

## Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland)

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### Abstract

*Background:* Calcium, phosphorus, fructose, and animal protein are hypothesized to be associated with prostate cancer risk, potentially via their influence on 1,25-dihydroxyvitamin D<sub>3</sub>. We examined these nutrients and overall diet and prostate cancer risk in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC Study).

*Materials and methods:* The ATBC Study was a randomized 2 × 2 trial of alpha-tocopherol and beta-carotene on lung cancer incidence conducted among Finnish male smokers; 27,062 of the men completed a food-use questionnaire at baseline, and comprise the current study population. There were 184 incident clinical (stage 2–4) prostate cancer cases diagnosed between 1985 and 1993. We used Cox proportional hazards models to examine associations between dietary intakes and prostate cancer.

*Results:* We did not observe significant independent associations for calcium and phosphorus and prostate cancer risk. However, men with lower calcium and higher phosphorus intake had a multivariate relative risk of 0.6 (95% CI 0.3–1.0) compared to men with lower intakes of both nutrients, adjusting for age, smoking, body mass index, total energy, education, and supplementation group. Of the other foods and nutrients examined, none was significantly associated with risk.

*Discussion:* This study provides, at best, only weak evidence for the hypothesis that calcium and phosphorus are independently associated with prostate cancer risk, but suggests that there may be an interaction between these nutrients.

### Introduction

Prostate cancer is one of the most commonly diagnosed cancers among men in Western countries [1, 2]. In Finland the age-adjusted incidence is approximately 61/100,000 person-years [3]. Age, race, and family history are the few established risk factors for prostate cancer [4]. Even though several dietary and lifestyle characteristics have been linked to the disease, there is still no consensus that these risk factors truly influence tumor development.

Giovannucci recently hypothesized that calcium, phosphorus, fructose, and animal protein intake all might affect prostate cancer risk through their influence on 1,25-dihydroxyvitamin D<sub>3</sub> (1,25-D) [5], an active metabolite of vitamin D thought to protect against prostate cancer [5–15]. Low circulating calcium and phosphorus levels stimulate production of 1,25-D [16], and dietary fructose can induce transient reductions in plasma phosphate [17]; higher animal protein intake can lower blood pH, which limits 1-alpha-hydroxylase activity [18, 19], which in turn can reduce 1,25-D production [20].

Two large studies (one cohort and one case-control study) in distinct populations recently observed two- to four-fold increases in advanced prostate cancer risk

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associated with total calcium intake, adjusted for phosphorus [21, 22]. Both studies also observed a trend toward decrease in risk associated with higher phosphorus intake, controlling for calcium, but the results were not significant. In the cohort study, fruit and fructose intakes were also protective for prostate cancer, in particular for advanced disease (RRs = approximately 0.6) [21].

One other large cohort study in the Netherlands did not observe a significant association for calcium specifically, but reported a positive significant trend for milk products [23]. Four other case-control studies [24–27] that examined calcium intake and prostate cancer risk did not observe a positive association, and one reported a significant inverse association [26]. Other studies on diet and prostate cancer have found positive associations between meat (a major source of animal protein) and dairy products (a major source of calcium and phosphorus); these have been reviewed recently by Giovannucci [5].

We investigated the associations between these nutrients hypothesized to influence 1,25-D (calcium, phosphorus, fructose, and animal protein), as well as other aspects of diet, and prostate cancer risk in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC Study).

## Materials and methods

### *Study population*

The ATBC Study was a 2 × 2 randomized, double-blinded placebo-controlled trial of alpha-tocopherol and beta-carotene supplementation on lung cancer incidence, conducted among male smokers, age 50–69, who were residing in southwestern Finland between 1985 and 1988. Men were excluded if they had a previous history of cancer or other serious disease that limited their participation, or used vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses. A total of 29,133 men were randomized to either alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both, or placebo, and the trial concluded in April 1993. The rationale, design, methods, and primary results of this trial have been published previously [28, 29].

### *Exposure assessment*

Twenty-seven thousand one hundred eleven of the 29,133 randomized men completed a self-administered food-use questionnaire at baseline. This questionnaire

had 276 food items and mixed dishes and an accompanying picture booklet with 122 photographs of food in three to five different portion sizes. Men were requested to report their typical portion size and frequency of consumption of each food item within the past 12 months. We also asked about their basic demographics, smoking habits, and medical history. The men completed the questionnaire at home, and two weeks later they returned it when they met with a study nurse who reviewed their responses with them. Food and nutrient consumption data were processed using the database at the National Public Health Institute of Finland. This provided us with the daily consumption of each food and nutrient. We examined six major food groups (dairy, red meat, fish and poultry, vegetables, fruits (including berries), and cereals), three major macronutrients (fat, protein, and carbohydrates), total energy, calcium, phosphorus, vitamin D, and fructose in this study.

The reproducibility and validity of this questionnaire have been evaluated previously [30]. In the reproducibility study the food-use questionnaire was administered three times, at three-month intervals, to 121 participants. The intra-class correlations were generally high, between 0.60 and 0.70 for most variables; the correlation was 0.66 for energy, 0.66 for protein, 0.72 for sucrose, and 0.70 for calcium. In the validity study 158 men completed 12 two-day diet records at uniform intervals over six months and completed the food-use questionnaire at the beginning and end of this period. The unadjusted Pearson correlation coefficients between food records and food-use questionnaire measurements ranged from 0.40–0.80; with adjustment for total energy, most correlations fell between 0.60 and 0.70. The correlations, adjusted for intra-individual variation, between measurements from the first food-use questionnaire and the food records were 0.7 for energy, 0.7 for protein, 0.6 for sucrose, 0.7 for calcium, 0.6 for fruits, 0.4 for beef/chicken/pork, and 0.7 for milk products.

### *Case assessment*

During the trial period (1985–1993), there were 233 incident cases of prostate cancer identified among the study population of 27,111 by the Finnish Cancer Registry and the Register of Causes of Death, which provide virtually 100% of case ascertainment nationally. Independently, two clinical oncologists reviewed the medical records of each prostate cancer patient to confirm the diagnosis and stage. Two independent pathologists also reviewed histopathologic and cytologic specimens to confirm cancer, histologic type, and histologic/cytologic grade.

We followed the American Joint Committee on Cancer 1992 [31] criteria for staging. Stage 0 and 1 tumors were those that were clinically inapparent; stage 2 tumors included clinically apparent cancers confined to the prostate; stage 3 tumors were those extending through the prostate capsule, and stage 4 tumors were those fixed into or invading adjacent structures other than the seminal vesicles and all those tumors with regional lymph node involvement or distant metastases. Of the 233 incident cases, we excluded from analysis one case with unknown staging and 48 who were classified as stage 0 or 1. We focused our analyses on only the stage 2–4 cases because they represented the clinically important tumors. Also, previous studies of the dietary risk factors of interest and prostate cancer had shown that associations were stronger when limiting analyses to the advanced or metastatic cases. We did examine the relative risks (RRs) for the 48 stage 0 and 1 cases separately, but because of small numbers, the estimates were unstable and did not add meaningfully to those presented here. Thus, the final population for analysis consisted of 27,062 men, among whom there were 184 stage 2–4 prostate cancer cases diagnosed during follow-up.

### Statistical methods

We log-transformed and then energy-adjusted all foods and nutrients employed in this analysis; we used the residual method to adjust all foods and nutrients by total energy intake and included quintiles of total energy in all dietary analyses [32]. We computed quintiles of the energy-adjusted foods and nutrients based on the intakes reported in the food-use questionnaire. The tests for trends were calculated using linear contrasts of the parameter estimates and Wald tests.

We counted follow-up time for each man starting from the date of randomization until diagnosis of prostate cancer, death, or 30 April 1993, whichever came first. We used Cox proportional hazards models to analyze associations between food and nutrient consumption and time to prostate cancer diagnosis. The hazard ratios and 95% confidence intervals (CIs) were used as estimates of relative risk (RRs). Other than age and supplementation group (beta-carotene, vitamin E, both, or placebo), there were few previously identified prostate cancer risk factors in this population to control for in the multivariate analyses [33]. We adjusted for body mass index (BMI), education, and smoking because they were associated with diet and moderately predictive of prostate cancer risk. Alcohol and residence (rural vs. urban) were specifically associated with calci-

um intake (Table 1), but were not included in the standard multivariate model because they were not significant risk factors for prostate cancer.

In the tables we provide the unadjusted crude nutrient and food medians within the energy-adjusted quintiles. Baseline age, number of years as a smoker, and BMI (weight divided by height squared, kg/m<sup>2</sup>) were also grouped into quintiles. There were 17 subjects with missing BMI and 59 subjects with missing number of years as a smoker; these were treated in separate missing categories in the analysis.

Dietary phosphorus and calcium were highly correlated due to their common food sources ( $r = 0.78$  in this population), and the two nutrients are also tightly linked metabolically [34, 35]. Previous studies suggest they may be independently associated with prostate cancer risk [21, 22]. To examine the potential for interaction between calcium and phosphorus, we

Table 1. Medians and percentages of dietary and lifestyle characteristics and total mortality by quintiles of energy-adjusted calcium intake among 27,062 men in the ATBC Study<sup>a</sup>

Quintiles of energy-adjusted calcium intake					
Medians	1	2	3	4	5
Age (years)	56.5	56.9	57.1	57.4	57.6
BMI (kg/m <sup>2</sup> )	25.8	25.8	25.8	26.1	26.4
Years as a smoker	36	36	37	36	37
Energy (kcal)	2653	2774	2778	2778	2632
Fat (g)	95	102	103	104	100
Protein (g)	88	97	102	105	108
Carbohydrates (g)	289	301	303	298	275
Calcium (mg)	802	1161	1365	1570	1841
Phosphorus (mg)	1729	1998	2134	2244	2343
Vitamin D (μg)	5.0	5.0	5.0	4.8	4.4
Fructose (g)	39	39	38	36	31
Dairy food (g)	310	603	766	922	1091
Red meat (g)	134	133	129	126	113
Fish and poultry (g)	47	47	46	44	40
Fruits (g)	102	112	112	106	96
Vegetables (g)	102	105	103	98	87
Cereals (g)	215	216	214	204	180
Alcohol (g)	17	13	11	9	7
<i>Percentages</i>					
Education					
<7 years	58.4	62.1	65.2	68.2	68.9
7–11 years	28.0	26.0	25.3	23.8	22.6
>11 years	13.6	12.0	9.5	8.0	8.5
Residence					
Rural	29.9	34.6	35.3	39.9	41.2
Urban	70.1	65.4	64.7	60.1	58.8
<i>Total mortality</i>					
Deaths/10,000 person-years	182	187	203	218	227

<sup>a</sup> ATBC Study = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study.

categorized men as having low and high intakes of each nutrient using the energy-adjusted medians as the cutpoints (calcium median = 1338 mg; phosphorus median = 2091 mg), then cross-classified each group creating four intake categories – low calcium/low phosphorus (used as the reference group), low calcium/high phosphorus, high calcium/low phosphorus, and high calcium/high phosphorus. We used the likelihood ratio test to test for interaction between these two nutrients and risk of prostate cancer.

## Results

Table 1 presents medians of dietary and lifestyle characteristics by quintiles of energy-adjusted total calcium intake. On average, men in the highest quintile of energy-adjusted calcium were slightly older and had greater intake of phosphorus, dairy products, and protein, and lower intake of red meat, fructose, vegetables, cereals, and alcohol than men in the lower quintile groups. Total mortality also increased with increasing quintiles of energy-adjusted calcium.

There was no consistent association or trend between intake of total energy, fat, protein, carbohydrates, dairy products, red meat, fish or poultry, fruits, vegetables, cereals, vitamin D, and fructose and stage 2–4 prostate cancer risk (Table 2). There were significantly elevated RRs for the fourth quintiles of fruits and carbohydrates, and significantly decreased risks for the third quintiles of red meat and protein. However, for each of these foods there was no significant trend, and the associations were attenuated and not statistically significant in the higher quintiles, suggesting these were chance occurrences.

There was no association for either calcium or phosphorus and total prostate cancer risk in the standard multivariate model (Table 3). When we mutually controlled for calcium and phosphorus in the model, there was some suggestion of an elevated risk for calcium intake, and a reduction in risk for phosphorus, but these effects were attenuated in the fifth quintiles (Table 3).

Compared to men with both low calcium and low phosphorus intakes, men with high calcium intake had prostate cancer risk levels of unity, regardless of their phosphorus intake (Table 4). However, men with low calcium and high phosphorus intakes had a multivariate RR of 0.6 (95% CI 0.3–1.0) compared to men with both low calcium and low phosphorus intakes. A formal test for interaction between low and high phosphorus and low and high calcium intakes and risk of clinical prostate cancer in the multivariate model was not significant ( $p = 0.09$ ).

## Discussion

The main aim of this study was to examine whether foods and nutrients involved in the regulation of 1,25-D, the most active vitamin D metabolite, could be meaningfully associated with prostate cancer risk, as proposed recently by Giovannucci [5]. The main hypothesis, that calcium, phosphorus, fructose, and animal protein might be associated with prostate cancer risk via 1,25-D rests on two suppositions – that 1,25-D has a beneficial effect on prostate cancer, and that dietary intakes can modify etiologically important levels of 1,25-D.

Evidence that vitamin D metabolites and their analogs may have a protective effect on prostate cancer risk comes primarily from *in-vivo* [36] and *in-vitro* experimental studies [8, 10–15, 37–39]. *In-vitro*, 1,25-D has anti-proliferative effects on prostate cancer cells [8, 10–15], can increase prostate-specific antigen production [8, 12] which is a marker of differentiation, and can reduce the invasiveness of DU145 prostate cancer cell lines, independent of its effects on cell proliferation [10]. Analogs of vitamin D<sub>3</sub> have also been shown to inhibit growth of prostate cancer cell lines [15, 37, 38]. *In-vivo* experiments confirm the anti-proliferative and pro-differentiating effects of 1,25-D on prostate epithelium, and vitamin D analogs inhibit the growth of induced prostate tumors and metastases in rats and mice [36, 40, 41].

Epidemiologic studies examining serum levels of 1,25-D and prostate cancer have been inconsistent [42–45], with only one study [44] clearly showing an inverse association. In this case-control study ( $n = 181$  cases) with stored prediagnostic sera [44], the authors reported substantially significantly reduced risks of prostate cancer, particularly for palpable tumors, in the presence of low 25(OH)-D (25-D), and among older men. Another study with 232 cases and prospectively collected blood samples reported suggestive inverse associations between serum 1,25-D and risk of prostate cancer, particularly for aggressive disease, but the results were not significant [43]. The two other studies reported no association, although one was small and did not consider aggressive cases separately [42]; and the other was conducted among Japanese-American men in Hawaii who had a much higher vitamin D status and much lower incidence of prostate cancer [45]. Thus, while *in-vitro* and *in-vivo* experimental studies suggest 1,25-D may have a beneficial effect on prostate tumor development, observational studies among humans, that have used a single serum measure of 1,25-D as the primary exposure, have been largely inconclusive.

1,25-D is produced from hydroxylation of 25-D in the kidney, is the most potent vitamin D metabolite, and is

Table 2. Multivariate relative risks of clinical (stage 2–4) prostate cancer by energy-adjusted foods and nutrients in a large population of Finnish smokers

Dietary intakes	Medians, multivariate relative risks <sup>a</sup> , and 95% CI <sup>b</sup> by quintiles of energy-adjusted foods and nutrients					Trend, <i>p</i>
	1	2	3	4	5	
Energy (kcal)	1906 1.0 –	2358 0.9 (0.6–1.4) <sup>c</sup>	2720 1.0 (0.6–1.5)	3139 1.0 (0.6–1.6)	3832 0.9 (0.6–1.5)	0.94
Fat (g)	79 1.0 –	95 1.2 (0.7–1.9)	103 1.4 (0.9–2.1)	110 1.0 (0.6–1.6)	121 1.1 (0.7–1.7)	0.89
Protein (g)	82 1.0 –	94 0.9 (0.6–1.3)	102 0.6 (0.4–1.0)	107 0.8 (0.5–1.3)	117 1.0 (0.7–1.6)	0.99
Carbohydrates (g)	234 1.0 –	276 1.0 (0.6–1.6)	298 1.0 (0.6–1.6)	317 1.6 (1.0–2.5)	343 1.1 (0.7–1.8)	0.22
Dairy (g)	275 1.0 –	588 1.4 (0.9–2.2)	770 1.1 (0.7–1.8)	919 1.1 (0.7–1.7)	1119 1.1 (0.7–1.7)	0.74
Red meat (g)	75 1.0 –	105 1.0 (0.6–1.4)	128 0.6 (0.4–1.0)	155 0.8 (0.5–1.2)	214 0.7 (0.5–1.1)	0.09
Fish and poultry (g)	16 1.0 –	31 1.1 (0.7–1.7)	45 1.0 (0.6–1.6)	62 0.9 (0.6–1.5)	95 1.2 (0.8–1.9)	0.72
Fruits (g)	25 1.0 –	67 1.4 (0.8–2.2)	108 1.3 (0.8–2.1)	151 1.8 (1.1–2.8)	230 1.3 (0.8–2.2)	0.13
Vegetables (g)	40 1.0 –	71 0.7 (0.5–1.2)	99 0.8 (0.5–1.2)	135 0.9 (0.6–1.5)	204 0.8 (0.5–1.3)	0.84
Cereals (g)	128 1.0 –	180 1.0 (0.6–1.7)	210 1.5 (0.9–2.3)	238 1.2 (0.7–1.9)	280 1.2 (0.7–1.9)	0.36
Vitamin D ( $\mu\text{g}$ )	2.4 1.0	3.7 0.8 (0.5–1.3)	4.9 0.7 (0.5–1.2)	6.3 0.9 (0.6–1.4)	9.2 0.8 (0.5–1.3)	0.86
Fructose (g)	18 1.0 –	29 0.9 (0.5–1.5)	37 1.3 (0.8–2.1)	46 1.4 (0.9–2.2)	60 1.0 (0.6–1.5)	0.54

<sup>a</sup> All food and nutrient models, with the exception of energy, were controlled for supplementation group (alpha-tocopherol, beta-carotene, both, or placebo), education (<7 years, 7–11 years, >11 years), and quintiles of age, body mass index, energy, and number of years as a smoker. The energy model was controlled for supplementation group (alpha-tocopherol, beta-carotene, both, or placebo), education (<7 years, 7–11 years, >11 years), quintiles of age, body mass index, and number of years as smoker.

<sup>b</sup> CI = confidence interval.

<sup>c</sup> Numbers in parentheses = 95 percent confidence intervals.

important for normal calcium metabolism [16]. It is hypothesized that nutrients involved in calcium regulation can modify circulating levels of 1,25-D [5]. Evidence that dietary factors can influence 1,25-D levels comes from physiology and feeding studies. High calcium

intake leads to suppression of 1,25-D, which consequently causes a decrease in intestinal absorption of calcium and avoids hypercalcemia [16]. At physiologic levels, change in calcium intake also correlates inversely with change in 1,25-D levels ( $r = -0.76$ ) [46]. We were

Table 3. Multivariate relative risks of clinical (stage 2–4) prostate cancer ( $n = 184$  cases) by quintiles of calcium and phosphorus among 27,062 Finnish male smokers in the ATBC Study<sup>a</sup>

Calcium		
Quintiles (median, mg)	Multivariate RR <sup>b</sup>	Multivariate RR <sup>b</sup> controlling for phosphorus
1 (802)	1.0	1.0
2 (1161)	1.2 (0.8–1.9) <sup>c</sup>	1.3 (0.8–2.1)
3 (1365)	1.0 (0.6–1.6)	1.2 (0.7–2.1)
4 (1570)	1.3 (0.8–2.0)	1.8 (1.0–3.2)
5 (1841)	1.1 (0.7–1.8)	1.6 (0.8–3.0)
Trend, $p$	0.58	0.13
Phosphorus		
Quintiles (median, mg)	Multivariate RR <sup>b</sup>	Multivariate RR <sup>b</sup> controlling for calcium
1 (1655)	1.0	1.0
2 (1945)	1.5 (1.0–2.2) <sup>c</sup>	1.3 (0.8–2.0)
3 (2131)	0.6 (0.4–1.0)	0.5 (0.3–0.9)
4 (2282)	0.8 (0.5–1.3)	0.6 (0.3–1.0)
5 (2468)	1.1 (0.7–1.8)	0.8 (0.4–1.5)
Trend, $p$	0.45	0.11

<sup>a</sup> ATBC Study = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study.

<sup>b</sup> Multivariate models control for supplementation group (alpha-tocopherol, beta-carotene, both, or placebo), education (<7 years, 7–11 years, >11 years), and quintiles of age, body mass index, energy, and number of years as smoker.

<sup>c</sup> Numbers in parentheses are 95 percent confidence intervals.

unable to examine change in calcium and 1,25-D levels over time; however, in a subset of the current study population ( $n = 197$ ), a single measure of serum 1,25-D was significantly, but not strongly, inversely correlated

Table 4. Cross-categorization of energy-adjusted calcium and phosphorus intakes and the multivariate relative risk<sup>a</sup> of clinical (stage 2–4) prostate cancer in the ATBC Study<sup>b</sup>

	Calcium <1338 mg	Calcium ≥1338 mg
Phosphorus <2091 mg	1.0 (39.1) <sup>c</sup>	0.9 (0.5–1.4) <sup>d</sup> (10.9) <sup>c</sup>
Phosphorus ≥2091 mg	0.6 (0.3–1.0) <sup>d</sup> (10.9) <sup>c</sup>	0.9 (0.7–1.2) <sup>d</sup> (39.1) <sup>c</sup>

$p$  for interaction = 0.09<sup>c</sup>

<sup>a</sup> Multivariate model controls for supplementation group (alpha-tocopherol, beta-carotene, both, or placebo), education (<7 years, 7–11 years, >11 years) and quintiles of age, body mass index, number of years as a smoker, and total energy.

<sup>b</sup> ATBC Study = Alpha-Tocopherol Beta-Carotene Cancer Prevention Study.

<sup>c</sup> Used the likelihood ratio test to test for interaction.

<sup>d</sup> 95 percent confidence intervals.

<sup>e</sup> Percentage of the population.

with dietary calcium intake ( $r = -0.14$  ( $p = 0.05$ )) (personal communication, J. Tangrea).

Phosphorus has a direct effect on 1,25-D production, and also influences both serum calcium and parathyroid hormone, which individually affect 1,25-D [5, 16, 35]. Hypophosphatemia stimulates production of 1,25-D, but this is a rare condition in normal Western diets. In contrast, at extremely high levels of phosphorus intake (e.g. double normal levels), phosphorus suppresses 1,25-D production but also increases parathyroid hormone secretion, which works to increase 1,25-D levels [47, 48]. Phosphate can bind calcium in the intestine [48], reducing bioavailable calcium, which may also increase 1,25-D production. Fructose may have a beneficial effect on prostate cancer risk because it can cause transient marked reductions in serum phosphorus, perhaps enough to stimulate 1,25-D [5, 17, 21]. Animal protein consumption can increase blood acidity, which may have a suppressive effect on 1,25-D levels [18–20]. In contrast, dietary vitamin D intake does not correlate well with 1,25-D levels because the latter is tightly regulated by calcium, phosphorus, and parathyroid hormone [16].

We found no association between total energy, fat, protein, carbohydrates, dairy products, red meat, fish and poultry, fruits, vegetables, cereals, vitamin D, and fructose and prostate cancer risk in this study. Previous case-control and cohort studies on total energy and prostate cancer risk have been ambiguous, and it is not surprising that we did not observe a significant association in this cohort [49]. Similarly, the correlation between fat and prostate cancer has not been entirely consistent, though there generally appears to be a positive association, especially for saturated or animal fat [49].

The lack of positive association between meat intake and prostate cancer risk, while contrary to the hypothesis regarding animal protein and 1,25-D, is consistent with the equivocal results of other case-control and prospective studies [49]. In a recent review, Giovannucci reported that only four out of nine case-control studies, and two out of eight cohort studies, observed significant positive associations between meat intake and risk of prostate cancer [5].

To our knowledge, only the Health Professionals Follow-up Study (HPFS) has also investigated the association between fructose and prostate cancer risk [5]. We observed no association for fructose; however, the levels of consumption were generally lower than those in the HPFS – total fructose in 1986 in the HPFS was 48 g/day versus 35 g/day in the current study. The lack of association between dietary vitamin D and risk is consistent with previous studies [21, 22]. Dietary intake of vitamin D is usually a poor measure of total vitamin

D because humans receive most of their vitamin D from casual sunlight exposure rather than diet [16].

Five out of ten case-control and five out of eight cohort studies have reported significant positive associations between some aspect of dairy intake and risk of prostate cancer [5, 23, 24, 50, 51]; this is one of the most consistent dietary predictors for prostate cancer in the published literature. The lack of association between dairy intake and prostate cancer risk in this cohort was surprising and remains unexplained; however, the overall range of intake in this population was uniformly higher than in previous studies.

One cohort [23] and three case-control [24, 25, 27] studies have reported null associations for calcium intake and prostate cancer risk. Two other studies have reported positive associations [21, 22] and, unlike the null studies, examined calcium in conjunction with phosphorus. In this investigation, we were able to study calcium and phosphorus together; however, we did not observe a clear association between these nutrients and risk of prostate cancer. While the RRs were generally positive for calcium and inverse for phosphorus, the trends were not significant and the associations were attenuated in the fifth quintiles.

One possible reason for this lack of clear association is that both calcium and phosphorus intakes in this population were higher than in the other two studies. In the current study, the HPFS [21], and the Swedish case-control study [22] the median daily unadjusted calcium intakes were 1338 mg, 764 mg, and 972 mg, respectively; the median intakes of phosphorus were 2094 mg, 1312 mg, and 1717 mg, respectively. In the HPFS the reference category was composed of men with an intake of less than 500 mg/day, whereas in the current study the median of the reference group was 802 mg/day. It is possible that calcium and phosphorus consumed at such high levels have different effects on risk. Also, it should be noted that the high calcium levels measured in this population were entirely from food intake, whereas the high levels of calcium intake in the HPFS were partly due to supplement use.

In the current study, men with higher calcium intake were not at particularly elevated risk of prostate cancer relative to those with lower calcium and lower phosphorus intakes. However, men with lower calcium and higher phosphorus intakes had a borderline significant 40% reduction in clinical prostate cancer risk relative to the reference group. This might be related, in part, to the ability of phosphorus to bind to calcium in the intestine, thereby prohibiting the suppressive effects of calcium on 1,25-D. While this result might be a chance finding, to our knowledge this observation was not reported in the two previously

cited studies on calcium, phosphorus, and prostate cancer [21, 22].

We cannot rule out the possibility that these results are due to chance; this study had a relatively small number of cases compared to the two previous positive studies. However, the prospective design minimizes concern for recall bias, and the detailed method of soliciting dietary intake information (questionnaire with picture book, plus review with a study nurse) reduces the level of misclassification of food consumption.

A final but important consideration for any differences between the results of this study and other prospective investigations of diet and prostate cancer is that this population was entirely composed of male smokers, with an average smoking history of 36 years. Smoking has been associated with greater risk of fatal prostate cancer [52–55], and tobacco may increase the virulence of tumors [56–60]. There is previous evidence that smoking can modify the effect of a nutritional risk factor for prostate cancer; supplemental vitamin E has been inversely associated with prostate cancer among smokers [33, 61], but not among non-smokers [61]. Thus, while calcium, dairy products, and fructose may be strong important predictors in other studies, they may play a weaker role here because of an undetected interaction with smoking.

Thus, in this population of Finnish smokers, calcium, dairy foods, phosphorus, fructose, and protein were not important predictors of prostate cancer risk. However, there was a suggestion of an interactive effect between calcium and phosphorus and prostate cancer risk, which may be important to consider in future investigations.

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