Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is a common disease of older men. Although the etiology remains unclear, nutritional factors may have an effect on the disease.

Objective: Because the literature on the relations between macronutrient intakes and BPH risk is limited, we examined these relations among men in the Health Professionals Follow-up Study.

Design: We followed men aged 40–75 y from baseline in 1986 to 1994. Total BPH cases (n = 3523) comprised men who reported BPH surgery (n = 1589) or who did not undergo surgery but scored 15–35 points on the lower urinary tract symptom questionnaire of the American Urological Association (n = 1934); noncases were men who scored ≤7 points (n = 24 388). Odds ratios (ORs) and 95% CIs were calculated by using multivariate logistic regression.

Results: The ORs rose with increasing total energy intake in a comparison of the highest and lowest quintiles for total BPH (OR: 1.29; 95% CI: 1.14, 1.45) and symptoms of BPH (1.43; 1.23, 1.66). Energy-adjusted total protein intake was positively associated with total BPH (1.18; 1.05, 1.33) and BPH surgery (1.26; 1.06, 1.49). Energy-adjusted total fat intake was not associated with risk of total BPH, but intakes of eicosapentaenoic, docosahexaenoic, and arachidonic acids were associated with a moderate increase in risk of total BPH.

Conclusions: We observed modest direct associations between BPH and intakes of total energy, protein, and specific long-chain polyunsaturated fatty acids. Because eicosapentaenoic, docosahexaenoic, and arachidonic acids are highly unsaturated fatty acids, our findings support a possible role of oxidative stress in the etiology of BPH. *Am J Clin Nutr* 2002;75:689–97.

KEY WORDS Benign prostatic hyperplasia, calories, energy, macronutrients, cohort study, protein, polyunsaturated fat, men, Health Professionals Follow-up Study

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disease of older men, characterized by overgrowth of the prostatic epithelium and fibromuscular tissue of the transition zone and periurethral area and by obstructive and irritative lower urinary tract symptoms (1). Autopsy data indicate that anatomic or microscopic evidence of BPH is present in 40% and 90% of men aged 50–60 and 80–90 y, respectively (2). More than 200 000 transurethral resections of the prostate for BPH are performed annually in the United States (3).

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The etiology of BPH is unclear, but it appears to represent a multifactorial process involving both mechanical and dynamic components (4). Enlarged prostate, a mechanical or static component of BPH, is influenced mainly by androgens and can be pharmacologically treated with 5α-reductase inhibitors to block intraprostatic conversion of testosterone to the more potent dihydrotestosterone (DHT) (5). Lower urinary tract symptoms due to a heightened tone of the prostatic smooth muscle, the dynamic component of BPH, are controlled by the sympathetic nervous system. α_1-Adrenergic receptor blockers, which are commonly used to alleviate these symptoms, act by relaxing prostatic smooth muscle (6).

Dietary and nutritional factors may have an effect on BPH etiology through a variety of mechanisms, but the literature on this topic is sparse (7–10). The absolute amount and composition of macronutrients may influence sympathetic nervous system activity and hormone concentrations. For example, a high total energy intake may elevate sympathetic nervous system activity and concentrations of testosterone (11). In addition, the macronutrient composition of the diet may be important. In particular, a high consumption of unsaturated fatty acids may contribute to lipid peroxidation of the cell membrane and of the components and fluidity of cell membranes, which may affect 5α-reductase activity (12). One group noted age-related changes in the fatty acid composition of the prostate epithelium and stroma in men with BPH (13).

Because the literature on relations between macronutrient intakes and BPH risk is limited, we examined the relations

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between macronutrient intakes and total BPH, BPH surgery, lower urinary tract symptoms, and enlarged prostate among men in the Health Professionals Follow-up Study.

SUBJECTS AND METHODS

Study population

The Health Professionals Follow-up Study is an ongoing prospective cohort study of 51 529 male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists. The participants, who were between 40 and 75 y of age at enrollment in 1986, completed a semiquantitative food-frequency questionnaire and provided information on age, race or ethnicity, weight, height, physical activity, cigarette smoking, alcohol consumption, and medical history (14). We collected updated information on exposure and disease biennially and on dietary intakes every 4 y via mailed follow-up questionnaires. The study was approved by the Human Research Committee at the Harvard School of Public Health.

On the 1988, 1990, 1992, and 1994 questionnaires, we asked participants whether they had undergone BPH surgery, usually a transurethral resection. In 1988 we mailed a confirmatory follow-up letter to a sample of respondents who reported such surgery. Of 99 randomly selected participants who confirmed having had a transurethral resection of the prostate, 77 granted us permission to review their medical records. We obtained medical records for 74 of these 77 participants, which confirmed the procedure. We subsequently considered the participant's self-report of BPH surgery as sufficient. Details of the cohort and follow-up techniques can be found elsewhere (15).

On the 1992 and 1994 questionnaires, we used a slightly modified version of the American Urological Association symptom index (16) to assess what percentage of the time (0%, 10%, 25%, 50%, 75%, or almost 100%) the participants experienced the following lower urinary tract symptoms during the past month: having a sensation of incomplete bladder emptying, having to urinate again after <2 h, stopping and starting several times during urination, difficulty postponing urination, having a weak urinary stream, and having to push or strain to begin urination. We also asked how many times per night the participant arose to urinate (0, 1, 2, 3, 4, 5, or ≥6). Each symptom was assigned a score of 0–5, corresponding to the percentage of the time that a symptom score was reported. We summed the points for each of the 6 lower urinary tract symptoms and the number of times per night the participant arose to urinate (we assigned a 5 for ≥5 times/night). The minimum possible score was 0 and the maximum was 35. On the 1992 questionnaire, we asked the men whether they had had an enlarged prostate detected by digital-rectal examination after 1986 and whether in the past 2 y they had had a digital-rectal examination.

At baseline we excluded men with an invalid dietary questionnaire (>70 blanks or an implausible energy intake) from 1986 (*n* = 1595), men who had a history of cancer (except for nonmelanoma skin cancer) or surgery for BPH before 1986 or prostate cancer during follow-up (*n* = 5237), and men who died (*n* = 442) before the 1988 questionnaire was mailed (the first opportunity to report BPH surgery). This left 44 488 men in the baseline population. Of the men who had not had BPH surgery throughout the follow-up period, we excluded those who did not respond to the questions about lower urinary tract symptoms in 1992, which left 33 344 men among whom to identify noncases and nonsurgery cases defined by symptoms.

Assessment of nutrients

The diet questionnaire used in the Health Professionals Follow-up Study was a 131-item validated semiquantitative food-frequency questionnaire aimed at accounting for >90% of the intake of major nutrients for the cohort (14, 17). For each food, a commonly used unit or portion size was specified, and participants were asked how often on average during the past year they consumed that amount of each food. Each item had 9 possible responses, ranging from never to ≥6 times/d. We also asked about the usual brand of breakfast cereal consumed; the brand, dose, duration, and frequency of multivitamin and individual vitamin supplement used; and the types of fat commonly used for cooking and at the table. The questionnaire also contained an open-ended section about foods that were not specified. We computed nutrient intakes by multiplying the frequency of consumption of the given portion size of each food by the nutrient content in that food with the use of values from US Department of Agriculture sources (18) and other data. In the present study we examined intakes of total energy (excluding energy from alcohol), total fat, total protein, and total carbohydrate in relation to BPH risk. Protein was further analyzed separately by animal protein and vegetable protein. We considered separately animal and vegetable fats; saturated, monounsaturated, and polyunsaturated fats; and the individual fatty acids palmitic (16:0), stearic (18:0), oleic (18:1), linoleic (18:2n−6), α-linolenic (18:3n−3), arachidonic (20:4n−6), eicosapentaenoic (EPA; 20:5n−3), and docosahexaenoic (DHA; 22:6n−3) acids. In all of the analyses, we used nutrients adjusted for energy with the use of the residuals method (11).

Classification of BPH cases and noncases

For the analyses we used 4 case definitions of BPH: *1*) surgery for enlarged prostate between the date of return of the 1986 baseline questionnaire and 31 December 1993 (*n* = 1589); *2*) high-moderate to severe lower urinary tract symptoms reported on the 1992 or 1994 questionnaire among those who did not undergo surgery for BPH (*n* = 1934); *3*) total BPH, consisting of surgery-defined cases and symptom-defined cases (*n* = 3523); and *4*) enlarged prostate detected by digital-rectal examination between 1986 and 1992 (*n* = 3180). The men were considered to have high-moderate to severe lower urinary tract symptoms if they scored 15–35 points on the American Urological Association symptoms index; men with a total symptom score of 8–14 points out of 35 (low-moderate symptoms; *n* = 5433) were not considered to be either cases or noncases.

Noncases were defined as men who had not had BPH surgery and whose total lower urinary tract symptom score in both 1992 and 1994 was between 0 and 7 points, or was between 0 and 7 points on the 1992 questionnaire if the 1994 symptom questions were not completed, irrespective of the result of the digital-rectal examination; 24 388 men fit these criteria. In the analysis of enlarged prostate, noncases were men who reported having had normal results from a digital-rectal examination in the past 2 y, irrespective of symptom score (*n* = 15 911).

Statistical analysis

We calculated odds ratios (ORs) and corresponding 95% CIs for each BPH definition and their associations with nutrient

TABLE 1
Age-standardized characteristics of the highest (Q5) and the lowest (Q1) quintiles of energy-adjusted nutrient intakes in the Health Professionals Follow-up Study, 1986[1]

	Total energy[2]		Total fat		Total protein		Total carbohydrate		Saturated fat		Polyunsaturated fat	
Characteristic	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5	Q1	Q5
Total BPH (%)	12.4	14.8	13.0	14.2	12.0	14.4	12.2	13.0[3]	13.2	13.6[3]	12.1	14.2
Race or ethnicity (%)												
Southern European	26.0	22.4	23.3	23.4[3]	22.5	25.3	22.9	23.3[3]	24.6	22.9[3]	22.2	24.5
Scandinavian	8.3	12.4	9.0	10.4	10.3	9.0	10.4	9.3	8.8	11.0	10.8	10.0[3]
Other white	55.0	58.1	58.1	58.3[3]	58.5	55.9	58.8	57.2[3]	56.6	59.0	57.9	56.8[3]
African American	1.1	0.6	0.8	0.6	1.0	0.7	0.5	1.0	0.9	0.6	0.8	0.6[3]
Asian	2.3	1.2	2.1	1.2	1.5	1.8[3]	1.1	2.1	2.6	0.7	1.9	1.7[3]
Other	7.3	5.2	6.7	6.1[3]	6.2	7.3	6.3	7.1[3]	6.6	5.7[3]	6.5	6.4[3]
Current smoker (%)	9.9	9.5[3]	6.1	12.9	11.4	7.5	15.6	4.1	5.1	13.5	10.2	7.9
Diabetes (%)	2.7	2.5	2.3	3.7	1.3	5.2	3.5	1.9	2.2	3.5	2.4	3.6
Vasectomy (%)	25.3	21.9	21.9	25.8	23.2	22.8[3]	27.1	20.6	22.0	24.7	21.0	25.5
Age (y)												
$\bar{x}$	54.2	52.3	54.3	53.1	53.1	54.6	54.0	53.7[3]	54.8	52.7	53.9	53.6[3]
SD	9.2	9.2	9.4	9.1	9.5	9.2	8.9	9.7	9.3	9.1	9.5	9.1
Alcohol intake (g/d)												
$\bar{x}$	11.1	11.5	15.7	7.2	17.0	7.3	22.6	4.7	14.8	8.0	15.2	8.8
SD	14.1	15.6	20.2	9.1	20.3	9.4	21.0	7.2	19.3	10.5	19.7	11.0
BMI (kg/m^2)												
$\bar{x}$	25.5	25.5[3]	24.7	26.0	25.1	25.9	26.0	24.7	24.6	26.0	25.3	25.5
SD	3.1	3.4	2.8	3.4	2.9	3.5	3.4	2.9	2.7	3.4	3.1	3.2
Physical activity (MET · h/wk)												
$\bar{x}$	18.4	21.3	25.7	15.1	19.0	20.6	16.2	24.1	26.5	14.9	20.5	19.4
SD	24.4	27.5	28.7	19.1	25.2	26.8	19.9	28.3	29.5	19.2	26.0	23.5
Energy intake (kJ/d)[2]												
$\bar{x}$	4915	11916	7746	7972	7779	7955	7591	8051	7817	7951	7850	8039
SD	652	1630	2512	2658	2629	2592	2558	2571	2546	2625	2546	2608
Energy-adjusted intake (g/d)												
Total fat												
$\bar{x}$	71.4	72.4	51.5	90.3	68.3	72.4	82.7	56.3	53.5	87.2	60.6	81.7
SD	14.9	13.3	7.4	7.1	14.2	14.4	13.5	10.4	9.7	9.1	14.0	11.9
Total protein												
$\bar{x}$	91.4	92.9	90.2	94.4	70.9	116.2	99.3	83.8	90.8	94.0	89.9	92.1
SD	17.5	16.6	18.0	15.4	6.8	11.1	18.4	14.6	18.7	15.1	16.8	16.3
Total carbohydrate												
$\bar{x}$	229	237	276	196	254	214	177	295	273	202	254	217
SD	46	39	43	28	45	39	21	24	44	32	49	37
Saturated fat												
$\bar{x}$	24.5	24.8	16.8	31.7	23.3	24.7	28.9	18.6	16.0	33.1	23.0	25.2
SD	6.6	5.8	3.6	4.8	6.1	6.4	6.2	4.7	2.8	3.7	7.2	5.5
Polyunsaturated fat												
$\bar{x}$	13.2	13.4	10.7	15.8	13.1	13.3	14.4	11.5	12.2	13.4	9.0	18.3
SD	3.5	3.6	2.4	4.2	3.9	3.3	4.2	2.9	3.5	3.4	1.1	3.0

[1] All factors except age were directly standardized to the age distribution of the 33 344 participants. BPH, benign prostatic hyperplasia; MET, metabolic equivalents. The trend in quintiles was significant ($P < 0.05$), except where noted otherwise.

[2] Does not include energy from alcohol.

[3] The trend in quintiles was not significant.

intakes from age- and energy-adjusted and multivariate logistic regression models. In the primary analyses, we considered the nutrients in quintiles. Because of the large number of cases, we also compared men in the top and bottom deciles of exposure to examine more extreme contrasts. Factors included in the multivariate logistic regression models were those for which distributions varied both by disease status and by nutrient intake or those that are risk factors for BPH in this population, ie, age (3-y categories), total energy (excluding that from alcohol), race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other) (19), physical activity in quintiles (20), cigarette smoking status [never, former, current (1–14, 15–34, and ≥35 cigarettes/d), and current unknown] (21), and alcohol consumption (5 categories) (21). In this cohort, central adiposity was positively associated with BPH (22). However, because waist circumference—from which central adiposity can be estimated, was available only for a subset of men, we used body mass index (BMI) instead. To determine whether the association between nutrient intake and BPH risk varied by level of obesity, we entered a series of indicator terms for cross-categories of BMI [tertiles of weight (in kg) divided by height squared (in m)] and nutrients (quintiles) in the multivariate logistic regression

TABLE 2
Odds ratios (ORs) and 95% CIs of total benign prostatic hyperplasia according to energy-adjusted macronutrient intakes in the Health Professionals Follow-up Study, 1986–1994

Macronutrient	Quintile of intake 1	2	3	4	5	P for trend[1]	Decile of intake (comparison of highest and lowest)
Total energy without alcohol (kJ/d)	5045	6494	7687	9094	11480	—	12740 and 4455
Number of cases	711	701	694	697	720	—	385 and 356
Age-adjusted OR (95% CI)	1.0	1.04 (0.93, 1.17)	1.04 (0.92, 1.17)	1.11 (0.98, 1.25)	1.25 (1.11, 1.40)	<0.001	1.46 (1.24, 1.72)
Multivariate OR 2[2] (95% CI)	1.0	1.06 (0.94, 1.19)	1.07 (0.95, 1.20)	1.14 (1.02, 1.29)	1.29 (1.14, 1.45)	<0.001	1.51 (1.28, 1.78)
Total fat (g/d)	53.6	64.5	71.6	78.3	88.3	—	93.5 and 47.6
Number of cases	715	675	691	703	739	—	378 and 370
Multivariate OR 1[3] (95% CI)	1.0	0.95 (0.84, 1.07)	0.97 (0.86, 1.09)	1.03 (0.92, 1.16)	1.11 (0.99, 1.25)	0.04	1.09 (0.93, 1.29)
Multivariate OR 2[2] (95% CI)	1.0	0.94 (0.83, 1.05)	0.94 (0.83, 1.05)	0.97 (0.86, 1.10)	1.02 (0.90, 1.15)	0.7	0.97 (0.82, 1.15)
Total protein (g/d)	72.6	83.6	91.6	100	113	—	120 and 67.3
Number of cases	640	637	721	727	798	—	414 and 317
Multivariate OR 1[3] (95% CI)	1.0	1.04 (0.92, 1.18)	1.15 (1.02, 1.30)	1.15 (1.02, 1.29)	1.26 (1.12, 1.42)	<0.001	1.33 (1.13, 1.57)
Multivariate OR 2[2] (95% CI)	1.0	1.03 (0.91, 1.17)	1.13 (1.00, 1.27)	1.11 (0.98, 1.25)	1.18 (1.05, 1.33)	0.004	1.23 (1.04, 1.46)
Total carbohydrate (g/d)	183	213	234	255	288	—	305 and 166
Number of cases	678	708	712	740	685	—	368 and 350
Multivariate OR 1[3] (95% CI)	1.0	1.11 (0.98, 1.25)	1.11 (0.98, 1.25)	1.18 (1.05, 1.33)	1.07 (0.95, 1.21)	0.2	1.12 (0.95, 1.32)
Multivariate OR 2[2] (95% CI)	1.0	1.05 (0.93, 1.18)	1.02 (0.90, 1.16)	1.07 (0.94, 1.21)	0.95 (0.83, 1.08)	0.5	0.95 (0.80, 1.14)
Animal protein (g/d)	46.7	58.2	66.7	75.6	89.5	—	97.4 and 40.8
Number of cases	684	631	699	738	771	—	399 and 337
Multivariate OR 1[3] (95% CI)	1.0	0.97 (0.85, 1.09)	1.09 (0.97, 1.23)	1.13 (0.99, 1.25)	1.20 (1.07, 1.36)	<0.001	1.32 (1.11, 1.57)
Multivariate OR 2[4] (95% CI)	1.0	0.96 (0.85, 1.08)	1.08 (0.95, 1.21)	1.07 (0.95, 1.21)	1.12 (0.99, 1.27)	0.02	1.22 (1.02, 1.45)
Vegetable protein (g/d)	18.0	21.6	24.2	27.1	32.3	—	35.4 and 16.3
Number of cases	660	651	738	720	754	—	376 and 316
Multivariate OR 1[3] (95% CI)	1.0	0.98 (0.86, 1.10)	1.10 (0.98, 1.24)	1.09 (0.97, 1.23)	1.11 (0.98, 1.26)	0.03	1.22 (1.02, 1.45)
Multivariate OR 2[4] (95% CI)	1.0	0.95 (0.84, 1.08)	1.06 (0.94, 1.20)	1.04 (0.92, 1.18)	1.05 (0.93, 1.20)	0.3	1.14 (0.95, 1.37)

[1] Estimated by entering the midpoint of each category as a continuous variable in the logistic regression model.

[2] The multivariate models included age (3-y intervals), race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), physical activity (quintiles), cigarette smoking [never, former, current (1–14, 15–34, and ≥35 cigarettes/d), and current unknown], alcohol consumption (quintiles), BMI (quintiles), and total energy intake (quintiles or deciles).

[3] The multivariate models included age and total energy intake.

[4] The multivariate models included age, race or ethnicity, physical activity, cigarette smoking, alcohol consumption, BMI, and intakes of total energy and animal and vegetable protein (quintiles or deciles).

models. We evaluated interactions between BMI and nutrient intake by entering the cross-product of BMI and the nutrient along with the main-effect terms as continuous variables in the multivariate logistic regression models. Because total energy intake was entered in the model, the OR for each quintile of a specific nutrient can be interpreted as the OR when the amount of energy (compared with the median of the lowest quintile) from the nutrient is substituted for the same amount of energy from the other nutrients not included in the model. To evaluate trend, the midpoints of each category of intake of each nutrient were entered as a single continuous variable in the logistic regression models. All analyses were conducted with the use of SAS release 6.12 (SAS Institute, Cary, NC).

RESULTS

Of the 33344 men with complete data, 3523 men were considered to have BPH; 1589 men reported having had surgery for BPH between 1986 and 1994, and 1934 men reported lower urinary tract symptoms classified as high-moderate to severe in 1992 or 1994. In addition, 5433 men reported lower urinary tract symptoms that were classified as low-moderate; these men were not included in the analysis. The 24388 remaining men were considered to be asymptomatic noncases. Of the 19091 men who had had a digital-rectal examination by 1992, 3180 reported having an enlarged prostate.

The mean age of the 33344 men at baseline in 1986 was 53.4 ± 9.3 y (median: 53 y), and the mean total daily energy (excluding that from alcohol), fat, protein, and carbohydrate intakes were 8030 ± 2355 kJ (median: 7687 kJ), 71.4 ± 13.8 g (median: 71.8 g), 92.2 ± 16.3 g (median: 91.3 g), and 234.4 ± 42.0 g (median: 234 g), respectively. Age-standardized means and prevalences of suspected BPH risk factors and other factors characterizing the participants in the highest and lowest quintiles of macronutrient intake are shown in **Table 1**. Most of the *P* values for trend were significant because of the large sample size.

In a comparison of the highest and lowest quintiles, the OR rose with increasing total energy intake for total BPH (OR: 1.29; **Table 2**) and for high-moderate to severe lower urinary tract symptoms (OR: 1.43; **Table 3**) after adjustment for age, race or ethnicity, physical activity, cigarette smoking, alcohol consumption, and BMI. However, associations with total energy intake were not observed for BPH surgery and enlarged prostate (Table 3). A comparison of extreme deciles showed consistent results for total BPH (OR: 1.51; Table 2) and for high-moderate to severe lower urinary tract symptoms (OR: 1.70; 95% CI: 1.39, 2.09; Table 3). The association between total energy intake and total BPH did not differ significantly by BMI.

TABLE 3
Multivariate odds ratios (ORs) and 95% CIs in a comparison of the highest and lowest quintiles of total benign prostatic hyperplasia (BPH) according to energy-adjusted nutrient intakes in the Health Professionals Follow-up Study, 1986–1994

	Case definition of BPH								
	BPH surgery			High-moderate to severe lower urinary tract symptoms			Enlarged prostate		
Nutrient intake	OR	95% CI	*P* for trend[1]	OR	95% CI	*P* for trend[1]	OR	95% CI	*P* for trend[1]
Total energy[2]	1.12	(0.95, 1.33)	0.2	1.43	(1.23, 1.66)	<0.001	1.12	(0.98, 1.27)	0.3
Total fat[2]	0.91	(0.77, 1.08)	0.3	1.12	(0.96, 1.31)	0.1	0.95	(0.83, 1.08)	0.4
Total protein[2]	1.26	(1.06, 1.49)	0.003	1.14	(0.98, 1.33)	0.09	1.01	(0.89, 1.14)	0.9
Total carbohydrate[2]	1.07	(0.88, 1.29)	0.6	0.85	(0.72, 1.01)	0.09	1.10	(0.95, 1.26)	0.2
Animal protein[3]	1.17	(0.98, 1.40)	0.01	1.10	(0.94, 1.29)	0.2	0.97	(0.85, 1.11)	0.8
Vegetable protein[3]	1.16	(0.96, 1.40)	0.05	0.97	(0.83, 1.15)	0.9	1.07	(0.93, 1.23)	0.5
Animal fat[4]	0.93	(0.78, 1.11)	0.2	0.98	(0.84, 1.16)	0.9	0.86	(0.75, 0.98)	0.03
Vegetable fat[4]	1.10	(0.93, 1.31)	0.3	1.14	(0.98, 1.34)	0.02	1.11	(0.98, 1.27)	0.3
Saturated fat[4]	0.76	(0.59, 0.99)	0.05	1.09	(0.86, 1.37)	0.6	1.03	(0.84, 1.24)	0.9
Monounsaturated fat[5]	1.05	(0.80, 1.40)	0.4	0.93	(0.72, 1.20)	0.9	0.88	(0.71, 1.09)	0.4
Polyunsaturated fat[5]	1.15	(0.94, 1.41)	0.4	1.18	(0.99, 1.41)	0.02	1.13	(0.97, 1.31)	0.2
Palmitic acid[2]	0.83	(0.70, 0.99)	0.05	0.99	(0.85, 1.15)	0.7	0.89	(0.78, 1.02)	0.07
Stearic acid[2]	0.77	(0.65, 0.92)	0.01	1.05	(0.90, 1.22)	0.3	0.96	(0.84, 1.09)	0.5
Oleic acid[2]	0.94	(0.79, 1.11)	0.7	1.09	(0.94, 1.27)	0.1	0.96	(0.85, 1.09)	0.6
Linoleic acid[2]	1.08	(0.91, 1.28)	0.4	1.14	(0.98, 1.32)	0.01	1.08	(0.95, 1.22)	0.3
α-Linolenic acid[2]	0.99	(0.84, 1.18)	0.9	1.17	(1.00, 1.36)	0.07	1.10	(0.97, 1.24)	0.2
Arachidonic acid[2]	1.13	(0.96, 1.34)	0.3	1.22	(1.05, 1.42)	0.02	0.97	(0.86, 1.10)	0.8
Eicosapentaenoic acid[2]	1.32	(1.11, 1.57)	<0.001	1.10	(0.94, 1.29)	0.3	1.14	(1.00, 1.30)	0.01
Docosahexaenoic acid[2]	1.32	(1.11, 1.57)	0.002	1.17	(1.01, 1.36)	0.06	1.23	(1.08, 1.40)	<0.001

[1] Estimated by entering the midpoint of quintiles 1 to 5 as a continuous variable in the logistic regression model.

[2] The multivariate models included age (3-y intervals), race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), physical activity (quintiles), cigarette smoking [never, former, current (1–14, 15–34, and ≥35 cigarettes/d), and current unknown], alcohol consumption (quintiles), BMI (quintiles), and total energy intake (quintiles).

[3] The multivariate models included age, race or ethnicity, physical activity, cigarette smoking, alcohol consumption, BMI, and intakes of total energy and animal and vegetable protein (quintiles).

[4] The multivariate models included age, race or ethnicity, physical activity, cigarette smoking, alcohol consumption, BMI, and intakes of total energy and animal and vegetable fat (quintiles).

[5] The multivariate models included age, race or ethnicity, physical activity, cigarette smoking, alcohol consumption, BMI, and intakes of total energy and saturated, monounsaturated, and polyunsaturated fat (quintiles).

No relation of total fat or carbohydrate intake to risk of total BPH (Table 2) or the other case definitions (Table 3) was observed after adjustment for total energy intake and all the covariates listed above. However, energy-adjusted total protein intake was positively associated with total BPH (OR: 1.18; Table 2) and BPH surgery (OR: 1.26; Table 3) after multivariate adjustment. The association was slightly stronger for animal protein intake than for vegetable protein intake. The results of the comparison of extreme deciles of protein intake were consistent with the quintile analyses (Table 2). The association between protein intake and BPH was similar across BMIs.

The ORs for specific case definitions of BPH differed by type of fat intake. Animal fat intake was not associated with total BPH (**Table 4**), BPH surgery, or high-moderate to severe lower urinary tract symptoms. However, animal fat intake was slightly inversely related to enlarged prostate after multivariate adjustment (OR: 0.86; 95% CI: 0.75, 0.98; *P* for trend = 0.03; Table 3). Vegetable fat intake was positively associated with total BPH and high-moderate to severe lower urinary tract symptoms, but not with BPH surgery or enlarged prostate, although the magnitudes of the associations were small. We observed similar patterns when comparing extreme deciles of animal and vegetable fat intakes.

Intakes of saturated and monounsaturated fats were not associated with total BPH (Table 4). Only saturated fat intake had a weak inverse relation with BPH surgery, and neither fat was significantly associated with other definitions of BPH (Table 3). On the other hand, polyunsaturated fat intake was slightly positively associated with total BPH (OR: 1.17; Table 4) and high-moderate to severe lower urinary tract symptoms (OR: 1.18, Table 3), but not with BPH surgery or enlarged prostate. However, the comparison of extreme deciles of intake showed that polyunsaturated fat intake was positively associated with all definitions of BPH [ORs: 1.36 for total BPH (Table 4), 1.36 for BPH surgery, 1.38 for high-moderate to severe lower urinary tract symptoms, and 1.25 for enlarged prostate].

Palmitic acid intake was not associated with total BPH (**Table 5**) or high-moderate to severe lower urinary tract symptoms, whereas marginal inverse associations were observed for BPH surgery (OR: 0.83; Table 3) and for enlarged prostate (OR: 0.89; Table 3). Stearic acid intake was significantly inversely associated with BPH surgery (OR: 0.77; Table 3). However, this association was not observed for the other BPH endpoints.

Because of the high correlation between oleic acid and total monounsaturated fat ($r = 0.99$) intakes, the relation of oleic acid intake with total BPH was almost the same as that with monounsaturated fat intake. Also, further analyses of the comparison between extreme deciles of oleic acid intake or *cis* and *trans* isomers showed no significant associations.

Intakes of linoleic and arachidonic acids were slightly positively associated with total BPH (OR: 1.11 and 1.18, respectively;

TABLE 4
Odds ratios (ORs) and 95% CIs of total benign prostatic hyperplasia according to intakes of different types of fat in the Health Professionals Follow-up Study, 1986–1994

Type of fat	Quintile of intake					*P* for trend[1]	Decile of intake (comparison of highest and lowest)
	1	2	3	4	5		
Animal fat (g/d)	25.7	34.5	40.5	47.0	57.1	—	62.6 and 21.6
Number of cases	737	699	719	677	691	—	378 and 335
Multivariate OR 1[2] (95% CI)	1.0	0.97 (0.86, 1.09)	1.02 (0.91, 1.15)	0.97 (0.86, 1.09)	1.04 (0.92, 1.17)	0.6	1.00 (0.85, 1.19)
Multivariate OR 2[3] (95% CI)	1.0	0.96 (0.85, 1.08)	1.00 (0.89, 1.12)	0.93 (0.82, 1.05)	0.95 (0.84, 1.08)	0.4	0.90 (0.76, 1.07)
Vegetable fat (g/d)	18.7	24.5	29.0	34.1	42.7	—	47.6 and 15.9
Number of cases	682	669	692	711	769	—	408 and 343
Multivariate OR 1[2] (95% CI)	1.0	1.02 (0.90, 1.15)	1.08 (0.96, 1.22)	1.15 (1.02, 1.30)	1.20 (1.06, 1.35)	<0.001	1.25 (1.06, 1.48)
Multivariate OR 2[3] (95% CI)	1.0	1.00 (0.89, 1.13)	1.05 (0.93, 1.19)	1.11 (0.98, 1.25)	1.12 (0.99, 1.27)	0.03	1.15 (0.97, 1.36)
Saturated fat (g/d)	16.8	21.3	24.3	27.3	32.0	—	34.7 and 14.4
Number of cases	743	696	692	705	687	—	328 and 378
Multivariate OR 1[2] (95% CI)	1.0	0.98 (0.86, 1.12)	1.01 (0.87, 1.17)	1.00 (0.85, 1.18)	1.00 (0.84, 1.20)	0.9	0.99 (0.77, 1.28)
Multivariate OR 2[4] (95% CI)	1.0	0.98 (0.85, 1.11)	0.97 (0.84, 1.13)	0.96 (0.81, 1.13)	0.93 (0.78, 1.12)	0.5	0.91 (0.70, 1.18)
Monounsaturated fat (g/d)	19.6	24.2	27.3	30.2	34.6	—	36.8 and 17.1
Number of cases	742	610	716	701	754	—	376 and 378
Multivariate OR 1[2] (95% CI)	1.0	0.80 (0.70, 0.92)	0.93 (0.80, 1.09)	0.91 (0.77, 1.09)	0.99 (0.81, 1.20)	0.7	0.85 (0.64, 1.13)
Multivariate OR 2[4] (95% CI)	1.0	0.80 (0.70, 0.93)	0.94 (0.80, 1.10)	0.90 (0.76, 1.08)	0.97 (0.79, 1.18)	0.8	0.84 (0.63, 1.11)
Polyunsaturated fat (g/d)	9.3	11.3	12.8	14.5	17.4	—	19.3 and 8.3
Number of cases	654	677	697	730	765	—	406 and 317
Multivariate OR 1[2] (95% CI)	1.0	1.07 (0.94, 1.21)	1.14 (1.01, 1.30)	1.18 (1.03, 1.34)	1.21 (1.05, 1.39)	0.006	1.42 (1.16, 1.73)
Multivariate OR 2[4] (95% CI)	1.0	1.06 (0.94, 1.21)	1.12 (0.99, 1.27)	1.16 (1.01, 1.32)	1.17 (1.02, 1.35)	0.03	1.36 (1.12, 1.67)

[1] Estimated by entering the midpoint of each category as a continuous variable in the logistic regression model.
[2] The multivariate models included age (3-y intervals) and total energy intake (quintiles).
[3] The multivariate models included age, race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), physical activity (quintiles), cigarette smoking [never, former, current (1–14, 15–34, and ≥35 cigarettes/d), and current unknown], alcohol consumption (quintiles), BMI (quintiles), and intakes of total energy (quintiles or deciles) and animal and vegetable fat (quintiles or deciles).
[4] The multivariate models included age, race or ethnicity, physical activity, cigarette smoking, alcohol consumption, BMI, and intakes of total energy and animal and saturated, monounsaturated, and polyunsaturated fat (quintiles or deciles).

Table 5) and with high-moderate to severe lower urinary tract symptoms (OR: 1.14 and 1.22; Table 3). These fatty acids were not associated with BPH surgery or enlarged prostate. α-Linolenic acid was weakly associated with high-moderate to severe lower urinary tract symptoms only (OR: 1.17; Table 3).

EPA and DHA correlated highly with each other ($r = 0.95$) because both are primarily from marine sources. As shown in Tables 3 and 5, EPA and DHA were both positively associated with total BPH, and the ORs were slightly higher for DHA. For EPA, the ORs (95% CIs) for total BPH were 1.20 (1.06, 1.35), for BPH surgery were 1.32 (1.11, 1.57), for high-moderate to severe lower urinary tract symptoms were 1.10 (0.94, 1.29), and for enlarged prostate were 1.14 (1.00, 1.30) in a comparison of extreme quintiles; the respective ORs for DHA were 1.23 (1.09, 1.39), 1.32 (1.11, 1.57), 1.17 (1.01, 1.36), and 1.23 (1.08, 1.40). The positive relations of EPA and DHA with total BPH were significant for all definitions except high-moderate to severe lower urinary tract symptoms. The ORs comparing extreme deciles for these 4 definitions of BPH were 1.15 (Table 5), 1.17, 1.15, and 1.15 for EPA, and 1.28 (Table 5), 1.38, 1.22, and 1.23 for DHA, respectively. These relations were consistent across BMIs.

DISCUSSION

Of the 33 344 members of the Health Professionals Follow-up Study, we observed direct associations between total energy intake and total BPH and high-moderate to severe lower urinary tract symptoms; between total and animal protein intakes and total BPH and BPH surgery; between EPA and DHA and total BPH, BPH surgery, and enlarged prostate; and between total polyunsaturated fats and all definitions of BPH.

Intakes of total energy and specific macronutrients may affect several aspects of the underlying etiology of BPH and lower urinary tract symptoms. Although the etiology of BPH is unclear, 2 aspects have been emphasized: a static component and a dynamic component. The static component probably results from overgrowth of the prostatic epithelium, which compresses the urethra. Prostatic epithelial cell proliferation is influenced by androgens, as evidenced by the absence of BPH in men who are castrated before puberty (23) and the small or absent prostate in men who are deficient in 5α-reductase type 2 (24, 25). On the other hand, the dynamic component of BPH appears to be related to the level of sympathetic nervous system activity. α_{1c}-Adrenoceptors have been identified as the major mediator of prostate contractility (26, 27), and contractility is dependent on norepinephrine concentrations (28). Adrenergic receptors are preferentially expressed in the prostate stroma, probably in smooth muscle cells (29), and the ratio of prostatic stroma to epithelium is higher in some men with symptomatic BPH (30).

The positive relation between total energy intake and total BPH is difficult to interpret because variation in total energy intake is due largely to differences in physical activity, body size, and energy efficiency (11). In this cohort, we previously reported an inverse association between physical activity and BPH (20) and a positive association between abdominal obesity and BPH (22).

TABLE 5
Odds ratios (ORs) and 95% CIs of total benign prostatic hyperplasia according to intakes of specific fatty acids in the Health Professionals Follow-up Study, 1986–1994

Fatty acid	Quintile of intake					*P* for trend[1]	Decile of intake (comparison of highest and lowest)
	1	2	3	4	5		
Palmitic acid (g/d)	9.5	11.9	13.5	15.1	17.5	—	18.8 and 8.2
Number of cases	758	687	704	694	680	—	339 and 386
Multivariate OR 1[2] (95% CI)	1.0	0.87 (0.77, 0.98)	0.96 (0.85, 1.08)	0.96 (0.86, 1.08)	0.99 (0.88, 1.12)	0.7	0.99 (0.84, 1.16)
Multivariate OR 2[3] (95% CI)	1.0	0.86 (0.77, 0.97)	0.93 (0.83, 1.05)	0.92 (0.81, 1.03)	0.91 (0.81, 1.03)	0.4	0.89 (0.75, 1.06)
Stearic acid (g/d)	4.0	5.3	6.2	7.0	8.4	—	9.1 and 3.3
Number of cases	752	675	681	721	694	—	353 and 362
Multivariate OR 1[2] (95% CI)	1.0	0.90 (0.80, 1.01)	0.93 (0.83, 1.05)	1.02 (0.90, 1.14)	1.00 (0.89, 1.13)	0.5	1.05 (0.89, 1.23)
Multivariate OR 2[3] (95% CI)	1.0	0.89 (0.79, 1.00)	0.90 (0.80, 1.02)	0.96 (0.85, 1.08)	0.91 (0.81, 1.03)	0.4	0.94 (0.79, 1.11)
Oleic acid (g/d)	17.6	22.1	25.0	27.8	32.0	—	34.1 and 15.3
Number of cases	740	617	715	690	761	—	386 and 371
Multivariate OR 1[2] (95% CI)	1.0	0.84 (0.75, 0.95)	0.97 (0.87, 1.09)	0.99 (0.88, 1.11)	1.09 (0.98, 1.23)	0.03	1.13 (0.96, 1.33)
Multivariate OR 2[3] (95% CI)	1.0	0.84 (0.74, 0.94)	0.95 (0.84, 1.07)	0.94 (0.83, 1.06)	1.01 (0.90, 1.14)	0.5	1.03 (0.87, 1.22)
Linoleic acid (g/d)	7.7	9.6	11.0	12.6	15.4	—	17.2 and 6.8
Number of cases	682	676	677	737	751	—	409 and 331
Multivariate OR 1[2] (95% CI)	1.0	1.00 (0.89, 1.13)	1.06 (0.94, 1.19)	1.14 (1.01, 1.28)	1.16 (1.03, 1.30)	0.003	1.32 (1.12, 1.55)
Multivariate OR 2[3] (95% CI)	1.0	0.99 (0.88, 1.12)	1.03 (0.91, 1.16)	1.11 (0.99, 1.25)	1.11 (0.99, 1.25)	0.02	1.25 (1.06, 1.48)
α-Linolenic acid (g/d)	0.69	0.86	1.01	1.19	1.51	—	1.71 and 0.62
Number of cases	741	715	690	678	699	—	374 and 381
Multivariate OR 1[2] (95% CI)	1.0	1.09 (0.97, 1.22)	1.11 (0.98, 1.24)	1.13 (1.01, 1.28)	1.15 (1.02, 1.29)	0.03	1.21 (1.03, 1.43)
Multivariate OR 2[3] (95% CI)	1.0	1.07 (0.95, 1.20)	1.07 (0.95, 1.20)	1.10 (0.97, 1.24)	1.08 (0.96, 1.22)	0.3	1.13 (0.96, 1.34)
Arachidonic acid (g/d)	0.05	0.07	0.08	0.10	0.13	—	0.15 and 0.04
Number of cases	645	681	719	676	802	—	383 and 295
Multivariate OR 1[2] (95% CI)	1.0	1.11 (0.98, 1.25)	1.13 (1.00, 1.27)	1.08 (0.96, 1.22)	1.22 (1.08, 1.37)	0.004	1.22 (1.03, 1.45)
Multivariate OR 2[3] (95% CI)	1.0	1.10 (0.98, 1.24)	1.12 (0.99, 1.26)	1.07 (0.94, 1.20)	1.18 (1.05, 1.33)	0.03	1.18 (0.99, 1.41)
Eicosapentaenoic acid (g/d)	0.02	0.04	0.07	0.10	0.17	—	0.27 and 0.01
Number of cases	611	699	678	755	780	—	403 and 330
Multivariate OR 1[2] (95% CI)	1.0	1.10 (0.97, 1.24)	1.04 (0.92, 1.18)	1.17 (1.03, 1.31)	1.19 (1.06, 1.35)	0.003	1.14 (0.97, 1.35)
Multivariate OR 2[3] (95% CI)	1.0	1.11 (0.98, 1.26)	1.06 (0.94, 1.20)	1.20 (1.06, 1.35)	1.20 (1.06, 1.35)	0.004	1.15 (0.98, 1.36)
Docosahexaenoic acid (g/d)	0.03	0.08	0.13	0.19	0.35	—	0.47 and 0.01
Number of cases	631	664	734	700	794	—	432 and 332
Multivariate OR 1[2] (95% CI)	1.0	1.05 (0.93, 1.19)	1.11 (0.96, 1.25)	1.04 (0.92, 1.17)	1.22 (1.09, 1.38)	<0.001	1.27 (1.08, 1.49)
Multivariate OR 2[3] (95% CI)	1.0	1.07 (0.94, 1.21)	1.13 (1.01, 1.28)	1.06 (0.94, 1.20)	1.23 (1.09, 1.39)	0.002	1.28 (1.08, 1.51)

[1] Estimated by entering the midpoint of each category as a continuous variable in the logistic regression model.
[2] The multivariate models included age (3-y intervals) and total energy intake (quintiles).
[3] The multivariate models included age, race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), physical activity (quintiles), cigarette smoking [never, former, current (1–14, 15–34, and ≥35 cigarettes/d), and current unknown], alcohol consumption (quintiles), BMI (quintiles), and total energy intake.

An increase in energy intake may enhance abdominal obesity and sympathetic nervous system activity, both of which may increase the risk of BPH. However, higher energy intakes related to physical activity do not appear to increase BPH risk. In the present study, we adjusted for BMI and physical activity. Also, the relation between energy intake and BPH was essentially the same in the analyses that were stratified by tertile of BMI (data not shown). Thus, it is not likely that total energy intake represented physical activity or body size in the present study. One possibility for the positive relation between total energy intake and total BPH is that activation of the sympathetic nervous system by a high energy intake (31) may cause the prostate smooth muscle to contract, resulting in a worsening of lower urinary tract symptoms. The positive relation of total BPH with total energy intake could also be indirect if low metabolic efficiency results in both higher symptomatic tone and higher energy intakes. The lack of an association between total energy intake and enlarged prostate suggests that the effect of energy intake is mediated through the dynamic rather than the static component of BPH.

Positive relations of total and animal protein intakes with total BPH and BPH surgery were observed. Because there were no associations between enlarged prostate and protein intake in this study, the etiology of BPH also could be explained by the dynamic rather than the static component of BPH. However, protein intake was not associated with high-moderate to severe lower urinary tract symptoms. Furthermore, the relation of dietary protein with sympathetic nervous system activity is reported to be less strong than that of dietary carbohydrate intake in humans (32) and rats (33) in short-term studies. Also, a study of vegetarians suggested that protein might lower sympathetic nervous system activity (34). These observations indicate that protein may not be associated with BPH surgery as a result of higher sympathetic nervous system activation. Another plausible role of protein may be related to its contribution to the osmolar concentration of the diet that increases the obligatory water loss, which may increase urination (100 g protein contains 16 g N that must be excreted, mostly as urea, contributing 500 mOsmol). Because the kidneys can only concentrate urine up to a certain osmolality, the osmolar concentration of the diet, which is largely related to protein and salt, induces an obligatory water loss. It is plausible that the osmolar load from a large protein meal as it is digested influences urinary flow, which may exacerbate any existing urinary symptoms. This mechanism is speculative because it is unclear whether the magnitude of changes in urinary flow is sufficient to produce symptoms.

EPA and DHA were associated with total BPH, BPH surgery, and enlarged prostate. These polyunsaturated fatty acids were most clearly related to enlarged prostate, suggesting a mechanism of BPH etiology different from that of the other nutrients. The high degree of unsaturation of EPA and DHA suggests a mechanism involving lipid peroxidation. Lipid peroxides may result in increases in tissue concentrations of NAD and NADPH, which increase 5α-reductase and prostatic DHT concentrations, thus possibly increasing epithelial and stromal growth (1). A hormonal etiology appears consistent with the finding that EPA and DHA were associated with the mechanical, or static, component rather than with the dynamic component of BPH. A weak positive association between vegetable fat and total BPH and high-moderate to severe lower urinary tract symptoms and enlarged prostate also might be due to peroxidation. Serum DHT is reported to be positively correlated with vegetable fat intake (35), but the relation between plasma hormones and BPH risk is controversial (36). The degree of unsaturation of fatty acids in cell membranes appears to influence 5α-reductase activity (13), which is a determinant of intracellular DHT concentrations in the prostate.

Besides a mechanism involving androgenic effects, numerous previous studies have shown that lipid peroxides are involved in the regulation of cellar proliferation and cytotoxicity. Dietary EPA and DHA are sources of lipid peroxides, and their cytotoxicity is concentration dependent (37) and may influence BPH through nonhormonal mechanisms (38). The results of an animal study suggest that $n-3$ polyunsaturated fatty acids suppress sympathetic nervous system activity (39), which does not support a positive effect on the dynamic component of BPH.

There are few reports on the relations between intake of foods or macronutrients and BPH. An ecologic study in China (7) suggests that the increasing prevalence of BPH in China may be attributed to the increased intakes of total energy, fat, and animal protein. A case-control study (n = 100 cases and 100 matched control subjects) conducted in Japan reported a positive association between BPH and regular milk consumption (OR: 2.3) and daily meat consumption (OR: 3.2) (8). A cohort study (9) reported a weak positive relation between beef consumption (consumption of ≥180 g/wk compared with nonconsumers) and BPH surgery (OR: 1.3; P = 0.05). A case-control study of 184 BPH patients and 244 control subjects found that butter, margarine, and seed oils were related to a higher risk of BPH; margarine and seed oils are sources of polyunsaturated fat (10).

Some strengths of our study were its large size, prospective assessment of diet, and ability to control for numerous potentially confounding factors. Although there is some degree of misclassification when both diet and BPH are assessed, the large sample size in the present study increased the likelihood that important associations would be detected even if they were attenuated by measurement error. Because diet was assessed prospectively, misclassification should have been largely nondifferential between cases and noncases. Thus, the true underlying associations may be even stronger than observed. To the extent that we could control for various factors, confounding did not appear to account for the observed associations, although this possibility cannot be entirely excluded. Although we made no direct clinical measures to diagnose BPH, our multiple assessments of various aspects of BPH enhanced the likelihood of our detecting any associations. The greatest credibility should be given to results that were consistent across all or most endpoints; the results for nutrients associated with only one endpoint should be viewed with more caution.

In this study, we reported on associations between BPH and macronutrient intakes. The associations were modest, and any changes in diet must be considered in conjunction with other important diseases, such as cancer and heart disease. Our findings on polyunsaturated fatty acids need to be explored further because unsaturated fats and fish oils are beneficial in preventing heart disease. If the associations related to fatty acids are due to oxidative stress, the role of antioxidants needs to be considered to arrive at the optimal diet, taking into account overall health.

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