Associations of Energy, Fat, Calcium, and Vitamin D with Prostate Cancer Risk[1]

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Abstract

This population-based, case-control study in King County, Washington examined associations of energy, fat, vitamin D, and calcium with risk of prostate cancer in 605 incident cases (ages 40–64 years) identified from the Seattle-Puget Sound Surveillance Epidemiology and End Results registry and 592 controls recruited from the same underlying population using random-digit telephone sampling. Self-administered food frequency questionnaires were used to assess diet over the 3–5-year period before diagnosis or interview date. Total energy was associated with increased risk for both local and regional/distant stage disease. The adjusted odds ratios [95% confidence intervals (CIs)] contrasting highest to lowest quintile of energy intake were 2.15 (95% CI, 1.35–3.43) for local and 1.96 (95% CI, 1.08–3.56) for regional/distant disease. Fat was associated with regional/distant disease only. Adjusted odds ratios comparing the highest to lowest quintiles of percentage energy from total, saturated, and monounsaturated fats were 2.01 (1.03–3.92), 1.82 (0.93–3.56), and 2.00 (1.03–3.87), respectively. For calcium, adjusted odds ratios contrasting the highest to lowest quartiles were 1.07 (0.63–1.84) for local and 2.12 (1.02–4.38) for regional/distant disease. There were no associations of vitamin D, total polyunsaturated fatty acids, or the highly unsaturated, long-chain eicosapentainoic and docosahexaenoic fatty acids with prostate cancer risk. These results suggest that high energy intake is a risk factor for both localized and nonlocalized prostate cancer, whereas dietary fat and calcium increase the risk of regional/distant disease only. These results are consistent with general dietary guidelines to moderate consumption of total energy and fat, and they motivate further research to consider the potential benefits and risks of high calcium intake.

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Introduction

The relationship between dietary fat consumption and prostate cancer risk remains unclear. Although ecological studies find strong associations of *per capita* fat consumption or biomarkers of fatty acid intake with prostate cancer incidence (1–3), results of case-control and prospective observational studies are far less consistent. A recent, comprehensive review reported that 24 of 32 studies found positive, although not necessarily statistically significant, relationships of dietary fat or intake of foods high in fat with prostate cancer risk (4). Many questions remain about the associations of fat with prostate cancer risk. One set of questions is related to whether effects of fat differ by level of saturation because many studies find associations only for saturated fat or for foods high in saturated fat. Another set of questions relates to whether there are unique effects for specific fatty acids, in particular for α-linolenic acid (5) and for the highly unsaturated, very long-chain EPA[3] and DHA (6–8). Finally, there are questions about whether associations attributed to fat are actually due to other components of foods that are high in fat. For example, 16 of 22 studies examining meat consumption and prostate cancer risk have reported positive associations (9), suggesting that compounds in meat or carcinogenic by-products of cooking meat could be causal agents (10).

Another possible dietary risk factor for prostate cancer is high calcium intake (11). The strongest evidence is from studies finding increased risks with higher milk consumption, total dietary calcium, and calcium from supplements (12–15). The evidence is not consistent, however, because several studies have not found associations of calcium with prostate cancer risk (16–18). Vitamin D, which affects both calcium absorption in the gut and calcium absorption from bone, may affect the relationship between calcium and prostate cancer risk (19, 20), although it is important to note that vitamin D is available from both dietary and nondietary sources. Given the inconsistency in the literature regarding calcium and prostate cancer risk, along with the very high relative risk reported in one study for both high intakes of dietary and supplemental calcium (12), it is important to examine this association in additional studies.

Here we give the final set of results on diet and prostate cancer risk from a population-based case-control study of men ages 40–64 years. Previous articles from this study have reported on dietary supplement use (21) and fruit and vegetable consumption (22). This article addresses the remaining diet-related hypotheses, specifically, associations of energy, total fat, types of fat, calcium, and vitamin D with prostate cancer risk.

[3] The abbreviations used are: EPA, eicosapentainoic acid; DHA, docosahexaenoic acid; PSA, prostate-specific antigen; FFQ, food frequency questionnaire; CI, confidence interval; %en, percentage of energy.

Materials and Methods

Data are from a population-based, case-control study of risk factors for prostate cancer, described in detail elsewhere (23). Eligible cases were white and African-American male residents of King County (Seattle), Washington, ages 40–64 years, who were newly diagnosed with histologically confirmed prostate cancer between January 1, 1993 and December 31, 1996. Cases were identified from the Seattle-Puget Sound Surveillance Epidemiology and End Results cancer registry. Only cases with a residential telephone were eligible because controls were selected using random-digit dialing. Furthermore, because the emphasis was on recruiting younger men, only a random 75% sample of cases ages 60–64 years was recruited. Of 917 cases selected for participation, 753 (82.1%) were interviewed. The median time between diagnosis and interview was 9 months. Reasons for nonresponse were physician refusal to allow contact (2.6%), case refusal (12.5%), inability to locate (1.5%), illness (0.4%), and death (0.2%). Controls were identified using random-digit dialing, frequency-matched to cases by age (same 5-year group), and recruited evenly throughout the ascertainment period for cases. Of the 21,116 residential numbers contacted, 94% provided household census data. Of the 1,025 eligible men identified, 941 (91.8%) agreed to receive mailed information about the study. Of those receiving information, 703 (74.7%) were interviewed. Reasons for nonresponse were refusal (24.2%), loss to follow-up (<1%), and illness (<1%).

Participants completed in-person interviews conducted by trained male interviewers. Information was collected on a broad range of topics, including demographic characteristics, height and weight, family history of prostate cancer, and 5-year history of screening using PSA and digital rectal examination. For cases, all time-sensitive questions used diagnosis date as the reference date. For controls, the reference date was randomly assigned from dates that approximated the distribution of cases' diagnosis dates. A calendar of life events was used to enhance recall. After the interview, participants were given a self-administered FFQ and asked to complete it at home and return it by mail. Extent of disease in cases was based on data abstracted by the Seattle/Puget Sound Surveillance Epidemiology and End Results cancer registry. Tumors were classified as localized (confined to the prostate), regional (spread beyond the prostatic capsule into surrounding tissue), and distant (metastatic). Classification of extent of disease incorporated data from surgery for men undergoing radical prostatectomy.

The FFQ asked about usual consumption over the 3–5-year period preceding the reference date. There were 99 food items, and 22 questions on food purchasing and preparation were used to adjust nutrient calculations (24, 25). Both food items and adjustment questions collected information on use of fat-modified foods and types and amounts of fat added in preparation or at the table because these can have large effects on FFQ-derived estimates of fat intake (26). Each food item had nine options for frequency (ranging from "never or less than once per month" to "2+ times per day" for foods, and "6+ times per day" for beverages) and three options for portion size. Daily nutrient intakes were calculated using algorithms developed at the Fred Hutchinson Cancer Research Center (25), using the nutrient database from the University of Minnesota Nutrient Data System (27). FFQs were completed by 654 cases (87%) and 625 controls (89%). For this study, participants were excluded if: (*a*) their energy intakes were less than 800 kcal or greater than 5000 kcal because their FFQs were considered to be unreliable ($n = 35$ cases and 31 controls); (*b*) stage of disease at diagnosis was missing ($n = 10$ cases); or (*c*) there were missing data on covariates ($n = 4$ cases and 2 controls). The final sample consisted of 605 cases and 592 controls.

To estimate intake of the marine fatty acids EPA and DHA, additional questions were asked about servings/week of sardines and herring, shellfish, and light- and dark-fleshed fish. EPA and DHA values were based on nutrient values in the University of Minnesota Nutrient Data System (27). Data on use of supplemental calcium, vitamin D, and fish oil supplements were also collected and incorporated into calculations of total intake. In addition, the frequencies of consuming standard portions of dairy products (milk, ice cream, and cheese), milk alone, and red meat were calculated from food frequency data.

Nutrient values, with the exceptions of percentages of energy from total, saturated, monounsaturated, and polyunsaturated fats, were log-transformed for all calculations. Mean nutrient intakes and SDs are given back-transformed to original units for ease of interpretation. Polytomous, unconditional logistic regression was used to calculate odds ratios for risks of local and regional/distant prostate cancer associated with nutrient intake. Associations were adjusted for the following covariates: (*a*) age (categorized in 5-year groups); (*b*) race (white and African American); (*c*) family history of prostate cancer (none, second-degree relative only, and first-degree relative); (*d*) education (12, 13–15, 16, and 17+ years); (*e*) body mass index (<24, 24–27, 28–29, and 30+ kg/m^2); and (*f*) number of screening PSA tests within 5 years before reference date (0, 1–2, 3–4, and 5+). Based on previously published results, analyses were also adjusted for the number of servings/day of vegetables (22) and for use of supplemental vitamin E, vitamin C, and zinc (21). Two analytic approaches were used to examine fat intake, the "nutrient density" and the "partition" methods (28). Analyses of percentage energy from fat were adjusted for total energy intake (nutrient density method), which can be interpreted as the effect of substituting fat for other sources of energy while keeping energy intake constant. Analyses of energy from fat were adjusted for nonfat sources of energy (partition method), which can be interpreted as the effect of increasing fat (with the corresponding energy from fat) while keeping other sources of energy constant. Analyses were based on quintiles of distributions in controls, and tests for trends across quintiles used the method of Breslow and Day (29). All *P*s are two-sided.

Results

Table 1 gives demographic characteristics, family history of prostate cancer, PSA testing, and stage of disease at diagnosis. More than 60% of study participants were <60 years old, and >50% were college graduates. Cases were more likely than controls to have a family history of prostate cancer, be African American, and have received PSA screening tests. The majority of cases had localized disease (stage A or B) confined to the prostate.

Table 2 gives the means and SDs of nutrient intakes. Calcium intake was significantly higher among cases than controls. Energy and fat intakes were modestly higher in cases than controls, although these differences were not statistically significant.

Table 3 gives associations of energy, percentage of energy from fat, and energy from fat with prostate cancer risk. Total energy intake was significantly associated with risk for both localized and regional/distant disease. Compared with men eating <1322 kcal/day, those eating ≥2439 kcal/day had a 115% increased risk of local cancer and a 96% increased risk of regional/distant cancers. The increased risk associated with

Table 1 Demographic and health-related characteristics of case and control participants

	Cases (%) (N = 605)	Controls (%) (N = 592)
Age (yrs)		
40–49	5.3	6.9
50–54	19.4	18.4
55–59	36.4	38.5
60–64	39.0	36.2
Race		
White	96[a]	98.5
African American	4	1.5
Family history of prostate cancer		
None	72.2[b]	84.3
First-degree relative	19.5	10.2
Second-degree relative only	8.3	5.6
Education (yrs)		
≤12	27.3	21.8
13–15	20.2	22.8
16	28.6	27.7
≥17	24.0	27.7
Body mass index (kg/m^2)		
18–23	27.3	21.8
24–26	38.0	34.8
27–29	21.7	24.8
≥30	16.7	18.6
PSA tests within previous 5 yrs		
None	29.1[b]	66.6
1–2	33.6	19.2
3–4	19.5	8.6
≥5	17.9	5.6
Stage of disease		
Local	73.1	
Regional	23.5	
Distant	3.3	

[a] χ^2 cases *versus* controls $P < 0.05$.
[b] χ^2 cases *versus* controls $P < 0.001$.

Table 2 Nutrient intake/day in case and control participants

	Cases (N = 605) ($\bar{X} \pm SD$)[a]	Controls (N = 592) ($\bar{X} \pm SD$)[a]
Energy (kcal)	1882 ± 719	1830 ± 669
Total fat (g) (%en)	76.1 ± 37.4	73.5 ± 36.3
	37.3 ± 7.9	37.2 ± 8.4
Saturated fat (g)	26.1 ± 13.8	25.3 ± 13.2
Monounsaturated fat (g)	28.4 ± 14.3	27.2 ± 13.8
Polyunsaturated fat (g)	15.3 ± 7.8	14.9 ± 7.9
EPA[b] + DHA[b] (g)	0.13 ± 0.11	0.13 ± 0.11
Calcium[b] (mg)	811 ± 419[c]	765 ± 383
Vitamin D[b] (mcg)	7.9 ± 5.7	7.3 ± 5.2

[a] Geometric means, except percentage energy from fat.
[b] From food plus supplements.
[c] $P < 0.05$ *versus* controls.

higher energy intake was evident only in the highest quintile. Dietary fat intake was associated with regional/distant disease only. The first statistical model, in which percentage energy from fat was controlled for total energy, shows a statistically significant 2-fold increase in risk comparing men in the lowest quintile (<29.6%en) with those in all higher quintiles, with no evidence of a trend with increasing fat intake. The second model, in which energy from fat was controlled for energy from nonfat sources, shows both a nearly statistically significant odds ratio of 2.03 contrasting the lowest to highest quintile and a nearly statistically significant trend across quintiles. There was no significant association of red meat consumption with prostate cancer risk. Comparing the highest to lowest quintiles of red meat intake, the adjusted odds ratios were 1.20 (95% CI, 0.68–2.10) for local disease and 1.23 (95% CI, 0.57–2.66) for regional/distant disease, with test for trends of $P = 0.26$ and $P = 0.31$, respectively.

Table 4 gives associations of prostate cancer risk with percentages of energy from saturated, monounsaturated, and saturated fat and with total intakes of EPA + DHA, vitamin D, and calcium. Results are given for fully adjusted models only, and all are controlled for total energy. Intakes of both saturated and monounsaturated fats, but not polyunsaturated fats, were associated with risk of regional/distant disease, although the trends did not reach the 5% level of statistical significance. There were no associations of prostate cancer risk with long-chain *o*-3 fatty acids (EPA + DHA) or vitamin D. There was a statistically significant increase in risk of regional/distant disease with increasing calcium intake, with a 112% increased risk contrasting the highest to lowest quintiles. There was no significant association of dairy product consumption with prostate cancer risk, but there was a significant association of milk consumption with regional/distant disease. Comparing men who drank 2 or more glasses of milk/day with those drinking <2 glasses of milk/week, the adjusted odds ratio was 2.11 (95% CI, 1.12–4.00), with modest evidence for a trend across intake categories ($P = 0.062$).

Table 5 gives associations of calcium intake, cross-classified by dietary and supplemental calcium intakes. Calcium from supplements is categorized as none, doses from multivitamins (<200 mg), and doses from antacids or other high-calcium sources. For regional/distant disease, there were consistent trends for increased, independent risks from both dietary and supplemental calcium. For local disease, there was some suggestion of a trend for increased risk from supplemental calcium, although the magnitudes of these trends were modest.

Discussion

The primary findings from this study were that high energy intake was associated with increased risks of both local and regional/distant prostate cancer, whereas dietary fat and calcium were associated with increased risk for regional/distant cancer only. The increased odds ratios associated with fat were similar for both saturated and monounsaturated fats, and there was no evidence that total polyunsaturated fats or *o*-3 fatty acids were associated with risk. Increased odds ratios associated with calcium intake were evident from both dietary and supplemental sources. Our interpretation of these results is that high energy intake increases prostate cancer risk overall, whereas high dietary fat and calcium intakes increase the risk of more clinically significant, advanced stages of disease.

Several studies have found associations of total energy intake with prostate cancer risk (30–32), reporting magnitudes of association similar to the approximate 2-fold increase between low and high quintiles of energy intake found in this study. Our study found similar effects for local and regional/distant disease, which is also consistent with previous studies. However, all studies have relied upon FFQs to assess energy intake, and this limits their interpretation. Correlations between FFQs and criterion measures such as food records and multiple 24-h dietary recalls are rarely over 0.40 (33). Furthermore, it is difficult to interpret energy intake alone because it is affected by other factors such as lean body mass and physical activity. Nevertheless, the consistency of experimental findings in animal models (34) makes an association of high energy intake

Table 3 Odds ratios for associations of energy, percentage energy from fat, and energy from fat with prostate cancer risk, by stage of disease

	Stage	Odds ratio (95% CI) Quintile 1	2	3	4	5	*P* for trend
Total energy[a] (kcal)							
Unadjusted	Local	1.00 (ref)	1.32 (0.89–1.96)	1.03 (0.69–1.55)	1.01 (0.67–1.52)	1.52 (1.03–2.24)	0.20
	Regional/distant	1.00 (ref)	0.96 (0.55–1.67)	0.65 (0.35–1.19)	1.04 (0.60–1.80)	1.39 (0.83–2.35)	0.22
Adjusted[b]	Local	1.00 (ref)	1.40 (0.90–2.17)	1.28 (0.80–2.03)	1.09 (0.68–1.74)	2.15 (1.35–3.43)	0.02
	Regional/distant	1.00 (ref)	0.99 (0.55–1.80)	0.79 (0.41–1.51)	1.22 (0.67–2.23)	1.96 (1.08–3.56)	0.03
Fat[a] (%en)							
Unadjusted	Local	1.00 (ref)	1.60 (1.08–2.36)	1.42 (0.95–2.10)	1.09 (0.73–1.64)	1.08 (0.72–1.63)	0.63
	Regional/distant	1.00 (ref)	2.09 (1.13–3.88)	2.00 (1.08–3.72)	1.85 (0.99–3.47)	2.11 (1.14–3.91)	0.05
Adjusted[b,c]	Local	1.00 (ref)	1.42 (0.92–2.19)	1.25 (0.80–1.94)	1.12 (0.71–1.79)	1.08 (0.67–1.72)	0.88
	Regional/distant	1.00 (ref)	2.07 (1.08–3.98)	1.86 (0.96–3.59)	2.05 (1.05–4.01)	2.01 (1.03–3.92)	0.07
Fat[a] (kcal)							
Unadjusted	Local	1.00 (ref)	1.05 (0.71–1.57)	1.27 (0.86–1.87)	1.03 (0.69–1.53)	1.24 (0.84–1.83)	0.37
	Regional/distant	1.00 (ref)	1.02 (0.58–1.80)	0.79 (0.44–1.44)	1.07 (0.61–1.87)	1.50 (0.88–2.54)	0.16
Adjusted[b,d]	Local	1.00 (ref)	1.15 (0.74–1.79)	1.43 (0.91–2.25)	1.12 (0.69–1.81)	1.34 (0.75–2.38)	0.41
	Regional/distant	1.00 (ref)	1.16 (0.64–2.12)	1.01 (0.52–1.93)	1.35 (0.71–2.56)	2.03 (0.96–4.30)	0.08

[a] Cutpoints for quintiles: energy (kcal), 1322, 1694, 1993, and 2439; fat (%en), 29.6, 35.9, 40.3, and 44.2; fat (g), 438, 604, 762, and 990.
[b] Adjusted for age, race, family history of prostate cancer, education, body mass index, number of screening PSA tests within 5 years before reference date, servings/day of vegetables, and use of supplemental vitamin E, vitamin C, and zinc.
[c] Adjusted, in addition, for total energy.
[d] Adjusted, in addition, for nonfat energy.

Table 4 Adjusted[a] odds ratios for association of specific fatty acids, vitamin D, and calcium with prostate cancer risk, by stage of disease

	Stage	Odds ratio (95% CI) Quintile 1	2	3	4	5	*P* for trend
Saturated fat[b] (%en)	Local	1.00 (ref)	1.27 (0.83–1.94)	0.71 (0.45–1.13)	0.98 (0.62–1.55)	1.09 (0.69–1.72)	0.86
	Regional/distant	1.00 (ref)	1.58 (0.82–3.03)	1.88 (0.98–3.58)	2.01 (1.04–3.87)	1.82 (0.93–3.56)	0.06
Monosaturated fat[b] (%en)	Local	1.00 (ref)	1.35 (0.87–2.10)	1.15 (0.73–1.81)	1.33 (0.84–2.11)	1.04 (0.65–1.69)	0.89
	Regional/distant	1.00 (ref)	1.80 (0.94–3.44)	1.43 (0.73–2.79)	1.90 (0.98–3.67)	2.00 (1.03–3.87)	0.06
Polyunsaturated fat[b] (%en)	Local	1.00 (ref)	0.97 (0.62–1.51)	1.07 (0.70–1.66)	1.27 (0.82–1.96)	0.91 (0.58–1.43)	0.88
	Regional/distant	1.00 (ref)	0.84 (0.45–1.57)	1.12 (0.62–2.02)	1.37 (0.77–2.45)	1.17 (0.64–2.12)	0.24
EPA[b,c] + DHA[b,c] (g)	Local	1.00 (ref)	0.85 (0.55–1.32)	0.75 (0.48–1.16)	1.08 (0.70–1.66)	1.05 (0.68–1.63)	0.51
	Regional/distant	1.00 (ref)	1.10 (0.62–1.94)	1.16 (0.66–2.05)	1.33 (0.75–2.35)	0.84 (0.44–1.58)	0.81
Vitamin D[b,c] (mcg)	Local	1.00 (ref)	0.80 (0.51–1.28)	1.10 (0.70–1.72)	0.70 (0.44–1.12)	1.06 (0.66–1.70)	0.98
	Regional/distant	1.00 (ref)	0.71 (0.37–1.38)	0.98 (0.53–1.83)	1.52 (0.84–2.75)	1.13 (0.59–2.15)	0.19
Calcium[b,c] (mg)	Local	1.00 (ref)	0.82 (0.52–1.30)	0.85 (0.54–1.36)	0.96 (0.59–1.56)	1.07 (0.63–1.84)	0.64
	Regional/distant	1.00 (ref)	1.26 (0.67–2.36)	1.08 (0.55–2.10)	1.55 (0.80–3.02)	2.12 (1.02–4.38)	0.04

[a] Adjusted for age, race, family history of prostate cancer, education, body mass index, number of screening PSA tests within 5 years before reference date, servings/day of vegetables, use of supplemental vitamin E, vitamin C, and zinc, and total energy.
[b] Cutpoints for quintiles: saturated fat (%en), 9.9, 12.3, 13.7, and 15.7; monounsaturated fat (%en), 10.8, 13.3, 14.9, and 16.7; polyunsaturated fat (%en), 5.6, 6.8, 8.1, and 9.7; EPA + DHA (g), 0.03, 0.09, 0.14, and 0.24; vitamin D (mcg), 3.9, 5.9, 9.7, and 14.2; calcium (mg), 518, 672, 850, and 1163.
[c] From food plus supplements.

with increased cancer risk in humans biologically plausible. For prostate cancer, one possible mechanism is through insulin-related growth factors. Energy intake is positively associated with levels of insulin-like growth factor I (35), and elevated insulin-like growth factor I has been associated with increased prostate cancer risk in several studies (36–38). Prospective studies that use more valid measures of energy intake, such as multiple 24-hour dietary recalls, are needed to better address possible associations of high energy intakes with increased prostate cancer risk.

This study examined two statistical models of fat and prostate cancer risk, contrasting (*a*) substituting fat for other macronutrients and keeping energy intake constant (percentage energy from fat controlled for total energy) with (*b*) adding fat along with the additional energy from fat (energy from fat controlled for energy from other sources). The interpretations of results from these two methods deserve comment. From the first model, we infer that a very low fat diet, regardless of total energy, reduces the risk of prostate cancer by approximately 50% but that above a threshold of approximately 30% of energy from fat, there is no additional increase in risk. From the second model, we infer that a high intake of energy from fat increases prostate cancer risk, but only above 760 kcal from fat per day. The finding for percentage of energy from fat suggests a direct biological effect from a very low fat diet. In contrast, the finding for high energy from fat may be indirect, operating through the association of total energy with cancer risk. Persons consuming large amounts of fat will most likely have high total energy intakes because fat contains far more energy/gram than other macronutrients. However, associations for total energy

Table 5 Odds ratios[a] for associations of dietary and supplemental calcium intakes with prostate cancer risk, by stage of disease

Calcium from food (mg/day) tertiles		Calcium from supplements (mg/day)		
		0	1–199	200+
		(*n* = 678)	(*n* = 441)	(*n* = 108)
0–563 mg	Local	1.00 (ref)[b]	1.09 (0.80–1.48)	1.58 (0.89–2.79)
	n cases	78	46	21
	Regional/distant	1.00 (ref)	1.26 (0.84–1.90)	1.38 (0.61–3.12)
	n cases/*n* controls	25/118	18/61	4/18
564–837 mg	Local	0.83 (0.58–1.19)	0.91 (0.57–1.45)	1.31 (0.66–2.61)
	n cases	81	49	11
	Regional/distant	0.91 (0.55–1.51)	1.15 (0.60–2.20)	1.26 (0.48–3.33)
	n cases/*n* controls	26/118	16/65	3/14
≥838 mg	Local	0.87 (0.57–1.34)	0.95 (0.56–1.59)	1.37 (0.66–2.84)
	n cases	83	60	14
	Regional/distant	1.62 (0.92–2.85)	2.04 (1.03–4.05)	2.23 (0.82–6.08)
	n cases/*n* controls	37/112	28/68	5/18

[a] Adjusted for age, race, family history of prostate cancer, education, body mass index, number of PSA screenings with 5 years before reference date, servings/day of vegetables, energy, percentage energy from fat, and supplemental vitamin E, vitamin C, and zinc.
[b] Data for local and regional/distant disease are odds ratio (95% CI).

and energy from fat with prostate cancer risk were not altogether consistent because total energy was associated with local and regional/distant cancers, whereas energy from fat was associated with advanced/regional disease only. Reasons for this inconsistency are not clear.

Our finding that fat intake was associated with advanced but not localized prostate cancer is somewhat consistent with other studies (4). Most previous studies have examined total prostate cancers and the subset of men with advanced disease but have not stratified analyses by extent of disease and examined associations for men with localized disease only. Thus, our finding of no association of fat with risk for localized disease is probably consistent with some earlier findings, which would have found similar results if they used our analytic strategy. Our finding of no association of polyunsaturated fats with prostate cancer risk is also consistent with the previous literature (4). However, we found similar effects for saturated and monounsaturated fats, in contrast to many other studies that found associations primarily for saturated fat (5) or for foods high in saturated fats such as dairy products and meat. Finally, we found no dose-response effects for increasing percentage energy from fat; rather, we found that men in the lowest quintile of intake were at reduced risk compared with all others. The mean fat intake in this sample was relatively high (37%en), and it could be that there is a threshold beyond which higher fat intake has little effect.

Studies on consumption of specific fatty acids and prostate cancer risk are inconsistent. Giovannucci *et al.* (5) reported that intake of α-linolenic acid is a strong risk factor for prostate cancer. However, there is good evidence that consumption of this fatty acid cannot be measured validly with a FFQ because it accounts for only about 0.5% of total energy intake and is obtained in very small amounts from a diverse range of foods (39). We chose, therefore, not to analyze this nutrient. Results for the very long-chain polyunsaturated fatty acids derived from marine sources, DHA and EPA, have been conflicting (8). Our questionnaire included detailed items on types of fish consumed and on use of supplemental DHA and EPA, and we found no associations.

Whereas there are several mechanisms that could explain how dietary fat could promote the development of prostate cancers from relatively indolent lesions to more invasive disease, one of the most likely is hormonal. High-fat diets increase circulating androgen levels (40, 41), and high testosterone levels may influence prostate cancer risk (42). Other possible mechanisms include effects of dietary fat or specific fatty acids on eicosanoid metabolism and cell membrane composition (43).

We also found evidence to support the hypothesis that high calcium intake increases the risk of regional/distant prostate cancer. Of 10 observational studies that have examined the association of calcium intake or supplementation with prostate cancer risk, three found significant associations of calcium with regional/distant disease, with relative risks contrasting high to low intake categories of 2.97 (12), 2.12 (13), and 1.42 (14). As reviewed by Chan and Giovannucci (11), many of the studies finding no significant association were too small to detect modest relative risks, and upon critical evaluation, the observational epidemiology is moderately consistent in supporting an association of calcium with prostate cancer risk. We know of only one experimental study evaluating the effect of calcium supplementation on prostate cancer, which was a secondary analysis of a randomized trial in 671 men testing 1200 mg calcium/day for prevention of colorectal polyps (44). Calcium supplementation reduced the risk of prostate cancer in this study, which reported a hazard ratio contrasting treated with untreated men of 0.54 (95% CI, 0.22–1.30) during the 4 years of treatment and 0.43 (95% CI, 0.20–0.94) with an additional year of follow-up (45). Thus, the evidence to date on calcium and prostate cancer remains equivocal. One proposed mechanism to explain such an association is that dietary calcium suppresses production of 1,25 dihydroxyvitamin D (46). Vitamin D decreases proliferation of normal and malignant prostate cells (47, 48), as well as the invasiveness of malignant cells (49). The public health implications of an association of calcium with increased prostate cancer risk are complex. Calcium supplements, which are promoted primarily for "bone health," are most commonly used by postmenopausal women to prevent osteoporosis (50). However, in a study of participants in the Prostate Cancer Prevention Trial, we found that over 20% of men also used calcium supplements regularly (51). Randomized trials of calcium supplements have found that calcium can prevent bone fractures in men (52) and reduce the recurrence of adenomatous polyps (44). Total calcium intake may also reduce the risk of distal colon cancers (53). Thus, any recommendation regarding calcium supplementation and dietary intake will need

to carefully examine both the potential benefits and risks of high calcium consumption.

The widespread use of PSA screening has created several challenges in the analysis and interpretation of epidemiological studies of prostate cancer risk. For example, in this study, 70% of cases had received PSA screening in the 5 years prior to their diagnosis (excluding PSA tests done within the year before their diagnosis date) compared with only 34% of controls. As a result of PSA screening, many men who are now diagnosed with prostate cancer may never have been diagnosed in the past. It is therefore important to stratify analyses by stage of disease because risk factors for PSA-detected early-stage disease could differ from those for more clinically advanced tumors. A related concern is that control participants not screened with PSA may have had undiagnosed, latent disease. We completed additional analyses that excluded control participants who had never received PSA screening and found no substantial differences in results. Finally, PSA screening is associated with healthful behavior, including higher fruit and vegetable and lower fat intakes, both in other population-based samples (54) and in the control group in this study. As expected, statistical control for number of PSA tests increased the strength of associations of energy and fat with prostate cancer risk.

One noteworthy aspect of this study is that it examined dietary risk factors in an age group at lower absolute risk for prostate cancer than those included in most published studies. The incidence of prostate cancer in men under 65 years of age is about 250/100,000 compared with 1,000/100,000 for men over 65 years of age (55). Studies of risk factors in lower incidence groups may allow more clear identification of environmental exposures related to risk (56). It is also possible that a higher proportion of prostate cancer in low incidence age groups is due to inherited susceptibility genes; however, such genes are thought to explain less than 34% of cancers diagnosed in men less than 70 years of age (57).

There are several limitations to this study. As in any case-control design that assesses exposure after onset of disease, differential dietary recall between cases and controls could bias results. In particular, men with cancer may have biased their report to include foods they believe are related to disease risk. Probably more important, however, is that controls who volunteer to participate are more likely to be a subset of potential controls interested in heath and likely to have diets low in energy and fat. Overall response rates in controls (completed interviews divided by eligible men identified) was 69%, which is similar those reported in other case-control studies but does allow the possibility of considerable selection bias. Finally, there are inherent limitations in the accuracy of FFQs, which require participants to estimate their usual dietary patterns over a period of several years in the past (58). For studies of diet and prostate cancer risk, prospective studies that use biologically based measures of dietary exposures are needed to avoid these limitations.

In summary, we found that energy intake was associated with increased risk of both localized and regional/distant prostate cancer, whereas high consumption of dietary fat and calcium was associated with the development of more aggressive disease only. This study provides justification for further research that attempts to elucidate the mechanisms whereby fat and calcium may promote tumor growth. These results are consistent with general dietary guidelines to moderate consumption of total energy and fat, and they motivate further research to consider the potential benefits and risks of high calcium intake.

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