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Original Contribution

Indications For and Use of Nonsteroidal Antiinflammatory Drugs and the Risk of Incident, Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial

Jeannette M. Schenk*, Gregory S. Calip, Catherine M. Tangen, Phyllis Goodman, J. Kellogg Parsons, Ian M. Thompson, and Alan R. Kristal

* Correspondence to Dr. Jeannette M. Schenk, Cancer Prevention Program, Fred Hutchinson Cancer Research Center, P.O. Box 19024, M4-B402, Seattle, WA 98109-1024 (e-mail: jschenk@fhcrc.org).

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The authors conducted a cohort study of nonsteroidal antiinflammatory drug (NSAID) use and risk of symptomatic benign prostatic hyperplasia (BPH), using data from 4,735 men without BPH at baseline in the placebo arm of the Prostate Cancer Prevention Trial (1993–2003). Incident BPH ($n = 471$) was defined as medical or surgical treatment or at least 2 International Prostate Symptom Score (I-PSS) values greater than or equal to 15. Proportional hazards models using time-dependent exposure for NSAID use were employed to estimate covariate-adjusted associations of NSAID-related medical conditions and NSAID use with BPH risk. Arthritis, other inflammation-related musculoskeletal conditions, and headaches were associated with increased BPH risk (hazard ratio (HR) = 1.77 (95% confidence interval (CI): 1.37, 2.29), HR = 1.57 (95% CI: 1.14, 2.17), and HR = 1.40 (95% CI: 1.09, 1.80), respectively). Use of any NSAID, use of aspirin, and use of nonaspirin NSAIDs were associated with significant increases in BPH risk (HR = 1.21 (95% CI: 1.01, 1.46), HR = 1.20 (95% CI: 1.00, 1.45), and HR = 1.34 (95% CI: 1.07, 1.69), respectively). Control for indications for NSAID use, including baseline I-PSS, attenuated the associations slightly, but all became nonsignificant. Among men with no indications for NSAID use, the hazard ratio for any NSAID use was 1.06 (95% CI: 0.82, 1.38). The modest associations of NSAID use with BPH risk in this cohort were probably due to confounding by indication, and NSAID use was not associated with BPH risk.

anti-inflammatory agents, non-steroidal; aspirin; inflammation; prostatic hyperplasia

Abbreviations: BPH, benign prostatic hyperplasia; I-PSS, International Prostate Symptom Score; NSAID, nonsteroidal antiinflammatory drug.

Benign prostatic hyperplasia (BPH) is one of the most common medical conditions among older men, affecting 40%–50% of 50-year-old men and up to 80% of men over age 70 years (1–3). Symptomatic BPH is caused by two components: enlargement of the prostate and heightened tone in prostate smooth muscle, both of which can obstruct urinary flow. Although the pathophysiology of BPH is uncertain, it is likely that chronic inflammation either causes or exacerbates lower urinary tract symptoms. The evidence underlying an etiologic role of inflammation in BPH is based on laboratory studies (4, 5), epidemiologic studies finding associations of biomarkers of chronic systemic inflammation with increased BPH symptoms (6) and incidence (7), and pathologic studies finding associations of prostate tissue inflammation with increased risk of BPH symptom progression and a higher International Prostate Symptom Score (I-PSS) (8). Treatment trials have found reduced BPH symptoms with nonsteroidal antiinflammatory drug (NSAID) monotherapy or improved treatment outcomes in combination with 5α-reductase inhibitors or α-adrenergic antagonists (9, 10). It is therefore reasonable to hypothesize that use of antiinflammatory agents, such as aspirin and other NSAIDs, could reduce BPH incidence.

There have been few epidemiologic studies of NSAID use and BPH. St. Sauver et al. (11) reported that daily use

of NSAIDs was significantly and inversely associated with several measures of BPH risk. In contrast, Meigs et al. (12) reported a nonsignificant 20% increased risk of BPH incidence associated with regular use of aspirin, Kang et al. (2) reported a significant 20% increased prevalence of BPH symptoms associated with both aspirin and ibuprofen, and Verhamme et al. (13) reported a significant 102% increased risk of incident acute urinary retention associated with cyclooxygenase 2 selective NSAIDs but no associations with other NSAIDs or aspirin. Overall, these findings are difficult to synthesize, because the studies used very different and often limited definitions of both BPH and NSAID use. Thus, whether or not NSAIDs are associated with BPH risk is uncertain.

NSAIDs are one of the most commonly used nonprescription drugs in the United States, and knowing whether they increase or decrease BPH risk is of considerable public health importance. Thus, we examined whether use of NSAID medications was associated with BPH risk, using data from the Prostate Cancer Prevention Trial. Our study had several unique strengths, including a definition of incident BPH based on BPH-specific medical treatments or significant, sustained elevations in I-PSS and the use of time-dependent NSAID exposure data in statistical models. We also examined whether the indications for NSAID use were associated with BPH risk and used these results to control for confounding by indication.

MATERIALS AND METHODS

Data were obtained from the Prostate Cancer Prevention Trial (1993–2003), a randomized, placebo-controlled trial testing the use of finasteride for primary prevention of prostate cancer (14). Briefly, 18,880 US men aged 55 years or older with a normal digital rectal examination, a prostate-specific antigen level of 3 ng/mL or less, no history of prostate cancer, and no severe BPH symptoms (defined as an I-PSS (15) of 20 or higher) were randomized to receive finasteride (5 mg/day) or placebo. Participants were followed for up to 7 years. Because finasteride is used for the treatment of BPH, these analyses were restricted to the 9,457 placebo arm participants. Men with BPH at baseline, defined as medical or surgical treatment for BPH ($n = 735$), self-reported medical history of BPH ($n = 1,979$), or an average I-PSS of 8 or more ($n = 1,779$), based on measurements taken at recruitment and randomization (3 months apart), were excluded, leaving 4,964 men eligible for this study.

Data collection

At baseline, data on age, race/ethnicity, physical activity, and history of smoking were collected using self-administered questionnaires, and height and weight were measured by clinic staff. Body mass index was calculated as weight (kg) divided by the square of height (m^2).

Open-ended data on current medication use were collected by interview at baseline. New medication use was ascertained at each follow-up contact (6-month and annual clinic visits and every 3- and 9-month phone contact between clinic visits), during which participants were asked, "Have you started any new medications since we last talked with you?" For these analyses, NSAIDs included carboxylic acids (i.e., aspirin and salicylates), propionic acid derivatives (i.e., ibuprofen), acetic acid derivatives (i.e., sulindac), enolic acid derivatives (i.e., meloxicam), fenamic acid derivatives (i.e., meclofenamate), nonacidic compounds (i.e., nabumetone), and selective cyclooxygenase 2 inhibitors (i.e., celecoxib). Different classes of NSAIDs, specifically aspirin and nonaspirin NSAIDs, were considered separately as well as in combination. Only NSAID use for more than 6 months before diagnosis of BPH was considered exposure.

The presence of medical conditions was recorded as part of the physical examination at the recruitment visit; at each subsequent contact, participants were asked about the diagnosis of several medical conditions, followed by "Have you had other significant medical problems?" Participants were also asked about the condition being treated when reporting medication use. For these analyses, musculoskeletal and other painful conditions commonly associated with NSAID use were classified as "arthritis" (osteoarthritis, rheumatoid arthritis, arthralgia, or joint pain), "general musculoskeletal complaints" (muscular discomfort, pain or cramping, pulled muscles, tendonitis, bursitis, repetitive motion injuries, or carpal tunnel syndrome), "headaches," and "sciatica" (pinched nerve or sciatica). These disorders were grouped into "inflammatory musculoskeletal conditions" (arthritis and other chronic musculoskeletal pain), "noninflammatory musculoskeletal conditions" (general musculoskeletal complaints), and "neurologic conditions" (headaches or sciatica). The date on which a condition was first reported was used to define the start of exposure.

Extensive medical data, including participant-reported physician's diagnosis of and treatment for BPH, were collected at the baseline visit and at each subsequent contact. In addition, at recruitment, baseline, and each annual clinic visit, participants completed the I-PSS questionnaire, a 7-item self-administered questionnaire assessing the frequency of lower urinary tract symptoms (incomplete bladder emptying, frequent urination, intermittency, urgency, weak urinary stream, hesitancy, and nocturia) over the past month. The I-PSS is a validated and reliable quantitative instrument for measuring male urinary symptoms (16), and it is the primary method by which BPH symptoms are assessed in clinical practice (16, 17).

Definition of incident BPH

The definition of incident BPH used in this study was developed a priori, before initiation of analyses, by an expert committee of research urologists, epidemiologists, and statisticians. Incident BPH was defined as the first of either 1) surgical treatment ($n = 36$; 7.6%), 2) medical treatment ($n = 214$; 45.4%), or 3) sustained, clinically significant BPH symptoms ($n = 221$; 47%). Surgical treatment included transuretheral prostatectomy, balloon dilation, and laser or open prostatectomy. Medical treatments included 5-α-reductase inhibitors (finasteride) and uroselective α blockers (tamsulosin); use of nonspecific α blockers (doxazosin, prazosin, terazosin) was also considered as BPH treatment if a physician's diagnosis of BPH or elevated I-

PSS measures (a single I-PSS value ≥15 or 2 I-PSS values ≥12) were reported preceding medication use. Men who reported use of nonspecific α blockers without concomitant evidence of BPH and men who reported a physician's diagnosis of BPH alone in the absence of treatment or symptoms were not included as having BPH events. We defined the onset of clinically significant BPH symptoms as the second report of an I-PSS greater than or equal to 15, consistent with prior publications (18, 19).

Statistical methods

All analyses were based on the time between randomization and the estimated time of incident BPH or a censoring event. For cases defined by treatment (medical or surgical), incidence time was assigned as the date of treatment. If treatment date was not reported, incidence time was assigned as the midpoint between the prior quarterly visit and the visit at which BPH treatment was reported. For cases defined by BPH symptoms, incidence time was assigned as the midpoint between the second elevated I-PSS and the preceding I-PSS (most often the previous year). Noncases were censored at the time of 1) treatment with nonselective α blockers without evidence of BPH; 2) prostate cancer diagnosis; 3) the last recorded I-PSS; or 4) death, with a maximum time under study of 7 years.

All models examined aspirin alone (ignoring nonaspirin NSAIDs), nonaspirin NSAIDs alone (ignoring aspirin), and any NSAIDs, using the date of first reported use to define the start of exposure. When we lacked information on whether and when NSAID use stopped, we assumed that exposure was continuous until the censoring date. Poisson regression models were used to calculate relative risks and 95% confidence intervals for associations between medical conditions and NSAID use. In these analyses, we considered men to have a medical condition if it was reported anytime during the study, because these conditions are mostly of slow onset and are diagnosed only after symptoms become sufficiently severe to come to medical attention; similarly, NSAID users were defined as men using NSAIDs at any time during the study. Cox proportional hazards models with time-dependent exposure were used to calculate the relative hazards of incident BPH associated with medical conditions and NSAID use. All proportional hazards models were adjusted for age (years; continuous), race/ethnicity (Caucasian, African-American, Hispanic, other), and body mass index (continuous). Neither physical activity nor smoking affected results, and therefore neither was included in the final models.

For models of the association between NSAID use and BPH risk, two approaches were used to investigate the potential effect of confounding by indication. Because preexisting medical conditions could affect baseline urinary symptoms and NSAIDs are used to treat urinary symptoms, models were first controlled for baseline I-PSS and then, further, for medical conditions directly. Second, we created a set of dummy variables to capture all 8 possible combinations of medical conditions, and using their interaction with time-dependent NSAID use, we estimated associations within medical conditions.

These analyses were restricted to the 4,735 men with available postrandomization follow-up and covariate data. All analyses were completed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina). A 2-sided *P* value less than 0.05 was considered statistically significant.

RESULTS

Distributions of participant characteristics at baseline, along with their unadjusted associations with BPH risk, are given in Table 1. Participants were mostly white, nonsmokers, and overweight or obese. Almost 60% reported no physical activity or only light physical activity, and half reported I-PSS values of 3 or less. The overall incidence of BPH was 18.6 per 1,000 person-years. BPH incidence was highest in men aged 65 years or more and in men with a baseline I-PSS of 6 or 7.

A total of 2,889 men (61%) reported use of any NSAID during the trial; 42% used NSAIDs at baseline and 19% initiated use postbaseline. For aspirin and nonaspirin NSAIDs, the percentages of users were 40% and 3% at baseline, respectively, and 9% and 23% initiated use postbaseline. Only 11.6% of men reported using both aspirin and nonaspirin NSAIDs at any time during the trial.

All reported medical conditions that are indications for NSAID use were significantly associated with increased NSAID use (Table 2). Both inflammation-related and noninflammation-related musculoskeletal conditions were associated with NSAID use; however, associations were weak or nonsignificant for aspirin and were much stronger and all significant for nonaspirin NSAIDs. Headaches and sciatica were significantly associated with nonaspirin NSAID use only. The counterintuitive observation that the associations of medical conditions with any NSAID use were intermediate in comparison with those for only aspirin use or only nonaspirin NSAID use was due to the different numbers of nonexposed men included in the these analyses: The analyses of aspirin considered nonaspirin NSAID users unexposed and, similarly, the analyses of nonaspirin NSAIDs considered aspirin users unexposed.

Table 3 gives covariate-adjusted associations of medical conditions with the risk of incident BPH. All conditions with a certain or likely inflammatory component, including arthritis, other chronic musculoskeletal pain, and headaches, were associated with a significantly increased risk of BPH. The increased risk ranged from 40% for headaches to 77% for arthritis. Neither noninflammatory musculoskeletal complaints nor sciatica was associated with BPH risk.

Table 4 gives the covariate-adjusted associations of NSAID use with risk of incident BPH. The results reported were controlled for age, race/ethnicity, and body mass index only (model 1), additionally controlled for baseline I-PSS (model 2), and additionally controlled for medical indications for NSAID use (model 3). In model 1, there were modest but statistically significant associations of NSAIDs with increased BPH risk. Use of any NSAID was associated with a 21% increase in risk, and increased risks associated with aspirin and nonaspirin NSAIDs were 20% and 34%, respectively. When baseline I-PSS and then medical indications for NSAID use were added as covariates to the

Table 1. Distributions of Baseline Characteristics and Their Associations With the Incidence of Benign Prostatic Hyperplasia, Prostate Cancer Prevention Trial, 1993–2003

	No. of Subjects	%	No. of BPH Events	Person-Years of Follow-up	Incidence Rate[a]
Total	4,735	100	471	25,365	18.6
Age, years					
55–59	1,706	36	110	9,411	11.7
60–64	1,497	32	150	8,018	18.7
65–69	1,532	32	211	7,936	26.6
Race/ethnicity					
White	4,371	92	427	23,646	18.1
Black	175	4	20	828	24.2
Hispanic	115	2	13	571	22.8
Other	74	2	11	320	34.4
Smoking status[b]					
Current smoker	397	8	41	2,034	20.2
Former/never smoker	4,337	92	430	23,325	18.4
Body mass index[c]					
Normal (<25)	1,177	25	117	6,421	18.2
Overweight (25–29.9)	2,470	52	250	13,214	18.9
Obese (≥30)	1,088	23	104	5,730	18.1
Physical activity[b]					
Sedentary	766	16	76	4,043	18.8
Light activity	2,021	43	195	10,793	18.1
Moderate activity	1,453	31	143	7,906	18.1
Very active	470	10	54	2,517	21.5
Baseline I-PSS					
0.0–3.9	2,385	50	119	13,155	9.0
4.0–5.9	1,349	28	158	7,234	21.0
6.0–7.0	1,001	21	194	4,976	39.0

Abbreviations: BPH, benign prostatic hyperplasia; I-PSS, International Prostate Symptom Score.
[a] Number of cases per 1,000 person-years.
[b] For smoking and physical activity, numbers of participants, BPH events, and person-years do not sum to the totals because of missing data.
[c] Weight (kg)/height $(m)^2$.

statistical models, all associations were slightly attenuated; however, no association remained statistically significant. Results did not differ when models included both aspirin and nonaspirin NSAIDs (data not shown).

An additional set of analyses examined associations of any NSAID use with BPH risk in strata defined by all 8 possible combinations of inflammatory musculoskeletal, noninflammatory musculoskeletal, and neurologic conditions (Table 5). The largest stratum included men who reported no indication for NSAID use, among whom there were no associations of NSAID use with BPH risk. There were elevated risks for BPH associated with aspirin and nonaspirin NSAID use among men reporting only inflammatory musculoskeletal conditions, men reporting only noninflammatory musculoskeletal conditions, and men reporting both; however, not all associations were statistically significant. The numbers of cases in other strata were small (<20), and the hazard ratios, though given in the table, had confidence intervals that were too large to allow interpretation.

DISCUSSION

In this large, prospective study of healthy men, we found no evidence that NSAID use was associated with reduced risk of incident, symptomatic BPH. Contrary to our expectations, NSAID use was associated with a statistically significant 23% increased risk of BPH, with similar associated risks for aspirin (29%) and nonaspirin NSAIDs (34%). However, statistical models that, to the best of our ability, controlled for confounding by medical indications for NSAID use yielded more nuanced results; these models suggested that the modest association of NSAID use with increased BPH risk in the total study sample was not causal but rather the result of confounding by indication.

Table 2. Associations of Medical Conditions With Use of Nonsteroidal Antiinflammatory Drugs ($n = 4,735$), Prostate Cancer Prevention Trial, 1993–2003

Indication for NSAID Use	Men Reporting the Condition		Use of Any NSAID ($n = 2,889$)			Use of Aspirin ($n = 2,344$)				Use of Nonaspirin NSAIDs ($n = 1,243$)		
	No.	%	%[a]	OR[b]	95% CI	%[a]	OR[b]	95% CI	*P* Value	%[a]	OR[b]	95% CI
Inflammation-related chronic musculoskeletal conditions												
Arthritis	655	14	75	2.11*	1.74, 2.54	52	1.09	0.92, 1.29	0.32	53	2.42*	2.21, 2.66
Chronic musculoskeletal pain	430	9	73	1.83*	1.47, 2.29	52	1.09	0.89, 1.33	0.40	47	1.97*	1.76, 2.20
Non-inflammation-related musculoskeletal conditions												
General musculoskeletal complaints	1,112	24	75	2.21*	1.90, 2.57	54	1.23	1.07, 1.40	0.003	49	2.53*	2.31, 2.76
Neurologic conditions												
Headaches	757	16	67	1.39*	1.18, 1.64	52	1.15	0.99, 1.35	0.07	35	1.44*	1.29, 1.61
Pinched nerve/sciatica	124	3	76	1.99*	1.36, 1.85	52	1.05	0.73, 1.50	0.80	52	2.05*	1.72, 2.45

Abbreviations: CI, confidence interval; OR, odds ratio; NSAID, nonsteroidal antiinflammatory drug.
* $P < 0.0001$.
[a] Percentage reporting NSAID use among those men reporting the medical condition.
[b] Adjusted for age.

In pharmacoepidemiology, confounding by indication describes a situation in which the indications for medication use are also associated with the disease under investigation (20, 21). This was most certainly true in this study, because all musculoskeletal conditions, as well as common painful neurologic conditions, were strongly associated with NSAID use. However, of these conditions, only those with a clear or likely inflammatory component were associated with BPH

Table 3. Associations of Medical Conditions With Risk of Benign Prostatic Hyperplasia, Prostate Cancer Prevention Trial, 1993–2003

Indication for NSAID Use	No. of BPH Events	Person-Years of Follow-up	Hazard Ratio for BPH[a]	95% Confidence Interval	*P* Value
Inflammation-related chronic musculoskeletal conditions					
Arthritis					
Yes	72	1,720	1.77	1.37, 2.29	<0.0001
No	399	23,645	1.00		
Chronic musculoskeletal pain					
Yes	42	1,099	1.57	1.14, 2.17	0.006
No	429	24,267	1.00		
Non-inflammation-related musculoskeletal conditions					
General musculoskeletal complaints					
Yes	85	3,510	1.01	0.79, 1.28	0.95
No	386	21,855	1.00		
Neurologic conditions					
Headaches					
Yes	74	2,574	1.40	1.09, 1.80	0.008
No	397	22,792	1.00		
Pinched nerve/sciatica					
Yes	8	357	0.83	0.41, 1.67	0.60
No	463	25,007	1.00		

Abbreviation: BPH, benign prostatic hyperplasia.
[a] Adjusted for age, race/ethnicity, and body mass index.

Table 4. Associations of Use of Nonsteroidal Antiinflammatory Drugs[a] With Risk of Benign Prostatic Hyperplasia, Prostate Cancer Prevention Trial, 1993–2003

	No. of BPH Events	Person-Years of Follow-up	Model of BPH Risk								
			Model 1[b]			Model 2[c]			Model 3[d]		
			HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Any NSAID use											
Yes	275	13,055	1.21	1.01, 1. 46	0.04	1.16	0.97, 1.40	0.11	1.16	0.96, 1.40	0.13
No	196	12,310	1.00			1.00			1.00		
Aspirin use											
Yes	236	11,111	1.20	1.00, 1.45	0.05	1.20	1.00, 1.45	0.05	1.18	0.98, 1.42	0.08
No	235	14,254	1.00			1.00			1.00		
Nonaspirin NSAID use											
Yes	96	3,688	1.34	1.07, 1.69	0.01	1.29	1.02, 1.62	0.03	1.25	0.98, 1.58	0.07
No	375	21,676	1.00			1.00			1.00		

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug.
[a] A first report of medication use within 6 months of a BPH or censoring event was not considered exposure.
[b] Results were adjusted for age, race/ethnicity, and body mass index.
[c] Results were additionally adjusted for baseline International Prostate Symptom Score.
[d] Results were additionally adjusted for inflammation-related and non-inflammation-related musculoskeletal conditions and neurologic conditions.

risk: The covariate-adjusted increases in the hazards of BPH ranged from 40% for headaches to 77% for arthritis. We used two approaches to control for confounding by indication. In the first, we added baseline I-PSS and medical indications as covariates to statistical models. We controlled for baseline I-PSS, which was very strongly associated with BPH incidence, because it reflects preexisting subclinical lower urinary tract symptoms, which could be treated with

Table 5. Associations of Use of Nonsteroidal Antiinflammatory Drugs[a] With Risk of Benign Prostatic Hyperplasia, According to Indications for NSAID Use, Prostate Cancer Prevention Trial, 1993–2003[b]

	Indication for NSAID Use											
	None (*n* = 2,630)			Inflammatory Conditions Only (*n* = 429)			Noninflammatory Conditions Only (*n* = 546)			Neurologic Conditions Only (*n* = 434)		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Total	229			52			46			43		
Any NSAID use	112	1.06	0.82, 1.38	37	1.79	0.98, 3.27	34	1.82	0.94, 3.52	26	1.31	0.71, 2.42
Aspirin use	104	1.10	0.85, 1.43	30	1.73	1.00, 3.01	31	2.10	1.13, 3.89	23	1.34	0.73, 2.44
Nonaspirin NSAID use	17	0.88	0.54, 1.44	17	1.54	0.86, 2.75	16	1.80	0.98, 3.31	7	1.13	0.50, 2.55
	Indication for NSAID Use											
	Inflammatory and Noninflammatory Conditions (*n* = 273)			Noninflammatory and Neurologic Conditions (*n* = 162)			Inflammatory and Neurologic Conditions (*n* = 130)			All Indications (*n* = 131)		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Total	40			16			28			17		
Any NSAID use	26	0.91	0.47, 1.74	9	0.69	0.26, 1.86	18	1.18	0.55, 2.57	13	1.81	0.60, 5.66
Aspirin use	16	0.64	0.24, 1.20	8	0.88	0.33, 2.34	16	1.34	0.63, 2.83	8	1.24	0.48, 3.21
Nonaspirin NSAID use	17	1.63	0.87, 3.07	5	1.16	0.40, 3.35	7	1.07	0.46, 2.54	10	2.20	0. 83, 5.81

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug.
[a] A first report of medication use within 6 months of a BPH or censoring event was not considered exposure.
[b] Results were adjusted for age, race/ethnicity, and body mass index.

NSAIDs. The effects of adding these covariates were very small; for example, the hazard ratio for any NSAID use was reduced from 1.21 ($P = 0.04$) to 1.16 ($P = 0.13$). Nevertheless, all associations of NSAIDs with BPH risk were no longer statistically significant. In the second approach, we stratified findings by the presence or absence of medical conditions. Using this approach, there was no association of NSAID use with BPH risk among men reporting no medical indications. NSAID use was associated with a nonsignificant 67% increased risk of BPH among men with inflammation-related musculoskeletal conditions only, suggesting that use of NSAIDs was reflecting the severity of these conditions and the likelihood that they would be treated with NSAIDs. If data were available on the severity and duration of medical conditions and on the dose of, duration of, and reasons for NSAID use, it would have been possible to better control for confounding by indication. However, using the data we had available, the evidence suggests that NSAID use does not substantially affect BPH risk.

Few previous studies have examined the use of NSAIDs and BPH risk, and each had characteristics that limit interpretation and make comparisons with our study difficult. Meigs et al. (12) reported an odds ratio of 1.2 (95% confidence interval: 0.8, 1.8) for the association of baseline aspirin use with cumulative incidence of BPH, defined as frequent or difficult urination or a physician's determination of an enlarged or swollen prostate, assessed a mean of 9 years postbaseline. However, given the nonspecific definition of BPH and the small number of aspirin users ($n = 18$; 1.3%) in that cohort, that study provides little support either for or against an association between NSAID use and BPH risk. In a cross-sectional study, Kang et al. (2) reported odds ratios of 1.2 (95% confidence interval: 1.1, 1.3) for the associations of regular aspirin and regular ibuprofen use during the previous year with a history of physician diagnosis of BPH; findings were similar using the endpoints of nocturia and history of BPH surgery. In this study, the temporal relations between NSAID use and BPH endpoints were uncertain, and the observed small increase in risk could be due to uncontrolled confounding by indication. Finally, St. Sauver et al. (11) reported significant inverse associations between NSAID use (primarily aspirin) and several indirect and direct measures of BPH in a cohort followed for over 12 years. Both the BPH endpoints and the statistical models used in the St. Sauver study differed substantially from those used in this study. In particular, St. Sauver et al. did not use time-varying exposures in their statistical models; instead, only men who used NSAIDs at baseline were considered exposed (11). As a result, NSAID use that was initiated during the 12 years following baseline was not captured, and all BPH cases occurring among these men would have contributed to the incidence of BPH among men considered unexposed. This could have led to an artifactual inverse association, if either NSAIDs or indications for NSAID use were associated with increased risk in that cohort. The substantial analytical differences between our study and those described above underscore the substantial challenges of investigating NSAID use and BPH risk in observational studies.

This study had several strengths. A principal strength is the careful and comprehensive definition of BPH incidence, which was developed through consensus among a panel of research urologists, epidemiologists, and statisticians. Only men with no clinical history of BPH and I-PSS values indicative of insignificant or no lower urinary tract symptoms at baseline were included, and only surgical treatment, medication use specific to BPH, or repeated I-PSS values of 15 or above qualified as a BPH endpoint. We recognize that there are other causes of lower urinary tract symptoms not related to BPH (22), but these are far less common causes of lower urinary tract symptoms than prostate hyperplasia, and we do not believe that they would substantially affect the interpretation of our BPH endpoint. Further, because men were screened annually by means of prostate-specific antigen testing and digital rectal examination, cancers detected during the study were almost all asymptomatic, and it is unlikely that cancer, rather than BPH, was the cause of elevated I-PSS values. Second, data on NSAID use were collected throughout the study (4 times per year) rather than at baseline alone, so we could capture use initiated postbaseline. Third, we identified and controlled for medical conditions that were associated with both NSAID use and BPH risk, and at least partly controlled for confounding by indication. Fourth, many characteristics of the Prostate Cancer Prevention Trial, including the large sample size and the emphasis on capturing prostate-related disease outcomes, contributed to the quality of data used in these analyses.

We also recognize many limitations of this study that should be considered when interpreting its results. First, we only captured the initiation of NSAID use, and therefore we had to assume that use continued thereafter. This is a reasonable assumption when NSAIDs are used to treat chronic conditions such as arthritis and headaches, but it may not be true for acute conditions such as muscle strain. Second, we did not capture data on NSAID dose and, particularly for aspirin, could not separate users of low-dose aspirin (81 mg) from users of regular aspirin (325 mg). It is likely that most of the men reporting aspirin use at baseline were using low-dose aspirin for heart disease prevention. Third, with the exception of aspirin at baseline, the collection of information on NSAID use and medical conditions was unstructured and subject to omission and error. Fourth, men were censored at the time of prostate cancer diagnosis. However, in a previous study, we reported no association of BPH with prostate cancer risk (23); therefore, this is unlikely to have biased the results. Fifth, there is no accepted, standard definition of incident BPH, and thus our study is not necessarily comparable to those previously published. Finally, there are limits to this study's generalizability. This was a study of older men that excluded a substantial proportion of participants who, at baseline, had already developed BPH or had I-PSS values above 7. In addition, participants in the Prostate Cancer Prevention Trial were healthy and well-educated men who were not representative of the racial, ethnic, social, or health-related characteristics of US men overall.

In conclusion, we found no evidence that use of NSAIDs reduces the risk of incident, symptomatic BPH. We observed a modestly increased risk of BPH among men using NSAIDs that could largely be explained by confounding by indication. We did find evidence that inflammatory musculoskeletal conditions such as arthritis were associated with

increased BPH risk, which is consistent with other evidence suggesting an association of BPH with inflammation. Nevertheless, our findings suggest that use of antiinflammatory drugs has little impact on the development of BPH. Ultimately, only a randomized trial would be able to determine whether NSAIDs could prevent or delay clinical BPH; however, based on the current evidence, we believe that such a trial would not be well motivated.

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Author affiliations: Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, Washington (Jeannette M. Schenk, Gregory S. Calip, Catherine M. Tangen, Phyllis Goodman, Alan R. Kristal); Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington (Gregory S. Calip, Alan R. Kristal); Division of Urologic Oncology, Moores Comprehensive Cancer Center, University of California, San Diego, La Jolla, California (J. Kellogg Parsons); Section for Surgery, San Diego Veterans Affairs Medical Center, La Jolla, California (J. Kellogg Parsons); and Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, Texas (Ian M. Thompson).

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REFERENCES

1. Kirby RS. The natural history of benign prostatic hyperplasia: what have we learned in the last decade? *Urology*. 2000; 56(5 suppl 1):3–6.
2. Kang D, Andriole GL, van de Vooren RC, et al. Risk behaviours and benign prostatic hyperplasia. *BJU Int*. 2004;93(9):1241–1245.
3. Pettaway CA, Lamerato LE, Eaddy MT, et al. Benign prostatic hyperplasia: racial differences in treatment patterns and prostate cancer prevalence. *BJU Int*. 2011; 108(8):1302–1308.
4. Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? *Eur Urol*. 2007;51(5):1202–1216.
5. De Nunzio C, Kramer G, Marberger M, et al. The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. *Eur Urol*. 2011;60(1):106–117.
6. Rohrmann S, De Marzo AM, Smit E, et al. Serum C-reactive protein concentration and lower urinary tract symptoms in older men in the Third National Health and Nutrition Examination Survey (NHANES III). *Prostate*. 2005; 62(1):27–33.
7. Schenk JM, Kristal AR, Neuhouser ML, et al. Biomarkers of systemic inflammation and risk of incident, symptomatic benign prostatic hyperplasia: results from the Prostate Cancer Prevention Trial. *Am J Epidemiol*. 2010;171(5):571–582.
8. Nickel JC, Roehrborn CG, O'Leary MP, et al. The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. *Eur Urol*. 2008;54(6):1379–1384.
9. Di Silverio F, Bosman C, Salvatori M, et al. Combination therapy with rofecoxib and finasteride in the treatment of men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). *Eur Urol*. 2005;47(1):72–78.
10. Ozdemir I, Bozkurt O, Demir O, et al. Combination therapy with doxazosin and tenoxicam for the management of lower urinary tract symptoms. *Urology*. 2009;74(2):431–435.
11. St. Sauver JL, Jacobson DJ, McGree ME, et al. Protective association between nonsteroidal antiinflammatory drug use and measures of benign prostatic hyperplasia. *Am J Epidemiol*. 2006;164(8):760–768.
12. Meigs JB, Mohr B, Barry MJ, et al. Risk factors for clinical benign prostatic hyperplasia in a community-based population of healthy aging men. *J Clin Epidemiol*. 2001;54(9): 935–944.
13. Verhamme KM, Dieleman JP, Van Wijk MA, et al. Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention. *Arch Intern Med*. 2005; 165(13):1547–1551.
14. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349(3):215–224.
15. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol*. 1992;148(5):1549–1557.
16. Barry MJ, Fowler FJ Jr, O'Leary MP, et al. Correlation of the American Urological Association symptom index with self-administered versions of the Madsen-Iversen, Boyarsky and Maine Medical Assessment program symptom indexes. Measurement Committee of the American Urological Association. *J Urol*. 1992;148(5):1558–1563.
17. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. *J Urol*. 2003;170(2):530–547.
18. Kristal AR, Arnold KB, Schenk JM, et al. Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the Prostate Cancer Prevention Trial. *J Urol*. 2007;177(4):1395–1400.
19. Kristal AR, Arnold KB, Schenk JM, et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the Prostate Cancer Prevention Trial. *Am J Epidemiol*. 2008;167(8):925–934.
20. Signorello LB, McLaughlin JK, Lipworth L, et al. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther*. 2002;9(3):199–205.
21. Psaty BM, Koepsell TD, Lin D, et al. Assessment and control for confounding by indication in observational studies. *J Am Geriatr Soc*. 1999;47(6):749–754.
22. Gades NM, Jacobsen DJ, Girman CJ, et al. Prevalence of conditions potentially associated with lower urinary tract symptoms in men. *BJU Int*. 2005;95(4):549–553.
23. Schenk JM, Kristal AR, Arnold KB, et al. Association of symptomatic benign prostatic hyperplasia and prostate cancer: results from the Prostate Cancer Prevention Trial. *Am J Epidemiol*. 2011;173(12):1419–1428.