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Dairy Products, Calcium, and Vitamin D and Risk of Prostate Cancer

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INTRODUCTION

Dairy intake has been consistently associated with increased risk of prostate cancer in many epidemiologic studies conducted during the past two decades. The anticarcinogenic properties of vitamin D have been studied in the laboratory for many years, and 1,25 dihydroxyvitamin D_3 (1,25 D), the most potent vitamin D metabolite, has consistently been shown to inhibit prostate cancer cell growth and development. Recently, it has been reported that calcium, and specifically dairy calcium, may increase the risk of prostate cancer. 1,25 D regulates calcium metabolism in the body, and, consequently, dietary calcium intake can suppress circulating 1,25 D levels. Thus, a hypothesis has emerged combining these different areas of research suggesting that calcium, particularly from dairy products, may elevate prostate cancer risk by reducing circulating 1,25 D. This hypothesis does not exclude, however, that calcium and 1,25 D may exert other independent effects on prostate cancer development. The following review will briefly summarize the large body of evidence on dairy intake and prostate cancer, which sets a background for the current studies on calcium. We will then address more specifically the experimental and epidemiologic research on vitamin D and prostate cancer and the recent epidemiologic studies on calcium intake and prostate cancer risk.

DAIRY PRODUCTS AND RISK OF PROSTATE CANCER

Seven (1–7) of 14 case-control (1–14), and five (15–19) of nine cohort (15–23) studies have reported statistically significant positive associations between some aspect of dairy intake and prostate cancer risk (table 1). Overall, 12 (1–12) of the 14 case-control studies (1–14) and seven (15–19, 21, 23) of the nine cohort studies (15–23) observed a positive association for some measure of dairy products and prostate cancer; this is one of the most consistent dietary predictors for prostate cancer in the published literature. In these studies, men with the highest dairy intakes had approximately double the risk of total prostate cancer, and up to a fourfold increase in risk of metastatic or fatal prostate cancer relative to low consumers (17, 24). It remains unknown which compounds in dairy products might be responsible for this association; however, several recent studies which have been able to investigate nutrients more thoroughly suggest that calcium, and perhaps phosphorous, may play important roles.

Originally, it was speculated that the fat content in milk may affect risk of prostate cancer. However, a few of the more recent studies with comprehensive dietary assessments present evidence to the contrary. In the Health Professionals Follow-up Study and a large Swedish case-control study, the association for dairy foods was independent of fat intake, as well as several other measured risk factors (6, 17). Most recently, in the Physicians' Health Study, fat and protein from dairy products were not risk factors for prostate cancer, and in the Health Professionals Follow-up Study and Physicians' Health Study, skim and low-fat milk were positively associated with prostate cancer risk (17, 19). Higher low-fat milk intake has been linked to higher levels of circulating insulin-like growth factor 1 (25), and plasma insulin-like growth factor 1 has been positively associated with elevated prostate cancer risk (26–28). Thus, the positive association between dairy/milk intake and prostate cancer risk may be partially due to increased levels of insulin-like growth factor 1; this hypothesis is speculative and requires further study.

A few studies also suggest that the association between dairy products and prostate cancer may be particularly strong among older men and for advanced or fatal prostate cancer (6, 17). This indicates a potential role for dairy products in the progression as well as the incidence of prostate cancer.

VITAMIN D AND PROSTATE CANCER

In 1990, Schwartz and Hulka (29) hypothesized that vitamin D deficiency may be related to risk of prostate cancer. They made the observation that black race, northern latitudes, and older age all appeared to be positively correlated with greater risk of prostate cancer as well as vitamin D deficiency. They suggested that lower levels of pre-vitamin D, which we receive from sunlight exposure, and 25 hydroxyvitamin D, which is produced in the liver through hydroxylation of pre-vitamin D, could influence production of 1,25 D (29). 1,25 D is produced by means of hydroxylation of 25 hydroxyvitamin D in the kidneys, is the most active vitamin D metabolite, is important for normal cal-

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Abbreviation: 1,25 D, dihydroxyvitamin D_3.

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TABLE 1. Dairy intake and risk of prostate cancer

Reference	Year	Location	Cases	Dairy intake
Case-control studies on dairy intake and risk of prostate cancer				
Rotkin (8)	1977	Illinois, California	111	Cases ate more cheeses (p* = 0.09), margarine (p = 0.04), butter (p = 0.09), and milk (NS†)
Schuman et al. (9)	1982	Minnesota	223	Cases ate more ice cream (NS)
Talamini et al. (1)	1986	Italy	166	Milk/dairy (RR† = 2.5, p = 0.05)
Mettlin et al. (2)	1989	New York	371	Whole milk (RR = 2.5, p < 0.05)
LaVecchia et al. (3)	1991	Italy	96	Milk (RR = 5.0, p < 0.05)
Talamini et al. (4)	1992	Italy	271	Milk (RR = 1.6, p < 0.03); no association with cheese, butter; among cases aged ≥70 years, milk (RR = 1.91, p = 0.03), butter (RR = 1.7, p = 0.14)
De Stafani et al. (5)	1995	Uruguay	156	Milk (RR = 1.7, p = 0.04)
Whittemore et al. (10)	1995	United States	1,655	Saturated fat from dairy—positive association
Chan et al. (6)	1998	Sweden	526 total prostate cancer 296 advanced prostate cancer	Dairy—total (RR = 1.49, p < 0.05); advanced (RR = 1.64, p < 0.05)
Ewings and Bowie (14)	1996	England	159	Milk (RR = 0.95, p = 0.95)
Deneo-Pellegrini et al. (13)	1999	Uruguay	175	Dairy (RR = 0.80, p = 0.60)
Hayes et al. (11)	1999	United States	932 total 449 blacks 483 whites	Dairy foods (RR = 1.4, p = 0.10) Among blacks (RR = 1.1, p = 0.57) Among whites (RR = 1.7, p = 0.07)
Jain et al. (7)	1999	United States	617	Milk (RR = 1.47, p = 0.02)
Tzonou et al. (12)	1999	Greece	320	OR for one quintile increment of milk/dairy products = 1.12, p = 0.08
Cohort studies on dairy intake and risk of prostate cancer				
Snowdon et al. (21)	1984	California	99 fatal	Positive associations with milk (RR = 1.4) and cheese (RR = 1.4) (both NS in multivariate analyses)
Mills et al. (20)	1989	California	180	No association with milk (RR = 0.8)
Severson et al. (15)	1989	Hawaii	174	Positive association with butter/margarine/cheese (RR = 1.5, p = 0.05); no association with milk (RR = 1.0)
Hsing et al. (22)	1990	Upper Midwest and northeastern United States	149 fatal	No association with dairy products (RR = 1.0)
Le Marchand et al. (16)	1994	Hawaii	198	Positive association with milk (RR = 1.4, p = 0.05)
Giovannucci et al. (17)	1998	United States		Positive association with milk
			423 advanced	Advanced (RR = 1.6, p = 0.002)
			201 metastatic	Metastatic (RR = 1.8, p = 0.01)
Shuurman et al. (18)	1999	The Netherlands	642	Milk and milk products (RR = 1.12, p = 0.02)
Chan et al. (23)	2000	Finland	184 stages II–IV	Dairy (RR = 1.1, p = 0.74)
Chan et al. (19)	In press	United States	1,012	Dairy (RR = 1.34, p = 0.05)

* p value for trend or association.
† RR, relative risk; NS, not statistically significant.

cium metabolism in the body (30), and may be protective for prostate cancer.

1,25 D has consistently been shown to inhibit prostate cancer growth and to induce cellular differentiation in laboratory experiments (31–40). 1,25 D receptors are expressed in normal and malignant prostate epithelial cells and have been shown to suppress proliferation of normal as well as LNCaP and PC-3 prostate cancer cell lines when activated (31). 1,25 D also stimulates production of prostate-specific antigen by LNCaP cells, which may indicate 1,25 D increases cellular differentiation (31).

In vivo, administration of 1,25 D analogs is associated with decreased induced prostate tumor growth in mice (41). Furthermore, Lokeshwar et al. (42) recently demonstrated that 1,25 D not only suppressed the growth of primary induced prostate tumors, but also metastases to the lungs, suggesting that 1,25 D may be important not just for prostate cancer initiation but also for progression.

Despite the compelling results from laboratory studies, the potential protective effect of vitamin D has been much more difficult to assess in human populations. Observational studies incorporating single serum measures of vitamin D

metabolites (25 hydroxyvitamin D and 1,25 D) have been inconsistent. In 1993, Corder et al. (43) reported substantial reductions in prostate cancer risk associated with high levels of prediagnostic 1,25 D among white and black men, in particular among older men and those with low 25 hydroxyvitamin D levels. Further examination of this population revealed that controls maintained steady 1,25 D levels throughout the year, whereas cases experienced a drop in 1,25 D levels during the summer months; both cases and controls had increases in their 25 hydroxyvitamin D levels during the summer (44).

Subsequent to these reports, however, three other studies on serum 1,25 D and risk of prostate cancer have been mostly null. Braun et al. (45) found no association, although there were only 61 cases in this report. In a study among Japanese-American men in Hawaii, Nomura et al. (46) found no evidence of association; however, the men in this study had markedly higher levels of vitamin D metabolites than those reported in other studies. This is likely due to the greater sun exposure men receive in Hawaii and might have influenced the ability to detect any association. Gann et al. (47) did not observe any association in the Physicians' Health Study, except a suggestion of reduced risk (not statistically significant) among the sub-group of men who also had high 25 hydroxyvitamin D levels. Thus, while there is a growing body of evidence that 1,25 D plays a role in prostate cancer initiation, promotion, and progression, the few studies conducted among humans using single serum measures of 1,25 D remain inconclusive. It is possible that different measures of vitamin D metabolites (e.g., serial or seasonal measurements) might reveal more consistent associations. It may also be important to consider vitamin D binding proteins because these can influence the bioavailability of vitamin D metabolites.

1,25 D function is mediated by the vitamin D receptor, which is expressed in both normal and malignant prostate cells. Several polymorphisms of the *VDR* gene have been linked to prostate cancer risk (48–51). Most recently, Habuchi et al. (51) reported that Japanese men who were BB or Bb in the *BsmI VDR* polymorphism had a statistically significant 70 percent reduced risk of prostate cancer ($p < 0.0001$), but reported no association for polymorphisms in the *TaqI* and *ApaI VDR* genes. In the Physicians' Health Study, Ma et al. (50) also observed no association for *TaqI*, but unlike the Japanese study, there was no overall association between polymorphisms in *BsmI* and risk of prostate cancer. However, among men with plasma 25 hydroxyvitamin D levels below the median, those who were BB versus bb in the *BsmI* gene had a statistically significant 57 percent reduction in risk of prostate cancer. This relation was stronger among the older men (relative risk = 0.18; 95 percent confidence interval: 0.05, 0.68); p value for interaction < 0.01). There was also some suggestion of an interaction between 1,25 D levels and this gene, although the p value was not statistically significant ($p = 0.15$). The functional consequences, if any, of the various *VDR* polymorphisms have yet to be elucidated, and further study is warranted.

Overall, there is reasonable evidence supporting a role for vitamin D, its metabolites, and its receptor in the development and progression of prostate cancer. Further experimental and epidemiologic research is recommended, including studies focused on potential gene-environment interactions.

CALCIUM AND PROSTATE CANCER

Recently, another approach to examining the vitamin D hypothesis has been to study dietary factors that regulate 1,25 D levels in humans, mainly calcium and phosphorous. When serum levels of calcium are low, 1,25 D acts on the bones, kidneys, and intestines to increase retention and absorption of calcium until serum levels return to a normal range (30). Similarly, if serum levels of calcium are high, production of 1,25 D is suppressed by reduced parathyroid hormone production. The physiologic link between serum calcium levels and 1,25 D is well established (30), and more recently, epidemiologic studies have observed a small but statistically significant inverse correlation between self-reported dietary intakes of calcium and serum levels of 1,25 D (r = approximately –0.15; $p < 0.05$) (19, 23). Dietary phosphorous can increase as well as decrease 1,25 D levels, depending on serum calcium and phosphorous status. Dietary vitamin D does not correlate with 1,25 D because the latter is tightly regulated and primarily responsible for serum calcium and phosphorous homeostasis.

Relatively few epidemiologic studies have recently examined calcium and phosphorous intake and risk of prostate cancer (table 2). One cohort (18) and three case-control (11, 52, 53) studies have reported null associations for calcium intake and prostate cancer risk, and one case-control study from Serbia observed a statistically significant inverse association (54). Two cohort studies (17, 19) and one large case-control study (6) reported moderate to strong positive associations; two other prospective and case-control studies reported suggestive positive associations, however, the trends were not significant (12, 23).

The strongest evidence for an association between calcium intake and risk of prostate cancer comes from the Health Professionals Follow-up Study, which had a comprehensive dietary assessment of calcium from food as well as multivitamins, calcium supplements, and other sources (e.g., antacids—TUMS® (SmithKline Beecham, Pittsburgh, Pennsylvania)) (17). In this study, men who consumed more than 2,000 mg of calcium daily had a multivariate relative risk of 4.6 (95 percent confidence interval: 1.9, 11.1) for metastatic and fatal prostate cancer compared with men consuming less than 500 mg of calcium daily. This association was independent of age, body mass index, total energy intake, fat, fructose, phosphorous, vitamin D, vitamin E, and lycopene intake. Independent associations were observed for calcium from supplements only and calcium from foods.

Kristal et al. (53) also examined the effect of specific calcium supplements in a large case-control study ($n = 697$), but observed no relation to prostate cancer risk. However, in this study the authors over-selected younger men with stage A or stage B disease (75 percent). Less than 10 percent of the cases and controls reported usage of calcium supplements, and the authors collected information only on frequency of supplement use rather than actual amounts of supplemental calcium

TABLE 2. Summary of case-control and cohort studies examining dietary or supplementary calcium intake and risk of prostate cancer

Study (reference no.)	Year	Location	Design	Cases	Association for dietary calcium intake and prostate cancer
Ohno et al. (52)	1998	Japan	Case-control	100	No association
Vlajinac et al. (54)	1997	Serbia	Case-control	101	RR* = 0.37, p† = 0.03
Chan et al. (6)	1998	Sweden	Case-control	526 total 296 advanced 115 metastatic	RR = 1.91, p = 0.03 RR = 2.12, p = 0.002 RR = 2.64, p = 0.008
Hayes et al. (11)	1999	United States	Case-control	932 total 449 blacks 483 whites	RR = 0.90, p = 0.58 RR = 0.60, p = 0.06 RR = 1.4, p = 0.22
Tzonou et al. (12)	1999	Greece	Case-control	326	RR = 1.23, p = 0.12
Kristal et al. (53)	1999	United States	Case-control	697	RR = 1.25 (95% CI: 0.73, 2.17) for more frequent calcium supplement use, among supplement users
Giovannucci et al. (17)	1998	United States	Cohort	1,369 total 423 advanced 201 metastatic	RR for calcium from diet and supplements: RR = 1.71, p = 0.36 RR = 2.97, p = 0.002 RR = 4.57, p < 0.001
Shuurman et al. (18)	1999	The Netherlands	Cohort	642 total 224 localized 210 advanced	RR = 1.09, p = 0.34 RR = 1.21, p = 0.10 RR = 0.83, p = 0.45
Chan et al. (23)	2000	Finland	Cohort	184 stages II–IV	RR = 1.60, p = 0.13
Chan et al. (19)	In press	United States	Cohort	1,012	RR = 1.32, p = 0.03

* RR, relative risk; CI, confidence interval.
† p value for trend or association.

taken daily. Such differences in study design between this case-control study and the Health Professionals Follow-up Study (which consisted of an older population with more advanced disease and detailed assessment of milligrams of calcium intake from food and various supplemental sources) may partially explain discrepancies in the results.

In a more recent investigation of the Physicians' Health Study, dairy intake, and specifically calcium from dairy products, was linked to greater risk of prostate cancer (19). Although this study did not have complete dietary assessment, we were able to demonstrate that calcium from dairy products, rather than fat or protein from dairy products, was positively associated with prostate cancer risk. Additionally, skim milk calcium appeared to be the single dairy item linked to prostate cancer as well as to lower levels of 1,25 D (whole milk, cheese, and ice cream, or calcium from these sources, were not associated with prostate cancer risk when examined individually). One cannot exclude the possibility that this was due to chance, or that perhaps skim milk was assessed with the least measurement error.

In three of the studies on calcium intake (6, 17, 23), consideration of phosphorous intake in the multivariate models appeared to enhance the association between calcium and prostate cancer risk. Additionally, there were suggestive inverse associations for phosphorous intake; however, the results were not consistently statistically significant (6, 17, 23). In the observational cohort of the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial, there was a borderline significant interaction between calcium and phosphorous intake and risk of prostate cancer (p = 0.09) (23). Phosphorous influences 1,25 D levels differently at the two extremes. Extremely low levels of circulating phosphate leads to increased 1,25 D production while very high intakes of phosphorous (double normal intake) tend to lower serum 1,25 D levels (55). Phosphorous can also bind to calcium in the intestine, decreasing bioavailability of calcium, which may lead to higher circulating 1,25 D levels. Thus, future studies on calcium and 1,25 D and risk of prostate cancer should also consider phosphorous intake.

CONCLUSION

In summary, there is reasonable evidence that both vitamin D metabolites and calcium, and specifically calcium from dairy sources, play important roles in the development of prostate cancer. Given current national enthusiasm to increase calcium consumption in efforts to prevent other chronic diseases (e.g., osteoporosis), further study of these factors is warranted, particularly in aging men. Additional studies that assess serum vitamin D metabolites, vitamin D binding proteins, *VDR* polymorphisms, dietary and supplemental calcium intakes, and phosphorous intake are recommended.

REFERENCES

1. Talamini R, La Vecchia C, Decarli A, et al. Nutrition, social factors, and prostatic cancer in a northern Italian population. Br J Cancer 1986;53:817–21.
2. Mettlin C, Selenskas S, Natarajan NS, et al. Beta-carotene and animal fats and their relationship to prostate cancer risk: a case-control study. Cancer 1989;64:605–12.
3. LaVecchia C, Negri E, D'Avanzo B, et al. Dairy products and the risk of prostatic cancer. Oncology 1991;48:406–10.
4. Talamini R, Franceschi S, LaVecchia C, et al. Diet and prostatic cancer: a case-control study in northern Italy. Nutr Cancer 1992;18:277–86.
5. De Stefani E, Fierro L, Barrios E, et al. Tobacco, alcohol, diet and risk of prostate cancer. Tumori 1995;81:315–20.
6. Chan JM, Giovannucci E, Andersson SO, et al. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer. Cancer Causes Control 1998;9:559–66.
7. Jain MG, Hislop GT, Howe GR, et al. Plant foods, antioxidants, and prostate cancer risk: findings from case-control studies in Canada. Nutr Cancer 1999;34:173–84.
8. Rotkin ID. Studies in the epidemiology of prostatic cancer: expanded sampling. Cancer Treat Rep 1977;61:173–80.
9. Schuman LM, Mandel JS, Radke A, et al. Some selected features of the epidemiology of prostatic cancer: Minneapolis-St. Paul, Minnesota, case-control study, 1976–1979. In: Magnus K, ed. Trends in cancer incidence: causes and practical implications. Washington, DC: Hemisphere Publishing, 1982:345–54.
10. Whittemore AS, Kolonel LN, Wu AH, et al. Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. J Natl Cancer Inst 1995;87:652–61.
11. 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.
12. Tzonou A, Signorello LB, Lagiou P, et al. Diet and cancer of the prostate: a case-control study in Greece. Int J Cancer 1999;80:704–8.
13. Deneo-Pellegrini H, De Stefani E, Ronco A, et al. Foods, nutrients and prostate cancer: a case-control study in Uruguay. Br J Cancer 1999;80:591–7.
14. Ewings P, Bowie C. Case-control study of cancer of the prostate in Somerset and east Devon. Br J Cancer 1996;74:661–6.
15. Severson RK, Nomura AMY, Grove JS, et al. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res 1989;49:1857–60.
16. Le Marchand L, Kolonel LN, Wilkens LR, et al. Animal fat consumption and prostate cancer: a prospective study in Hawaii. Epidemiology 1994;5:276–82.
17. 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.
18. Schuurman AG, van den Brandt PA, Dorant E, et al. Animal products, calcium, and protein and prostate cancer risk in The Netherlands Cohort Study. Br J Cancer 1999;80:1107–13.
19. Chan JM, Stampfer MJ, Ma J, et al. Dairy products, calcium, and prostate cancer in the Physicians' Health Study. Am J Clin Nutr (in press).
20. Mills PK, Beeson WL, Phillips RL, et al. Cohort study of diet, lifestyle, and prostate cancer in Adventist men. Cancer 1989;64:598–604.
21. Snowdon DA, Phillips RL, Choi W. Diet, obesity, and risk of fatal prostate cancer. Am J Epidemiol 1984;120:244–50.
22. Hsing AW, McLaughlin JK, Schuman LM, et al. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. Cancer Res 1990;50:6836–40.
23. 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.
24. Giovannucci E. Dietary influences of $1,25(OH)_2$ vitamin D and prostate cancer: a hypothesis. Cancer Causes Control 1998;9:567–82.
25. Heaney R, McCarron DA, Dawson-Hughes B, et al. Dietary changes favorably affect bone remodeling in older adults. J Am Diet Assoc 1999;99:1228–33.
26. Chan JM, Stampfer MJ, Giovannucci E, et al. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279:563–6.
27. Mantzoros CS, Tzonou A, Signorello LB, et al. Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. Br J Cancer 1997;76:1115–18.
28. Wolk A, Mantzoros CS, Andersson SO, et al. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. J Natl Cancer Inst 1998;90:911–15.
29. Schwartz GG, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). Anticancer Res 1990;10:1307–11.
30. Holick MF. Vitamin D. In: Shils ME, Olson JA, Shike M, et al., eds. Modern nutrition in health and disease. 9th ed. Baltimore, MD: Williams and Wilkins, 1999:329–45.
31. 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, NY: Plenum Press, 1995:53–63.
32. Schwartz GG, Oeler TA, Uskokovic MR, et al. Human prostate cancer cells: inhibition of proliferation by vitamin D analogs. Anticancer Res 1994;14:1077–81.
33. 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.
34. Esquenet M, Swinnen JV, Heyns W, et al. 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.
35. Peehl DM, Skowronski RJ, Leung GK, et al. Antiproliferative effects of 1,25-dihydroxyvitamin D_3 on primary cultures of human prostatic cells. Cancer Res 1994;54:805–10.
36. Miller GJ, Stapleton GE, Hedlund TE, et al. 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. Hsieh TC, Ng CY, Mallouh C, et al. 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.
38. 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.
39. Schwartz GG, Wang MH, Zhang M, et al. 1α,25-dihydroxyvitamin D (calcitriol) inhibits the invasiveness of human prostate cancer cells. Cancer Epidemiol Biomarkers Prev 1997;6:727–32.
40. Bahnson RR, Oeler T, Trump D, et al. Inhibition of human prostatic carcinoma cell lines by 1,25-dihydroxyvitamin D_3 and vitamin D analogs. (Abstract). J Urol 1993;149(suppl):471a.
41. Schwartz GG, Hill CC, Oeler TA, et al. 1,25-Dihydroxy-16-ene-23-yne-vitamin D_3 and prostate cancer cell proliferation in vivo. Urology 1995;46:365–9.
42. Lokeshwar BL, Schwartz GG, Selzer MG, et al. Inhibition of prostate cancer metastasis in vivo: a comparison of 1,25-dihydroxyvitamin D (calcitriol) and EB 1089. Cancer Epidemiol Biomarkers Prev 1999;8:241–8.
43. 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.
44. Corder EH, Friedman GD, Vogelman JH, et al. Seasonal variation in vitamin D, vitamin D-binding protein, and dehydroepiandrosterone: risk of prostate cancer in black and white men. Cancer Epidemiol Biomarkers Prev 1995;4:655–9.

45. Braun MM, Helzlsouer KJ, Hollis BW, et al. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). Cancer Causes Control 1995;6: 235–9.
46. 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.
47. Gann PH, Ma J, Hennekens CH, et al. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epidemiol Biomarkers Prev 1996;5:121–6.
48. 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.
49. Taylor JA, Hirvonen A, Watson M, et al. Association of prostate cancer with vitamin D receptor gene polymorphism. Cancer Res 1996;56:4108–10.
50. 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.
51. 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.
52. Ohno Y, Yoshida O, Oishi K, et al. Dietary beta-carotene and cancer of the prostate: a case-control study in Kyoto, Japan. Cancer Res 1988;48:1331–6.
53. Kristal AR, Stanford JL, Cohen JH, et al. Vitamin and mineral supplement use is associated with reduced risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 1999;8: 887–92.
54. Vlajinac HD, Marinkovic JM, Ilic MD, et al. Diet and prostate cancer: a case-control study. Eur J Cancer 1997;33: 101–7.
55. Portale AA, Halloran BP, Murphy MM, et al. Oral intake of phosphorus can determine the serum concentration of 1,25-dihydroxyvitamin D by determining its production rate in humans. J Clin Invest 1986;77:7–12.