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Prostate Cancer

Dietary Intake of Calcium, Vitamin D, Phosphorus and the Risk of Prostate Cancer

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Abstract

Objectives: A relation of prostate cancer risk with calcium, vitamin D and phosphorus has been suggested, but remains controversial.

Methods: A case-control study was conducted in Italy in 1991–2002. Cases were 1294 men with incident prostate cancer, and controls were 1451 men admitted to hospital for acute non-neoplastic diseases. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression.

Results: Compared to the lowest one quintile of dietary calcium intake the OR was 1.18 for the highest, 1.01 for an increment of 622 mg/day of calcium, and 1.29 (95% CI 0.78–2.13) for 2000 mg/day or more of calcium. The OR of prostate cancer for the highest quintile of dietary intake of vitamin D and phosphorus were 1.33 and 1.20 respectively.

Conclusions: This study shows no material association of dietary intake of calcium, vitamin D and phosphorus with prostate cancer risk.

Keywords: Calcium; Case-control study; Phosphorus; Prostate cancer; Risk factors; Vitamin D

1. Introduction

A positive association between milk and dairy product intake and the risk of prostate cancer has been reported in ecological, case-control and cohort studies [1,2]. This has been related to the influence on prostate carcinogenesis exerted by either their high fat content, or the balance between calcium and vitamin D, although these hypotheses are not mutually exclusive [3]. In several studies the association with milk and dairy products was apparently stronger than that with other sources of animal fat, including meat [3], suggesting that intake is not sufficient to explain the increased prostate cancer risk. On the other hand, laboratory evidence indicates that high circulating levels of vitamin D and its active metabolite $1,25(OH)_2$-vitamin D ($1,25(OH)_2D$) (500- to 1000-fold more active than vitamin D) inhibits prostate carcinogenesis in vitro by reducing prostate cellular proliferation and enhancing cellular differentiation [4].

The balance of circulating levels of calcium, phosphorus, fructose and animal protein, with vitamin D and $1,25(OH)_2D$ is complex. Measures of vitamin D levels are difficult, since only part of biologically available vitamin D comes from dietary sources, part

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being produced in the skin through sun exposure [3]. Within a range of typical intakes, calcium modulates $1,25(OH)_2D$ levels; on the other hand, low dietary calcium transiently reduces plasma calcium, which, through the action of parathyroid hormone, increases the conversion rate of $1,25(OH)_2D$ from vitamin D [3,5], in turn enhancing intestinal absorption of calcium. Another important regulator of $1,25(OH)_2D$ levels is phosphorus, as low blood phosphate levels increase $1,25(OH)_2D$ production and blood levels [6], and high phosphate levels are relatively minor inhibitors of $1,25(OH)_2D$ synthesis.

Thus, a proposed hypothesis is that a diet low in calcium and phosphorus increases vitamin D and $1,25(OH)_2D$ circulating levels and consequently decreases the risk of prostate cancer [3]. However, epidemiological evidence on the impact of dietary calcium and phosphorus on $1,25(OH)_2D$ levels is unclear, and their role on prostate carcinogenesis too.

In a case-control study conducted in Italy, we observed a direct association between milk and dairy product consumption and prostate cancer risk, but no relation with cheese and meat intake [7]. In the same study we found no association of protein, total fats and saturated fatty acid intake with prostate cancer risk [8]. It is therefore unclear which ingredient of dairy products may be specifically related to prostate cancer risk. We analysed the data of this study to assess the relation between calcium, phosphorus and vitamin D dietary intake and prostate cancer risk, taking into account the potential confounding effect of several covariates.

2. Subjects and methods

The data were derived from a case-control study of prostate cancer, conducted between 1991 and 2002 in four Italian areas: greater Milan (northern Italy), the provinces of Pordenone and Gorizia (North-eastern Italy), the province of Latina (central Italy) and the urban area of Naples (southern Italy) [7,8]. Cases were 1294 men (median age 66, range 46 to 74 years), with incident, histologically confirmed prostate cancer, admitted to the major teaching and general hospitals in the areas under surveillance. Controls were 1451 men (median age 63, range 46 to 74 years), residing in the same geographical areas and admitted to the same network of hospitals of cases for a wide spectrum of acute conditions unrelated to known or likely risk factors for prostate cancer. Among controls, 21% had traumatic conditions, 32% non-traumatic orthopedic disorders, 17% acute surgical conditions and 29% miscellaneous other illnesses (such as eye, ear, nose, throat and dental disorders). All interviews for cases and controls were conducted in hospital by trained interviewers using a structured questionnaire; less than 5% of cases and controls approached refused interview, and the response rates did not vary across hospitals and geographic areas.

The structured questionnaire included information on sociodemographic factors, self-reported anthropometric variables, general lifestyle habits, such as smoking, alcohol and coffee consumption, frequency of intake of selected food items, personal medical history and family history of cancer. Information on diet referred to the two years before the onset of the disease that led to hospital admission and included the frequency of consumption of 78 foods, food groups, or dishes, including major dietary sources of calcium in the Italian diet (milk, cheese, yoghurt), and foods with the highest content of vitamin D (fish, eggs, milk) and phosphorus (milk, cheese, eggs). Specific questions on intake of milk (full fat, skimmed) and all types of cheese (including hard and soft cheese and portion size) were asked to patients, together with other questions on minor dietary sources of calcium [9]. The detailed questionnaire allowed to estimate the intake of selected nutrients and of total energy, using Italian food composition databases [9].

2.1. Data analysis

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were estimated using unconditional multiple logistic regression models [10], including terms for quinquennia of age, centre, education, body mass index (kg/m^2), tobacco smoking, physical activity, total energy, and family history of prostate cancer in first degree relatives. The nutrients of interest were entered in the models either in quintiles or in continuous. In the latter case, the measurement unit was set to the difference in intake between the upper cut-point of the forth quintile and that of the first one.

3. Results

The relation between the intake of calcium, vitamin D and phosphorus and the risk of prostate cancer is reported in Table 1. Compared to the lowest quintile of calcium intake, the multivariate OR for increasing quintiles of intake were 1.14, 1.01, 0.94 and 1.18, with no significant trend in risk; the OR was 1.01 for an increment of 622 mg/day of calcium, approximately corresponding to an intake of 60–100 g of cheese or to 100–150 ml of milk, and the OR for calcium intake of 2000 mg/day or more was 1.29 (95% CI 0.78–2.13). The OR for increasing quintiles of vitamin D intake were 1.22, 1.05, 1.27 and 1.32, with no significant trend in risk, and the OR for an increment of 2.1 μg/day was 1.06. The OR for increasing quintiles of phosphorus intake were 1.04, 0.83, 1.11 and 1.20, with no significant trend in risk, and the OR for an increment of 692 mg/day was 1.05.

The risk estimates for calcium intake were not heterogeneous in strata of age, education, body mass index, total energy intake, and family history of prostate cancer (Table 2). The OR was 1.00 (95% CI 0.92–1.10) for the highest quintile of calcium intake for prostate cancer cases with a Gleason score 2–6 (based on 538 cases), and 1.03 (95% CI 0.93–1.15) for those with a Gleason score ≥ 7 (based on 384 cases).

Table 1

Distribution of 1294 cases of prostate cancer and 1451 controls, and corresponding odds ratios (OR) with 95% confidence intervals (CI), according to intake of calcium, vitamin D and phosphorus, Italy, 1991–2002

Micronutrient	Quintile of intake						Continuous OR[b]
	1 (low)	2	3	4	5 (high)	χ^2_{trend} (p value)	
Calcium							
Cases:controls	195:290	263:291	254:290	261:290	321:290		
Upper cut-point (mg/day)	678.47	875.61	1067.60	1300.00			
OR[a] (95% CI)	1[c]	1.14 (0.88–1.49)	1.01 (0.77–1.32)	0.94 (0.70–1.25)	1.18 (0.88–1.59)	0.15 ($p = 0.70$)	1.01 (0.95–1.09)
Vitamin D							
Cases:controls	199:290	260:290	234:291	293:290	308:290		
Upper cut-point (μg/day)	1.98	2.63	3.18	4.05			
OR[a] (95% CI)	1[c]	1.22 (0.94–1.59)	1.05 (0.80–1.38)	1.27 (0.97–1.66)	1.32 (1.01–1.75)	3.50 ($p = 0.06$)	1.06 (1.00–1.13)
Phosphorus							
Cases:controls	198:290	248:291	244:289	307:291	297:290		
Upper cut-point (mg/day)	1204.66	1413.51	1609.22	1897.00			
OR[a] (95% CI)	1[c]	1.04 (0.78–1.38)	0.83 (0.60–1.16)	1.11 (0.77–1.59)	1.20 (0.79–1.84)	0.74 ($p = 0.39$)	1.05 (0.95–1.16)

[a] Estimates from multiple logistic regression models including terms for age, centre, education, body mass index, tobacco smoking, physical activity, total energy, and family history of prostate cancer.
[b] OR for a difference in intake equal to the difference between the upper cut-point of the forth quintile and that of the first (622 mg/day for calcium, 2.1 μg/day for vitamin D, and 692 mg/day for phosphorus).
[c] Reference category.

4. Comment

This study found no consistent association between calcium, vitamin D and phosphorus dietary intake and prostate cancer risk, at least within the range of intakes observed in this population, as all the point estimates for subsequent levels were close to unity and there was no significant trend in risk.

Epidemiological studies on the relation of calcium, vitamin D and phosphorus with prostate cancer risk

Table 2

Odds ratio (OR) of prostate cancer, and corresponding 95% confidence intervals (CI), according to intake of calcium in strata of selected covariates, Italy, 1991–2002

	Cases:controls	Quintile of calcium intake, OR[a] (95% CI)						Continuous OR[b]
		1 (low)	2	3	4	5 (high)	χ^2_{trend} (p value)	
Age (years)								
<65	529:790	1[c]	1.05 (0.71–1.56)	1.17 (0.78–1.75)	0.78 (0.51–1.20)	1.20 (0.77–1.88)	0.05 ($p = 0.83$)	1.14 (0.93–1.40)
≥65	765:661	1[c]	1.24 (0.87–1.77)	0.90 (0.62–1.30)	1.03 (0.70–1.51)	1.11 (0.74–1.67)	0.003 ($p = 0.96$)	1.00 (0.83–1.21)
Education (years)								
<7	636:844	1[c]	1.06 (0.74–1.51)	0.97 (0.67–1.42)	0.93 (0.63–1.38)	1.20 (0.80–1.81)	0.29 ($p = 0.59$)	1.08 (0.90–1.30)
≥7	658:607	1[c]	1.20 (0.81–1.78)	1.00 (0.67–1.50)	0.89 (0.58–1.36)	1.03 (0.66–1.61)	0.27 ($p = 0.60$)	1.02 (0.82–1.26)
Body mass index (kg/m^2)								
<26	318:678	1[c]	0.99 (0.68–1.44)	0.85 (0.58–1.26)	0.97 (0.64–1.48)	0.99 (0.64–1.54)	0.005 ($p = 0.94$)	1.00 (0.90–1.10)
≥26	672:768	1[c]	1.30 (0.89–1.88)	1.12 (0.76–1.64)	0.90 (0.61–1.34)	1.35 (0.89–2.03)	0.22 ($p = 0.64$)	1.06 (0.88–1.29)
Total energy intake (kcal/day)								
<2487.07	618:754	1[c]	1.32 (0.98–1.77)	0.96 (0.70–1.32)	1.01 (0.70–1.44)	1.47 (0.93–2.33)	0.27 ($p = 0.60$)	1.22 (0.96–1.54)
≥2487.07	676:697	1[c]	1.17 (0.67–2.04)	1.43 (0.84–2.43)	1.24 (0.74–2.08)	1.44 (0.86–2.38)	1.69 ($p = 0.19$)	1.09 (0.93–1.28)
Family history of prostate cancer								
No	204:1423	1[c]	1.08 (0.83–1.41)	1.01 (0.77–1.33)	0.93 (0.70–1.24)	1.13 (0.84–1.53)	0.09 ($p = 0.76$)	1.07 (0.93–1.24)
Yes	90:28	1[c]	8.10 (0.67–97.86)	0.28 (0.03–2.97)	0.30 (0.03–2.72)	1.28 (0.10–15.80)	0.90 ($p = 0.34$)	0.83 (0.34–2.04)

[a] Estimates from multiple logistic regression models including terms for age, centre, education, body mass index, cigarette smoking, physical activity, total energy and family history of prostate cancer.
[b] OR for an increment of 622 mg/day (the difference in intake equal to the difference between the upper cut-point of the forth quintile and that of the first).
[c] Reference category.

have produced conflicting results. The results of most relevant studies, ten cohort [11–20] and eleven case-control studies [21–31], are summarized in Table 3. The relation with calcium intake was considered in at least twelve studies [14–19,21,22,25,26,28,29]: of these, seven reported risk estimates above unity [14,16,17,19,22,26,28], significant in four [14,17,19,22]; four studies reported risk estimates around unity [15,18,25,29], and one study reported estimates significantly below unity [21]. Various

Table 3

Calcium, phosphorus and vitamin D intake and prostate cancer risk: main results from selected studies

Author, year, reference	Country	Cases	Variable[a]		Relative risk (95% confidence interval)	Observations
Cohort studies						
Corder et al., 1993 [11]	USA	181	25(OH)D	Serum levels	1.7[b] highest quartile	Kaiser Permanente Medical
			$1,25(OH)_2D$	Serum levels	0.3[b] highest quartile	Care program.
Braun et al., 1995 [12]	USA	61	25(OH)D	Serum levels	2.4 (0.8–8.2) highest quintile	Population based campaign
			$1,25(OH)_2D$	Serum levels	1.5 (0.5–4.5) highest quintile	to collect serum in Washington County.
Gann et al., 1996 [13]	USA	232	25(OH)D	Plasma levels	0.92 (0.56–1.50) highest quartile	Physicians' Health study.
			$1,25(OH)_2D$	Plasma levels	0.88 (0.53–1.45) highest quartile	
Giovannucci et al., 1998 [14]	USA	1792	Total calcium	Dietary intake	1.71 (1.19–2.46) ≥2000 mg/day	Health Professional
			Vitamin D	Dietary intake	1.21 (0.92–1.58) ≥800 IU/day	follow-up study. No
			Phosphorus	Dietary intake	0.94 (0.71–1.26) >1800 mg/day	trend in risk for calcium.
Schuurman et al., 1999 [15]	The Netherlands	642	Calcium	Dietary intake	1.09 (0.79–1.50) highest quintile	The Netherlands cohort study.
Chan et al., 2000 [16]	Finland	184	Calcium	Dietary intake	1.6 (0.8–3.0) highest quintile	Alpha-Tocopherol
			Vitamin D	Dietary intake	0.8 (0.5–1.3) highest quintile	Beta-Carotene cancer
			Phosphorus	Dietary intake	0.8 (0.4–1.5) highest quintile	prevention (ATBC) study.
Chan et al., 2001 [17]	USA	1012	Calcium	Dietary intake	1.29 (1.04–1.62) >600 mg/die	Physicians' Health study.
Berndt et al., 2002 [18]	USA	69	Calcium	Dietary intake	0.92 (0.48–1.77) highest tertile	Baltimore longitudinal
			Vitamin D	Dietary intake	1.21 (0.64–2.30) highest tertile	study of aging.
			Phosphorus	Dietary intake	1.22 (0.64–2.31) highest tertile	
Rodriguez et al., 2003 [19]	USA	3811	Calcium	Dietary intake	1.2 (1.0–1.6) total ≥2000 mg/die 1.6 (1.1–2.3) diet ≥2000 mg/die	Cancer prevention study II nutrition cohort.
Platz et al., 2004 [20]	USA	460	25(OH)D	Plasma levels	1.19 (0.79–1.79) highest quartile	Health professional
			$1,25(OH)_2D$	Plasma levels	1.25 (0.82–1.90) highest quartile	follow-up study.
Case-control studies						
Vlajinac et al., 1997 [21]	Serbia	101	Calcium	Dietary intake	0.37 (0.14–0.94) highest tertile	Hospital-based; significant
			Vitamin D	Dietary intake	0.70 (0.39–1.24) highest tertile	linear trend for
			Phosphorus	Dietary intake	1.69 (0.44–6.43) highest tertile	calcium intake.
Chan et al., 1998 [22]	Sweden	526	Calcium	Dietary intake	1.91 (1.23–2.97) highest quartile	Population-based; significant linear trend.
Nomura et al., 1998 [23]	USA	136	25(OH)D	Serum levels	0.8 (0.4–1.8) highest quartile	Nested in a cohort of
			$1,25(OH)_2D$	Serum levels	1.0 (0.5–2.1) highest quartile	Japanese men living in the Hawaii.
Deneo-Pellegrini et al., 1999 [24]	Uruguay	175	Vitamin D	Dietary intake	0.7 (0.4–1.2) highest quartile	Hospital-based.
Hayes et al., 1999 [25]	USA	932	Calcium	Dietary intake	0.9 (not significant) highest quartile	Population-based.
Kristal et al., 1999 [26]	USA	697	Calcium	Supplements	1.25 (0.73–2.17) users	Population-based.
Ahonen et al., 2000 [27]	Finland	149	25(OH)D	Serum levels	0.6 (0.2–1.0) highest quartile	Nested in the Helsinki heart study.
Tavani et al., 2001 [28]	Italy	288	Calcium	Dietary intake	1.12 (0.67–1.88) highest quintile	Hospital-based.
Kristal et al., 2002 [29]	USA	605	Calcium	Dietary intake	1.07 (0.63–1.84) highest quintile	Population-based.
			Vitamin D	Dietary intake	1.06 (0.66–1.70) highest quintile	
Tuohimaa et al., 2004 [30]	Norway, Finland, Sweden	622	25(OH)D	Serum levels	U shaped curve lowest risk at 40–60 nmol/l	Nested in the nordic specimen banks for cancer causes and controls.
Jacobs et al., 2004 [31]	USA	83	25(OH)D	Plasma levels	0.75 (0.29–1.91) highest tertile	Nested in the nutritional
			1alpha, 25(OH)(2)D(3)	Plasma levels	1.06 (0.42–2.66) highest tertile	prevention of cancer (NCP) trial.

[a] 25(OH) vitamin D = 25(OH)D; $1,25(OH)_2$-vitamin D = $1,25(OH)_2D$.

[b] Computed from published data.

measures of vitamin D (vitamin D intake, 25(OH)D and 1,25$(OH)_2$D circulating levels) were obtained in at least fourteen studies [11–14,16,18,20,21,23,24,27, 29–31]: four studies reported non-significant direct relations [12,14,18,20]; five studies inverse relations [13,16,21,24,27], four studies reported risks around unity [11,23,29,31], none significant, and one study reported an U-shaped curve [30]. Of the four studies measuring phosphorus intake [14,16,18,21], two reported risk estimates above unity [18,21] and the other two studies below unity [14,16], none significant.

An association between calcium and prostate cancer has been mainly observed for more advanced disease [14] or for very high intakes [14,17,19]. However, we found no different risk for patients with Gleason score below and over 7, and no increased risk for patients reporting an intake of more than 2000 mg/day of calcium. This observation, however, does not exclude that calcium could cause tumors to progress independently of grade.

In this analysis, calcium, phosphorus and vitamin D intake was computed by a food frequency questionnaire tested for validity [32] and reproducibility [33]: the Pearson correlation coefficient for validity of calcium intake was 0.54 [32]. Milk and cheese, in the Italian diet, account for about 70% of total calcium intake [34], and phosphorus is plentiful in diary products and meat and, at normal intakes, it is also well absorbed by the gut [6]. In this population less than 15% of dietary calcium derived from milk and over 50% from cheese [34]. This may explain the different findings for calcium intake and milk, moderately related to prostate cancer risk in this population (OR 1.15 for the highest quintile of intake) [7]. A potential explanation is that the bioavailability of calcium from cheese may be reduced by concomitant intake of other foods (particularly those with high fibre content) compared to milk, which in Italy is consumed mostly alone or with carbohydrates at breakfast and not during meals. Other explanations include the higher concentration in cheese of several micronutrients and dietary correlates of milk and cheese intake. Other sources of calcium in Italy, such as yoghurt, citrus fruit or green salad, accounted only for 2–3% of calcium intake and were included in the computing of calcium intake [9,34]. There was no information on the use of calcium supplements, but their use was extremely limited in Italy, i.e. less than 5% of the population [9,35].

Vitamin D dietary intake does not represent circulating levels, as it is also synthesized in the skin in a reaction catalyzed by ultraviolet light, and it undergoes several well regulated hydroxylation reactions to become biologically active [3]. Thus, given the complex biological regulation of vitamin D levels, which involves also fructose and animal protein intake, our results on vitamin D dietary intake should be taken with cautions. Moreover, vitamin D intake was very low and would not be expected to influence circulating 25(OH)D by more than 1–2 ng/ml, while the typical observable range is about ten times higher, and it would be likely that any association observed with vitamin D would be confounded by the source of vitamin D. There are differences in vitamin D expression in prostate cancer, and this might also explain, at least in part, the lack of association between prostate cancer and nutrients that may influence 1,25$(OH)_2$D levels.

A potential difficulty in these studies is to disentangle the individual effect of dietary calcium, phosphorus and vitamin D, as milk and diary products are the major sources of dietary calcium and phosphorus and an important source of dietary vitamin D, too [9]. A limitation of this study is also that a number of undetected prostate cancer cases might be present in the control group, since case diagnosis by PSA may have been more common in the case group than in the control group, and that subjects undergoing PSA might be more health-conscious and may have healthier life-style, including diet. Screening for prostate cancer is not widespread in Italy, although occasional case finding through PSA testing is increasingly common. However, high education is strongly related to PSA utilization and allowance for this variable has been accurately done.

Although we used hospital controls, patients admitted for conditions potentially influencing dietary habits were specifically excluded from the comparison group; cases and controls were drawn from the same catchment areas, their interviews were conducted in the same hospital setting, their participation was almost complete. The food frequency questionnaire was satisfactorily valid [32] and reproducible [33] and allowance for several confounding factors, including fruit consumption (the major source of fructose, another modulator of vitamin D levels, together with animal proteins) did not notably modify the relative risk estimates. The OR for calcium consumption after further allowance for phosphorus intake were 1.14, 0.99, 0.84, 1.00 for increasing quintiles of intake, compared to the lowest one, thus materially different from those presented in Table 1. The OR for the highest quintile of intake, after allowance for age, centre and total energy intake were 1.24 (95% CI 0.95–1.61) for calcium, 1.37 (95% CI 0.91–2.07) for phosphorus and 1.57 (95% CI 1.20–2.05) for vitamin D, not materially different from the fully adjusted ones. The exclusion from the control group of subjects admitted for traumas or for orthopedic non traumatic conditions (which may have different calcium/vitamin D levels) did not materially change the risk estimates.

5. Conclusions

In this case-control study there is no evidence that dietary calcium and phosphorus, at levels consumed by this population, may exert unfavourable effects on prostate carcinogenesis. Thus, our results do not support the hypothesis that milk and cheese consumption influence prostate cancer risk through their high calcium or phosphorus content, even at intakes higher than 1300 mg/day of calcium and higher than 1897 mg/day of phosphorus. However, additional prospective studies in this field are needed.

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