Dairy products, calcium and prostate cancer risk

KA Koh1, HD Sesso2,3, RS Paffenbarger Jr3,4 and I-M Lee*,2,3

1Harvard University, 8 Garden Street, Cambridge, MA 02138, USA; 2Department of Medicine, Division of Preventive Medicine, Brigham and Women’s Hospital and Harvard Medical School, 900 Commonwealth, Avenue East, Boston, MA 02215, USA; 3Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA; 4Division of Epidemiology, Department of Health Research Policy, HRP Redwood Building, T213B, Stanford, CA 94305, USA

In a prospective study of 10,011 men with 815 prostate cancer cases, despite plausible biological mechanisms, neither increasing intake levels of dairy products nor calcium from dairy products (P trend; 0.23 and 0.64, respectively), or calcium supplements was associated with prostate cancer risk (relative risk, 1.05; 95% confidence interval, 0.84–1.31).

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Prostate cancer is the most commonly diagnosed non-skin cancer among men in North America, Europe, and parts of Africa, with the United States having the highest prostate cancer incidence in the world (Gronberg, 2003). Although its incidence is increasing steadily in almost all countries, few modifiable predictors for the disease have been identified (Gronberg, 2003). Well-established risk factors, such as age, family history, race, and country of residence, are not amenable to modification and have limited utility as primary prevention strategies.

Calcium intake, a modifiable dietary factor, has recently been proposed as a risk factor for prostate cancer. Evidence from in vitro and animal studies suggests that risk may be increased by higher levels of calcium, since these suppress 1,25-dihydroxy-vitamin D3, the most active form of vitamin D3, that inhibits the proliferation of prostate cancer cells and promotes their differentiation (Schwartz et al, 1995, 1997; Giovannucci, 1998). However, recent studies have yielded inconsistent results (Gao et al, 2005), although few studies have considered intake from calcium supplementation, that can provide higher doses than dietary intake. Given calcium’s importance in the prevention of diseases such as osteoporosis, we conducted a study of the question in a large cohort of men.

MATERIALS AND METHODS

Subjects

The Harvard Alumni Health Study, initiated in the 1960s, is an ongoing cohort study of men who entered Harvard University, United States, as undergraduates between 1916 and 1950. Health information is obtained from subjects via questionnaires mailed at periodic intervals. The present study utilises data from a questionnaire mailed in 1988 that included detailed information on diet, and eligible subjects were 12,805 men who responded. We excluded men reporting cancer at baseline (n = 1,731) and those not providing information on dairy product intake (n = 60). Of the remaining 11,014 men, we successfully followed 10,011 (90.9%) for the development of prostate cancer; these men represent the subjects for the present analysis.

Assessment of calcium intake and other factors

The 1988 questionnaire assessed diet using an abbreviated version (23 food items) of a validated semiquantitative frequency questionnaire (Willett et al, 1985, 1987). Men indicated their usual daily intake of seven different dairy products (whole milk, low fat milk, cream, ice cream, yogurt, cheese and butter) using pre-specified responses ranging from ‘almost never’ to ‘six or more times per day.’ On the original, longer version of the questionnaire, 13 dairy items were assessed. However, we believe our assessment of calcium intake using the seven items is reasonably valid. While we did not directly validate our 7-item questionnaire against the longer questionnaire, a previous study that assessed fewer items – milk (including whole, skim and milk with cereal), cheese and ice cream – was able to account for 82% of the variation in calcium consumption in male physicians (Chan et al, 2001).

We estimated calcium intake in mg day−1 based on the frequency of consumption of each dairy product and the calcium composition of specified portions of each dairy product, using data from the US Department of Agriculture (US). In addition to dairy products, we asked alumni about use of calcium supplements (occasional use, use of ordinary daily dose, or use of high daily dose).

From the 1988 questionnaire, we also obtained information on potential confounders, including weight, height, physical activity, cigarette smoking, alcohol intake, and paternal history of prostate cancer.
Ascertainment of prostate cancer

Men reported physician-diagnosed prostate cancer on subsequent health questionnaires in 1993 and 1998. A previous validation study has shown that such self-reports were confirmed by attending physicians in 91% of cases (Lee et al, 1992). In addition, we obtained death certificates for men who died through 1998 to ascertain cases of fatal prostate cancer.

Data analyses

In separate analyses, we considered intakes of (1) dairy products, (2) calcium from dairy products, and (3) calcium supplements, in relation to prostate cancer risk. For dairy products, we created a dairy score, representing servings of dairy products per day, by summing the frequency of consumption of the seven dairy products, and categorised men into approximate quartiles (Table 1). Similarly, we grouped men into approximate quartiles of calcium intake, in mg day\(^{-1}\), based on the frequency of consumption of each dairy product and the calcium composition of each dairy product (Table 2). For supplements, because only 8% of men reported using supplemental calcium (with most taking an ordinary daily dose), we grouped men as non-users or users. We used Cox proportional hazards regression models to estimate the ordinary daily dose), we grouped men as non-users or users. We used Cox proportional hazards regression models to estimate the relative risks (RR) and 95% confidence intervals for developing prostate cancer associated with dairy and calcium intakes. Initially, we adjusted for age (in continuous years) only, but later for the following potential confounders: body mass index (BMI), smoking (never, past, or current), total energy intake (in quartiles), alcohol intake (none, 1–3, 4–6, or ≥seven drinks week\(^{-1}\)), physical activity (≥1000 kcal/week), red meat intake (≥3 servings/month, 1–2 servings month, or ≥3 servings month\(^{-1}\)), vegetable intake (≤six servings week, 1–2 servings week, or ≥three servings week\(^{-1}\)), and paternal history of prostate cancer (no or yes). We repeated the above analyses, examining only fatal prostate cancer, owing to the suggestion from some previous studies that the association may be stronger with advanced or fatal prostate cancer (Giovannucci et al, 1998; Schuurman et al, 1999; Chan et al, 2001; Rodriguez et al, 2003).

RESULTS

Among the 10011 men, the mean age at baseline in 1988 was 67 years. Table 1 shows the baseline characteristics of subjects according to dairy product intake. Men in the highest quartile of dairy consumption tended to be older, were more likely to smoke, and were less likely to be overweight. They also consumed more red meat and vegetables, and were more likely to have a paternal history of prostate cancer. There were no clear trends for physical activity and alcohol consumption.

Table 1 Baseline characteristics of men in 1988 according to dairy product intake, Harvard Alumni Health Study

| Characteristic          | 0–<1.25 (n = 2460) | 1.25–<2.00 (n = 2537) | 2.00–<3.25 (n = 2416) | ≥3.25 (n = 2598) |
|-------------------------|--------------------|-----------------------|-----------------------|-----------------|
| Mean age (s.d.) (years) | 66.0 (7.5)         | 66.9 (7.9)            | 67.3 (8.0)            | 68.7 (8.4)      |
| Cigarette smoking (%)   | 7.6                | 7.6                   | 6.7                   | 10.1            |
| Overweight or obese (%) | 46.0               | 43.4                  | 42.6                  | 39.4            |
| Physical activity ≥1000 kcal/week (%) | 67.3 | 70.2                  | 69.3                  | 66.2            |
| Alcohol intake (%)      | 71.4               | 73.0                  | 73.7                  | 70.4            |
| Red meat intake ≥3 servings/week (%) | 21.2 | 25.3                  | 33.4                  | 38.7            |
| Vegetable intake ≥3 servings/day (%) | 14.2 | 12.6                  | 13.7                  | 18.6            |
| Paternal history of prostate cancer (%) | 3.2   | 4.8                   | 4.5                   | 4.2             |

\(^a\)Body mass index ≥25 kg m\(^{-2}\). \(^b\)Sufficient to meet recommended level of physical activity.

Table 2 RR of total prostate cancer according to dairy product and calcium intake, Harvard Alumni Health Study

| Dairy product intake (servings/day)\(^b\) | Age-adjusted RR (95% confidence interval) | Multivariate RR\(^a\) (95% confidence interval) |
|-----------------------------------------|-----------------------------------------|-----------------------------------------------|
| 0–<1.125 (189 cases)                   | 1.00 (referent)                         | 1.00 (referent)                                |
| 1.25–<2.00 (183 cases)                 | 0.91 (0.74–1.12)                       | 0.91 (0.71–1.15)                              |
| 2.00–<3.25 (220 cases)                | 1.14 (0.90–1.39)                       | 1.11 (0.87–1.42)                              |
| ≥3.25 (223 cases)                     | 1.07 (0.88–1.31)                       | 1.11 (0.85–1.46)                              |

| Dairy calcium intake (mg/day)\(^b\) | Age-adjusted RR (95% confidence interval) | Multivariate RR\(^a\) (95% confidence interval) |
|-----------------------------------|-----------------------------------------|-----------------------------------------------|
| 0–199 (209 cases)                 | 1.00 (referent)                         | 1.00 (referent)                                |
| 200–499 (167 cases)               | 0.83 (0.68–1.02)                       | 0.81 (0.64–1.02)                              |
| 500–999 (238 cases)               | 0.97 (0.81–1.17)                       | 0.97 (0.73–1.14)                              |
| ≥600 (201 cases)                  | 0.96 (0.79–1.17)                       | 0.91 (0.70–1.18)                              |

RR = relative risks. \(^a\)Adjusted for age; smoking; body mass index; physical activity; intakes of alcohol, red meat and vegetables; total caloric intake; and paternal history of prostate cancer. \(^b\)Summed from intakes of milk, low-fat milk, cream, yogurt, cheese, ice cream, and butter. Median: 849 mg day\(^{-1}\); interquartile range: 710–1146 mg day\(^{-1}\).

During follow-up through 1998, 815 incident cases of prostate cancer developed, of which 99 cases were fatal. Table 2 shows no significant relation between higher intakes of dairy products and risk of prostate cancer, whether in age- or multivariate-adjusted analyses (P trend = 0.16 and 0.23, respectively). In multivariate analyses, men in the highest quartile had an RR of prostate cancer of 1.11 (95% confidence interval, 0.85–1.46), compared with the lowest quartile. When individual dairy products were examined, there were also no significant associations (data not shown).

For calcium intake, Table 2 shows that levels of intake were not significantly associated with prostate cancer risk, either in age- or multivariate-adjusted analyses (P trend = 0.93 and 0.64, respectively). Calcium supplement use was also not significantly related to risk (multivariate RR = 1.05 (0.84–1.31)).

When we repeated the above analyses, examining only fatal (instead of all) prostate cancer, we continued to observe no significant associations between dairy product or calcium intakes and risk of fatal prostate cancer (P trend = 0.64 and 0.52, respectively; Table 3).

DISCUSSION

This large study does not support the hypothesis that higher intakes of calcium are associated with an increased risk of prostate...
In vitro vitamin D₃ or its analogues reduces the growth of prostate gland cancerous prostate epithelial cells and promotes their differentiation (Renehan et al, 2003). Additionally, higher intakes of milk and calcium may increase insulin-like growth factor-1 (IGF-1) (Gunnell et al, 2003), which may be associated with increased prostate cancer risk (Renehan et al, 2004). Findings from previous studies have been conflicting. While some large cohort studies (with >500 cases) have reported significant positive associations between dairy products and/or calcium intake and prostate cancer (Giovannucci et al, 1998; Chan et al, 2001), others have not (Schuurman et al, 1999; Michaud et al, 2001; Rodriguez et al, 2003). A recent clinical trial of calcium supplementation (1200 mg day⁻¹) in the prevention of colorectal adenomas found no significant increase in prostate cancer (70 cases) risk with supplementation in secondary analyses, and even a suggestion of a protective effect (Baron et al, 2005). A 2005 meta-analysis of prospective cohort studies reported increased RR of 1.11 (95% confidence interval, 1.00–1.22) and 1.39 (1.09–1.77) for all prostate cancer among men with the highest intakes of dairy products and calcium, respectively, and stronger associations for advanced prostate cancers (RR = 1.33 and 1.46, respectively) (Gao et al, 2005). However, with the inclusion of a 2006 Australian study that found no association with calcium intake (Severi et al, 2006), the findings for all prostate cancer were weakened (RR = 1.09 (1.00–1.20) for dairy products; 1.32 (1.05–1.67) for calcium) (Severi et al, 2006). The present study agrees with the Australian data, in showing no significant relation between calcium intake and risk.

Strengths of the present study include its prospective design, large number of cases (including fatal cases), and high rates of follow-up. Additionally, dietary information was ascertained using a validated food frequency questionnaire, and information was available on several potential confounders. The study also included many older men (baseline age 67 years), who are at greater risk for prostate cancer (Gronberg, 2003).

One potential limitation is that the calcium intake may have been too low in the present study. The highest category of calcium intake from dairy products was >600 mg day⁻¹ (median 849 mg day⁻¹; interquartile range 710–1416 mg day⁻¹). Thus, many men would have had intakes below US recommendations, and several would have had intakes falling below UK recommendations (Prentice, 2002). However, a previous large study did observe a significantly increased risk at >600 mg day⁻¹ calcium intake (Chan et al, 2001), making it less likely that the range of intakes was reasonable for our null findings. Further, since we relied on self-reported diet, random misclassification may have occurred, biasing findings to the null. However, the large number of cases offers some assurance that an association of moderate magnitude, as has been reported in previous studies (Giovannucci et al, 1998), would not have been missed. Finally, we were specifically interested in advanced prostate cancer, but did not have information on the stage or grade of prostate cancers diagnosed in the present study. However, we were able to ascertain fatal prostate cancers, which would reasonably reflect advanced disease.

In conclusion, this study does not support the biologically plausible hypothesis that a high calcium intake increases prostate cancer risk. Further studies should include other populations, such as Blacks, in whom prostate cancer rates are higher (Hayes et al, 1999; Gronberg, 2003), to extend the generalisability of the present findings.

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REFERENCES

Baron JA, Beach M, Wallace K, Grau MV, Sandler RS, Mandel JS, Heber D, Greenberg ER (2005) Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiol Biomarkers Prev 14: 586–589

Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL (2001) Dairy products, calcium, and prostate cancer risk in the Physicians’ Health Study. Am J Clin Nutr 74: 549–554

Gao X, LaValley MP, Tucker KL (2005) Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. J Natl Cancer Inst 97: 1768–1777

Giovannucci E (1998) Dietary influences of 1,25(OH)2 vitamin D in relation to prostate cancer: a hypothesis. Cancer Causes Control 9: 567–582
Giovannucci E, Rimm EB, Wolk A, Ascherio A, Stampfer MJ, Colditz GA, Willett WC (1998) Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 58: 442–447

Gronberg H (2003) Prostate cancer epidemiology. Lancet 361: 859–864

Gunnell D, Oliver SE, Peters TJ, Donovan JL, Persad R, Maynard M, Gillatt D, Pearce A, Hamdy FC, Neal DE, Holly JM (2003) Are diet-prostate cancer associations mediated by the IGF axis? A cross-sectional analysis of diet, IGF-I and IGFBP-3 in healthy middle-aged men. Br J Cancer 88: 1682–1686

Hayes RB, Ziegler RG, Gridley G, Swanson C, Greenberg RS, Swanson GM, Schoenberg JB, Silverman DT, Brown LM, Pottem LM, Liff J, Schwartz AG, Fraumeni Jr F, Hoover RN (1999) Dietary factors and risks for prostate cancer among blacks and whites in the United States. Cancer Epidemiol Biomarkers Prev 8: 25–34

Lee IM, Paffenbarger Jr RS, Hsieh CC (1992) Physical activity and risk of prostatic cancer among college alumni. Am J Epidemiol 135: 169–179

Lucia MS, Anzano MA, Slayter MV, Anver MR, Green DM, Shrader MW, Logsdon DL, Driver CL, Brown CC, Peer CW (1995) Chemopreventive activity of tamoxifen, N-(4-hydroxyphenyl)retinamide, and the vitamin D analogue Ro24-5531 for androgen-promoted carcinomas of the rat seminal vesicle and prostate. Cancer Res 55: 5621–5627

Michaud DS, Augustsson K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E (2001) A prospective study on intake of animal products and risk of prostate cancer. Cancer Causes Control 12: 557–567

Prentice A (2002) What are the dietary requirements for calcium and vitamin D? Calcif Tissue Int 70: 83–88

Renehan AG, Zwahlen M, Minder C, O’Dwyer ST, Shalet SM, Egger M (2004) Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 363: 1346–1353

Rodriguez C, McCullough ML, Mondul AM, Jacobs EJ, Fakhraabadi-Shokoohi D, Giovannucci EL, Thun MJ, Calle EE (2003) Calcium, dairy products, and risk of prostate cancer in a prospective cohort of United States men. Cancer Epidemiol Biomarkers Prev 12: 597–603

Schuurman AG, van den Brandt PA, Dorant E, Goldbohm RA (1999) Animal products, calcium and protein and prostate cancer risk in The Netherlands Cohort Study. Br J Cancer 80: 1107–1113

Schwartz GG, Hill CC, Oeler TA, Becich MJ, Bahnson RR (1995) 1,25-Dihydroxy-16-ene-23-yne-vitamin D3 and prostate cancer cell proliferation in vivo. Urology 46: 365–369

Schwartz GG, Wang MH, Zang M, Singh RK, Siegal GP (1997) 1 alpha, 25-Dihydroxyvitamin D (calcitriol) inhibits the invasiveness of human prostate cancer cells. Cancer Epidemiol Biomarkers Prev 6: 727–732

Severi G, English D, Hopper J, Giles G (2006) Re: Prospective studies of dairy product and calcium intakes and prostate cancer risk: A meta-analysis. J Natl Cancer Inst 98: 794–795

US Department of Agriculture, Agricultural Research Service (1998) USDA Nutrient Database for Standard Reference, Release 12, Nutrient Data Laboratory http://www.nal.usda.gov/fnic/foodcomp accessed 22 September 2005

Willett WC, Reynolds RD, Cottrell-Hoehner S, Sampson L, Browne ML (1987) Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. J Am Diet Assoc 87: 43–47

Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE (1985) Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 122: 51–65

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