# Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies[1–4]

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**ABSTRACT**

**Background:** Dairy product and calcium intakes have been associated with increased prostate cancer risk, but whether specific dairy products or calcium sources are associated with risk is unclear.

**Objective:** In the Continuous Update Project, we conducted a meta-analysis of prospective studies on intakes of dairy products and calcium and prostate cancer risk.

**Design:** PubMed and several other databases were searched up to April 2013. Summary RRs were estimated by using a random-effects model.

**Results:** Thirty-two studies were included. Intakes of total dairy products [summary RR: 1.07 (95% CI: 1.02, 1.12; $n$ = 15) per 400 g/d], total milk [summary RR: 1.03 (95% CI: 1.00, 1.07; $n$ = 14) per 200 g/d], low-fat milk [summary RR: 1.06 (95% CI: 1.01, 1.11; $n$ = 6) per 200 g/d], cheese [summary RR: 1.09 (95% CI: 1.02, 1.18; $n$ = 11) per 50 g/d], and dietary calcium [summary RR: 1.05 (95% CI: 1.02, 1.09; $n$ = 15) per 400 mg/d] were associated with increased total prostate cancer risk. Total calcium and dairy calcium intakes, but not nondairy calcium or supplemental calcium intakes, were also positively associated with total prostate cancer risk. Supplemental calcium was associated with increased risk of fatal prostate cancer.

**Conclusions:** High intakes of dairy products, milk, low-fat milk, cheese, and total, dietary, and dairy calcium, but not supplemental or nondairy calcium, may increase total prostate cancer risk. The diverging results for types of dairy products and sources of calcium suggest that other components of dairy rather than fat and calcium may increase prostate cancer risk. Any additional studies should report detailed results for subtypes of prostate cancer. *Am J Clin Nutr* 2015;101:87–117.

**Keywords** calcium, dairy products, milk, prostate cancer, WCRF/AICR Continuous Update Project

## INTRODUCTION

Prostate cancer is the second most-common cancer in men worldwide with approximately 900,000 new cases diagnosed in 2008 accounting for 13.8% of all cancers in men (1). Ecologic studies have shown up to a 70-fold variation in the incidence of prostate cancer worldwide with low rates in parts of Asia and Africa and high rates in North America, Australia, New Zealand, and Northern Europe (2). Migration studies suggested increased risk in Asians who move to the United States (3–5), and secular trend studies have reported an increased incidence and mortality within countries over time (6–8). These observations suggest a possible influence of modifiable exposures, including diet, on prostate cancer risk, but to date, few dietary risk factors for prostate cancer have been firmly established (9).

Ecologic studies have reported high correlations between intake of dairy foods and milk and prostate cancer risk (10–12), but data from observational case-control and cohort studies have been inconclusive. In the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[5] report "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective" from 2007 (9), it was stated that there is probable evidence that diets high in calcium increase risk and limited suggestive evidence that milk and dairy products increase risk (9). However, no recommendation was provided for calcium and dairy intakes because the evidence for prostate cancer conflicted with decreased risk of colorectal cancer with high milk intake. We have recently confirmed reduced risk of colorectal cancer with intakes of total dairy products and milk in an updated meta-analysis of prospective studies, and we showed evidence that the reduction in risk was largest at the highest intakes (13). Eighteen additional studies (21 publications) (14–34) have been published on dairy or calcium intakes and prostate cancer risk since the completion of the second WCRF/AICR report), and for this reason, we decided to conduct an updated systematic review and meta-analysis of the evidence. Specifically, we wanted to conduct more-detailed analyses of *1*) the

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[5] Abbreviations used: ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; EPIC, European Prospective Investigation into Cancer and Nutrition; IGF-I, insulin-like growth factor I; PSA, prostate specific antigen; WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.

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dose-response relation between dairy and calcium intakes and prostate cancer risk, *2*) types of dairy products and sources of calcium intake in relation to prostate cancer risk overall and by stage, and *3*) to investigate potential confounding by other factors and heterogeneity between studies by conducting subgroup and meta-regression analyses.

## METHODS

### Search strategy

We updated the systematic literature review published in 2007 (9) by searching the PubMed database up to April 2013 for prospective studies of dairy product and calcium intake and prostate cancer risk (incidence or mortality). A predefined protocol was used for the review (http://www.dietandcancerreport.org/cup/current_progress/prostate_cancer.php) and included details of the search terms used. We also reviewed reference lists of relevant articles and published systematic reviews and meta-analyses for additional studies (35–38). We followed standard criteria for conducting and reporting meta-analyses (39).

### Study selection

Studies were eligible for inclusion if they *1*) had a prospective design (randomized trials, cohort studies, case-cohort studies, and nested case-control studies) and *2*) presented estimates of the RR (such as a HR or risk ratio) with 95% CIs for the association between dairy products or calcium and prostate cancer incidence or mortality. For the dose-response analysis, a quantitative measure of intake had to be provided. When we identified duplicate publications, we generally selected the publication with the largest number of cases, but exceptions were made if information needed for the dose-response analysis was not available in the publication. Forty-five potentially relevant full-text publications (14–34, 40–63) were identified. We excluded 2 studies of dietary factors after prostate cancer diagnosis and risk of progression, recurrence, or death (58, 60), 4 duplicate publications (34, 59, 61, 63), and one study that only compared types of dairy products (skim compared with whole milk) (62). Although a more-recent study with a larger number of cases has been published from a Finnish study (59), we used the older publication (23) because the newest publication adjusted all analyses for calcium intake (which might be an overadjustment). One study was excluded from the analysis because cases prevalent at the time of dietary assessment were included in the analysis (33). For the dose-response analysis, we further excluded 3 publications (15, 19, 56) because there was only 2 categories of exposure. One study was excluded in the analysis of total dairy because it reported on total dairy and eggs combined, but it was included in the analysis of milk and cheese (54). For one study (32, 49), we used the older publication (49) for the analysis of dairy calcium because quantities were not provided in the most-recent publication (32).

### Data extraction

The following data were extracted from each study: first author's last name, publication year, country where the study was conducted, study name, follow-up period, sample size, sex, age, number of cases, dietary-assessment method (type, number of food items, and whether it had been validated), type of dairy product or calcium source (e.g., total dairy, milk, cheese, total, dietary, dairy, nondairy, and supplemental calcium), quantity of intake, RR and 95% CIs, and variables adjusted for in the analysis (**Table 1**). The search and data extraction of articles published up to June 2006 was conducted by several reviewers at the University of Bristol during the systematic literature review for the WCRF/AICR report (http://www.dietandcancerreport.org/downloads/SLR/Prostate_SLR.pdf). The search from June 2006 to April 2013 was conducted by one of the authors (DANR). Data were extracted by 2 authors (DANR and DA).

### Statistical methods

We used random-effects models to calculate summary RRs and 95% CIs associated with dairy product and calcium intake (64). The ln of the RR from each study was weighted by the inverse of its variance and unweighted by a variance component that corresponded to the amount of heterogeneity between studies and pooled across studies. A 2-tailed $P < 0.05$ was considered statistically significant. For one study that reported results separately for localized and advanced cancers but not for total prostate cancer (31), we combined the 2 results first by using a fixed-effects model before pooling with other studies.

We used the method described by Greenland and Longnecker (65) to compute study-specific slopes (linear trends) and 95% CIs from the lns of RRs and CIs across categories of dairy product and calcium intakes. The method required that the distribution of cases and person-years or noncases and RRs with variance estimates for ≥3 quantitative exposure categories were known. We estimated the distribution of cases or person-years in studies that did not report these variables. The median or mean dairy product or calcium intake in each category of intake was assigned to the corresponding RR for each study when it was reported. For studies that reported intake by ranges, we estimated the midpoint in each category by calculating the average of the lower and upper bounds. When the highest or lowest category was open ended, it was assumed that the open-ended interval length had the same length as the adjacent interval. If intakes were reported in densities (i.e., g/1000 kcal), we estimated reported intakes to absolute intakes by using the mean or median energy intake reported in the publication (28). When studies reported intakes in servings and times per day or week and did not provide a serving size, we converted intakes to grams of intake per day by using standard units of 244 g (or 244 mL) for milk and yogurt, 43 g for cheese (2 slices), and 177 g for total dairy products on the basis of serving sizes reported in the United States Department of Agriculture Food and Nutrient Database for Dietary Studies (66). Results from dose-response analyses are presented for a 400-g/d, 200-g/d, 100-g/d, 50-g/d, and 400-mg/d increment for total dairy, total milk, yogurt, cheese, and calcium, respectively. A potential nonlinear dose-response relation between dairy and calcium intakes and prostate cancer was examined by using fractional polynomial models (67). We determined the best-fitting second-order fractional polynomial regression model, which was defined as the one with the lowest deviance. A likelihood ratio test was used to assess the difference between nonlinear and linear models to test for nonlinearity (67). Separate analyses were conducted for total prostate cancer and nonadvanced, advanced, metastatic, and fatal cancers. For

**TABLE 1**
Prospective studies of dairy product and calcium intake and PC risk

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Song, 2013, United States (32) | Physicians' Health Study | 1982–2010, 28-y follow-up | 21,660, age: 40–84 y, 2806 cases | FFQ | Total PC | All dairy food | >2.5 vs. ≤0.5 servings/d | 1.12 (0.93, 1.35) | Age, cigarette smoking, vigorous exercise, alcohol, race, BMI, diabetes, red meat, total energy, assignment in aspirin trial and $\beta$-carotene trial. Whole milk and skim/low fat milk were mutually adjusted. |
| | | | | | | Whole milk | ≥1 serving/d vs. rarely | 0.95 (0.81, 1.10) | |
| | | | | | | Skim, low-fat milk | ≥1 serving/d vs. rarely | 1.19 (1.06, 1.33) | |
| | | | | | | Hard cheese | ≥1 serving/d vs. rarely | 1.05 (0.85, 1.30) | |
| | | | | | | Ice cream | ≥1 serving/d vs. rarely | 1.03 (0.80, 1.32) | |
| | | | | | | Dairy calcium | Quintile 5 vs. 1 | 1.14 (0.97, 1.34) | |
| | | | | | Localized PC | All dairy food | >2.5 vs. ≤0.5 servings/d | 1.13 (0.91, 1.39) | |
| | | | | | | Whole milk | ≥1 serving/d vs. rarely | 0.89 (0.74, 1.07) | |
| | | | | | | Skim- and low-fat milk | ≥1 serving/d vs. rarely | 1.19 (1.04, 1.35) | |
| | | | | | Advanced PC | All dairy food | >2.5 vs. ≤0.5 servings/d | 0.68 (0.36, 1.27) | |
| | | | | | | Whole milk | ≥1 serving/d vs. rarely | 0.83 (0.49, 1.41) | |
| | | | | | | Skim- and low-fat milk | ≥1 serving/d vs. rarely | 0.99 (0.67, 1.45) | |
| | | | | | Fatal PC | All dairy food | >2.5 vs. ≤0.5 servings/d | 1.73 (0.90, 3.35) | |
| | | | | | | Whole milk | ≥1 serving/d vs. ≤1 serving/wk | 1.49 (0.97, 2.28) | |
| | | | | | | Skim- and low-fat milk | ≥1 serving/d vs. ≤1 serving/wk | 1.04 (0.71, 1.51) | |
| Butler, 2010, Singapore (30) | Singapore Chinese Health Study | 1993/1998 −2007, 11 y | 27,293, age: 45–75 y, 298 cases | Validated FFQ, 165 food items | Total PC | Total calcium | 659 vs. 211 mg/d | 1.25 (0.89, 1.74) | Age, dialect group, interview year, education, weekly supplement use |
| | | | | | | Dietary calcium | 651 vs. 210 mg/d | 1.23 (0.88, 1.72) | |
| | | | | | Localized PC | Total calcium | 659 vs. 211 mg/d | 1.43 (0.81, 2.52) | |
| | | | | | Advanced PC | Total calcium | 659 vs. 211 mg/d | 1.18 (0.75, 1.87) | |

*(Continued)*

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Kristal, 2010, United States (31) | Prostate Cancer Prevention Trial | 1994–2003, 7 y | 9559, age ≥ 55 y, 1703 cases, 127/1576 high-/low-grade cases | FFQ, 99 food items | Gleason score: 2–7 | Total calcium | >1357 vs. <689 mg/d | 1.17 (0.97, 1.42) | Age, race-ethnicity, treatment arm, BMI, energy intake |
| | | | | | | Dietary calcium | >1165 vs. <598 mg/d | 1.27 (1.02, 1.57) | |
| | | | | | | Calcium supplements | >199 vs. <150 mg/d | 1.11 (0.96, 1.29) | |
| | | | | | Gleason score: 8–10 | Total calcium | >1357 vs. <689 mg/d | 0.46 (0.24, 0.89) | |
| | | | | | | Dietary calcium | >1165 vs. <598 mg/d | 0.43 (0.21, 0.89) | |
| | | | | | | Calcium supplements | >199 vs. <150 mg/d | 0.77 (0.46, 1.32) | |
| Park, 2009, United States (28) | NIH-AARP Diet and Health Study | 1995–96–2003, 8 y | 293,907, age: 50–71 y, 17,189 cases | Validated FFQ, 124 food items | Total PC | Dairy foods | 1.4 vs. 0.2 servings/1000 kcal per day | 1.06 (1.01, 1.12) | Age, race-ethnicity, education, marital status, BMI, FH–cancer, diabetes, physical activity, ALA, alcohol, red meat, total energy, smoking, PSA test, tomatoes, selenium |
| | | | | | | Total calcium | 1530 vs. 526 mg/d | 1.03 (0.98, 1.08) | |
| | | | | | | Dietary calcium | 1247 vs. 478 mg/d | 1.04 (0.98, 1.09) | |
| | | | | | | Supplemental calcium | ≥1000 vs. 0 mg/d | 0.96 (0.88, 1.05) | |
| Chae, 2009, United States (29) | CLUE II | 1989–2002, ∼14 y | Nested case-control study: 269 cases, 440 controls Mean age: 64.1/64.7 y | Validated FFQ, 61 food items | Total PC | Dietary calcium | ≥878.7 vs. <424.0 mg/d | 1.08 (0.66, 1.75) | Age, ethnicity, date of blood donation |

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**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Kurahashi, 2008, Japan (26) | Japan Public Health Center-Based Prospective Study | 1990–1993–2004, 7.5 y | 43,435, age: 45–75 y; 329 cases, 90 advanced cancers, and 227 localized cancers | Validated FFQ, 138 food items | Total PC | Total dairy products | 339.8 vs. 12.8 g/d | 1.63 (1.14, 2.32) | Age, area, smoking status, drinking frequency, marital status, green tea, genistein, energy |
| | | | | | | Milk | 290.5 vs. 2.3 g/d | 1.53 (1.07, 2.19) | |
| | | | | | | Cheese | 6.2 vs. 1.9 g/d | 1.32 (0.93, 1.89) | |
| | | | | | | Yogurt | 31.5 vs. 1.9 g/d | 1.52 (1.10, 2.12) | |
| | | | | | | Calcium | 725.1 vs. 282.8 mg/d | 1.24 (0.85, 1.81) | |
| | | | | | Localized PC | Total dairy products | 339.8 vs. 12.8 g/d | 1.69 (1.10, 2.59) | |
| | | | | | | Calcium | 725.1 vs. 282.8 mg/d | 1.25 (0.80, 1.97) | |
| | | | | | Advanced PC | Total dairy products | 339.8 vs. 12.8 g/d | 1.41 (0.73, 2.73) | |
| | | | | | | Calcium | 725.1 vs. 282.8 mg/d | 1.14 (0.54, 2.41) | |
| Allen, 2008, Europe (27) | European Prospective Investigation into Cancer and Nutrition | 1989–2004, ∼8.7 y | 142,251, median age: 52 y, 2727 cases, 1131/541 localized/advanced cases | Validated FFQ, diet histories | Total PC | Milk and milk beverages | 466 vs. 34 g/d | 1.01 (0.89, 1.16) | Age, center, education, marital status, height, weight, energy intake |
| | | | | | | Yogurt | 135 vs. 10 g/d | 1.17 (1.04, 1.31) | |
| | | | | | | Cheese | 57 vs. 15 g/d | 1.04 (0.90, 1.20) | |
| | | | | | | Calcium | 1320 vs. 780 mg/d | 1.17 (1.00, 1.35) | |
| | | | | | | | Per 300 mg/d | 1.04 (1.01, 1.08) | |
| | | | | | | Dairy calcium | 880 vs. 300 mg/d | 1.18 (1.03, 1.36) | |
| | | | | | | | Per 300 mg/d | 1.04 (1.01, 1.08) | |
| | | | | | | Nondairy calcium | 550 vs. 380 mg/d | 1.02 (0.85, 1.23) | |
| | | | | | | | Per 300 mg/d | 1.04 (0.90, 1.19) | |
| | | | | | Localized PC | Calcium | Per 300 mg/d | 1.07 (0.96, 1.19) | |
| | | | | | | Dairy calcium | Per 300 mg/d | 1.06 (0.96, 1.17) | |
| | | | | | | Nondairy calcium | Per 300 mg/d | 1.14 (0.66, 1.99) | |
| | | | | | Advanced PC | Calcium | Per 300 mg/d | 1.05 (0.91, 1.22) | |
| | | | | | | Dairy calcium | Per 300 mg/d | 1.04 (0.91, 1.19) | |
| | | | | | | Nondairy calcium | Per 300 mg/d | 1.04 (0.47, 2.29) | |
| Smit, 2007, Puerto Rico (72) | The Puerto Rico Heart Health Program | 1965–1968−2005, | 9777, age: 35–79 y, 167 deaths | 24-h recall | Fatal PC | Dairy products | ≥7 vs. ≤7 servings/d | 1.75 (0.76, 2.63) | Age, education, BMI, urban or rural living, physical activity, smoking, energy intake |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Ahn, 2007, United States (24) | Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial | 1993–2001−2002, up to 8.9 y | 29,509, age: 55–74 y, 1910 cases, 791 aggressive cancers, 1089 nonaggressive cancers | FFQ, 137 food items | Total PC | Total dairy | ≥2.75 vs. ≤0.98 servings/d | 1.12 (0.97, 1.30) | Age, race, study center, FH–PC, BMI, smoking status, physical activity, diabetes history, red meat, total energy, education, no. of screening examinations during follow-up |
| | | | | | | Low-fat dairy | ≥1.00 vs. ≤0.08 servings/d | 1.23 (1.07, 1.41) | |
| | | | | | | High-fat dairy | ≥0.53 vs. ≤0.10 servings/d | 1.07 (0.92, 1.23) | |
| | | | | | | Total calcium | ≥2001 vs. ≤750 mg/d | 0.89 (0.66, 1.19) | |
| | | | | | | Dietary calcium | ≥2001 vs. ≤750 mg/d | 1.22 (0.83, 1.79) | |
| | | | | | | Supplemental calcium | ≥801 vs. 0 mg/d | 0.94 (0.68, 1.29) | |
| | | | | | Nonaggressive PC | Total dairy | ≥2.75 vs. ≤0.98 servings/d | 1.20 (0.99, 1.46) | |
| | | | | | | Low-fat dairy | ≥1.00 vs. ≤0.08 servings/d | 1.30 (1.09, 1.55) | |
| | | | | | | High-fat dairy | ≥0.53 vs. ≤0.10 servings/d | 1.03 (0.85, 1.24) | |
| | | | | | | Total calcium | ≥2001 vs. ≤750 mg/d | 1.08 (0.75, 1.56) | |
| | | | | | | Dietary calcium | ≥2001 vs. ≤750 mg/d | 1.52 (0.94, 2.47) | |
| | | | | | | Supplemental calcium | ≥801 vs. 0 mg/d | 0.88 (0.57, 1.36) | |
| | | | | | Aggressive PC | Total dairy | ≥2.75 vs. ≤0.98 servings/d | 1.02 (0.81, 1.28) | |
| | | | | | | Low-fat dairy | ≥1.00 vs. ≤0.08 servings/d | 1.12 (0.90, 1.39) | |
| | | | | | | High-fat dairy | ≥0.53 vs. ≤0.10 servings/d | 1.13 (0.91, 1.42) | |
| | | | | | | Total calcium | ≥2001 vs. ≤750 mg/d | 0.61 (0.37, 1.02) | |
| | | | | | | Dietary calcium | ≥2001 vs. ≤750 mg/d | 0.83 (0.42, 1.64) | |
| | | | | | | Supplemental calcium | ≥801 vs. 0 mg/d | 1.02 (0.63, 1.63) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Park, 2007, United States (22) | NIH-AARP Diet and Health Study | 1995/1996–2001, 6 y | 293,888, age: 50–71 y, 10,180 cases, 8754 nonadvanced, 1426 advanced, and 178 fatal cases | Validated FFQ, 124 food items | Total PC | Whole milk | ≥2 vs. 0 servings/d | 0.91 (0.76, 1.09) | Age, race/ ethnicity, education, marital status, BMI, vigorous physical activity, smoking, alcohol consumption, diabetes history, FH–PC, PSA screening, tomatoes, red meat, fish, vitamin E, ALA, total energy |
| | | | | | | Low-fat milk | ≥2 vs. 0 servings/d | 1.03 (0.95, 1.13) | |
| | | | | | | Skim milk | ≥2 vs. 0 servings/d | 1.01 (0.93, 1.10) | |
| | | | | | | Cheese | ≥0.75 vs. <0.1 servings/d | 1.08 (0.96, 1.22) | |
| | | | | | | Yogurt | ≥0.5 vs. 0 servings/d | 1.01 (0.89, 1.15) | |
| | | | | | | Dairy calcium | ≥800 vs. <250 mg/d | 1.06 (0.99, 1.14) | |
| | | | | | | Nondairy calcium | ≥600 vs. <250 mg/d | 0.82 (0.69, 0.98) | |
| | | | | | Nonadvanced PC | Dairy foods | ≥3 vs. <0.5 servings/d | 1.02 (0.93, 1.12) | |
| | | | | | | Whole milk | ≥2 vs. 0 servings/d | 0.91 (0.75, 1.10) | Calcium from supplements also adjusted for dietary calcium |
| | | | | | | Low-fat milk | ≥2 vs. 0 servings/d | 1.06 (0.96, 1.17) | Dairy and nondairy calcium were mutually adjusted |
| | | | | | | Skim milk | ≥2 vs. 0 servings/d | 0.98 (0.89, 1.07) | |
| | | | | | | Cheese | ≥0.75 vs. <0.1 servings/d | 1.09 (0.96, 1.24) | Total calcium also adjusted for vitamin D |
| | | | | | | Yogurt | ≥0.5 vs. 0 servings/d | 1.01 (0.88, 1.16) | |
| | | | | | | Total calcium | ≥2000 vs. <250 mg/d | 0.93 (0.81, 1.07) | |
| | | | | | | Supplemental calcium | ≥1000 vs. 0 mg/d | 0.99 (0.86, 1.13) | |
| | | | | | | Dairy calcium | ≥800 vs. <250 mg/d | 1.06 (0.98, 1.14) | |
| | | | | | | Nondairy calcium | ≥600 vs. <250 mg/d | 0.82 (0.68, 0.99) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Advanced PC | Dairy foods | ≥3 vs. <0.5 servings/d | 0.89 (0.70, 1.13) | |
| | | | | | | Whole milk | ≥2 vs. 0 servings/d | 0.93 (0.58, 1.49) | |
| | | | | | | Low-fat milk | ≥2 vs. 0 servings/d | 0.87 (0.68, 1.12) | |
| | | | | | | Skim milk | ≥2 vs. 0 servings/d | 1.23 (0.99, 1.54) | |
| | | | | | | Cheese | ≥0.75 vs. <0.1 servings/d | 1.03 (0.75, 1.42) | |
| | | | | | | Yogurt | ≥0.5 vs. 0 servings/d | 1.02 (0.72, 1.43) | |
| | | | | | | Total calcium | ≥2000 vs. <250 mg/d | 1.20 (0.86, 1.68) | |
| | | | | | | Supplemental calcium | ≥1000 vs. 0 mg/d | 1.07 (0.77, 1.48) | |
| | | | | | | Dairy calcium | ≥800 vs. <250 mg/d | 1.08 (0.90, 1.30) | |
| | | | | | | Nondairy calcium | ≥600 vs. <250 mg/d | 0.82 (0.51, 1.33) | |
| | | | | | Fatal PC | Dairy foods | ≥3 vs. <0.5 servings/d | 1.27 (0.67, 2.39) | |
| | | | | | | Whole milk | ≥2 vs. 0 servings/d | 0.77 (0.24, 2.49) | |
| | | | | | | Low-fat milk | ≥2 vs. 0 servings/d | 0.87 (0.47, 1.62) | |
| | | | | | | Skim milk | ≥2 vs. 0 servings/d | 1.03 (0.54, 1.96) | |
| | | | | | | Cheese | ≥0.75 vs. <0.1 servings/d | 1.24 (0.56, 2.75) | |
| | | | | | | Yogurt | ≥0.5 vs. 0 servings/d | 0.78 (0.25, 2.50) | |
| | | | | | | Total calcium | ≥2000 vs. <250 mg/d | 1.05 (0.54, 2.05) | |
| | | | | | | Supplemental calcium | ≥1000 vs. 0 mg/d | 1.46 (0.83, 2.57) | |
| | | | | | | Dairy calcium | ≥800 vs. <250 mg/d | 1.24 (0.81, 1.91) | |
| | | | | | | Nondairy calcium | ≥600 vs. <250 mg/d | 1.32 (0.67, 2.62) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Park, 2007, United States (21) | Multiethnic Cohort Study | 1993–2002, 8 y | 82,483, age: 45–75 y | Validated FFQ, ≥180 food items | Total PC | Dairy products | ≥332 vs. <49 g/d | 1.03 (0.92, 1.16) | Age, time since cohort entry, ethnicity, FH–PC, education, BMI, smoking status, energy intake |
| | | | | | | Total milk | ≥256 vs. <17 g/d | 1.07 (0.95, 1.19) | |
| | | | 4404 cases | | | Low-fat/nonfat milk | ≥243 vs. 0 g/d | 1.16 (1.04, 1.29) | |
| | | | 738 advanced cancers | | | Whole milk | ≥163 vs. 0 g/d | 0.88 (0.77, 1.00) | |
| | | | | | | Yogurt | ≥40 vs. 0 g/d | 0.96 (0.83, 1.09) | |
| | | | | | | Cheese | ≥14 vs. 0 g/d | 1.01 (0.91, 1.12) | |
| | | | 3405 localized cancers | | | Total calcium | ≥1301 vs. <470 mg/d | 1.04 (0.91, 1.20) | |
| | | | | | | Supplemental calcium | ≥200 vs. 0 mg/d | 0.99 (0.90, 1.08) | Mutually adjusted |
| | | | | | | Calcium from foods | ≥1123 vs. <417 mg/d | 1.02 (0.87, 1.19) | Mutually adjusted |
| | | | | | Localized PC | Dairy products | ≥332 vs. <49 g/d | 1.06 (0.93, 1.22) | |
| | | | | | | Total milk | ≥256 vs. <17 g/d | 1.09 (0.96, 1.24) | |
| | | | | | | Low-/nonfat milk | ≥243 vs. 0 g/d | 1.28 (1.13, 1.45) | |
| | | | | | | Whole milk | ≥163 vs. 0 g/d | 0.84 (0.73, 0.98) | |
| | | | | | | Yogurt | ≥40 vs. 0 g/d | 0.92 (0.79, 1.07) | |
| | | | | | | Cheese | ≥14 vs. 0 g/d | 0.99 (0.88, 1.11) | |
| | | | | | | Total calcium | ≥1301 vs. <470 mg/d | 1.10 (0.94, 1.29) | |
| | | | | | | Supplemental calcium | ≥200 vs. 0 mg/d | 1.00 (0.90, 1.11) | |
| | | | | | | Calcium from foods | ≥1123 vs. <417 mg/d | 1.06 (0.89, 1.27) | |
| | | | | | Advanced PC | Dairy products | ≥332 vs. <49 g/d | 0.97 (0.72, 1.31) | |
| | | | | | | Total milk | ≥256 vs. <17 g/d | 1.01 (0.76, 1.34) | |
| | | | | | | Low-/nonfat milk | ≥243 vs. 0 g/d | 0.81 (0.61, 1.09) | |
| | | | | | | Whole milk | ≥163 vs. 0 g/d | 0.99 (0.74, 1.34) | |
| | | | | | | Yogurt | ≥40 vs. 0 g/d | 0.95 (0.68, 1.34) | |
| | | | | | | Cheese | ≥14 vs. 0 g/d | 1.07 (0.83, 1.37) | |
| | | | | | | Total calcium | ≥1301 vs. <470 mg/d | 0.91 (0.65, 1.28) | |
| | | | | | | Supplemental calcium | ≥200 vs. 0 mg/d | 0.87 (0.69, 1.10) | |
| | | | | | | Calcium from foods | ≥1123 vs. <417 mg/d | 0.97 (0.66, 1.43) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Neuhouser, 2007, United States (20) | Carotene and Retinol Efficacy Trial | 1994–2005, 11 y | 12,025 smokers, age: 45–69 y, 890 cases | FFQ, 110 items | Total PC | Total dairy | ≥2.2 vs. <0.9 servings/d | 0.82 (0.66, 1.02) | Age, energy intake, BMI, smoking, FH–PC. Models for disease severity also included race-ethnicity. |
| | | | | | Nonaggressive PC | Total dairy | ≥2.2 vs. <0.9 servings/d | 1.04 (0.74, 1.47) | |
| | | | | | Aggressive PC | Total dairy | ≥2.2 vs. <0.9 servings/d | 0.59 (0.40, 0.85) | |
| Rohrmann, 2007, United States (19) | CLUE II | 1989–2004, 13 y | 3892, age ≥ 35 y, 199 cases | Validated FFQ, 60 food items | Total PC | Dairy products | 3.3 vs. 0.3 servings/d | 1.08 (0.78, 1.54) | Age, energy intake, tomato products, BMI at age 21 y, SFA |
| | | | | | | Cheese | ≥5 vs. ≤1/wk | 1.43 (1.01, 2.03) | |
| | | | | | | Milk | ≥5 vs. ≤1/wk | 1.26 (0.91, 1.74) | |
| | | | | | | Total calcium | ≥957.58 vs. <685.77 mg/d | 0.99 (0.70, 1.41) | |
| | | | | | | Dairy calcium | Tertile 3 vs. 1 | 1.08 (0.76, 1.54) | Age |
| | | | | | | Calcium supplements | Yes vs. no | 0.86 (0.62, 1.19) | Age |
| | | | | | Low-stage PC | Dairy products | 3.3 vs. 0.3 servings/d | 1.31 (0.71, 2.41) | |
| | | | | | | Cheese | ≥5 vs. ≤1/wk | 0.93 (0.51, 1.67) | |
| | | | | | | Milk | ≥5 vs. ≤1/wk | 1.66 (0.93, 2.93) | |
| | | | | | | Total calcium | ≥957.58 vs. <685.77 mg/d | 1.16 (0.63, 2.15) | |
| | | | | | | Dairy calcium | Tertile 3 vs. 1 | 1.50 (0.82, 2.72) | |
| | | | | | | Calcium supplements | Yes vs. no | 1.02 (0.56, 1.85) | |
| | | | | | High-stage PC | Dairy products | 3.3 vs. 0.3 servings/d | 1.28 (0.63, 2.59) | |
| | | | | | | Cheese | ≥5 vs. ≤1/wk | 1.71 (0.88, 3.32) | |
| | | | | | | Milk | ≥5 vs. ≤1/wk | 1.41 (0.73, 2.72) | |
| | | | | | | Total calcium | ≥957.58 vs. <685.77 mg/d | 1.06 (0.55, 2.04) | |
| | | | | | | Dairy calcium | Tertile 3 vs. 1 | 1.10 (0.57, 2.11) | |
| | | | | | | Calcium supplements | Yes vs. no | 1.01 (0.60, 1.69) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Mitrou, 2007, Finland (23) | Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study | 1985–1988−1999, 17 y | 29,133 smokers, age: 50–69 y; 1267 cases, 300 advanced cancers, 561 nonadvanced cancers | Validated FFQ 276 food items | Total PC | Total dairy | 1220.2 vs. 380.9 g/d | 1.26 (1.04, 1.51) | Age, trial intervention group, physical activity at work and leisure, BMI, history of type 2 diabetes, FH–PC, height, smoking, total no. of cigarettes per day, marital status, education, urban residence, total energy intake |
| | | | | | | Total milk | 993.5 vs. 152.6 g/d | 1.08 (0.91, 1.30) | |
| | | | | | | Whole milk | 667.9 vs. 0 g/d | 1.05 (0.86, 1.29) | |
| | | | | | | Low-fat milk | 773.1 vs. 75.9 g/d | 1.18 (0.97, 1.44) | |
| | | | | | | Butter | 71.7 vs. 5.1 g/d | 1.00 (0.84, 1.20) | |
| | | | | | | Ice cream | 9.3 vs. 0 g/d | 0.90 (0.75, 1.08) | |
| | | | | | | Cream | 47.7 vs. 1.2 g/d | 1.09 (0.91, 1.30) | |
| | | | | | | Cheese | 54.6 vs. 3.0 g/d | 1.13 (0.95, 1.36) | |
| | | | | | | Sour milk products | 423.1 vs. 0 g/d | 1.07 (0.90, 1.28) | |
| | | | | | | Dairy calcium | 1613.7 vs. 565.8 mg/d | 1.28 (1.07, 1.54) | |
| | | | | | | Dietary calcium | ≥2000 vs. <1000 mg/d | 1.63 (1.27, 2.10) | |
| | | | | | Nonadvanced PC | Dietary calcium | ≥2000 vs. <1000 mg/d | 1.59 (1.10, 2.29) | |
| | | | | | Advanced PC | Dietary calcium | ≥2000 vs. <1000 mg/d | 1.25 (0.73, 2.16) | |
| | | | | | Low-grade PC | Dietary calcium | ≥2000 vs. <1000 mg/d | 1.43 (1.01, 2.02) | |
| | | | | | High-grade PC | Dietary calcium | ≥2000 vs. <1000 mg/d | 1.53 (0.80, 2.95) | |
| Iso, 2007, Japan (25) | Japan Collaborative Cohort Study | 1988/1990–NR, ∼12.5 y | 42,289, age: 40–79 y, 154 deaths | Validated FFQ, 33 food items | Fatal PC | Milk | ≥5 vs. <3/wk | 0.84 (0.57, 1.22) | Age |
| | | | | | | Yogurt | ≥5 vs. <3/wk | 1.31 (0.63, 2.71) | |
| | | | | | | Cheese | ≥3–4 vs. <1/wk | 0.70 (0.32, 1.52) | |
| | | | | | | Butter | ≥3–4 vs. <1/wk | 1.29 (0.72, 2.30) | |
| Koh, 2006, United States (15) | The Harvard Alumni Health Study | 1988–1998, 10 y | 10,011, mean age: 67 y, 815 cases | FFQ, 23 food items | Total PC | Dairy products | ≥3.25 vs. 0 to <1.25 servings/d | 1.11 (0.85, 1.46) | Age; smoking; BMI; physical activity; intakes of alcohol, red meat, vegetables, and total calories; paternal history of PC |
| | | | | | | Dairy calcium | ≥600 vs. 0–199 mg/d | 1.12 (0.51, 2.47) | |
| | | | | | Fatal PC | Dairy products | ≥3.25 vs. 0 to <1.25 servings/d | 0.91 (0.70, 1.18) | |
| | | | | | | Dairy calcium | ≥600 vs. 0–199 mg/d | 0.81 (0.38, 1.71) | |
| | | | | | | Calcium supplements | Yes vs. no | 1.05 (0.84, 1.31) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Severi, 2006, Australia (14) | Melbourne Collaborative Cohort Study | 1990–1994–2004, 10.9 y | 14,642, age: 27–75 y, 674 cases | FFQ, 121 food items | Total PC | Dairy products | 56 vs. 10 times/wk | 0.99 (0.78, 1.26) | Age, country of birth, total energy intake Additional adjustment for educational level, BMI, fat and fat-free mass, smoking status and history, and alcohol did not materially change estimated rate ratios |
| | | | | | | Butter | 7.5 vs. 0 times/wk | 1.11 (0.85, 1.46) | |
| | | | | | | Calcium | 1238 vs. 507 mg/d | 0.98 (0.72, 1.33) | |
| | | | 563 nonaggressive cases | | Nonaggressive PC | Dairy products | 56 vs. 10 times/wk | 1.07 (0.82, 1.39) | |
| | | | | | | Butter | 7.5 vs. 0 times/wk | 1.14 (0.85, 1.54) | |
| | | | | | | Calcium | 1238 vs. 507 mg/d | 1.06 (0.77, 1.47) | |
| | | | 107 aggressive cases | | Aggressive PC | Dairy products | 56 vs. 10 times/wk | 0.77 (0.45, 1.31) | |
| | | | | | | Butter | 7.5 vs. 0 times/wk | 1.03 (0.53, 2.00) | |
| | | | | | | Calcium | 1238 vs. 507 mg/d | 0.74 (0.43, 1.27) | |
| Tande, 2006, United States (18) | ARIC study | 1987/1989–2000, 12.1 y | 6429, age: 45–64 y, 385 cases | Validated FFQ, 61 items | Total PC | Milk | ≥1.0 vs. <0.07 servings/d | 1.46 (1.06, 2.01) | Age, race |
| Kesse, 2006, France (16) | SU.VI.MAX study | 1994/1995−2004, 7.7 y | 2776, age: 45–60 y, 69 cases | 5 × 24-h dietary record | Total PC | Dairy products | >396 vs. <160 g/d | 2.16 (0.96, 4.85) | Age, occupation, group of treatment, smoking status, physical activity, energy from fat, energy from other sources, ethanol intake, BMI, FH–PC in first degree relative |
| | | | | | | | Per 200 g/d | 1.35 (1.02, 1.78) | |
| | | | | | | Milk | >253 vs. <25 g/d | 1.13 (0.54, 2.34) | |
| | | | | | | | Per 100 g/d | 1.04 (0.89, 1.23) | |
| | | | | | | Cheese | >71 vs. <25 g/d | 0.90 (0.42, 1.91) | |
| | | | | | | | Per 30 g/d | 1.06 (0.87, 1.31) | |
| | | | | | | Fresh cheese | >50 vs. 0 g/d | 2.38 (1.23, 4.62) | |
| | | | | | | | Per 100 g/d | 1.34 (0.83, 2.15) | |
| | | | | | | Yogurt | >100 vs. <0 g/d | 1.81 (0.87, 3.76) | |
| | | | | | | | Per 125 g/d | 1.67 (1.16, 2.40) | |
| | | | | | | Total calcium | >1081 vs. <725 mg/d | 2.43 (1.05, 5.62) | |
| | | | | | | Dairy calcium | >696 vs. <354 mg/d | 2.94 (1.16, 7.51) | |
| | | | | | | Nondairy calcium | >440 vs. <294 mg/d | 1.12 (0.60, 2.11) | |

*(Continued)*

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Giovannucci, 2006, United States (17) | Health Professionals Follow-Up Study | 1986–2002, 16 y | 47,750, age: 45–70 y, 3544 cases | Validated FFQ, 131 food items | Total PC | Dairy food | 3.72 vs. 0.50 servings/d | 1.07 (0.95, 1.20) | Age, time period, BMI at age 21 y, vigorous physical activity, height, cigarette pack-years in the previous 10 y, FH–PC, diabetes, total calories, red meat, fish, ALA, zinc supplements, tomato sauce |
| | | | | | | Total calcium | ≥2000 vs. 500–749 mg/d | 1.28 (1.02, 1.60) | |
| | | | | | Nonadvanced PC | Total calcium | ≥2000 vs. 500–749 mg/d | 1.13 (0.88, 1.47) | |
| | | | 523 advanced cancers | | Advanced PC | Dairy food | 3.72 vs. 0.50 servings/d | 1.21 (0.89, 1.64) | |
| | | | | | | Total calcium | ≥2000 vs. 500–749 mg/d | 2.02 (1.28, 3.19) | |
| | | | | | | Dietary calcium | ≥933 vs. <585 mg/d | 1.46 (1.12, 1.90) | |
| | | | | | | Supplemental calcium | ≥401 vs. 0 mg/d | 1.22 (0.93, 1.62) | |
| | | | 312 fatal cancers | | Fatal PC | Total calcium | ≥2000 vs. 500–749 mg/d | 2.02 (1.14, 3.58) | |
| | | | | | | Dietary calcium | ≥933 vs. <585 mg/d | 1.36 (0.97, 1.92) | |
| | | | | | | Supplemental calcium | ≥401 vs. 0 mg/d | 1.51 (1.09, 2.10) | |
| Tseng, 2005, United States (57) | National Health and Nutrition Examination Epidemiologic Follow-up Study | 1982/1984–1992, 7.7 y | 3612, age: 25–74 y, 131 cases | Validated FFQ, 105 food items | Total PC | Dairy | 21 vs. 5 servings/wk | 2.2 (1.2, 3.9) | Age, race, energy intake, design variables, region, education, recreational sun exposure, recreational and usual level of physical activity, smoking status, current alcohol intake |
| | | | | | | Total milk | 14 vs. 0.5 servings/wk | 1.8 (1.1, 2.9) | |
| | | | | | | Low-fat milk | 7 vs. 0 servings/wk | 1.5 (1.1, 2.2) | |
| | | | | | | Whole milk | 7 vs. 0 servings/wk | 0.8 (0.5, 1.3) | |
| | | | | | | Cheese | 4 vs. 0.25 servings/wk | 1.1 (0.6, 1.9) | |
| | | | | | | Ice cream | 3 vs. 0.1 servings/wk | 1.0 (0.7, 1.5) | |
| | | | | | | Cottage cheese | 1 vs. 0 servings/wk | 1.2 (0.8, 1.8) | |
| | | | | | | Cream | 0.5 vs. 0 servings/wk | 0.9 (0.6, 1.3) | |
| | | | | | | Yogurt | 0.25 vs. 0 servings/wk | 1.0 (0.6, 1.9) | |
| | | | | | | Calcium | 920.6 vs. 455.4 mg/d | 2.2 (1.4, 3.5) | |
| | | | | | | Calcium from low-fat milk | 264.9 vs. 0 mg/d | 1.7 (1.1, 2.6) | |
| | | | | | | Calcium from whole milk | 193.8 vs. 0 mg/d | 0.8 (0.5, 1.3) | |
| | | | | | | Calcium from all other dairy | 337.8 vs. 50.1 mg/d | 0.9 (0.6, 1.5) | |

*(Continued)*

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Calcium from nondairy sources | 417.9 vs. 264.9 mg/d | 0.8 (0.5, 1.3) | |
| | | | | | | Calcium supplement use | Yes vs. no | 0.9 (0.4, 2.3) | |
| Baron, 2005, United States (56) | Calcium Polyp Prevention Study | 1988–2003, ≤12 y | Randomized trial, 672, mean age: 61.8 y, 70 cases | FFQ | Total PC | Calcium supplements | 1200 vs. 0 mg/d | 0.83 (0.52, 1.32) | Unadjusted |
| | | | | | | Dietary calcium | ≥990.8 vs. <675.2 mg/d | 1.20 (0.64, 2.23) | Age, treatment, calories |
| Allen, 2004, Japan (54) | Life Span Study | 1963, 1965, or 1979–1996, ∼14 y | 18,115, 18–99 y, 196 cases | Validated FFQ, ≥8 food items | Total PC | Milk | Almost daily vs. <2 times/wk | 0.87 (0.62, 1.21) | Age, migration |
| | | | | | | Butter, cheese | Almost daily vs. <2 times/wk | 0.84 (0.52, 1.37) | |
| Leitzmann, 2004, United States (55) | Health Professionals Follow-Up Study | 1986–2000, 14 y | 47,866, age: 40–75 y, 448 advanced cancers | Validated FFQ, 131 food items | Advanced PC | Cheese | ≥1 time/d vs. <1 time/mo | 1.19 (0.66, 2.13) | Age, time period, major ancestry, FH–PC, BMI at age 21 y, height, D2, vasectomy, smoking, vigorous physical activity, total energy, supplemental vitamin E |
| | | | | | | Skim milk | | 1.07 (0.82, 1.39) | |
| Rodriguez, 2003, United States (53) | Cancer Prevention Study 11 Nutrition Cohort | 1992/1993–1999, ∼7 y | 65,321, age: 50–74 y, 3811 cases 569 advanced PC cases | Validated FFQ, 68 food items | Total PC | Dairy food | ≥4.0 servings/d vs. <3 servings/wk | 1.1 (0.9, 1.3) | Age at entry, race, FH–PC, total energy, total fat intake, education, phosphorus, total vitamin D |
| | | | | | | Total calcium | ≥2000 vs. <700 mg/d | 1.2 (1.0, 1.6) | |
| | | | | | | Dietary calcium | ≥2000 vs. <700 mg/d | 1.6 (1.1, 2.3) | |
| | | | | | | Calcium supplements | ≥500 vs. 0 mg/d | 1.1 (1.0, 1.3) | |
| | | | | | Advanced PC | Dairy food | ≥4.0/d vs. <3/wk | 0.9 (0.5, 1.4) | |
| | | | | | | Total calcium | ≥2000 vs. <700 mg/d | 1.6 (0.9, 3.0) | |
| | | | | | | Dietary calcium | ≥2000 vs. <700 mg/d | 2.2 (0.9, 5.3) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Rodriguez, 2002, United States (52) | Cancer Prevention Study I | 1959–1972, 13 y | 417,018, median age: 52 y, 1751 deaths | FFQ | Fatal PC | Dairy products | ≥28 vs. <7/wk | 1.20 (0.95, 1.53) | Age, education, FH–PC, smoking, BMI, vegetables, pork |
| Rodriguez, 2002, United States (52) | Cancer Prevention Study II | 1982–1996, 14 y | 447,780, median age: 57 y, 3594 deaths | FFQ | Fatal PC | Dairy products | ≥28 vs. <7/wk | 1.00 (0.82, 1.23) | Age, education, FH–PC, smoking, BMI, vegetables, pork |
| Berndt, 2002, United States (51) | Baltimore Longitudinal Study of Aging | 1994–NR, NR | 454, age: 46–92 y, 69 cases | Validated FFQ | Total PC | Calcium | 1121 vs. 525 mg/d | 0.92 (0.48, 1.77) | Age, energy intake |
| | | | | | | Milk, cheese, yogurt | 4.30 vs. 1.01 servings/d | 1.26 (0.57, 2.79) | |
| | | | | | | Milk | 2.99 vs. 0.26 servings/d | 1.20 (0.58, 2.47) | |
| Michaud, 2001, United States (50) | Health Professionals Follow-Up Study | 1986–1996, 10 y | 51,529, age: 40–75 y, 249 metastatic PC | Validated FFQ, 131 food items | Metastatic PC | Dairy products | >69 vs. <19 g/d | 1.43 (0.91, 2.3) | Age, calories, calcium, smoking, tomato sauce, vigorous exercise |
| | | | | | | Butter | ≥5 servings/wk vs. 0 servings/mo | 1.42 (1.0, 2.0) | |
| | | | | | | Ice cream (1 cup) | ≥5 servings/wk vs. 0 servings/mo | 1.28 (0.71, 2.3) | |
| | | | | | | Skim- and low-fat milk | >2 servings/d vs. 0 servings/mo | 1.25 (0.83, 1.9) | |
| | | | | | | Whole milk | >4 servings/wk vs. 0 servings/mo | 1.25 (0.80, 1.9) | |
| | | | | | | Cottage, ricotta cheese | ≥2 servings/wk vs. 0 servings/mo | 1.06 (0.75, 1.5) | |
| | | | | | | Other cheese | ≥5 servings/wk vs. ≤3 servings/mo | 1.29 (0.88, 1.9) | |
| | | | | | | Cream cheese | ≥1 serving/wk vs. 0 servings /mo | 1.20 (0.81, 1.8) | |
| Chan, 2001, United States (49) | Physicians' Health Study | 1984–1995, 11 y | 20,885, age: 53 y, 1012 cases | FFQ | Total PC | Skim milk | ≥1 serving/d vs. 0 servings/d | 1.32 (1.12, 1.56) | Age, smoking, vigorous exercise, randomized assignment to aspirin, β-carotene/placebo, BMI, food score |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Schuurman, 1999, The Netherlands (48) | Netherlands Cohort study | 1986–1992, 6.3 y | 58,279, age: 55–69 y; 642 cases 226 localized cancers, 213 advanced cancers | Validated FFQ, 150 food items | Total PC | Milk and milk products | 566 vs. 74 g/d | 1.12 (0.81, 1.56) | Age, FH–PC, socioeconomic status |
| | | | | | | | Per 50 g/d | 1.00 (0.98, 1.03) | |
| | | | | | | Cheese | 43 vs. 2 g/d | 1.21 (0.87, 1.79) | |
| | | | | | | | Per 20 g/d | 1.02 (0.93, 1.13) | |
| | | | | | | Low-fat cheese | Per 20 g/d | 1.01 (0.77, 1.32) | |
| | | | | | | Fermented whole milk | Per 50 g/d | 0.87 (0.76, 1.00) | |
| | | | | | | Fermented low-fat milk | Per 50 g/d | 1.01 (0.96, 1.07) | |
| | | | | | | Whole milk | Per 50 g/d | 1.00 (0.96, 1.03) | |
| | | | | | | Low-fat milk | Per 50 g/d | 1.01 (0.97, 1.05) | |
| | | | | | | Whole yogurt | Per 50 g/d | 0.88 (0.76, 1.01) | |
| | | | | | | Dietary calcium | 1329 vs. 602 mg/d | 1.09 (0.79, 1.50) | |
| | | | | | Localized PC | Milk and milk products | Per 50 g/d | 1.01 (0.98, 1.05) | |
| | | | | | | Cheese | Per 20 g/d | 1.20 (1.06, 1.37) | |
| | | | | | | Low-fat cheese | Per 20 g/d | 1.07 (0.78, 1.47) | |
| | | | | | | Fermented whole milk | Per 50 g/d | 0.96 (0.79, 1.15) | |
| | | | | | | Fermented low-fat milk | Per 50 g/d | 1.01 (0.94, 1.09) | |
| | | | | | | Whole milk | Per 50 g/d | 0.97 (0.92, 1.03) | |
| | | | | | | Low-fat milk | Per 50 g/d | 1.03 (0.97, 1.09) | |
| | | | | | | Dietary calcium | 1329 vs. 602 mg/d | 1.21 (0.79, 1.86) | |
| | | | | | Advanced PC | Milk and milk products | Per 50 g/d | 0.99 (0.95, 1.03) | |
| | | | | | | Cheese | Per 20 g/d | 1.05 (0.66, 1.68) | |
| | | | | | | Low-fat cheese | Per 20 g/d | 0.95 (0.60, 1.52) | |
| | | | | | | Fermented whole milk | Per 50 g/d | 0.84 (0.66, 1.05) | |
| | | | | | | Fermented low-fat milk | Per 50 g/d | 1.03 (0.95, 1.11) | |
| | | | | | | Whole milk | Per 50 g/d | 1.00 (0.95, 1.06) | |
| | | | | | | Low-fat milk | Per 50 g/d | 0.99 (0.93, 1.06) | |
| | | | | | | Dietary calcium | 1329 vs. 602 mg/d | 0.83 (0.52, 1.34) | |
| Grönberg, 1996, Sweden (47) | The Swedish Twin Registry | 1967–1970 | Nested case-control study; 406 cases, 1208 controls; age: 42–81 y | FFQ, ∼10 food items | Total PC | Milk | 5–9 vs. 0 glasses/d | 0.84 (0.44, 1.57) | |

(*Continued*)

**TABLE 1** (*Continued*)

| First author, publication year, country or region (reference) | Study name | Follow-up period | Study size, age, and no. of cases | Dietary assessment | PC stage or grade | Exposure | Quantity | RR (95% CI) | Adjustment for confounders |
|---|---|---|---|---|---|---|---|---|---|
| Le Marchand, 1994, United States (46) | Hawaii Household Survey | 1975/1980–1992, 13 y | 20,316, age >45 y, 198 cases | FFQ, 13 food items | Total PC | Milk, total PC | >1 glass/d vs. 0 glasses/d | 1.4 (1.0, 2.1) | Age, ethnicity, income |
| | | | | | Localized PC | Milk, age ≤72.5 y | >1 glass/d vs. 0 glasses/d | 1.9 | |
| | | | | | | Milk, age >72.5 y | >1 glass/d vs. 0 glasses/d | 0.7 | |
| | | | | | Regional/distant PC | Milk, age ≤72.5 y | >1 glass/d vs. 0 glasses/d | 2.8 | |
| | | | | | | Milk, age >72.5 y | >1 glass/d vs. 0 glasses/d | 0.6 | |
| Hsing, 1990, United States (45) | Lutheran Brotherhood Cohort Study | 1966–1986, 20 y | 17,633, age ≥35 y, 149 deaths | FFQ, 35 food items | Fatal PC | Dairy | 86–189 vs. ≤26 servings/mo | 1.0 (0.6, 1.7) | Age, tobacco use |
| Ursin, 1990, Norway (44) | NA | 1967–1978, ∼12 y | 13,235, age: 35–74 y, 196 cases | FFQ | Total PC | Milk | ≥2 glasses/d vs. <1 glasses/d | 1.02 (0.76, 1.37)[2] | Age, residence, cigarette smoking |
| Thompson, 1989, United States (43) | Lipid Research Clinics Prevalence Study | 1972–1987, 14 y | 1776, age: 50–84 y, 54 cases | Interview | Total PC | Whole milk | Per cup/d | 0.9 (0.7, 1.1)[3] | Age, diabetes, heart disease, SBP, plasma cholesterol, BMI, current smoking, eggs |
| Mills, 1989, United States (42) | Adventist Health Study | 1976–1982, 6 y | 14,000, age: ≥25 y, 180 cases | FFQ | Total PC | Whole milk | At least daily vs. never | 0.80 (0.54, 1.19) | Age |
| Severson, 1989, United States (41) | Honolulu Heart Program | 1965/1968–1986, ∼17.5 y | 7999, born 1900–1919, 174 cases | FFQ, 20 food items | Total PC | Butter, margarine, and cheese | ≥5 times/wk vs. ≤1 time/wk | 1.47 (0.97, 2.25) | Age |
| | | | | | | Milk | ≥5 times/wk vs. ≤1 time/wk | 1.00 (0.73, 1.38) | |
| Snowdon, 1984, United States (40) | Adventist Mortality Study | 1960–1980, 20 y | 6763, age ≥30 y, 99 deaths | FFQ | Fatal PC | Milk | ≥3 glasses/d vs. <1 glass/d | 2.4 (1.3, 4.3) | Age |
| | | | | | | Cheese | ≥3 times/wk vs. <1 time/wk | 1.5 (0.9, 2.6) | |

[1]ALA, α-linolenic acid; ARIC, Atherosclerosis Risk in Communities; CLUE II, Campaign Against Cancer and Heart Disease; D2, type 2 diabetes; FFQ, food-frequency questionnaire; FH, family history; NA, not applicable; NR, not reported; PC, prostate cancer; PSA, prostate specific antigen; SBP, systolic blood pressure; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants Study.

[2]Estimated CI.

[3]RR (90% CI).

the analysis of nonadvanced prostate cancers, we included studies that reported on low-stage, low-grade, and localized cancers, whereas for the analysis of advanced prostate cancers, we included studies that reported on high-stage, high-grade, non-localized, and advanced cancers.

Statistical heterogeneity in studies was assessed by using $I^2$, which was the amount of total variation that was explained by between-study variation and the $Q$ test (68). We conducted subgroup and meta-regression analyses by study characteristics to investigate potential sources of heterogeneity. Small study bias, such as publication bias, was assessed with funnel plots, Egger's test (69), and Begg's test (70), and results were considered to indicate potential small study bias at $P < 0.10$. We used the trim-and-fill method to assess the potential influence of small study bias on results (71), with the assumption that these effects were due to publication bias. We conducted sensitivity analyses by excluding one study at a time to explore whether results were robust to the influence of single studies. Subgroup and meta-regression analyses by study characteristics were conducted to investigate potential sources of heterogeneity. Stata version 10.1 software (StataCorp) was used for statistical analyses.

## RESULTS

Thirty-two prospective studies (37 publications) (14–32, 40–57) could be included in the analysis of dairy product and calcium intake and prostate cancer risk (Table 1, **Supplemental Figure 1**). Five of these studies reported only on prostate cancer mortality (4 publications) (25, 40, 45, 52), and one study reported only on advanced prostate cancer (55), and these were included in subgroup analyses by stage or mortality (**Tables 2** and **3**). Six of the studies were from Europe, 21 studies were from the United States, 4 studies were from Asia, and one study was from Australia. A summary of study characteristics of included studies is provided in Table 1.

### Total dairy products

Fifteen cohort studies (14–17, 19–21, 23, 24, 26, 28, 32, 51, 53, 57) investigated total dairy product intake and prostate cancer risk and included 38,107 cases in 848,395 participants. The summary RR for highest compared with lowest intakes was 1.09 (95% CI: 1.02, 1.17), with moderate heterogeneity ($I^2$ = 43%, $P$-heterogeneity = 0.04 (**Supplemental Figure 2**A). In the dose-response analysis, the summary RR was 1.07 (95% CI: 1.02, 1.12, $I^2$ = 44%, $P$-heterogeneity = 0.04, $n$ = 15) per 400 g/d (**Figure 1**). The summary RR for the dose-response analysis ranged from 1.06 (95% CI: 1.02, 1.10) when the NHANES I (57) was excluded to 1.07 (95% CI: 1.02, 1.12) when the Cancer Prevention Study 2 Nutrition Cohort (53) was excluded. There was an indication of small study effects with Egger's test ($P$ = 0.08) and Begg's test ($P$ = 0.02). The exclusion of one small and outlying study (57) made Egger's test nonsignificant (Egger's test = 0.22, Begg's test = 0.08), and the summary estimate remained similar (summary RR: 1.06; 95% CI: 1.02, 1.10), but heterogeneity was reduced ($I^2$ = 27%). Alternatively, by using the trim-and-fill method, the summary RR became 1.04 (95% CI: 0.99, 1.09) when 5 studies were added to the analysis. There was no evidence of a nonlinear association between total dairy product intake and prostate cancer risk ($P$-nonlinearity = 0.99) (**Figure 2**A, **Supplemental Table 1**). There was no association in the 7 studies (6 publications) that investigated high compared with low dairy product intakes and fatal prostate cancer (Table 2) (15, 22, 32, 45, 52, 72), and results were similar in the dose-response analysis (Figure 1).

### Milk

Fifteen cohort studies (16, 18, 19, 22, 23, 26, 27, 41, 44, 46–48, 51, 54, 57) were included in the analysis of milk intake and prostate cancer risk, including a total of 11,392 cases in 566,146 participants. One of these studies was excluded from the dose-response analysis because only a high compared with low comparison was reported (44). The summary RR for high compared with low intakes was 1.11 (95% CI: 1.03, 1.21) with low heterogeneity ($I^2$ = 21%, $P$-heterogeneity = 0.22) (Supplemental Figure 2B). The summary RR for a 200-g/d increase in intake was 1.03 (95% CI: 1.00, 1.06; $P$-association = 0.04) with no evidence of heterogeneity ($I^2$ = 9%, $P$-heterogeneity = 0.36) (**Figure 3**). In a sensitivity analysis, the summary RR ranged from 1.02 (95% CI: 1.00, 1.05) when the NHANES (57) was excluded to 1.04 (95% CI: 1.00, 1.07) when the EPIC (European Prospective Investigation into Cancer and Nutrition) study was excluded (27). There was an indication of small study effects with Egger's test ($P$ = 0.06) but not Begg's test ($P$ = 0.66). The exclusion of the same small study (57) as in the total dairy analysis made Egger's test nonsignificant ($P$ = 0.12) and slightly attenuated results (summary RR: 1.02; 95% CI: 1.00, 1.05; $I^2$ = 0%). Alternatively, by using the trim-and-fill method, 2 studies were added to the analysis, and the association was attenuated and no longer significant (summary RR: 1.02; 95% CI: 0.98, 1.06). There was some indication of a nonlinear association between milk intake and prostate cancer risk ($P$-nonlinearity = 0.08) with risk increasing rapidly at low intakes but flattening from ∼200 g/d (Figure 2B, **Supplemental Table 2**). There was no association between milk intake and fatal prostate cancer (Table 2, Figure 3) (25, 40).

### Whole milk

Eight cohort studies (21–23, 32, 42, 43, 48, 57) were included in the analysis of whole=milk intake and prostate cancer and included 19,664 cases in 448,719 participants. Two studies reported only continuous estimates and were excluded from the high compared with low analysis (43, 48). The summary RR for high compared with low intakes was 0.92 (95% CI: 0.85, 0.99; $I^2$ = 0%, $P$-heterogeneity = 0.69) (**Supplemental Figure 3**A). The summary RR was 0.98 (95% CI: 0.95, 1.01; $I^2$ = 0%, $P$-heterogeneity = 0.48) per 200 g/d (**Supplemental Figure 4**). The summary RR ranged from 0.97 (95% CI: 0.93, 1.02) when the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study (23) was excluded to 0.99 (95% CI: 0.96, 1.02) when the Multiethnic Cohort Study (21) was excluded. There was some evidence of publication bias with Egger's test ($P$ = 0.04) but not Begg's test ($P$ = 0.11). There was no evidence of a nonlinear association between whole-milk intake and prostate cancer risk ($P$-nonlinearity = 0.32) (Figure 2C, **Supplemental Table 3**). There was no significant association between whole-milk intake and fatal prostate cancer (Supplemental Figure 4) (22, 32).

**TABLE 2**
Subgroup analyses of milk and dairy product intakes and prostate cancer risk (high compared with low)[1]

| | Dairy products | | | | | Milk | | | | | Cheese | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | RR (95% CI) | $I^2$, % | P-heterogeneity[2] | P-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$, % | P-heterogeneity[2] | P-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$, % | P-heterogeneity[2] | P-heterogeneity[3] |
| All studies | 15 | 1.09 (1.02, 1.17) | 42.9 | 0.04 | — | 15 | 1.11 (1.03, 1.21) | 20.6 | 0.22 | — | 11 | 1.07 (1.01, 1.13) | 0 | 0.56 | — |
| Duration of follow-up, y | | | | | | | | | | | | | | | |
| <10 | 8 | 1.14 (1.03, 1.26) | 53.7 | 0.04 | 0.43 | 7 | 1.13 (1.00, 1.28) | 33.6 | 0.17 | 0.88 | 7 | 1.05 (0.98, 1.12) | 0 | 0.62 | 0.44 |
| ≥10 | 7 | 1.06 (0.96, 1.17) | 35.7 | 0.16 | | 8 | 1.11 (0.98, 1.25) | 17.7 | 0.29 | | 4 | 1.11 (0.97, 1.28) | 16.5 | 0.31 | |
| Outcome | | | | | | | | | | | | | | | |
| Nonadvanced | 8 | 1.08 (1.00, 1.18) | 20.5 | 0.27 | 0.83/0.74[4] | 3 | 1.14 (0.98, 1.32) | 7.8 | 0.34 | 0.99/0.92[4] | 3 | 1.03 (0.95, 1.12) | 0 | 0.52 | 0.15/0.52[4] |
| Advanced | 10 | 0.92 (0.79–1.08) | 34.5 | 0.13 | | 3 | 1.09 (0.86, 1.38) | 0 | 0.60 | | 4 | 1.18 (1.00, 1.41) | 0 | 0.58 | |
| Metastatic | 1 | 1.43 (0.91, 2.30) | — | — | | 0 | — | — | — | | 1 | 1.29 (0.88, 1.90) | — | — | |
| Fatal | 7 | 1.11 (0.97, 1.27) | 0 | 0.60 | | 2 | 1.38 (0.49, 3.86) | 88.1 | 0.004 | | 3 | 1.17 (0.75, 1.81) | 20.8 | 0.28 | |
| Geographic location | | | | | | | | | | | | | | | |
| Europe | 2 | 1.42 (0.92, 2.20) | 38.1 | 0.20 | 0.47 | 6 | 1.04 (0.94, 1.14) | 0 | 0.96 | 0.24 | 4 | 1.08 (0.97, 1.20) | 0 | 0.48 | 0.94 |
| America | 11 | 1.06 (1.01, 1.12) | 21.5 | 0.24 | | 7 | 1.22 (1.05, 1.41) | 34.3 | 0.17 | | 5 | 1.06 (0.98, 1.13) | 0 | 0.44 | |
| Asia | 2 | 1.25 (0.77, 2.03) | 80.8 | 0.02 | | 2 | 1.15 (0.66, 2.00) | 80.4 | 0.02 | | 2 | 1.09 (0.70, 1.68) | 54.1 | 0.14 | |
| Cases, *n* | | | | | | | | | | | | | | | |
| <500 | 5 | 1.51 (1.13, 2.01) | 36.2 | 0.18 | 0.18 | 11 | 1.20 (1.04, 1.38) | 27.8 | 0.18 | 0.11 | 5 | 1.14 (0.89, 1.46) | 28.9 | 0.23 | 0.18 |
| 500 to <1500 | 4 | 1.02 (0.81, 1.29) | 66.1 | 0.03 | | 2 | 1.09 (0.93, 1.27) | 0 | 0.85 | | 2 | 1.15 (0.98, 1.34) | 0 | 0.72 | |
| ≥1500 | 6 | 1.07 (1.02, 1.11) | 0 | 0.94 | | 2 | 1.04 (0.96, 1.14) | 0 | 0.52 | | 4 | 1.04 (0.97, 1.11) | 0 | 0.88 | |
| Adjustment for potential confounding factors | | | | | | | | | | | | | | | |
| Alcohol | | | | | | | | | | | | | | | |
| Yes | 5 | 1.20 (0.99, 1.45) | 55.5 | 0.06 | 0.61 | 2 | 1.55 (1.01, 2.37) | 7.2 | 0.30 | 0.12 | 4 | 1.06 (0.96, 1.18) | 0 | 0.67 | 1.00 |
| No | 10 | 1.08 (1.00, 1.17) | 41.9 | 0.08 | | 13 | 1.09 (1.02, 1.17) | 18.2 | 0.27 | | 7 | 1.08 (0.99, 1.17) | 16.1 | 0.31 | |
| Smoking | | | | | | | | | | | | | | | |
| Yes | 10 | 1.11 (1.01, 1.22) | 61.7 | 0.005 | 0.82 | 6 | 1.12 (0.99, 1.26) | 43.9 | 0.11 | 0.69 | 7 | 1.06 (0.99, 1.13) | 0 | 0.63 | 0.72 |
| No | 5 | 1.09 (0.99, 1.20) | 0 | 0.93 | | 9 | 1.10 (0.98, 1.23) | 17.5 | 0.29 | | 4 | 1.11 (0.94, 1.32) | 28.8 | 0.24 | |
| BMI, weight, WHR | | | | | | | | | | | | | | | |
| Yes | 10 | 1.07 (1.01, 1.14) | 29.2 | 0.18 | 0.34 | 5 | 1.06 (0.99, 1.14) | 0 | 0.79 | 0.21 | 7 | 1.06 (1.00, 1.12) | 0 | 0.45 | 0.44 |
| No | 5 | 1.27 (1.00, 1.63) | 60.3 | 0.04 | | 10 | 1.19 (1.02, 1.38) | 34.9 | 0.13 | | 4 | 1.15 (0.94, 1.41) | 0 | 0.51 | |
| Physical activity | | | | | | | | | | | | | | | |
| Yes | 8 | 1.13 (1.04, 1.22) | 41.2 | 0.10 | 0.36 | 3 | 1.25 (0.90, 1.75) | 46.8 | 0.15 | 0.61 | 5 | 1.08 (0.99, 1.18) | 0 | 0.76 | 0.69 |
| No | 7 | 1.05 (0.93, 1.19) | 48.0 | 0.07 | | 12 | 1.10 (1.01, 1.20) | 18.4 | 0.26 | | 6 | 1.08 (0.97, 1.20) | 24.9 | 0.25 | |
| Diabetes | | | | | | | | | | | | | | | |
| Yes | 5 | 1.08 (1.03, 1.13) | 0 | 0.47 | 0.70 | 1 | 1.08 (0.90, 1.29) | | | 0.77 | 2 | 1.10 (0.96, 1.26) | 0 | 0.61 | 0.66 |
| No | 10 | 1.12 (0.97, 1.30) | 56.6 | 0.01 | | 14 | 1.13 (1.03, 1.23) | 26.1 | 0.17 | | 9 | 1.06 (0.99, 1.13) | 2.7 | 0.41 | |
| PSA test | | | | | | | | | | | | | | | |
| Yes | 2 | 1.07 (1.02, 1.12) | 0 | 0.49 | 0.85 | 0 | — | — | — | NC | 1 | 1.08 (0.96, 1.22) | — | — | 0.80 |
| No | 13 | 1.11 (1.01, 1.23) | 49.7 | 0.02 | | 15 | 1.11 (1.03, 1.21) | 20.6 | 0.22 | | 10 | 1.06 (0.99, 1.13) | 0 | 0.47 | |
| Meat | | | | | | | | | | | | | | | |
| Yes | 5 | 1.07 (1.02, 1.12) | 0 | 0.95 | 0.86 | 0 | — | — | — | NC | 2 | 1.07 (0.97, 1.19) | 0 | 0.82 | 0.88 |
| No | 10 | 1.14 (1.00, 1.31) | 62.0 | 0.005 | | 15 | 1.11 (1.03, 1.21) | 20.6 | 0.22 | | 9 | 1.07 (0.99, 1.15) | 7.1 | 0.38 | |

*(Continued)*

**TABLE 2** (*Continued*)

| | Dairy products | | | | | Milk | | | | | Cheese | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | RR (95% CI) | $I^2$, % | *P*-heterogeneity[2] | *P*-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$, % | *P*-heterogeneity[2] | *P*-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$, % | *P*-heterogeneity[2] | *P*-heterogeneity[3] |
| Tomatoes | | | | | | | | | | | | | | | |
| Yes | 3 | 1.06 (1.01, 1.11) | 0 | 0.99 | 0.64 | 1 | 1.26 (0.91, 1.74) | — | — | 0.46 | 2 | 1.18 (0.91, 1.53) | 55.0 | 0.14 | 0.40 |
| No | 12 | 1.13 (1.02, 1.25) | 53.9 | 0.01 | | 14 | 1.11 (1.02, 1.20) | 22.9 | 0.21 | | 9 | 1.05 (0.98, 1.12) | 0 | 0.68 | |
| α-Linolenic acid | | | | | | | | | | | | | | | |
| Yes | 2 | 1.06 (1.01, 1.11) | 0 | 0.89 | 0.64 | 0 | — | — | — | NC | 1 | 1.08 (0.96, 1.22) | — | — | 0.80 |
| No | 13 | 1.12 (1.02, 1.24) | 49.8 | 0.02 | | 15 | 1.11 (1.03, 1.21) | 20.6 | 0.22 | | 10 | 1.06 (0.99, 1.13) | 0 | 0.47 | |
| Energy intake | | | | | | | | | | | | | | | |
| Yes | 14 | 1.10 (1.02, 1.17) | 46.9 | 0.03 | 0.94 | 8 | 1.12 (1.01, 1.24) | 28.5 | 0.20 | 0.82 | 10 | 1.07 (1.01, 1.13) | 0 | 0.56 | 0.36 |
| No | 1 | 1.12 (0.51, 2.47) | — | — | | 7 | 1.10 (0.95–1.28) | 23.3 | 0.25 | | 1 | 0.84 (0.52, 1.36) | — | — | |

[1]NC, not calculated; PSA, prostate specific antigen; WHR, waist-to-hip ratio.
[2]Within each subgroup.
[3]Between subgroups with metaregression analysis.
[4]*P*-heterogeneity between nonadvanced and fatal prostate cancers.

## Low-fat milk

Six cohort studies (21–23, 32, 48, 57) were included in the analysis of low-fat milk and prostate cancer risk and included 19,430 cases in 432,943 participants. One study only reported a continuous result and was excluded from the dose-response analysis (48). Two of these studies reported on skim and low-fat milk combined (21, 32). The summary RR for high compared with low intakes was 1.14 (95% CI: 1.05, 1.25; $I^2$ = 51%, *P*-heterogeneity = 0.09) (Supplemental Figure 3B). The summary RR per 200 g/d was 1.06 (95% CI: 1.01, 1.11; $I^2$ = 67%, *P*-heterogeneity = 0.01) (**Supplemental Figure 5**). The summary RR ranged from 1.04 (95% CI: 1.00, 1.08) when the Physicians Health Study was excluded to 1.08 (95% CI: 1.02, 1.14) when the NIH-AARP Diet and Health Study was excluded. There was evidence of a nonlinear association between low-fat milk and prostate cancer (*P*-nonlinearity $<$ 0.0001) with a flattening of the curve between 300 and 400 g/d (Figure 2D, **Supplemental Table 4**). There was no significant association between low-fat milk and fatal prostate cancer (Supplemental Figure 5) (22, 32).

## Cheese

Eleven cohort studies (16, 19, 21–23, 26, 27, 32, 48, 54, 57) were included in the analysis of cheese intake and prostate cancer risk and included 22,950 cases in 887,759 participants. The summary RR for high compared with low intakes was 1.07 (95% CI: 1.01, 1.13), and there was no evidence of heterogeneity ($I^2$ = 0%, *P*-heterogeneity = 0.56) (**Supplemental Figure 6**A). The summary RR was 1.10 (95% CI: 1.03, 1.18; $I^2$ = 0%, *P*-heterogeneity = 0.93) per 50 g/d (**Supplemental Figure 7**). The summary RR ranged from 1.09 (95% CI: 1.02, 1.17) when the CLUE 11 (Campaign Against Cancer and Heart Disease) cohort (19) was excluded to 1.11 (95% CI: 1.02, 1.20) when the NIH-AARP Diet and Health study (22) was excluded. There was no evidence of small study effects with either Egger's test (*P* = 0.57) or Begg's test (*P* = 0.44). There was no evidence of a nonlinear association between cheese intake and prostate cancer risk (*P*-nonlinearity = 0.32) (**Supplemental Table 5**, **Supplemental Figure 8**A). There was no significant association between cheese intake and fatal prostate cancer (Table 2, Supplementary Figure 7) (22, 25, 40).

## Yogurt

Six cohort studies were included in the analysis of yogurt intake and prostate cancer risk (16, 21, 22, 26, 27, 48) (one of these studies only provided a continuous result and was not included in the analysis of highest compared with lowest intakes (48). The summary RR for high compared with low intakes was 1.12 (95% CI: 0.97, 1.29) with high heterogeneity ($I^2$ = 67%, *P*-heterogeneity = 0.02) (Supplemental Figure 6B). The summary RR per 100 g/d was 1.08 (95% CI: 0.93, 1.24) and also with high heterogeneity ($I^2$ = 82%, *P*-heterogeneity $<$ 0.0001) (**Supplemental Figure 9**). The summary RR ranged from 1.02 (95% CI: 0.89, 1.18) when the NHANES was excluded (57) to 1.14 (95% CI: 0.88, 1.48) when the NIH-AARP Diet and Health Study (22) was excluded. There was no evidence of small study effects with Begg's test (*P* = 0.62) or Egger's test (*P* = 0.45). There was no evidence of a nonlinear association between yogurt intake and

**TABLE 3**
Subgroup analyses of total, dietary, and supplemental calcium intakes and prostate cancer incidence (high compared with low)[1]

| | Total calcium | | | | | Dietary calcium | | | | | Supplemental calcium | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | RR (95% CI) | $I^2$ (%) | P-heterogeneity[2] | P-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$ (%) | P-heterogeneity[2] | P-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$ (%) | P-heterogeneity[2] | P-heterogeneity[3] |
| All studies | 9 | 1.10 (1.01, 1.21) | 50.4 | 0.04 | — | 15 | 1.18 (1.08, 1.30) | 53.4 | 0.008 | — | 9 | 1.00 (0.95, 1.05) | 0 | 0.68 | — |
| Duration of follow-up, y | | | | | | | | | | | | | | | |
| <10 | 6 | 1.05 (0.98, 1.14) | 26.8 | 0.23 | 0.05 | 10 | 1.16 (1.04, 1.28) | 52.0 | 0.03 | 0.60 | 6 | 1.01 (0.96, 1.06) | 0 | 0.54 | 0.63 |
| ≥10 | 3 | 1.25 (1.09, 1.43) | 3.2 | 0.36 | | 5 | 1.24 (1.00, 1.54) | 43.0 | 0.14 | | 3 | 0.96 (0.81, 1.14) | 0 | 0.49 | |
| Outcome | | | | | | | | | | | | | | | |
| Nonadvanced | 6 | 1.05 (0.96, 1.14) | 0 | 0.42 | 0.75/ 0.37[4] | 6 | 1.21 (1.06, 1.37) | 15.3 | 0.32 | 0.66/0.59[4] | 6 | 1.02 (0.96, 1.08) | 0 | 0.85 | 0.21/0.04[4] |
| Advanced | 7 | 1.03 (0.73, 1.45) | 72.2 | 0.001 | | 9 | 1.00 (0.77, 1.31) | 55.4 | 0.02 | | 7 | 0.99 (0.88, 1.11) | 0 | 0.61 | |
| Metastatic | 0 | | | | | 0 | | | | | 0 | | | | |
| Fatal | 2 | 1.39 (0.77, 2.50) | 28.4 | 0.24 | | 1 | 1.36 (0.97, 1.92) | — | — | | 2 | 1.50 (1.13, 1.99) | 0 | 0.92 | |
| Geographic location | | | | | | | | | | | | | | | |
| Europe | 1 | 2.43 (1.05, 5.62) | — | — | 0.92 | 3 | 1.28 (1.02, 1.61) | 65.1 | 0.06 | 0.45 | 0 | — | — | — | NC |
| America | 8 | 1.08 (1.00, 1.18) | 47.3 | 0.08 | | 9 | 1.16 (1.02, 1.32) | 52.6 | 0.03 | | 9 | 1.00 (0.95, 1.05) | 0 | 0.68 | |
| Asia | 1 | 1.25 (0.89, 1.75) | — | — | | 3 | 1.13 (0.93, 1.37) | 0 | 0.52 | | 0 | — | — | — | |
| Cases, *n* | | | | | | | | | | | | | | | |
| <500 | 3 | 1.25 (0.87–1.79) | 49.1 | 0.14 | 0.34 | 6 | 1.29 (1.03, 1.61) | 27.8 | 0.23 | 0.26 | 3 | 0.85 (0.66, 1.10) | 0 | 0.99 | 0.39 |
| 500 to <1500 | 0 | — | — | — | | 3 | 1.22 (0.88, 1.68) | 72.9 | 0.03 | | 1 | 1.05 (0.84, 1.31) | — | — | |
| ≥1500 | 6 | 1.09 (1.00, 1.19) | 55.6 | 0.05 | | 6 | 1.11 (1.01, 1.21) | 40.6 | 0.14 | | 5 | 1.01 (0.96–1.06) | 0.5 | 0.40 | |
| Adjustment for potential confounding factors | | | | | | | | | | | | | | | |
| Alcohol | | | | | | | | | | | | | | | |
| Yes | 7 | 1.12 (1.01, 1.23) | 31.7 | 0.19 | 0.69 | 2 | 1.46 (0.70, 3.03) | 90.1 | 0.001 | 0.79 | 2 | 0.96 (0.88, 1.05) | 0 | 0.82 | 0.27 |
| No | 2 | 1.42 (0.63, 3.21) | 75.1 | 0.05 | | 13 | 1.18 (1.08, 1.28) | 18.5 | 0.26 | | 7 | 1.02 (0.96, 1.09) | 0 | 0.64 | |
| Smoking | | | | | | | | | | | | | | | |
| Yes | 4 | 1.14 (0.98, 1.32) | 76.0 | 0.006 | 0.75 | 5 | 1.27 (1.03, 1.57) | 82.1 | <0.0001 | 0.59 | 4 | 0.98 (0.92, 1.04) | 0 | 0.88 | 0.23 |
| No | 5 | 1.09 (0.97, 1.22) | 0 | 0.50 | | 10 | 1.16 (1.06, 1.28) | 0 | 0.84 | | 5 | 1.05 (0.96, 1.15) | 0 | 0.50 | |
| BMI, weight, WHR | | | | | | | | | | | | | | | |
| Yes | 7 | 1.08 (0.98, 1.20) | 57.2 | 0.03 | 0.42 | 6 | 1.15 (1.03, 1.29) | 65.8 | 0.01 | 0.55 | 6 | 0.99 (0.94, 1.05) | 0 | 0.71 | 0.28 |
| No | 2 | 1.22 (1.00, 1.47) | 0 | 0.85 | | 9 | 1.24 (1.05, 1.46) | 32.4 | 0.16 | | 3 | 1.07 (0.95, 1.22) | 0 | 0.48 | |
| Physical activity | | | | | | | | | | | | | | | |
| Yes | 4 | 1.13 (0.92, 1.39) | 78.1 | 0.003 | 0.92 | 4 | 1.41 (1.01, 1.98) | 86.2 | <0.0001 | 0.24 | 4 | 0.97 (0.90, 1.05) | 0 | 0.90 | 0.33 |
| No | 5 | 1.09 (0.99, 1.19) | 0 | 0.73 | | 11 | 1.13 (1.04, 1.22) | 0 | 0.71 | | 5 | 1.02 (0.96, 1.09) | 2.2 | 0.39 | |
| Diabetes | | | | | | | | | | | | | | | |
| Yes | 3 | 1.09 (0.90, 1.31) | 79.7 | 0.007 | 0.80 | 3 | 1.26 (0.92, 1.72) | 83.7 | 0.002 | 0.78 | 2 | 0.96 (0.88, 1.05) | 0 | 1.00 | 0.26 |
| No | 6 | 1.10 (1.00, 1.22) | 9.1 | 0.36 | | 12 | 1.17 (1.06, 1.29) | 27.1 | 0.18 | | 7 | 1.03 (0.96, 1.09) | 0 | 0.65 | |
| PSA test | | | | | | | | | | | | | | | |
| Yes | 2 | 1.03 (0.98, 1.08) | 0 | 0.34 | 0.15 | 2 | 1.04 (0.99, 1.10) | 0 | 0.42 | 0.36 | 2 | 0.96 (0.88, 1.05) | 0 | 1.00 | 0.26 |
| No | 7 | 1.16 (1.04, 1.29) | 35.4 | 0.16 | | 13 | 1.22 (1.09, 1.36) | 45.1 | 0.04 | | 7 | 1.03 (0.96, 1.09) | 0 | 0.65 | |
| Meat | | | | | | | | | | | | | | | |
| Yes | 3 | 1.09 (0.90, 1.31) | 79.7 | 0.007 | 0.80 | 2 | 1.04 (0.99, 1.10) | 0 | 0.42 | 0.36 | 3 | 0.97 (0.90, 1.05) | 0 | 0.76 | 0.34 |
| No | 6 | 1.10 (1.00, 1.22) | 9.1 | 0.36 | | 13 | 1.22 (1.09, 1.36) | 45.1 | 0.04 | | 6 | 1.02 (0.96, 1.09) | 0 | 0.53 | |

*(Continued)*

**TABLE 3** (*Continued*)

| | Total calcium | | | | | Dietary calcium | | | | | Supplemental calcium | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | RR (95% CI) | $I^2$ (%) | *P*-heterogeneity[2] | *P*-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$ (%) | *P*-heterogeneity[2] | *P*-heterogeneity[3] | No. of studies | RR (95% CI) | $I^2$ (%) | *P*-heterogeneity[2] | *P*-heterogeneity[3] |
| Tomatoes | | | | | | | | | | | | | | | |
| Yes | 3 | 1.12 (0.93, 1.34) | 77.2 | 0.01 | 0.92 | 1 | 1.04 (0.98, 1.09) | | | 0.27 | 2 | 0.95 (0.87, 1.04) | 0 | 0.52 | 0.19 |
| No | 6 | 1.10 (0.97, 1.23) | 29.0 | 0.22 | | 14 | 1.22 (1.09, 1.35) | 40.6 | 0.06 | | 7 | 1.03 (0.97, 1.09) | 0 | 0.78 | |
| β-linolenic acid | | | | | | | | | | | | | | | |
| Yes | 2 | 1.15 (0.91, 1.45) | 88.4 | 0.003 | 0.73 | 1 | 1.04 (0.98, 1.09) | — | — | 0.27 | 1 | 0.96 (0.88, 1.05) | — | — | 0.28 |
| No | 7 | 1.08 (0.98, 1.20) | 17.6 | 0.30 | | 14 | 1.22 (1.09, 1.35) | 40.6 | 0.06 | | 8 | 1.02 (0.96, 1.09) | 0 | 0.73 | |
| Energy intake | | | | | | | | | | | | | | | |
| Yes | 7 | 1.10 (0.98, 1.23) | 60.2 | 0.02 | 0.79 | 12 | 1.20 (1.07, 1.34) | 62.2 | 0.002 | 0.85 | 7 | 0.99 (0.94, 1.05) | 0 | 0.68 | 0.45 |
| No | 2 | 1.12 (0.96, 1.32) | 0 | 0.48 | | 3 | 1.17 (0.99, 1.38) | 0 | 0.91 | | 2 | 1.04 (0.88, 1.24) | 10.9 | 0.29 | |

[1]NC, not calculated; PSA, prostate specific antigen; WHR, waist-to-hip ratio.
[2]Within each subgroup.
[3]Between subgroups with metaregression analysis.
[4]*P*-heterogeneity between nonadvanced and fatal prostate cancers.

prostate cancer (*P*-nonlinearity = 0.45) (**Supplemental Table 6**, Supplemental Figure 8B).

## Other dairy products

Other specific types of dairy products were only investigated in a limited number of studies. The summary RR for high compared with low intakes was 1.14 (95% CI: 0.88, 1.49; $I^2$ = 88%, *P*-heterogeneity = 0.005) for skim milk (22, 49), 0.95 (95% CI: 0.83, 1.09; $I^2$ = 0%, *P*-heterogeneity = 0.70) for ice cream (23, 57), and 1.03 (95% CI: 0.89, 1.20; $I^2$ = 0%, *P*-heterogeneity = 0.53) for butter (14, 23) in relation to total prostate cancer and 1.16 (95% CI: 0.98, 1.38; $I^2$ = 0%, *P*-heterogeneity = 0.43) for skim milk in relation to advanced prostate cancer (22, 55) (**Table 4**).

## Total calcium

Nine cohort studies were included in the analysis of total calcium (diet and supplements) intake and prostate cancer risk (16, 17, 19, 21, 24, 28, 30, 31, 53) and included 33,127cases in 750,275 participants. The summary RR for high compared with low intakes was 1.10 (95% CI: 1.01, 1.21; $I^2$ = 50%, *P*-heterogeneity = 0.04) (**Supplemental Figure 10**A). In the dose-response analysis, the summary RR per 400 mg/d was 1.02 (95% CI: 1.01, 1.04) with no evidence of heterogeneity ($I^2$ = 12%, *P*-heterogeneity = 0.33) (**Figure 4**). The summary RR ranged from 1.02 (95% CI: 1.01, 1.03) when the Health Professionals Follow-Up Study (17) was excluded to 1.03 (95% CI: 1.02, 1.05) when the NIH-AARP Diet and Health Study (28) was excluded. There was no evidence of small study effects with Egger's test ($P$ = 0.26) or Begg's test ($P$ = 0.12). There was evidence of a nonlinear association between total calcium intake and prostate cancer risk (*P*-nonlinearity $<$ 0.0001), and risk increased monotonically but more steeply at higher intakes (**Figure 5**A, **Supplemental Table 7**).

## Dietary calcium

Fifteen cohort studies were included in the analysis of dietary calcium and prostate cancer risk (14, 21, 23, 24, 26–31, 48, 51, 53, 56, 57) and included 35,493 cases in 800,879 participants. The summary RR high compared with low intakes was 1.18 (95% CI: 1.08, 1.30) with moderate heterogeneity ($I^2$ = 53%, *P*-heterogeneity = 0.008) (Supplemental Figure 10B). The summary RR per 400 mg/d was 1.05 (95% CI: 1.02, 1.09) with moderate to high heterogeneity ($I^2$ = 49%, *P*-heterogeneity = 0.02) (**Figure 6**). There was no indication of small study effects with Egger's test ($P$ = 0.11) or Begg's test ($P$ = 0.37). The heterogeneity was largely explained by one American study (57), and when excluded, the summary RR was 1.04 (95% CI: 1.02, 1.06; $I^2$ = 6%, *P*-heterogeneity = 0.38). The summary RR ranged from 1.03 (95% CI: 1.01, 1.05) when the ATBC study (23) was excluded to 1.05 (95% CI: 1.03, 1.08) when the NIH-AARP Diet and Health Study (28) was excluded. There was evidence that the association between dietary calcium intake and prostate cancer risk was nonlinear (*P*-nonlinearity $<$ 0.0001), and risk increased significantly above ∼1200 mg/d but was most pronounced above 2000 mg/d (Figure 5B, **Supplemental Table 8**).

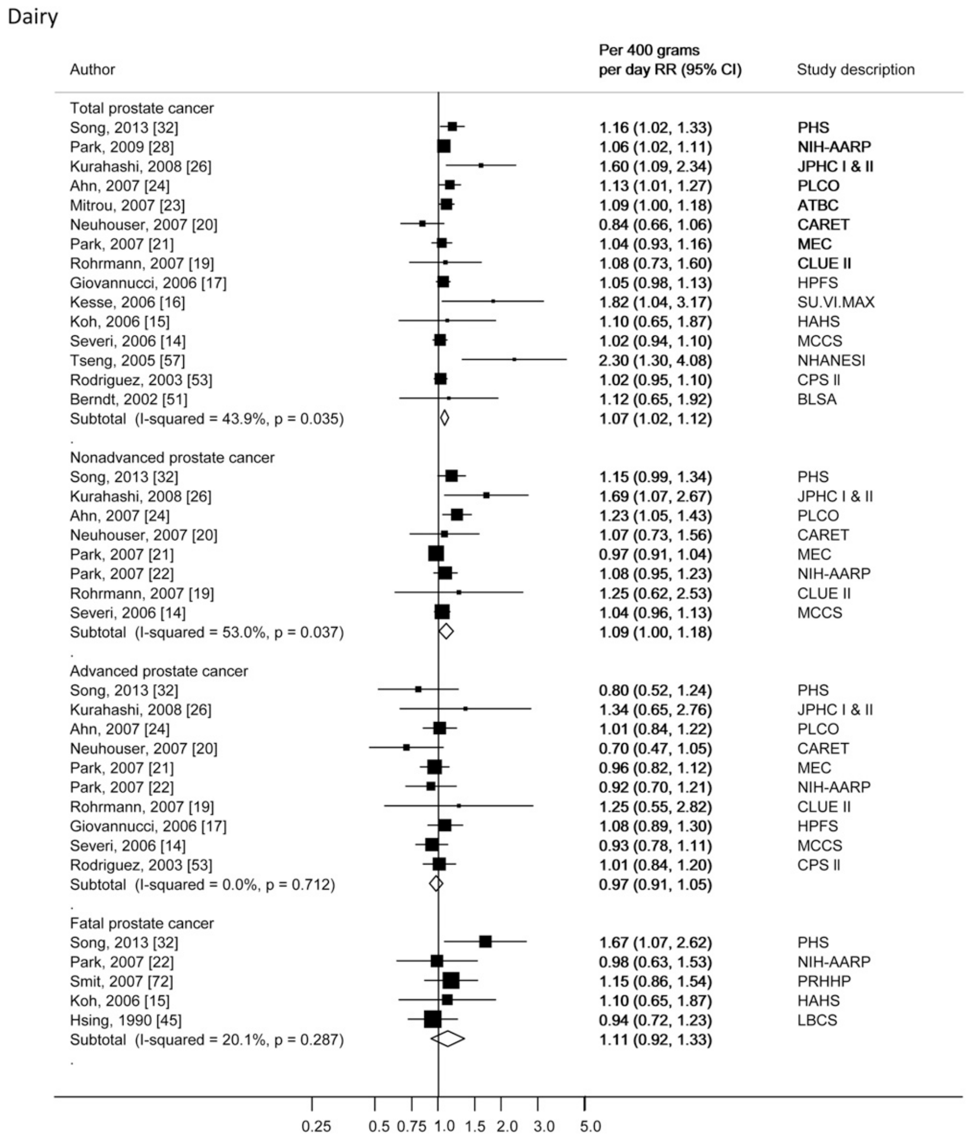


**FIGURE 1** Intake of total dairy products and prostate cancer risk. The RR from each study is represented by a black square and the 95% CIs by the line through the square. Summary RRs (center of open diamond) and 95% CIs (width of open diamond) were calculated per 400-g/d intake by using a random-effects model. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BLSA, Baltimore Longitudinal Study on Aging; CARET, Carotene and Retinol Efficacy Trial; CLUE II, Campaign Against Cancer and Heart Disease; CPS II, Cancer Prevention Study II; HAHS, The Harvard Alumni Health Study; HPFS, Health Professionals Follow-Up Study; JPHC, Japan Public Health Center-Based Prospective Study; LBCS, Lutheran Brotherhood Cohort Study; MCCS, Melbourne Collaborative Cohort Study; MEC, Multiethnic Cohort Study; NIH-AARP, NIH-AARP Diet and Health Study; PHS, Physicians' Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PRHHP, The Puerto Rico Heart Health Program; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants Study.

## Dairy calcium

Seven cohort studies investigated the association between dairy calcium and prostate cancer risk (15, 16, 19, 22, 23, 27, 49) and included 10,493 cases in 479,666 participants. One study was excluded from the dose-response analysis because only a high compared with low comparison was reported (19). The summary RR for high compared with low intakes was 1.13 (95% CI: 1.02, 1.24) with moderate heterogeneity ($I^2$ = 46%, *P*-heterogeneity = 0.08) (**Supplemental Figure 11**A). The summary RR per 400 mg/d was 1.06 (95% CI: 1.02, 1.09) with little evidence of heterogeneity ($I^2$ = 33%, *P*-heterogeneity = 0.19) (**Supplemental Figure 12**A). The summary RR ranged from 1.05 (95% CI: 1.01, 1.09) when the ATBC study was excluded (23) to 1.07 (95% CI: 1.02, 1.13) when the NIH-AARP Diet and Health Study was excluded (28). There was no evidence of small study effects with Egger's test (*P* = 0.31) or Begg's test (*P* = 0.13). There was no evidence of a nonlinear association between dairy calcium intake and prostate cancer risk (*P*-nonlinearity = 0.29) (Figure 5C, **Supplemental Table 9**).

## Nondairy calcium

Four cohort studies investigated the association between nondairy calcium and prostate cancer risk (16, 22, 27, 57) and included 13,067 cases in 442,796 participants. The summary RR for high compared with low intakes was 0.91 (95% CI: 0.79, 1.05; $I^2$ = 15%, *P*-heterogeneity = 0.32) (Supplemental Figure 11B). The summary RR for a 400=mg/d increase in nondairy calcium

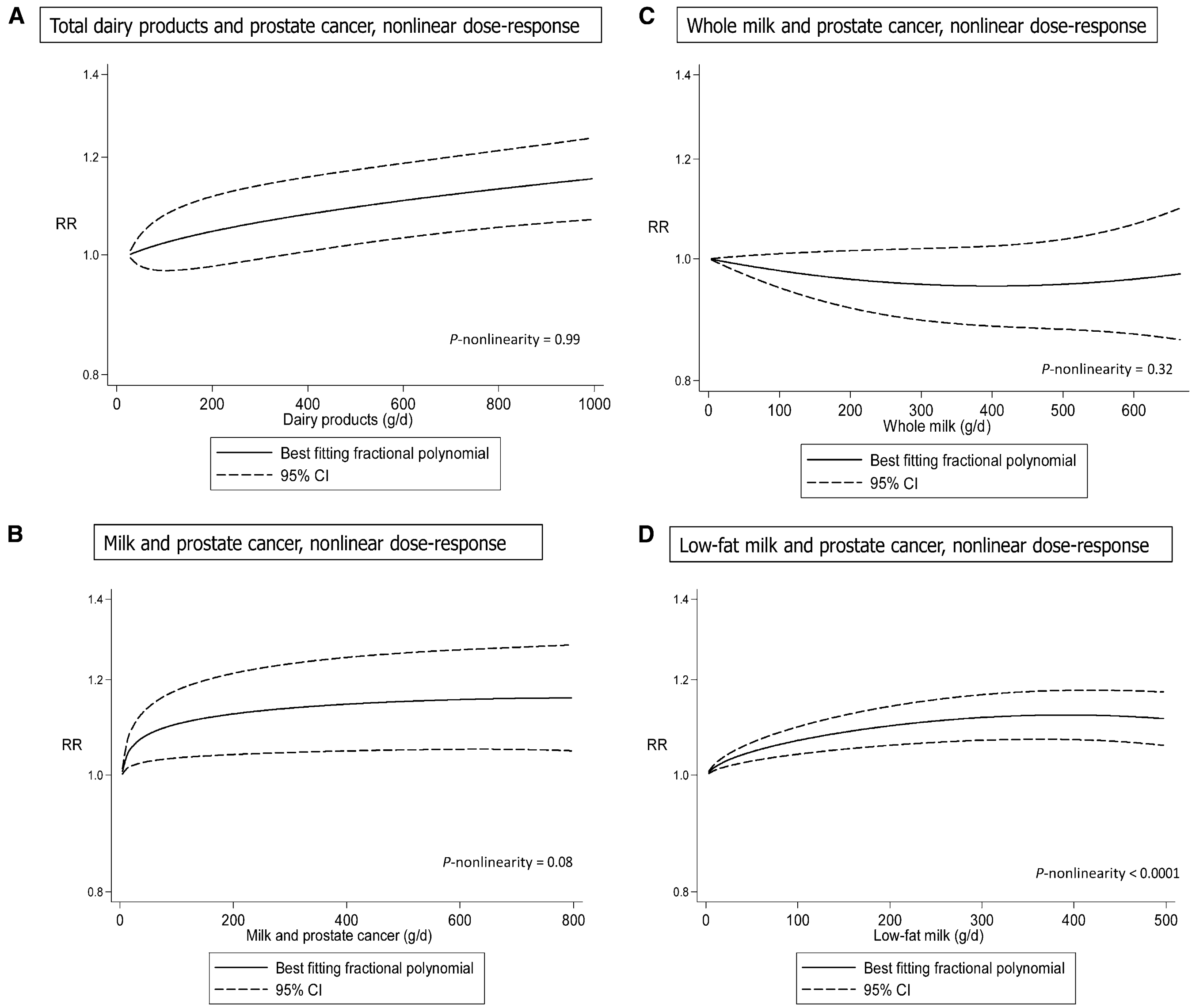


**FIGURE 2** Nonlinear analysis [summary RRs (full lines) and 95% CIs (dashed lines)] of total dairy products (A), milk (B), whole milk (C), and low-fat milk (D) and total prostate cancer risk. The dose-response curve was calculated by using fractional polynomial models, and the test for nonlinearity was based on a log-likelihood test.

was 0.97 (95% CI: 0.90, 1.04; $I^2$ = 0%, *P*-heterogeneity = 0.59) (**Supplemental Figure 13**). The summary RR ranged from 0.95 (95% CI: 0.88, 1.03) when the EPIC study was excluded (27) to 1.04 (95% CI: 0.87, 1.25) when the NIH-AARP Diet and Health Study was excluded (28). There was no evidence of small study effects with Egger's test (*P* = 0.92) or Begg's test (*P* = 1.00), although the number of studies was small. Although the test for nonlinearity was significant (*P*-nonlinearity < 0.0001), there was no association over most of the range of nondairy calcium, and the slight inverse association at very high intakes (>700 mg/d) was driven by one study only (Figure 5D, **Supplemental Table 10**).

## Supplemental calcium

Eight cohort studies (15, 19, 21, 22, 24, 31, 53, 57) and one randomized trial (56) were included in the analysis of supplemental calcium intake and prostate cancer risk and included 30,232 cases in 498,516 participants. Five studies were excluded from the dose-response analysis because there was only a comparison of supplement use compared with not (<3 categories of exposure) (15, 19, 53, 56, 57). The summary RR for high compared with low intakes (or use compared with nonuse) was 1.00 (95% CI: 0.95, 1.05) with no evidence of heterogeneity ($I^2$ = 0%, *P*-heterogeneity = 0.68) (**Supplemental Figure 14**). The summary RR per 400 mg/d was 0.99 (95% CI: 0.96, 1.01; $I^2$ = 0%, *P*-heterogeneity = 0.63) (**Supplemental Figure 15**). The summary RR ranged from 0.99 (95% CI: 0.93, 1.06) when the NIH-AARP Diet and Health Study was excluded (28) to 0.99 (95% CI: 0.96, 1.01) when the Prostate Cancer Prevention Trial was excluded (56). There was no evidence of small study effects with Egger's test (*P* = 0.36) or Begg's test (*P* = 0.31). There was no evidence of a nonlinear association between supplemental calcium intake and prostate cancer risk (*P*-nonlinearity = 0.74) (**Supplementary Table 11**, **Supplemental Figure 16**). Supplemental calcium was associated with increased risk of fatal prostate cancer (summary RR: 1.50; 95% CI: 1.13, 1.99; $I^2$ = 0%, *P*-heterogeneity = 0.92); however, the result was based on only 2 studies (Table 3, Supplemental Figure 15) (17, 22).

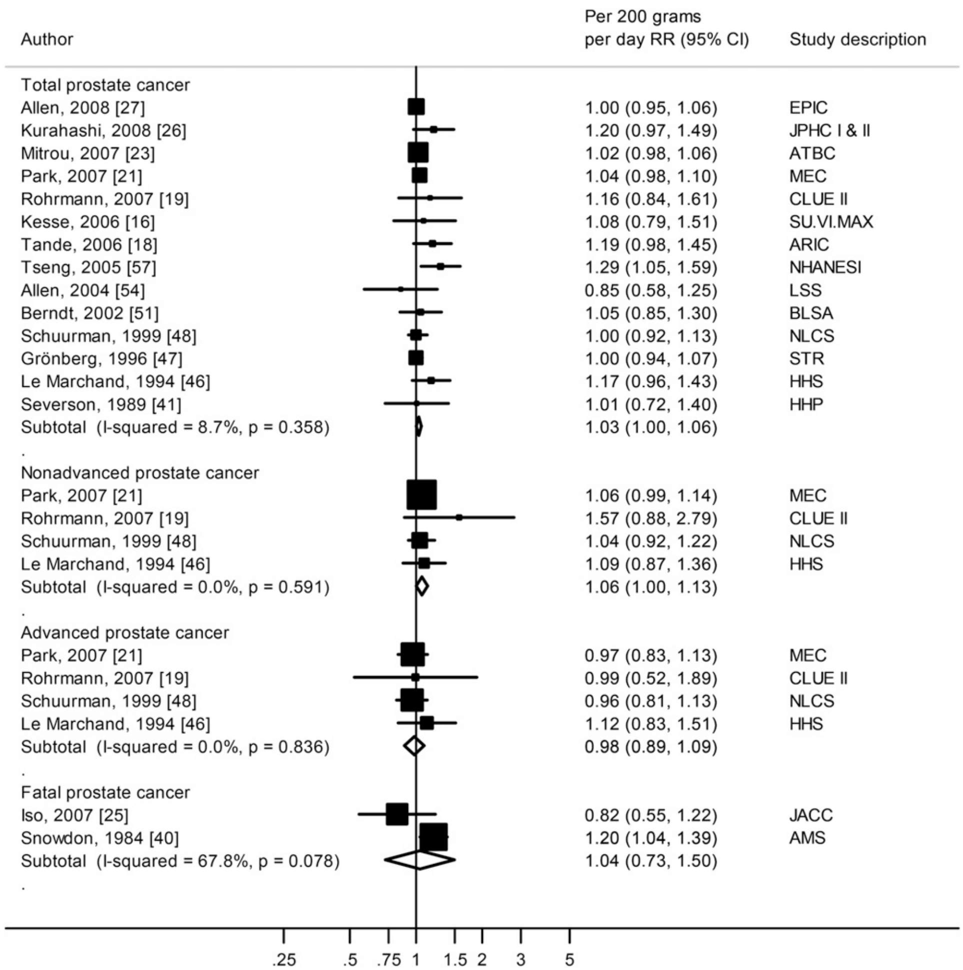


**FIGURE 3** Intake of milk and prostate cancer risk. The RR from each study is represented by a black square and the 95% CIs by the line through the square. Summary RRs (center of open diamond) and 95% CIs (width of open diamond) were calculated per 200-g/d intake by using a random-effects model. AMS, Adventist Mortality Study; ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BLSA, Baltimore Longitudinal Study on Aging; CLUE II, Campaign Against Cancer and Heart Disease; EPIC, European Prospective Investigation into Cancer and Nutrition; HHP, Honolulu Heart Program; HHS, Hawaii Household Survey; JACC, Japan Collaborative Cohort study; JPHC, Japan Public Health Center-Based Prospective Study; LSS, Life Span Study; MEC, Multiethnic Cohort Study; NLCS, Netherlands Cohort Study; STR, The Swedish Twin Registry; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants Study.

## Subgroup, sensitivity, and meta-regression analyses

In subgroup analyses of total dairy products, milk, and cheese and prostate cancer, there were positive associations in most strata, although results were not significant in many of subgroups (Table 2). There was no evidence that results differed by subgroups (*P*-heterogeneity $\geq$ 0.11). There was no evidence of a difference between subgroups in the analyses of dietary calcium; however, for total calcium, results were stronger in the subgroup of studies with $\geq$10 compared with $<$10 y of follow-up (*P*-heterogeneity = 0.05) (Table 3). For supplemental calcium, there was consistent evidence of no association across subgroups except in the analysis of fatal prostate cancer in which there was increased risk (*P*-heterogeneity = 0.04) compared with for nonadvanced cancers; however, this result was based on only 2 studies. In a sensitivity analysis, we included one study that did not quantify skim-milk intake but compared intake of skim milk with whole milk and prostate cancer risk (62) (and was originally excluded). The summary RR was 1.30 (95% CI: 0.96, 1.75; $I^2$ = 87%, *P*-heterogeneity $<$ 0.0001).

Because some studies reported results for dairy foods adjusted for calcium intake as an exploratory analysis to investigate whether the calcium content of dairy products may have accounted for the association with prostate cancer risk, we conducted additional analyses by comparing results with and without adjustment for calcium. The summary RR for high compared with low intakes of total dairy products was 1.15 (95% CI: 1.02, 1.29; $I^2$ = 58%, *P*-heterogeneity = 0.04) without adjustment for calcium and 0.99 (95% CI: 0.92, 1.07; $I^2$ = 0%, *P*-heterogeneity = 0.65) with adjustment for calcium (16, 17, 22–24, 57), whereas the summary RR for total milk was 1.27 (95% CI: 0.88, 1.84; $I^2$ = 46%, *P*-heterogeneity = 0.15) without adjustment for calcium and 0.86 (95% CI: 0.71, 1.05; $I^2$ = 0%, *P*-heterogeneity = 0.99) with adjustment for calcium (16, 23, 57).

To assess possible biased reporting, we conducted additional analyses in the 6 studies (16, 19, 20, 23, 26, 57) that were common in the analysis of total dairy products, milk, and cheese intakes. Summary RRs in the dose-response analyses were 1.19 (95% CI: 1.02, 1.38) for total dairy products, 1.06 (95% CI: 1.00, 1.12) for milk, and 1.12 (95% CI: 0.99, 1.27) for cheese. With the restriction of analyses to the 5 studies (21, 24, 28, 30, 31) that were common for the analyses of total and dietary calcium, the summary RR was 1.01

**TABLE 4**
Other dairy products and prostate cancer

| | Total prostate cancer | | | | Advanced prostate cancer | | | |
|---|---|---|---|---|---|---|---|---|
| Type of dairy product | No. of studies | RR (95% CI) | $I^2$ | *P*-heterogeneity | No. of studies | RR (95% CI) | $I^2$ | *P*-heterogeneity |
| Skim milk | 2 | 1.14 (0.88, 1.49) | 87.5 | 0.005 | 2 | 1.16 (0.98, 1.38) | 0 | 0.43 |
| Ice cream | 3 | 0.95 (0.83, 1.09) | 0 | 0.70 | 0 | — | — | — |
| Butter | 2 | 1.03 (0.89, 1.20) | 0 | 0.53 | 1 | 1.03 (0.53, 2.00) | — | — |

(95% CI: 1.00, 1.03) for total calcium and 1.02 (95% CI: 1.00, 1.05) for dietary calcium. With the restriction of analyses to the 6 studies (21, 24, 28, 31, 56, 57) that were common for the analyses of dietary and supplementary calcium, the summary RR was 1.05 (95% CI: 0.99, 1.12) for dietary calcium and 0.99 (95% CI: 0.93, 1.04) for high supplemental calcium compared with low supplemental calcium.

## DISCUSSION

We showed increased risk of prostate cancer with high intakes of total dairy products, milk, cheese, low-fat milk and skim milk combined, total calcium, dietary calcium, and dairy calcium but a significant inverse association with whole milk. No association was observed between other subtypes of dairy products (skim milk, ice cream, and butter) and prostate cancer risk, but the number of studies was limited. With the use of fractional polynomial models, we showed evidence of a nonlinear positive association between milk, total calcium, and dietary calcium and prostate cancer. Risk increased rapidly when increasing milk intake from 0 to 100–200 g/d but reached a plateau with little additional increase in risk. This result was in contrast to results for the other dairy foods for which associations appeared to be linear. For total and dietary calcium, we observed nonlinear positive associations that were most pronounced at the higher intakes (approximately ≥1500 mg/d); however, dairy calcium appeared

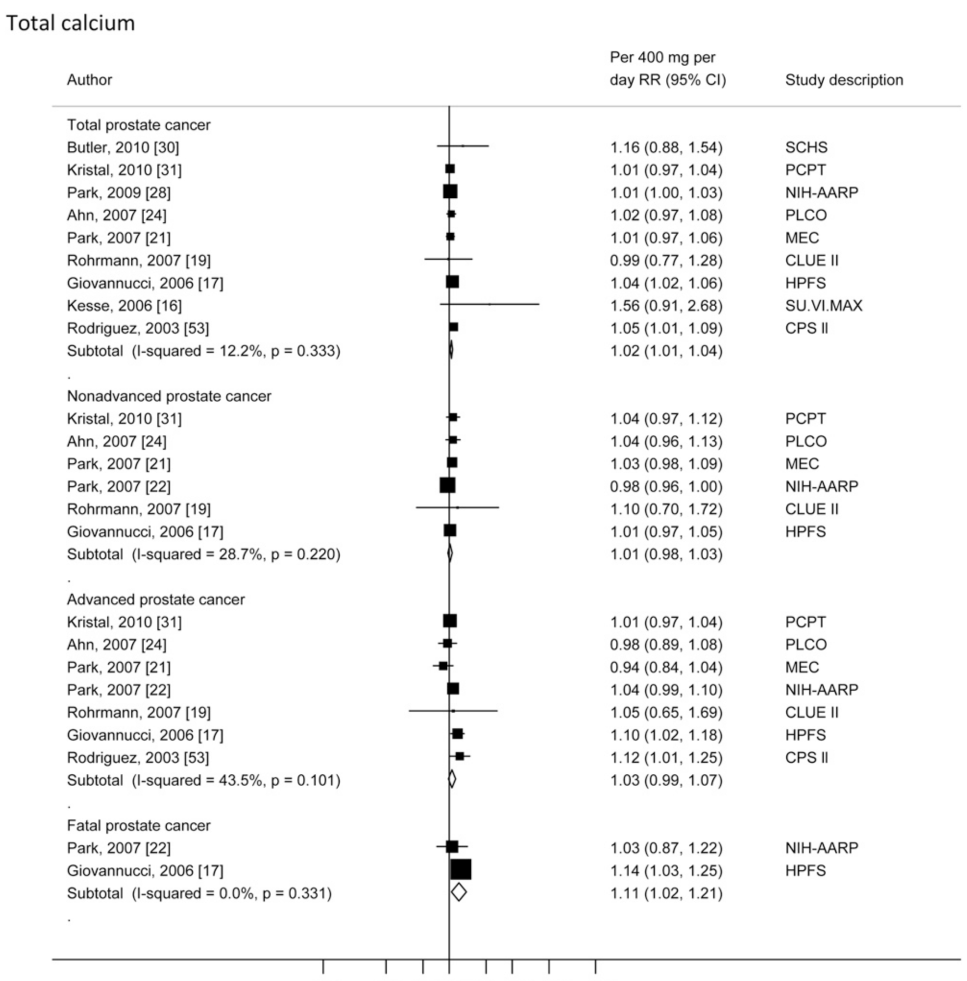


**FIGURE 4** Intake of total calcium and prostate cancer risk. Summary RRs (dashed line) and 95% CIs (open diamonds) were calculated per 400-mg/d intake by using a random-effects model. CLUE II, Campaign Against Cancer and Heart Disease; CPS II, Cancer Prevention Study II; HPFS, Health Professionals Follow-Up Study; MEC, Multiethnic Cohort Study; NIH-AARP, NIH-AARP Diet and Health Study; PCPT, Prostate Cancer Prevention Trial; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SCHS, Singapore Chinese Health Study; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants Study.

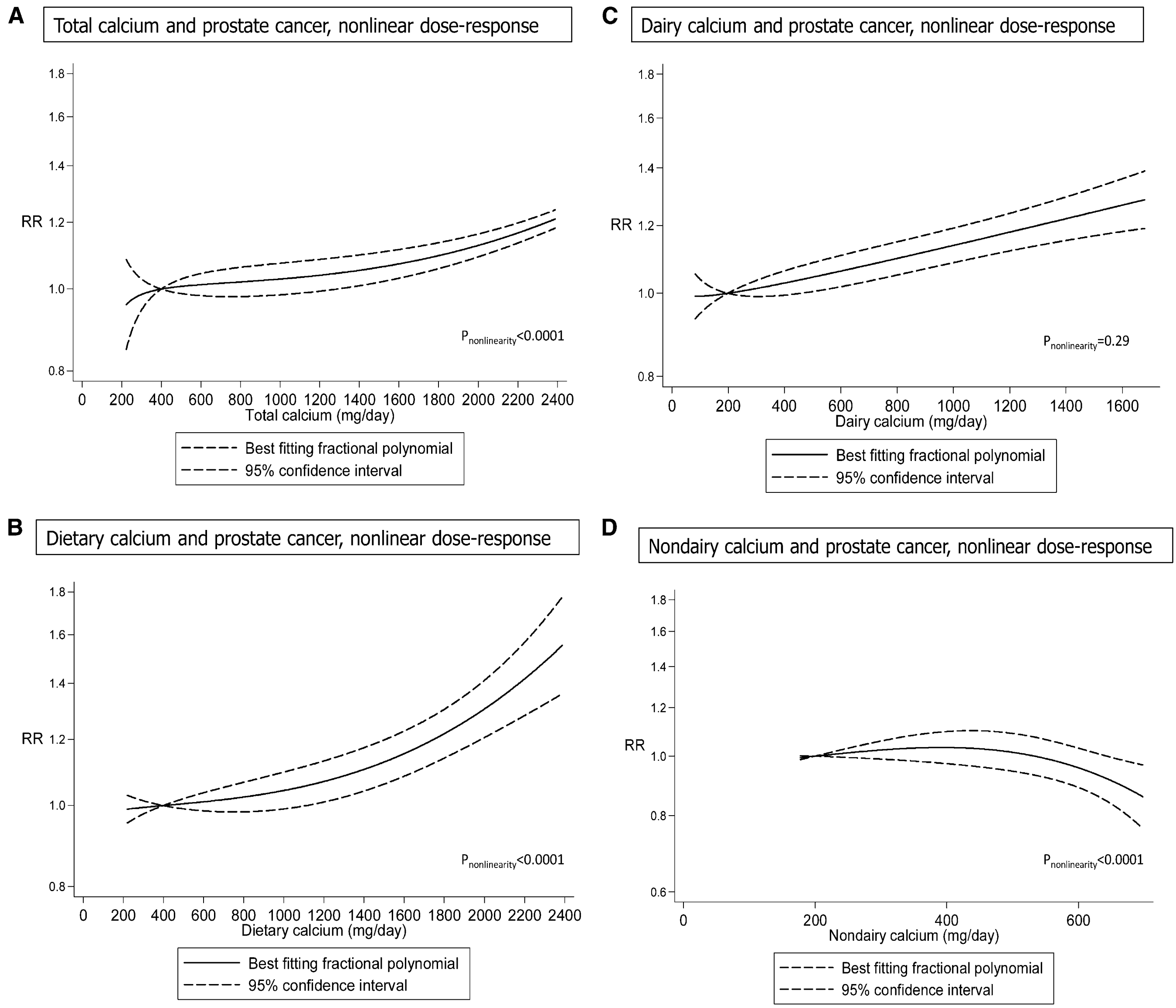


**FIGURE 5** Nonlinear analysis [summary RRs (full lines) and 95% CIs (dashed lines)] of total calcium (A), dietary calcium (B), dairy calcium (C), and nondairy calcium (D) and total prostate cancer risk. The dose-response curve was calculated by using fractional polynomial models, and the test for nonlinearity was based on a log-likelihood test.

to be associated with a linear increase in risk. Supplemental calcium was not significantly associated with total prostate cancer risk; however, there was evidence of increased fatal prostate cancer risk, but this result was based on only 2 studies.

Because this was a meta-analysis of observational studies, our findings may have had several limitations. Dairy food and calcium intakes may be associated with other risk factors such as physical activity, smoking, alcohol, intakes of meat and tomatoes, or prostate specific antigen (PSA) testing (21, 22, 53, 61), which might have confounded the associations we showed. However, we showed no evidence that results differed in several subgroups according to adjustment for potential confounding factors, and for total dairy, results generally persisted across subgroups of adjustment, whereas for the other dairy variables and calcium intakes, there were fewer studies that adjusted for potential confounding and may have limited the statistical power in these subgroups. Dairy food intake may be positively associated with screening practices such as the PSA test (22), and a positive association between dairy products and prostate cancer risk might simply have reflected more cancers being detected if the analyses did not adjust for such testing. However, results for dairy products persisted in the 2 studies that adjusted for PSA testing (24, 28), and there was no evidence that results differed by adjustment for PSA testing. Nevertheless, for most of exposures, there were very few studies that adjusted for PSA testing, and this lack makes any conclusions difficult. PSA testing is much more common in the United States (38%) than in Europe (6–16%) (27), but results persisted in European studies as well, in which the impact of any such bias would have been less, and there was no evidence that results differed by geographic location.

It has been hypothesized that some risk factors including dairy products and calcium intakes may be more strongly associated with advanced prostate cancers than nonadvanced cancers (34). In our analyses, there were fewer studies that presented results stratified by stage or grade, and in most analyses, we did not have sufficient statistical power to clarify whether this was the case or

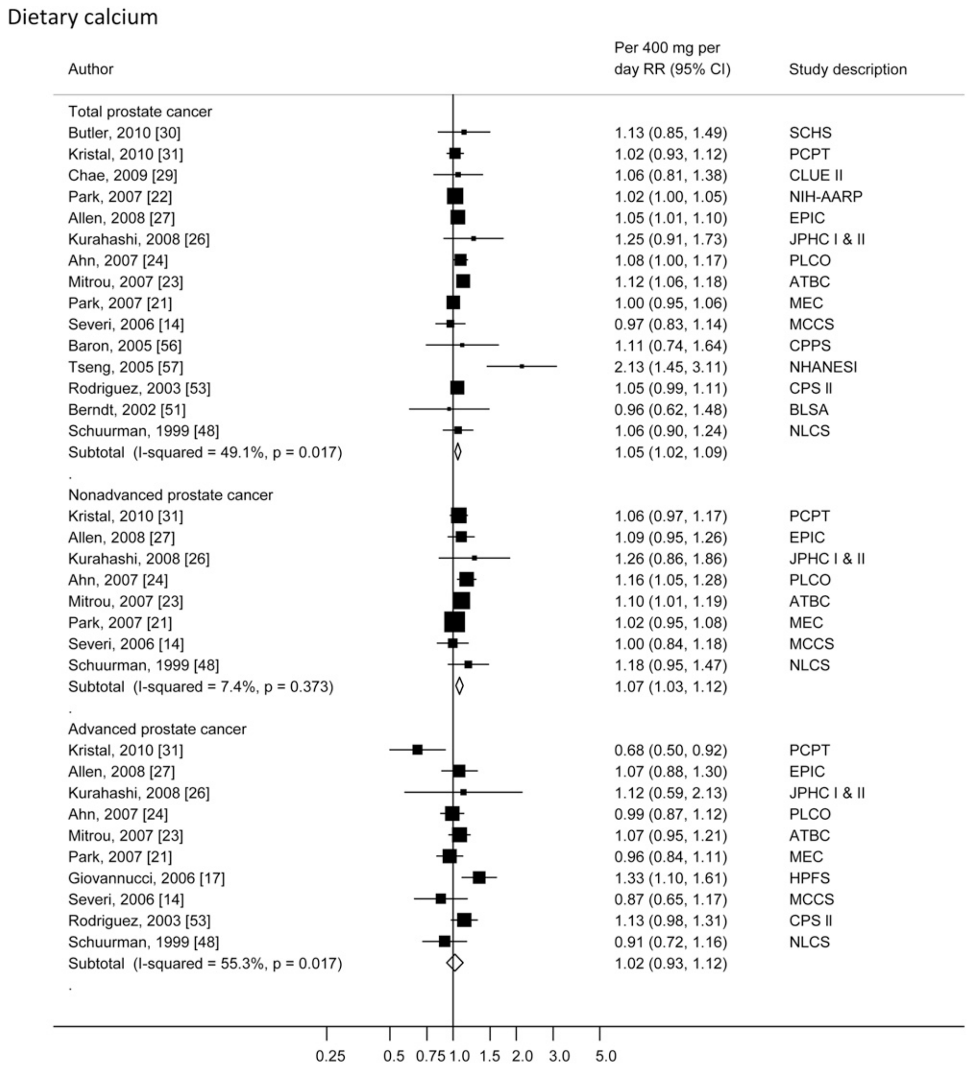


**FIGURE 6** Intake of dietary calcium and prostate cancer risk. Summary RRs (dashed line) and 95% CIs (open diamonds) were calculated per 400-mg/d intake by using a random-effects model. ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BLSA, Baltimore Longitudinal Study on Aging; CLUE II, Campaign Against Cancer and Heart Disease; CPPS, Calcium Polyp Prevention Study; CPS II, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-Up Study; JPHC, Japan Public Health Center-Based Prospective Study; MEC, Multiethnic Cohort Study; MCCS, Melbourne Collaborative Cohort Study; NIH-AARP, NIH-AARP Diet and Health Study; NLCS, Netherlands Cohort Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PCPT, Prostate Cancer Prevention Trial; SCHS, Singapore Chinese Health Study.

not. Only in the subgroup analysis of supplemental calcium and fatal prostate cancer was there evidence of heterogeneity between fatal and non-advanced cancers; however, this finding needs additional study because there were only 2 studies in the subgroup of fatal prostate cancer.

Publication bias or small study effects can be a problem in meta-analyses of published literature and may lead to exaggerated summary estimates. In this analysis, we showed some evidence of possible publication bias or small study effects in analyses of total dairy and milk; however, this bias appeared to be explained by one outlying study, and when this study was excluded, the test for publication bias was no longer significant, and summary estimates remained similar. Most of the results also remained similar when we used the trim-and-fill method. In addition, there was a possibility of the selective publication of results for subtypes of dairy products or subtypes of calcium, although it was also possible that differences in questionnaires in different studies partly may have contributed to differences in how results were presented in publications. Of the 28 studies that reported on some type of dairy product intake in relation to any type of prostate cancer outcome (such as incidence, advanced, or mortality) 18 studies reported on total dairy products, 14 studies reported on total milk, 12 studies reported on cheese, and 9 studies reported on yogurt. Of the 19 studies that reported on some type of calcium intake, 9 studies reported on total calcium, 15 studies reported on dietary calcium, but only 4 studies reported on nondairy calcium. In sensitivity analyses of studies that were common for the analyses of dairy products, milk, and cheese, RRs were somewhat stronger than in the analysis that included all studies, which suggested potential reporting bias. In addition, there were few studies that reported results for specific types of dairy products (except for milk and cheese), and therefore, we may have had limited statistical power to detect associations with these items.

Measurement errors in the dietary assessment was another limitation of our results. Less than 50% of studies included in our meta-analysis stated that they used validated food-frequency questionnaires, and only one of the studies corrected the results for measurement error (27). In the EPIC study, the HR per 300 mg total calcium intake /d increased from 1.04 (95% CI: 1.01, 1.08) to 1.09 (95% CI: 1.01, 1.16) with correction for measurement error, which suggested the attenuation of RRs by measurement errors. In addition, regression dilution bias because of changes in dairy and calcium intakes during follow-up may have further attenuated associations, but only one study used repeated measurements of dietary intake (50) and stated that associations did not differ when different analytic approaches were used.

Several mechanisms might explain increased risk of prostate cancer with high dairy food intakes. Dairy products are an important source of calcium, which has been hypothesized to increase risk through the downregulation of circulating vitamin D concentration (73). Several (17, 74), but not all (24), studies reported lower vitamin D concentrations with higher calcium intake. High vitamin D concentrations may regulate gene expression, inhibit cellular proliferation, and induce the differentiation of normal and neoplastic cells (75, 76). However, a recent meta-analysis showed no significant association between dietary or blood concentrations of vitamin D and prostate cancer risk (77). We showed no association between supplemental calcium intakes and total prostate cancer risk, and although increased risk was observed for fatal prostate cancer, this result was based on only 2 studies and needs additional study. In contrast to the positive associations for total and dietary calcium, there was no association with intake of nondairy calcium. This result might have suggested that other components of dairy products than calcium contribute to risk. Although we showed an attenuation of risk estimates for dairy intake when we adjusted for calcium intake, calcium intake may be highly correlated with other possibly etiologically relevant dairy components, and therefore, it is difficult to conclude that high calcium intake per see is the causal factor. A number of experimental and observational studies have reported increased circulating concentrations of insulin-like growth factor I (IGF-1) with intake of milk and dairy products (78), and this effect was confirmed in a meta-analysis of cross-sectional studies and randomized trials (79). In addition, lower IGF-I concentrations have been observed in vegans who do not use dairy products compared with in both omnivores and lactovegetarians (80). IGF-1 promotes proliferation and inhibits apoptosis in vitro in both normal and prostate cancer cells (81, 82) and has been associated with increased prostate cancer risk in epidemiologic studies (83, 84). A pooled analysis of 12 prospective studies showed 38% increased risk of prostate cancer with high concentrations of IGF-1 (85). Although high dietary fat intake has been hypothesized to increase prostate cancer risk, there is currently little evidence to support an association between fat intake and prostate cancer risk (9, 86), and in addition, we showed an inverse association in the high compared with low analysis of whole-milk intake but a significant positive association with low-fat milk and a nonsignificant positive association with skim milk in this analysis.

Strengths of this meta-analysis included the prospective design of included studies, which avoided recall bias and reduced risk of selection bias. With the large number of studies (and cases and participants), we had adequate statistical power to detect significant associations in the main analyses, although this was not the case for some of subtypes of dairy products and some subgroup analyses. To our knowledge, this is also the first meta-analysis to explore a potential nonlinear association between dairy and calcium intakes and prostate cancer risk, conduct separate analyses by sources of calcium intake, and conduct comprehensive subgroup analyses by study characteristics and types of dairy products. Our results suggest that it is important to consider both adverse and beneficial effects of dairy product and calcium intake before recommendations to modify intake of dairy products are made. Additional studies of dairy products, including subtypes of dairy product and calcium (and other dairy components) intakes in relation to other cancers and chronic diseases, total cancer incidence, and overall mortality might provide further evidence of what is the optimal intake for overall health.

In conclusion, we showed increased risk of prostate cancer with intakes of total dairy, milk, cheese, low fat and skim milk combined, total calcium, dietary calcium, and dairy calcium but no association with supplemental calcium or nondairy calcium and an inverse association for whole milk. A positive association between supplemental calcium and fatal prostate cancer needs additional study. Diverging results for types of dairy products and sources of calcium suggest that other components of dairy than fat and calcium may increase prostate cancer risk. Additional prospective studies are needed on types of dairy products and various sources of calcium in relation to risk of subtypes of prostate cancer and, in particular, advanced and fatal cancers.

The authors' responsibilities were as follows—DANR: performed the updated literature search; DANR and DA: performed the updated data extraction; DA: performed the updated study selection, conducted statistical analyses, wrote the first draft of the original manuscript, had primary responsibility for the final content of the manuscript, and took responsibility for the integrity of data and accuracy of the data analysis; RV: was database manager for the project; DCG: was expert statistical advisor and contributed toward statistical analyses; and all authors: contributed to the revision of the manuscript and had full access to all data in the study. TN is the primary investigator of the Continuous Update Project. None of the authors reported a conflict of interest related to the study. The views expressed in this review are the opinions of the authors. The views may not represent the views of World Cancer Research Fund International/American Institute for Cancer Research and may differ from those in future updates of the evidence related to food, nutrition, physical activity, and cancer risk. The sponsor of this study had no role in the decisions about the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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