American Journal of Epidemiology
Vol. 149, No. 2

Alcohol Consumption, Cigarette Smoking, and Risk of Benign Prostatic Hyperplasia

Elizabeth A. Platz,[1,2] Eric B. Rimm,[1-3] Ichiro Kawachi,[3,4] Graham A. Colditz,[1,3] Meir J. Stampfer,[1-3] Walter C. Willett,[1-3] and Edward Giovannucci[2,3]

Alcohol consumption and cigarette smoking were evaluated in relation to development of benign prostatic hyperplasia (BPH) among 29,386 members of the Health Professionals Follow-up Study. Men who were 40–75 years old in 1986 and free of prior BPH surgery, diagnosed cancer at baseline, and prostate cancer at baseline and during follow-up were followed for incidence of BPH surgery from 1986 to 1994. Cases were men who reported BPH surgery between 1986 and 1994 (n = 1,813) or who scored ≥15 points of 35 on seven lower urinary tract symptom questions modified from the American Urological Association symptom index in 1992 and 1994 (n = 1,786); noncases were men who scored ≤7 points (n = 20,840). After controlling for age, race/ethnicity, body mass index, physical activity, and mutually for alcohol intake and smoking, moderate alcohol consumption was inversely related with total BPH (30.1–50 g/day vs. 0: odds ratio (OR) = 0.59, 95% confidence interval (CI) 0.51–0.70; p trend < 0.0001), although the relation was attenuated at high intake (≥50.1 g/day vs. 0: OR = 0.72, 95% CI 0.57–0.90). Current cigarette smoking was positively related to total BPH only among those who smoked 35 or more cigarettes/day (compared with never smokers: OR = 1.45, 95% CI 1.07–1.97). These findings suggest that moderate alcohol consumption and avoidance of smoking may benefit BPH. *Am J Epidemiol* 1999;149:106–15.

alcohol drinking; cohort studies; prostatectomy; prostatic hyperplasia; risk factors; smoking

The incidence of benign prostate hyperplasia (BPH) rises steeply with age (1) and, in the United States, results annually in more than 200,000 transurethral resections of the prostate (2). BPH encompasses both prostate enlargement and obstructive and irritative lower urinary tract symptoms, although little correlation exists between prostate volume and extent of symptoms (3, 4). Prostatic enlargement, particularly of the epithelial component, is likely influenced by the changing androgen and estrogen balance in the aging male. The lower urinary tract symptoms of BPH reflect both the greater prostate mass impinging on the urethra and increased prostatic smooth muscle tone mediated by sympathetic nervous system activity (5).

Factors that alter steroid hormone concentrations might be expected to affect the development or progression of BPH. In experimental settings, acute and repeated alcohol intake transiently reduces circulating testosterone (6–8), and men with alcoholic cirrhosis have diminished testosterone levels (9). Alcohol also increases circulating estrogen concentrations in pre- (10) and postmenopausal (11) women and likely in men (A. Field, Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, personal communication, 1998). Male cigarette smokers generally have higher plasma testosterone concentrations than do nonsmokers (12, 13).

Several epidemiologic studies have examined the relation between alcohol consumption and surgery for BPH, with most (14–18), but not all (19), showing an inverse relation. Studies evaluating the relation between alcohol and clinically detected or symptomatic BPH have not been consistent, with some finding a positive relation (20, 21) and others no relation (19, 22). Numerous studies have evaluated the relation between smoking and either surgery for BPH (14–19, 23–27) or clinically detected or symptomatic BPH (19–22, 25, 27–29) and generally have shown a moderate inverse association with current smoking or no effect of smoking. The majority of these studies, how-

Received for publication December 16, 1997, and accepted for publication June 8, 1998.

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; OR, odds ratio.

[1] Department of Epidemiology, Harvard School of Public Health, Boston, MA.
[2] Department of Nutrition, Harvard School of Public Health, Boston, MA.
[3] Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA.
[4] Department of Health and Social Behavior, Harvard School of Public Health, Boston, MA.
Reprint requests to Dr. Elizabeth A. Platz, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115.

ever, have not examined the spectrum of BPH, including surgery for BPH and symptomatic BPH within the same population, have not evaluated the potential for bias in the alcohol and BPH relation resulting from men with BPH avoiding alcohol and other beverages, and have not considered potential confounding of the smoking and BPH relation by alcohol or physical activity.

Thus, the etiologic roles of alcohol consumption and cigarette smoking in BPH remain to be clarified. We therefore evaluated the relation between BPH, defined either by surgery or by lower urinary tract symptoms, and alcohol consumption and cigarette smoking status among participants in the prospective Health Professionals Follow-up Study, 1986–1994. We considered the frequency and sources of alcohol and current smoking status and lifetime smoking history.

MATERIALS AND METHODS

Study population

Participants were a subset of the Health Professionals Follow-up Study, an ongoing prospective study of heart disease and cancer among 51,529 male dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists. At enrollment in 1986, the men, who were 40–75 years old, completed a semiquantitative food frequency questionnaire and provided information including age, weight, height, alcohol consumption, use of cigarettes, physical activity, and medical history. We collect biennially updated exposure and disease information by mail.

On the 1988, 1990, 1992, and 1994 questionnaires, we asked each participant whether he had undergone surgery for prostatic enlargement. 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 prostatectomy on the subsequent letter, 77 granted permission to review medical records. For 74 of the 77 cases, we were able to obtain medical records, all of which confirmed the surgery. We subsequently considered the participant's self-report of surgery as sufficient.

On the 1992 and 1994 questionnaires, we asked each participant how frequently, by percentage (0, 10, 25, 50, 75, or almost 100 percent of the time), he experienced the following lower urinary tract symptoms (slightly modified from the American Urological Association (30) to fit the constraints of our mailed questionnaire) over the past month: sensation of incomplete bladder emptying, having to urinate again after less than 2 hours, stopping and starting several times during urination, difficulty postponing urinating, weak urinary stream, and having to push or strain to begin urination. We also asked how many times per night the participants had to get up to urinate (0, 1, 2, 3, 4, 5, ≥6). For each BPH symptom, we assigned a score of 0–5 corresponding to the 0–100 percent of the time that a symptom was reported to be experienced. To obtain a total BPH symptom score, we summed the points for each of the six lower urinary tract symptoms and the number of times per night the participant got up to urinate (we assigned 5 for ≥5 times per night). The minimum possible score was 0 and the maximum was 35. On the 1992 questionnaire, we asked men to indicate whether they had an enlarged prostate detected by digital-rectal examination after 1986 and whether they had a rectal examination in the last 2 years.

At baseline, we excluded men with an invalid dietary questionnaire in 1986 (n = 1,595); men who had a history of cancer or surgery for BPH before 1986 (except nonmelanoma skin cancer) or had a history of prostate cancer through 1994 (n = 5,171); and men who died before the 1988 questionnaire was mailed (for opportunity to report BPH surgery; n = 506). This left 44,514 men in the baseline population. Among men without BPH surgery throughout the follow-up period, we excluded those who did not respond to the questions on lower urinary tract symptoms in 1992 (n = 11,542). We further excluded 1,414 men who did not provide complete information on alcohol intake or cigarette smoking, leaving 29,386 men among whom to identify symptomatic cases and noncases.

Classification of BPH cases

Four BPH case definitions were used: 1) surgery for prostatic enlargement (e.g., transurethral resection) between 1986 and December 31, 1993; 2) among those who did not undergo surgery for BPH, symptomatic BPH in 1992 and/or 1994; 3) total BPH, consisting of surgery-defined cases and high-moderate/severe lower urinary tract symptom-defined cases; and 4) prostatic enlargement detected by rectal examination between 1986 and 1992, excluding those who underwent surgery for BPH. Using the cutpoints for symptom severity described by the American Urological Association (30), we further classified symptomatic BPH cases as having 1) high-moderate/severe lower urinary tract symptoms (≥15 of 35 points), 2) severe lower urinary tract symptoms (≥20 of 35 points), 3) severe obstructive symptoms (≥12 of 20 points for sensation of incomplete bladder emptying, stopping and starting several times during urination, weak urinary stream, and had to push or strain to begin urination), or 4) severe irritative symptoms (≥9 of 15 points for having to urinate again after less than 2 hours, finding it

difficult to postpone urinating, number of times per night got up to urinate). Men with 8–14 points of 35 (n = 4,947) were not considered to be cases or noncases.

Noncases were defined as men without BPH surgery whose total lower urinary tract symptom scores in both 1992 and 1994 were 0–7 points or, for those men who did not complete the 1994 lower urinary tract symptom questions, then 0–7 points in 1992. Additionally, in analysis of prostatic enlargement, noncases were those who reported having had a negative rectal examination in the past 2 years, irrespective of symptoms.

Assessment of intake of alcohol and other beverages

In 1986 participants were asked to report their daily frequency of intake of alcohol and other beverages in portion sizes specified on the semiquantitative food frequency questionnaire. This method of assessment of alcohol intake has been shown to have a high degree of validity and is reproducible in a subset from this cohort (31). Quintiles of servings/day of total beverages (excluding alcoholic beverages) and caffeinated beverages (coffee, tea, cola, and low calorie cola) were determined. We multiplied servings of specified portions of alcoholic beverages by grams/serving (beer = 13.2, red and white wine = 10.8, and liquor = 15.1 g/serving) to obtain alcohol intake in grams/day. Participants were also asked to report on how many days of the week they consumed alcohol.

Assessment of cigarette smoking history

In 1986 participants were asked to report whether they had smoked 20 packs of cigarettes or more in their lifetimes and, if yes, whether they currently smoke or had smoked in the past. For current and former smokers, we ascertained the average number of cigarettes/day in each decade of life and calculated pack-years smoked. We asked former smokers when they quit.

Statistical analysis

We calculated age-standardized means and proportions for demographic and lifestyle factors by categories of alcohol consumption or cigarette smoking. We calculated the odds ratio and corresponding 95 percent confidence interval for each endpoint and their associations with alcohol and smoking from age-adjusted and multiple logistic models controlling for age, race/ethnicity, body mass index (weight (kg)/height (m)^2), physical activity (metabolic equivalent (MET)-hours/week), and mutually for alcohol and smoking. In this cohort, body mass index is directly related (32) and physical activity (33) inversely related to risk of BPH. Other potentially confounding factors were evaluated for confounding by inclusion in multiple logistic models. Because any inverse association between alcohol and BPH might reflect the tendency for men with any degree of lower urinary tract symptoms to reduce their alcohol intake as well as beverage intake, we also evaluated the relation between intake of total beverages excluding alcohol and intake of caffeinated beverages in multiple logistic models.

To evaluate trends, the midpoints of each category of alcohol intake or number of cigarettes smoked or pack-years were entered as a single continuous variable in the logistic models. A term for past smokers was also included in the model to evaluate trend for current smoking. To determine if the effect of alcohol intake or smoking varies by age or body mass index, or whether the effect of alcohol varies by levels of smoking and vice versa, we ran stratified analyses. Multiplicative interaction was assessed using models with and without cross-product terms for age, body mass index, alcohol intake, and smoking, and the Wald test was used to test if the coefficient for the cross-product differed from the null. All analyses were conducted using SAS release 6.12 software (SAS Institute, Cary, North Carolina).

RESULTS

Among the 29,386 men with complete data on smoking and alcohol intake, 3,599 men were considered to have BPH. Of these, 1,813 had surgery for BPH between 1986 and 1994, and 1,786 had symptoms but no surgery. Thirty-six percent of the symptomatic men had severe symptoms. An enlarged prostate detected by digital-rectal examination was reported by 2,684 men. Age-standardized characteristics of the men by categories of alcohol intake and smoking status are shown in tables 1 and 2, respectively.

Alcohol and other beverages

In multivariate models controlling for age, race/ethnicity, smoking, body mass index, and physical activity, there was a strong inverse association between moderate alcohol intake (g/day) in 1986 and total BPH (30.1–50 g/day vs. 0: odds ratio (OR) = 0.59, 95 percent confidence interval (CI) 0.51–0.70); surgery for BPH (OR = 0.53, 95 percent CI 0.43–0.66); symptomatic BPH (high-moderate/severe: OR = 0.67, 95 percent CI 0.55–0.82); and enlarged prostate (OR = 0.73, 95 percent CI 0.62–0.87). The inverse association with alcohol intake was stronger for severe symptomatic BPH (OR = 0.57, 95 percent CI 0.40–0.80), particularly for

TABLE 1. Age-standardized* characteristics by alcohol intake, Health Professionals Follow-up Study, 1986–1994

Alcohol intake (g/day)	Total benign prostatic hyperplasia† (%)	Age (years)	Major race/ethnicity (%)						Mean body mass index (kg/m²)
			Southern European	Scandinavian	Other Caucasian	African American	Asian	Other	
0	13.6	53.4	23.9	11.7	57.4	0.9	2.7	3.4	25.6
0.1–5	12.8	52.5	26.2	8.8	59.3	0.9	1.8	3.1	25.5
5.1–10	13.0	52.5	25.3	9.8	60.0	0.8	1.2	3.0	25.3
10.1–15	11.6	52.9	23.5	11.4	60.4	0.6	1.0	3.2	25.3
15.1–30	11.5	53.4	23.9	11.5	60.7	0.6	0.7	2.6	25.3
30.1–50	9.2	54.8	20.3	13.6	62.2	0.4	1.0	2.5	25.4
≥50.1	11.1	54.7	19.6	11.1	65.3	0.3	0.5	3.1	25.6

Alcohol intake (g/day)	Mean physical activity (MET‡-hours/week)	Mean energy intake§ (kcal/day)	Mean % of calories from fat§ (%)	Mean dietary fiber intake¶ (g/day)	Current smoker (%)	Total beverages (servings/day)	Caffeinated beverages (servings/day)	Diabetes (%)	Vasectomy (%)
0	17.3	1,941	32.9	22.3	6.0	6.5	1.9	4.4	20.9
0.1–5	19.1	1,919	32.7	22.0	6.7	6.6	2.0	2.9	22.8
5.1–10	21.2	1,909	33.2	21.3	7.3	6.7	2.1	1.7	24.2
10.1–15	21.6	1,889	33.7	20.8	7.6	6.6	2.1	1.7	26.2
15.1–30	21.7	1,932	34.4	20.1	9.1	6.7	2.3	1.7	26.8
30.1–50	19.6	1,881	35.1	17.6	17.3	7.1	2.6	2.0	28.4
≥50.1	18.5	1,950	34.9	15.3	19.9	7.3	2.8	2.3	29.2

* *All factors except age were directly standardized to the age distribution of the 29,386 participants.*
† Total, either surgery for benign prostatic hyperplasia or high-moderate/severe lower urinary tract symptoms in 1992 or 1994.
‡ MET, metabolic equivalent.
§ Excluding calories from alcohol.
¶ Adjusted for total energy intake.

TABLE 2. Age-standardized* characteristics by cigarette smoking status, Health Professionals Follow-up Study, 1986–1994

Current smoking status	Total benign prostatic hyperplasia† (%)	Age (years)	Major race/ethnicity (%)					
			Southern European	Scandinavian	Other Caucasian	African American	Asian	Other
Never	12.4	51.8	24.2	11.2	59.5	0.7	1.8	2.7
Former	12.3	54.6	24.5	10.3	60.1	0.7	1.3	3.2
Current (cigarettes/day)								
1–14	10.6	53.2	24.0	11.1	58.9	1.0	1.9	3.2
15–34	11.8	53.2	22.1	10.5	60.1	1.0	1.9	4.3
≥35	14.4	54.2	23.0	9.6	62.7	0.6	0.4	3.7

Current smoking status	Mean body mass index (kg/m²)	Mean physical activity (MET‡-hours/week)	Mean energy intake§ (kcal/day)	Mean % of calories from fat§ (%)	Mean dietary fiber intake¶ (g/day)	Mean alcohol intake (g/day)	Diabetes (%)	Vasectomy (%)
Never	25.2	20.3	1,947	32.8	21.7	8.4	2.3	22.3
Former	25.7	20.1	1,889	33.8	20.7	14.5	2.9	26.4
Current (cigarettes/day)								
1–14	25.2	18.1	1,869	34.9	18.9	16.8	2.9	26.8
15–34	25.2	13.0	1,906	36.4	17.2	17.6	2.5	25.7
≥35	25.8	10.6	1,978	37.3	15.5	24.0	4.1	24.0

* All factors except age were directly standardized to the age distribution of the 29,386 participants.
† Total, either surgery for benign prostatic hyperplasia or high-moderate/severe lower urinary tract symptoms in 1992 or 1994.
‡ MET, metabolic equivalent.
§ Excluding calories from alcohol.
¶ Adjusted for total energy intake.

severe obstructive symptoms (OR = 0.50, 95 percent CI 0.36–0.70), than for those with high-moderate/severe symptoms only. Above 50 g/day, the inverse relations between all definitions of BPH and alcohol intake were somewhat attenuated compared with 30.1–50 g/day (table 3). These relations did not vary by age or body

TABLE 3. Relation between alcohol intake and benign prostatic hyperplasia, Health Professionals Follow-up Study, 1986–1994

Alcohol intake in 1986 (g/day)	Benign prostatic hyperplasia			
	No. of cases	Age-adjusted odds ratio	Multivariate odds ratio*	95% confidence interval†
		Total		
0	922	1.00	1.00	
0.1–5	873	0.95	0.94	0.84–1.05
5.1–10	516	0.93	0.93	0.82–1.06
10.1–15	393	0.79	0.80	0.70–0.92
15.1–30	501	0.79	0.80	0.70–0.91
30.1–50	275	0.59	0.59	0.51–0.70
≥50.1	119	0.73	0.72	0.57–0.90
p trend‡		0.0001	0.0001	
		Surgery		
0	481	1.00	1.00	
0.1–5	443	0.95	0.94	0.81–1.10
5.1–10	272	0.97	0.97	0.81–1.15
10.1–15	197	0.78	0.80	0.66–0.96
15.1–30	236	0.72	0.73	0.61–0.87
30.1–50	132	0.52	0.53	0.43–0.66
≥50.1	52	0.60	0.60	0.43–0.82
p trend		0.0001	0.0001	
		High-moderate/severe symptoms		
0	441	1.00	1.00	
0.1–5	430	0.95	0.95	0.82–1.09
5.1–10	244	0.89	0.90	0.76–1.06
10.1–15	196	0.80	0.82	0.68–0.98
15.1–30	265	0.87	0.88	0.75–1.04
30.1–50	143	0.67	0.67	0.55–0.82
≥50.1	67	0.87	0.85	0.64–1.12
p trend		0.0008	0.001	
		Severe symptoms		
0	162	1.00	1.00	
0.1–5	156	0.94	0.93	0.74–1.16
5.1–10	91	0.91	0.91	0.69–1.18
10.1–15	72	0.80	0.81	0.61–1.08
15.1–30	96	0.85	0.85	0.65–1.11
30.1–50	46	0.58	0.57	0.40–0.80
≥50.1	22	0.78	0.72	0.45–1.14
p trend		0.003	0.002	
		Severe obstructive symptoms		
0	187	1.00	1.00	
0.1–5	191	0.98	0.97	0.79–1.20
5.1–10	94	0.80	0.80	0.62–1.03
10.1–15	78	0.75	0.75	0.57–0.98
15.1–30	101	0.78	0.76	0.59–0.98
30.1–50	47	0.54	0.50	0.36–0.70
≥50.1	22	0.70	0.63	0.40–0.99
p trend		0.0001	0.0001	

Table continues

TABLE 3. Continued

Alcohol intake in 1986 (g/day)	Benign prostatic hyperplasia			
	No. of cases	Age-adjusted odds ratio	Multivariate odds ratio*	95% confidence interval†
		Severe irritative symptoms		
0	311	1.00	1.00	
0.1–5	310	0.97	0.97	0.82–1.15
5.1–10	169	0.89	0.90	0.73–1.09
10.1–15	133	0.78	0.80	0.64–0.99
15.1–30	171	0.80	0.81	0.67–0.99
30.1–50	103	0.67	0.67	0.52–0.85
≥50.1	48	0.87	0.82	0.59–1.14
p trend‡		0.001	0.0009	
		Enlarged prostate		
0	604	1.00	1.00	
0.1–5	672	1.01	1.01	0.89–1.14
5.1–10	393	0.98	0.98	0.85–1.13
10.1–15	324	0.90	0.90	0.78–1.05
15.1–30	393	0.91	0.91	0.79–1.05
30.1–50	221	0.72	0.73	0.62–0.87
≥50.1	77	0.72	0.72	0.55–0.94
p trend		0.0001	0.0001	

* Odds ratio adjusted for age (3-year intervals), race/ethnicity (southern European, Scandinavian, African American, Asian, other, other Caucasian), smoking (former, current 1–14, 15–34, ≥35 cigarettes/day, never smoker), body mass index (quintiles), and physical activity (quintiles).

† For multivariate model.

‡ Calculated by entering the midpoint of each category as a single ordinal variable in a logistic model.

mass index. By servings per day, beer and liquor were associated with a decreased risk of total BPH (table 4).

The inverse relations between alcohol and total BPH, surgery for BPH, symptomatic BPH, and enlarged prostate were also observed for the number of days on which alcohol was consumed. The odds ratio of total BPH for men who drank alcohol 7 days per week compared with none was 0.70 (95 percent CI 0.61–0.79, p trend < 0.0001).

In an analysis restricted to men who reported that their alcohol intake had not changed in the 10 years preceding baseline (n = 15,073), the strong inverse relation between alcohol intake and BPH persisted for each definition; in a comparison of 30.1–50 g/day with none, the odds ratio of total BPH was 0.69 (95 percent CI 0.56–0.87, p trend < 0.0001). The relation for alcohol intake reported in 1986 and surgery for BPH was similar for cases that arose during each 2-year follow-up period.

Because an inverse relation between alcohol and BPH might result if men with lower urinary tract symptoms reduced their consumption of alcohol as well as beverage intake, we examined the relation between beverage intake and BPH. In multivariate models controlling for age, race/ethnicity, smoking, body mass index, physical activity, and alcohol intake,

TABLE 4. Relation between alcohol source and total benign prostatic hyperplasia, Health Professionals Follow-up Study, 1986–1994

No. of drinks in 1986	Alcohol source									
	Beer			White wine			Red wine		Liquor	
	No. of cases*	Odds ratio†	95% CI‡	No. of cases	Odds ratio	95% CI	No. of cases	Odds ratio	No. of cases	Odds ratio	95% CI
0–3/month	2,374	1.00		2,514	1.00		2,830	1.00	2,192	1.00	
1/week	375	0.98	0.86–1.12	427	0.98	0.85–1.13	307	1.03	289	0.95	0.82–1.10
2–4/week	428	0.95	0.84–1.08	345	0.80	0.69–0.93	229	1.11	435	0.90	0.79–1.01
5–7/week	247	0.93	0.80–1.08	173	0.97	0.80–1.17	92	1.18	373	0.79	0.69–0.90
>1/day	76	0.59	0.46–0.76	44	0.89	0.63–1.26	25	0.84	261	0.71	0.61–0.83
p trend§			0.0001			0.21		0.85			0.0001

* Cases do not sum to total because of missing report for some alcohol types; indicator variables were included in the logistic regression model for "missings."
† Odds ratio for alcohol type mutually adjusted for all others and for age (3-year intervals), race/ethnicity (southern European, Scandinavian, African American, Asian, other, other Caucasian), smoking (former, current 1–14, 15–34, ≥35 cigarettes/day, never smoker), body mass index (quintiles), and physical activity (quintiles).
‡ CI, confidence interval.
§ Calculated by entering the midpoint of each category as a single ordinal variable in a logistic model.

there was no association between total BPH and number of servings/day of total beverages (excluding alcoholic beverages), caffeinated beverages, coffee (caffeinated), or water consumed. The relation of total beverage consumption with incidence of BPH surgery did not vary among the 2–year periods of follow-up.

Cigarette smoking

In multivariate models compared with never smokers, after controlling for age, race/ethnicity, body mass index, physical activity, and alcohol intake, for all BPH case definitions the elevated risk of BPH was largely confined to those currently smoking ≥35 cigarettes/day (table 5). Among those smoking ≥35 cigarettes/day, the odds ratio for total BPH was 1.45 (95 percent CI 1.07–1.97), which was somewhat greater for symptomatic BPH (OR = 1.57, 95 percent CI 1.07–2.29) than for surgery for BPH (OR = 1.33, 95 percent CI 0.87–2.04). Former smokers did not appear to be at an increased risk compared with never smokers. There was no evidence that the relation of currently smoking ≥35 cigarettes/day with total BPH varied by alcohol consumption (p-interaction = 0.9). Compared with nondrinkers with a smoking status other than currently smoking ≥35 cigarettes/day, for men who currently smoked ≥35 cigarettes/day and who were nondrinkers, the odds ratio was 1.43 (95 percent CI 0.73–2.90); for men who were never or former smokers or who smoked <35 cigarettes/day and consumed alcohol, the odds ratio was 0.71 (95 percent CI 0.57–0.89); and for men who smoked ≥35 cigarettes/day and who consumed alcohol, the odds ratio was 1.08 (95 percent CI 0.74–1.58).

In multivariate models, the relation between lifetime cumulative smoking and total BPH was modest (≥40 pack-years vs. never smokers: OR = 1.16, 95 percent CI 1.03–1.31, p trend = 0.03). However, the risk of symptomatic BPH increased with increasing number of pack-years smoked (≥40 pack-years vs. never smokers: OR = 1.37, 95 percent CI 1.17–1.61, p trend = 0.0002). There was no relation between pack-years smoked and surgery for BPH (≥40 pack-years vs. none: OR = 0.97, 95 percent CI 0.82–1.14, p trend = 0.78).

Mutually adjusting for current smoking and cumulative pack-years, only currently smoking ≥35 cigarettes/day was associated with an increased risk of total BPH (OR = 1.48, 95 percent CI 0.97–2.26). Among current smokers, there was no relation between total BPH and pack-years smoked compared with never smokers. After mutually controlling for pack-years smoked and time since quitting, among former smokers, there was no relation between total BPH and either pack-years or time since quitting, when compared with never smokers.

TABLE 5. Relation between cigarette smoking in 1986 and benign prostatic hyperplasia, Health Professionals Follow-up Study, 1986–1994

Smoking status	Benign prostatic hyperplasia			
	No. of cases	Age-adjusted odds ratio	Multivariate odds ratio*	95% confidence interval†
Total				
Never	1,579	1.00	1.00	
Former	1,734	1.00	1.06	0.97–1.15
Current (cigarettes/day)				
1–14	79	0.84	0.90	0.70–1.16
15–34	144	0.84	0.88	0.73–1.07
≥35	63	1.38	1.45	1.07–1.97
p trend‡		0.97	0.55	
Surgery				
Never	805	1.00	1.00	
Former	871	0.92	0.97	0.87–1.09
Current (cigarettes/day)				
1–14	46	0.96	1.06	0.76–1.48
15–34	62	0.68	0.74	0.56–0.98
≥35	29	1.20	1.33	0.87–2.04
p trend		0.17	0.54	
High-moderate/severe symptoms				
Never	774	1.00	1.00	
Former	863	1.09	1.13	1.02–1.26
Current (cigarettes/day)				
1–14	33	0.70	0.74	0.51–1.07
15–34	82	0.98	1.00	0.79–1.28
≥35	34	1.54	1.57	1.07–2.29
p trend		0.26	0.17	
Severe symptoms				
Never	269	1.00	1.00	
Former	315	1.14	1.20	1.01–1.43
Current (cigarettes/day)				
1–14	14	0.86	0.92	0.53–1.60
15–34	32	1.08	1.15	0.79–1.68
≥35	15	1.96	2.11	1.22–3.65
p trend		0.07	0.03	
Severe obstructive symptoms				
Never	300	1.00	1.00	
Former	351	1.20	1.29	1.10–1.52
Current (cigarettes/day)				
1–14	16	0.89	0.98	0.58–1.63
15–34	34	1.07	1.14	0.79–1.65
≥35	19	2.26	2.42	1.48–3.96
p trend		0.02	0.006	
Severe irritative symptoms				
Never	527	1.00	1.00	
Former	609	1.10	1.15	1.01–1.30
Current (cigarettes/day)				
1–14	20	0.62	0.66	0.42–1.05
15–34	62	1.09	1.14	0.86–1.50
≥35	27	1.80	1.86	1.22–2.84
p trend‡		0.04	0.02	
Enlarged prostate				
Never	1,207	1.00	1.00	
Former	1,283	0.99	1.03	0.94–1.13
Current (cigarettes/day)				
1–14	64	0.85	0.88	0.67–1.17
15–34	97	0.79	0.82	0.65–1.04
≥35	33	0.95	1.00	0.68–1.47
p trend		0.08	0.21	

Table continues

TABLE 5. Continued

* Odds ratio adjusted for age (3-year intervals), race/ethnicity (southern European, Scandinavian, African American, Asian, other, other Caucasian), body mass index (quintiles), physical activity (quintiles), and alcohol intake (quintiles).

† For multivariate model.

‡ Estimated by entering midpoint of each category of current smoking as a continuous variable in the logistic model. A term for past smokers was also included in the model.

DISCUSSION

Among 29,386 members of the Health Professionals Follow-up Study, we observed an inverse relation between alcohol consumption, incident surgery for BPH, prevalent symptomatic BPH, and enlarged prostate. These relations persisted among men who had not changed their alcohol intake in the 10 years preceding the start of follow-up. Currently smoking ≥35 cigarettes/day was associated with an increased risk of BPH symptoms but not enlarged prostate. Exsmokers were not at an elevated risk of BPH compared with never smokers. Our results are generally consistent with the findings of other groups for the relation between BPH and alcohol, but they differ from the majority of studies evaluating the association between BPH and cigarette smoking.

Our analysis was limited to men who underwent surgery for BPH or who answered the questions on lower urinary tract symptoms in 1992 or 1994. Almost a third of the base population did not provide information on lower urinary tract symptoms. These nonrespondents did not, however, differ materially from

respondents on the amount of alcohol consumed per day (11.5 (standard error, 16.5) vs. 11.9 (standard error, 16.0) g/day), the proportion of former smokers (44.1 vs. 43.1 percent), or the proportion currently smoking ≥35 cigarettes/day (1.9 vs. 1.4 percent).

Because we are uncertain of the time of onset of BPH symptoms relative to assessment of baseline alcohol intake, and because alcohol may act as a diuretic, it is possible that our findings resulted from men with early symptoms of BPH reducing or eliminating their intake of alcohol, while men who are symptom free may continue to drink. However, when we restricted the analysis to men who reported not having changed their intake of alcohol in the 10 years preceding baseline, the inverse relation between alcohol intake and symptomatic BPH or surgery for BPH persisted and was of the same magnitude. For surgery for BPH, the association with baseline alcohol intake was constant over each 2–year period of follow-up; if our findings were an artifact of assessment of reduced alcohol intake after the onset of symptoms, we would expect that the odds ratio would have approached the null with subsequent follow-up periods. In addition, we did not observe an inverse relation between intake of other beverages, including water and coffee, and BPH, a pattern that would be suggestive of general avoidance of fluids among men with early lower urinary tract symptoms.

Androgens play a role in the development and maintenance of BPH particularly in the prostatic epithelium, which is supported by androgen receptor expression in prostatic epithelium (34, 35), reduction in hyperplastic prostate mass, primarily of the epithelium, with androgen deprivation (36), and the absence of BPH in men who are castrated before puberty (37) or who are deficient in 5α-reductase-2 (38, 39). Early work on risk factors for BPH suggested that men with alcoholic cirrhosis of the liver, which leads to decreased testosterone concentrations and in some cases increased estrogen concentrations (9), were less likely to have BPH nodules at autopsy, although study methods did not always take into account differing age distributions among cases and controls and findings were not entirely consistent between studies (40, 41). Experimentally, both acute and repeated intake of higher levels of alcohol (e.g., 1.3 g/kg) results in transient plasma testosterone concentration depression (6–8) via decreased production and increased metabolism (8). Indeed, we observed an inverse relation between alcohol intake and enlarged prostate, the component of BPH that is most influenced by androgen balance.

It is unlikely that the apparent benefit of moderate alcohol consumption on BPH is mediated by effects on the sympathetic nervous system. High alcohol intake raises blood pressure, and even acute moderate consumption increases blood pressure, heart rate, and muscle sympathetic nervous system activity (42). The attenuation of the beneficial effect of alcohol on BPH at an intake over 50 g/day perhaps may be due to the elevation in sympathetic nervous system activity, resulting in heightened prostatic smooth muscle tone. Moreover, no attenuation was seen for enlarged prostate, which would not be expected to be affected by the sympathetic nervous system.

Of the published epidemiologic studies (14–22), six have observed an inverse relation of alcohol with BPH, either surgery (14–18) or symptoms (20). Our results are most consistent with the findings of Chyou et al. (17), who reported a relative risk of BPH surgery of 0.64 (95 percent CI 0.52–0.78, p trend < 0.0001) comparing men who drank ≥25 oz (740 ml) of alcohol per month with nondrinkers in a prospective cohort study of 6,581 Japanese-American men living in Hawaii. Sidney et al. (15), in a large cohort study within a health maintenance organization, observed that those who drank ≥3 drinks/day had a statistically significant 25 percent reduced risk of histologic BPH, and an inverse relation was observed by alcohol source, either beer, wine, or spirits. Gann et al. (18), in a nested case-control study of 320 matched pairs, and Morrison (16), in a study of 910 cases and 2,003 controls, both observed inverse relations between surgery for BPH and alcohol, but these relations did not consistently decrease with increasing alcohol intake. In a cross-sectional study of 514 Korean men, Lee et al. (20) noted an inverse association of symptomatic BPH with beer consumption.

A major criticism of the studies that have evaluated the relation between cigarette smoking and surgery for BPH is that smokers may be more likely to have comorbid diseases due to their smoking that select against undergoing prostatectomy for BPH (16), or that smokers may have differing thresholds of seeking relief from bothersome lower urinary tract symptoms. In our analysis, we explored surgery and symptoms separately, as well as the combined endpoint of surgery plus symptoms, which more likely captures the full spectrum of symptomatic BPH and limits the extent of these biases. Indeed, we observed that the association of current smoking and pack-years with BPH risk was greater for symptomatic disease than for prostatectomy, even though bothersome lower urinary tract symptoms underlie both endpoints.

In this large study, we were able to control for many suspected BPH risk factors. The major sources of confounding of the association between BPH and smoking, evident in comparing the age-adjusted and multivariate models, were alcohol and physical activity. Not

controlling for alcohol would result in underestimating, and not controlling for physical activity would result in overstating, the positive relation with smoking ≥35 cigarettes per day. Race/ethnicity and body mass index included in the multivariate models, and dietary fat and fiber intake, and diabetes and vasectomy, other purported risk factors for BPH, did not confound the BPH-smoking relation.

Cigarette smoking affects plasma steroid hormone levels, including higher testosterone concentration (12, 13), and nicotine has been shown to lead to dihydrotestosterone accumulation in the prostate of the dog (43). An elevation in prostate androgens, particularly the more potent dihydrotestosterone, would be compatible with an elevated risk of BPH, most likely manifested as prostatic enlargement, among smokers compared with nonsmokers. To the contrary, Mittler et al. (44) showed that dogs that chronically inhaled cigarette smoke had lower testosterone concentrations and smaller prostates than did unexposed kennel mates. Similarly, some studies reported lower prostate volume among smokers (28, 45), while others found no correlation between prostate size and current smoking (29) or smoking history or intensity (46). We did not observe a relation between smoking and having had an enlarged prostate detected by digital-rectal examination, suggesting that smoking may influence BPH through a different pathway.

An alternative explanation for the positive relation between currently smoking ≥35 cigarettes/day and risk of BPH is that nicotine increases sympathetic nervous system activity (47) and, thus, may affect prostate tone, or other cigarette smoke constituents may irritate the bladder, in both cases worsening the urgency, frequency, and nocturia symptoms. However, we noted that the obstructive symptoms, retention, hesitancy, weak stream, and straining, were more strongly associated with current smoking than were the irritative symptoms, although the difference by symptom type is not statistically significant, possibly because the number of severe obstructive and irritative cases was small at the extremely high end of smoking.

Epidemiologic studies that have evaluated the relation between smoking and BPH have used surgery (14–19, 23–27) or clinically detected or symptomatic BPH (19–22, 25, 27–29) as the outcome. Of these, nine have shown some evidence of a lower risk of BPH among current smokers (14, 15, 19, 21, 24–26, 28, 29), although none have demonstrated a statistically significant relation with intensity or duration of smoking. However, two studies suggested that men who currently smoked ≥1.5 packs/day (28) or ≥1 pack/day (20) had a higher risk of symptomatic BPH compared with nonsmokers, which is consistent with our observation. A combination of selection against smokers undergoing prostatectomy combined with negative confounding by alcohol consumption may account for some portion of the inverse association seen in other studies. From our study, the age-adjusted odds ratio for surgery for BPH among men who currently smoke compared with never smokers is 0.84 and, with further control for alcohol, the odds ratio increases to 0.94. Similarly, among men who currently smoke ≥35 cigarettes/day and compared with nonsmokers, the age-adjusted odds ratio increases from 1.19 to 1.39 after controlling for alcohol intake.

Our findings suggest that moderate alcohol consumption and avoidance of smoking will reduce the risk of BPH and progression to surgery. Whether alcohol and constituents of cigarette smoke produce their effect on BPH through hormonal alterations or other mechanisms remains to be determined.

ACKNOWLEDGMENTS

This work was supported by Public Health Service (PHS) grant DK45779 from the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health (NIH), Department of Health and Human Services (DHHS); by PHS grant CA55075 from the National Cancer Institute, NIH, DHHS; by PHS grant HL35464 from the National Heart, Lung, and Blood Institute, NIH, DHHS; and by Special Institution grant 18 from the American Cancer Society. E. A. P. is supported by a National Service Award (T32 CA 09001–20).

The authors are indebted to Jill Arnold, Elizabeth Frost-Hawes, Mira Kaufman, Kerry Demers, Alvin Wing, and Mildred Wolff for their expert help.

REFERENCES

1. Bostwick D. Pathology of benign prostatic hyperplasia. In: Kirby R, McConnell J, Fitzpatrick J, et al, eds. Textbook of benign prostatic hyperplasia. Oxford: ISIS Medical Media, Ltd, 1996:91–104.
2. Graves EJ, Gillum BS. Detailed diagnoses and procedures, National Hospital Discharge Survey, 1995. Vital Health Stat 13 1997;130:1–146.
3. Girman C, Jacobsen S, Guess H, et al. Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. J Urol 1995;153:1510–15.
4. Simpson R, Fisher W, Lee A, et al. Benign prostatic hyperplasia in an unselected community-based population: a survey of urinary symptoms, bothersomeness and prostatic enlargement. Br J Urol 1996;77:186–91.
5. Caine M. The present role of alpha-adrenergic blockers in the treatment of benign prostatic hypertrophy. J Urol 1986;136:1–4.
6. Ida Y, Tsujimaru S, Nakamaura K, et al. Effects of acute and repeated alcohol ingestion on hypothalamic-pituitary-gonadal

and hypothalamic-pituitary-adrenal functioning in normal males. Drug Alcohol Depend 1992;31:57–64.
7. Mendelson J, Mello N, Ellingboe J. Effects of acute alcohol intake on pituitary-gonadal hormones in normal males. J Pharmacol Exp Ther 1977;202:676–82.
8. Gordon G, Altman K, Southren A, et al. Effect of alcohol (ethanol) administration on sex-hormone metabolism in normal men. N Engl J Med 1976;295:793–7.
9. Green G. Mechanism of hypogonadism in cirrhotic males. Gut 1977;18:843–53.
10. Reichman M, Judd J, Longcope C, et al. Effects of alcohol consumption on plasma and urinary hormone concentration in premenopausal women. J Natl Cancer Inst 1993;85:722–7.
11. Ginsburg E, Mello N, Mendelson J, et al. Effects of alcohol ingestion on estrogens in postmenopausal women. JAMA 1996;276:1747–51.
12. Dai WS, Gutai JP, Kuller LH, et al. Cigarette smoking and serum sex hormones in men. Am J Epidemiol 1988;128:796–805.
13. Field AE, Colditz GA, Willett WC, et al. The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab 1994;79:1310–16.
14. Greenwald P, Kirmss V, Polan A, et al. Cancer of the prostate among men with benign prostatic hyperplasia. J Natl Cancer Inst 1974;53:335–40.
15. Sidney S, Quesenberry C, Sadler M, et al. Risk factors for surgically treated benign prostatic hyperplasia in a prepaid health care plan. Urology 1991;38(suppl):13–19.
16. Morrison A. Risk factors for surgery for prostatic hypertrophy. Am J Epidemiol 1992;135:974–80.
17. Chyou P, Nomura A, Stemmermann G, et al. A prospective study of alcohol, diet, and other lifestyle factors in relation to obstructive uropathy. Prostate 1993;22:253–64.
18. Gann P, Hennekens C, Longcope C, et al. A prospective study of plasma hormone levels, nonhormonal factors, and development of benign prostatic hyperplasia. Prostate 1995;26:40–9.
19. Glynn RJ, Campion EW, Bouchard GR, et al. The development of benign prostatic hyperplasia among volunteers in the Normative Aging Study. Am J Epidemiol 1985;121:78–90.
20. Lee E, Park M, Shin C, et al. A high-risk group for prostatism: a population-based epidemiological study in Korea. Br J Urol 1997;79:736–41.
21. Porta M, Fernandez E, Alonso J, et al. Re: Risk factors for benign prostatic hypertrophy. (Letter). Am J Epidemiol 1994;139:114–15.
22. Araki H, Watanabe H, Mishina T, et al. High-risk group for benign prostatic hypertrophy. Prostate 1983;4:253–64.
23. Seitter W, Barrett-Connor E. Cigarette smoking, obesity, and benign prostatic hypertrophy: a prospective population-based study. Am J Epidemiol 1992;135:500–3.
24. Daniell H. More stage A prostatic cancers, less surgery for benign hypertrophy in smokers. J Urol 1993;149:68–72.
25. Morrison A. Prostatic hypertrophy in greater Boston. J Chronic Dis 1978;31:357–62.
26. Ross R, Bernstein L, Paganini-Hill A, et al. Effects of cigarette smoking on "hormone related" disease in a southern California retirement community. In: Wald N, Baron J, eds. Smoking and hormone related disorders. Oxford: Oxford University Press, 1990:183–96.
27. Armenian H, Lilienfeld A, Diamond E, et al. Epidemiologic characteristics of patients with prostatic neoplasms. Am J Epidemiol 1975;102:47–54.
28. Roberts R, Jacobsen S, Rhodes T, et al. Cigarette smoking and prostatism: a biphasic association? Urology 1994;43:797–801.
29. Roberts R, Tsukamoto T, Kumamoto Y, et al. Association between cigarette smoking and prostatism in a Japanese community. Prostate 1997;30:154–9.
30. Barry M, Fowler F, O'Leary M, et al. The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 1992;148:1549–57.
31. Giovannucci E, Colditz G, Stampfer M, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. Am J Epidemiol 1991;133:810–17.
32. Giovannucci E, Rimm E, Chute C, et al. Obesity and benign prostatic hypertrophy. Am J Epidemiol 1994;140:989–1002.
33. Platz E, Kawachi I, Rimm E, et al. Physical activity and benign prostatic hyperplasia. Arch Intern Med 1998;158:2349–56.
34. Kyprianou N, Davies P. Association states of androgen receptors in nuclei of human benign hypertrophic prostate. Prostate 1986;8:363–80.
35. Frydenberg M, Foo T, Jones A, et al. Benign prostatic hyperplasia-video image analysis and its relationship to androgen and epidermal growth factor receptor expression. J Urol 1991;146:872–6.
36. Peters C, Walsh P. The effect of nafarelin acetate, a luteinizing-hormone-releasing hormone agonist, on benign prostatic hyperplasia. N Engl J Med 1987;317:599–604.
37. Wilson J. The pathogenesis of benign prostatic hyperplasia. Am J Med 1980;68:745–56.
38. Imperato-McGinley J, Guerrero L, Gautier T, et al. Steroid 5–alpha-reductase deficiency in man: an inherited form of male pseudohermaphroditism. Science 1974;186:1213–15.
39. Andersson S, Berman DM, Jenkins EP, et al. Deletion of steroid 5 alpha-reductase 2 gene in male pseudohermaphroditism. Nature 1991;354:159–61.
40. Frea B, Annoscia S, Stanta G, et al. Correlation between liver cirrhosis and benign prostatic hyperplasia: a morphological study. Urol Res 1987;15:311–14.
41. Guess HA. Epidemiology and natural history of benign prostatic hyperplasia. Urol Clin North Am 1995;22:247–61.
42. Grassi G, Somers V, Renk W, et al. Effects of alcohol intake on blood pressure and sympathetic nerve activity in normotensive humans: a preliminary report. J Hypertens 1989;7(suppl): S20–1.
43. Meikle A, Liu X, Taylor G, et al. Nicotine and cotinine effects on 3–alpha-hydroxysteroid dehydrogenase in canine prostate. Life Sci 1988;43:1845–50.
44. Mittler J, Pogach L, Ertel N. Effects of chronic smoking on testosterone metabolism in dogs. J Steroid Biochem 1983;18:759–63.
45. Daniell H. Larger prostatic adenomas in obese men with no associated increase in obstructive uropathy. J Urol 1993;149:315–17.
46. Matzkin H, Cytron S, Simon D. Is there an association between cigarette smoking and gland size in benign prostatic hyperplasia? Prostate 1996;29:42–5.
47. Haass M, Kubler W. Nicotine and sympathetic neurotransmission. Cardiovasc Drugs Ther 1997;10:657–65.