American Journal of Epidemiology
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Vol. 164, No. 8
DOI: 10.1093/aje/kwj258
Advance Access publication August 11, 2006

Original Contribution

Protective Association between Nonsteroidal Antiinflammatory Drug Use and Measures of Benign Prostatic Hyperplasia

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Received for publication August 11, 2005; accepted for publication March 24, 2006.

In 1990–2002, the authors conducted a population-based cohort study of 2,447 Caucasian men in Olmsted County, Minnesota, to determine whether daily users of nonsteroidal antiinflammatory drugs (NSAIDs) were at lower risk than nondaily NSAID users of developing benign prostatic hyperplasia. Participants completed validated questionnaires during a home visit, including information about daily NSAID use. A random subset of 634 men also participated in a clinical evaluation including transrectal ultrasonography and assessment of serum prostate-specific antigen levels. Examinations and questionnaires were repeated biennially through 2002. Benign prostatic hyperplasia measures included development of moderate/severe urinary symptoms (American Urological Association Symptom Index score >7), low maximum urinary flow rate (<12 ml/second), prostate volume >30 ml, or prostate-specific antigen level >1.4 ng/ml. After adjustment for age, daily NSAID use was inversely associated with onset of moderate/severe urinary symptoms (hazard ratio (HR) = 0.73, 95% confidence interval (CI): 0.64, 0.82), low maximum flow rate (HR = 0.51, 95% CI: 0.43, 0.61), increased prostate volume (HR = 0.53, 95% CI: 0.41, 0.68), and elevated prostate-specific antigen level (HR = 0.52, 95% CI: 0.40, 0.68). In age-specific analyses, inverse associations between NSAID use and urinary measures tended to be stronger in the oldest age groups, although this interaction was statistically significant for only obstructive symptoms and treatment. Results suggest that NSAID use may prevent or delay development of benign prostatic hyperplasia.

anti-inflammatory agents, non-steroidal; cohort studies; data collection; men; prostate-specific antigen; prostatic hyperplasia; questionnaires

Abbreviations: AUASI, American Urological Association Symptom Index; BPH, benign prostatic hyperplasia; CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal antiinflammatory drugs; PSA, prostate-specific antigen.

Benign prostatic hyperplasia (BPH) is one of the most common diseases affecting aging men. In a study of men residing in Olmsted County, Minnesota, 26 percent of those aged 40–49 years experienced moderate to severe lower urinary tract symptoms, and this proportion increased to 45 percent among those aged 70–79 years (1). As the US population ages, the number of affected men is expected to rise substantially, and, by 2030, more than 11 million men are expected to meet American Health Care Policy and Research guidelines for discussing BPH treatment options (2).

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BPH therefore causes substantial morbidity among aging men, accounting for more than $1 billion in direct health care expenditures in 2000 (3).

Pathologically, BPH is defined by cellular proliferation in the prostate gland. As the prostate gland increases in volume, it may impinge on the urethra and limit urinary flow. Increased urinary resistance in the urethra may also cause bladder wall changes that result in bladder detruser dysfunction, which may also be responsible for development of lower urinary tract symptoms (3). However, there is not a perfect correlation between increased prostate size and the severity and bother of lower urinary tract symptoms, because it is possible for men to experience substantial urinary symptoms even without a detectably enlarged prostate gland (4). Because the correlation is not perfect between increase in prostate size and presence of bothersome symptoms, BPH is typically diagnosed clinically by using a constellation of noninvasive measures, including onset of lower urinary tract symptoms, increased prostate size, and decreased urinary flow rates in the absence of other obvious causes (3, 5). Additionally, we have previously found that prostate-specific antigen (PSA) levels may serve as a biochemical marker of prostate volume in the absence of prostate cancer (6, 7).

The biologic mechanisms leading to the development of BPH have not been completely elucidated; however, both chronic and acute inflammation have been frequently noted in prostate biopsy sections and in tissue obtained during prostatic resection for treatment of BPH (8–12). Inflammation may therefore lead to the development of BPH or, alternatively, arise as the result of BPH disease progression. If inflammation plays an important role in the development or worsening of BPH, antiinflammatory agents may offer useful adjunct medical therapies for treatment of this syndrome.

Although study results are not completely consistent, accumulating evidence suggests that use of nonsteroidal antiinflammatory drugs (NSAIDs) may be associated with a decreased risk of prostate cancer (13–16). The precise pathways by which NSAIDs may function to reduce prostate cancer risk have not been elucidated, but NSAIDs may inhibit proliferation and induce apoptosis in hyperplastic cells (17). A similar mechanism of reduced proliferation and increased apoptosis might therefore also decrease the development of BPH. Few data are available, however, examining the association between NSAID use and BPH. Meigs et al. (18) found no association between aspirin use and subsequent positive responses on questions related to BPH among men participating in the Massachusetts Male Aging Study. Kang et al. (19) found a 10–20 percent increased odds of nocturia, physician-diagnosed BPH, or transurethral prostatectomy among men using aspirin or ibuprofen and participating in the Prostate, Lung, Colorectal, and Ovarian screening trial. These studies, however, were limited by relatively nonspecific measures of BPH and a lack of incidence data on BPH development.

Given the association between BPH and inflammation, studies suggesting a beneficial effect of NSAID use on prostate cancer, and the paucity of data related to NSAID use and BPH, we examined the question of whether NSAID users would be at a lower risk than non-NSAID users of developing BPH in a population-based cohort of aging men.

MATERIALS AND METHODS

Study population

Our study population consisted of men enrolled in the Olmsted County Study of Urinary Symptoms and Health Status among Men. This long-term cohort study of men residing in Olmsted County, Minnesota, is one of the most comprehensive studies of urinary health to date in an unselected population (5). Details of the study are available in previous publications (20, 21).

Briefly, the cohort was assembled by identifying a stratified random sample of all male Olmsted County residents 40–79 years of age on January 1, 1990, using the resources of the Rochester Epidemiology Project (22). Men with a previous history of prostatectomy, prostate cancer, or other urologic conditions (bladder cancer or surgery, other bladder disorders, or urethral surgery or strictures) were excluded, leaving 3,874 eligible men. Of these men, 2,115 (55 percent) agreed to participate in an in-home interview, which included verbal questions about family history of urologic disease and medication use and measurement of peak urinary flow rates with a portable urometer. Participants also completed a self-administered questionnaire regarding lower urinary tract symptom severity (a modification of the American Urological Association Symptom Index (AUASI)). The AUASI has been previously validated for assessing urologic symptom severity, has excellent test-retest reliability, is able to discriminate between men with BPH and controls, and is sensitive to changes in symptom severity (23). An item about the frequency of physician visits (excluding hospitalizations) in the previous year was also included in the baseline questionnaires.

A random sample of men who participated in the in-home portion of the study were also invited to participate in a detailed clinical examination including determination of PSA levels, a digital rectal examination, and a transrectal sonographic examination of the prostate; 475 (88 percent) of the 537 men who were contacted participated in this portion of the study. For this study, transrectal sonographic measures of prostate volume were used in all analyses reported. All measures were taken by a single technician throughout the study period, and coefficients of variation for this procedure were $\leq$5 percent.

Examinations and questionnaires were repeated biennially through 2002. In addition, to replace men who either died or dropped out of the study during the follow-up period, additional men were randomly sampled from the community and were invited to participate during the first 4 years of the study. Questionnaire and in-home information was therefore available for 2,447 men, and in-depth information (including PSA level and prostate volume) was available for 634. Finally, all men in the study were passively followed through their community medical records for the occurrence of urologic events.

Ascertainment of NSAID use

At the initial visit, study participants were asked (by structured interview) to report all prescribed and over-the-counter

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medications that were used on a daily basis. The dosage, unit of administration, starting date, and directions for use of each medication were recorded when such information was available. When possible, medication information was recorded directly from the label of the bottle. Medication use was then reassessed by questionnaire during the fifth biennial follow-up period (round 6). Participants who reported daily NSAID use at baseline were considered ''exposed.''

Measures of BPH

Longitudinal BPH measures included development over time of moderate to severe urinary symptoms, as assessed by the AUASI. Scores between 8 and 19 on this index are considered ''moderate,'' whereas scores $\geq$20 are considered ''severe.'' For this study, these two categories were combined in the analyses, and scores $>$7 were considered moderate/severe symptoms (23). Other outcomes examined were time to a low maximum urinary flow rate ($<$12 ml/second), a prostate volume $>$30 ml (enlarged prostate), or a serum PSA level $>$1.4 ng/ml (the upper 25th percentile for this cohort at baseline). These variables have been shown to be modestly correlated, with cross-sectional correlation coefficients ranging from 0.19 for the correlation between prostate volume and AUASI to $-$0.35 for the correlation between AUASI and maximum urinary flow rate (24). In addition, subsets of symptom types were examined, including development of moderate to severe irritative symptoms (Irritative Symptom Index score $>$3) and moderate to severe obstructive symptoms (Obstructive Symptom Index score $>$4). Risk of treatment (surgery or BPH medications, including self-treatment with herbal medications thought to improve prostate health) and acute urinary retention were also examined as endpoints.

Analyses

The men were followed up from the start of the study until the first occurrence of a BPH event (as described above) or the last study visit. The medical records of men added later to the cohort were abstracted back to January 1, 1990. Therefore, the initial date for all men in the analyses was January 1, 1990. Observations for men who developed prostate cancer ($n = 149$) or bladder cancer, had a procedure or surgery to treat an enlarged prostate, began medications for treatment of BPH, died, or were lost to follow-up were censored at the date of these events. Because each BPH measure (moderate/severe symptoms, low maximum flow rate, enlarged prostate, etc.) reflects an aspect of BPH, time to event for each of these variables was first considered separately as an individual outcome and then examined together. Therefore, hazard ratios and 95 percent confidence intervals were first estimated separately for each BPH event by using Cox proportional hazards models. A second analysis was performed in which time to the first of any BPH event, time to the second of at least any two BPH events, and time to the third of any three BPH events were examined as outcomes. Because of the observed strong confounding of NSAID use by age, results were age adjusted by using age as a continuous variable. Results were also adjusted for other potential confounders, including the frequency of baseline physician visits and the presence of diabetes, hypertension, or coronary heart disease.

To assess the potential effect modification of the association between NSAID use and BPH outcomes by age, the results were stratified according to age-decade at the start of the study, and interaction-term p values were calculated. Additionally, hazard ratios and 95 percent confidence intervals were estimated by using Cox proportional hazards models to assess associations of duration, type, and dose of NSAIDs with BPH outcomes.

Finally, to estimate associations of NSAID use with increases or decreases in AUASI scores, maximum flow rate, PSA, and prostate volume over time, a least-squares regression line was estimated for each man by regressing the measurement on time from baseline (25, 26). An estimate of annual change in AUASI, maximum flow rate, PSA, and prostate volume (intercept and slope) was obtained for each man with two or more observations before prostatic treatment or diagnosis of prostate cancer or death/dropout. The distribution of slopes was determined for the entire study cohort and was stratified by age at baseline. Because of skewed distributions, a log transformation was applied to maximum flow rate, PSA level, and prostate volume measurements before analysis. A line plot portraying the average annual change in each BPH measure over time, stratified by baseline 10-year age groups, was generated based on the least-squares slope measurements.

Bivariate and multivariable logistic regression analyses were used to assess the association between NSAID use and a rapid increase in AUASI, a rapid increase in prostate volume, a rapid decline in maximum flow rate, and a rapid increase in PSA level. Cutoffs of the 80th percentiles for a rapid increase (AUASI, volume, and PSA) and the 20th percentile for a rapid decline (maximum urinary flow rate) were examined. Mixed-effect regression models were used to corroborate our estimates of slope. No associations were observed between NSAID use and annual change in these measures (data not shown). All analyses were performed by using SAS version 8.2 software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Overall, 796 (33 percent) of the men in our study reported using NSAIDs daily at the time of study enrollment. Of the men who participated in the in-clinic portion of the study, 201 (32 percent) reported daily NSAID use. The majority of NSAID users (80 percent) took aspirin daily. Of this group, 45 (7 percent) men took a low-dose aspirin. Other NSAIDs used included ibuprofen, naproxen, and diclofenac sodium. NSAID users were older than non-NSAID users: 20 percent of men 40–49 years of age took daily NSAIDs, whereas 57 percent of men aged 70 years or older took an NSAID daily (table 1). After we adjusted for age, NSAID users were also more likely to have visited a physician more than once in the year prior to enrollment (table 1) but less likely to have moderate/severe urinary symptoms, a decreased maximum

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TABLE 1. Characteristics of male NSAID* users and non-NSAID users in Olmsted County, Minnesota, 1990–2002

Characteristic	NSAID use		Non-NSAID use		Chi-square *p* value	Age-adjusted chi-square *p* value
	No.	%	No.	%		
Age (years)						
40–49	229	20.03	914	79.97	<0.0001	
50–59	204	34.00	396	66.00		
60–69	218	48.66	230	51.34		
≥70	145	56.64	111	43.36		
More than one physician visit per year (at baseline)	420	40.31	622	59.69	<0.0001	<0.0001
BPH* medication or herbal medication use	166	40.79	241	59.21	<0.0001	0.10
AUASI* score >7	356	24.02	1,126	75.98	0.83	0.01
Irritative symptom score >3	357	22.01	1,265	77.99	0.12	0.0001
Obstructive symptom score >4	406	25.39	1,193	74.61	0.69	0.01
Nocturia symptom score >1	288	27.51	759	72.49	0.27	0.004
Maximum urinary flow rate <12 ml/second	183	25.07	547	74.93	0.02	<0.0001
Prostate volume >30 ml†	78	22.48	269	77.52	0.21	0.001
PSA* level >1.4 ng/ml†	74	23.95	235	76.05	0.16	0.002
Treatment (surgery or medications)	190	35.45	346	64.55	0.03	0.33
Acute urinary retention	54	42.19	74	57.81	0.01	0.94

* NSAID, nonsteroidal antiinflammatory drug; BPH, benign prostatic hyperplasia; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Data reflect only those 631 men who participated in the in-clinic examinations.

flow rate, increased prostate volume, or elevated PSA level compared with non-NSAID users (table 1).

After adjustment for age, NSAID use was significantly inversely associated with onset of moderate/severe urinary symptoms (hazard ratio (HR) = 0.73, 95 percent confidence interval (CI): 0.64, 0.82), onset of low maximum flow rate (HR = 0.51, 95 percent CI: 0.43, 0.61), increased prostate volume (HR = 0.53, 95 percent CI: 0.41, 0.68), elevated serum PSA level (HR = 0.52, 95 percent CI: 0.40, 0.68), and treatment for BPH (HR = 0.79, 95 percent CI: 0.65, 0.95) (table 2). NSAID use was not associated with development of acute urinary retention. Further adjustment for baseline physician visits, diabetes, hypertension, and coronary heart disease slightly increased the strength of the associations observed in the age-adjusted analyses (table 2).

Age-specific associations between NSAID use and development of urinary outcomes were also examined. A statistically significant interaction between age and NSAID use was observed for the obstructive symptom score ($p = 0.03$) and treatment outcomes ($p = 0.0001$); NSAID use was associated with a decrease in each of these outcomes for men in the oldest age group but not in the youngest age group (table 3).

We next examined associations between NSAID use and time to the first of any urologic outcome, time to the second of at least any two urologic outcomes, and time to the third of at least three urologic outcomes. NSAID use was associated with a decreased risk of developing any urologic endpoint (HR = 0.71, 95 percent CI: 0.63, 0.79), at least two urologic endpoints (HR = 0.69, 95 percent CI: 0.59, 0.80), and at least three urologic endpoints (HR = 0.60, 95 percent CI: 0.47, 0.76), suggesting that the inverse association between NSAID use and BPH outcomes was consistent regardless of how strictly BPH endpoints were defined.

We also examined associations between NSAID use and each of our outcome measures by repeating the analysis using data for a subset of those men who reported NSAID use at baseline and at the round 6 follow-up (approximately 12 years following initial enrollment) to determine whether long-term NSAID use was more strongly associated with urologic outcomes compared with shorter-term NSAID use. Our results were virtually identical to those obtained by examining only baseline daily use of NSAIDs (table 4). Additionally, we examined the subsets of men who reported using only aspirin or using only another NSAID, and we found similar results for both aspirin and nonaspirin users (table 5). Finally, we examined associations of using low-dose aspirin (≤85 mg/day) and using a higher dose (>85 mg/day) with the BPH outcomes. Results were generally not statistically significant for men who took low-dose aspirin (except for AUASI scores); however, point estimates were of a similar magnitude and in the same direction as associations observed for using higher-dose aspirin (table 6).

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TABLE 2. Associations between NSAID* use and risk of urologic outcomes for men in Olmsted County, Minnesota, 1990–2002

BPH* outcome	Non-NSAID use		NSAID use		Age-adjusted hazard ratio	95% CI*	Multivariable-adjusted hazard ratio†	95% CI
	No. of events	No. of person-years	No. of events	No. of person-years				
AUASI* score >7	1,126	10,341	356	3,511	0.73	0.64, 0.82	0.64	0.56, 0.73
Irritative symptom score >3	1,265	9,588	357	3,061	0.72	0.64, 0.81	0.63	0.55, 0.72
Obstructive symptom score >4	1,193	9,561	406	3,410	0.77	0.68, 0.86	0.70	0.61, 0.79
Nocturia symptom score >1	759	12,753	288	4,583	0.72	0.62, 0.82	0.59	0.51, 0.69
Maximum urinary flow rate <12 ml/second	547	6,600	183	2,902	0.51	0.43, 0.61	0.46	0.39, 0.56
Prostate volume >30 ml	269	2,456	78	901	0.53	0.41, 0.68	0.46	0.34, 0.60
PSA* level >1.4 ng/ml	235	2,713	74	1,123	0.52	0.40, 0.68	0.48	0.36, 0.64
Treatment (surgery or medications)	346	15,024	190	7,102	0.79	0.65, 0.95	0.80	0.66, 0.98
Acute urinary retention	74	15,521	54	7,404	0.94	0.65, 1.35	0.93	0.62, 1.37

* NSAID, nonsteroidal antiinflammatory drug; BPH, benign prostatic hyperplasia; CI, confidence interval; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Adjusted for age, baseline number of physician visits, diabetes, hypertension, and coronary heart disease.

Finally, we examined the association between NSAID use and large changes over time in AUASI score, maximum flow rate, prostate volume, and PSA levels. After we adjusted for age and urinary variable status at baseline, NSAID use was associated with a decrease in large changes in prostate volume and maximum flow rate; however, these results were not statistically significant (table 7).

DISCUSSION

These data suggest that daily use of NSAIDs is associated with a decreased risk of developing moderate to severe urologic symptoms, a low maximum urinary flow rate, a high prostate volume, and an elevated PSA level. Specifically, NSAID use was associated with an approximately 35 percent

TABLE 3. Associations between NSAID* use and risk of urologic outcomes, stratified by age, for men in Olmsted County, Minnesota, 1990–2002

BPH* outcome	Results stratified by age (years)†							
	40–49		50–59		60–69		≥70	
	Hazard ratio	95% CI*	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
AUASI* score >7	0.87	0.69, 1.09	0.81	0.64, 1.03	0.61	0.48, 0.77	0.62	0.46, 0.84
Irritative symptom score >3	0.73	0.58, 0.91	0.77	0.60, 0.97	0.69	0.55, 0.86	0.63	0.47, 0.85
Obstructive symptom score >4‡	0.93	0.76, 1.13	0.85	0.68, 1.06	0.68	0.54, 0.85	0.56	0.41, 0.75
Nocturia symptom score >1	0.80	0.59, 1.08	0.82	0.62, 1.08	0.62	0.49, 0.79	0.60	0.44, 0.83
Maximum urinary flow rate <12 ml/second	0.56	0.38, 0.83	0.39	0.26, 0.58	0.62	0.46, 0.84	0.46	0.33, 0.64
Prostate volume >30 ml	0.61	0.37, 1.01	0.54	0.32, 0.92	0.51	0.32, 0.81	0.41	0.23, 0.76
PSA* level >1.4 ng/ml	0.47	0.27, 0.83	0.61	0.36, 1.03	0.49	0.30, 0.80	0.51	0.28, 0.93
Treatment (surgery or medications)‡	1.42	0.97, 2.08	0.87	0.63, 1.21	0.67	0.49, 0.92	0.44	0.28, 0.70
Acute urinary retention	1.53	0.67, 3.49	1.06	0.42, 2.70	0.64	0.34, 1.21	1.01	0.54, 1.89

* NSAID, nonsteroidal antiinflammatory drug; BPH, benign prostatic hyperplasia; CI, confidence interval; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Data in this table are age stratified but also age adjusted (using continuous age) within each age stratum.

‡ Statistically significant ($p < 0.05$) interaction term p value.

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TABLE 4. Hazard ratios and 95% confidence intervals for men who reported NSAID* use only at baseline and those who reported NSAID use at both baseline and round 6 (long-term users of NSAIDs), Olmsted County, Minnesota, 1990–2002

Event	Non-NSAID use		Baseline NSAID use				NSAID use at both baseline and round 6			
	No. of events	No. of person-years	No. of events	No. of person-years	Multivariable adjusted†		No. of events	No. of person-years	Multivariable adjusted†	
					Hazard ratio	95% CI*			Hazard ratio	95% CI
AUASI* score >7	1,126	10,341	195	1,830	0.61	0.52, 0.72	161	1,680	0.64	0.53, 0.77
Irritative symptom score >3	1,265	9,588	203	1,617	0.63	0.54, 0.74	154	1,444	0.61	0.51, 0.73
Obstructive symptom score >4	1,193	9,561	225	1,754	0.69	0.59, 0.80	181	1,656	0.68	0.57, 0.81
Nocturia symptom score >1	759	12,753	156	2,316	0.58	0.48, 0.70	132	2,267	0.57	0.46, 0.70
Maximum urinary flow rate <12 ml/second	547	6,600	116	1,438	0.55	0.44, 0.68	67	1,463	0.35	0.27, 0.46
Prostate volume >30 ml	269	2,456	38	438	0.38	0.26, 0.56	40	463	0.54	0.38, 0.78
PSA* level >1.4 ng/ml	235	2,713	35	493	0.46	0.32, 0.67	39	630	0.51	0.35, 0.73
Treatment (surgery or medications)	346	15,024	102	3,741	0.76	0.60, 0.97	88	3,361	0.82	0.63, 1.07
Acute urinary retention	74	15,521	39	3,756	1.14	0.74, 1.77	15	3,651	0.58	0.32, 1.08

* NSAID, nonsteroidal antiinflammatory drug; CI, confidence interval; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Adjusted for continuous age, baseline number of physician visits, diabetes, hypertension, and coronary heart disease.

reduction in the risk of developing moderate to severe urinary symptoms, after adjusting for potential confounders. The overall decrease in urinary symptoms did not appear to be due to a decrease in any one type of symptom, because NSAIDs were associated with decreases in irritative, obstructive, and nocturia symptom scores. In addition, the men in this study also experienced a reduction of approximately 50 percent in their risk of developing a decreased maximum flow rate, a large prostate volume, and an elevated PSA level, as well as a reduction of 20 percent in treatment for BPH. The decreased risk of developing these urologic outcomes was consistent whether the endpoints were examined singly or were combined, and it remained consistent regardless of whether the NSAID used was aspirin or nonaspirin.

TABLE 5. Hazard ratios and 95% confidence intervals for men who reported aspirin use only at baseline and those who reported nonaspirin NSAID* use and urologic outcomes, Olmsted County, Minnesota, 1990–2002

Event	Non-NSAID use		Aspirin use				Nonaspirin NSAID use			
	No. of events	No. of person-years	No. of events	No. of person-years	Multivariable adjusted†		No. of events	No. of person-years	Multivariable adjusted†	
					Hazard ratio	95% CI*			Hazard ratio	95% CI
AUASI* score >7	1,126	10,341	277	2,778	0.60	0.52, 0.70	79	733	0.72	0.57, 0.91
Irritative symptom score >3	1,265	9,588	281	2,425	0.61	0.52, 0.70	76	636	0.71	0.56, 0.90
Obstructive symptom score >4	1,193	9,561	309	2,648	0.66	0.57, 0.76	97	761	0.75	0.61, 0.94
Nocturia symptom score >1	759	12,753	226	3,626	0.55	0.47, 0.65	62	957	0.69	0.52, 0.90
Maximum urinary flow rate <12 ml/second	547	6,600	145	2,278	0.44	0.36, 0.54	38	624	0.55	0.39, 0.77
Prostate volume >30 ml	269	2,456	69	735	0.47	0.34, 0.63	9	166	0.43	0.22, 0.84
PSA* level >1.4 ng/ml	235	2,713	64	896	0.47	0.35, 0.64	10	227	0.55	0.29, 1.04
Treatment (surgery or medications)	346	15,024	153	5,606	0.83	0.67, 1.02	37	1,496	0.69	0.48, 0.99
Acute urinary retention	74	15,521	43	5,925	0.86	0.56, 1.32	11	1,482	1.02	0.53, 1.99

* NSAID, nonsteroidal antiinflammatory drug; CI, confidence interval; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Adjusted for continuous age, baseline number of physician visits, diabetes, hypertension, and coronary heart disease.

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TABLE 6. Multivariable-adjusted hazard ratios for the associations between different doses of aspirin and BPH* outcomes for men in Olmsted County, Minnesota, 1990–2002

BPH outcome	Non-NSAID* use		≤85 mg/day				>85 mg/day			
	No. of events	No. of person-years	No. of events	No. of person-years	Multivariable adjusted†		No. of events	No. of person-years	Multivariable adjusted†	
					Hazard ratio	95% CI*			Hazard ratio	95% CI
AUASI* score >7	1,126	10,341	98	1,297	0.45	0.28, 0.73	259	2,576	0.72	0.60, 0.86
Irritative symptom score >3	1,265	9,588	86	1,137	0.46	0.27, 0.78	266	2,288	0.79	0.67, 0.93
Obstructive symptom score >4	1,193	9,561	117	1,210	0.53	0.34, 0.84	289	2,466	0.74	0.63, 0.87
Nocturia symptom score >1	759	12,753	79	1,698	0.47	0.28, 0.77	209	3,369	0.70	0.57, 0.85
Maximum urinary flow rate <12 ml/second	547	6,600	56	1,066	0.55	0.31, 1.00	133	2,156	0.52	0.41, 0.66
Prostate volume >30 ml	269	2,456	30	333	0.49	0.18, 1.34	65	687	0.46	0.32, 0.68
PSA* level >1.4 ng/ml	235	2,713	30	455	0.66	0.27, 1.63	59	843	0.49	0.33, 0.72
Treatment (surgery or medications)	346	15,024	61	2,545	0.57	0.29, 1.12	144	5,199	0.89	0.69, 1.15
Acute urinary retention	74	15,521	15	2,673	0.55	0.16, 1.86	40	5,518	1.10	0.67, 1.78

* BPH, benign prostatic hyperplasia; NSAID, nonsteroidal antiinflammatory drug; CI, confidence interval; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Adjusted for continuous age, baseline number of physician visits, diabetes, hypertension, and coronary heart disease.

Overall, men in the older age groups tended to have greater decreased risks of each of the outcomes examined compared with men in the younger age groups, although the interaction between age and NSAID use was significant for only the obstructive symptoms and treatment for BPH outcomes. Older men are more likely in general to have other medical conditions that require daily NSAID treatment (such as arthritis or heart disease). These men may therefore have been exposed to a longer duration of NSAID use compared with the younger men in our study and may thus have received more benefit from this use. In addition, older men are more likely than younger men to develop lower urinary tract problems; therefore, we may have been able to detect associations with increased precision in older men compared with younger men.

Decreased associations between NSAID use and urologic outcomes were consistent whether data for long-term or shorter-term NSAID users were examined. Additionally, aspirin use was generally associated with a larger decrease in risk of outcomes compared with other NSAID use; however, men who used other NSAIDs also experienced a generally decreased risk of urologic outcomes as well.

Limited dose data were available; however, after we examined associations between aspirin dose and outcomes, low-dose aspirin also appeared to be associated with a reduced risk of outcomes, although many of the results were not statistically significant. Because only 45 men reported using low-dose aspirin, the lack of significance is not surprising, but the protective point estimates suggest that even low-dose aspirin may reduce the risk of urologic outcomes.

Although we observed a decreased risk of ever developing a BPH outcome among daily NSAID users, we did not observe statistically significant associations between NSAID use and substantial increases or decreases in specific measures of BPH. However, each of these measures of BPH varied considerably within individuals. In addition, each of these measurements fluctuated substantially within men over time. Therefore, it is possible that associations between NSAID use and changes in these outcomes may exist but may not have been found in these analyses given the considerable noise in each of these measures.

The overall decrease in risk we observed between NSAID use and urologic outcomes is consistent with previous studies that have found an inverse association between NSAID

TABLE 7. Association between NSAID* use and progression of lower urinary tract outcomes for men in Olmsted County, Minnesota, 1990–2002

Variable	Odds ratio†	95% CI*
AUASI* score slope ≤80th percentile	1.00	Reference
AUASI score slope >80th percentile	1.18	0.94, 1.48
PSA* slope ≤80th percentile	1.00	Reference
PSA slope >80th percentile	1.01	0.64, 1.60
Maximum urinary flow rate slope ≥20th percentile	1.00	Reference
Maximum urinary flow rate slope <20th percentile	0.64	0.39, 1.03
Prostate volume slope ≤80th percentile	1.00	Reference
Prostate volume slope >80th percentile	0.67	0.41, 1.09

* NSAID, nonsteroidal antiinflammatory drug; CI, confidence interval; AUASI, American Urological Association Symptom Index; PSA, prostate-specific antigen.

† Adjusted for age and urinary variable status at baseline.

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use and risk of prostate cancer (13–16). The protective association between NSAID use and decreased risk of prostate cancer has been postulated to be due to the ability of NSAIDs to inhibit cyclooxygenase-2, resulting in a decrease in prostaglandin synthesis (17). Other investigators have also described the ability of specific NSAIDs to inhibit androgen receptor expression and activity in human prostate cancer cell lines (27, 28). Decreased prostaglandin synthesis and inhibition of the prostate androgen receptors may result in decreased growth of the prostate and a subsequent reduction in development of lower urinary tract outcomes. In addition, NSAIDs have been associated with increased apoptosis via both cyclooxygenase-2–dependent and –independent pathways (17). Because decreased apoptosis may be associated with development of BPH (29), NSAIDs may also decrease development of BPH outcomes by increasing apoptosis in prostatic cells. Alternatively, NSAID use may affect other components of the genitourinary system unrelated strictly to prostate volume. For example, Di Silverio et al. (30) demonstrated that men who took the cyclooxygenase-2 inhibitor rofecoxib in conjunction with finasteride experienced faster relief of BPH symptoms compared with men who took finasteride alone, suggesting that an inflammatory component is related to development of BPH symptoms.

The results of this study do differ from those reported by Meigs et al. (18) and Kang et al. (19), however, who previously found no and a slightly increased odds of BPH outcomes, respectively, among men who used aspirin. Our study may differ from that of Meigs et al. because the number of men using aspirin in the Massachusetts Male Aging Study was quite small ($n = 18$), resulting in relatively low power to detect an association with urologic outcomes if associations exist (18). Kang et al. relied on self-report of both aspirin use and BPH outcomes, allowing for the possibility that men with perceived urinary problems might be higher users of medical care and therefore also more likely to report use of aspirin for another condition (19). Additionally, in both of these studies, prevalent rather than incident BPH outcomes were examined, BPH outcomes were less specific than those used in our study, and it is not clear how frequency of aspirin use was defined. Such differences between these studies and ours may account for these discrepancies in study results. For example, daily use of aspirin may be necessary to see an improvement in urinary symptoms, and including less than daily users in this category might dilute such an association.

Strengths of our study include the population-based setting in which it was conducted, which ensured that the men represented the full BPH disease spectrum. In contrast, clinic-based studies of BPH tend to focus on men with more severe BPH symptoms who seek care from urologic specialists. Urologic specialists primarily examine and treat men with substantial urologic problems. Therefore, an association between NSAID use and urologic symptoms could easily be missed in studies examining populations skewed toward severely affected men, because representation of nondiseased men would be limited. In addition, this well-established cohort of men made it possible for us to examine them for longitudinal development of BPH outcomes over a 12-year period. Finally, aspirin use in this population was similar to that observed in previous Midwest population-based studies, suggesting that our results may be generalizable to other populations with similar characteristics. In our study, 635 (26 percent) of the men used a daily aspirin, while an additional 7 percent used another daily NSAID. This proportion of men using a daily aspirin is slightly higher than the 19.5 percent prevalence of daily aspirin use observed in Wisconsin residents 45 years of age or older in 1991 but was very similar to the 25 percent prevalence in Michigan residents of the same age in 1994 (31).

Potential limitations of our study include our inability to examine changes in NSAID use over time because only those data on NSAID use at baseline and at the round 6 follow-up periods were available. In addition, we were not able to examine a dose-response relation between duration of NSAID use and development of BPH measures because it was not possible to determine the start date for NSAID use, changes in NSAID dose, and cumulative NSAID dose for most of the men in the study, precluding our ability to examine associations of recency of NSAID use and cumulative dose with urologic outcomes.

It is also possible that our study results are due to the effects of an uncontrolled confounder. For example, the men in our study might have been more likely to make frequent physician visits and receive a diagnosis of, and treatment for, BPH, as well as a suggestion to use daily NSAIDs to prevent other health problems. After adjustment for age, our data did not suggest that men who took daily NSAIDs were more likely to also receive BPH medications (table 1). However, our data did indicate that men who took NSAIDs were more likely to visit the physician more than once in the year prior to recruitment (table 1). After adjustment for more frequent visits, diabetes, hypertension, and coronary heart disease, our results actually became slightly stronger (table 2).

Although further studies are necessary to determine whether NSAID use truly decreases the development of BPH, and the mechanisms by which this decrease might occur, these data suggest that NSAID use may prevent, delay, or retard hyperplastic and/or inflammatory processes in the prostate, resulting in a decreased incidence of BPH.

ACKNOWLEDGMENTS

This project was supported by research grants from the Public Health Service, National Institutes of Health (DK58859, AR30582, and RR000585).

The authors thank the Olmsted County Study personnel for their help with the study and Sondra Buehler for her assistance in preparing this manuscript.

Conflict of interest: none declared.

REFERENCES

1. Sarma AV, Wei JT, Jacobson DJ, et al. Comparison of lower urinary tract symptom severity and associated bother between community-dwelling black and white men: the Olmsted

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County Study of Urinary Symptoms and Health Status and the Flint Men's Health Study. Urology 2003;61:1086–91.
2. Jacobsen SJ, Girman CJ, Guess HA, et al. New diagnostic and treatment guidelines for benign prostatic hyperplasia: potential impact in the United States. Arch Intern Med 1995;155: 477–81.
3. Wei JT, Calhoun EA, Jacobsen SJ. Benign prostatic hyperplasia. In: Litwin MS, Saigal CS, eds. Urologic diseases in America. Washington, DC: US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, US Government Publishing Office, 2004: 43–67. (NIH publication no. 04-5512).
4. Guess HA. Benign prostatic hyperplasia: antecedents and natural history. Epidemiol Rev 1992;14:131–53.
5. Emberton M, Andriole GL, de la Rosette J, et al. Benign prostatic hyperplasia: a progressive disease of aging men. Urology 2003;61:267–73.
6. Oesterling JE, Martin SK, Bergstralh EJ, et al. The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. JAMA 1993;269:57–60.
7. Lieber MM, Jacobsen SJ, Roberts RO, et al. Prostate volume and prostate-specific antigen in the absence of prostate cancer: a review of the relationship and prediction of long-term outcomes. Prostate 2001;49:208–12.
8. Gerstenbluth RE, Seftel AD, MacLennan GT, et al. Distribution of chronic prostatitis in radical prostatectomy specimens with up-regulation of bcl-2 in areas of inflammation. J Urol 2002;167:2267–70.
9. Nickel JC, Downey J, Young I, et al. Asymptomatic inflammation and/or infection in benign prostatic hyperplasia. BJU Int 1999;84:976–81.
10. Anim JT, Udo C, John B. Characterisation of inflammatory cells in benign prostatic hyperplasia. Acta Histochem 1998; 100:439–49.
11. Wang W, Bergh A, Damber JE. Chronic inflammation in benign prostate hyperplasia is associated with focal upregulation of cyclooxygenase-2, Bcl-2, and cell proliferation in the glandular epithelium. Prostate 2004;61:60–72.
12. Di Silverio F, Gentile V, De Matteis A, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. Eur Urol 2003;43:164–75.
13. Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. Br J Cancer 2004;90:93–9.
14. Roberts RO, Jacobson DJ, Girman CJ, et al. A population-based study of daily nonsteroidal anti-inflammatory drug use and prostate cancer. Mayo Clin Proc 2002;77:219–25.
15. Irani J, Ravery V, Pariente JL, et al. Effect of nonsteroidal anti-inflammatory agents and finasteride on prostate cancer risk. J Urol 2002;168:1985–8.
16. Perron L, Bairati I, Moore L, et al. Dosage, duration and timing of nonsteroidal antiinflammatory drug use and risk of prostate cancer. Int J Cancer 2003;106:409–15.
17. Zha S, Yegnasubramanian V, Nelson WG, et al. Cyclooxygenases in cancer: progress and perspective. Cancer Lett 2004; 215:1–20.
18. 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;54:935–44.
19. Kang D, Andriole GL, Van De Vooren RC, et al. Risk behaviours and benign prostatic hyperplasia. BJU Int 2004;93: 1241–5.
20. Jacobsen SJ, Girman CJ, Guess HA, et al. Natural history of prostatism: factors associated with discordance between frequency and bother of urinary symptoms. Urology 1993;42: 663–71.
21. Chute CG, Panser LA, Girman CJ, et al. The prevalence of prostatism: a population-based survey of urinary symptoms. J Urol 1993;150:85–9.
22. Melton LJ III. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996;71:266–74.
23. 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;148:1549–57.
24. Girman CJ, Jacobsen SJ, Guess HA, et al. Natural history of prostatism: relationship among symptoms, prostate volume and peak urinary flow rate. J Urol 1995;153:1510–15.
25. Feldman HA. Families of lines: random effects in linear regression analysis. J Appl Physiol 1988;64:1721–32.
26. Ware JH. Linear models for the analysis of longitudinal studies. Am Stat 1985;39:95–101.
27. Pan Y, Zhang JS, Gazi MH, et al. The cyclooxygenase 2-specific nonsteroidal anti-inflammatory drugs celecoxib and nimesulide inhibit androgen receptor activity via induction of c-Jun in prostate cancer cells. Cancer Epidemiol Biomarkers Prev 2003;12:769–74.
28. Zhu W, Smith A, Young CY. A nonsteroidal anti-inflammatory drug, flufenamic acid, inhibits the expression of the androgen receptor in LNCaP cells. Endocrinology 1999;140: 5451–4.
29. Kyprianou N, Tu H, Jacobs SC. Apoptotic versus proliferative activities in human benign prostatic hyperplasia. Hum Pathol 1996;27:668–75.
30. 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: 72–9.
31. Prevalence of aspirin use to prevent heart disease—Wisconsin, 1991, and Michigan, 1994. MMWR Morb Mortal Wkly Rep 1997;46:498–502.

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