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Original Contribution

Use of Aspirin and Other Nonsteroidal Antiinflammatory Medications in Relation to Prostate Cancer Risk

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Recent interest has focused on the role that inflammation may play in the development of prostate cancer and whether use of aspirin or other nonsteroidal antiinflammatory drugs (NSAIDs) affects risk. In a population-based case-control study designed to investigate the relation between these medications and prostate cancer risk, detailed exposure data were analyzed from 1,001 cases diagnosed with prostate cancer between January 1, 2002, and December 31, 2005, and 942 age-matched controls from King County, Washington. A significant 21% reduction in the risk of prostate cancer was observed among current users of aspirin compared with nonusers (95% confidence interval (CI): 0.65, 0.96). Long-term use of aspirin (>5 years: odds ratio = 0.76, 95% CI: 0.61, 0.96) and daily use of low-dose aspirin (odds ratio = 0.71, 95% CI: 0.56, 0.90) were also associated with decreased risk. There was no evidence that the association with aspirin use varied by disease aggressiveness, but there was effect modification ($P_{interaction} = 0.02$) with a genetic variant in prostaglandin-endoperoxide synthase 2 (*PTGS2*) (rs12042763). Prostate cancer risk was not related to use of either nonaspirin NSAIDs or acetaminophen. These results contribute further evidence that aspirin may have chemopreventive activity against prostate cancer and highlight the need for additional research.

anti-inflammatory agents, non-steroidal; aspirin; odds ratio; polymorphism, genetic; prostaglandin-endoperoxide synthases; prostatic neoplasms

Abbreviations: CI, confidence interval; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio; PSA, prostate-specific antigen; SNP, single nucleotide polymorphism.

Prostate cancer is the most frequent noncutaneous cancer in men (1), and discovery of modifiable determinants of risk could present an opportunity to prevent or delay the onset of this common disease. Established risk factors such as ancestry or family history are not modifiable, and the evidence for dietary and lifestyle risk factors is inconclusive (2). However, in recent years the role of inflammation in cancer etiology has gained attention, and several studies have suggested that nonsteroidal antiinflammatory drugs (NSAIDs) may have chemopreventive activity (3). Use of NSAIDs has been associated with a reduced risk of prostate cancer in some, but not all, studies (4). Eight studies that evaluated aspirin use and prostate cancer reported 15%–55% reductions in risk (5–12), 2 studies found increases in risk (13, 14), and 5 reported no association (15–19).

Given the potential role of the inflammation pathway in the development of prostate cancer, a population-based case-control study was conducted to evaluate the effects of aspirin and other NSAID use on prostate cancer risk. The relation between use of these medications and clinical characteristics of prostate cancer was also explored. In addition, genetic variants in 2 cyclooxygenase genes (*PTGS1, PTGS2)* that may alter aspirin effects were examined.

MATERIALS AND METHODS

Study population

Caucasian and African-American men 35–74 years of age residing in King County, Washington, who were diagnosed

with histologically confirmed prostate cancer between January 1, 2002, and December 31, 2005, were ascertained from the Seattle–Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry. Of the 1,327 eligible patients identified, 1,001 (75.4%) were interviewed. The reasons for nonresponse were patient refusal (14.9%), patient was too ill or had other problems (2.6%), patient could not be located (2.3%), physician refusal to allow patient contact (1.8%), and patient died (1.7%) or moved (1.3%) before the interview could be conducted. DNA for genotyping was available for 827 (83%) interviewed cases.

Controls were Caucasian and African-American male residents of King County, Washington, who had never been diagnosed with prostate cancer. They were identified by using random digit telephone dialing (20), recruited evenly throughout the ascertainment period for cases, and frequency matched to cases by age (5-year groups). Household census information was obtained for 81% of residences contacted. Of the 1,507 eligible men identified, 942 (62.5%) completed the interview. Reasons for nonparticipation included subject refusal (21.7%), the person providing household census data refused to allow contact of the eligible man (10.5%), language problem, moved, or was lost to follow-up (3.3%), illness (1.7%), or death (0.3%). DNA for genotyping was available for 787 (84%) interviewed controls.

In-person interviews conducted by trained male interviewers using a standardized questionnaire were completed by participants. Questions pertained to the time prior to the reference date, that is, the date of prostate cancer diagnosis for cases and, for controls, a preassigned random date that approximated the distribution of cases' diagnosis dates and included the following: demographic and lifestyle information, family history of cancer, medical history, use of selected medications, and prostate cancer screening history (prostate-specific antigen (PSA) and digital rectal examination). Clinical information on cases, including Gleason score, stage of disease, and PSA at diagnosis, was obtained from the cancer registry. The study was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study participants. Genotyping was approved by the National Human Genome Research Institute Institutional Review Board.

Assessment of aspirin and other NSAID use

Lifetime use of aspirin and other NSAID medications was obtained, including ever use (i.e., use at least once per week for $\geq$3 months), type used (i.e., brand or generic name), duration of each episode of use (i.e., start and stop dates, age at start and stop, or total duration of use), and frequency of use (i.e., number of pills taken each time and number of times taken per day, week, month, or year). Current use was defined as use within the year prior to the reference date. Time since first or last use of aspirin or other NSAIDs was defined as the years elapsed from the date of first or last use, respectively, until the reference date. Total duration of aspirin or other NSAID use was calculated as the sum of nonoverlapping periods of use. Total duration of use of a specific medication, for example, low-dose aspirin, or of a specific pattern of use, for example, daily use, was calculated in a similar manner, but only periods of use corresponding to the exposure of interest were considered.

Genotyping

DNA isolated from peripheral blood was used for genotyping single nucleotide polymorphisms (SNPs) in *PTGS2*, selected to maximize coverage of genetic variation ($r^2 > 0.80$). Three nonsynonymous coding SNPs in *PTGS1* were also selected. Genotyping was performed at the National Human Genome Research Institute, National Institutes of Health (E. A. O.'s laboratory), with the SNPlex system (Applied Biosystems, Foster City, California). Identification of the SNP allele was carried out with the Applied Biosystems 3730*xl* DNA analyzer, with GeneMapper software used for allele assignment (www.appliedbiosystems.com). Quality control included genotyping 84 blind duplicates, which showed 100% agreement for all SNPs. Four SNPs in *PTGS2* (rs1119231, rs20417, rs2206593, rs2745557) with call rates less than 95% were excluded. The remaining 15 SNPs had greater than 98% completion levels and were in Hardy-Weinberg equilibrium in Caucasian controls ($P > 0.05$).

Statistical analyses

Odds ratios and 95% confidence intervals from unconditional logistic regression (21) were used to evaluate the association between prostate cancer and use of aspirin or other NSAIDs. Potential confounding factors that changed the risk estimates in relation to use of aspirin or other NSAIDs by 10% or more when added one at a time were incorporated in the final model. Potential confounders included race, smoking status, education, income, marital status, prostate cancer screening history (none, digital rectal examination only, PSA testing), and several indications and contraindications for use of NSAIDs. All regression models were adjusted for age at the reference date (5-year groups). Statistically significant associations were those with $P < 0.05$ (2-sided test). The goodness of fit of regression models was evaluated with the Hosmer-Lemeshow test. All statistical calculations were performed by using SAS, version 9.1.3, software (SAS Institute, Inc., Cary, North Carolina).

The association between use of aspirin and other NSAIDs and clinical characteristics of prostate cancer was examined by stratifying cases on the Gleason score ($\leq$7 (3 + 4) vs. $\geq$7 (4 + 3)), stage (local vs. regional/distant), and a composite measure of disease aggressiveness (less aggressive: Gleason score $\leq$7 (3 + 4) and localized stage and PSA level $<$20 ng/mL vs. more aggressive: Gleason score $\geq$7 (4 + 3) or regional or distant stage or PSA level $\geq$20 ng/mL). Polytomous regression was used to compare NSAID use in each group of cases with use in controls (22). We also considered whether associations between NSAID use and prostate cancer risk differed according to genetic variants in *PTGS1* or *PTGS2* in Caucasian cases and controls. This was tested formally with a likelihood ratio test of the interaction term in a model with the main effects compared with the reduced model with main effects only.

Table 1. Selected Characteristics of Population-based Prostate Cancer Cases and Controls in King County, Washington, 2002–2005

Characteristic	Cases (n = 1,001)		Controls (n = 942)		Odds Ratio[a]	95% CI
	No.	%	No.	%		
Age, years, at reference date						
35–49	93	9.3	96	10.2		
50–54	108	10.8	113	12.0		
55–59	184	18.4	174	18.5		
60–64	218	21.8	187	19.9		
65–69	210	21.0	202	21.4		
70–74	188	18.8	170	18.0		
Race						
Caucasian	843	84.2	844	89.6	1.00	Referent
African American	158	15.8	98	10.4	1.69	1.29, 2.23
First-degree family history of prostate cancer						
No	775	77.4	833	88.4	1.00	Referent
Yes	226	22.6	109	11.6	2.25	1.75, 2.89
Annual income, $						
<15,000	48	5.0	47	5.1	0.86	0.56, 1.34
15,000–29,999	85	8.9	93	10.1	0.77	0.54, 1.08
30,000–49,999	189	19.7	169	18.4	0.95	0.72, 1.25
50,000–74,999	212	22.1	206	22.5	0.88	0.68, 1.13
75,000–99,999	141	14.7	157	17.1	0.76	0.57, 1.02
≥100,000	284	29.6	245	26.7	1.00	Referent
Missing	42		25			
Education						
≤ High school	196	19.6	181	19.2	1.00	Referent
Some college	241	24.1	210	22.3	1.07	0.81, 1.40
College degree	262	26.2	261	27.7	0.94	0.72, 1.22
Graduate degree	301	30.1	289	30.7	0.97	0.75, 1.25
Body mass index, kg/m^2						
<25	287	28.7	259	27.5	1.00	0.81, 1.24
25.0–29.9	492	49.2	444	47.1	1.00	Referent
30.0–34.9	168	16.8	186	19.8	0.81	0.64, 1.04
≥35.0	54	5.4	53	5.6	0.91	0.61, 1.36
Recent exercise, times/week[b]						
None	262	26.2	246	26.1	1.00	Referent
1–2	315	31.5	283	30.0	1.05	0.83, 1.33
3–4	251	25.1	244	25.9	0.97	0.76, 1.25
≥5	173	17.3	169	17.9	0.96	0.73, 1.27
Smoking status						
Nonsmoker	428	42.8	429	45.6	1.00	Referent
Former smoker	462	46.2	394	41.9	0.94	0.70, 1.26
Current smoker	111	11.1	118	12.5	1.16	0.96, 1.41
Prostate cancer screening[c]						
None	133	13.3	136	14.4	1.00	Referent
Digital rectal examination only	159	15.9	263	27.9	0.62	0.46, 0.85

Table continues

Table 1. Continued

Characteristic	Cases (n = 1,001)		Controls (n = 942)		Odds Ratio[a]	95% CI
	No.	%	No.	%		
PSA test	709	70.8	543	57.6	1.36	1.04, 1.78
Migraines						
Never	929	92.8	876	93.2	1.00	Referent
Ever	72	7.2	64	6.8	1.06	0.74, 1.50
Arthritis (rheumatoid or osteoarthritis)						
Never	833	84.2	767	82.3	1.00	Referent
Ever	156	15.8	165	17.7	0.86	0.68, 1.10
Gastroesophageal reflux disease						
Never	819	81.9	759	80.7	1.00	Referent
Ever	181	18.1	181	19.3	0.92	0.73, 1.16
Gastrointestinal ulcer						
Never	886	88.5	855	91.1	1.00	Referent
Ever	114	11.4	84	8.9	1.29	0.96, 1.74
Heart attack						
Never	932	93.2	862	91.5	1.00	Referent
Ever	68	6.8	80	8.5	0.76	0.54, 1.08
Stroke						
Never	968	96.7	907	96.6	1.00	Referent
Ever	32	3.2	32	3.4	0.93	0.57, 1.53
Gleason score						
3–4	7	0.7				
5–6	518	52.0				
7 (3 + 4)	294	29.5				
7 (4 + 3)	78	7.8				
8–10	99	9.9				
Missing	5					
Stage of cancer						
Local	819	81.8				
Regional	160	16.0				
Distant	22	2.2				
PSA value, ng/mL[d]						
<4.0	134	14.3	720	91.6		
4.0–9.9	592	63.1	55	7.0		
10.0–19.9	143	15.2	10	1.3		
≥20.0	69	7.4	1	0.1		
Missing	63		156			
Prostate cancer aggressiveness[e]						
Less aggressive	686	68.5				
More aggressive	315	31.5				

Abbreviation: CI, confidence interval; PSA, prostate-specific antigen.
[a] Adjusted for age at reference date.
[b] Exercise frequency 1 year before reference date.
[c] Prostate cancer within 5 years before reference date.
[d] Measured at diagnosis for cases and at interview for controls.
[e] Less aggressive = Gleason ≤7 (3 + 4), local stage, and PSA <20 ng/mL; more aggressive = Gleason ≥7 (4 + 3) or regional/distant stage or PSA ≥20 ng/mL.

Table 2. Comparison of Selected Demographic Factors and Medical Conditions in Population-based Controls According to Use of Aspirin or Other NSAIDs, King County, Washington, 2002–2005

Characteristic	Users[a] (n = 561)		Nonusers[a] (n = 381)		P Value[b]
	No.	%	No.	%	
Mean age, years, at reference date	63		58		
Age, years, at reference date					3.3×10^{-15}
35–49	28	5.0	68	17.9	
50–54	47	8.4	66	17.3	
55–59	97	17.3	77	20.2	
60–64	126	22.5	61	16.0	
65–69	145	25.9	57	15.0	
70–74	118	21.0	52	13.7	
Race					0.0009
Caucasian	528	94.4	316	88.8	
African American	33	5.6	65	11.2	
First-degree family history of prostate cancer					0.33
No	500	89.3	333	87.2	
Yes	61	10.7	48	12.8	
Annual income, $					0.03
<15,000	28	17.4	19	15.6	
15,000–29,999	51	14.7	42	19.4	
30,000–49,999	101	15.6	68	18.2	
50,000–74,999	124	17.3	82	15.8	
75,000–99,999	85	15.8	72	17.9	
≥100,000	152	19.2	93	13.1	
Missing	16		5		
Education					0.02
≤ High school	98	21.2	83	30.6	
Some college	129	26.4	81	22.9	
College degree	153	25.6	108	24.2	
Graduate degree	180	26.8	109	22.4	
Body mass index, kg/m^2					0.87
<25	275	23.3	169	24.5	
25.0–29.9	140	22.0	119	29.8	
30.0–34.9	111	25.1	75	24.8	
≥35.0	35	27.6	18	20.9	
Recent exercise, times/week[c]					0.60
None	151	24.9	95	25.1	
1–2	155	23.8	128	26.9	
3–4	149	26.2	95	23.1	
≥5	106	25.0	63	24.9	
Smoking status					0.89
Nonsmoker	247	33.2	182	33.6	
Former smoker	246	33.1	148	33.7	
Current smoker	67	33.7	51	32.8	
Prostate cancer screening[d]					6.1×10^{-5}
None	55	27.5	81	40.7	
Digital rectal examination only	134	32.9	129	33.9	
PSA	372	39.7	171	25.4	
No. of PSA tests[d]					1.1×10^{-5}
0	107	20.5	131	32.1	

Table continues

Table 2. Continued

Characteristic	Users[a] (n = 561)		Nonusers[a] (n = 381)		P Value[b]
	No.	%	No.	%	
1–2	94	23.9	67	26.8	
3–4	83	25.3	46	24.6	
≥5	194	30.4	57	16.5	
Missing	83		80		
PSA value, ng/mL[e]					0.04
0–0.4	88	18.7	64	14.0	
0.5–0.9	150	20.2	90	12.1	
1.0–1.9	133	18.6	72	14.2	
2.0–3.9	79	16.6	44	16.7	
4.0–9.9	29	13.3	26	21.1	
≥10.0	6	12.6	5	21.9	
Missing	76		80		
Migraines					0.008
Never	512	91.0	364	95.8	
Ever	47	9.0	17	4.2	
Arthritis (rheumatoid or osteoarthritis)					3.2×10^{-9}
Never	422	76.3	345	91.4	
Ever	133	23.7	32	8.6	
Gastroesophageal reflux disease					0.31
Never	440	79.8	319	82.8	
Ever	119	20.2	62	17.2	
Gastrointestinal ulcer					0.56
Never	510	91.7	345	90.0	
Ever	50	8.3	34	10.0	
Inflammatory bowel disease					0.98
Never	544	97.3	370	96.9	
Ever	16	2.7	11	3.1	
Arrhythmia (any)					0.003
Never	470	84.9	346	90.4	
Ever	88	15.1	35	8.6	
Congestive heart failure					0.007
Never	550	98.2	381	100.0	
Ever	10	1.8	0		
Heart attack					2.4×10^{-8}
Never	488	89.2	374	98.1	
Ever	73	10.8	7	1.9	
Hypertension					3.5×10^{-10}
Never	302	55.7	297	76.6	
Ever	258	44.3	84	23.4	
Stroke					0.01
Never	533	95.1	374	98.1	
Ever	26	4.9	6	1.9	

Abbreviations: NSAID, nonsteroidal antiinflammatory drug; PSA, prostate-specific antigen.

[a] Proportions are age adjusted; total numbers of aspirin or NSAID users vary because of missing data.

[b] Likelihood ratio statistic-based test comparing users with nonusers, except for "congestive heart failure," where Fisher's exact test was used.

[c] Exercise frequency 1 year prior to reference date.

[d] Prostate cancer screening within 5 years before reference date.

[e] PSA measured at interview.

RESULTS

Compared with controls, cases were more likely to be African American, to report a first-degree family history of prostate cancer, and to have undergone PSA testing prior to the reference date (Table 1). Cases and controls did not differ with respect to the other factors shown or *PTGS1* or *PTGS2* SNP genotypes (data not shown). With respect to the clinical characteristics of prostate cancer, almost a third of cases were classified as having more aggressive disease.

Among controls, 51.6% and 21.0% reported ever using aspirin or another NSAID, respectively. Table 2 presents the distribution of selected factors among controls by exposure status. Compared with nonusers, users were older and more likely to be Caucasian, to have higher income and educational levels, and to have undergone PSA screening. Users of aspirin/NSAIDs also tended to have lower plasma PSA values than did nonusers ($P = 0.04$). No differences were observed with respect to family history of prostate cancer, body mass index, smoking status, or genotypes (data not shown). However, use was associated with an increased prevalence of several medical conditions, including hypertension, arthritis, heart attack, arrhythmia, congestive heart failure, migraines, and stroke.

Use of aspirin

Ever use of aspirin was associated with an 18% reduction in the relative risk of prostate cancer (odds ratio (OR) = 0.82, 95% confidence interval (CI): 0.68, 0.99) (Table 3). Daily use of aspirin (OR = 0.78, 95% CI: 0.64, 0.95) and daily low-dose use (OR = 0.71, 95% CI: 0.56, 0.90) were associated with further risk reductions.

Current use of aspirin was associated with a 21% decrease in the risk of prostate cancer relative to nonusers (OR = 0.79, 95% CI: 0.65, 0.96), although former users had no reduction in risk (OR = 1.15, 95% CI: 0.74, 1.80). Long-term use of aspirin was also associated with a significant reduction in risk, with men who used aspirin for greater than 5 years having an odds ratio = 0.76 (95% CI: 0.61, 0.96). There were no significant patterns of risk in relation to time since first or last use of aspirin. Because duration and recency of use were correlated, joint effects were evaluated. The strongest reduction in risk was in current users with greater than 5 years of use (OR = 0.74, 95% CI: 0.58, 0.94); current users reporting 5 or fewer years of use had an odds ratio = 0.85 (95% CI: 0.67, 1.08). The relative risk in former users did not differ from the null regardless of duration of use.

Use of nonaspirin NSAIDs

There were no associations between use of nonaspirin NSAIDs and prostate cancer risk (OR = 1.05, 95% CI: 0.84, 1.32) (Table 4). Because the majority of nonaspirin NSAID use was for ibuprofen (controls, 50.5%; cases, 45.8%), this drug was examined separately; however, no association was found ($OR_{ever\ use} = 0.94$, 95% CI: 0.69, 1.27). In addition, there was no evidence of any relation to prostate cancer risk of using acetaminophen ($OR_{ever\ use} = 1.03$, 95% CI: 0.75, 1.41; $OR_{>5\ years'\ use} = 1.15$, 95% CI: 0.71, 1.48) (data not shown).

Clinical features of disease

No significant differences in risk estimates were observed when men with relatively less versus more aggressive disease were compared with controls (Table 5). Daily low-dose aspirin use was associated with decreased odds ratios for both less and more aggressive prostate cancer. No associations were observed when use of NSAIDs other than aspirin was examined in cases stratified by clinical features compared with controls.

Effect modification by genetic variants in *PTGS1* and *PTGS2*

The effects of aspirin on prostate cancer risk may be influenced by genetic polymorphisms within cyclooxygenase genes. To evaluate this possibility, we stratified Caucasian cases and controls who ever versus never used aspirin according to *PTGS1* and *PTGS2* SNP genotypes (Table 6). For comparison, the relative risk estimate associated with ever use of aspirin in Caucasian cases and controls with DNA, regardless of genotype, was 0.75 (95% CI: 0.61, 0.92); use of aspirin did not differ between subjects who did compared with those who did not have DNA available. Aspirin users homozygous for the major G allele at rs12042763 had a greater reduction in risk (OR = 0.60) compared with users with any T allele (OR = 0.86) when compared with nonusers ($P_{interaction} = 0.02$).

DISCUSSION

In this study, men who reported ever use of aspirin had a statistically significant 18% reduction in the relative risk of prostate cancer. Current users (defined as use within the year prior to the reference date: cases, 43.3%; controls, 47.7%) had a 21% reduction in risk, long-term users (>5 years' use) had a 24% decrease in risk, and users of daily low-dose aspirin had a 29% reduction in risk relative to nonusers. These risks did not vary substantially by disease aggressiveness. One SNP in *PTGS2*, rs12042763 located 2.3 kilobases 5′ of the transcript start site, showed a statistically significant interaction with aspirin use. There was no relation between use of nonaspirin NSAIDs and prostate cancer risk.

Ever use of aspirin was previously examined in 2 case-control studies that reported significant reductions in prostate cancer risk, with odds ratios of 0.66 (95% CI: 0.51, 0.86) (12) and 0.84 (95% CI: 0.75, 0.96) (11). In 3 other studies, reductions in risk ranged from 9%–24% but did not reach statistical significance (5, 10, 17). A single study reported a significant increase in risk of prostate cancer (OR = 1.33, 95% CI: 1.07, 1.64) for ever use of prescription-only aspirin and other NSAIDs (23). Elevated, although nonsignificant, relative risks have also been reported by others (13, 14). Only 2 prior studies (8, 10) evaluated current use, and both found reductions in risk, although the cohort study result did not reach significance (10).

Table 3. Association Between Use of Aspirin and Prostate Cancer in a Population-based Case-Control Study in King County, Washington, 2002–2005

Aspirin Use	Cases[a] (n = 1,000)		Controls[a] (n = 942)		Odds Ratio[b]	95% CI	Odds Ratio[c]	95% CI
	No.	%	No.	%				
Ever use[d]								
Never	516	51.6	456	48.4	1.00	Referent	1.00	Referent
Ever	484	48.4	486	51.6	0.84	0.70, 1.02	0.82	0.68, 0.99
Daily aspirin	406	44.0	420	47.9	0.82	0.68, 1.00	0.78	0.64, 0.95
Daily low-dose aspirin[e]	211	29.0	230	33.5	0.76	0.60, 0.96	0.71	0.56, 0.90
Age at first use, years								
Nonuser	516	51.8	456	48.6	1.00	Referent	1.00	Referent
<50	122	12.2	124	13.2	0.87	0.66, 1.15	0.85	0.64, 1.13
50–64	268	26.9	290	30.9	0.77	0.62, 0.96	0.75	0.60, 0.94
≥65	91	9.1	69	7.3	1.15	0.79, 1.67	1.11	0.76, 1.62
Recency of use								
Nonuser	516	51.6	456	48.4	1.00	Referent	1.00	Referent
Former user	51	5.1	37	3.9	1.19	0.77, 1.86	1.15	0.74, 1.80
Current user[f]	433	43.3	449	47.7	0.81	0.67, 0.98	0.79	0.65, 0.96
Duration of use, years								
Continuous					0.99	0.98, 1.00	0.99	0.98, 1.00
Nonuser	516	51.7	456	48.5	1.00	Referent	1.00	Referent
≤5	242	24.2	229	24.4	0.90	0.72, 1.13	0.88	0.70, 1.11
>5	241	24.1	255	27.1	0.79	0.63, 1.00	0.76	0.61, 0.96
Time since first use, years								
Nonuser	516	51.8	456	48.6	1.00	Referent	1.00	Referent
0.1–0.9	21	2.1	30	3.2	0.60	0.34, 1.07	0.52	0.29, 0.92
1–4.9	197	19.8	181	19.3	0.93	0.73, 1.18	0.92	0.72, 1.19
5–9.9	122	12.2	130	13.8	0.79	0.59, 1.05	0.75	0.56, 1.00
≥10	141	14.1	142	15.1	0.84	0.64, 1.10	0.82	0.62, 1.09

Abbreviation: CI, confidence interval.

[a] The number of cases and controls varies because of missing information: 1 case who did not know whether or not he had ever used aspirin was excluded from all analyses; and 1 case and 2 controls who reported using aspirin but did not know for how long and 2 cases and 1 control who reported ever use of aspirin but did not know when the period of use began were also excluded from specific analyses.

[b] Adjusted for age at reference date.

[c] Adjusted for age at reference date, race, and prostate cancer screening within 5 years before reference date.

[d] "Ever use" was defined as use of aspirin at least once per week for a period of 3 months or longer.

[e] "Low-dose aspirin" refers to a formulation containing 81 mg of aspirin.

[f] "Current use" is defined as use within the year before reference date.

Several studies have considered duration of aspirin use (8, 10, 12, 14, 19). Of the studies that detected a reduction in prostate cancer risk (8, 12), only one (12) found a significant inverse association (for ≥6 pill-years: OR = 0.54, 95% CI: 037, 0.78). The association in the study by García Rodríguez and González-Pérez (8), although not significant, was similar in magnitude to the one found in our study (for ≥4 years' aspirin use: OR = 0.83). No relation with exposure duration was found in one prospective cohort study (for ≥1 years: relative risk = 0.97, 95% CI: 0.65, 1.43), with a limited number of cases (n = 50) (19). The remaining studies reported nonsignificant increases in risk associated with prolonged aspirin use, with a relative risk = 1.27 for 4 or more years' use (10) and an odds ratio = 1.17 for 10 or more years' use (14). In another case-control study (7), current, long-term aspirin use determined from prescription records was associated with a significant reduction in risk compared with nonusers ($OR_{\text{daily use for 8 years}} = 0.82$, 95% CI: 0.71, 0.95).

Use of daily low-dose aspirin was associated with the lowest risk of prostate cancer in our study (OR = 0.71, 95% CI: 0.56, 0.90), which is consistent with earlier reports (6, 8, 9, 18, 24–27). The strongest inverse associations between aspirin use and prostate cancer risk reported to date have been for daily low-dose aspirin use, with odds ratios of 0.34 (95% CI: 0.23, 0.58) (24) and 0.37 (95% CI: 0.22, 0.62) (26). Although both studies considered use of aspirin and other NSAIDs jointly, 88% of users in the study by Roberts et al. (26) were aspirin users. Men who take aspirin daily may be more likely to use low-dose aspirin, which could be

Table 4. Association Between Use of Nonaspirin NSAIDs and Prostate Cancer in a Population-based Case-Control Study in King County, Washington, 2002–2005

NSAID Use (Nonaspirin)	Cases[a] (*n* = 998)		Controls[a] (*n* = 941)		Odds Ratio[b]	95% CI	Odds Ratio[c]	95% CI
	No.	%	No.	%				
Ever use[d]								
Never	786	78.8	743	79.0	1.00	Referent	1.00	Referent
Ever	212	21.2	198	21.0	1.02	0.82, 1.27	1.05	0.84, 1.32
Daily NSAID	98	11.1	73	8.9	1.27	0.92, 1.75	1.32	0.95, 1.83
Cox-2 specific[e]	38	4.6	26	3.4	1.39	0.84, 2.32	1.47	0.88, 2.47
Age at first use, years								
Nonuser	786	79.0	743	79.5	1.00	Referent	1.00	Referent
<50	101	10.2	88	9.4	1.13	0.83, 1.54	1.19	0.86, 1.63
50–64	81	8.1	78	8.3	0.96	0.69, 1.34	0.97	0.70, 1.36
≥65	27	2.7	26	2.8	0.95	0.54, 1.67	0.99	0.56, 1.76
Recency of use								
Nonuser	786	78.8	743	79.0	1.00	Referent	1.00	Referent
Former user	66	6.6	56	6.0	1.14	0.78, 1.64	1.23	0.85, 1.80
Current user[f]	146	14.6	142	15.1	0.97	0.76, 1.25	0.99	0.76, 1.28
Duration of use, years								
Continuous user					0.99	0.98, 1.01	0.99	0.98, 1.01
Nonuser	786	78.8	743	79.1	1.00	Referent	1.00	Referent
≤5	111	11.1	99	10.5	1.07	0.80, 1.42	1.11	0.83, 1.49
>5	100	10.0	97	10.3	0.98	0.73, 1.32	1.01	0.74, 1.37
Time since first use, years								
Nonuser	786	79.0	743	79.5	1.00	Referent	1.00	Referent
0.1–4.9	67	6.7	68	7.3	0.92	0.65, 1.32	0.96	0.67, 1.37
5–9.9	52	5.2	40	4.3	1.25	0.82, 1.92	1.26	0.82, 1.95
≥10	90	9.0	84	9.0	1.02	0.75, 1.40	1.07	0.78, 1.48

Abbreviations: CI, confidence interval; Cox-2, cyclooxygenase 2; NSAID, nonsteroidal antiinflammatory drug.

[a] Three cases and 1 control who did not know whether they had ever used nonaspirin NSAIDs were excluded from all analyses.

[b] Adjusted for age at reference date.

[c] Adjusted for age at reference date, race, and prostate cancer screening within 5 years before reference date.

[d] "Ever use" was defined as use of nonaspirin NSAIDs at least once per week for a period of 3 months or longer.

[e] Use of Bextra (Pfizer, Inc., New York, NY), Celebrex (Pfizer), and/or Vioxx (Merck & Co., Inc., Whitehouse Station, NJ) at least once per week for 3 months or longer.

[f] "Current use" is defined as use within the year prior to reference date.

important in terms of biologic mechanisms. In a recent randomized trial, lipid molecules that promote the resolution phase of inflammation were synthesized in response to low-dose aspirin (28), but no significant effect was detected at higher doses (29).

Among studies that have evaluated nonaspirin NSAID use, results have been conflicting (5, 7–12, 19). Ever use of nonaspirin NSAIDs was associated with significant 29% (11) and 21% (12) reductions in the relative risk of prostate cancer and of advanced prostate cancer. In contrast, 2 studies using pharmacy databases to define exposure reported borderline significant 14%–20% increases in risk associated with current use compared with never use (7, 8).

In summary, the majority of studies including our own observed a lower risk of prostate cancer in relation to current use and daily low-dose aspirin use. Similar, although less consistent, results have been noted when duration of aspirin use was examined. However, the data are less consistent for use of nonaspirin NSAIDs. The differing results across studies of aspirin or other NSAIDs may be due to differences in exposure measurement (e.g., assessment of duration, dose, frequency), study design and methodology (e.g., interviews vs. pharmacy databases to define exposure), populations (e.g., differences in the prevalence of aspirin/NSAID use), and/or study power.

Results from experimental studies support a beneficial role of aspirin/NSAIDs against prostate carcinogenesis, as they show that these agents inhibit cell proliferation, induce apoptosis, and decrease metastasis (30). The anticancer effects of aspirin and other NSAIDs are thought to occur primarily through their direct inhibition of PTGS1 and PTGS2 enzymes. Through their inhibition of these enzymes, aspirin/NSAIDs block the synthesis of proinflammatory prostaglandins (31–33). Historically, only *PTGS2* was

Table 5. Association Between Use of Aspirin or Other NSAIDs and Prostate Cancer Aggressiveness in a Population-based Case-Control Study in King County, Washington, 2002–2005

	Controls		Less Aggressive Cases[a]				More Aggressive Cases[a]			
	No.	%	No.	%	Odds Ratio[b]	95% CI	No.	%	Odds Ratio[b]	95% CI
Aspirin use[c]										
Ever use										
Never	456	48.4	343	50.1	1.00	Referent	173	54.9	1.00	Referent
Ever	486	51.6	342	49.9	0.84	0.68, 1.04	142	45.1	0.78	0.59, 1.02
Daily aspirin	435	48.8	293	46.1	0.79	0.63, 0.99	130	42.9	0.77	0.58, 1.02
Daily low-dose aspirin	226	33.1	148	30.1	0.73	0.56, 0.95	62	26.4	0.71	0.50, 1.01
Recency										
Nonuser	456	48.4	343	43.8	1.00	Referent	173	54.9	1.00	Referent
Former user	37	3.9	36	4.6	1.15	0.70, 1.88	15	4.8	1.08	0.58, 2.04
Current user	449	47.7	306	39.0	0.81	0.65, 1.01	127	40.3	0.75	0.57, 0.99
Duration of use, years										
Continuous					0.99	0.98, 1.00			0.99	0.98, 1.01
Nonuser	456	48.5	343	43.8	1.00	Referent	173	55.1	1.00	Referent
≤5	229	24.4	172	21.9	0.91	0.71, 1.18	70	22.3	0.82	0.59, 1.14
>5	255	27.1	170	21.7	0.78	0.60, 1.01	71	22.6	0.73	0.52, 1.03
NSAID use[d]										
Ever use										
Nonuser	743	79.0	537	78.6	1.00	Referent	249	79.0	1.00	Referent
Ever, any	198	21.0	146	21.4	1.05	0.82, 1.34	66	21.0	1.06	0.78, 1.46
Cox-2 specific	26	3.4	28	5.0	1.54	0.88, 2.70	10	3.9	1.33	0.62, 2.82
Recency										
Nonuser	743	79.0	537	78.6	1.00	Referent	249	79.0	1.00	Referent
Former users	56	6.0	49	7.2	1.22	0.83, 1.78	17	5.4	1.89	0.41, 8.63
Current users	142	15.1	97	14.2	0.98	0.75, 1.26	49	15.6	1.62	0.52, 5.02
Duration of use, years										
Continuous					1.00	0.98, 1.02			0.98	0.96, 1.01
Nonuser	743	79.0	537	78.6	1.00	Referent	249	79.3	1.00	Referent
≤5	99	10.5	71	10.4	1.03	0.74, 1.44	40	12.7	1.26	0.85, 1.88
>5	97	10.3	75	11.0	1.08	0.78, 1.51	25	8.0	0.84	0.53, 1.34

Abbreviations: CI, confidence interval; Cox-2, cyclooxygenase 2; NSAID, nonsteroidal antiinflammatory drug; PSA, prostate-specific antigen.

[a] Less aggressive = Gleason score ≤7 (3 + 4), local stage, and PSA <20 ng/mL; more aggressive = Gleason score ≥7 (4 + 3) or regional/distant stage or PSA ≥20 ng/mL at diagnosis.

[b] Adjusted for age at reference date, race, and prostate cancer screening within 5 years before reference date.

[c] For controls, less aggressive cases, and more aggressive cases, the respective totals were as follows: $n = 942$, $n = 685$, and $n = 315$.

[d] For controls, less aggressive cases, and more aggressive cases, the respective totals were as follows: $n = 941$, $n = 683$, and $n = 315$.

thought to be involved in the process of inflammation; however, there is evidence of a role for *PTGS1* in both inflammation and carcinogenesis (34–37). Given the importance of *PTGS1* and *PTGS2* to the pharmacology of these medications, genetic polymorphisms of these genes might modify the effects of aspirin or other NSAIDs on cancer risk (38, 39). Some reports also indicate that such polymorphisms may alter prostate cancer risk (40, 41), but this has not been consistent (42). Interestingly, the highest level of PTGS2 protein in the body is in the prostate (43), with even higher levels in neoplastic prostate tissue (44).

Several strengths and limitations should be considered when interpreting these results. Strengths of our study include its size and the fact that it was designed to test the association between use of aspirin and other NSAIDs in relation to risk of prostate cancer. Concerns relate to potential selection, detection, or recall bias. The 62.5% participation level among controls raises the possibility that men who completed the interview may have differed from those who did not with respect to use of aspirin/NSAIDs. If interviewed controls were more likely to use aspirin than controls who did not participate, this would have led to an overestimate of the inverse association we observed. However, the 52% prevalence of aspirin use observed in our controls is similar to that of other population-based studies (10, 16). Potential detection bias may arise if the likelihood

Table 6. Association Between Ever Use of Aspirin and Prostate Cancer Among Caucasians, According to Genotypes of Selected *PTGS1* and *PTGS2* Gene Variants, in a Population-based Case-Control Study in King County, Washington, 2002–2005

Exposure	MAF[a]	MAF[b]	Cases, no.	Controls, no.	Odds Ratio[c]	95% CI	$P_{interaction}$
Ever use of aspirin							
Never[d]			362	314	1.00	Referent	
Ever			349	404	0.75	0.61, 0.92	
PTGS1							
rs1236913 (Trp8Arg)	0.071	0.075					0.52
CC			296	340	0.74	0.58, 0.94	
TT + TC			48	63	0.56	0.29, 1.08	
rs3842787 (Pro17Leu)	0.061	0.068					0.36
CC			303	353	0.67	0.53, 0.85	
TT + TC			39	49	1.08	0.53, 2.24	
rs5789 (Leu237Met)[e]	0.028	0.030					0.43
CC			322	373	0.71	0.56, 0.89	
CA			14	21	0.71	0.24, 2.12	
PTGS2							
rs6685280	0.227	0.203					0.66
AA			204	242	0.75	0.56, 1.00	
CC + CA			126	139	0.67	0.46, 0.97	
rs964570	0.083	0.070					0.69
GG			293	347	0.69	0.55, 0.88	
AA + GA			52	56	0.73	0.39, 1.37	
rs6425043[e]	0.038	0.031					0.45
AA			319	379	0.70	0.56, 0.88	
AG			26	22	0.78	0.31, 1.94	
rs1119231	0.151	0.130					0.56
GG			256	303	0.73	0.56, 0.95	
AA + AG			85	94	0.64	0.42, 0.99	
rs12042763	0.260	0.254					0.02
GG			177	233	0.60	0.44, 0.81	
TT + TG			165	169	0.86	0.61, 1.20	
rs689462	0.026	0.029					0.13
AA			330	376	0.73	0.58, 0.91	
CC + CA			9	23	0.20	0.05, 0.75	
rs689466	0.179	0.192					0.32
AA			237	276	0.73	0.56, 0.96	
GG + GA			107	127	0.66	0.44, 0.98	
rs2745557	0.181	0.207					0.53
GG			225	251	0.63	0.48, 0.83	
AA + AG			110	145	0.80	0.54, 1.19	
rs4648261[e]	0.024	0.027					0.09
GG			329	374	0.75	0.59, 0.94	
GA			14	29	0.17	0.05, 0.57	
rs2066826	0.139	0.129					0.51
GG			254	307	0.72	0.55, 0.93	
AA + AG			81	92	0.63	0.40, 0.98	
rs5275	0.348	0.330					0.10
TT			150	170	0.87	0.62, 1.22	
CC + CT			195	232	0.59	0.44, 0.80	
rs689470	0.025	0.028					0.07
CC			329	376	0.73	0.58, 0.91	
TT + TC			8	23	0.13	0.03, 0.55	

Abbreviations: CI, confidence interval; MAF, minor allele frequency.

[a] For Caucasian cases.

[b] For Caucasian controls.

[c] Adjusted for age at reference date and prostate cancer screening history within the 5 years prior to reference date.

[d] Nonusers of aspirin are the reference group in each model (stratified by genotype), but totals vary according to the number of men with genotype data available.

[e] No men were homozygous for the minor allele.

of being diagnosed with prostate cancer is related to aspirin/NSAID use. In this study, control men who used NSAIDs were significantly more likely to have undergone prostate cancer screening compared with nonusers (Table 2), so results were adjusted for screening history. Finally, if recall bias resulted in controls underreporting aspirin use, then the reduced relative risk that we observed may be an underestimate of the potential beneficial effects of aspirin against prostate cancer.

In conclusion, the significant inverse association between prostate cancer risk and use of aspirin that we observed provides additional support for the role of inflammation in the development of this cancer. Because aspirin toxicity appears to be dose related (45), the consistent reduction in risk observed among daily low-dose users in this and other studies bears directly on the future potential of aspirin in cancer prevention. If aspirin delays the onset or progression of prostate cancer through its antiinflammatory activities, this may offer another agent to be tested in prevention trials. Aspirin is a widely used and inexpensive medication, and the potential public health implications of an effective chemopreventive agent for prostate cancer are considerable. Thus, further exploration of this medication in relation to prostate cancer prevention is warranted.

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