ABSTRACT

Laboratory and clinical data indicate an antitumor effect of 1,25(OH)\textsubscript{2} vitamin D (1,25(OH)\textsubscript{2}D) on prostate cancer. High calcium intake suppresses formation of 1,25(OH)\textsubscript{2}D from 25(OH)D, thereby decreasing the 1,25(OH)\textsubscript{2}D level. Ingestion of fructose reduces plasma phosphate transiently, and hypophosphatemia stimulates 1,25(OH)\textsubscript{2}D production. We thus conducted a prospective study among 47,781 men of the Health Professionals Follow-Up Study free of cancer in 1986 to examine whether calcium and fructose intake influenced risk of prostate cancer. Between 1986 and 1994, 1369 non-stage A1 and 423 advanced (extraprostatic) cases of prostate cancer were diagnosed. Higher consumption of calcium was related to advanced prostate cancer (multivariate relative risk (RR), 2.97; 95% confidence interval (CI), 1.61–5.50 for intakes ≥2000 mg/day versus <500 mg/day; P, trend, 0.002) and metastatic prostate cancer (RR, 4.57; CI, 1.88–11.1; P, trend, <0.001). Calcium from food sources and from supplements independently increased risk. High fructose intake was related to a lower risk of advanced prostate cancer (multivariate RR, 0.51; CI, 0.33–0.80, for intakes >70 versus ≤40 g/day; P, trend, 0.007). Fruit intake was inversely associated with risk of advanced prostate cancer (RR, 0.63; 95% CI, 0.43–0.93; for >5 versus ≤1 serving per day), and this association was accounted for by fructose intake. Non-fruit sources of fructose similarly predicted lower risk of advanced prostate cancer. A moderate positive association between energy-adjusted fat intake and prostate cancer was attenuated and no longer statistically significant when controlled for calcium and fructose. Our findings provide indirect evidence for a protective influence of high 1,25(OH)\textsubscript{2}D levels on prostate cancer and support increased fruit consumption and avoidance of high calcium intake to reduce the risk of advanced prostate cancer.

INTRODUCTION

1,25(OH)\textsubscript{2}D\textsuperscript{3} has a well-established role in calcium and phosphorus homeostasis, but many cell types possess functional vitamin D receptors and are responsive to the actions of 1,25-(OH)\textsubscript{2}D\textsuperscript{1} (1). Typically, higher levels of 1,25-(OH)\textsubscript{2}D inhibit cellular proliferation and induce differentiation for normal and neoplastic prostate cells in vitro (2–5). Moreover, limited studies in rodents support antitumor potency of 1,25(OH)\textsubscript{2}D analogues against prostate cancer (6, 7), and older men who have high circulating 1,25(OH)\textsubscript{2}D are at reduced risk of poorly differentiated and clinically advanced prostate cancer (8, 9). Additional preliminary evidence of a role of 1,25(OH)\textsubscript{2}D is that genetic polymorphisms of the vitamin D receptor gene, which may correlate with activity of the receptor, also predict risk of prostate cancer (10, 11).

If circulating 1,25(OH)\textsubscript{2}D confers these benefits, adequate intake of vitamin D or production in the skin through sunlight exposure may help prevent prostate cancer. Although some geographic evidence suggests that sunlight may be beneficial (12), ecological, case-control, and cohort studies consistently find higher intakes of dairy products, the major dietary source of vitamin D, associated with an enhanced risk of prostate cancer (13). This apparent paradox may be resolved by considering that 1,25(OH)\textsubscript{2}D, rather than the precursor 25(OH)D, is biologically relevant. As shown in Fig. 1, 1,25(OH)\textsubscript{2}D is tightly regulated, primarily through the activity of renal 1-α-hydroxylase, which is stimulated to hydroxylate 25(OH)D to 1,25(OH)\textsubscript{2}D when the circulating concentration of calcium is low (14, 15). Because of its precise regulation, 1,25(OH)\textsubscript{2}D is not correlated with vitamin D intake or 25(OH)D levels. Instead, because dairy products are the major source of calcium, their overall effect is to suppress 1,25(OH)\textsubscript{2}D levels.

Another potentially important dietary factor is phosphorus, because reductions in circulating phosphate increase 1,25(OH)\textsubscript{2}D levels appreciably (16, 17). Because phosphorus is generally abundant in most diets and is well absorbed intestinally, dietary-induced hypophosphatemia is rare. Moreover, phosphatase may bind calcium, reducing its bioavailability, and low phosphate stimulates parathyroid hormone; these properties tend to decrease circulating 1,25(OH)\textsubscript{2}D, making the overall impact of dietary phosphorus on circulating phosphate or 1,25(OH)\textsubscript{2}D levels unclear. Dietary fructose can reduce plasma phosphate levels by 30 to 50% for more than 3 h due to the rapid shift of phosphate from the extracellular to intracellular compartment (18, 19). This hypophosphatemia occurs because fructose is very rapidly phosphorylated in the liver, catalyzed by fructokinase (20), which by-passes the phosphofructokinase regulatory step in glycolysis (21).

Based on the evidence supporting antitumor properties of 1,25(OH)\textsubscript{2}D (1–11), we examined dietary calcium, vitamin D, phosphorus, and fructose in relation to risk of prostate cancer in the ongoing Health Professionals Follow-Up Study.

PATIENTS AND METHODS

Study Population and Follow-up of the Cohort. The Health Professionals Follow-Up Study, an ongoing prospective cohort study (22), consists of 51,529 U.S. male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, who were 40–75 years in 1986. Through mailed questionnaires, these men provided information on age, marital status, height and weight, ancestry, medications, disease history, physical activity, and diet. For this analysis, we excluded men who had a diagnosis of cancer (other than nonmelanoma skin cancer) or who did not adequately complete the diet questionnaire (3% of total), leaving 47,781 for follow-up. Follow-up questionnaires were sent in 1988, 1990, 1992, and 1994 to ascertain new cases of a variety of diseases, including prostate cancer. The response rate through 1994 was 94%. Deaths in the cohort were reported by family members in response to the follow-up questionnaires or were discovered through the postal system or the National Death Index, a highly sensitive method (23) used to identify deaths among nonrespondents. Through these measures, over 98% of the deaths are ascertained.

Dietary Assessment. Diet was assessed with a self-administered semi-quantitative food frequency questionnaire. Men were asked how often on average, over the past year, they consumed each item on a list of 131 commonly consumed foods and beverages. In addition, we assessed frequency

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2 To whom requests for reprints should be addressed, at Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115.

The abbreviations used are: 1,25-(OH)\textsubscript{2}D, 1,25(OH)\textsubscript{2} vitamin D; RR, relative risk; CI, confidence interval; BMI, body mass index.
of supplement use and included an open-ended section for commonly eaten foods not listed. Nutrient intakes were the product of the frequency of intake and the nutrient composition (24) of the specified portion size. Analyses were conducted using energy-adjusted nutrient intakes based on residuals from the regression of nutrient intake on total caloric intake (25).

We conducted a validation study of 121 men in the cohort to compare questionnaire-based intakes to those estimated from two 1-week diet records (26). Correlation coefficients between the energy-adjusted calcium intakes measured by diet records (de-attenuated for week-to-week variability) and by the second questionnaire were 0.61 for calcium with supplements and 0.63 for calcium without supplements, and 0.63 for phosphorys. Composition for vitamin D was not available from diet records, but correlation coefficients between the questionnaire and the diet records for dairy foods, the major dietary source of vitamin D, was 0.70 (27).

Fructose is ingested as a monosaccharide or as part of sucrose. Because fructose is readily liberated from sucrose in the small intestine, fructose from sucrose has similar metabolic properties as monosaccharide fructose (28). The major dietary sources of total fructose are fruits, carbonated beverages, sweet bakery products, candy, and added sugar. The median intake of total fructose represented 9.5% of total energy intake, with a range from 4.9% in the tenth percentile to 16.1% in the ninetieth, comparable with national data (28).

Although diet record values for fructose and sucrose were not available for comparison, the major dietary sources of sucrose were measured well (27).

We evaluated potential confounding from nondietary factors (tobacco use, physical activity, and vasectomy) and various dietary factors hypothesized to be related to prostate cancer risk (total energy and fat, types of fat, vitamin E, and lycopene). We also assessed current BMI and BMI at age 21 years, which was strongly inversely related to advanced prostate cancer risk in this population (31).

RESULTS

Calcium. As shown in Table 1, high calcium consumption was related to less tobacco use, higher level of physical activity, higher consumption of multivitamins, fiber, phosphorus, vitamin E, and lycopene. In age-adjusted and multivariate analyses (Table 2), consumption of calcium was related to higher risk of total, advanced, and metastatic prostate cancer, especially at intakes exceeding 2000 mg/day.

Table 1 Age-standardized characteristics according to low and high intake of total calcium, total fructose, fruit fructose, and non-fruit fructose in the Health Professionals Follow-up Study (1986)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Calcium (mg)*</th>
<th>% energy from calcium</th>
<th>% energy from fructose</th>
<th>% energy from sucrose</th>
<th>Current smokers (%)</th>
<th>Past smokers (%)</th>
<th>BMI (kg/m²)</th>
<th>BMI (kg/m²) at age 21</th>
<th>Physical activity (MET-hours/week)</th>
<th>Multivitamin use (%)</th>
<th>Vitamin E (%)</th>
<th>Total fat (g)</th>
<th>% energy from fat</th>
<th>Carbohydrates (g)</th>
<th>Fiber (g)*</th>
<th>Phosphorus (mg)*</th>
<th>Vitamin D (IU)</th>
<th>Vitamin E (IU)</th>
<th>Lycopene (µg)*</th>
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<tr>
<td>Low</td>
<td>432</td>
<td>2474</td>
<td>915</td>
<td>842</td>
<td>818</td>
<td>965</td>
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<td>960</td>
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<td>Low</td>
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<td>Current smokers</td>
<td>Past smokers</td>
<td>BMI</td>
<td>BMI (kg/m²) at age 21</td>
<td>Physical activity (MET-hours/week)</td>
<td>Multivitamin use (%)</td>
<td>Vitamin E (%)</td>
<td>Total fat (g)</td>
<td>% energy from fat</td>
<td>Carbohydrates (g)</td>
<td>Fiber (g)*</td>
<td>Phosphorus (mg)*</td>
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<td>19.0</td>
<td>24.5</td>
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<td>20.9</td>
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<td>19.4</td>
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<tr>
<td>Total fat (g)</td>
<td>73.5</td>
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<td>75.0</td>
<td>64.8</td>
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<tr>
<td>% energy from fat</td>
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<td>35.8</td>
<td>26.0</td>
<td>32.8</td>
<td>30.3</td>
<td>220.6</td>
<td>245.6</td>
<td>214.2</td>
<td>267.6</td>
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<td>20.9</td>
<td>23.6</td>
<td>17.0</td>
<td>28.9</td>
<td>21.2</td>
<td>19.6</td>
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<td>Fiber (g)*</td>
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<td>24.0</td>
<td>20.9</td>
<td>23.6</td>
<td>17.0</td>
<td>28.9</td>
<td>21.2</td>
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<td>1131</td>
<td>1818</td>
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<td>Phosphorus (mg)*</td>
<td>1131</td>
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<td>1429</td>
<td>1309</td>
<td>1340</td>
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<td>1484</td>
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<td>193</td>
<td>835</td>
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<td>307</td>
<td>419</td>
<td>415</td>
<td>295</td>
<td>61</td>
<td>108</td>
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<tr>
<td>Vitamin D (IU)</td>
<td>193</td>
<td>835</td>
<td>378</td>
<td>330</td>
<td>307</td>
<td>419</td>
<td>415</td>
<td>295</td>
<td>61</td>
<td>108</td>
<td>87</td>
<td>79</td>
<td>144</td>
<td>127</td>
<td>127</td>
<td>79</td>
<td>61</td>
<td>108</td>
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<tr>
<td>Vitamin E (IU)</td>
<td>61</td>
<td>371</td>
<td>108</td>
<td>87</td>
<td>79</td>
<td>144</td>
<td>127</td>
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<td>4650</td>
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<td>4445</td>
<td>4525</td>
<td>4650</td>
<td>5140</td>
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</table>

*Adjusted for total energy intake.

For fruit and non-fruit fructose, this represents percentage of energy from fruit and non-fruit fructose, respectively.
day. The RR's for an equivalent increase of calcium from dairy and nondairy sources (including supplements) were similar; the multivariate RR for metastatic prostate cancer was 1.8 (95% CI, 1.0-3.3; \( P = 0.05 \)) for a 1000-mg increment of dairy calcium and 1.7 (95% CI, 1.0-2.8) per 1000-mg increment of nondairy calcium. Increasing calcium from foods and supplements independently increased the risk of prostate cancer (Table 3).

Total consumption of milk, 83% from skim and low-fat milk, was associated with higher risk of advanced prostate cancer (RR, 1.6; 95% CI, 1.2-2.1 for \( >2 \) versus 0 glasses per day; \( P = 0.002 \)) and metastatic prostate cancer (RR, 1.8; 95% CI, 1.2-2.8; \( P = 0.001 \)). We examined whether other components of dairy products, including vitamin A, protein, vitamin D, phosphorus, and saturated fat, could have accounted for the association. Including each of these in multivariate models with calcium, calcium intake persisted unchanged as a significant risk factor in every model.

**Phosphorus.** Intake of phosphorus was unrelated to risk of total prostate cancer (multivariate RR for \( >1800 \) versus \( <1200 \) mg/day, 0.94; 95% CI, 0.71-1.26; \( P = 0.31 \)) for advanced prostate cancer, the age-adjusted model suggested a slightly elevated risk of 1.10 (not significant) at high intakes, but in the multivariate model, an inverse association was suggested (RR, 0.67; 95% CI, 0.40-1.13). The difference between the age-adjusted and the multivariate RR's was due primarily to confounding from calcium intake.

**Vitamin D.** Total vitamin D intake was not associated with risk of total prostate cancer (multivariate RR, 1.21; 95% CI, 0.92-1.58 for \( \geq 800 \) versus \( <150 \) IU/day; \( P = 0.87 \)) or advanced prostate cancer (RR, 1.48; 95% CI, 0.91-2.39; \( P = 0.64 \)). Also, vitamin D intake was not related to risk of metastatic prostate cancer (\( P = 0.28 \)). No association was observed for vitamin D intake from supplements only (\( P = 0.30, 0.41, \) and 0.25, for total, advanced, and metastatic prostate cancer, respectively) or from supplements (\( P = 0.84, 0.70, \) and 0.84).

**Fructose.** As seen in Table 1, high consumers of fructose were considerably less likely to be or have been smokers, tended to be more physically active and slightly leaner, and had lower intake of fat and higher consumption of carbohydrates, fiber, and lycopene. High consumption of energy-adjusted fructose was related to lower age-adjusted risk of total prostate cancer (Table 4). Additional models (not shown), which included nondietary risk factors including current BMI, smoking status, vasectomy, and physical activity level, yielded similar results as the age-adjusted models. Controlling for various dietary factors, including dietary fat, yielded almost identical results as the age-adjusted analysis. High fructose consumption had an even stronger inverse association with advanced and metastatic prostate cancer (Table 4). Both free fructose (\( P = 0.04 \)) and fructose from sucrose (\( P = 0.006 \)) had similar inverse associations with advanced prostate cancer in multivariate models.

Total carbohydrates, which had a correlation of 0.74 with total fructose, also was inversely associated with advanced forms of prostate cancer (RR, 0.74 for a 100-g increment; \( P = 0.02 \)), but the relationship with total carbohydrates was attenuated when we controlled for fructose (RR, 0.92; \( P = 0.66 \)).

Although controlling for known and suspected risk factors for prostate cancer, including fat intake, did not alter our results for fructose, the possibility remained that unknown risk factors associated with fructose intake accounted for this relationship. High consumers of total fructose were more likely to have generally "healthy lifestyles," but fructose from fruit and non-fruit sources (predominantly sweets, carbonated soft drinks, and added sugar) had divergent lifestyle and dietary patterns (see Table 1). We examined fructose from fruit and non-fruit sources simultaneously as separate predictors of advanced prostate cancer in a multivariate logistic regression model that included age and total energy. Men in the top decile of consumption were at lower risk of advanced prostate cancer relative to men with the lowest intakes for fructose (RR, 0.55; 95% CI, 0.33-0.92; \( P = 0.04 \)) and for non-fruit fructose (RR, 0.54; 95% CI, 0.36-0.84; \( P = 0.02 \)). Modeling both sources as continuous variables yielded similar results for fruit fructose (for a 30-g increment in fructose intake: RR, 0.78; 95% CI, 0.61-0.99) and non-fruit fructose (RR, 0.78; 95% CI, 0.63-0.96).

Total fruit intake was inversely associated with risk of advanced prostate cancer.
RISK OF PROSTATE CANCER AND CALCIUM AND FRUCTOSE INTAKE

Table 5 RR and 95% CI of prostate cancer for a 33 g (15% of energy) increment of total fat, a 50-g (10% of energy) increment of fructose, and a 1000-mg increment of calcium

<table>
<thead>
<tr>
<th>Total fat</th>
<th>Total fructose</th>
<th>Total calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total prostate cancer (n = 1363)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.09 (0.94-1.25)</td>
<td>1.07 (0.91-1.26)</td>
</tr>
<tr>
<td>RR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.00 (0.86-1.17)</td>
<td>0.74 (0.61-0.91)</td>
</tr>
<tr>
<td><strong>Advanced prostate cancer (n = 411)</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.17 (1.09-1.33)</td>
<td>1.48 (1.14-1.92)</td>
</tr>
<tr>
<td>RR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.60 (0.42-0.87)</td>
<td>1.52 (1.17-1.97)</td>
</tr>
<tr>
<td><strong>Metastatic prostate cancer (n = 201)</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.50 (1.04-2.18)</td>
<td>1.84 (1.28-2.62)</td>
</tr>
<tr>
<td>RR (95% CI)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.57 (0.35-0.93)</td>
<td>1.88 (1.32-2.66)</td>
</tr>
</tbody>
</table>

- <sup>a</sup> RR from a multivariate model based on the indicated variable (fat, fructose, or calcium) as a continuous variable controlling for age, BMI at age 21, intakes of energy, phosphorus, vitamin D, vitamin E, and lycopene. The increments for fat, fructose, and calcium represent approximately the difference between the 90th and 10th percentiles of intake for these nutrients.
- <sup>b</sup> P ≤ 0.001.
- <sup>c</sup> From multivariate model as above (a) including total fat, fructose, and calcium simultaneously.
- <sup>d</sup> 0.01 < P ≤ 0.05.
- *0.001 < P ≤ 0.01.

prostate cancer (age- and energy-adjusted RR, 0.63; 95% CI, 0.43–0.93, for >5 relative to ≤1 serving per day), but this inverse association did not persist when total fructose was included in this model (RR, 0.87; 95% CI, 0.55–1.36). This finding suggests that the association seen for fruit is due to the fructose content of this food. Fructose from carbonated beverages alone (a component of non-fruit fructose) yielded a similar inverse association (RR, 0.72; 95% CI, 0.51–1.03).

The inverse association between fructose intake and risk of total and advanced prostate cancer did not vary appreciably across levels of calcium, phosphorus, total fat, and lycopene intake, and no statistically significant interactions were noted between fructose and any of these variables.

**Fat.** Energy-adjusted fat intake was inversely correlated (r = −0.41) with energy-adjusted fructose intake. As reported in an earlier follow-up period of this cohort (1986–1990; Ref. 22), energy-adjusted total fat was significantly related to advanced and metastatic prostate cancer, although in a multivariate analysis (without fructose and calcium intake) the magnitude of the association was less than that observed during earlier follow-up periods (Table 5). Simultaneous control for fat, fructose, and calcium yielded little change of the results for calcium and fructose, but the positive association between total fat intake and advanced prostate cancer became attenuated and was no longer statistically significant (Table 5). These results were similar when we substituted animal fat and saturated fat for total fat in the multivariate model (data not shown). These findings for calcium and fructose also persisted when we substituted total fat in the models with α-linolenic acid, for which we had previously reported strong associations with prostate cancer (22, 32). However, associations for α-linolenic acid persisted but were attenuated (multivariate RR for high versus low quintile of α-linolenic acid was 1.33; 95% CI, 0.97–1.81; P, trend = 0.08) for advanced cancer and RR = 1.55 (95% CI, 0.97–2.49; P, trend = 0.07) for metastatic prostate cancer.

**DISCUSSION**

The hypothesis that higher levels of circulating 1,25(OH)₂D reduces the risk of prostate cancer is unproven but supported by an increasing body of *in vitro*, animal, epidemiological, and genetic evidence (1–11), as summarized in the introduction. We thus examined whether dietary factors that may influence 1,25(OH)₂D risk are related to prostate cancer risk in a large cohort study.

The most obvious dietary factor to influence circulating 1,25(OH)₂D is calcium. The predicted plasma levels of 1,25(OH)₂D based on published data (plasma 1,25(OH)₂D pmol/l = 99–40 × calcium intake mmol/kg/day; Refs. 3 and 33) for our extreme categories of intake (medians, 445 and 2346 mg/day) were 39.1 and 28.6 pg/ml. In the two studies that showed lower risks of advanced prostate cancer associated with higher 1,25(OH)₂D levels (8, 17), the cutoff values for the extreme quartiles were >39 and <27 pg/ml (8) and 40.2 and 28.6 (17). Thus, the range of calcium intake in our cohort predicts a magnitude of difference in plasma levels of 1,25(OH)₂D, which have been directly correlated with prostate cancer risk. In this study, we found dietary and supplementary calcium each associated with higher risk of extraprostatic, metastatic, and fatal prostate cancer. The association with supplementary sources indicated that calcium, and not another factor in dairy products, accounted for the increased risk.

Another major determinant of 1,25(OH)₂D level is circulating phosphate. A reduction in phosphate levels stimulates renal 1-α-hydroxylase to convert 25(OH)D to 1,25(OH)₂D, thus raising circulating 1,25(OH)₂D (34). Low blood phosphate levels induced experimentally by atypically low phosphorus intakes (300 mg), coupled with agents that decreased gut absorption of phosphorus, have been shown to sharply increase 1,25(OH)₂D blood levels by 80% (34). In the same subjects, increasing baseline phosphorus intake from 1500 to 3000 mg/day decreased 1,25(OH)₂D by 29%. Because of the limited range of phosphorus intake in our population (about 1200 to 1800 mg/day) and the potentially competing effects of dietary phosphorus on 1,25(OH)₂D by binding intestinal calcium and by suppressing parathyroid hormone, the overall impact of phosphorus on 1,25(OH)₂D are unclear (14). Perhaps these complexities may explain why we did not observe an association between dietary phosphorus and prostate cancer risk.

Dietary phosphorus deficiency severe enough to lower phosphorus levels is probably rare, but significant transient reductions of 1–2 mg/dl in plasma phosphate (which averages about 3.5 mg/dl) occur daily. These fluctuations are likely due primarily to fructose consumption because the high rate of fructose phosphorylation catalyzed by fructokinase (14, 15) leads to a sequestration of inorganic phosphate into the liver (35). Indeed, i.v. or oral consumption of relatively high levels of fructose (e.g., 50 g) in controlled situations is known to induce a profound hypophosphatemia. Several lines of evidence illustrate that the hypophosphatemic effect of fructose occurs in free-living individuals consuming typical dietary intakes of fructose. For example, one of the well-established consequences of reduced phosphate level is activation of AMP deaminase and nucleotidase, which induces increased uric acid production and hyperuricemia (21). Among normal individuals with typical diets, higher intakes of fructose correlate with increases in serum uric acid, strongly suggesting that fructose intakes in mixed diets appreciably influences phosphate levels (18, 19, 36).

In this prospective study, we found that high fructose consumption, from either fruit or non-fruit sources, was associated with a reduced risk of prostate cancer, particularly with advanced disease. Beyond controlling for suspected risk factors, we further considered the possibility that fructose was acting as an indirect marker of an actual unconsidered risk factor. This putative risk factor would have to be strongly and similarly correlated with fructose from fruit and non-fruit sources because the relationship with prostate cancer risk was virtually identical for these two sources of fructose. Compared to the corresponding low consumers, the high consumers of fructose from non-fruit sources were less physically active, more likely to smoke, and were relatively inactive. The very divergent lifestyle patterns between high fruit and non-fruit fructose consumers reduces the biological plausibility of a strong association.
likelihood that a strong unrecognized determinant of prostate cancer would be equally correlated with fruit and non-fruit fructose, to produce confounding, while being uncorrelated with numerous other behaviors and dietary patterns.

It is important to emphasize that we only examined the link between dietary fructose and prostate cancer risk here and did not study the proposed intervening steps. We do not know whether any influence of fructose on 1,25(OH)2D levels through hypophosphatemia would be of sufficient magnitude to influence prostate cancer risk. Also, we cannot rule out alternative mechanisms. Nonetheless, the characteristic metabolic, physiological, and clinical consequences of fructose taken either p.o. or i.v. are clearly related to the very high activity of hepatic fructokinase and the resulting sequestration of phosphate (21). Given the importance of hypophosphatemia in determining renal 1-α-hydroxylase activity, this proposed mechanism clearly deserves consideration, although other potential mechanisms should not be excluded.

We did not observe any relationship between prostate cancer and vitamin D from foods or supplements at total intakes ranging from <150 to >800 IU/day. This is not surprising because dietary vitamin D influences 25(OH)D levels but not 1,25(OH)2D, except perhaps at extremes.

Previous studies of prostate cancer have not examined calcium, but many have assessed the major calcium sources, milk and other dairy products. Per capita milk consumption correlated more highly with national rates of prostate cancer mortality (r = 0.66) than other foods rich in animal fats and cholesterol (meats, r = 0.39; eggs, r = 0.01; Ref. 37). A correlation study of prostate cancer among regions in Italy found the strongest independent dietary correlations for milk (r = 0.75) and cheese consumption (r = 0.69; Ref. 38). The most consistent dietary predictor of elevated prostate cancer risk from six case-control and three prospective studies is high milk or dairy consumption (13). Magnitudes of RRs between high and low consumption for milk have been approximately 2-fold (13), similar to our study. However, when we considered the additional intake of non-dairy and supplementary calcium, more striking RRs emerged, presumably because of the greater contrast.

To our knowledge, the hypothesis that high intakes of fructose reduces risk of prostate cancer had not been tested previously, and there is sparse data regarding fruit intake. One study reported a significant positive association between fruit intake and prostate cancer risk (39), and another reported a nonsignificant positive association (40). Two studies reported no relationship (41, 42), but a non-significant inverse association was observed with dried fruits in the latter study. Unlike our study, these studies tended to rely on reported aggregate intakes than of individual items. If fructose is the relevant factor, it is unclear how well fruit intake in these studies correlated with overall fructose consumption.

Although an association with fat intake was noted with advanced prostate cancer, fructose but not fat intake was the independent predictor of risk in multivariate analysis. Moreover, fat intake was strongly inversely correlated with fruit fructose (Pearson r = −0.44) but only weakly related to non-fructose fructose (r = −0.11); thus, the similar inverse associations with prostate cancer for both fruit and non-fructose fructose argues strongly against fat intake directly accounting for the fructose association. We hypothesize that diets high in dairy products and meat and low in fruits are associated with increased risk of prostate cancer because these diets tend to be high in calcium and phosphorus and low in fructose, and thus associated with lower circulating 1,25(OH)2D levels. In previous studies (13), including in the Health Professionals Follow-Up Study, fat intake may have represented an indirect marker of a dietary pattern high in animal products and low in fructose. However, we cannot definitively exclude an independent role for α-linolenic acid or some close correlate of this fatty acid.

Our findings, if confirmed, have several implications. They provide indirect support for an influence of dietary determinants of 1,25(OH)2D levels on prostate cancer carcinogenesis. They also suggest that diets high in animal fat increase the risk of prostate cancer indirectly through their low fructose and high calcium content. Most importantly, these results indicate an additional health benefit of increased fruit consumption and suggest a potential adverse effect of high calcium intakes specifically among middle-aged and older men. Given the morbidity and mortality caused by prostate cancer, these hypotheses warrant further investigation.

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Calcium and Fructose Intake in Relation to Risk of Prostate Cancer


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