Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in US men[1–3]

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ABSTRACT

Background: Nutrients with antioxidant properties or that influence cell growth and differentiation might reduce the risk of benign prostatic hyperplasia (BPH).

Objective: The objective was to evaluate the association of fruit, vegetable, and micronutrient intakes with BPH.

Design: The participants were members of the Health Professionals Follow-Up Study and were aged 46–81 y in 1992. In 1992 and biennially thereafter, the men reported having surgery for an enlarged prostate, and in 1992 and on 3 subsequent questionnaires they completed the American Urological Association symptom index (AUASI). BPH cases were men who reported having surgery or who had an AUASI score of 15–35 ($n = 6092$). Control subjects were men who had not had surgery and never had an AUASI score >7 ($n = 18\,373$). Men with a score of 8–14 were excluded ($n = 7800$). Intakes of fruit, vegetables, and antioxidants were assessed with a food-frequency questionnaire in 1986. We calculated odds ratios (ORs) of BPH and 95% CIs using logistic regression.

Results: Vegetable consumption was inversely associated with BPH (fifth compared with first quintile—OR: 0.89; 95% CI: 0.80, 0.99; P for trend = 0.03), whereas fruit intake was not. Consumption of fruit and vegetables rich in β-carotene (P for trend = 0.004), lutein (P for trend = 0.0004), or vitamin C (P for trend = 0.05) was inversely related to BPH. With increasing vitamin C intake from foods, men were less likely to have BPH (P for trend = 0.0009). Neither α- nor γ-tocopherol intake from foods was associated with BPH (P for trend = 0.05 and 0.84, respectively).

Conclusion: Our findings are consistent with the hypothesis that a diet rich in vegetables may reduce the occurrence of BPH. *Am J Clin Nutr* 2007;85:523–9.

KEY WORDS Benign prostatic hyperplasia, micronutrients, fruit, vegetables

INTRODUCTION

Benign prostatic hyperplasia (BPH) is common in older men and often results in lower urinary tract symptoms (LUTS). Both an enlarged prostate and an increased tone of the prostate smooth muscle are thought to contribute to this bothersome condition. The cause of BPH is largely unknown, but fruit and vegetable consumption has been found to be inversely associated with BPH in 3 small case-control studies (1–3), whereas no association was observed for vegetable and fruit juice consumption in a Hawaiian cohort study (4). Previously, a high intake of polyunsaturated fatty acids (PUFAs) was observed to be associated with a higher risk of BPH in the Health Professionals Follow-Up Study (5), and it was hypothesized that oxidative damage might contribute to the disorder of BPH. Fruit and vegetables provide nutrients with antioxidant properties, such as vitamin E and lycopene, and nutrients that might influence cell growth and differentiation, such as lycopene, may beneficially influence the disorders underlying BPH.

Thus, we examined the association of fruit and vegetable consumption and the intake of micronutrients with BPH in a large US cohort study. This examination allowed us not only to evaluate the overall associations but also to assess in depth these associations with sufficient power in potentially interesting subgroups.

SUBJECTS AND METHODS

Study population

Men who were included in the analysis are participants in the Health Professionals Follow-Up Study, a large prospective cohort study comprising 51 529 dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists aged between 40 and 75 y at enrollment in 1986. At baseline, all participants completed a semiquantitative food-frequency questionnaire (FFQ) (6) and provided information on age, race or ethnicity, weight, height, physical activity, cigarette smoking, alcohol consumption, and medical history. Every 2 y, questionnaires were mailed to collect updated information on exposure and new diagnoses. Every 4 y, FFQs were mailed to collect updated diet information, although in the analysis we used only the baseline FFQ to lower the possibility that BPH was already present at the time of the dietary assessment. The study was

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approved by the Human Subjects Committee at the Harvard School of Public Health and the Johns Hopkins Bloomberg School of Public Health.

Cases and controls for these analyses were derived from the 32 265 men with information on fruit and vegetable consumption at baseline in 1986 and BPH between 1992 and 2000. Men were excluded if they had been diagnosed with cancer before baseline or with prostate cancer through 2000 (n = 7178), died before 1992 (n = 2027), or did not return the 1992 questionnaire, which was the first to request information on LUTS (n = 8738). Furthermore, men who had had surgery for an enlarged prostate before 1992, men with an invalid FFQ in 1986, or men with missing information on other covariables were excluded (n = 1312).

Case ascertainment

On the 1992, 1994, 1998, and 2000 questionnaires, we asked men to complete the American Urological Association symptom index (AUASI) (7), which was slightly modified to fit the constraints of our questionnaire, to assess what percentage of the time (0%, 10%, 25%, 50%, 75%, or almost 100%) the participants experienced the following LUTS 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 LUTS and the number of times per night the participant arose to urinate (we assigned a 5 for ≥5 times per night). The minimum possible score was 0 and the maximum was 35. In 1998 and 2000, we also asked the men to report whether they used either α-blockers or finasteride to treat BPH.

In 1988 and every 2 y subsequently, the participants were asked whether they had undergone surgery for an enlarged prostate. Self-reported surgery for an enlarged prostate was validated in a subset of men in 1988 that showed this information was reliable (8). Briefly, 77 of 99 randomly selected men who had reported having had surgery for prostatic enlargement consented to the review of their medical records. All of the 74 records that could be obtained confirmed the self-reported surgery. To be parallel to the symptoms analyses, we included surgery cases from 1992 and onward only.

In the present analysis, we used several different definitions of BPH: *1*) surgery—surgery for an enlarged prostate between 1992 and 2000; *2*) LUTS—high-moderate to severe LUTS (AUASI score ≥ 15) on ≥1 of 4 possible questionnaires between 1992 and 2000 (but no surgery) or use of medications to treat BPH in 1998 or 2000; *3*) total BPH—the combined endpoint of either surgery or symptoms; and *4*) incident total BPH—men who did not report surgery or symptoms in 1992 and 1994 but who reported surgery or symptoms later during follow-up. Noncases were men who had never reported surgery for prostatic enlargement, whose AUASI score has always been between 0 and 7, and who did not report taking medications to treat BPH on the 1998 and 2000 questionnaires. Men with an intermediate AUASI score of 8–14 were not considered to be case or control subjects to increase the specificity of the case definition.

Assessment of fruit and vegetable consumption

In 1986, participants completed a 131-item validated semiquantitative FFQ (6). For each food item, a commonly used unit or serving size was specified. The participants were asked to indicate how often, on average, they consumed each food, with 9 possible response categories ranging from "never" to "6 or more times per day." Information on dose and duration of vitamin supplement intake also was assessed on the baseline FFQ. Nutrient intake was calculated by multiplying the given consumption frequency of each food by its nutrient content for the specified serving size derived from US Department of Agriculture sources and other data (6).

Statistical analysis

Fruit and vegetable consumption and micronutrient intake were categorized into quintiles of intake based on the distribution of the entire Health Professionals Follow-Up Study cohort in 1986. We restricted the analyses to the fruit and vegetable intakes as assessed at baseline in 1986 because we primarily studied prevalent BPH (ie, it was not known when the symptoms started). Thus, we did not use updated information of fruit and vegetable consumption to limit reverse causation as much as possible. In addition, using baseline information allowed us to examine cases of incident BPH, that is, men who did not report LUTS or surgery in 1992 and 1994 but did so subsequently (ie, in 1998 or 2000). Fruit and vegetable consumption was grouped into total fruit and vegetable consumption as well as into groups of fruit and vegetables that are rich in specific micronutrients, such as rich in vitamin C. Furthermore, we grouped fruit and vegetables by botanical groups.

We calculated odds ratios (ORs) and corresponding 95% CIs using logistic regression to evaluate the association of fruit and vegetable consumption and micronutrient intake with each definition of BPH. The models were adjusted for age (3-y categories), race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), cigarette smoking [never, former, and current (1–15, 16–34, or >35 cigarettes/d or unknown amount)], body mass index (in quintiles), leisure-time physical activity (in quintiles), alcohol consumption (nonconsumers and 0.1–5.0, 5.1–15.0, 15.1–30.0, 30.1–50.0, or >50.1 g alcohol/d), energy intake (in quintiles), intake of protein (in quintiles), and intake of PUFAs (in quintiles). To test for trend, we entered the midpoint of each category of fruit, vegetable, and micronutrient intake as a single continuous variable into the logistic regression model, the coefficient for which was evaluated by the Wald test. Previously, a positive association between PUFA intake and the risk of BPH was observed in this cohort (5). To examine whether PUFA intake is an effect modifier of the association of fruit and vegetable consumption and micronutrient intake with BPH, we ran logistic regression models stratified by PUFA intake (below median and equal or above median). The presence of multiplicative interaction was assessed by including a cross-product term for PUFA intake and fruit, vegetable, and micronutrient intakes in a logistic regression model along with the main effect terms. The statistical significance of the coefficient for the cross-product term was evaluated by the Wald test. All analyses were conducted with the use of SAS version 9.1 (SAS Institute, Cary, NC).

TABLE 1
Baseline characteristics of participants by quintiles of total fruit and vegetable intake in 1986: Health Professionals Follow-Up Study[1]

	Quintiles of total fruit and vegetable intake				
	1 (*n* = 6493)	2 (*n* = 6460)	3 (*n* = 6467)	4 (*n* = 6385)	5 (*n* = 6457)
Median intake (servings/d)	2.8	4.2	5.5	7.0	9.8
Age (y)[2]	51.7 ± 0.11[3]	52.9 ± 0.11	53.5 ± 0.11	53.7 ± 0.12	54.4 ± 0.12
Total BPH (%)[4]	24.9	25.9	24.8	26.0	26.0
Race or ethnicity (%)					
African American	0.8	0.7	0.8	0.5	0.8
Asian	2.1	1.6	1.3	1.2	1.3
Southern European	22.8	22.5	23.4	23.6	24.4
Scandinavian	11.0	10.7	10.2	10.1	9.9
Other	6.3	5.8	5.9	6.5	6.5
Other white	57.0	58.7	58.4	58.1	57.1
Current smoker (%)	14.4	10.7	8.2	7.0	4.8
Alcohol intake (g/d)	12.2 ± 0.19	12.0 ± 0.19	11.8 ± 0.19	11.0 ± 0.19	10.6 ± 0.19
Physical activity (MET h/wk)	14.5 ± 0.30	16.9 ± 0.30	19.2 ± 0.30	21.5 ± 0.31	26.7 ± 0.30
BMI (kg/m^2)	25.6 ± 0.04	25.5 ± 0.04	25.4 ± 0.04	25.3 ± 0.04	25.3 ± 0.04
Polyunsaturated fat intake (g/d)	13.2 ± 0.04	13.3 ± 0.04	13.3 ± 0.04	13.3 ± 0.04	13.0 ± 0.04
Protein intake (g/d)	88.6 ± 0.20	90.7 ± 0.20	92.2 ± 0.20	94.0 ± 0.20	95.3 ± 0.20
Fiber intake (g/d)	15.6 ± 0.07	18.4 ± 0.07	20.6 ± 0.07	22.7 ± 0.07	27.3 ± 0.07
Current use of multivitamins (%)	37.0	40.0	41.2	42.8	46.0

[1] Includes 32 265 men with information on fruit and vegetable consumption on the baseline food-frequency questionnaire. BPH, benign prostatic hyperplasia; MET, metabolic equivalent. Means and percentages (except mean age and race distribution) were calculated by using the SAS procedure general linear model (PROC GLM), with adjustment for age.
[2] All *P* values of tests for differences between groups were < 0.0001.
[3] $\bar{x}$ ± SEM (all such values).
[4] Diagnosis of BPH based on history of surgery for an enlarged prostate, high-moderate to severe lower urinary tract symptoms, and use of medications to treat BPH.

RESULTS

Of 32 265 eligible men, 6092 had BPH indicated either by surgery for an enlarged prostate (n = 3145) or a high-moderate to severe AUASI score (n = 2947), and of these 1161 had incident BPH. A total of 18 373 were considered to be noncases. The remaining men had low-to-moderate symptoms and were excluded from the analysis. Age-adjusted characteristics of the study participants are shown in **Table 1**. Men who consumed more servings of fruit and vegetables were older, were less likely to currently smoke cigarettes, drank less alcohol, were more physically active, had slightly lower body mass index, and were more likely to use multivitamins.

Total consumption of fruit and vegetables was not associated with the odds of total BPH (**Table 2**). For vegetable intake, the OR of total BPH decreased statistically significantly with increasing consumption of vegetables in the multivariable model. Vegetable consumption was inversely associated with LUTS (OR: 0.87; 95% CI: 0.76, 1.00; *P* for trend = 0.04) but not with surgery for an enlarged prostate (fifth compared with first quintile, OR: 0.90; 95% CI: 0.78, 1.03; *P* for trend = 0.11). No association was present for vegetables and incident BPH (OR: 0.96; 95% CI: 0.78, 1.18; *P* for trend = 0.62). In contrast to vegetable consumption, men who consumed higher amounts of fruit and fruit juice were not less likely to have BPH than were men who consumed lower amounts of fruit (Table 2).

Consumption of fruit and vegetables rich in β-carotene, rich in lutein, and rich in vitamin C was associated with a lower OR of total BPH (Table 2). Increasing intakes of fruit and vegetables rich in β-carotene and lutein were inversely related to both LUTS (*P* for trend = 0.01 and 0.01, respectively) and surgery (*P* for trend = 0.02 and 0.003, respectively). Men with higher intakes of fruit and vegetables rich in vitamin C were less likely to have symptoms (*P* for trend = 0.03) but not surgery (*P* for trend = 0.34). We observed an inverse association of fruit and vegetables rich in β-carotene with incident total BPH (Table 2). No associations with incident total BPH were present for fruit and vegetables rich in lutein or for fruit and vegetables rich in vitamin C (Table 2). Among foods that are rich in lutein, β-carotene, or both, cooked spinach (*P* for trend = 0.02), raw spinach (*P* for trend = 0.0004), Brussels sprouts (*P* for trend = 0.06), peas (*P* for trend < 0.0001), and peaches (*P* for trend = 0.01) were related to a lower OR of total BPH. Furthermore, increasing consumption of orange juice tended to be inversely associated with total BPH (*P* for trend = 0.06).

We evaluated whether fruit and vegetable botanical groups were associated with total or incident total BPH. The consumption of rutaceae (oranges, orange juice, grapefruit, and grapefruit juice; *P* for trend = 0.05), legumes (string beans, peas, beans, and alfalfa sprouts; *P* for trend = 0.01), cruciferous vegetables (broccoli, sauerkraut, cole slaw, cooked cabbage, cauliflower, Brussels sprouts, and kale; *P* for trend = 0.006), and "other vegetables" (corn, mixed vegetables, mushrooms, yams, cooked spinach, raw spinach, iceberg lettuce, romaine lettuce, and garlic; *P* for trend = 0.002) were associated with a lower OR of total BPH. These botanical groups were also generally inversely associated with incident BPH, but none of the associations was statistically significant.

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TABLE 2
Association of fruit and vegetable consumption with total and incident benign prostatic hyperplasia (BPH): Health Professionals Follow-Up Study, 1992–2000[1]

	Total BPH						Total incident BPH					
	Quintile of fruit and vegetable intake (servings/d)					*P* for trend	Quintile of fruit and vegetable intake (servings/d)					*P* for trend
	1	2	3	4	5		1	2	3	4	5	
Fruit and vegetable[2]	2.8	4.2	5.5	7.0	9.8		2.8	4.2	5.5	7.0	9.8	
Cases/noncases (*n*)	1102/3944	1215/3682	1202/3705	1244/3504	1329/3538		224/3944	238/3682	235/3705	216/3504	248/3538	
Multivariable OR[3]	1.00	1.03	0.93	0.97	0.93	0.14	1.00	1.02	0.94	0.89	0.94	0.40
95% CI	Ref	0.93, 1.14	0.84, 1.03	0.88, 1.08	0.84, 1.04		Ref	0.85, 1.24	0.77, 1.14	0.72, 1.09	0.76, 1.17	
Vegetables[4]	1.6	2.4	3.2	4.3	6.1		1.6	2.4	3.2	4.3	6.1	
Cases/noncases (*n*)	1212/3776	1173/3711	1207/3684	1234/3593	1266/3609		232/3776	235/3711	220/3684	228/3593	246/3609	
Multivariable OR[3]	1.00	0.98	0.94	0.95	0.89	0.03	1.00	1.02	0.90	0.94	0.96	0.62
95% CI	Ref	0.89, 1.08	0.85, 1.04	0.86, 1.05	0.80, 0.99		Ref	0.84, 1.24	0.74, 1.10	0.77, 1.15	0.78, 1.18	
Fruit and fruit juices[5]	0.7	1.4	2.1	2.8	4.3		0.7	1.4	2.1	2.8	4.3	
Cases/noncases (*n*)	1001/4010	1150/3746	1235/3610	1376/3536	1330/3471		232/4010	214/3746	224/3610	242/3536	249/3471	
Multivariable OR[3]	1.00	1.05	1.08	1.09	1.04	0.64	1.00	0.86	0.89	0.90	0.93	0.78
95% CI	Ref	0.95, 1.17	0.97, 1.19	0.98, 1.21	0.93, 1.16		Ref	0.71, 1.05	0.73, 1.09	0.74, 1.09	0.75, 1.14	
Fruit[6]	0.4	0.8	1.3	1.9	3.1		0.4	0.8	1.3	1.9	3.1	
Cases/noncases (*n*)	964/4034	1142/4000	1220/3466	1374/3533	1392/3340		217/4034	247/4000	200/3466	262/3533	235/3340	
Multivariable OR[3]	1.00	1.03	1.16	1.14	1.06	0.32	1.00	1.02	0.89	1.06	0.91	0.50
95% CI	Ref	0.93, 1.15	1.04, 1.29	1.02, 1.26	0.95, 1.19		Ref	0.84, 1.23	0.73, 1.09	0.87, 1.29	0.74, 1.13	
Fruit and vegetables rich in β-carotene[7]	0.2	0.4	0.6	1.0	1.6		0.2	0.4	0.6	1.0	1.6	
Cases/noncases (*n*)	1129/3834	1183/3661	1330/4012	1138/3180	1312/3686		240/3834	222/3661	263/4012	204/3180	232/3686	
Multivariable OR[3]	1.00	1.00	0.95	0.96	0.87	0.004	1.00	0.90	0.92	0.86	0.80	0.03
95% CI	Ref	0.90, 1.11	0.86, 1.04	0.87, 1.07	0.78, 0.96		Ref	0.74, 1.09	0.77, 1.11	0.71, 1.06	0.65, 0.98	
Fruit and vegetables rich in lutein[8]	0.2	0.4	0.6	0.9	1.4		0.2	0.4	0.6	0.9	1.4	
Cases/noncases (*n*)	1266/3902	965/3024	1359/4213	1206/3587	1296/3647		237/3902	192/3024	250/4213	235/3587	247/3647	
Multivariable OR[3]	1.00	0.95	0.92	0.89	0.83	0.0004	1.00	1.01	0.93	0.97	0.92	0.43
95% CI	Ref	0.85, 1.05	0.84, 1.02	0.81, 0.99	0.75, 0.92		Ref	0.82, 1.23	0.77, 1.13	0.80, 1.17	0.76, 1.13	
Fruit and vegetables rich in lycopene[9]	0.3	0.5	0.7	1.1	1.6		0.3	0.5	0.7	1.1	1.6	
Cases/noncases (*n*)	1187/3713	1159/3629	1204/3934	1230/3576	1312/3521		226/3713	226/3629	217/3934	248/3576	244/3521	
Multivariable OR[3]	1.00	1.03	0.96	0.96	0.98	0.42	1.00	1.03	0.96	0.96	0.98	0.67
95% CI	Ref	0.93, 1.14	0.87, 1.07	0.87, 1.07	0.88, 1.09		Ref	0.93, 1.14	0.87, 1.07	0.87, 1.07	0.88, 1.09	
Fruit and vegetables rich in vitamin C[10]	0.5	1.1	1.4	2.0	3.1		0.5	1.1	1.4	2.0	3.1	
Cases/noncases (*n*)	1161/3850	1089/3666	1268/3634	1280/3623	1294/3600		240/3850	204/3666	228/3634	228/3623	261/3600	
Multivariable OR[3]	1.00	0.90	0.97	0.91	0.89	0.05	1.00	0.82	0.87	0.85	0.94	0.99
95% CI	Ref	0.82, 1.00	0.88, 1.08	0.82, 1.01	0.80, 0.99		Ref	0.68, 1.00	0.72, 1.05	0.70, 1.03	0.78, 1.15	
Citrus fruit[11]	0.1	0.4	0.9	1.1	1.9		0.1	0.4	0.9	1.1	1.9	
Cases/noncases (*n*)	1246/3978	1108/3678	1264/3633	1154/3553	1320/3531		249/3978	214/3678	222/3633	224/3553	252/3531	
Multivariable OR[3]	1.00	0.98	0.98	0.88	0.94	0.09	1.00	0.92	0.88	0.89	0.96	0.75
95% CI	Ref	0.89, 1.09	0.89, 1.08	0.79, 0.97	0.85, 1.04		Ref	0.76, 1.11	0.72, 1.06	0.73, 1.08	0.79, 1.16	

[1] Diagnosis of total BPH based on a history of surgery for an enlarged prostate, high-moderate to severe lower urinary tract symptoms, and use of medications to treat BPH. Diagnosis of incident BPH based on report of no surgery or symptoms in 1992 and 1994 but report of surgery or symptoms later during follow-up. OR, odds ratio; Ref, reference.

[2] Pizza, tomatoes, tomato juice, tomato sauce, eggplant, green pepper, red chili sauce, watermelon, cantaloupe melon, yellow squash, apples, apple juice, strawberries, peaches, oranges, orange juice, grapefruit, grapefruit juice, string beans, peas, beans, alfalfa sprouts, broccoli, sauerkraut, cole slaw, cooked cabbage, cauliflower, Brussels sprouts, kale, carrots, celery, corn, mixed vegetables, mushrooms, yams, cooked spinach, raw spinach, iceberg lettuce, romaine lettuce, garlic, avocado, bananas, other juices, blueberries, and raisins.

[3] Multivariable logistic regression models adjusted for age (3-y categories), race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), cigarette smoking [never, former, and current (1–15, 16–34, or >35 cigarettes/d or unknown amount], BMI (in quintiles), leisure-time physical activity (in quintiles), alcohol consumption (nonconsumers and 0.1–5.0, 5.1–15.0, 15.1–30.0, 30.1–50.0, or ≥50.1 g alcohol/d), energy intake (in quintiles), intake of protein (in quintiles), and intake of polyunsaturated fatty acids (in quintiles). *P* values for trend were from a Wald test of the coefficient for the exposure variable entered into the logistic regression model as an ordinal variable with values equal to the midpoint of each category.

[4] Pizza, tomatoes, tomato juice, tomato sauce, eggplant, green pepper, red chili sauce, yellow squash, string beans, peas, beans, alfalfa sprouts, broccoli, sauerkraut, cole slaw, cooked cabbage, cauliflower, Brussels sprouts, kale, carrots, celery, corn, mixed vegetables, mushrooms, yams, cooked spinach, raw spinach, iceberg lettuce, romaine lettuce, and garlic.

[5] Oranges, orange juice, grapefruit, grapefruit juice, apples, apple juice, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.

[6] Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, blueberries, and raisins.

[7] Carrots, yellow squash, yams, cooked spinach, raw spinach, cantaloupe melon, kale, romaine lettuce, and peaches.

[8] Cooked spinach, raw spinach, kale, broccoli, Brussels sprouts, celery, peas, and yellow squash.

[9] Pizza, tomatoes, tomato juice, tomato sauce, watermelon, and grapefruit.

[10] Cantaloupe melon, oranges, orange juice, grapefruit, grapefruit juice, strawberries, other juices, broccoli, green pepper, Brussels sprouts, and cauliflower.

[11] Oranges, orange juice, grapefruit, and grapefruit juice.

The intake of vitamin C from foods, but not from supplements, was associated with a decreased OR of total BPH (**Table 3**), surgery (P for trend = 0.03), and LUTS (P for trend = 0.001) but not total incident BPH (Table 3). The intake of lutein and zeaxanthin was inversely associated with total BPH (Table 3), surgery (P for trend = 0.001), and LUTS (P for trend < 0.0001) but not incident total BPH (Table 3). Among foods contributing to lycopene intake, consumption of tomato juice (P for trend = 0.06) but not tomato sauce (P for trend = 0.70) tended to be related to a decreased OR of total BPH.

The intake of γ-tocopherol (which is mostly from foods) was not associated with the odds of BPH; the slight positive association of α-tocopherol with total BPH was of borderline significance (Table 3). Also no statistically significant association was observed with incident BPH for tocopherols (Table 3). Because the main dietary source of tocopherols is vegetable oils, we evaluated the association of α- and γ-tocopherol intakes with total BPH stratified by the intake of different types of fat. No effect modification was observed by intake of total PUFA, n−6 fatty acids, or α-linolenic acids (data not shown). We observed a statistically significant interaction between α-tocopherol intake and total n−3 fatty acid intake (P for interaction = 0.03); men with a low intake of total n−3 fatty acids had a higher OR of total BPH for α-tocopherol intake (fifth compared with first quintile, OR: 1.13; 95% CI: 1.00, 1.28; P for trend = 0.04) than did men who had had a high intake of total n−3 fatty acids (fifth compared with first quintile, OR: 0.94; 95% CI: 0.77, 1.13; P for trend = 0.56). A similar but less strong interaction was noted for γ-tocopherol intake and n−3 fatty acid intake (P for interaction = 0.05).

We further examined whether the associations of micronutrient intake were modified by PUFA intake. No statistically significant effect modification by PUFAs was observed ($P > 0.05$ for all), except for vitamin C from food (below the median intake of PUFAs, fifth compared with first quintile of vitamin C, OR: 0.92; 95% CI: 0.81, 1.06; at or above the median intake of PUFAs, fifth compared with first quintile of vitamin C, OR: 0.73; 95% CI: 0.61, 0.86; P for interaction = 0.02) and for lutein and zeaxanthin (below the median intake of PUFAs, fifth compared with first quintile of lutein and zeaxanthin, OR: 0.89; 95% CI: 0.78, 1.02; at or above the median intake of PUFAs, fifth compared with first quintile of lutein and zeaxanthin, OR: 0.73; 95% CI: 0.62, 0.86; P for interaction = 0.03).

DISCUSSION

In this large study, we observed that the consumption of vegetables, in general, and of fruit and vegetables rich in β-carotene, lutein, and vitamin C was modestly inversely associated with total BPH. We also observed that men with a high intake of vitamin C from foods and of lutein and zeaxanthin were statistically significantly less likely to have BPH. In contrast, neither the intake of α- nor γ-tocopherol was associated with the risk of BPH in this group of men.

The association between fruit and vegetable consumption and BPH has been investigated in only a small number of studies. In a Japanese case-control study (100 cases, 100 control subjects), men who irregularly consumed green and yellow vegetables were more likely to have BPH than were men who ate them regularly (OR: 3.91; $P < 0.01$) (2). A case-control study conducted in Greece (184 cases, 246 control subjects) did not observe an inverse association between vegetable consumption and surgery for BPH (OR: 1.00; 95% CI: 0.87, 1.15), but fruit consumption was inversely associated with surgery for BPH (OR: 0.84; 95% CI: 0.72, 0.97) (3). In a cohort study in Hawaii (6581 men, including 846 cases), neither Japanese American men with a high vegetable consumption nor with a high intake of fruit drinks had a lower risk of BPH than did men who did not consume vegetables or fruit drinks (4). Finally, a Finnish population-based cross-sectional study (2137 men) observed an inverse association between vegetable consumption and BPH (OR: 0.68; 95% CI: 0.54, 0.86) (1).

Oxidative damage is thought to be associated with the development of BPH. De Marzo et al (9) suggested that the prostate may be particularly vulnerable to oxidative stress especially in the setting of chronic intraprostatic inflammation. Thus, nutrients with antioxidant properties may beneficially affect the disorders underlying BPH and its symptoms. It was previously shown in this cohort of US men that a higher intake of PUFAs was associated with a moderately increased risk of BPH (5), suggesting that lipid peroxidation involvement may be important. The increased intake of micronutrients that protect against lipid peroxidation might, thus, be associated with a decreased risk of BPH and its symptoms. Accordingly, it was observed that a diet with a high intake of fruit and vegetables was associated with less oxidative damage as measured by urinary 8-hydroxy-2'-deoxyguanosine excretion (10) and with decreased plasma malondialdehyde concentration (11), an end product of PUFA peroxidation. An elevated malondialdehyde concentration was observed in patients with BPH (12).

In addition to an inverse association of vegetable consumption with BPH in general, we observed that men who consumed high amounts of fruit and vegetables rich in vitamin C were less likely to have BPH. A similar, but weaker association was observed in the Greek case-control study (OR: 0.88; 95% CI: 0.57, 1.37) (3). These findings are consistent with several observations related to oxidant burden. Plasma vitamin C concentration was shown to be inversely associated with malondialdehyde concentration (11). In addition, vitamin C supplementation of 500 mg/d during a period of 2 mo was related to reduced in vivo lipid peroxidation (13). It is of interest that the effect of vitamin C intake from foods was stronger in men with a PUFA intake above the median. In contrast to the reduced risk of BPH with higher consumption of fruit and vegetables rich in vitamin C, a high intake of vitamin C from supplements was associated with a slightly elevated risk of BPH in our study. The intake of vitamin C in the middle quintiles was similar from foods and from supplements, however. A possible explanation for this discrepant finding for high intake by source is that fruit and vegetables rich in vitamin C provide other plant constituents that might beneficially influence BPH.

Men with a high intake of lutein and zeaxanthin were less likely to have BPH in this investigation than were men with a low intake. This effect was stronger in men with a high intake of PUFA than in men with PUFA intake below the median. Both carotenoids were found to be associated with less oxidative stress as measured by plasma malondialdehyde concentration (11). We did not observe statistically significant associations of α- or γ-tocopherol intake with the risk of BPH. In contrast to our results, Lagiou et al (3) observed an inverse, although not statistically significant, association between vitamin E intake and surgery for BPH (OR: 0.55; 95% CI: 0.23, 1.27), and a cross-sectional evaluation of data from the third National Health and Nutrition Examination Survey found an inverse association of

TABLE 3
Association of micronutrient intake with total and incident benign prostatic hyperplasia (BPH): Health Professionals Follow-Up Study, 1992–2000[1]

	Total BPH						Incident BPH					
	Categories of micronutrient intake					*P* for trend	Categories of micronutrient intake					*P* for trend
	1	2	3	4	5		1	2	3	4	5	
Total vitamin C (mg/d)	95	157	227	403	1168		95	157	227	403	1168	
Cases/noncases (*n*)	1131/4019	1161/3670	1245/3618	1251/3565	1304/3501		229/4019	224/3670	229/3618	238/3565	241/3501	
Multivariable OR[2]	1.00	0.97	1.03	1.03	1.07	0.08	1.00	0.97	0.99	1.03	1.06	0.39
95% CI	Ref	0.88, 1.07	0.93, 1.14	0.93, 1.14	0.97, 1.19		Ref	0.80, 1.17	0.82, 1.20	0.85, 1.25	0.87, 1.28	
Vitamin C from food (mg/d)	79	121	154	193	265		79	121	154	193	265	
Cases/noncases (*n*)	1188/3890	1231/3826	1215/3628	1277/3531	1181/3498		245/3890	223/3826	229/3628	232/3531	232/3498	
Multivariable OR[2]	1.00	0.94	0.93	0.91	0.84	0.0009	1.00	0.85	0.89	0.88	0.87	0.33
95% CI	Ref	0.85, 1.03	0.84, 1.03	0.83, 1.01	0.75, 0.93		Ref	0.70, 1.03	0.73, 1.08	0.73, 1.07	0.72, 1.06	
Vitamin C from supplements (mg/d)	0	50	150	500	1100		0	50	150	500	1100	
Cases/noncases (*n*)	2763/8918	743/2285	850/2453	904/2332	832/2385		536/8918	155/2285	156/2453	152/2332	162/2385	
Multivariable OR[2]	1.00	0.95	1.11	1.11	1.06	0.08	1.00	1.05	1.05	1.02	1.09	0.46
95% CI	Ref	0.86, 1.05	1.01, 1.23	1.01, 1.22	0.97, 1.17		Ref	0.87, 1.27	0.87, 1.27	0.84, 1.23	0.91, 1.31	
Total carotene (IU/d)	3732	5729	7731	11207	18409		3732	5729	7731	11207	18409	
Cases/noncases (*n*)	1132/3952	1191/3899	1163/3685	1286/3549	1320/3288		238/3952	234/3899	220/3685	229/3549	240/3288	
Multivariable OR[2]	1.00	0.96	0.88	0.95	0.95	0.73	1.00	0.93	0.87	0.90	0.96	0.94
95% CI	Ref	0.87, 1.06	0.80, 0.98	0.86, 1.05	0.86, 1.06		Ref	0.77, 1.13	0.71, 1.05	0.74, 1.09	0.79, 1.16	
α-Carotene (μg/d)	293	473	634	1019	2040		293	473	634	1019	2040	
Cases/noncases (*n*)	1171/3792	1132/3814	1193/3781	1273/3613	1323/3373		241/3792	234/3814	220/3781	221/3613	245/3373	
Multivariable OR[2]	1.00	0.93	0.91	0.95	0.96	0.87	1.00	0.93	0.84	0.86	0.95	0.99
95% CI	Ref	0.84, 1.03	0.82, 1.00	0.86, 1.05	0.87, 1.07		Ref	0.77, 1.12	0.69, 1.02	0.71, 1.05	0.78, 1.15	
β-Carotene (μg/d)	2040	3134	4219	5779	9175		2040	3134	4219	5779	9175	
Cases/noncases (*n*)	1159/3952	1210/3824	1167/3684	1285/3599	1271/3314		245/3952	237/3824	204/3684	244/3599	231/3314	
Multivariable OR[2]	1.00	0.97	0.88	0.92	0.93	0.24	1.00	0.92	0.79	0.92	0.91	0.63
95% CI	Ref	0.87, 1.07	0.79, 0.97	0.83, 1.02	0.84, 1.03		Ref	0.77, 1.11	0.65, 0.96	0.76, 1.11	0.74, 1.10	
β-Cryptoxanthin (μg/d)	11	33	56	93	171		11	33	56	93	171	
Cases/noncases (*n*)	1185/3849	1194/3744	1265/3701	1248/3641	1200/3438		236/3849	207/3744	258/3701	212/3641	248/3438	
Multivariable OR[2]	1.00	0.99	0.99	0.92	0.87	0.002	1.00	0.99	0.99	0.92	0.87	0.90
95% CI	Ref	0.89, 1.09	0.90, 1.09	0.83, 1.02	0.79, 0.97		Ref	0.89, 1.09	0.90, 1.09	0.83, 1.02	0.79, 0.97	
Lycopene (μg/d)	3498	6158	8669	12221	18772		3498	6158	8669	12221	18772	
Cases/noncases (*n*)	1405/3248	1249/3715	1192/3827	1123/3850	1123/3733		240/3248	223/3715	238/3827	225/3850	235/3733	
Multivariable OR[2]	1.00	0.92	0.95	0.90	0.92	0.13	1.00	0.90	1.01	0.97	1.04	0.44
95% CI	Ref	0.83, 1.01	0.86, 1.05	0.81, 0.99	0.83, 1.01		Ref	0.74, 1.08	0.84, 1.23	0.80, 1.18	0.85, 1.25	
Lutein and zeaxanthin (μg/d)	1308	2271	3184	4347	6788		1308	2271	3184	4347	6788	
Cases/noncases (*n*)	1234/3807	1290/3697	1241/3646	1179/3678	1148/3545		251/3807	229/3697	251/3646	193/3678	237/3545	
Multivariable OR[2]	1.00	1.00	0.96	0.87	0.82	<0.0001	1.00	0.90	0.99	0.74	0.91	0.18
95% CI	Ref	0.90, 1.10	0.87, 1.06	0.79, 0.96	0.74, 0.90		Ref	0.75, 1.09	0.82, 1.19	0.60, 0.90	0.75, 1.10	
Total vitamin A (IU/d)	6241	9223	12706	17326	27099		6241	9223	12706	17326	27099	
Cases/noncases (*n*)	1077/4149	1161/3769	1214/3704	1304/3513	1336/3238		245/4149	228/3769	224/3704	225/3513	239/3238	
Multivariable OR[2]	1.00	0.99	0.97	1.00	1.04	0.31	1.00	0.92	0.87	0.86	0.98	0.99
95% CI	Ref	0.89, 1.09	0.88, 1.08	0.90, 1.10	0.94, 1.15		Ref	0.76, 1.11	0.72, 1.06	0.71, 1.04	0.80, 1.19	
α-Tocopherol (mg/d)	7.5	9.6	12.3	27.7	412.4		7.5	9.6	12.3	27.7	412.4	
Cases/noncases (*n*)	1093/4095	1102/3819	1289/3536	1234/3648	1374/3275		249/4095	192/3819	238/3536	229/3648	253/3275	
Multivariable OR[2]	1.00	0.92	1.00	0.99	1.06	0.05	1.00	0.72	0.87	0.86	0.96	0.15
95% CI	Ref	0.82, 1.02	0.90, 1.12	0.89, 1.10	0.95, 1.17		Ref	0.59, 0.89	0.70, 1.06	0.71, 1.05	0.79, 1.16	
γ-Tocopherol (mg/d)[3]	6.9	9.5	11.5	13.7	17.2		6.9	9.5	11.5	13.7	17.2	
Cases/noncases (*n*)	1234/3412	1177/3719	1234/3772	1240/3760	1207/3710		220/3412	210/3719	243/3772	247/3760	241/3710	
Multivariable OR[2]	1.00	0.96	1.02	1.04	0.99	0.84	1.00	0.96	1.12	1.16	1.06	0.46
95% CI	Ref	0.87, 1.07	0.91, 1.14	0.92, 1.17	0.86, 1.14		Ref	0.78, 1.18	0.90, 1.40	0.92, 1.48	0.81, 1.39	

[1] Diagnosis of total BPH based on a history of surgery for an enlarged prostate, high-moderate to severe lower urinary tract symptoms, and use of medications to treat BPH. Diagnosis of incident BPH based on report of no surgery or symptoms in 1992 and 1994 but report of surgery or symptoms later during follow-up. OR, odds ratio; Ref, reference.

[2] Multivariable logistic regression models adjusted for age (3-y categories), race or ethnicity (southern European, Scandinavian, other white, African American, Asian, and other), cigarette smoking [never, former, and current (1–15, 16–34, or >35 cigarettes/d or unknown amount)], BMI (in quintiles), leisure-time physical activity (in quintiles), alcohol consumption (nonconsumers, 0.1–5.0, 5.1–15.0, 15.1–30.0, 30.1–50.0, or ≥50.1 g alcohol/d), energy intake (in quintiles), intake of protein (in quintiles), and intake of polyunsaturated fatty acids (in quintiles). *P* values for trend were from a Wald test of the coefficient for the exposure variable entered into the logistic regression model as an ordinal variable with values equal to the midpoint of each category.

[3] The primary source of γ-tocopherol is food.

plasma vitamin E concentration and the occurrence of BPH in men aged ≥60 y (14).

This study has several strengths. Because of its large sample size, it offers the opportunity to examine the association across extreme differences in intake. Making use of the large sample size, we examined the association of food and micronutrient intake with BPH by quintiles and deciles of intake. However, we did not note stronger associations when considering deciles instead of quintiles of intake (data not shown). Furthermore, we had the opportunity to investigate, in addition to the intake from foods, the effect of dietary supplements on BPH. The long follow-up of the Health Professionals Follow-Up Study, with baseline assessment in 1986, allowed us to examine the association of fruit and vegetable consumption and micronutrient intake with incident total BPH in addition to total BPH. Although total vegetable intake was not inversely associated with incident BPH, in general, similar associations were observed for fruit and vegetable consumption and micronutrient intake with total BPH and with incident total BPH. However, because the number of incident total BPH cases was smaller than the number of total BPH cases, the associations for incident total BPH were usually not statistically significant. BPH is a condition that starts in men's young adulthood (15). Although we observed inverse associations among several aspects of diet of middle-aged men, it might be more important to examine diet during the time period of BPH initiation, especially in the context of BPH prevention. However, our work may be informative about the role of modifiable factors in the progression to symptomatic BPH. In conclusion, our findings are consistent with the hypothesis that a diet rich in vegetables and in β-carotene, lutein, and vitamin C derived from foods may reduce the occurrence of BPH.

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REFERENCES

1. Koskimaki J, Hakama M, Huhtala H, Tammela TL. Association of dietary elements and lower urinary tract symptoms. Scand J Urol Nephrol 2000;34:46–50.
2. Araki H, Watanabe H, Mishina T, Nakao M. High-risk group for benign prostatic hypertrophy. Prostate 1983;4:253–64.
3. Lagiou P, Wuu J, Trichopoulou A, Hsieh CC, Adami HO, Trichopoulos D. Diet and benign prostatic hyperplasia: a study in Greece. Urology 1999;54:284–90.
4. Chyou PH, Nomura AM, Stemmermann GN, Hankin JH. A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. Prostate 1993;22:253–64.
5. Suzuki S, Platz EA, Kawachi I, Willett WC, Giovannucci E. Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. Am J Clin Nutr 2002;75:689–97.
6. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–36.
7. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol 1992;148:1549–57.
8. Platz EA, Kawachi I, Rimm EB, et al. Physical activity and benign prostatic hyperplasia. Arch Intern Med 1998;158:2349–56.
9. De Marzo AM, Coffey DS, Nelson WG. New concepts in tissue specificity for prostate cancer and benign prostatic hyperplasia. Urology 1999;53:29–42.
10. Huang H-Y, Helzlsouer KJ, Appel LJ. The Effects of vitamin C and vitamin E on oxidative DNA damage: results from a randomized controlled trial. Cancer Epidemiol Biomarkers Prev 2000;9:647–52.
11. Block G, Dietrich M, Norkus EP, et al. Factors associated with oxidative stress in human populations. Am J Epidemiol 2002;156:274–85.
12. Merendino RA, Salvo F, Saija A, et al. Malondialdehyde in benign prostate hypertrophy: a useful marker? Mediators Inflamm 2003;12:127–8.
13. Huang H-Y, Appel LJ, Croft KD, Miller ER III, Mori TA, Puddey IB. Effects of vitamin C and vitamin E on in vivo lipid peroxidation: results of a randomized controlled trial. Am J Clin Nutr 2002;76:549–55.
14. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between serum concentrations of micronutrients and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey. Urology 2004;64:504–9.
15. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol 1984;132:474–9.