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Finasteride Reduces the Risk of Incident Clinical Benign Prostatic Hyperplasia

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Abstract

Background—Despite the high prevalence of clinical benign prostatic hyperplasia (BPH) among older men, there remains a notable absence of studies focused on BPH prevention.

Objective—To determine if finasteride prevents incident clinical BPH in healthy older men.

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Design, setting, and participants—Data for this study are from the Prostate Cancer Prevention Trial. After excluding those with a history of BPH diagnosis or treatment, or an International Prostate Symptom Score (IPSS) ≥ 8 at study entry, 9253 men were available for analysis.

Outcome measurements and statistical analysis—The primary outcome was incident clinical BPH, defined as the initiation of medical treatment, surgery, or sustained, clinically significant urinary symptoms (IPSS >14). Finasteride efficacy was estimated using Cox proportional regression models to generate hazards ratios (HRs).

Results and limitations—Mean length of follow-up was 5.3 yr. The rate of clinical BPH was 19 per 1000 person-years in the placebo arm and 11 per 1000 person-years in the finasteride arm ($p < 0.001$). In a covariate-adjusted model, finasteride reduced the risk of incident clinical BPH by 40% (HR: 0.60; 95% confidence interval, 0.51–0.69; $p < 0.001$). The effect of finasteride on incident clinical BPH was attenuated in men with a body mass index ≥ 30 kg/m² ($p_{\text{interaction}} = 0.04$) but otherwise did not differ significantly by physical activity, age, race, current diabetes, or current smoking. The post hoc nature of the analysis is a potential study limitation.

Conclusions—Finasteride substantially reduces the risk of incident clinical BPH in healthy older men. These results should be considered in formulating recommendations for the use of finasteride to prevent prostate diseases in asymptomatic older men.

Keywords

Prostatic hyperplasia; Finasteride; 5 α -reductase inhibitor; Prevention and control; Prostatic neoplasm

1. Introduction

Benign prostatic hyperplasia (BPH) is a chronic disease that affects as many as 75% of men by age 70 yr, and in the United States, it results in more than \$4 billion in treatment costs annually [1–4]. Lower urinary tract symptoms (LUTS), the most common clinical manifestation of BPH, are independently associated with increased risks of mortality, falls, diminished quality of life, depression, and impaired activities of daily living [5–8].

Despite the high prevalence of BPH among older men, there remains a conspicuous absence of studies focused on BPH prevention. Several lines of evidence support the consideration of finasteride, a 5 α -reductase inhibitor (5-ARI) that blocks the conversion of the sex steroid hormone testosterone to dihydrotestosterone (DHT), for the primary prevention of BPH. First, DHT is a potent androgen that promotes prostate growth and is an essential component of BPH pathogenesis [9]. Second, finasteride significantly decreases serum and intraprostatic DHT concentrations, reduces prostate volume, and is approved for the treatment of clinical BPH [10,11]. Third, studies of asymptomatic older men have reported strong direct associations of serum DHT and DHT metabolite concentrations with BPH risk, suggesting that DHT suppression might delay or prevent clinical BPH onset [12,13]. Finally, clinical trials of prostate cancer prevention and clinical BPH have demonstrated that finasteride decreases the risks of severe BPH sequelae, including acute urinary retention, urinary infection, and noncancer prostate surgery [10,14,15].

The efficacy of finasteride for the primary prevention of clinical BPH has not been investigated. It is not known whether finasteride prevents or delays LUTS onset or other adverse events among men with no or mild symptoms [10,14,15].

We report results from a secondary analysis of the Prostate Cancer Prevention Trial (PCPT). The PCPT, which collected extensive data on LUTS and medical and surgical treatments for BPH, constitutes a robust and unique resource for the evaluation of the efficacy of finasteride for the primary prevention of symptomatic BPH.

2. Materials and methods

2.1. Study population

Data are from the PCPT, a randomized placebo-controlled trial testing whether finasteride reduces prostate cancer risk [14]. Extensive demographic and medical data, including diagnosis of and treatment for BPH, were collected at the baseline, 6-mo, and annual clinic visits and at every 3- and 9-mo phone contact between clinic visits. Baseline body mass index (BMI) was calculated as weight (in kilograms) divided by height (meters squared) and categorized as normal (BMI <25 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese (BMI ≥30 kg/m²). Baseline physical activity was categorized into four levels: sedentary, light, moderate, and very active [16].

2.2. Assessment of benign prostatic hyperplasia symptoms and definition of incident benign prostatic hyperplasia

At the recruitment, baseline, and annual clinic visits, participants completed the International Prostate Symptom Score (IPSS). We excluded participants who at baseline reported BPH medical treatment, BPH surgery, or IPSS ≥8. We defined incident clinical BPH as the first event of report of medical treatment, surgery, or sustained, clinically significant BPH symptoms. Medical treatment included uroselective α-blockers (tamsulosin) and 5-ARIs (finasteride). We defined a report of nonspecific α-blocker therapy (doxazosin, prazosin, or terazosin) as BPH if there was concomitant evidence of BPH by either self-report or by symptoms (one report of an IPSS ≥14 or any two reports of an IPSS ≥12 at any time prior to the report of medication use). Surgical treatments included transurethral prostatectomy, open prostatectomy, urethral balloon dilation, and laser prostatectomy. We defined the onset of clinically significant BPH symptoms as the second report of an IPSS ≥14 [17,18].

2.3. Statistical analysis

We based all analyses on the time between randomization and either BPH incidence or censoring event. For cases defined by treatment (medical or surgical), we defined incidence time as the date of treatment. If treatment date was not reported, we defined incidence time as the midpoint between the prior quarterly visit and the visit when BPH treatment was reported. For cases defined by IPSS, we defined incidence time as the midpoint between the second elevated IPSS and preceding IPSS (most often the previous year) to account for the fact that onset of clinical BPH likely occurred at a point during the time interval between assessments rather than on the exact date of completion of the second IPSS questionnaire.

We censored noncases at the first event of (1) medical treatment with a nonspecific BPH drug outside of the study without evidence of BPH, (2) prostate cancer diagnosis, or (3) the last recorded IPSS (which included patients who had died).

We calculated incidence rates as the annual incidence per 1000 person-years of observation. We used chi-square tests to determine whether the baseline distribution of covariates differed between finasteride and placebo arms. We used Cox proportional hazards models to compare unadjusted and covariate-adjusted hazards ratios (HRs) between finasteride and placebo arms. All models were adjusted for age, race, BMI, physical activity, current smoking status, and diabetes; controlling for additional factors associated with BPH, including family history of prostate cancer, baseline IPSS, and baseline prostate-specific antigen (PSA), did not affect results.

Additional models tested whether the effect of finasteride differed by age, race, BMI, diabetes, physical activity, and smoking status by adding an interaction term to the proportional hazards model. Interaction tests were based on *p* values for the interaction of treatment and a categorical variable for age, BMI, and physical activity or a dummy variable for race, diabetes, and smoking status.

We calculated the number of men needed to treat (NNT) to prevent one additional BPH case as the inverse of the difference in survivorship at time *t* between finasteride and placebo arms for a specified population, using the full model to determine parameter estimates. We calculated the 95% confidence intervals (CIs) for the NNT using the standard errors from the survival distribution. All analyses used SAS v.9.2 software (SAS Institute Inc, Cary, NC, USA).

3. Results

3.1. Study population

Of the 18 882 men enrolled in the PCPT, 9253 (49%) reported a baseline IPSS <8, did not have a history of physician-diagnosed or treated BPH, were not taking BPH medications at baseline, had completed at least 50% of annual IPSS assessments, and were not missing baseline covariate data (Fig. 1).

3.2. Demographic, health, and lifestyle characteristics at baseline

Distributions of age, race, BMI, diabetes prevalence, smoking, and physical activity were similar in the finasteride and placebo arms (Table 1). Participants were mostly white, overweight or obese, and nonsmokers. Mean age was 62.3 yr (standard deviation [SD]: 5.4) and mean BMI was 27.8 kg/m² (SD: 4.1).

3.3. Cumulative incidence and hazards ratios

There were a total of 469 events of incident clinical BPH among 25 237 person-years of follow-up (18.6 per 1000 person-years) in the placebo arm and 263 events among 23 550 person-years of follow-up (11.2 per 1000 person-years) in the finasteride arm (Fig. 2a). In both unadjusted and adjusted proportional hazards models, finasteride decreased the risk of incident clinical BPH by 40% (Table 2). Among men 65 yr of age, there were a total of

208 events of incident clinical BPH among 7907 person-years of follow-up (26.3 per 1000 person-years) in the placebo arm and 108 events among 7238 person-years of follow-up (14.9 per 1000 person-years) in the finasteride arm (Fig. 2b). In these older men, finasteride decreased the risk of incident clinical BPH by 44% (HR: 0.56; 95% CI, 0.44–0.70; $p < 0.001$) after multivariable adjustment.

In additional analyses censoring men who went off treatment, the protective effect of finasteride on clinical BPH risk was numerically larger, decreasing the risk of incident symptomatic BPH by 43% in unadjusted and multivariate adjusted models, respectively (Table 2). The inclusion of men with a baseline IPSS between 8 and 12 only slightly reduced the efficacy of finasteride (HR_{adj}: 0.67; 95% CI, 0.60–0.74; $p < 0.0001$).

3.4. Subgroup analyses

Analyses of finasteride and clinical BPH risk among strata defined by age, race/ethnicity, BMI, diabetes, physical activity, and smoking status demonstrated that the effect of finasteride on incident BPH was attenuated in obese men (HR_{adj}: 0.79; 95% CI, 0.59–1.06, $p_{\text{interaction}} = 0.04$). The effects of finasteride on incident clinical BPH did not significantly differ by age, race, diabetes, physical activity, or current smoking (Table 3). An additional analysis showed no significant associations of baseline PSA with risk of incident clinical BPH (area under the curve = 0.5) or finasteride effect ($p_{\text{interaction}} = 0.06$).

3.5. Number needed to treat

The NNT to prevent one case of clinical BPH over 7 yr was 58 (95% CI, 35–177) for men 55–59 yr of age, 42 (95% CI, 25–123) for men 60–64 yr, and 31 (95% CI, 19–83) for men 65 yr. In addition, for men 65 yr, the 5- and 6-yr NNT values were 54 (95% CI, 32–152) and 40 (95% CI, 25–111), respectively.

4. Discussion

This study is the first experimental analysis to investigate the primary prevention of clinical BPH. Based on a large randomized double-blind clinical trial, the daily use of 5 mg of finasteride reduced the incidence of clinical BPH by 40%. Among men 65 yr of age, finasteride decreased the risk by 44%. The effect of finasteride on incident clinical BPH did not differ significantly by age, race, diabetes, physical activity, or current smoking. Based on 7 yr of treatment, the NNT to prevent one clinical BPH case ranged from 58 for men 55–59 yr of age to 31 for men 65 yr.

These data provide the first clinical evidence that BPH may be prevented and directly inform the ongoing scientific and health policy dialogue with respect to the use of 5-ARIs for the chemoprevention of prostate cancer [19,20]. Two large randomized clinical trials and a systematic review demonstrated a decreased risk of incident prostate cancer with the use of prophylactic 5-ARI therapy [14,15,21]. Although not approved by the US Food and Drug Administration (FDA) for the prevention of prostate cancer (www.drugs.com/pro/finasteride), the American Urological Association (AUA) and the American Society of Clinical Oncology have recommended that some asymptomatic men may benefit from a conversation about the benefits and risks of finasteride for prostate cancer prevention [22].

Based on our findings, finasteride could be considered as a single prophylactic agent for two of the most common and costly diseases of elderly men: BPH and prostate cancer. Such a consideration must be weighed against the potential risks of finasteride treatment including sexual dysfunction, gynecomastia, and a modestly increased incidence of diagnosis of high-grade prostate cancer (for which the FDA has issued an advisory) [14,21,22]. Nevertheless, in light of these data, future scientific, clinical, and health policy deliberations of finasteride prophylaxis should incorporate decreased incidence of clinical BPH as a potential benefit.

Within this context, it is worth noting that the 7-yr NNT values of finasteride for clinical BPH prevention are comparable with published NNT values for aspirin, statins, diuretics, and β -blockers for the primary prevention of cardiovascular disease [23–25]. Because our definition of symptomatic BPH was more conservative than published clinical guidelines, it is possible that our analyses underestimated the magnitude of the risk reductions, overestimated the NNT values, and thus underestimated the potential population benefits of finasteride prophylaxis. It is also reasonable to postulate that combining primary prevention of clinical BPH and prostate cancer into a single outcome (ie, incidence of any prostate disease) would further decrease the NNT values and present a more favorable cost-benefit profile. However, although BPH prevention is an important public health endeavor, its overall morbidity is less than that of myocardial infarction or stroke, and further studies of cost effectiveness are needed with respect to finasteride-mediated prevention of LUTS, BPH medication use, and BPH surgery.

We also observed an apparent diminished efficacy of finasteride for clinical BPH prevention among obese men. This finding is novel and suggests that obesity potentially attenuates the effect of 5-ARIs on BPH. A preponderance of—but not all—published studies supports a positive association of obesity with prevalent and incident BPH as measured by multiple different clinical end points [17,26]. It is possible that the potential mechanisms by which obesity increases the risk of BPH, including inflammatory pathways and alterations in endogenous sex steroid hormone levels, may counteract the beneficial outcomes of finasteride [27]. For example, obesity increases serum estrogen concentrations through peripheral aromatization of serum testosterone, and changes in intraprostatic estrogen might promote prostate growth independently of the DHT pathways through which finasteride exerts its clinical effects [9]. Further identification of men with differential responses to finasteride prophylaxis would potentially increase the utility of using finasteride for clinical BPH prevention by identifying particular groups of men most likely to benefit.

Notable strengths of this study include its use of data from a large randomized clinical trial, a conservative definition of BPH requiring multiple reports of clinically significant LUTS, and a focus on participants who were free of clinically significant BPH symptoms at baseline. One limitation of this study was the post hoc nature of the analysis. Another limitation is the generalizability of the results because the PCPT enrolled relatively healthy, predominantly white men, which potentially diminishes the external validity of the findings. Still, a healthy study population also may strengthen the applicability of the findings to the general population because most community-dwelling older men are relatively healthy compared with less independent age-matched peers. In these analyses the finasteride effect was independent of age and race. Finally, because there are no consensus recommendations

for defining BPH in clinical research, and urinary symptoms may be nonspecific, misclassification of cases may have occurred. Yet misclassification events would likely have been nondifferential with respect to the finasteride and placebo arms and therefore not have biased the results. We also minimized the likelihood of misclassification by using a definition of clinical BPH that was more conservative than those used in prior clinical trials [10], most observational studies [3], and evidence-based practice guidelines such as the AUA [28]. The conservative character of our definition, in fact, might have underestimated the true number of cases in both arms and led to a cumulative incidence less than what might be encountered in clinical practice.

5. Conclusions

In this analysis of data from the PCPT, finasteride substantially reduced the incidence of clinical BPH. These findings should be considered in formulating recommendations for using finasteride to prevent clinical BPH and prostate cancer in older men.

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Take-home message

Finasteride reduces the risk of incident symptomatic benign prostatic hyperplasia by 40% in healthy asymptomatic older men. These data should be considered in formulating recommendations for the use of finasteride to prevent prostate diseases in asymptomatic older men.

Fig. 1.
Composition of analytic cohort: the Prostate Cancer Prevention Trial (PCPT). IPSS = International Prostate Symptom Score.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Finasteride group							
No. at risk	4562	4096	3768	3455	3206	2990	2690
No. BPH events	22	25	41	37	36	50	52
Placebo group							
No. at risk	4691	4391	4099	3767	3457	3201	2859
No. BPH events	24	34	69	91	87	79	85

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Finasteride group							
No. at risk	1391	1248	1175	1077	994	912	813
No. BPH events	11	8	15	14	18	18	24
Placebo group							
No. at risk	1521	1408	1306	1192	1079	977	853
No. BPH events	9	15	31	45	43	33	32

Fig. 2.

(a) Unadjusted cumulative incidence of symptomatic benign prostatic hyperplasia (BPH) comparing finasteride with placebo for the entire analytic cohort ($n = 9253$); (b) unadjusted cumulative incidence of symptomatic benign prostatic hyperplasia in finasteride and placebo arms among men ≥ 65 yr at baseline ($n = 2912$).

Table 1
Incidence of symptomatic benign prostatic hyperplasia by demographic and health-related characteristics and stratified by treatment arm in the Prostate Cancer Prevention Trial

	Placebo (n = 4691)							Finasteride (n = 4562)							p value*
	Mean (SD)	Range	n	%	Events	Person-years	Rate	Mean (SD)	Range	n	%	Events	Person-years	Rate	
Age, yr	62.4 (5.4)	54–85						62.3 (5.4)	54–83						0.17
54–59			1686	36	111	9352	11.9			1691	37	73	8809	8.3	
60–64			1484	32	150	7978	18.8			1480	32	82	7504	10.9	
65+			1521	32	208	7907	26.3			1391	30	108	7238	14.9	
Race/ethnicity															
White			4336	92	425	23 537	18.1			4218	92	240	21 847	11.0	0.96
African American			172	4	20	817	24.5			163	4	13	790	16.5	
Hispanic			112	2	13	565	23.0			115	3	8	581	13.8	
Other			71	2	11	318	34.6			66	1	2	332	6.0	
BMI, kg/m ²	27.7 (4.1)	16.5–54.4						27.8 (4.1)	16.6–57.9						0.69
<25			1162	25	115	6330	19.4			1121	25	59	5912	10.0	
25–29			2454	52	249	13 174	18.9			2324	51	122	11971	10.2	
30+			1075	23	105	5703	18.4			1117	24	82	5667	14.5	
Diabetes															0.42
No			4252	91	427	22 719	18.8			4153	91	230	21 224	10.8	
Yes			439	9	42	2518	16.7			409	9	33	2326	14.2	
Physical activity															0.38
Sedentary			764	16	77	4034	19.1			809	18	57	4129	13.8	
Light			2013	43	195	10 799	18.1			1810	40	102	9205	11.1	
Moderate			1447	31	143	7904	18.1			1430	31	78	7001	10.3	
High			467	10	54	2500	21.6			513	11	26	2424	9.9	
Current smoker															0.97
Yes			397	8	40	2038	19.6			385	8	29	1884	15.4	
No			4294	92	429	23 199	18.5			4177	92	234	21 666	10.8	
Family history of prostate cancer															0.17
Yes			705	15	63	3902	16.1			733	16	42	3940	10.7	

	Placebo (n = 4691)						Finasteride (n = 4562)						p value*		
	Mean (SD)	Range	n	%	Events	Person-years	Rate	Mean (SD)	Range	n	%	Events		Person-years	Rate
No			3986	85	406	21 335	19.0			3829	84	221	19610	11.3	
Baseline PSA	1.2 (0.7)	0.3–4						1.2 (0.7)	0.3–4						0.33
<1.0 ng/ml			2219	47	188	12 152	15.5			2135	47	118	10 986	10.7	ng/mL
1.0–2.0 ng/ml			1764	38	182	9402	19.4			1712	38	97	9042	10.7	
>2.0 ng/ml			708	15	99	3682	26.9			715	16	48	3522	13.6	ng/mL
Baseline IPSS	3.8 (2)	0–7.5	2366	50	120	13 100	9.2	3.8 (2)	0–7.5	2305	51	59	12 201	4.8	0.50
0.0–3.9			1343	29	157	7233	21.7			1318	29	89	6688	13.3	
4.0–5.9			982	21	192	4904	39.2			939	21	115	4660	24.7	
6.0–7.0															
Total			4691	100	469	25 237	18.6			4562	100	263	23 550	11.2	

SD = standard deviation; BMI = body mass index; PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score.

* The p values were calculated using χ^2 tests for continuous variables (age, BMI, baseline IPSS), chi-square tests for nominal categorical variables (race, current smoking status, and family history of prostate cancer), and Cochran-Mantel-Haenszel tests for ordered categorical variables (age, BMI, diabetes, physical activity, baseline IPSS) and compare the mean (continuous variables) or distribution of covariates between finasteride and placebo arm.

Table 2
Model of the association of finasteride with benign prostatic hyperplasia, unadjusted and adjusted for covariates

	Hazard ratio	95% CI	<i>p</i> value
Intent-to-treat analysis			
Unadjusted	0.60	0.52–0.70	<0.0001
Multivariate adjusted*	0.60	0.51–0.69	<0.0001
Noncompliant men censored			
Unadjusted	0.57	0.49–0.67	<0.0001
Multivariate adjusted ^a	0.57	0.48–0.66	<0.0001

CI = confidence interval.

* Adjusted for race, body mass index, diabetes, physical activity, and current smoking status.

Table 3
Effects of finasteride treatment within strata defined by age, race, body mass index, diabetes, physical activity, and current smoking status

	Finasteride	
	Hazard ratio	95% CI
Age, yr		
54–59	0.68	0.51–0.92
60–64	0.58	0.44–0.75
65+	0.56	0.45–0.71
	$p_{\text{interaction}} = 0.34^a$	
Race/ethnicity		
White	0.60	0.52–0.71
African American	0.65	0.32–1.30
Hispanic	0.58	0.24–1.40
Other	0.21	0.05–0.93
	$p_{\text{interaction}} = 0.58^b$	
Body mass index, kg/m ²		
<25	0.51	0.37–0.70
25–29	0.55	0.44–0.69
30	0.79	0.59–1.06
	$p_{\text{interaction}} = 0.04^a$	
Diabetes		
No	0.57	0.49–0.67
Yes	0.82	0.52–1.29
	$p_{\text{interaction}} = 0.16^b$	
Physical activity		
Sedentary	0.75	0.53–1.05
Light	0.60	0.47–0.76
Moderate	0.55	0.42–0.73
High	0.47	0.30–0.75
	$p_{\text{interaction}} = 0.09^a$	
Current smoker		
No	0.58	0.49–0.68
Yes	0.77	0.48–1.25
	$p_{\text{interaction}} = 0.26^b$	

CI = confidence interval.

^aThe p interaction values derived from interaction of treatment and ordered variable for age, body mass index, physical activity, and baseline International Prostate Symptom Score.

^bThe p interaction values derived from interaction of treatment and categorical variable for race, diabetes, and smoking status.