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Original Contribution

Dietary Patterns, Supplement Use, and the Risk of Symptomatic Benign Prostatic Hyperplasia: Results from the Prostate Cancer Prevention Trial

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This study examined dietary risk factors for incident benign prostatic hyperplasia (BPH) in 4,770 Prostate Cancer Prevention Trial (1994–2003) placebo-arm participants who were free of BPH at baseline. BPH was assessed over 7 years and was defined as medical or surgical treatment or repeated elevation (>14) on the International Prostate Symptom Score questionnaire. Diet, alcohol, and supplement use were assessed by use of a food frequency questionnaire. There were 876 incident BPH cases (33.6/1,000 person-years). The hazard ratios for the contrasts of the highest to lowest quintiles increased 31% for total fat and 27% for polyunsaturated fat and decreased 15% for protein (all $p_{trend} < 0.05$). The risk was significantly lower in high consumers of alcoholic beverages (0 vs. ≥2/day: hazard ratio (HR) = 0.67) and vegetables (<1 vs. ≥4/day: HR = 0.68) and higher in daily (vs. <1/week) consumers of red meat (HR = 1.38). There were no associations of supplemental antioxidants with risk, and there was weak evidence for associations of lycopene, zinc, and supplemental vitamin D with reduced risk. A diet low in fat and red meat and high in protein and vegetables, as well as regular alcohol consumption, may reduce the risk of symptomatic BPH.

alcohol drinking; diet; dietary supplements; prostatic hyperplasia

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HR, hazard ratio; IPSS, International Prostate Symptom Score; PCPT, Prostate Cancer Prevention Trial.

Benign prostatic hyperplasia (BPH) is one of the most common medical conditions in older men. Estimates of BPH prevalence range from 40 percent to 50 percent at 50 years of age to as high as 80 percent for men aged 70 years (1, 2). Both the high prevalence of BPH and the associated costs of medical care (approximately 4 billion dollars per year in the United States) strongly motivate research to better understand the causes of BPH and identify modifiable risk factors to prevent or delay the disease (3). The current literature on BPH risk factors is quite limited. Most reports have been based on case series, cross-sectional associations, or hospital-based case-control studies, and few studies have examined the risk of incident BPH using case definitions that reflect current medical practice and validated symptom questionnaires. The only well-established modifiable risk factor for BPH is obesity and, in particular, abdominal obesity (4–7). Of the studies examining diet, only two have examined dietary risk factors for incident BPH (8, 9). Large studies of diet and BPH incidence are needed to clarify how diet may affect BPH risk.

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Symptomatic BPH is caused by two components: enlargement of the prostate and heightened tone in prostate smooth muscle, both of which can obstruct urinary flow. Although the pathogenesis of BPH is not well understood, age-related changes in hormonal and other growth-regulatory factors are the likely cause of cellular proliferation (10). Thus, dietary patterns that alter the hormonal milieu, such as a high-fat diet, or other regulator factors, such as insulin-like growth factors, could conceivably affect BPH risk. Prostate smooth muscle tone is controlled by the sympathetic nervous system, which is directly affected by many diet-related factors including energy intake, hyper- and hypoglycemia, and obesity (11, 12). BPH may also be caused or exacerbated by chronic inflammation and subsequent oxidative damage (13), and thus dietary factors such as ω-3 fatty acids, polyunsaturated fats, and antioxidants may also affect risk. Clearly, there are many mechanisms whereby dietary patterns could affect the risk of symptomatic BPH.

Here, we give results of a prospective cohort study examining the 7-year incidence of symptomatic BPH among men participating in the Prostate Cancer Prevention Trial (PCPT). Data from the PCPT include rigorous assessment of both the symptoms and treatment of BPH, as well as extensive information on diet and other lifestyle factors that may affect BPH risk. This report examines whether dietary patterns, supplement use, and alcohol consumption affect the risk of incident, symptomatic BPH in a population of healthy men aged 55 years or older.

MATERIALS AND METHODS

Data are from placebo arm participants in the PCPT, a randomized, placebo-controlled trial testing whether finasteride, a 5α-reductase inhibitor, could reduce the 7-year period prevalence of prostate cancer. Details regarding study design and participant characteristics have been described previously (14). Briefly, 18,880 men aged 55 years or older with normal digital rectal examinations and prostate-specific antigen levels of 3 ng/ml or below, as well as no history of prostate cancer, severe BPH (defined as an International Prostate Symptom Score (IPSS) of 19 or lower), or clinically significant coexisting conditions (judged by the clinic physician to affect survival until or eligibility for the end-of-study biopsy at 7 years postrandomization), were randomized to receive finasteride (5 mg/day) or placebo. During the PCPT, a prostate biopsy was recommended for participants with an abnormal digital rectal examination or a prostate-specific antigen level of 4.0 ng/ml or greater; all men were requested to undergo biopsy at 7 years postrandomization.

Data collection

Extensive data are available on the demographic and lifestyle characteristics of PCPT participants. Details regarding age, race/ethnicity, education, and history of smoking were collected at baseline by self-administered questionnaires. The level of physical activity was assessed by use of a six-item questionnaire and categorized as ''sedentary,'' ''light,'' ''moderate,'' and ''very active'' (15). Height and weight were measured at the baseline clinic visit.

At 1 year postrandomization, men completed a 15-page diet and supplement questionnaire, and clinic staff measured height, weight, and body circumferences as part of an ancillary study protocol. Diet was assessed with a food frequency questionnaire (FFQ) developed specifically for this population of older men. This FFQ consisted of questions on the usual consumption over the past year of 99 foods or food groups and nine beverages, along with 13 questions on food preparation and purchasing and three questions on usual consumption of fruits, vegetables, and fried foods. Algorithms for analysis of this questionnaire are available at http://www.fhcrc.org/science/shared_resources/nutrition/ffq/tech_doc.pdf. The dietary supplement questionnaire and its analysis have been described in detail previously (16). In brief, participants reported usual pills per day for multivitamins and antioxidant mixtures and both pills per day and dose for β-carotene, vitamin C, vitamin E, calcium, and zinc. In addition, participants reported whether they used stress-type multivitamins, vitamin D, fish oil, B-complex, iron, vitamin A, selenium, or niacin at least three times a week. We conducted an inter- and intramethod reliability study in 150 randomly selected men, to compare nutrients calculated from the initial FFQ, from six 24-hour recalls collected over the following year and from an additional FFQ completed after all 24-hour recalls had been collected. Based on the 128 men who completed at least five 24-hour recalls, correlations between the first FFQ and 24-hour recalls (adjusted for energy and deattenuated for measurement error in the 24-hour recalls) were as follows: total fat, 0.71; polyunsaturated fat, 0.66; monounsaturated fat, 0.66; saturated fat, 0.75; alcohol, 0.84; carbohydrate, 0.70; lycopene, 0.58; β-carotene, 0.58; vitamin D, 0.57; docosahexaenoic acid (DHA) plus eicosapentaenoic acid (EPA), 0.87; vitamin C, 0.62; calcium, 0.62; vitamin C, 0.40; and zinc, 0.87. Correlations between repeat FFQs were above 0.60 for all nutrients with the exception of 0.54 for EPA plus DHA.

Extensive medical data, including physician diagnosis of and treatment for BPH, prostatitis, diabetes, cardiovascular disease, and cancer, were collected at the baseline clinic visit, each annual and 6-month clinic visit, and every 3- and 9-month phone contact between scheduled clinic visits. At recruitment, randomization, and each annual follow-up clinic visit, participants completed the seven-item IPSS self-administered questionnaire (17).

Incident BPH was defined as either the first report of treatment or the second report of an IPSS of 15 or higher. Treatments included use of α-blockers, finasteride, or any surgical intervention (transurethral prostatectomy, balloon dilation, or laser prostatectomy). Men who reported a physician diagnosis of BPH alone, in the absence of symptoms or treatment, were not included as cases in this analysis. We did complete analyses that included men reporting a physician diagnosis only as BPH cases and report the few differences in the Results section below.

Statistical methods

All analyses were based on the time between randomization and the estimated time of incident BPH. For cases defined by the IPSS, we assigned incidence time as the

TABLE 1. Demographic and health-related characteristics of the study sample and their associations with the incidence of symptomatic benign prostatic hyperplasia, Prostate Cancer Prevention Trial placebo arm, 1994–2003

	Sample		Incident benign prostatic hyperplasia		
	No.	%	Events (no.)	Person-years (no.)	Rate/1,000 person-years
Total sample	4,770	100	876	26,079	33.6
Age (years)					
54–59	1,681	35.2	242	9,472	25.5
60–64	1,489	31.2	250	8,144	30.7
≥65	1,600	34.5	384	8,463	45.4
Race/ethnicity					
African American	153	3.2	37	770	48.0
Hispanic	98	2.1	22	529	41.6
Caucasian	4,460	93.5	808	24,486	33.0
Other	59	1.2	9	293	30.7
Current smoker					
Yes	381	8.0	73	2,022	36.1
No	4,382	92.0	803	24,047	33.4
Waist/hip ratio					
<0.95	2,065	43.3	356	11,458	31.1
0.95–0.99	1,693	35.5	307	9,229	33.3
1.00–1.04	834	17.5	174	4,467	39.0
≥1.05	178	3.7	39	925	42.2
Body mass index (kg/m^2)					
<25	1,150	24.1	196	6,450	30.4
25–29	2,486	52.1	452	13,589	33.3
30–34	879	18.4	177	4,661	38.0
≥35	255	5.3	51	1,379	37.0

midpoint between the second elevated IPSS and preceding IPSS (most often the previous year). For cases defined by treatment, which was assessed every 3 months, we assigned incidence time as the midpoint between the two annual visits when BPH treatment was first reported. Follow-up was censored at the last reported IPSS or at the time of prostate cancer diagnosis. We calculated simple incidence rates as the annual incidence per 1,000 person-years of observation. We used Cox proportional hazards models to calculate the associations of diet with the relative hazards of BPH; $p < 0.05$ was considered statistically significant, and p values are reported in the text rounded to the third decimal place.

This study is based on 9,457 placebo arm participants, from whom we excluded 33.8 percent with a history of BPH at baseline (542 for surgery, 12 for medication use, 1,090 for an IPSS of 15 or higher at either the recruitment or randomization visit, and 1,548 who reported a previous BPH diagnosis). We excluded an additional 502 men who were missing at least half of the expected number of postrandomization IPSS values, leaving 5,763 participants. We then excluded 993 men with missing data (404 missing food frequency questionnaires, 281 with unreliable dietary data (energy <800 or >5,000 kcal), and 308 missing complete anthropometry data), leaving 4,770 men for analyses. Most men missing diet and anthropometry measures were enrolled at study sites that chose not to participate in the special dietary and anthropometry assessment protocols.

RESULTS

There were 876 incident BPH cases during the 7 years of follow-up, corresponding to an incidence rate of 33.6 per 1,000 person-years. Most BPH endpoints were based on medical treatment (52 percent) or elevated IPSS (41 percent), and only 7 percent were based on surgery. Table 1 gives distributions of participants' baseline demographic and health-related characteristics, as well as the unadjusted incidence rates for BPH stratified by these characteristics. The mean age of participants was 62.6 (standard deviation: 5.5) years and ranged from 54 years to 86 years. Only 24 percent of men were normal weight (body mass index: <25 kg/m^2), and 21 percent had a waist/hip ratio of 1.0 or greater. BPH incidence rates increased with increasing age, body mass index, and waist/hip ratio, and they were higher in African Americans and Hispanics compared with Caucasians.

Table 2 gives the adjusted hazard ratios for BPH associated with energy and macronutrient intake. There was no association of energy intake with BPH risk. For each macronutrient, we give results from two statistical models, labeled ''percent energy'' and ''total energy.'' Percent energy models examine the percentage of energy from each macronutrient (for alcohol, models used categorized drinks per day), use a linear term for total energy as a covariate, and can be interpreted as the effect of substituting energy from each specific macronutrient for other macronutrients. Total energy models examine energy from each macronutrient (for alcohol, models used categorized drinks per day), use a linear term for energy from all other macronutrients as a covariate, and can be interpreted as the effect of increasing energy from a specific macronutrient while keeping the energy from each other macronutrient constant. In percent energy models, there were statistically significant increases in BPH risk associated with high percentages of energy from total and polyunsaturated fats and significant decreases in risk associated with a high percentage of energy from protein and number of alcoholic drinks per day (all $p_{trend} < 0.05$). Comparing men in the highest and lowest quintiles, risk was 31 percent higher for total fat ($p = 0.018$), 27 percent higher for polyunsaturated fat ($p = 0.025$), and 15 percent lower for protein ($p = 0.134$); compared with less than 1 drink/month, consuming two or more drinks/day was associated with a 33 percent ($p < 0.001$) reduction in risk. Overall, this pattern of findings was similar in the total energy models. We also fit a model with linear terms for energy from fat, carbohydrate, and protein, plus alcohol categorized by drinks per week, and found significant associations with fat (4.5 percent increase per 100 kcal, $p = 0.003$), protein (5.1 percent decrease per 100 kcal, $p = 0.008$), and alcohol (comparing $<$1/month with $\geq$2/day: 30 percent reduction, $p = 0.002$). Finally, we examined whether the finding of increased risk associated with total fat was attributable to saturated, monounsaturated, or polyunsaturated fats specifically. We fit a set of percent energy models that controlled for total fat and a single total energy model that included energy from each type of fat; however, in all of these models, there were no significant associations of any specific type of fat with risk (data not shown).

Table 3 gives associations of micronutrients with BPH risk. We give results for nutrients for which we hypothesized an association with BPH risk because of antioxidant, anti-inflammatory, or growth-regulatory properties. We report results for diet alone and for ''total'' (diet plus supplements) where appropriate. Results for dietary vitamin E and selenium are not reported because, on the basis of very poor correlations between FFQ-based dietary intake of these nutrients and serum concentrations (18–23), we believe they cannot be assessed using an FFQ. Both dietary and total zinc were associated with reduced BPH risk. Compared with men in the lowest quintile of total zinc intake, those in the highest quintile had a 32 percent ($p = 0.002$) lower BPH risk. Total but not dietary vitamin D was associated with reduced risk. Compared with men in the lowest quintile of total vitamin D intake, those in the highest quintile had an 18 percent reduced BPH risk ($p_{trend} = 0.032$). There was a suggestive but not statistically significant 18 percent reduction in BPH risk associated with high lycopene intake ($p_{trend} = 0.056$). This association was modestly stronger when physician diagnosis of BPH was included as an endpoint (quintile 1 vs. quintile 5: hazard ratio (HR) = 0.79, 95 percent confidence interval (CI): 0.63, 0.98; $p_{trend} = 0.023$). Neither vitamin C, calcium, nonlycopene carotenoids, nor long-chain ω-3 fatty acids were associated with risk.

Table 4 gives associations of dietary supplement use with BPH risk. Supplement use is categorized as low, corresponding to no or infrequent use of a supplement, medium, corresponding to the amounts generally obtained from multivitamins, and high, corresponding to amounts that are generally only possible from using high-dose single supplements. The exceptions were EPA plus DHA and single vitamin D supplements, for which we had data only on whether they were used at least three times per week. Thus, EPA plus DHA was coded as 0 or 0.5 g/day, and vitamin D from a single supplement was coded as 0 or 10 μg/day. Because the vitamin D content of multivitamins is also 10 μg, only men who used both multivitamins and single vitamin D supplements could be in the high-dose vitamin D category. There were no associations of supplement use with BPH risk, with the exception of a trend for decreasing BPH risk with increasing dose of supplemental vitamin D ($p_{trend} = 0.048$). We also examined results excluding multivitamin users, because regular multivitamin users have, by definition, at least moderate intakes of many micronutrients. In these analyses (not shown), there were no associations of any supplement with BPH risk. In particular, the hazard ratio contrasting users with nonusers of vitamin D supplements was 1.00 (95 percent CI: 0.65, 1.52).

Table 5 gives associations of food groups often associated with prostate health. Compared with men eating red meat less than once per week, men eating red meat at least daily had a 38 percent increased BPH risk ($p = 0.044$) and, compared with men eating fewer than one serving of vegetables per day, men eating four or more servings had a 32 percent decreased BPH risk ($p = 0.011$). There were no clear dose-response effects for either red meat or vegetables; however, the largest associations were in the contrasts between extreme quintiles. In analyses adding physician-diagnosed BPH as an endpoint, the association with red mean was attenuated and no longer statistically significant ($<$1 vs. $\geq$4 servings/day: HR = 1.30, 95 percent CI: 0.97, 1.75), while there was a significant dose response for vegetables with reduced risk ($p_{trend} = 0.023$). Neither cruciferous vegetables, fruit, nor dairy products were associated with BPH risk.

DISCUSSION

In this large prospective study, we found that diets high in total fat were associated with increased risk of symptomatic BPH and that diets high in protein and alcohol were associated with decreased risk. In analyses of foods, high vegetable consumption was associated with lower risk, and high red meat consumption was associated with increased risk. There were no associations of antioxidant nutrients, including supplemental vitamin E and selenium or total vitamin C,

TABLE 2. Association of energy and macronutrient intake with risk of total incident symptomatic benign prostatic hyperplasia, Prostate Cancer Prevention Trial placebo arm, 1994–2003

	Macronutrient intake					p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Energy						
Total energy (kcal)	<1,442	1,442–1,849	1,850–2,272	2,273–2,831	≥2,832	
HR* (95% CI*)†	Referent	0.91 (0.74, 1.12)	0.86 (0.70, 1.07)	0.86 (0.70, 1.06)	1.05 (0.86, 1.29)	0.800
Cases/men (nos.)	186/954	172/948	160/955	162/955	196/958	
Total fat						
Percent energy	<25.7	25.7–30.9	31.0–34.9	35.0–38.1	≥38.2	
HR (95% CI)†	Referent	1.21 (0.98, 1.51)	1.19 (0.95, 1.48)	1.22 (0.98, 1.53)	1.31 (1.05, 1.63)	0.034
Cases/men (nos.)	147/966	183/947	175/952	179/953	192/952	
Total energy (kcal)	<410	410–567	568–745	746–989	≥990	
HR (95% CI)‡	Referent	1.06 (0.86, 1.32)	1.08 (0.86, 1.36)	1.10 (0.86, 1.41)	1.60 (1.19, 2.15)	0.014
Cases/men (nos.)	169/953	174/955	171/961	158/950	204/951	
Saturated fat						
Percent energy	<8.0	8.0–9.7	9.8–11.2	11.3–12.9	≥13	
HR (95% CI)†	Referent	0.93 (0.75, 1.16)	0.96 (0.77, 1.19)	1.09 (0.88, 1.34)	1.08 (0.87, 1.33)	0.214
Cases/men (nos.)	171/956	160/960	171/954	186/943	188/957	
Total energy (kcal)	<128	128–181	182–240	241–326	≥327	
HR (95% CI)‡	Referent	0.98 (0.79, 1.22)	0.84 (0.66, 1.08)	0.86 (0.65, 1.13)	1.02 (0.70, 1.50)	0.416
Cases/men (nos.)	178/954	177/946	162/963	160/956	199/951	
Monounsaturated fat						
Percent energy	<9.6	9.6–11.7	11.8–13.4	13.5–15.2	≥15.3	
HR (95% CI)†	Referent	1.09 (0.88, 1.36)	1.03 (0.82, 1.28)	1.30 (1.05, 1.61)	1.14 (0.92, 1.42)	0.074
Cases/men (nos.)	155/962	179/953	157/938	206/958	179/959	
Total energy (kcal)	<153	153–216	217–285	286–381	≥382	
HR (95% CI)‡	Referent	0.99 (0.79, 1.24)	0.93 (0.72, 1.21)	0.87 (0.63, 1.19)	1.02 (0.64, 1.62)	0.426
Cases/men (nos.)	171/953	177/956	173/957	157/950	198/954	
Polyunsaturated fat						
Percent energy	<5.1	5.1–6.1	6.2–7.1	7.2–8.3	≥8.4	
HR (95% CI)†	Referent	1.16 (0.94, 1.43)	0.96 (0.77, 1.20)	1.15 (0.93, 1.43)	1.27 (1.03, 1.57)	0.043
Cases/men (nos.)	159/966	180/950	155/954	181/952	201/948	
Total energy (kcal)	<85	85–116	117–151	152–206	≥207	
HR (95% CI)‡	Referent	1.08 (0.87, 1.34)	0.93 (0.73, 1.19)	0.96 (0.73, 1.26)	1.13 (0.79, 1.61)	0.949
Cases/men (nos.)	168/954	184/959	160/953	165/951	199/953	
Carbohydrates						
Percent energy	<41.5	41.5–46.0	46.1–50.5	50.6–56.1	≥56.2	
HR (95% CI)†	Referent	0.96 (0.78, 1.19)	0.94 (0.76, 1.17)	0.94 (0.76, 1.16)	1.07 (0.87, 1.32)	0.647
Cases/men (nos.)	175/960	177/955	168/944	169/952	187/959	
Total energy (kcal)	<690	690–900	901–1,100	1,101–1,372	≥1,373	
HR (95% CI)‡	Referent	0.87 (0.70, 1.09)	1.00 (0.80, 1.25)	0.95 (0.74, 1.22)	1.16 (0.86, 1.55)	0.347
Cases/men (nos.)	187/955	158/952	174/945	162/953	195/965	
Protein						
Percent energy	<14.6	14.6–16.1	16.2–17.6	17.7–19.4	≥19.5	
HR (95% CI)†	Referent	1.02 (0.83, 1.25)	0.92 (0.75, 1.13)	0.85 (0.69, 1.05)	0.85 (0.69, 1.05)	0.037
Cases/men (nos.)	187/958	190/949	180/957	158/954	161/952	
Total energy (kcal)	<236	236–311	312–385	386–489	≥490	
HR (95% CI)‡	Referent	0.76 (0.61, 0.94)	0.68 (0.53, 0.86)	0.67 (0.51, 0.87)	0.67 (0.47, 0.95)	<0.001
Cases/men (nos.)	196/952	171/952	157/953	167/959	185/954	
Alcohol (drinks)	<1/month	1–3/month	1–6/week	7–13/week	≥14/week	
HR (95% CI)†	Referent	0.74 (0.58, 0.96)	0.85 (0.72, 1.01)	0.83 (0.68, 1.01)	0.67 (0.45, 0.84)	<0.001
Cases/men (nos.)	324/1,540	72/449	240/1,333	136/738	104/710	
HR (95% CI)‡	Referent	0.74 (0.58, 0.96)	0.86 (0.72, 1.01)	0.83 (0.68, 1.02)	0.68 (0.57, 0.85)	0.001
Cases/men (nos.)	324/1,540	72/449	240/1,333	136/738	104/710	

* HR, hazard ratio; CI, confidence interval.

† Controlled for age, race/ethnicity, waist/hip ratio, and total energy (equivalent to the percent energy model).

‡ Controlled for age, race/ethnicity, waist/hip ratio, and energy from other macronutrients (equivalent to the total energy model).

TABLE 3. Association of energy and micronutrient intake with risk of total incident symptomatic benign prostatic hyperplasia, Prostate Cancer Prevention Trial placebo arm, 1994–2003

	Micronutrient intake					p_{trend}
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Vitamin C (mg/day)						
Diet	<69.8	69.8–104.1	104.2–142.0	142.1–193.9	≥194.0	
HR* (95% CI*)†	Referent	1.05 (0.85, 1.30)	0.93 (0.75, 1.16)	0.98 (0.79, 1.23)	1.02 (0.81, 1.29)	0.899
Cases/men (nos.)	172/955	183/964	162/937	178/958	181/956	
Total	≤104.4	104.5–169.1	169.2–297.1	297.2–711.0	≥711.1	
HR (95% CI)†	Referent	0.92 (0.75, 1.13)	0.73 (0.59, 0.91)	0.91 (0.74, 1.12)	0.92 (0.74, 1.14)	0.477
Cases/men (nos.)	192/968	182/956	154/950	177/945	171/951	
Zinc (mg/day)						
Diet	<8.8	8.8–11.7	11.8–14.6	14.7–18.8	≥18.9	
HR (95% CI)†	Referent	0.77 (0.62, 0.95)	0.68 (0.54, 0.86)	0.69 (0.53, 0.90)	0.69 (0.50, 0.96)	0.018
Cases/men (nos.)	201/952	167/953	159/959	170/956	179/950	
Total	<11.5	11.5–17.5	17.6–24.9	25.0–33.2	≥33.3	
HR (95% CI)†	Referent	0.70 (0.56, 0.87)	0.81 (0.66, 1.01)	0.79 (0.63, 0.98)	0.68 (0.54, 0.87)	0.026
Cases/men (nos.)	206/951	159/963	181/963	173/943	157/950	
Carotenoids (excluding lycopene) (μg/day)						
Diet	<4,748	4,748–7,088	7,089–9,724	9,725–14,056	≥14,057	
HR (95% CI)†	Referent	0.91 (0.73, 1.12)	0.88 (0.71, 1.09)	0.94 (0.75, 1.16)	0.89 (0.71, 1.12)	0.455
Cases/men (nos.)	181/953	172/960	168/957	182/951	173/949	
Total	<6,496	6,496–10,499	10,500–15,499	15,500–28,499	≥28,500	
HR (95% CI)†	Referent	0.89 (0.72, 1.10)	0.79 (0.64, 0.98)	0.95 (0.77, 1.17)	0.88 (0.71, 1.09)	0.437
Cases/men (nos.)	181/912	164/906	169/996	196/996	166/960	
Lycopene (μg/day)						
Diet	<3,540	3,540–5,616	5,617–8,175	8,176–12,588	≥12,589	
HR (95% CI)†	Referent	1.01 (0.82, 1.24)	0.96 (0.77, 1.19)	0.90 (0.72, 1.13)	0.82 (0.65, 1.03)	0.056
Cases/men (nos.)	180/958	190/963	174/945	169/946	163/958	
Calcium (mg/day)						
Diet	<542	542–733	734–940	941–1,237	≥1,238	
HR (95% CI)†	Referent	1.02 (0.82, 1.26)	0.93 (0.73, 1.17)	0.87 (0.67, 1.12)	0.95 (0.71, 1.26)	0.393
Cases/men (nos.)	174/958	179/953	169/944	166/951	188/964	
Total	<617	617–842	843–1,085	1,086–1,445	≥1,446	
HR (95% CI)†	Referent	0.95 (0.76, 1.17)	0.86 (0.68, 1.08)	0.88 (0.69, 1.12)	0.96 (0.74, 1.25)	0.647
Cases/men (nos.)	182/955	174/963	159/941	176/962	185/949	
Vitamin D (μg/day)						
Diet	<2.7	2.7–3.9	4.0–5.2	5.3–7.3	≥7.4	
HR (95% CI)†	Referent	0.99 (0.80, 1.22)	0.92 (0.73, 1.14)	0.93 (0.74, 1.18)	0.96 (0.75, 1.24)	0.656
Cases/men (nos.)	171/951	178/954	170/951	172/963	185/951	
Total	<3.6	3.6–5.9	6.0–11.7	11.8–15.5	≥15.6	
HR (95% CI)†	Referent	0.90 (0.73, 1.10)	0.88 (0.71, 1.09)	0.77 (0.62, 0.96)	0.82 (0.66, 1.03)	0.032
Cases/men (nos.)	191/954	182/960	178/953	156/951	169/952	
EPA* plus DHA* (g/day)						
Diet	<0.05	0.05–0.10	0.11–0.16	0.17–0.27	≥0.28	
HR (95% CI)†	Referent	0.84 (0.68, 1.03)	0.99 (0.81, 1.21)	0.80 (0.65, 1.00)	0.83 (0.67, 1.04)	0.117
Cases/men (nos.)	190/957	167/949	194/955	158/951	167/958	
Total	<0.05	0.05–0.10	0.11–0.18	0.19–0.34	≥0.35	
HR (95% CI)†	Referent	0.85 (0.69, 1.05)	0.96 (0.78, 1.18)	0.85 (0.68, 1.05)	0.95 (0.77, 1.18)	0.672
Cases/men (nos.)	187/955	166/950	182/956	162/952	179/957	

* HR, hazard ratio; CI, confidence interval; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
† Controlled for age, race/ethnicity, waist/hip ratio, and total energy.

TABLE 4. Association of dietary supplement use with the risk of total incident symptomatic benign prostatic hyperplasia, Prostate Cancer Prevention Trial placebo arm, 1994–2003

	Supplement use			p_{trend}
	Low	Medium	High	
Multivitamin (pills/week)	<1	1–5	≥6	
HR* (95% CI*)†	Referent	0.86 (0.65, 1.14)	0.92 (0.80, 1.06)	0.224
Cases/men (nos.)	515/2,686	55/336	306/1,748	
Vitamin C (mg/day)	<60	60–250	>250	
HR (95% CI)†	Referent	0.84 (0.70, 1.00)	1.01 (0.87, 1.17)	0.944
Cases/men (nos.)	409/2,135	178/1,082	289/1,553	
Vitamin E (mg/day)	<8	8–30	>30	
HR (95% CI)†	Referent	0.94 (0.79, 1.12)	0.95 (0.82, 1.11)	0.486
Cases/men (nos.)	426/2,241	176/983	274/1,546	
Calcium (mg/day)	<150	150–199	≥200	
HR (95% CI)†	Referent	0.82 (0.69, 0.97)	1.05 (0.87, 1.26)	0.713
Cases/men (nos.)	548/2,879	181/1,141	147/750	
Zinc (mg/day)	<15	15–23	>23	
HR (95% CI)†	Referent	0.93 (0.80, 1.08)	0.92 (0.73, 1.16)	0.310
Cases/men (nos.)	523/2,760	271/1,520	82/490	
EPA* plus DHA* (g/day)	0	0.5		
HR (95% CI)†	Referent	1.23 (0.97, 1.57)		0.085
Cases/men (nos.)	802/4,415	74/355		
Selenium (μg/day)	<10	10–30	>30	
HR (95% CI)†	Referent	0.83 (0.71, 0.97)	1.01 (0.83, 1.25)	0.336
Cases/men (nos.)	528/2,725	238/1,444	110/601	
Vitamin D (μg/day)	<2.5	2.5–10	≥11	
HR (95% CI)†	Referent	0.88 (0.77, 1.02)	0.82 (0.60, 1.11)	0.047
Cases/men (nos.)	528/2,721	305/1,763	43/286	

* HR, hazard ratio; CI, confidence interval; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

† Controlled for age, race/ethnicity, and waist/hip ratio.

with risk. Dietary but not supplemental zinc was associated with reduced risk, and use of vitamin D supplements was associated with reduced risk. Finally, there was a suggestion that high intake of lycopene, but not other carotenoids, was associated with reduced risk.

Before discussing the consistency of our findings with those in the published literature, it is important to note that research on dietary patterns and BPH is very limited. Most reports are from small case-control studies in which cases were men undergoing surgical treatment (24–27) or from cross-sectional studies examining associations of lower urinary tract symptoms with current diet (28, 29) or serum micronutrient concentrations (30). Two studies used a longitudinal design to examine true BPH incidence, using either surgery (8) or the combination of medical and surgical treatment plus the development of severe lower urinary tract symptoms (9) as BPH endpoints. For dietary assessment, two studies used a FFQ (9, 25, 31), one used serum micronutrients (30), and the rest collected limited information on specific foods or food groups. Given these differences in study design, BPH endpoints, and dietary assessment methods, inconsistencies in findings across studies are expected.

Our finding that total fat was associated with increased BPH risk, with no evidence that associations were specific to type of fat, was in part consistent with the two previous studies that have examined macronutrients and BPH risk. The large study by Suzuki et al. (31) reported modest increases in the 6-year period prevalence of BPH associated with high intakes of energy, animal protein, polyunsaturated fat, and long-chain ω-3 fatty acids. Lagiou et al. (25), in a very small case-control study, reported a nonsignificant increased risk associated with high intake of polyunsaturated fat. Our finding that regular alcohol consumption was associated with reduced risk was consistent with findings from many studies that have examined this question (8, 26, 29, 32, 33) and probably due to the effects of alcohol on the production and metabolism of testosterone (34). We did examine whether the alcohol finding could be attributed to avoiding beverages to reduce symptoms; however, BPH incidence was not associated with consumption of either tea or

TABLE 5. Association of food use with the risk of incident symptomatic benign prostatic hyperplasia, Prostate Cancer Prevention Trial placebo arm, 1994–2003

	Frequency of consumption (servings)					p_{trend}
Red meat (servings/week)	<1	1.0–2.9	3.0–4.9	5.0–6.9	≥7	
HR* (95% CI*)†	Referent	1.26 (0.97, 1.63)	1.01 (0.77, 1.33)	0.99 (0.74, 1.33)	1.38 (1.01, 1.88)	0.557
Cases/men (nos.)	71/438	291/1,462	202/1,196	145/889	166/784	
Dairy (servings/day)	<1	1.0–1.9	2.0–2.9	≥3		
HR (95% CI)†	Referent	1.02 (0.87, 1.19)	1.00 (0.79, 1.26)	0.94 (0.72, 1.24)		0.762
Cases/men (nos.)	377/2,116	321/1,703	102/535	75/415		
Vegetables (servings/day)	<1	1.0–1.9	2.0–2.9	3.0–3.9	≥4	
HR (95% CI)†	Referent	0.76 (0.62, 0.93)	0.85 (0.69, 1.06)	0.79 (0.60, 1.03)	0.68 (0.50, 0.92)	0.095
Cases/men (nos.)	136/646	303/1,771	257/1,331	104/574	75/447	
Cruciferous vegetables (servings/week)	<1	1.0–1.9	2.0–2.9	3.0–3.9	≥4	
HR (95% CI)†	Referent	0.90 (0.77, 1.07)	1.12 (0.90, 1.39)	0.94 (0.69, 1.28)	0.88 (0.66, 1.16)	0.592
Cases/men (nos.)	464/2,443	207/1,218	101/491	46/264	57/353	
Fruit (servings/day)	<1	1.0–1.9	2.0–2.9	≥3		
HR (95% CI)†	Referent	0.83 (0.71, 0.97)	0.87 (0.71, 1.07)	1.02 (0.82, 1.27)		0.776
Cases/men (nos.)	330/1,717	291/1,726	132/732	122/594		

* HR, hazard ratio; CI, confidence interval.
† Controlled for age, race/ethnicity, waist/hip ratio, and total energy.

coffee. We did not confirm the previous finding of an increased risk associated with long-chain ω-3 fatty acids, and our finding of a decreased risk associated with high protein intake is novel and requires replication.

Both our study and previously published studies do not support an association of antioxidant nutrients with BPH risk. In the only other longitudinal study, Rohrmann et al. (9) reported decreased risks for 8-year BPH period prevalence associated with high intakes of vitamin C from foods (but not supplements) and individual carotenoids (but not lycopene and β-carotene) and no associations with tocopherols. They also found no significant associations of antioxidants with BPH incidence. Lagiou et al. (25) reported no significant associations with antioxidants, although there were nonsignificant reduced risks associated with high intakes of vitamins C and E. Rohrmann et al. (30) reported no significant cross-sectional associations of serum antioxidants with lower urinary tract symptoms, although men in the lowest quintiles of α-tocopherol, lycopene, and selenium were approximately twice as likely to report symptoms as were men with higher serum antioxidant levels. We judge it unlikely that dietary antioxidants play an important role in preventing symptomatic BPH.

Results from previous studies of specific foods and food groups are generally consistent with our finding that diets high in vegetables are associated with lower BPH risk. The largest studies reported an 11 percent reduction in BPH prevalence when comparing the lowest and highest quintiles of vegetable intake (9) and a 30 percent reduced risk of symptoms when comparing less than daily with daily consumption of fresh vegetables (28). There is also some support of our finding that high intake of red meat increases risk (28, 31).

Our findings on dietary zinc and supplemental vitamin D are difficult to interpret. The correlation between dietary zinc and protein, controlled for energy, was 0.52; in models that included dietary zinc and protein, both associations were attenuated and not statistically significant and, in models that included total zinc and protein, only protein was significant ($p = 0.017$). Combined with the observation that supplemental zinc was not associated with risk, it is possible that the dietary zinc finding is the result of collinearity with protein. It is also possible that there is a threshold above which zinc has no additional effect on risk. In analyses cross-classifying men by dietary and supplemental zinc intake using quintile 1 of dietary zinc without supplements as the comparison group, the hazard ratios were 0.69 (95 percent CI: 0.52, 0.91) for quintile 1 with supplements, 0.60 (95 percent CI: 0.48, 0.77) for quintiles 2–5 without supplements, and 0.61 (95 percent CI: 0.48, 0.78) for quintiles 2–5 with supplements. Vitamin D supplementation was associated with reduced risk, but our calculated dose of total vitamin D is imprecise, and the association was observed only among men who used both multivitamins and single vitamin D supplements. Larger studies with more detailed data on supplement use, including frequency, dose, and duration, will be needed to further address whether high-dose vitamin D supplementation is associated with BPH risk.

Many of the dietary factors that we found to be associated with BPH risk can affect both steroid hormone concentrations and the sympathetic nervous system. The dietary pattern characterized by low fat, moderate alcohol, and high vegetables is associated with less obesity (15), lower serum estrogens and androgens, and higher sex hormone binding globulin (34, 35) and probably also less sympathetic nervous stimulation (36). It is possible that these physiologic

effects moderate both the hormonally regulated prostate growth and heightened smooth muscle tone that cause BPH. Planned future analyses, based on assays of serum steroid hormone, cytokine, and adipokine concentrations, may provide insight into whether these mechanisms underlie associations of diet with BPH risk.

There are several strengths to this study, including the longitudinal design, the large sample size, the standardized and frequent assessments of BPH treatment and symptoms, and the use of incident rather than prevalent BPH as a study endpoint. There are also several limitations. First, all information used to define BPH endpoints was based on self-report, including medical and surgical treatment and lower urinary tract symptoms. We used specific interviewer-administered probes to collect treatment information every 3 months during the duration of the trial, but we did not have access to medical records to validate responses. We also used a standardized and well-validated, self-administered questionnaire to collect symptom data annually, but reporting of symptoms is highly subjective and may differ across racial, ethnic, and socioeconomic groups. Second, we used data from a FFQ to assess diet. Although we did not analyze nutrients that are very poorly ascertained by FFQ, we and many others are concerned by recent studies suggesting that FFQs correlated poorly with unbiased biomarkers of diet and perform poorly compared with dietary records (37). Finally, our assessment of supplement use was incomplete, and in particular we lacked frequency and dose information for selenium, vitamin D, and fish oil.

In conclusion, we found evidence that a dietary pattern high in vegetables and protein, moderate in alcohol, and low in fat and red meat may protect men from developing symptomatic BPH. We found no evidence that antioxidant nutrients, from either supplements or food, were associated with reduced BPH risk, nor did we find evidence that consumption of long-chain ω-3 fatty acids, zinc, or calcium was associated with reduced risk. Although confirmatory studies are needed, it is possible that dietary modification could be useful for preventing BPH and the management of BPH symptoms.

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