Fruit and vegetable consumption, intake of micronutrients, and benign prostatic hyperplasia in US men\textsuperscript{1–3}

Sabine Rohrmann, Edward Giovannucci, Walter C Willett, and Elizabeth A Platz

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 \textasciitilde 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 \textasciitilde 6092). Control subjects were men who had not had surgery and never had an AUASI score \textasciitilde 7 \textasciitilde 373). Men with a score of 8–14 were excluded \textasciitilde 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—\textit{OR}: 0.89; 95% CI: 0.80, 0.99; \textit{P} for trend = 0.03), whereas fruit intake was not. Consumption of fruit and vegetables rich in \textit{β}-carotene \textit{(P} for trend = 0.004), lutein \textit{(P} for trend = 0.0004), or vitamin C \textit{(P} for trend = 0.05) was inversely related to BPH. With increasing vitamin C intake from foods, men were less likely to have BPH \textit{(P} for trend = 0.0009). Neither \textit{α}-nor \textit{γ}-tocopherol intake from foods was associated with BPH \textit{(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. \textit{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 \textasciitilde 1–3), whereas no association was observed for vegetable and fruit juice consumption in a Hawaiian cohort study \textasciitilde 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 \textasciitilde 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) \textit{(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 funded by Public Health Service grants DK44779 and CA55075 from the Department of Health and Human Services, the National Institutes of Health.

\textsuperscript{1}From the Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (SR and EAP); the Division of Clinical Epidemiology, German Cancer Research Center, Heidelberg, Germany (SR); the Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston, MA (WCW and EG); the Channing Laboratory, Department of Medicine, Brigham & Women’s Hospital, Boston, MA (WCW and EG); and Harvard Medical School, Boston, MA (WCW and EG).

\textsuperscript{2}Supported by Public Health Service grants DK44779 and CA55075 from the Department of Health and Human Services, the National Institutes of Health.

\textsuperscript{3}Reprints not available. Address correspondence to EA Platz, Johns Hopkins Bloomberg School of Public Health, Department of Epidemiology, 615 North Wolfe Street, Room E6138, Baltimore, MD 21205. E-mail: eplatz@jhsp.edu.

Received June 8, 2006.

Accepted for publication September 18, 2006.

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 semi-quantitative 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).
RESULTS

Of 32,265 eligible men, 6,092 had BPH indicated either by surgery for an enlarged prostate (n = 3,145) or a high-moderate to severe AUASI score (n = 2,947), and of these 11,616 had incident BPH. A total of 18,373 were considered to be noncases. The baseline characteristics of participants by quintiles of total fruit and vegetable intake in 1986: Health Professionals Follow-Up Study are shown in Table 1. Men who consumed more servings of fruits 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 fruits 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: 0.89; 95% CI: 0.66, 1.19; P for trend = 0.11). No association was present for vegetables and incident BPH (OR: 0.89; 95% CI: 0.68, 1.19; 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 fruits 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, cauliflower, 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.

### TABLE 1

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

<table>
<thead>
<tr>
<th>Quintiles of total fruit and vegetable intake</th>
<th>1 (n = 6493)</th>
<th>2 (n = 6460)</th>
<th>3 (n = 6467)</th>
<th>4 (n = 6385)</th>
<th>5 (n = 6457)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median intake (servings/d)</td>
<td>2.8</td>
<td>4.2</td>
<td>5.5</td>
<td>7.0</td>
<td>9.8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51.7 ± 0.11</td>
<td>52.9 ± 0.11</td>
<td>53.5 ± 0.11</td>
<td>53.7 ± 0.12</td>
<td>54.4 ± 0.12</td>
</tr>
<tr>
<td>Total BPH (%)</td>
<td>24.9</td>
<td>25.9</td>
<td>24.8</td>
<td>26.0</td>
<td>26.0</td>
</tr>
<tr>
<td>Race or ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0.8</td>
<td>0.7</td>
<td>0.8</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Asian</td>
<td>2.1</td>
<td>1.6</td>
<td>1.3</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Southern European</td>
<td>22.8</td>
<td>22.5</td>
<td>23.4</td>
<td>23.6</td>
<td>24.4</td>
</tr>
<tr>
<td>Scandinavian</td>
<td>11.0</td>
<td>10.7</td>
<td>10.2</td>
<td>10.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Other</td>
<td>6.3</td>
<td>5.8</td>
<td>5.9</td>
<td>6.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Other white</td>
<td>57.0</td>
<td>58.7</td>
<td>58.4</td>
<td>58.1</td>
<td>57.1</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>14.4</td>
<td>10.7</td>
<td>8.2</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (g/d)</td>
<td>12.2 ± 0.19</td>
<td>12.0 ± 0.19</td>
<td>11.8 ± 0.19</td>
<td>11.0 ± 0.19</td>
<td>10.6 ± 0.19</td>
</tr>
<tr>
<td>Physical activity (MET h/wk)</td>
<td>14.5 ± 0.30</td>
<td>16.9 ± 0.30</td>
<td>19.2 ± 0.30</td>
<td>21.5 ± 0.31</td>
<td>26.7 ± 0.30</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 ± 0.04</td>
<td>25.5 ± 0.04</td>
<td>25.4 ± 0.04</td>
<td>25.3 ± 0.04</td>
<td>25.3 ± 0.04</td>
</tr>
<tr>
<td>Polyunsaturated fat intake (g/d)</td>
<td>13.2 ± 0.04</td>
<td>13.3 ± 0.04</td>
<td>13.3 ± 0.04</td>
<td>13.3 ± 0.04</td>
<td>13.0 ± 0.04</td>
</tr>
<tr>
<td>Protein intake (g/d)</td>
<td>88.6 ± 0.20</td>
<td>90.7 ± 0.20</td>
<td>92.2 ± 0.20</td>
<td>94.0 ± 0.20</td>
<td>95.3 ± 0.20</td>
</tr>
<tr>
<td>Fiber intake (g/d)</td>
<td>15.6 ± 0.07</td>
<td>18.4 ± 0.07</td>
<td>20.6 ± 0.07</td>
<td>22.7 ± 0.07</td>
<td>27.3 ± 0.07</td>
</tr>
<tr>
<td>Current use of multivitamins (%)</td>
<td>37.0</td>
<td>40.0</td>
<td>41.2</td>
<td>42.8</td>
<td>46.0</td>
</tr>
</tbody>
</table>

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 ± 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.
### TABLE 2

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

<table>
<thead>
<tr>
<th>Quintile of fruit and vegetable intake (servings/d)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quotient of fruit and vegetable intake (servings/d)</th>
<th>Total BPH</th>
<th>Total incident BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
| Prism, tomato sauce, tomato juice, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, oranges, orange juice, grapefruit, grapefruit juice, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, oranges, orange juice, grapefruit, grapefruit juice, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
| Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
| Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
| Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
| Cooked spinach, raw spinach, kale, broccoli, Brussel sprouts, celery, peas, and yellow squash.
| Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
| Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
| Oranges, grapefruit, and other citrus fruits.

### Notes
1. Diagnosis of BPH based on a history of surgery for an enlarged prostate, 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.
2. Pizza, tomatoes, tomato sauce, tomato juice, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, oranges, orange juice, grapefruit, grapefruit juice, strawberries, peaches, oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
3. Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
4. Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
5. Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
6. Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
7. Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
8. Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
9. Carrots, yellow squash, sweet potatoes, cooked vegetables, nuts, seeds, beans, choline, garlic, broccoli, cauliflower, Brussel sprouts, kale, carrot, corn, mixed vegetables, tomatoes, tomatoes, tomato sauce, eggplant, green pepper, red chilli paste, salad dressing, yellow squash, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.
10. Oranges, grapefruit, apples, strawberries, peaches, watermelon, cantaloupe melon, avocado, bananas, other juices, blueberries, and raisins.

### References
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, 1992–20001

<table>
<thead>
<tr>
<th>Micronutrient</th>
<th>Total BPH</th>
<th>P for trend</th>
<th>Incident BPH</th>
<th>Categories of micronutrient intake</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Categories of micronutrient intake</td>
<td></td>
<td></td>
<td>Categories of micronutrient intake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total vitamin C (mg/d)</strong></td>
<td>195</td>
<td>157</td>
<td>227</td>
<td>403</td>
<td>1168</td>
</tr>
<tr>
<td>Cases/noncases (n)</td>
<td>1113/4019</td>
<td>1161/3670</td>
<td>1245/3618</td>
<td>1251/3565</td>
<td>1304/3501</td>
</tr>
<tr>
<td>Multivariable OR2</td>
<td>1.00</td>
<td>0.97</td>
<td>1.03</td>
<td>1.03</td>
<td>1.07</td>
</tr>
<tr>
<td>95% CI</td>
<td>Ref</td>
<td>0.88</td>
<td>1.07</td>
<td>0.93</td>
<td>1.14</td>
</tr>
<tr>
<td>Vitamin C from food (mg/d)</td>
<td>79</td>
<td>121</td>
<td>154</td>
<td>193</td>
<td>265</td>
</tr>
<tr>
<td>Cases/noncases (n)</td>
<td>1188/3890</td>
<td>1231/3826</td>
<td>1215/3628</td>
<td>1277/3531</td>
<td>1181/3498</td>
</tr>
<tr>
<td>Multivariable OR2</td>
<td>1.00</td>
<td>0.94</td>
<td>0.93</td>
<td>0.93</td>
<td>0.97</td>
</tr>
<tr>
<td>95% CI</td>
<td>Ref</td>
<td>0.85</td>
<td>1.03</td>
<td>0.84</td>
<td>1.03</td>
</tr>
</tbody>
</table>

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.

We thank the research team of the Health Professional Follow-Up Study for their expert help.

SR and EAP were responsible for the statistical analysis and interpretation of data and drafted the manuscript. WCW and EG were responsible for the study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, and obtaining the funding for the study. None of the authors had a conflict of interest in connection with this study.

REFERENCES