

# Lower Urinary Tract

In many men from the PLCO screening trial authors from the USA identified risk factors for BPH.

Their findings are interesting; Asian Americans were at the lowest risk of clinical BPH, with alcohol and possibly cigarettes related to a lower risk for the condition.

Three further papers investigate various epidemiological aspects of LUTS. I think that it is important for we urologists to have a sound epidemiological knowledge of this subject, to answer the increasingly educated questions of our patients.

A further paper from Barcelona describes the results of a urodynamic study in patients with bladder calculi. The authors found that bladder stones are not necessarily associated with BOO, and that the results of urodynamic testing are not influenced by their presence.

## Risk behaviours and benign prostatic hyperplasia

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### OBJECTIVE

To identify risk factors for benign prostatic hyperplasia (BPH).

### SUBJECTS AND METHODS

Medical history data, including reported urological conditions and treatments, and risk factor data were collected from 34 694 participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a randomized controlled trial designed to evaluate methods for the early detection of cancer.

### RESULTS

Asian men had the lowest risks (odds ratio, 95% confidence interval) for nocturia (0.7, 0.5–0.9), physician-diagnosed BPH (0.3, 0.2–0.5) and transurethral prostatectomy (TURP, 0.2, 0.1–0.6), while risks for Whites and Blacks were similar for most measures of BPH. Greater alcohol intake was associated with decreased nocturia ( $P$  trend = 0.002), BPH ( $P$  trend < 0.001) and TURP ( $P$  trend < 0.001). Current tobacco use was associated with decreased nocturia (0.8, 0.7–0.9), BPH (0.7, 0.6–0.8) and TURP (0.6, 0.4–0.8) but dose-response patterns were weak.

### CONCLUSION

Asian-Americans have the lowest risk of clinical BPH. Alcohol and possibly cigarettes are related to a lower risk for BPH.

### KEYWORDS

smoking, alcohol, BPH, PLCO, risk

### INTRODUCTION

BPH, which manifests as prostatic enlargement, is an extremely common condition resulting in  $\approx$ 200 000 TURPs annually in the USA [1]. Autopsy studies show anatomical or microscopic evidence of BPH in  $\approx$ 20% of men aged 40–50 years, increasing to  $\approx$ 80% prevalence in men aged 70–80 years, but only 25–50% of men with microscopic BPH present with clinical manifestations [2]. Although BPH is common there is no uniform definition of the condition; both pathological and clinical descriptions are used, and volumetric definitions of enlargement also vary [3].

Race, ethnicity, cigarette smoking and alcohol consumption are suggested risk factors for BPH [2,4–11] but interpreting epidemiological

TABLE 1 Distribution of age and race for BPH cases and controls (PLCO trial, 1993–2000), adjusted for age (5-year intervals)

Factors	N	N cases, OR (95% CI)					
		Nocturia		Physician BPH		TURP	
<b>Age group</b>							
55–59	11 303	2 651	1.0	827	1.0	40	1.0
60–64	11 043	3 232	1.7 (1.5–1.9)	1617	2.8 (2.4–3.1)	200	7.6 (4.6–12.6)
65–69	7 968	2 919	2.8 (2.5–3.1)	1646	5.0 (4.3–5.7)	342	22.9 (13.9–37.5)
70–74	4 380	1 954	4.7 (4.2–5.3)	1175	9.2 (7.9–10.7)	391	62.0 (37.7–101.9)
<i>P</i> trend		<0.001		<0.001		<0.001	
<b>Race</b>							
White	30 769	9 141	1.0	4761	1.0	902	1.0
Black	1 415	647	2.0 (1.6–2.5)	206	1.5 (1.1–1.9)	27	1.2 (0.7–2.1)
Hispanic	757	285	1.6 (1.2–2.1)	103	1.3 (0.9–1.9)	19	1.8 (0.9–3.9)
Asian	1 452	539	0.7 (0.5–0.9)	175	0.3 (0.2–0.5)	23	0.2 (0.1–0.6)
Others*	301	144	1.3 (0.8–2.1)	20	0.3 (0.1–0.7)	2	0.3 (0.1–1.4)
Total	34 694	10 756		5265		973	

\*Pacific islander/American Indian/Alaskan Native; centre (Alabama, Colorado, Detroit, MI, Georgetown University, Hawaii, Marshfield, Minnesota, Pittsburgh, PA, Utah, and Washington).

results has been hampered by the lack of uniform definitions of disease. We investigated the association of these factors with BPH among the 34 694 participants who underwent a standardized procedure for prostate-cancer screening in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a randomized controlled trial designed to evaluate methods for the early detection of cancer [12]. Because the PLCO trial included screening with a DRE and PSA, and the collection of historical medical information on BPH, we were also able to relate risk factor patterns to several clinical variables reflecting BPH.

## SUBJECTS AND METHODS

The National Cancer Institute is conducting a major evaluation of selected screening procedures for the early detection of several cancers, the PLCO trial [12]. The trial includes >75 000 participants in the screening arm (about equally men and women aged 55–74 years) and an equal number of unscreened controls. Questionnaire data and biological samples are collected in this population for use in studies on the aetiology of cancer and related diseases, and for evaluating early markers of cancer development [13]. Questionnaires included information on ethnicity, education, marital status, current and past smoking behaviour, alcohol use,

history of cancer and other diseases, use of selected drugs, and history of previous screening examinations.

In the intervention arm, men are screened for prostate cancer by a DRE and PSA, in conjunction with screening for lung cancer (by chest X-ray) and colorectal cancer (by flexible sigmoidoscopy). Between September 1993 and December 2000, 37 789 men were randomized to the screening arm of the PLCO trial at 10 screening centres [14].

## RISK FACTORS

Based on questionnaire data, race was defined for this study as: Non-Hispanic White, Non-Hispanic Black, Hispanic, Asian, or Native American (Pacific Islander, American Indian, Alaskan Native). Tobacco use was defined as never, past or current use of cigarettes, or never use of cigarettes, but use of cigars or pipe. The usual number of cigarettes was categorized as 1–10, 11–20, 21–30 and >30 cigarettes/day. The usual alcohol intake was determined separately for wine, beer and liquor. The frequency of beverage-specific consumption and amount consumed per drink (i.e. small, medium, large portion) were used to derive estimates of 'standard' drinks per week and associated alcohol intake (in grams). Results were summed over beverage types to determine the total alcohol consumption.

## DISEASE CLASSIFICATION

Based on questionnaire information, nocturia was defined as usually urinating more than once at night, during the past year. A history of BPH was based on the questionnaire report of the subject being told by a physician that he had an enlarged prostate or BPH. A history of surgical treatment was based on a questionnaire report of having had a TURP.

## SELECTION OF STUDY SUBJECTS

Among the 37 789 men randomized to the screening arm of the trial, 34 694 (91.8%) subjects were assessed for this report; 3095 men were excluded for the following reasons: (a) history of cancer (except basal-cell skin cancer) before study entry (983, 2.6%); (b) failure to respond to questions on nocturia, history of BPH or TURP (1168, 3.1%); and (c) failure to provide information on race (914, 2.4%). Cases of BPH were defined by a history of nocturia ( $\geq 2$  voids at night), physician-reported BPH, or reported history of TURP. Controls for this study were men who reported none of these conditions and who also had a PSA level of <2 ng/mL at the baseline examination. Subjects with greater PSA values were excluded because elevated PSA and BPH are related.

TABLE 2 Distribution of aspirin use, and the relation between smoking and alcohol consumption, for BPH cases and controls (PLCO trial, 1993–2000), adjusted for age (5-year intervals)

Factors	N or N (%) cases	OR (95% CI)		
		Nocturia	Physician BPH	TURP
Aspirin†		1.2 (1.2–1.3)	1.2 (1.1–1.3)	1.2 (1.0–1.5)
Ibuprofen		1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.1 (0.9–1.3)
<b>Smoking</b>				
Never	10 117	1.0	1.0	1.0
Current	4 050	0.8 (0.7–0.9)	0.7 (0.6–0.8)	0.6 (0.4–0.8)
Former	17 770	1.1 (1.0–1.2)	1.0 (0.9–1.1)	0.9 (0.8–1.1)
Cigar/pipe	2 748	1.1 (1.0–1.3)	1.0 (0.8–1.1)	1.0 (0.7–1.3)
<b>Cigarettes/day‡</b>				
Never	10 117	1.0	1.0	1.0
1–10	619	0.9 (0.7–1.2)	0.7 (0.5–1.0)	0.5 (0.2–1.2)
11–20	1 585	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.7 (0.4–1.1)
21–30	1 045	0.9 (0.7–1.2)	0.7 (0.5–0.9)	0.6 (0.3–1.1)
≥31	795	1.0 (0.8–1.3)	0.8 (0.6–1.1)	0.5 (0.2–1.1)
<i>P</i> trend		0.011	<0.001	0.062
<b>Alcohol (g/day)</b>				
<5	9 655	1.0	1.0	1.0
5–15	2 716	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.7 (0.5–0.9)
>15–30	2 333	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.7 (0.6–0.9)
>30–45	1 117	0.8 (0.7–0.9)	0.7 (0.6–0.9)	0.6 (0.4–0.9)
>45–60	867	0.8 (0.7–1.0)	0.7 (0.6–0.9)	0.6 (0.3–0.9)
≥60	1 084	0.8 (0.7–1.0)	0.6 (0.5–0.7)	0.4 (0.3–0.7)
<i>P</i> trend		0.002	<0.001	<0.001
<b>Types of alcohol</b>				
<b>Beer</b>				
0 or <1/ week	11 534 (66.1)	1.0	1.0	1.0
1/ week	1 649 (9.5)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.8 (0.6–1.2)
2–4/ week	2 273 (13.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.9 (0.7–1.2)
5+ / week	1 983 (11.4)	0.9 (0.8–1.0)	0.7 (0.6–0.8)	0.7 (0.5–0.9)
<i>P</i> trend		0.011	<0.001	0.052
<b>Wine</b>				
0 or <1/ week	14 223 (81.6)	1.0	1.0	1.0
1/ week	978 (5.6)	0.8 (0.7–1.0)	1.0 (0.8–1.2)	1.1 (0.7–1.6)
2–4/ week	1 276 (7.3)	0.9 (0.8–1.1)	1.0 (0.9–1.2)	1.3 (1.0–1.8)
5+ / week	962 (5.5)	0.9 (0.8–1.1)	1.0 (0.8–1.2)	0.6 (0.4–0.9)
<i>P</i> trend		0.086	0.981	0.035
<b>Liquor</b>				
0 or <1/ week	13 184 (75.6)	1.0	1.0	1.0
1/ week	1 035 (5.9)	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.6 (0.4–0.9)
2–4/ week	1 573 (9.0)	0.9 (0.8–1.0)	0.8 (0.7–1.0)	0.7 (0.5–1.0)
5+ / week	1 647 (9.4)	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.6 (0.4–0.8)
<i>P</i> trend		0.010	<0.001	0.002

\*Pacific islander/American Indian/Alaskan Native; centre (Alabama, Colorado, Detroit, MI, Georgetown University, Hawaii, Marshfield, Minnesota, Pittsburgh, PA, Utah, and Washington); smoking (never, current, former, cigar/pipe), and alcohol consumption (<5, 5–14, 15–29, 30–44, 45–59, ≥60 g/day); †regular use of aspirin in last year, regular use of ibuprofen in last year; ‡Cigarettes consumed per day among current smokers.

## STATISTICAL ANALYSIS

Odds ratios (ORs) and corresponding 95% CI were calculated from multiple logistic models,

with statistical control, where indicated, for age groups (55–59, 60–64, 65–69, 70–74 years), race/ethnicity (White, Black, Hispanic, Asian, and \*Pacific Islander, American Indian,

Alaskan Native), screening centre, usual alcohol intake (<5, 5–14, 15–29, 30–44, 45–59, ≥60 g/day), cigarette use (never, current, former, cigar/pipe), regular use of aspirin in last year, and regular use of ibuprofen in last year. Additional adjustments of body mass index (kg/m<sup>2</sup>, by quartiles), marital status (married or living as married, living as single), and education (<8, 8–11, 12, >12 years) made no significant difference. To assess the relation between specific types of alcohol (beer, wine, liquor) and BPH, risks were evaluated for one beverage type while adjusting for the other beverage types. To evaluate trends the midpoints of each category of alcohol intake or numbers of cigarettes smoked per day were entered as a single continuous variable in the logistic model.

## RESULTS

Among the 34 694 men included in the study, nocturia was most commonly reported (31%, 10 756), followed by physician-diagnosed BPH (15%, 5265) and a history of TURP (2.8%, 973). The reported prevalence of nocturia, BPH and TURP increased strongly with increasing age ( $P < 0.001$ ); risks for these conditions were greater by 5-, 9- and 62-fold, respectively, in men aged 70–74 years than in men aged 55–59 years (Table 1). When combined case definitions were used (i.e. nocturia + BPH, nocturia + TURP, BPH + TURP), risks for these conditions were greater by 13-, 55- and 70-fold, respectively, in the oldest group (data not shown). Compared with Whites, Asians reported a lower frequency of all three conditions, and BPH and TURP also tended to be lower in Native Americans and Pacific islanders (Table 1). African-Americans and Hispanics reported 60–100% greater nocturia, with weaker or absent associations for BPH and TURP.

Aspirin and ibuprofen use were associated with modest increases in the risk of nocturia, BPH and TURP (Table 2). Results were similar when the use of either of these NSAIDs was considered (data not shown). Current cigarette use was associated with a lower prevalence of nocturia, BPH and TURP (Table 2) but the pattern of risks did not decrease systematically with increasing number of cigarettes smoked. There were no associations among ex-smokers or exclusive smokers of cigars and pipes. Greater alcohol

intake was negatively associated with BPH, TURP and less strongly with nocturia. The associations for tobacco and alcohol use were each adjusted for the other, indicating independent effects of these factors. The protective effects of alcohol were noted particularly for beer and liquor consumption; there was no clear pattern with wine (Table 2).

## DISCUSSION

This study of 34 694 men in the PLCO trial suggests that a man's age, race/ethnicity, and tobacco and alcohol use are determinants of symptomatic BPH. BPH increased dramatically with age, was lowest among Asians and consumers of alcohol, and tended to be lower among current cigarette smokers.

The three measures of BPH characterize different aspects of this condition and in part may also reflect other disease processes [15], differences in perception of discomfort and access to medical care. Nevertheless, results for these risk factors tend to be relatively consistent across disease definition groups, reinforcing the causal relationship of these risk factors with BPH.

We and others [6] found that race-specific rates for BPH tend to parallel the rates observed for prostate cancer incidence and mortality [16], suggesting that some risk factors for the two conditions may be shared. Steroidal hormones, their metabolism and receptor-based activity are likely components of both conditions, but it is unclear whether specific mechanistic pathways for the two diseases are congruent [17]. In addition to hormonal differentials, stromal/epithelial content may also vary by race/ethnic group; Japanese men are reported to have a greater epithelial to stromal ratio than Caucasians [18]. Asian-Americans may also have diets that are higher in anti-oestrogenic foods thought to inhibit prostate growth [19].

The present results on alcohol are consistent with previous epidemiological reports, generally showing a lower prevalence of BPH among consumers (Table 3) [3,5,8–10,20–27]. Alcohol consumption is also associated in humans with increased serum oestrogen and decreased levels of testosterone and sex hormone-binding globulin [28,29], and in animal studies alcohol suppresses testosterone and depletes testicular gonadotrophin receptors [30,31].

TABLE 3 Previous studies on the relation between smoking, alcohol and BPH

Ref	Design	BPH definition	N, cases	Smoking	Alcohol
[3]	cohort	Clinical BPH	198	II	no
[5]	cohort	BPH surgery	1813	P(heavy)	II
		Moderate/severe symptoms by AUA	1786	no	II
[23]	cohort	BPH surgery	320	no	I
[22]	cohort	BPH surgery			
	(Japanese American)		846	no	II
[10]	cohort	BPH surgery	1027	II	I (heavy)
[8]	case-control	BPH surgery (Greek)	184	no	no
[26]	case-control	BPH surgery	910	I	II
[9]	cross-sectional	IPSS (Austrian)	939	P	P
[24]	cross-sectional	IPSS (Japanese)	N/A	II	~
[21]	cross-sectional	IPSS (Korean)	119	no	II
[25]	cross-sectional	BPH surgery (Turkey)	68	I	~
[20]	cross-sectional	Prostate size by TRUS	195	no	~
[27]	cross-sectional	AUA (Caucasians)	2115	I	~

P, positive association; I, inverse association; II, strong inverse association; no, no association; ~ not addressed.

Previous studies of cigarette use and BPH are less consistent than the studies of alcohol, showing overall tobacco-related associations that were either null [6,9,21–24,32] or protective [4,25–27,33] (Table 3). In the one other large study of tobacco use in which alcohol was adjusted for, the overall effect of tobacco was null, with a suggestion of increased risk in a surgically treated subgroup [6].

Aspirin suppresses prostatic cancer cell proliferation [34] and other NSAIDs may have a similar effect, but the present study showed a modest excess risk for BPH among aspirin and ibuprofen users. A protective effect of NSAIDs for BPH seems unlikely.

A significant limitation of epidemiological approaches to understanding the causes of BPH is the uncertain relationship between disease indicators and underlying pathological processes. By examining several BPH measures and their combinations in the same population, the present study was able to assess the overall consistency of causal associations. However, a limitation to this approach is that all the disease indicators assessed were related to the symptomatic component of BPH; further advances in identifying risk factors for BPH will require studies that consider both morphometric and symptomatic components of this disease.

Although we had available prostate size estimates from the PLCO screening DRE, this information was not used here because of large inter-rater variation in individual estimates, consistent with other reports [35].

In conclusion, our study shows that BPH risk is lowest in Asian-Americans and that moderate alcohol consumption may reduce the BPH risk.

## CONFLICT OF INTEREST

None declared.

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e-mail: hayesr@mail.nih.gov
- Abbreviations:** PLCO, Prostate, Lung, Colorectal, and Ovarian (trial); OR, odds ratio.