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Dairy Products, Dietary Calcium and Vitamin D Intake as Risk Factors for Prostate Cancer: A Meta-Analysis of 26,769 Cases From 45 Observational Studies

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Dairy Products, Dietary Calcium and Vitamin D Intake as Risk Factors for Prostate Cancer: A Meta-Analysis of 26,769 Cases From 45 Observational Studies

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In this study, we examined the available evidence and sources of heterogeneity for studies of dairy products, calcium, and vitamin D intake and the risk of prostate cancer. We pooled data from 45 observational studies using a general variance-based, meta-analytic method employing CIs. Summary relative risks (RRs) were calculated for specific dairy products such as milk and dairy micronutrients. Sensitivity analyses were performed to test the robustness of these summary measures of effect. Cohort studies showed no evidence of an association between dairy [RR = 1.06; 95% confidence interval (CI) = 0.92–1.22] or milk intake (RR = 1.06; 95% CI = 0.91–1.23) and risk of prostate cancer. This was supported by pooled results of case-control analyses (RR = 1.14; 95% CI = 1.00–1.29), although studies using milk as the exposure of interest were heterogeneous and could not be combined. Calcium data from cohort studies were heterogeneous. Case-control analyses using calcium as the exposure of interest demonstrated no association with increased risk of prostate cancer (RR = 1.04; 95% CI = 0.90–1.15). Dietary intake of vitamin D also was not related to prostate cancer risk (RR = 1.16; 95% CI = 0.98–1.38). The data from observational studies do not support an association between dairy product use and an increased risk of prostate cancer.

INTRODUCTION

Prostate cancer is one of the most common malignancies in the United States, Canada, and Western Europe, with age-adjusted incidence rates of approximately 170 cases per 100,000 among North American males (1). This is in contrast to the much lower incidence seen among Japanese and Chinese men, with age-adjusted rates of approximately 10 per 100,000 (2). Interestingly, migration studies have suggested a role for environmental/dietary factors in the etiology of this disease because, for instance, Japanese immigrants to the United States experience a substantial increase in risk versus their native counterparts (3).

In addition, research by Wynder et al. (4) indicated that invasive prostate cancer may have a distinct etiology (vs. in situ disease), with observational studies having supported a possible role for diet. More specifically, it is thought that dietary factors may influence the promotion and progression of prostatic cancer rather than its initiation (4).

Dietary intake of dairy products and calcium has been suggested as a possible risk factor for prostate cancer. In 2007, the American Institute for Cancer Research concluded that there was limited data suggestive of increased risk based on the available ecological, and a subset of epidemiological, reports as well as the possible biological mechanisms put forth to support it (5). Nonetheless, although the proposed biological pathways underlying the dairy nutrient/prostate cancer association appear plausible (e.g., suppression of circulating 1,25-di-hydroxyvitamin D [1,25(OH)2D] levels by dietary calcium thereby decreasing 1,25(OH)2D's ability to suppress tumor growth via its ability to induce differentiation), varied interpretations of the existing observational data have been put forth both supporting as well as questioning the validity of a dairy product/prostate cancer relationship (6,7).

Clarity on the issue of the health effects of dairy products and dietary calcium intake carries important disease prevention implications because, for instance, the Dietary Guidelines

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for Americans (DGA) advises 3 cups per day of fat-free or equivalent milk products, a level attained by only a minority of Americans (8,9). Likewise, dairy products and dietary calcium are also promoted as a means for maintaining and enhancing bone health in the pediatric age group and preventing osteoporotic fracture among adults (10).

Given the large size of the relevant biomedical literature, we conducted a meta-analysis designed to evaluate the relationship between dietary intake of dairy products and dairy micronutrients on prostate cancer risk.

METHODS

The methods used in the design and execution of this study have been described previously (11,12). A study protocol was developed outlining a meta-analysis examining the risk of developing adenocarcinoma of the prostate associated with dietary intake of dairy products, calcium, and vitamin D. Eligibility criteria for inclusion were determined prospectively as were the data elements to be extracted.

Two researchers performed data extraction, with differences resolved by consensus. Other data collected but not included in the eligibility criteria were number of patients and location for each study; dietary assessment methods; length of follow-up and cohort description (when applicable); type of statistical adjustments, if any, to the individual study odds ratios (OR) or relative risks (RR); as well as source of controls for case-control studies.

Literature Search

Literature retrieval was performed by previously described methods (12). A MEDLARS search was conducted of English language literature published between January 1966 and February 2007, review of CancerLit, and the CD-ROM version of Current Contents. The Cochrane database was searched from January 1966 to February 2003. Search terms were *dairy products* [calcium, dietary], *dietary fats, vitamin D*, and *prostate neoplasms*. If a series of articles was published, data were retrieved from the most recent article. Hand searches of bibliographies of published reports, review articles, and textbooks were also performed.

The initial citations (abstracts) were screened by a physician-investigator. Rejected formats included in vitro and animal studies, review articles, letters to the editor, abstracts, and non-peer-reviewed articles. Eligibility criteria included published observational studies or clinical trials enrolling adult patients (18 yr or older) with histologically proven adenocarcinoma of the prostate; availability of data on exposures of interest including dairy products (broadly defined), dietary calcium and/or vitamin D intake; availability of ORs or RRs with 95% CIs for each report or availability of raw data to calculate these parameters; and availability of data on outcome of interest including incident of prostate cancer or death from prostate cancer.

Statistical Analysis

Data analysis was performed using a general, variance based, meta-analytic procedure using CIs described by Greenland (11). For each study, ORs were derived reflecting the risk of prostate cancer associated with dietary intake of dairy products, calcium, and/or vitamin D followed by calculation of the natural logarithm of the estimated RR as well as calculation of an estimate of the variance. When both crude and adjusted RRs were provided, the most fully adjusted value was used. The estimate of the 95% CI from each study was employed to calculate the variance of each study's measure of effect.

We calculated a weight for each included report as 1/variance followed by a summation of the weights. We then determined the product of the study weight and the natural logarithm of the estimated RR and then summed these products. Finally, summary RRs and 95% CI were determined. A statistical test for homogeneity was performed (Q). This procedure tests the hypothesis that the effect sizes are equal in all of the included studies (13). If Q exceeds the upper tail critical value of chi-square ($P < 0.10$) at $k - 1$ *df*, the observed variance in study effect sizes is greater than what would be expected by chance if all studies shared a common population effect size. If the hypothesis that the studies are homogenous is rejected, the studies are not measuring an effect of the same size. In this instance, calculation of a pooled estimate of effect (i.e., RRs) may be of questionable validity.

RESULTS

The initial literature search yielded 645 citations in the form of abstracts. Initial screening of these reduced the total to 98 citations, which were subsequently entered onto an "initial accept log." Full papers were obtained for all 98 and further screened for eligibility.

Only 1 randomized trial was located (14) randomizing 672 men to receive either 1,200 mg of calcium per day or placebo for 4 yr (12-yr follow-up). The results showed that calcium supplementation was not associated with increased risk of prostate cancer, and there was a suggestion of a protective effect, that is, OR of 0.83(95% CI = 0.52–1.32) (14). These data were not further incorporated into the pooled analysis.

A total of 23 cohort studies were found (15–37). Reference 14 was excluded from the analysis because Giovannucci et al. (21) was a follow-up of this report. Likewise, Ref. 30 was an update of the Alpha-Tocopherol Beta-Carotene Cancer Prevention cohort from 2000 (16). Therefore, only Ref. 30 was pooled. This left a total of 21 cohort studies for inclusion (see Table 1).

The search yielded 26 case-control analyses meeting specified inclusion criteria (38–63). The report by Hayes et al. (38) only provided ORs without 95% CIs. CIs could not be calculated based on data presented in the manuscript and therefore, the study was dropped from the analysis. Bosetti et al. (39) was a reanalysis of Ref. 61 without new relevant data. Therefore, only data from Ref. 39 was pooled. Table 2 provides a summary of the included case-control studies.

TABLE 1
Characteristics of 21 Cohort Studies Included in Meta-Analysis Examining Dietary Dairy/Calcium Intake and Prostate Cancer Risk[a]

Cohort Studies

Author (Reference), Year of Publication	Cohort Description	Country	No. Cases	Length of Follow-Up	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
Allen et al. (17) 2004	Lifespan Study Cohort; Adult Health Study; 18,115 men; mean age at entry 51; mean age at diagnosis 75	Japan	196	16.9 yr	FFQ interview-based and self-administered, validated, corrected for milk 0.32	Incident prostate CA; diagnosis verified via tumor registry, medical records, pathology	Milk	0.87 (0.62–1.21)	Age, calendar period, city of residence, radiation dose, and education level; no adjustment for energy intake
							Butter/cheese	0.84 (0.54–1.37)	
Berndt et al. (18) 2002	Baltimore Longitudinal Study of Aging; mean age of those completing FFQ was 67.6 yr	United States	69	NG	FFQ interview-based, validated	Prostate CA; 22 incident cases; 42 cases completed FFQ after diagnosis	Milk	1.20 (0.58–2.47)	Energy, age, physical activity, phosphorus and fat intakes
							Calcium (dietary)	0.92 (0.48–1.77)	
							Milk, cheese, yogurt	1.26 (0.57–2.79)	
							Vitamin D	1.21 (0.64–2.30)	
Chan et al. (19) 2006	Health Professionals Follow-Up Study; 51,529 men; mean age 68 at diagnosis	United States	392	6.4 yr	FFQ self-administered; validated; corrected for calcium 0.53; for saturated fat 0.71; 0.61 total fat	Prostate CA progression, i.e., PSA failure, clinical occurrence, or death	Milk	1.25 (0.93–1.69)	Age, energy, prediagnostic diet, clinical factors
Chan et al. (20) 2001	Physicians Health Study; 22,071 men, age 40–84	United States	1,012	11 yr	FFQ not validated	Prostate cancer verified by medical records	Dairy	1.27 (0.97–1.66)	Age, smoking, BMI, food score, assigned treatment, energy (indirect)

(*Continued on next page*)

TABLE 1
Characteristics of 21 Cohort Studies Included in Meta-Analysis Examining Dietary Dairy/Calcium Intake and Prostate Cancer Risk[a] *(Continued)*

Cohort Studies

Author (Reference), Year of Publication	Cohort Description	Country	No. Cases	Length of Follow-Up	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
							Calcium (dairy)	1.29 (1.04–1.62) (<600 mg/day vs. 1,150 mg/day)	
							Dairy (localized)	1.42 (0.98–2.04)	
							(advanced)	1.38 (0.95–2.01)	
							Calcium (localized)	1.47 (1.08–1.98)	
							(advanced)	1.30 (0.94–1.78)	
							Skim milk (none vs. 1 or more serving/day)	1.32 (1.12–1.56)	
Giovannucci et al. (21) 2006	Health Professionals Follow-Up Study; 51,529 men (91% White); 40–75 yr at baseline; dietary info updated every 4 yr	United States	3,544	16 yr	FFQ self-administered, validated, non-A1	Prostate cancer, death from prostate cancer; verified by medical records	Calcium (total)	1.28 (1.02–1.60)	Age, time period, BMI, energy, height, smoking, family Hx, Hx diabetes, race, total calories, red meat, fish, zinc, tomato sauce
							Calcium (fatal)	2.02 (1.14–3.58)	
							Calcium (nonadvanced disease)	1.13 (0.88–1.47)	
							Calcium (advanced disease)	2.02 (1.28–3.19)	
							Dairy (total)	1.07 (0.95–1.20)	
							Dairy (advanced disease)	1.08 (0.75–1.55)	
Giovannucci et al. (22) 1993	Health Professions Follow-Up Study (as previously)	United States	300, all advanced disease (stage C, D, or death)	4 yr	FFQ self-administered, validated	Prostate cancer, death from prostate cancer; National Death Index	Dairy (fat)	1.06 (0.56–1.98)	Age, total energy, BMI, marital status, ancestry, smoking, alcohol, physical activity, residence

Hsing et al. (23) 1990	Lutheran Brotherhood cohort; 17,633 White men, aged 35 or older, median age at entry 51; from upper Midwest and Northeast; smoking and alcohol was only assessed once (i.e., in 1966 via questionnaire)	United States	149	20 yr	FFQ self-administered, not validated	Prostate cancer, death via death certificate	Dairy (milk and ice cream); 89–189 times/month vs. < 26	1.0 (0.6–1.7)	Age, smoking at baseline
Keese et al. (24) 2006	SU.VI.MAX study cohort; 12,741 subjects, 5,028 men; 2,776 men included in this study	France	69	7.7 yr	FFQ unvalidated, self-administered	Prostate cancer verified by medical records, death certificates, pathology reports	Dairy (milk, cheese, yogurt)	2.16 (0.96–4.85)	BMI, age, occupation, alcohol, smoking, family Hx, physical activity, energy, meat and vegetable consumption, CA
							Milk	1.13 (0.54–2.34)	
							Cheese	0.90 (0.42–1.91)	
							Fresh cheese	2.38 (1.23–4.62)	
							Yogurt	1.81 (0.87–3.76)	
							Calcium (total)	2.43 (1.05–5.62)	
							Calcium (from dairy)	2.94 (1.16–7.51)	
							Calcium (nondairy)	1.12 (0.60–2.11)	
Koh et al. (25) 2006	Harvard Alumni Health Study; 12,805 men, 10,011 included in this study; mean age 67 yr; dietary info obtained only once from a single questionnaire in 1988	United States	815	20 yr	FFQ self-administered, not validated	Prostate cancer, death from prostate cancer (self-reported)	Dairy	1.11 (0.85–1.46)	Age, smoking, alcohol, red meat, total calorie intake, family Hx

(Continued on next page)

TABLE 1

Characteristics of 21 Cohort Studies Included in Meta-Analysis Examining Dietary Dairy/Calcium Intake and Prostate Cancer Risk[a] *(Continued)*

Author (Reference), Year of Publication	Cohort Description	Country	No. Cases	Length of Follow-Up	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
Cohort Studies									
							Calcium (from dairy)	0.91 (0.70–1.18)	
							Calcium (from supplements)	1.05 (0.84–1.31)	
							Calcium (fatal)	0.81 (0.38–1.71)	
Leitzmann et al. (26) 2004	Health Professionals Follow-Up Study cohort (as previously); diet assessed in 1986, 1990, and 1994	United States	2,965	14 yr	FFQ self-administered, validated	Prostate cancer, death from prostate cancer, verified with medical records	Skim milk	1.07 (0.82–1.39) (advanced disease)	Age, time period, family Hx, BMI, height, Hx diabetes, Hx vasectomy, smoking, physical activity, energy, vitamin E
							Cheese	1.19 (0.66–2.13) (advanced disease)	
LeMarchand et al. (27) 1994	Population-based cohort assembled via the Hawaii State Department of Health; 95% participation rate; linked to SEER program, state marriage and divorce files, voter registration, and Hawaii Tumor Registry;. ≥ 45 yr old; exposure data collected only once; 20,316 men	United States (Hawaii)	198 (36% White)	21 yr	FFQ mostly via interview, not validated	Prostate cancer verified via Tumor Registry	Milk	1.4 (1.0–2.1)	Age, income, ethnicity

Michaud et al. (28) 2001	Health Professionals Follow-Up Study cohort (as previously)	United States	1,897	10 yr (update through 1996	FFQ validated (as previously); total of 3 dietary assessments over time	Prostate, death from prostate cancer (as previously)	Dairy	1.04 (0.89–1.2)	Age, calories, smoking, tomato sausce, exercise, CA, saturated fat, alpha-linolenic acid
							Dairy (advanced disease)	1.38 (1.04–1.8)	
							Dairy (stage D and fatal)	1.66 (1.1–2.5)	
							Butter	1.42 (1.0–2.0)	
							Ice cream	1.28 (0.71–2.2)	
							Skim milk	1.25 (0.83-1.9)	
							Whole milk	1.25 (0.80–1.9)	
							Cheese (ricotta or cottage cheese)	1.06 (0.75–1.4)	
							Cheese (other)	1.29 (0.88–1.9)	
							Cheese (cream)	1.20 (0.81–1.8)	
Mills et al. (29) 1989	Seventh Day Adventist Cohort (CA, 1976); 15,000 men, 25 yr old or older at entry	United States	180	6 yr	FFQ self-administered, not validated	Prostate cancer verified by medical records, Tumor Registry	Milk	0.80 (0.54–1.19)	Age
Mitrou et al. (30) 2007	ATBC Study Cohort; 29,133 White male smokers, 50–69 yr at entry	Finland	1,267	17 yr	FFQ self-administered, validated	Prostate cancer verified by medical records, Finnish Cancer Registry	Milk (total)	1.08 (0.91–1.30)	Age, CA trial intervention group, physical activity, Hx diabetes, family Hx of prostate CA, height, BMI, smoking, marital status, education, urban residence, energy, CA

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TABLE 1
Characteristics of 21 Cohort Studies Included in Meta-Analysis Examining Dietary Dairy/Calcium Intake and Prostate Cancer Risk[a] (*Continued*)

Cohort Studies

Author (Reference), Year of Publication	Cohort Description	Country	No. Cases	Length of Follow-Up	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
							Milk (whole)	1.05 (0.86–1.29)	
							Milk (low fat)	1.18 (0.97–1.44)	
							Milk (sour milk products)	1.07 (0.90–1.28)	
							Dairy (total)	1.26 (1.04–1.51)	
							Butter	1.00 (0.84–1.20)	
							Ice cream	0.90 (0.75–1.08)	
							Cream	1.09 (0.91–1.30)	
							Cheese	1.13 (0.95–1.36)	
							Dairy fat	1.20 (1.00–1.43)	
							Calcium (from dairy)	1.28 (1.07–1.54)	
							(supplements alone)	0.96 (0.81–1.15)	
							(dietary)	1.63 (1.27–2.10)	
Rodriguez et al. (31) 2003	Cancer Prevention Study II Nutrition Cohort; 65,321 men, aged 50–74 at enrollment	United States	3,811	6 yr	FFQ self-administered, validated	Prostate cancer verified with medical records, cancer registry	Dairy (whole milk, low-fat milk, skim milk, cheese, low-fat regular yogurt, ice cream)	1.1 (0.9–1.3) (total)	Age, family Hx, energy, fat, education, vitamin D, phosphorus
								0.9 (0.5–1.4) (advanced disease)	
							Calcium (total)	1.2 (1.0–1.6) (total)	
								1.6 (0.9–3.0) (advanced disease)	
							Calcium (dietary)	1.6 (1.1–2.3)	
								2.2 (0.9–5.3) (advanced disease)	
							Calcium (supplements alone)	1.1 (1.0–1.3)	

Rohrmann et al. (32) 2007	CLUE II Study, Washington, County, MD; 10,457 men, 6,818 eligible for this study; of these, 5,620 completed an FFQ; after exclusions, 3,892 or 57% of eligible subjects were included in the analysis; age 35+, mean age 53.8 yr; 99.2% White	United States	199	15 yr	FFQ self-administered, validated; data collected once in 1989	Prostate cancer via linkage to the Washington Co. Cancer Registry, Maryland Cancer Registry; death certificates, and National Death Index	Dairy (cheese, whole milk, 2% milk, skim, cream, ice cream)	1.08 (0.78–1.54)	Age, energy, saturated fat, tomato products, BMI
								1.28 (0.63–2.59) (advanced disease)	
								1.31 (0.71–2.41) (localized disease)	
							Calcium (total)	0.99 (0.70–1.41)	
								1.06 (0.55–1.04) (advanced disease)	
								1.16 (0.63–2.15) (localized disease)	
							Calcium (supplements alone)	0.86 (0.62–1.19)	
							Cheese	1.43 (1.01–2.03)	
								1.71 (0.88–3.32) (advanced disease)	
								0.93 (0.51–1.67) (localized disease)	
							Milk	1.26 (0.91–1.74)	
								1.41 (0.73–2.72) (advanced disease)	
								1.66 (0.93–2.93) (localized disease)	

(Continued on next page)

TABLE 1
Characteristics of 21 Cohort Studies Included in Meta-Analysis Examining Dietary Dairy/Calcium Intake and Prostate Cancer Risk[a] (*Continued)*

Cohort Studies

Author (Reference), Year of Publication	Cohort Description	Country	No. Cases	Length of Follow-Up	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
Schuurman et al. (33) 1999	Netherlands Cohort Study; 58,279 men, aged 55–69 yr at enrollment	Netherlands	642	6.3 yr	FFQ self-administered, validated;, dietary info collected once in 1965	Prostate cancer verified by cancer registries and the Dutch national pathology database	Milk, Milk products (whole, low fat, skim, chocolate, buttermilk, dry curd, whole and skimmed yogurt)	1.12(0.81–1.56)	Age, family Hx, SES, energy
							Milk, milk products (localized disease)	1.01 (0.98–1.05)	
								(advanced disease)	0.99 (0.95–1.03)
							Cheese	1.21 (0.87–1.70)	
								(localized disease)	0.94 (0.68–1.29)
								(advanced disease)	1.05 (0.66–1.68)
							Calcium (all tumors)	1.09 (0.79–1.50)	
								(localized disease)	1.21 (0.79–1.34)
								(advanced disease)	0.83 (0.52–1.34)
Severson et al. (34) 1989	HHP cohort Hawaii; 7,999 men of Japanese ancestry, aged 46–68 yr at enrollment	United States—Hawaii	174	17.5 yr	FFQ via interview, not validated	Prostate cancer verified via tumor registry	Milk	1.0 (0.73–1.38)	Age
							Butter, margarine, cheese	1.47 (0.97–2.25)	
							Ice cream	1.31 (0.84–2.03)	
Snowden et al. (35) 1984[c]	Seventh Day Adventist Cohort; 6,763 White men, ages 60–99 yr at entry	United States	99	21 yr	FFQ self-administered, data collected once in 1960, not validated	Death from prostate cancer verified via California Death certificate file	Milk	2.4 (1.3–4.3)	Age

							Cheese	1.5 (0.9–2.6)	
Tseng et al. (36) 2005[d]	NHANES I, NHEFS cohort; 14,407 in NHEFS cohort, 5,811 men aged 25–74 yr at entry (57.8 mean); Follow-up interviews conducted 1986, 1987, 1992	United States	131	7.7 yr	FFQ via interview 1982–84, 1986, 1987, 1992, validated	Prostate cancer via National Death Index, medical records, death certificates; only 65% of cancer cases confirmed via medical or pathology records	Dairy (low-fat, whole milk, cheese, ice cream, cottage cheese, cream, yogurt)	2.2 (1.2–3.9)	Age, race, energy, residence, education, sun exposure, level of activity, smoking, alcohol
							Milk (total)	1.8 (1.1–2.9)	
							Milk/low-fat	1.5 (1.1–2.2)	
							Milk (whole)	0.8 (0.5–1.3)	
							Cheese	1.1 (0.6–1.9)	
							Ice cream	1.0 (0.7–1.5)	
							Cottage cheese	1.2 (0.8–1.8)	
							Cream	0.9 (0.6–1.3)	
							Yogurt	1.0 (0.6–1.9)	
							Vitamin D	1.3 (0.8–2.1)	
Veierod et al. (37) 1997	Norwegian Health Screening Cohort; 25,708 men aged 16–56 yr at entry.; mean 56 yr at the end of follow-up	Norway	72	9.0 yr	FFQ self-administered at entry, validated	Prostate cancer, death from prostate cancer verified via Cancer Registry of Norway and Central Bureau of Statistics	Milk (skim)	2.2 (1.3–3.7)	Age, time-scale variable attained age, BMI
							Milk (whole + skim)	1.2 (0.6–2.2)	

[a]Abbreviations are as follows: RR, relative risk; CI, confidence interval; FFQ, Food Factor Questionnaire; CA, cancer; NG, not given; PSA, prostate-specific antigen; BMI, body mass index; Hx, history; SU.VI.MAX, Supplementation en Vitamines et Mineraux Antioxydants study; ATBC, Alpha-Tocopheral, Beta-Carotene Cancer Prevention Study; HHP, Honolulu Heat Program; NHANES I, National Health and Nutrition Examination Survey I; NHEFS, National Health and Nutrition Examination Survey Epidemiological Follow-up Study.

[b]Highest vs. lowest intake categories.

[c]Mortality study.

[d]Milk RRs adjusted for calcium (provide separate analysis for dairy foods adjusted for calcium intake).

TABLE 2
Characteristics of 24 Case-Control Studies Included in Meta-Analysis Examining Dairy/Calcium Intake and Prostate Cancer Risk[a]

Reference	Location	No. Cases/ Controls	Source of Controls	Controls Screened for Prostate CA (Y/N)	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
Andersson (40) 1995	Sweden	256/252	P	Y	FFQ[c] not validated	Prostate CA pathologically confirmed	Total dairy	0.8 (0.4–1.3)	Age
							Whole milk	0.8 (0.5–1.4)	
							Cheese	0.8 (0.4–1.6)	
							Butter	0.6 (0.4–1.1)	
							Cream	0.7 (0.4–1.2)	
Bosetti (41) 2004	Italy	1,294/1,451	H	N	FFQ validated	Prostate CA pathologically confirmed	Milk/dairy	1.15 (0.90–1.46)	Age, study center, education, social class, BMI, family Hx of prostate cancer, total calorie intake
							Cheese	1.12 (0.85–1.47)	
Chan (42) 1998	Sweden	526/536	P	Y	FFQ valildated	Prostate CA pathologically confirmed	Dairy	1.49 (1.01–2.19)	Age, energy, family Hx or prostate CA, smoking
							(advanced disease)	1.64 (1.02–2.64)	
							(metastatic disease)	1.52 (0.78–2.98)	
							Calcium	1.91 (1.23–2.97)	
							(advanced disease)	2.12 (1.25–3.61)	
							(metastatic disease)	2.64 (1.24–5.61)	
							Vitamin D	1.37 (0.89–1.81)	
Deneo-Pellegrini et al. (43) 1999	Uruguay	175/233	H	N	FFQ not validated	Prostate CA pathologically confirmed	Dairy	0.8 (.04–1.6)	Age, residence, urban/rural status, education, family Hx prostate CA, BMI, total energy intake
							Vitamin D	0.7 (0.4–1.2)	
DeStefani (44) 1995	Uruguay	156/302	H	N	FFQ not validated	Prostate CA pathologically confirmed	Milk	1.7 (1.1–2.9)	Age, residence, education, smoking, beer consumption

Ewings (45) 1996	United Kingdom	159/325	H	N	FFQ not validated	Prostate CA pathologically confirmed	Milk	0.95 (0.50–1.83)	Age
							Milk (skim)	0.72 (0.44–1.18)	
							Cream	0.56 (0.15–1.79)	
Hodge et al. (46) 2004	Australia	858/905	P	N	Interview validated	Prostate CA pathologically confirmed; excluded patients with low-grade/Gleason < 5 tumors	Dairy	1.0 (0.8–1.3)	Age, group, yr, country of birth, socioeconomic group, energy, family Hx prostate CA
							Butter	1.0 (0.7–1.2)	
							Calcium	1.0 (0.7–1.3)	
Gronberg et al.(47) 1996	Sweden	406/1,218	P	N	FFQ not validated	Prostate CA pathologically confirmed	Milk	0.84 (.044–1.57)	Age
Jain (48) 1999	Canada	617/636	P	N	Interview validated instrument	Prostate CA pathologically confirmed	Milk	1.47 (1.11–1.94)	Age, energy, vasectomy, smoking, marital status, study area, BMI, education, multivitamin use, area of studies, selected nutrients
							Yogurt	1.05 (0.86–1.28)	
							Cream	0.82 (0.68–1.00)	
							Cheese	0.92 (0.70–1.21)	
Kristal et al. (49) 1999	United States	697/666	P	N	Interview not validated	Prostate CA pathologically confirmed	Calcium (including supplements)	1.04 (0.61–1.78)	Age, fat, energy, family Hx of prostate cancer, BMI, PSA in previous 5 yr, education
							Calcium (supplements only)	1.25 (0.73–2.17)	
Kristal et al. (50) 2002	United States	605/592	P	N	Interview FFQ validated	Prostate CA pathologically confirmed	Calcium (total–including supplements)	1.07 (0.63–1.84)	Age, race, family Hx, education, BMI, number of PSA tests, vegetable intake, vitamin E and C intake, zinc, and total energy

(Continued on next page)

TABLE 2
Characteristics of 24 Case-Control Studies Included in Meta-Analysis Examining Dairy/Calcium Intake and Prostate Cancer Risk[a] (*Continued*)

Reference	Location	No. Cases/ Controls	Source of Controls	Controls Screened for Prostate CA (Y/N)	Dietary Assessment	Outcome	Dairy Type	RR[b] (95% CI)	Controlled or Matched Variables
							Localized disease		
							Regional/distant disease	2.12 (1.02–4.38)	
							Calcium (from food only)	0.87 (0.57–1.34)	
							Localized disease		
							Regional/distant disease	1.62 (0.92–2.85)	
							Vitamin D	1.06 (0.66–1.70)	
							Localized disease		
							Regional/distant disease	1.13 (0.59–2.15)	
LaVecchia et al. (51) 1991	Italy	96/292	H	N	Interview FFQ not validated	Prostate CA pathologically confirmed	Milk	5.0 (1.5–16.6)	Age, area of residence, education, BMI
							Cheese	0.6 (0.3–1.1)	
							Butter	1.5 (0.4–5.2)	
Mettlin et al. (52) 1989	United States	371/371	H	N	FFQ validated instrument	Prostate CA pathologically confirmed	Milk whole only	1.92 (1.05–3.50)	Age, residence
							Skim	0.93 (0.40–2.16)	
							Reduced fat only	0.97 (0.56–1.67)	
Mishina et al. (53) 1985	Japan	100/100	H	N	Interview, no other info, nonvalidated instrument	Prostate CA pathologically confirmed	Milk	1.18 (0.67–2.07)	Age, residence NG
Ohno et al. (54) 1988	Japan	100/100	H	N	Interview FFQ validated Instrument	Prostate CA pathologically confirmed	Eggs/milk	0.93 (0.53–1.64) (BPH controls)	Age
								0.80(0.46–1.40) (hospital controls)	
Ramon et al. (55) 2000	Spain	217/434	P	N	Interview FFQ validated instrument	As previously	Calcium	0.74 (0.5–1.1)	Age, residence, caloric intake, family Hx, BMI

Tavani et al. (56) 2001	Italy	288/762	H	N	Interview nonvalidated instrument	As previously	Calcium	1.1 (0.67–1.88)	Age, study center, BMI, education, meat intake
Sonoda et al. (57) 2004	Japan	140/140	H	Y[d]	Interview FFQ validated instrument	As previously	Milk	0.33 (0.10–1.10)	Age, smoking, energy
							Dairy	1.37 (0.69–2.71)	
Talamini et al. (58) 1992	Italy	271/685	H	N	Interview FFQ nonvalidated instrument	As previously	Milk	1.67 (1.01–2.77)	Age, residence, education, BMI
							Cheese	0.77 (0.46–1.31)	
							Butter	0.72 (0.36–1.46)	
Talamini et al. (59) 1986	Italy	166/202	H	N	Interview nonvalidated instrument	As previously	Milk/cheese	2.46 (1.29–4.69)	Age, marital status, BMI, occupation, meat and vegetable consumption
Tavani et al. (60) 2005	Italy	1,294/1,451	H	N	Interview FFQ validated instrument	As previously	Calcium	1.18 (0.88–1.59)	Age, center, education, BMI, smoking, physical activity, energy, family Hx prostate CA
							Vitamin D	1.32 (1.01–1.75)	
Tzonou et al. (61) 1999	Greece	320/246	H	N	Interview FFQ validated instrument	As previously	Calcium	1.23 (0.94–1.73)	Age, height, education, energy intake, polyunsaturated fat, vitamin E
Vlajinac et al. (62) 1997	Serbia	101/202	H	N	Interview FFQ validated instrument	As previously	Vitamin D	0.70 (0.39–1.24)	Energy, protein, saturated fats, sugar, fiber, retinal, vitamin E, folic acid, B12, Na, K, P, Mg, Fe
							Calcium	0.37 (0.14–0.99)	
Walker et al. (63) 2005	Canada	80/334	H	Y	Questionnaire, FFQ interview validated instrument	As previously	Calcium	1.02 (0.54–1.92)	Age, alcohol intake, energy, protein, carbohydrates, fat, cholesterol, fiber

[a]Abbreviations are as follows: CA, cancer; Y, yes; N, no; RR, relative risk; CI, confidence interval; FFQ, Food Factor Questionnaire; P, population; Hospital; Hx, history; BMI, body mass index; PSA, prostate-specific antigen.

[b]Dietary information based on intake during adolescence.

[c]Via PSA.

To examine the relationship between dairy associated nutrients and prostate cancer risk, the RR/ORs for the highest intake category vs. the lowest intake category from each study were statistically combined. A summary estimate of effect greater than 1.0 reflects an increased risk of prostate cancer with intake of the specific dairy type/nutrient analyzed.

Cohort Studies

A total of 11 cohort studies utilized a dairy exposure category (19–21,23,24,27,29–32,36). As illustrated in Table 3, a broadly based exposure variable such as dairy is problematic because the definition of dairy products varied widely across studies. For instance, Hsing et al. (23) included only milk and ice cream as dairy products, whereas Michaud et al. (28) defined dairy as whole milk, low-fat milk, skim milk, cream, ricotta cheese, other cheese, sherbet, ice milk, ice cream, yogurt, cottage cheese, cream cheese, and butter.

Initially pooling all 11 homogeneous reports ($P = 0.33$) gave a summary relative risk of 1.11 (95% CI = 1.03–1.19). Restricting the analysis to only those studies using validated dietary questionnaires (21,28,30,31,36) did not change the summary RR (data not shown). Despite the fact that the pooled RR for dairy in the cohort studies remained slightly positive, several important caveats must be considered that call into question the validity of this finding. Substantial variation exists in the definition of dairy products across reports. It is clear, therefore, that if only certain dairy products are associated with prostate cancer and others are not, study results will vary depending on the definition of *dairy* employed and the proportion of specific dairy types making up this exposure category in any given report. This could potentially account for differences in outcome seen across the cohort studies as noted in Table 1.

Also arguing against a causal relationship is a lack of a clear dose response across studies (64). None of the available cohort studies showed a clear trend in dose response with the exception of Schuurman et al. (33). Although Tseng et al. (36) showed a marginal trend, design differences, as alluded to previously, preclude firm conclusions based on this information. In addition, Ref. 30 provided information on calcium adjusted dairy (see Table 4). This adjustment resulted in substantial attenuation of the dairy associated RR to 1.4 (95% CI = 0.6–3.4). Pooling the 4 cohort studies providing an analysis of calcium-adjusted dairy, that is, Refs. 24,28,30 and 36 (see Table 4), yielded a nonsignificant RR of 1.06 (95% CI = 0.92–1.22).

Next, the 11 homogeneous studies examining milk were statistically pooled (Refs. 17,18,24,27–30,32,34,36,37). Individual study RRs ranged from 0.8 to 2.4 (35). Pooling all reports yielded a nonsignificant RR of 1.06 (95% CI = 0.91–1.23). We also ran separate analyses for "total milk" and "whole milk" for Refs. 30 and 37. This did not result in any change in the summary RR.

Three reports provided calcium adjusted relative risks for milk intake (24,28,36) (see Table 4). All included study RRs were less than 1.0 with nonsignificant CIs. Pooling these 3 studies yielded a substantially attenuated summary RR of 0.86 (95% CI = 0.67–1.11).

Four studies contained data on dairy associated calcium intake, that is, Refs. 24–25, 30, and 36. This gave an RR of 1.18 (95% CI = 1.06–1.33), although the data were heterogeneous ($P = 0.02$). Given the small number of studies, identifying the specific source or sources of heterogeneity is not possible. As discussed earlier, differences in the definition of dairy could confound this calcium analysis and account for some of the observed heterogeneity.

The remaining 5 studies with calcium data reported "total calcium" (21,31,32,36) or "dietary calcium" (33). Although pooling these latter 5 homogenous reports showed a statistically significant RR, that is, 1.15 (95% CI = 1.02–1.30), no clear dose response was shown across reports. Due to the small number of studies with comparable exposure categories and the statistical heterogeneity discussed previously, further pooling the available calcium data from the cohort studies was not possible. One must also consider that insufficient data exist regarding the potential influence of nondietary calcium supplements on prostate cancer risk.

A total of 7 cohort studies provided homogeneous data on cheese intake (as a single item; see Table 1) (24,26,28,30,32,33,34). The resultant RR was 1.11 (95% CI = 0.99–1.25).

Case-Control Studies

The case-control studies are presented in Table 2. Of these, 8 are population based (40,42,46–50,55), with approximately half of the reports utilizing a validated dietary questionnaire.

Of these 24 studies, 5 contained a dairy exposure category (i.e., Refs. 40, 42, 43, 46, 57). Pooling homogeneous data from these reports yielded an RR of 1.14 (95% CI = 1.00–1.29). Stratifying the analysis by hospital-based vs. population-based studies gave RRs of 1.20 (95% CI = 0.99–1.43) and 1.08 (95% CI = 0.90–1.30), respectively. As in the cohort analyses, all but 1 of the case-control studies showed no dose-response relationship, further supporting a lack of association between dairy product use and prostate cancer risk.

Table 2 lists the 10 case-control studies with data on milk intake (40,44,45,47,48,51–53,57,58). Two reports, that is, Andersson et al. (40) and Mettlin et al. (52) specified "whole milk" rather than simply "milk." Reference 51 provided a separate analysis for "skim milk" as well (to be discussed following). Pooling all 10 studies showed a summary RR of 1.28 (95% CI = 1.06–1.55), although Q indicated heterogeneity ($P = 0.04$). This is reflected, to some degree, in the wide variation in individual study relative risks.

Without knowing the particular proportion of subjects using various milk types among reports using a milk exposure category, it is not possible to further explore. We do not have calcium-adjusted data for the case-control studies examining milk as the exposure of interest. Given the findings among the cohort analyses, it is certainly possible that the observed

TABLE 3
Definitions of "Dairy" Exposure Category Across Cohort Studies

Reference	Items Included in "Dairy"
Chan et al. (20)	Whole milk, skim milk, cold breakfast cereal, cheese, ice cream
Giovannucci et al. (21)	Whole milk, skim/low-fat milk, cream, sour cream, sherbet, ice milk, ice cream, yogurt, cottage cheese, cream cheese, other cheese
Giovannucci et al. (22)	Whole milk, skim or low-fat milk, cream, sour cream, sherbet or ice milk, ice cream, yogurt, cottage or ricotta cheese, cream cheese, butter, other cheese
Hsing et al. (23)	Milk, ice cream
Keese et al. (24)	Milk, cheese, fresh cheese, yogurt
Koh et al. (25)	Whole milk, low-fat milk, cream, ice cream, yogurt, cheese, butter
Michaud et al. (28)	Whole milk, low-fat milk, skim milk, cream, sour cream, ricotta cheese, other cheese, sherbet, ice milk, ice cream, yogurt, cottage cheese, cream cheese, butter
Mitrou et al. (30)	Total milk, whole milk, low-fat milk, butter, ice cream, cream, cheese, sour milk
Rodriguez et al. (31)	Whole milk, low-fat milk, skim milk, cheese, low-fat yogurt, ice cream
Rohrmann et al. (32)	Whole milk, 2% milk, skim milk, cream, ice cream
Shuurman et al. (33)	Whole milk, low-fat milk, skim milk, cream, butter milk, chocolate milk, dry curd whole and skim yogurt, fat cheese, low-fat cheese
Tseng et al. (36)	Whole milk, evaporated milk, low-fat milk, skim milk, cream, sour cream, dry milk, buttermilk, cheese or cheese dishes, yogurt, cottage cheese, ice cream

heterogeneity could be attributed in large part to differences in calcium content, and this in turn could produce a spurious association due to the demographic differences in milk type use across reports as discussed previously. Pooling the population-based reports (40,47,48) gave an RR of 0.92 (95% CI = 0.66–1.29) vs. an RR of 1.49 (95% CI = 1.24–1.80) among the hospital-based reports with persistent heterogeneity ($P = 0.02$). There was wide variation in the types of controls used across the hospital-based reports. For instance, the control subjects utilized by DeStefani et al. (44) were almost entirely patients with malignancies other

TABLE 4
Comparison of Calcium Adjusted and Unadjusted Relative Risks for the Association of "Dairy" Intake and Prostate Cancer from the Available Cohort Studies[a]

Reference	Dairy Type	Unadjusted RR (CI)	Calcium Adjusted RR (CI)
Keese et al. (24)	Dairy products	2.16 (0.96–4.85)	1.33 (0.52–3.45)
	Milk	1.13 (0.54–2.34)	0.83 (0.39–1.77)
	Cheese	0.90 (0.42–1.91)	0.65 (0.29–1.44)
	Fresh cheese	2.38 (1.23–4.62)	2.13 (1.09–4.15)
	Yogurt	1.81 (0.87–3.76)	1.46 (0.68–3.14)
Michaud et al. (28)	Dairy	1.04 (0.89–1.20)	1.07 (0.88–1.3)
Mitrou et al. (30)	Total dairy	1.26 (1.04–1.51)	0.87 (0.66–1.14)
	Total milk	1.08 (0.91–1.30)	0.86 (0.70–1.07)
	Whole milk	1.05 (0.86–1.29)	0.93 (0.76–1.13)
	Low-fat milk	1.18 (0.97–1.44)	1.00 (0.81–1.23)
	Butter	1.00 (0.84–1.20)	1.04 (0.87–1.25)
	Ice cream	0.90 (0.75–1.08)	0.90 (0.75–1.08)
	Cream	1.09 (0.91–1.30)	1.11 (0.93–1.33)
	Cheese	1.13 (0.95–1.36)	1.04 (0.86–1.25)
	Sour milk	1.07 (0.90–1.28)	0.97 (0.81–1.22)
Tseng et al. (36)	Dairy	2.2 (1.2–3.9)	1.4 (0.6–3.4)
	Total milk	1.8 (1.1–2.9)	0.9 (0.4–1.9)
	Low-fat milk	1.5 (1.1–2.2)	1.1 (.07–1.7)

[a]Abbreviations are as follows: RR, relative risk; CI, confidence interval.

than prostate cancer, whereas no other hospital-based analysis used controls with malignant disease. Likewise, some reports excluded controls with urological diseases (57), whereas others included patients with benign prostatic hypertrophy (45,52). Clearly, the large differences across studies in choice of controls could contribute to the observed heterogeneity. Overall, therefore, the data do not support an association between milk intake and increased risk of prostate cancer.

A total of 10 reports analyzed calcium as listed in Table 2 (42,46,49,50,55,56,60,61,62,63). Pooling homogeneous data ($P = 0.34$) from all 10 reports resulted in an RR of 1.04 (95% CI = 0.90–1.15). Only 2 reports (49,50) provided separate analyses for calcium from food sources versus nonfood (supplement) sources. Interestingly, Kristal et al. (49) demonstrated an increased OR of 1.23 for calcium supplement use vs. 1.04 for "total calcium" intake (including from supplements) as did Ref. 50. In the latter case, total calcium gave an OR of 1.07 (95% CI = 0.63–1.84) vs. 0.87 (95% CI = 0.57–1.34) for calcium from food sources alone. Because there are no other data available related to supplement-derived calcium vs. dietary calcium, no further analysis was possible.

We pooled 5 case-control studies using "cheese" as the variable of interest (40,41,48,51,58). Combining all 5 studies showed an RR of 0.74 (95% CI = 0.62–0.87), although the data were heterogeneous ($P = 0.02$). Almost all of the observed heterogeneity was due to Refs. 41 and 48, the 2 largest in terms of sample size in the group (data not shown). Dropping these 2 reports from the analysis shows little change in the RRs, that is, RR = 0.73 (95% CI = 0.51–1.04), although the statistical heterogeneity disappears. The data suggest no clear relationship between cheese intake and prostate cancer risk.

Vitamin D

Finally, we identified all observational studies examining the relationship between vitamin D intake and prostate cancer risk. Relative risks from 6 reports were pooled (36,42,43,50,60,62). The resultant RR was 1.16 (95% CI = 0.98–1.38; Q = 5.43, $P = 0.37$). It must also be considered that only subjects in the highest vitamin D exposure category in Kristal et al. (50) had vitamin D intakes at or above the recommended intake of 400 IU per day for adults over age 50 (e.g., 568 IU per day in Kristal et al. [50]). All other studies showed relatively low vitamin D intakes among patients in the highest vs. lowest intake category as defined by individual authors, ranging from 132 IU/day (62) to 376 IU/day in the report by Berndt et al. (18). Therefore, the true effects of vitamin D on prostate cancer risk cannot be determined from the available data.

DISCUSSION

At present, few risk factors for prostate cancer are known, with age being 1 of the most important. As discussed earlier, a number of ecological studies (65–67) and observational analyses (21) suggest that dairy products and some dairy nutrients, such as calcium, may be risk factors for prostate cancer. A dietary etiology for this disease is also supported by studies of migrant populations, and biological mechanisms have been described to provide a basis to the epidemiological observations (2,67). The latter includes calcium's ability to suppress the formation of 1,25(OH)2D3 from 25-hydroxycholecalciferol with subsequent loss of its antiproliferative effects (66). Nonetheless, the finding of an association between dairy products and prostate cancer is inconsistent across studies of varying designs and employing different populations (68–70). In addition, the previously noted hypothesis that relatively high consumption of calcium could promote the development of prostate cancer via reduction in the production of 1,25-dihydroxyvitamin D (by its inhibition of secretion and circulating levels of parathyroid hormone and/or via a direct negative impact of the increased extracellular calcium concentration on 25(OH)-1-alpha-hydroxylase activity) is questionable (71). As discussed by Bonjour et al. (71), the existing human data do not show that large variations in calcium intake result in corresponding large changes in circulating levels of 1,25-(OH)2D sufficient to influence the biological risk of developing prostate cancer.

To potentially clarify the relationship between intake of dairy products and dairy-associated nutrients and the risk of prostate cancer, in this meta-analysis, we pooled data from 45 observational studies. Overall, these data provide no clear evidence of a relationship between these dietary factors and an increased risk of prostate cancer.

Numerous methodological issues complicate interpretation of studies on this topic. For instance, the risk may depend on the classification of the exposure variable used to define the type of dairy product. Among the cohort studies, Veierod et al. (37) found a statistically significant relationship between skim milk vs. whole milk use and prostate cancer risk, RR = 2.2 (95% CI = 1.3–3.7). Likewise, Chan et al. (20) included 5 dairy products in the dairy exposure group. Although when analyzed as a single variable (dairy), a nonstatistically significant result was seen, RR = 1.27 (95% CI = 0.97–1.66), individually, a positive association with prostate cancer risk was found only for skim milk, RR = 1.32 (95% CI = 1.12–1.56).

A number of studies have also supported the idea that dairy product consumption is related to various demographic variables. For instance, Elbon et al. (72) in a study of elderly Americans found that 4 factors significantly increased the probability of drinking lower fat milks vs. whole milk. These factors were nutrition knowledge, income, interest in reducing dietary cholesterol, and being female (72). Ford (73) also showed that calcium intake among Whites was positively associated with educational achievement. In addition, Lee et al. (74), utilizing the Continuing Survey of Food Intakes by Individuals, demonstrated 1) total fat intake of reduced fat milk drinkers is significantly lower than that of whole milk drinkers, 2) reduced fat milk drinkers consume more fruits and vegetables and less red meat, and 3) many skim milk drinkers have achieved the U.S. dietary goal for fat intake, that is, energy intake from fat <30% (74). Data from the Physicians Health Study found that men who consumed the most servings of dairy products per day smoked less, exercised more, and were more likely to be current users of vitamins (20). Half of the dairy intake among this cohort was from skim milk (20). If individuals engaging in such "healthy" behaviors also seek medical attention more frequently, including periodic rectal exams or prostate-specific antigen (PSA) screenings, a detection bias could also be operative and explain the weak association seen in some of the dairy studies. This possibility is supported by Chan et al. (20) who documented more frequent screening among those with higher calcium intakes.

Further arguing against a relationship between dairy and prostate cancer risk is the negative findings derived from pooling the available dairy case-control studies and the complete attenuation of calculated summary RRs with use of calcium-adjusted measures of association. In addition, most reports did not report dose-response relationships for any of the nutrient types examined.

Examination of the pooled calcium data also showed no clear association with prostate cancer risk. Data from cohort studies evaluating dairy-associated calcium were strongly heterogeneous and could not be combined. It is possible that differences in use of specific dairy calcium sources across study populations could partially account for this along with differing definitions of dairy as seen in Table 3. "Total calcium" yielded an RR of 1.15 (95% CI = 1.02–1.30), although this exposure category does not stratify by calcium from supplements. Therefore, the validity of using risk estimates of total calcium for making inferences on diary-associated calcium on prostate cancer risk is questionable.

This meta-analysis is the largest comprehensive overview of published data examining the influence of dairy products and dairy associated nutrients on prostate cancer risk (68,69). Prior published pooled analyses (68,69), as well as this one, have highlighted many of the methodological limitations inherent in any review of this data set. As noted previously, wide variation exists across studies in adjustments made to individual study estimates of effect. Study variables are also inconsistently catalogued; for instance, dairy exposure category components were seen to differ widely across reports. There was also wide variation in dietary instruments used, with some being validated, whereas others were not. In addition, different instruments vary in the types of nutrient emphasized (75).

Additionally, much of the literature predates the widespread use of PSA screening in the United States. Few studies provide information on proportion of cases (controls) screened for prostate cancer and the stage distribution of cancer cases included in individual analyses. If some demographic and dietary variables are associated with certain health behaviors such as seeking prostate cancer screening, information on stage distribution across study populations could provide important insights into whether a "screening artifact" is operative. Unfortunately, such information is lacking.

Overall, weak positive effects seen in some of the reviewed observational studies could be due to uncontrolled confounding or other sources of bias. These findings, coupled with the questionable proposed biological basis for a dairy/prostate cancer association, provide little support for a causal role of these dietary factors in the etiology of prostate cancer.

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