different measurements of intake and outcomes used. In addition, intake levels ranged widely across the studies included in our meta-analysis. For example, the lowest intake categories ranged

Table 3. Dose–response relationships between dairy product or calcium intakes and prostate cancer risk*

Analysis	Dairy products, serving/d				Calcium, 100 mg/d			
	No. of studies	References	Coefficient (SE)	P_{trend}	No. of studies	References	Coefficient (SE)	P_{trend}
Main analysis	8	*14*, *23–29*	0.068 (0.025)	.029	4	*8*, *23*, *26*, *28*	0.0103 (0.002)	.014
Sensitivity analysis								
With intercept term	8	*14*, *23–29*	0.055 (0.030)	.110	4	*8*, *23*, *26*, *28*	0.0133 (0.007)	.159
All studies	10	*9*, *10*, *14*, *23–29*	0.049 (0.020)	.027	6	*8*, *9*, *14*, *23*, *26*, *28*	0.0159 (0.004)	.013
Dairy product intake includes ice cream intake	8	*14*, *23–29*	0.059 (0.022)	.029	NA	NA	NA	NA
Only U.S. studies	7	*14*, *23–25*, *27–29*	0.053 (0.035)	.185	NA	NA	NA	NA

*SE = standard error; NA = not applicable.

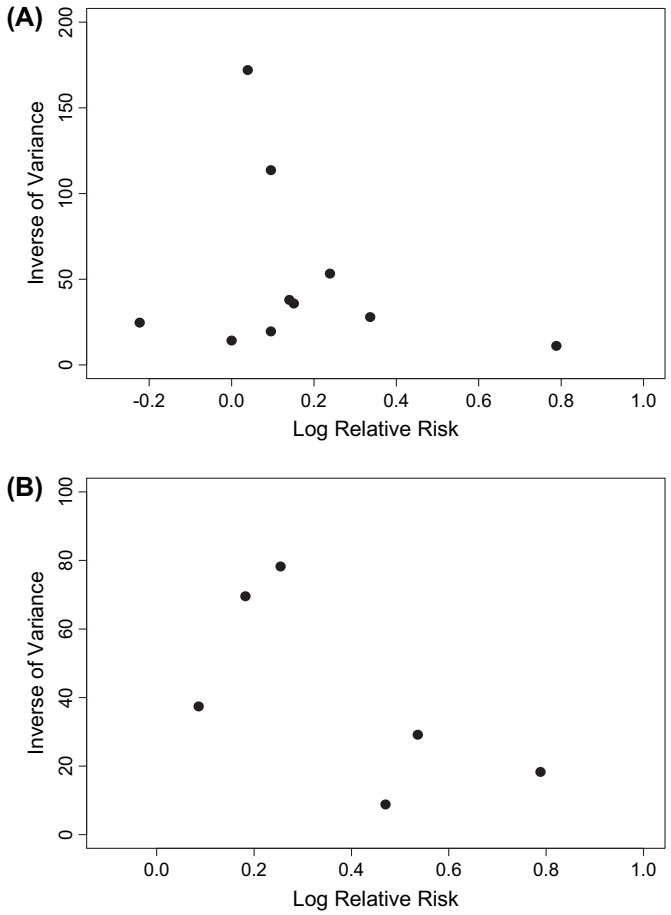

Fig. 3. Funnel plots of the log relative risk (for the highest versus the lowest intake categories) versus the inverse of variance. **A**) All dairy intake studies. **B**) All calcium intake studies.

from 0 to 1.5 servings/d for dairy products and from 228 to 802 mg/d for calcium. Although statistical tests did not suggest heterogeneity among the studies, we used random-effects models, which consider both within- and between-study variation *(32)*, for the pooled relative risk estimates and the dose–response analyses.

A fourth limitation is that measurement units for dairy intake and reported dairy items varied across studies. To account for this variation, we converted the different units of measurement to number of servings per day, and computed the amount of milk, cheese, and yogurt intake for each study based on intake distributions determined from the U.S. national data. Such conversions inevitably introduce misclassification, which may lead to an underestimation of the associations. Moreover, the proportions of dairy intake may also vary across ethnicities and regions, thereby introducing errors. Because our dairy intake distribution categories were based on the U.S. dietary pattern, we conducted a sensitivity study to examine the dose–response relationship between dairy intake and prostate cancer risk among the studies conducted in the United States. The estimated coefficients decreased only slightly from those obtained in our analyses of all studies. Therefore, the contribution of U.S. and non-U.S. studies did not produce errors in our analysis.

Fifth, our results are also limited because we were not able to examine the effect of prostate-specific antigen (PSA) screening on associations between dairy product and calcium intakes and the risk of prostate cancer. Only one study *(28)* conducted a subgroup analysis for men who had a PSA screening versus those who did not. However, Etzioni et al. *(57)* reported that PSA screening, which has been used widely in the United States after 1991, leads to overdiagnosis of prostate cancer *(56)*. Detection bias, therefore, may be introduced to our study, which may lead to an underestimate of the associations, as suggested by Rodriguez et al. *(28)*. They found a statistically significant relationship between calcium intake and prostate cancer among men who reported not having had PSA screening before 1992 (P_{trend}<.01) but not among men who had a PSA screening test (P_{trend} = .93) *(28)*.

Sixth, our study is limited by the inclusion of only those studies that were published in English, although we did include two studies that were conducted outside of the United States. Results of the meta-regression analysis suggested that study location did not have a statistically significant effect on the pooled relative risks for dairy or calcium intake. We repeated a Medline literature search for non–English-language studies, using the same search terms. Fourteen additional articles were found, but none met our inclusion criteria, based on a examination of their abstracts and titles.

Finally, our study is limited because of the small sample size. Only 10 publications examined associations with dairy intake, and only six publications examined associations with calcium intake. Thus, further sensitivity analysis restriction led to loss of statistical significance for pooled relative risks, although the risk estimates changed only slightly. Because of the small sample size, we had limited power to conclusively reject the null hypothesis of no publication bias. Therefore, we set statistical significance for publication bias at P<.1. We also presented funnel plots, which suggested consistent results for dairy product intake but not for calcium intake. The presence of possible publication bias could have led to an overestimate of the risk for calcium intake.

Several hypotheses have been proposed to explain the relationship between dairy product or calcium intakes and the increased risk of prostate cancer. Suppression of the production of plasma 1,25-dihydroxyvitamin D_3 by plasma calcium is one possible mechanism underlying the association between dairy product and calcium intakes and the risk of prostate cancer *(3,7)*. High 1,25-dihydroxyvitamin D_3 concentrations may inhibit cellular proliferation and induce differentiation of normal and neoplastic prostate cells *(8)*. Alternatively, higher intakes of milk and calcium have been associated with increased plasma levels of insulin-like growth factor-I *(58,59)*. Results of a recent meta-analysis showed that high plasma concentrations of insulin-like growth factor-I were associated with a 49% increased risk of prostate cancer *(60)*. Finally, it is possible that estrogen in milk may be another mechanism through which dairy intake may contribute to the etiology of prostate cancer *(61)*.

Calcium is an important nutrient, and dairy products are the major source of calcium in most Western countries. It is well documented that increased calcium intakes are associated with reduced risks of osteoporosis, hypertension, and colorectal cancer *(17,62–65)*. On the other hand, two cohort studies have found positive associations between the risk of Parkinson's disease and greater dairy intake in men *(66,67)*. In addition, high intakes of cow's milk have been hypothesized to contribute to male reproductive disorders because of its high estrogen content *(68)*. Several prospective studies have found that higher milk intake was also associated with an increased risk of ovarian cancer *(69–71)*. Given the high prevalence of prostate cancer in American men,

these findings, together with our findings, suggest caution before one embraces the new recommendations to increase dairy intake, especially among older men. More research, both population based and mechanistic, is needed to carefully examine both the potential benefits and risks of increasing intakes of dairy foods.

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