Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study[1-3]

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ABSTRACT

Background: A high calcium intake, mainly from dairy products, may increase prostate cancer risk by lowering concentrations of 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], a hormone thought to protect against prostate cancer. The results of epidemiologic studies of this hypothesis are inconclusive.

Objective: We investigated the association between dairy product and calcium intakes and prostate cancer risk in the Physicians' Health Study, a cohort of male US physicians.

Design: At baseline, the men answered abbreviated dietary questionnaires. During 11 y of follow-up, we documented 1012 incident cases of prostate cancer among 20 885 men. We estimated dairy calcium intake on the basis of consumption of 5 major dairy products and used logistic regression to estimate relative risk.

Results: At baseline, men who consumed >600 mg Ca/d from skim milk had lower plasma 1,25$(OH)_2D_3$ concentrations than did those consuming ≤150 mg Ca/d [71 compared with 85 pmol/L (30.06 compared with 35.64 pg/mL); $P = 0.005$]. Compared with men consuming ≤0.5 daily servings of dairy products, those consuming >2.5 servings had a multivariate relative risk of prostate cancer of 1.34 (95% CI: 1.04, 1.71) after adjustment for baseline age, body mass index, smoking, exercise, and randomized treatment assignment in the original placebo-controlled trial. Compared with men consuming ≤150 mg Ca/d from dairy products, men consuming >600 mg/d had a 32% higher risk of prostate cancer (95% CI: 1.08, 1.63).

Conclusions: These results support the hypothesis that dairy products and calcium are associated with a greater risk of prostate cancer. *Am J Clin Nutr* 2001;74:549–54.

INTRODUCTION

Prostate cancer remains the most common cancer among men in the United States and is a leading cause of cancer death. Few modifiable risk factors have been well established, although several dietary risk factors have been investigated in the past decade. Greater intakes of dairy products, meat, fat, and total energy and lower intakes of tomato products, lycopene, selenium, and vitamin E have all been linked to higher prostate cancer risk (1–3).

Countries with a high per capita consumption of dairy products have higher incidence rates of prostate cancer than do countries in which few dairy products are consumed. Twelve of 14 epidemiologic studies, summarized in a review (4), reported relative risks (RRs) of 1.5–2.5 comparing high with low dairy product intake. Dairy products are a major source of calcium; dietary calcium could influence prostate cancer development by down-regulating the production of 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], a hormone thought to protect against prostate cancer (4, 5).

The prospective Health Professionals Follow-up Study (HPFS) reported a multivariate RR of metastatic prostate cancer of 4.57 (95% CI: 1.88, 11.1) for men consuming >2000 mg Ca/d compared with <500 mg/d (6). In an analysis limited to calcium from supplements only, the association remained strong, indicating that calcium, and not some correlate in dairy products, enhanced risk. A large, population-based, case-control study in Sweden found a similar association for dietary calcium (7), and both studies reported the strongest associations for advanced or metastatic prostate cancer.

In contrast with these results, an analysis of baseline dietary data from the Finnish α-Tocopherol β-Carotene Cancer Prevention Trial (8) showed a statistically nonsignificant positive association for calcium intake and prostate cancer risk (for high versus low quintiles, RR = 1.6; 95% CI: 0.8, 3.0). This study included only 184 cases, however, and calcium intake was uniformly higher than in the other populations. The results of the Netherlands Cohort Study showed a significant positive trend for milk products ($P = 0.02$), but not for calcium (9). Three case-control studies—in the United States (10), Greece (11), and Japan (12)—found no significant association between

dietary calcium and prostate cancer risk, whereas a Serbian case-control study observed a statistically significant inverse trend for calcium and prostate cancer (13). The Greek study, however, did observe a positive nonsignificant association for milk and dairy product intake and risk of prostate cancer (11). A US case-control study reported no association between calcium supplement use and prostate cancer risk (14). In summary, the evidence for an association between calcium intake and prostate cancer risk, although suggestive, remains conflicting and limited. Thus, we investigated dairy product and dietary calcium intakes and prostate cancer risk in a distinct US population of male physicians.

SUBJECTS AND METHODS

Subjects

The Physicians' Health Study was a randomized, blinded, placebo-controlled trial of aspirin and β-carotene conducted among 22071 US male physicians beginning in 1982; the primary trial results were published previously (15, 16). Men completed brief follow-up questionnaires after the 18-wk run-in period and annually thereafter through 31 December 1995.

For the current investigation, we limited the study population to the 20885 men who returned the relevant abbreviated dietary questionnaires, did not have a diagnosis of cancer at baseline, and provided information on body mass index. Follow-up was >99% complete during the 11-y period from baseline—which was the return date of the 24-mo questionnaire (≈1984)—through 31 December 1995 (16). The study design and methods used in this investigation were reviewed and approved by the Human Research Committee of Brigham and Women's Hospital.

Identification of prostate cancer cases

During follow-up, we documented 1012 incident self-reported cases of prostate cancer among the 20885 men in our study population. When a participant reported a new diagnosis of prostate cancer, we requested permission to obtain hospital records and pathology reports for review by the study investigators. Information on tumor grade and stage at diagnosis was extracted, and the diagnosis of prostate cancer was confirmed by medical chart review in 99.1% (1003/1012) of cases. To examine possible different effects of dairy product and calcium intakes on advanced compared with nonadvanced cancer, we considered a man to have advanced disease if he fulfilled at least one of the following criteria: *1*) he was diagnosed with stage C or D prostate cancer (on the basis of the Whitmore-Jewett classification scheme; 17), *2*) his tumor had poor histologic differentiation at diagnosis, or *3*) he had a Gleason tumor grade of ≥7 at diagnosis. Of the 1012 total incident cases, 411 were advanced and 437 were nonadvanced; we were unable to classify 164 cases because of insufficient information.

Dietary assessment methods

The men completed short self-administered questionnaires annually, which assessed dietary and other lifestyle habits. At 18 wk and 24 mo, the men reported their consumption of cold breakfast cereal, whole milk, and skim milk; at 12 mo, they reported intakes of cheese and ice cream. Cold breakfast cereal was considered a major contributor to dairy product consumption because of the milk that is usually consumed with cereal; the original milk questions assessed consumption of only glasses of milk. For cereal, whole milk, and skim milk, we averaged intake values from the 18-wk and 24-mo questionnaires because the average was likely to better reflect overall long-term intake than either value alone (18). We considered these 5 foods to be the main contributors to dairy product intake and combined their information to create a dairy score, representing servings of dairy products per day.

We were also interested specifically in the effects of calcium on prostate cancer risk. To estimate how well these 5 dairy foods captured total calcium intake, we used the comprehensive dietary database from the HPFS from 1986. The HPFS had information on the consumption of 131 food items, including 13 dairy products. To examine the adequacy of using the 5 foods alone to estimate total dietary calcium intake, we created a linear regression model in which total dietary calcium was the dependent variable and intakes of whole milk, skim milk, cold breakfast cereal, cheese, and ice cream were the independent variables. The R^2 was 0.82, indicating that these foods accounted for ≈82% of the variation in calcium consumption and would provide a reasonable estimate of calcium intake. Thus, for the current investigation, we estimated individual daily calcium intake by summing the daily calcium contributions from each of these 5 dairy foods. One serving of cold breakfast cereal contributed the same amount of calcium as one serving of skim milk; 73% of the men consumed whole milk less than once per week, and only 6% of the men consumed whole milk once per day or more. The total calcium contributed by each dairy food was the product of the frequency of consumption of each food and the calcium composition (19) of specified portions of each food.

Statistics

To examine the effects of dairy product and calcium intakes on prostate cancer risk, we used unconditional logistic regression models to calculate odds ratios and 95% CIs as estimates of RR. The RR provides an estimate of the magnitude of the association between exposure and disease by comparing the risk of disease in one group exposed to some factor (eg, high dairy product intake) with the risk of disease in another group not exposed to the factor. Thus, an RR of 1.0 indicates a null result or no difference in disease risk by that factor. CIs provide an estimate of the precision of the RRs; CIs that do not include the null value of 1.0 are statistically significant at the 0.05 level. We also examined linear trends by considering the medians of the categories for each nutrient or food as continuous variables in a logistic regression model. All statistics were calculated by using SAS (version 6.12; SAS Institute Inc, Cary, NC). A 0.05% significance level was used for all tests.

We controlled for the following baseline characteristics: age (in 12, 3-y categories), randomized treatment assignment in the original trial (aspirin: yes or no; β-carotene: yes or no), quintiles of body mass index (in kg/m²), smoking (never, past, current, and missing), and exercise (exercised vigorously 1–3 times/mo, 1–4 times/wk, 5–7 times/wk, or missing). We controlled for body mass index and exercise to minimize potential confounding due to total energy intake.

The dietary questionnaires were not comprehensive; thus, we were unable to adjust for total energy directly. To minimize misclassification due to general over- and underreporting and to partially adjust for potential confounding by total energy or food intake, we created a food score that was the sum of servings per

TABLE 1
Baseline characteristics of 20 885 men in the Physicians' Health Study, by category of dairy product intake

	Dairy product intake (servings/d)[1]				
	0–0.50 (n = 2980)	0.51–1.00 (n = 4287)	1.01–1.50 (n = 4232)	1.51–2.50 (n = 5798)	>2.50 (n = 3588)
Age (y)	52 ± 9[2]	52 ± 9	53 ± 9	54 ± 10	55 ± 10
BMI (kg/m^2)	24.8 ± 3.0	25.1 ± 3.0	25.1 ± 3.0	24.8 ± 3.0	24.9 ± 3.1
Dairy calcium intake score (mg/d)	62 ± 35	176 ± 53	309 ± 65	507 ± 99	928 ± 253
Smoking (%)[3]					
Never	45	46	49	53	54
Past	40	42	40	39	35
Current	15	12	11	9	10
Exercise (%)[4]					
1–3 times/mo	34	30	27	25	23
1–4 times/wk	52	56	56	57	56
5–7 times/wk	13	14	16	17	20
Multiple vitamin use (%)[5]					
Never	68	66	66	63	60
Past	15	16	15	16	17
Current	17	18	19	21	23
Vitamin E supplement use (%)[6]	4.2	4.5	4.9	5.2	5.1

[1] Represents dairy product and calcium intakes, based on the consumption of 5 major dairy foods (skim milk, whole milk, cheese, ice cream, and cold breakfast cereal), assessed in 1982–1984. Because of the large sample size, differences across categories of dairy product intake were statistically significant.
[2] $\bar{x} \pm$ SD.
[3] Data were missing for 34 men.
[4] Data were missing for 174 men.
[5] Data were missing for 68 men.
[6] Men were considered users of vitamin E supplements if they reported taking vitamin E for >6 mo at baseline.

month of the 29 other food items asked about during the first 2 y. These foods included chicken, 3 types of fish, beef, processed meats, cookies, chips, nuts, fried foods, and 13 types of fruit and vegetables. We included quintiles of this food score in a secondary analysis of dairy product and calcium intakes to approximately control for total food and energy consumption. This method was examined and used previously in a Swedish case-control study of dairy product intake, calcium intake, and prostate cancer risk (7). In that study, which included a comprehensive diet assessment, we observed that adjusting for major food groups such as meat, vegetables and fruit, dairy products, and grains had approximately the same effect on the main associations as adjusting for total energy.

Data on usage of supplemental vitamin E were collected in 1982 and there is some evidence that supplemental vitamin E might protect against prostate cancer (20–22). However, <5% of the men used supplemental vitamin E, and inclusion of this variable in our multivariate models did not alter the main results; thus, we did not retain vitamin E in the final multivariate models.

Our primary analysis was to examine dairy product and calcium intakes and prostate cancer risk. We categorized dairy product intake into approximate quintiles; cutoffs for the dairy calcium categories were based on the amount of calcium in 0.5, 1, and 2 servings of milk (single servings of skim and whole milk were considered to contain 307.5 and 291 mg Ca, respectively). We were also interested in whether any associations were stronger for advanced cases, as was reported in other studies (6, 7).

A proposed mechanism for a positive association between dairy product intake and risk of prostate cancer is that calcium intake suppresses the production of $1,25(OH)_2D_3$. In a previous nested case-control study (23), we examined the relation between vitamin D metabolites and prostate cancer. To examine the biological plausibility of this hypothesized mechanism, we examined the association between intake of calcium and plasma $1,25(OH)_2D_3$ and 25-hydroxyvitamin D [25(OH)D; the precursor of $1,25(OH)_2D_3$] concentrations.

RESULTS

The baseline characteristics of the study population by categories of dairy product intake are presented in **Table 1**. Men who consumed the most servings of dairy products per day tended to smoke slightly less, exercise more frequently, and be older and were more likely to be current users of multivitamins than were men who consumed the least servings of dairy products.

Men in the highest categories of dairy product and calcium intakes had a statistically significant $\approx 30\%$ greater risk of prostate cancer than did those in the lowest consumption categories (**Table 2**). We observed significant, positive linear trends for both dairy product and calcium intakes. Each additional 500 mg Ca from dairy products consumed per day corresponded to a 16% increase in risk of prostate cancer ($P = 0.03$). When we further adjusted for quintiles of the food score, the results were similar although slightly attenuated.

We considered the possibility that the elevated RRs reflected simply an increased risk associated with greater overall food consumption. When we examined several other foods (chicken, fish, and eggs) individually, however, we found no such general increase in risk with increasing quartiles of consumption, and adjustment for total food intake had little effect on the estimates for calcium (Table 2).

Because the dietary data were not complete, we could not examine total fat or protein intake as potential confounders of the dairy product and calcium associations. However, we did calculate intakes of dairy fat and dairy protein from the 5 dairy foods used to compute dairy calcium. Neither of these was significantly

TABLE 2
Dairy product and calcium intake and the relative risk (RR) of prostate cancer for 20 885 men in the Physicians' Health Study[1]

	Age-adjusted RR	Multivariate RR[2]	Multivariate food-adjusted RR[3]
Dairy product intake (servings/d)			
0–0.50 ($n = 102$)	1.00	1.00	1.00
0.51–1.00 ($n = 175$)	1.20 (0.93, 1.55)	1.20 (0.93, 1.54)	1.15 (0.88, 1.51)
1.01–1.50 ($n = 213$)	1.35 (1.06, 1.72)	1.34 (1.05, 1.71)	1.32 (1.01, 1.71)
1.51–2.50 ($n = 312$)	1.34 (1.06, 1.69)	1.32 (1.05, 1.67)	1.29 (1.00, 1.66)
>2.50 ($n = 210$)	1.36 (1.06, 1.74)	1.34 (1.04, 1.71)	1.27 (0.97, 1.66)
P for trend[4]	0.04	0.05	0.14
Dairy calcium intake (mg/d)			
0–150 ($n = 155$)	1.00	1.00	1.00
151–300 ($n = 206$)	1.24 (1.00, 1.54)	1.24 (1.00, 1.54)	1.21 (0.96, 1.53)
301–600 ($n = 377$)	1.34 (1.10, 1.63)	1.33 (1.09, 1.61)	1.35 (1.09, 1.66)
>600 ($n = 274$)	1.34 (1.09, 1.65)	1.32 (1.08, 1.63)	1.29 (1.04, 1.62)
P for trend[4]	0.02	0.03	0.05

[1] Dairy product and calcium intakes are based on the consumption of 5 major dairy foods (skim milk, whole milk, cheese, ice cream, and cold breakfast cereal) assessed in 1982–1984. 95% CI in parentheses.

[2] Adjusted for baseline measures of age in 12, 3-y categories, smoking (never, past, current, or missing), vigorous exercise (1–3 times/mo, 1–4 times/wk, 5–7 times/wk, or missing), body mass index (quintiles), and randomized treatment assignment in the original trial (aspirin, β-carotene, or placebo).

[3] Adjusted for all of the above plus quintiles of the food score. Analysis based on 18 761 men, including 889 incident prostate cancer cases, after excluding men with missing food score data.

[4] Trends based on the medians of the categories.

associated with risk of prostate cancer [the food-adjusted multivariate RRs for being in the highest versus lowest quartile of consumption were 1.06 (95% CI: 0.86, 1.30) for dairy fat and 1.21 (95% CI: 0.98, 1.48) for dairy protein]. We could not include butter or cream in these analyses because <6000 men responded to this question in 1983.

When we considered the individual association of each of the 5 dairy foods with prostate cancer risk, only skim milk was significantly positively related when men who consumed one or more servings per day were compared with nonconsumers (multivariate RR: 1.32; 95% CI: 1.12, 1.56). Skim milk (from cereal and individual glasses) was the major contributor to dairy product intake (accounting for 48% of total dairy product intake) and contains more calcium than any of the other dairy items. Calcium from skim milk (from cereal and individual glasses) accounted for 57% of the total assessed dairy calcium intake.

Dairy product intake was equally associated with risk of advanced and nonadvanced prostate cancer. The multivariate RRs for being in the highest versus the lowest consumption group of dairy products were 1.38 (95% CI: 0.95, 2.01) and 1.42 (95% CI: 0.98, 2.04) for advanced and nonadvanced cases, respectively. For calcium intake, the multivariate RRs comparing extreme categories were 1.30 (95% CI: 0.94, 1.78) and 1.47 (95% CI: 1.08, 1.98) for advanced and nonadvanced cases, respectively.

To investigate the possible suppression of production of $1,25(OH)_2D_3$ by calcium, we examined the cross-sectional association between dairy calcium intake and plasma $1,25(OH)_2D_3$ concentrations in a subset ($n = 373$) of the study population who provided blood samples at baseline, had vitamin D metabolites measured in a previous investigation (23), had complete data on baseline dairy product intake, and did not subsequently develop prostate cancer. Although the serum and dietary information was collected at baseline when all men were clinically free of cancer, we limited our analysis to those men who did not develop prostate cancer later because some men may have been harboring latent undiagnosed prostate cancer.

In a linear regression model adjusted for age, body mass index, and smoking status, dairy calcium was significantly inversely associated with $1,25(OH)_2D_3$ concentrations: for every 300-mg increase in total daily calcium consumption from dairy products, $1,25(OH)_2D_3$ concentrations declined 2 pmol/L (1.02 pg/mL; $\beta = -0.0034$, $P = 0.007$). The association was stronger when we examined $1,25(OH)_2D_3$ and calcium intake from skim milk, probably because the single skim milk variable was assessed with less measurement error than the total calcium variable, which includes measurement error from each of its component foods. Men consuming >600 mg Ca/d from skim milk had a lower age-standardized mean concentration of $1,25(OH)_2D_3$ (71 pmol/L, or 30.06 pg/mL) than did men consuming ≤150 mg Ca/d from skim milk (85 pmol/L, or 35.64 pg/mL). Calcium from skim milk was significantly inversely correlated with plasma concentrations of $1,25(OH)_2D_3$ (Pearson correlation coefficient = –0.15, $P = 0.004$). In a multivariate linear regression model adjusted for age, body mass index, and smoking, $1,25(OH)_2D_3$ concentrations declined 3 pmol/L (1.44 pg/mL) per 300-mg/d increase in calcium from skim milk ($\beta = -0.0048$, $P = 0.005$). As expected, skim milk calcium was not correlated with plasma concentrations of 25(OH)D (Pearson correlation coefficient = 0.06, $P = 0.26$); most 25(OH)D is derived from sun exposure, and to a lesser extent from diet.

DISCUSSION

Our results, which are consistent with the results of previous studies (4, 6–8), support the hypothesis that intakes of dairy products and of calcium are positively associated with prostate cancer risk. The positive associations for dairy products, and dairy calcium especially, remained even after adjustment for the total food score. Thus, our inability to control for total energy probably introduced little or no bias, and random misclassification of the main exposure as the result of incomplete dairy calcium assessment would lead to an underestimate of any true association (24).

Data from the HPFS comprehensive dietary database indicated that we captured most of the interindividual variation in calcium consumption with our 5 dairy foods. The HPFS and Physicians' Health Study populations are both composed of mostly white male US health professionals; thus, it is reasonable to assume that the interindividual variances for calcium consumption in these populations are similar. The lack of information on calcium from nondairy foods was of less concern because vegetable calcium is substantially less bioavailable than is dairy calcium (25).

We could not contrast categories as extreme as those in the HPFS because we did not collect information on supplemental calcium intake. This probably added a moderate amount of misclassification to our analysis, which would lead to an underestimation of any true association. However, within the range of calcium intake in our cohort, the RRs were similar to comparable groups in the HPFS. In the HPFS, men consuming 500–999 mg total Ca/d compared with <500 mg/d had a multivariate RR of 1.20 for total prostate cancer and of 1.49 for metastatic prostate cancer (6).

Given the high correlation between dairy product and calcium intakes, we cannot exclude the possibility that some other component of dairy foods (eg, dairy fat) accounted for the observed associations. However, skim milk was the dairy food most strongly related to risk, and dairy fat and dairy protein were not significantly associated with risk. Additionally, in the Swedish study and the HPFS, the effect of calcium was independent of total fat and other major nutrients (6, 7).

In the HPFS, supplemental calcium intake was associated with greater risk of metastatic prostate cancer independent of dietary calcium consumption (6), whereas in a large case-control study ($n = 697$ cases), Kristal et al (14) observed no such association. However, the latter study had low power to examine associations with metastatic disease because 75% of the cases were stage A or B and <10% of the case and control subjects used calcium supplements. In the current investigation, we assessed only dairy product and dairy calcium intakes, but observed significant positive associations.

The serum calcium concentration is tightly regulated and is unlikely to influence prostate cancer development directly. Rather, if the association between calcium and risk is causal, then a third factor probably mediates the effect. Physiologic concentrations of dietary calcium can suppress the production of circulating $1,25(OH)_2D_3$ (26), and the results of in vitro, in vivo, and epidemiologic studies suggest that $1,25(OH)_2D_3$ may protect against prostate cancer (4, 5, 23, 27–37).

$1,25(OH)_2D_3$ is the most active form of vitamin D and is important for calcium and phosphorous metabolism (38). When the circulating calcium concentration is low, $1,25(OH)_2D_3$ acts on the bones, kidneys, and intestines to increase it (38). However, if the circulating calcium concentration is high, $1,25(OH)_2D_3$ production is suppressed by the down-regulation of parathyroid hormone (38). Despite the tight regulation of the plasma calcium concentration, in this population, we observed cross-sectional, inverse associations between total dietary and skim milk calcium intakes and a single measure of plasma $1,25(OH)_2D_3$ ($r = -0.15$, $P = 0.004$). The α-Tocopherol β-Carotene Cancer Prevention Trial observed a similar inverse correlation for plasma $1,25(OH)_2D_3$ and dietary calcium intake ($r = -0.14$, $P = 0.05$) (8). Although modest in magnitude, this correlation indicates that a modifiable dietary risk factor can influence the $1,25(OH)_2D_3$ concentration. Furthermore, the absolute difference in $1,25(OH)_2D_3$

concentration between extreme categories of calcium consumption from skim milk was ≈13 pmol/L (≈5.5 pg/mL). Previous investigations of serum $1,25(OH)_2D_3$ concentrations and prostate cancer risk examined $1,25(OH)_2D_3$ in quantiles, with intermediate quantile ranges of 14–19 pmol/L (6–8 pg/mL) (5, 23). Thus, a 13-pmol/L (5.5-pg/mL) change in $1,25(OH)_2D_3$ concentration is within the range predicted to have a significant etiologic effect on prostate cancer risk.

In vitro, $1,25(OH)_2D_3$ and its analogues inhibit cellular proliferation and promote the differentiation of prostate cancer cells (30, 32–37, 39–41). In rodents, administration of $1,25(OH)_2D_3$ or its analogues is associated with reduced growth of colon and prostate gland tumors (42–44). In humans, higher circulating concentrations of prediagnostic $1,25(OH)_2D_3$ were linked with a lower risk of prostate cancer in 1 study (5), but not in 3 others (23, 29, 45). Thus, a growing body of experimental evidence suggests that high circulating $1,25(OH)_2D_3$ concentrations may be beneficial in opposing prostate cancer development, but the results of studies in humans in which a single serum measure of $1,25(OH)_2D_3$ was used are conflicting.

On the other hand, specific polymorphisms of the vitamin D receptor gene are significantly inversely associated with prostate cancer risk (28, 46, 47), particularly in men with low concentrations of 25(OH)D (48). There is also evidence for an interaction between vitamin D metabolite concentrations and vitamin D receptor genotype and prostate cancer risk (48).

In conclusion, this report supports and extends previous observations that high intakes of dairy products, and of calcium from dairy foods specifically, are associated with an increased risk of prostate cancer. These findings may serve to interject a note of caution into the current enthusiastic promotion of a higher intake of calcium in the United States. Additional prospective investigations of this hypothesis, including a more comprehensive assessment of diet and supplement usage, are warranted.

REFERENCES

1. Ross RK, Schottenfeld D. Prostate cancer. In: Schottenfeld D, Fraumeni JFJ, eds. Cancer epidemiology and prevention. 2nd ed. New York: Oxford University Press, 1996:1180–206.
2. Key T. Risk factors for prostate cancer. Cancer Surv 1995;23:63–77.
3. Clinton SK, Giovannucci E. Diet, nutrition, and prostate cancer. Annu Rev Nutr 1998;18:413–40.
4. Giovannucci E. Diet, 1,25(OH)₂ vitamin D and prostate cancer: a hypothesis. Cancer Causes Control 1998;9:567–83.
5. Corder EH, Guess HA, Hulka BS, et al. Vitamin D and prostate cancer: a prediagnostic study with stored sera. Cancer Epidemiol Biomarkers Prev 1993;2:467–72.
6. Giovannucci E, Rimm EB, Wolk A, et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Res 1998;58:442–7.
7. Chan JM, Giovannucci E, Andersson S-O, Yuen J, Adami H-O, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer. Cancer Causes Control 1998;9:559–66.
8. Chan JM, Pietinen P, Virtanen M, et al. Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorous (Finland). Cancer Causes Control 2000;11:859–67.
9. Schuurman AG, van den Brandt PA, Dorant E, Goldbohm RA. Animal products, calcium, and protein and prostate cancer risk in the Netherlands Cohort Study. Br J Cancer 1999;80:1107–13.

10. Hayes RB, Ziegler RG, Gridley G, et al. Dietary factors and risk for prostate cancer among blacks and whites in the United States. Cancer Epidemiol Biomarkers Prev 1999;8:25–34.

11. Tzonou A, Signorello LB, Lagiou P, Wuu J, Trichopoulos D, Trichopoulou A. Diet and cancer of the prostate: a case-control study in Greece. Int J Cancer 1999;80:704–8.

12. Ohno Y, Yoshida O, Oishi K, Okada K, Yamabe H, Schroeder FH. Dietary beta-carotene and cancer of the prostate: a case-control study in Kyoto, Japan. Cancer Res 1988;48:1331–6.

13. Vlajinac HD, Marinkovic JM, Ilic MD, Kocev NI. Diet and prostate cancer: a case-control study. Eur J Cancer 1997;33:101–7.

14. Kristal AR, Stanford JL, Cohen JH, Wicklund K, Patterson RE. Vitamin and mineral supplement use is associated with reduced risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 1999;8:887–92.

15. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321:129–35.

16. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996; 334:1145–9.

17. Catalona WJ, Avioli LV. Diagnosis, staging, and surgical treatment of prostatic carcinoma (clinical conference). Arch Intern Med 1987; 147:361–3.

18. Willett WC. Nutritional epidemiology. In: Rothman KJ, Greenland S, eds. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven Publishers, 1998:623–42.

19. US Department of Agriculture. Composition of foods: raw, processed, and prepared, 1963–1988. Agriculture handbook no. 8 series. Washington, DC: US Government Printing Office, 1989.

20. Chan JM, Stampfer MJ, Ma J, Rimm EB, Willett WC, Giovannucci EL. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. Cancer Epidemiol Biomarkers Prev 1999;8:893–9.

21. Eichholzer M, Stahelin HB, Gey KF, Ludin E, Bernasconi F. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. Int J Cancer 1996;66:145–50.

22. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. J Natl Cancer Inst 1998;90:440–6.

23. Gann PH, Ma J, Hennekens CH, Hollis BW, Haddad JG, Stampfer MJ. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epidemiol Biomarkers Prev 1996;5:121–6.

24. Rothman KJ. Modern epidemiology. Boston: Little, Brown and Company, 1986.

25. Brody T. Calcium and phosphate. In: Nutritional biochemistry. 2nd ed. Boston: Academic Press, 1999:761–94.

26. Brody T. Vitamin D. In: Nutritional biochemistry. 2nd ed. Boston: Academic Press, 1999:565–85.

27. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Cancer 1992;70:2861–9.

28. Ingles SA, Ross RK, Yu MC, et al. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. J Natl Cancer Inst 1997;89:166–70.

29. Braun MM, Helzlsouer KJ, Hollis BW, Comstock GW. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). Cancer Causes Control 1995;6:235–9.

30. Feldman D, Skowronski RJ, Peehl DM. Vitamin D and prostate cancer. In: American Institute for Cancer Research, ed. Diet and cancer: molecular mechanisms of interactions. New York: Plenum Press, 1995:53–63.

31. Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). Anticancer Res 1990;10:1307–11.

32. Skowronski RJ, Peehl DM, Feldman D. Vitamin D and prostate cancer: 1,25 dihydroxyvitamin D_3 receptors and actions in human prostate cancer cell lines. Endocrinology 1993;132:1952–60.

33. Peehl DM, Skowronski RJ, Leung GK, Wong ST, Stamey TA, Feldman D. Antiproliferative effects of 1,25-dihydroxyvitamin D_3 on primary cultures of human prostatic cells. Cancer Res 1994;54:805–10.

34. Hsieh T-C, Ng C-Y, Mallouh C, Tazaki H, Wu JM. Regulation of growth, PSA/PAP and androgen receptor expression by 1α,25-dihydroxyvitamin D_3 in androgen-dependent LNCaP cells. Biochem Biophys Res Commun 1996;223:141–6.

35. Esquenet M, Swinnen JV, Heyns W, Verhoeven G. Control of LNCaP proliferation and differentiation: actions and interactions of androgens, 1α,25-dihydroxycholecalciferol, *all-trans* retinoic acid, 9-*cis* retinoic acid, and phenylacetate. Prostate 1996;28:182–94.

36. Miller GJ, Stapleton GE, Hedlund TE, Moffatt KA. Vitamin D receptor expression, 24-hydroxylase activity, and inhibition of growth by 1α,25-dihydroxyvitamin D_3 in seven human prostatic carcinoma cell lines. Clin Cancer Res 1995;1:997–1003.

37. Bahnson RR, Oeler T, Trump D, Smith D, Schwartz GG. Inhibition of human prostatic carcinoma cell lines by 1,25-dihydroxyvitamin D_3 and vitamin D analogs. J Urol 1993;149(suppl):471a (abstr).

38. Holick MF. Vitamin D. In: Shils ME, Olson JA, Shike M, Ross AC, eds. Modern nutrition in health and disease. 9th ed. Baltimore: Williams & Wilkins, 1999:329–45.

39. Schwartz GG, Oeler TA, Uskokovic MR, Bahnson RR. Human prostate cancer cells: inhibition of proliferation by vitamin D analogs. Anticancer Res 1994;14:1077–81.

40. Skowronski RJ, Peehl DM, Feldman D. Actions of vitamin D_3 analogs on human prostate cancer cell lines: comparison with 1,25-dihydroxyvitamin D_3. Endocrinology 1995;136:20–6.

41. Schwartz GG, Wang M-H, Zhang M, Singh RK, Siegal GP. 1α,25-Dihydroxyvitamin D (calcitriol) inhibits the invasiveness of human prostate cancer cells. Cancer Epidemiol Biomarkers Prev 1997;6: 727–32.

42. Schwartz GG, Hill CC, Oeler TA, Becich MJ, Bahnson RR. 1,25-Dihydroxy-16-ene-23-yne-vitamin D_3 and prostate cancer cell proliferation in vivo. Urology 1995;46:365–9.

43. Kawaura A, Tanida T, Sawada K, Oda M, Shimoyama T. Suppression of colonic carcinogenesis by vitamin D in rats. J Nutr Sci Vitaminol (Tokyo) 1992;Spec No:331–2.

44. Lucia MS, Anzano MA, Slayter MV, et al. Chemopreventive acitivity 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 1995;55:5621–7.

45. Nomura AMY, Stemmermann GN, Lee J, et al. Serum vitamin D metabolite levels and the subsequent development of prostate cancer. Cancer Causes Control 1998;9:425–32.

46. Taylor JA, Hirvonen A, Watson M, Pittman G, Mohler JL, Bell DA. Association of prostate cancer with vitamin D receptor gene polymorphism. Cancer Res 1996;56:4108–10.

47. Habuchi T, Suzuki T, Sasaki R, et al. Association of vitamin D receptor gene polymorphism with prostate cancer and benign prostatic hyperplasia in a Japanese population. Cancer Res 2000;15: 305–8.

48. Ma J, Stampfer MJ, Gann PH, et al. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. Cancer Epidemiol Biomarkers Prev 1998;7:385–90.