A Large Cohort Study of Aspirin and Other Nonsteroidal Anti-inflammatory Drugs and Prostate Cancer Incidence

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Background: **Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has consistently been associated with a reduced risk of colon cancer. Recent epidemiologic studies have suggested that the use of NSAIDs, particularly aspirin, may also be associated with a reduced risk of prostate cancer, but the evidence remains limited.** ***Methods:*** **We examined the association between NSAID use and prostate cancer incidence among 70 144 men in the American Cancer Society's Cancer Prevention Study II Nutrition Cohort. Information on NSAID use was obtained from a questionnaire completed at study enrollment in 1992–1993 and was updated using follow-up questionnaires in 1997 and 1999. We calculated rate ratios (RRs) and 95% confidence intervals (CIs) for prostate cancer incidence associated with NSAID use, adjusting for age and potential prostate cancer risk factors.** ***Results:*** **During follow-up from 1992–1993 through August 31, 2001, 4853 cases of incident prostate cancer were identified. Neither current aspirin use nor current use of NSAIDs (aspirin and other NSAIDs combined) was associated with prostate cancer risk, even at the highest usage level (60 or more pills per month). However, long-duration regular use (30 or more pills per month for 5 or more years) of NSAIDs was associated with reduced risk of prostate cancer (RR = 0.82, 95% CI = 0.71 to 0.94). Long-duration regular use of aspirin was also associated with reduced risk of prostate cancer (RR = 0.85, 95% CI = 0.73 to 0.99). The absolute rate of prostate cancer (standardized to the age distribution of study participants using 5-year age categories) was 1013 per 100 000 person-years among men who had never reported NSAID use, and 847 per 100 000 person-years among long duration regular NSAID users.** ***Conclusions:*** **These results support the hypothesis that long duration regular NSAID use is associated with modestly reduced risk of prostate cancer. [J Natl Cancer Inst 2005;97:975–80]**

Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been consistently associated with reduced risk of colon cancer in observational epidemiologic studies *(1)*, and aspirin use has been shown to reduce risk of colorectal polyp recurrence in two randomized trials *(2,3)*. There is some evidence from laboratory studies that NSAIDs might also influence prostate carcinogenesis, including inhibition of prostate cancer growth and metastasis in rodent models *(4–6)*. Potential biologic mechanisms include inhibition of cyclooxygenase 2 (COX-2), which is involved in inflammation *(7)*.

Results from large epidemiologic studies suggest that aspirin use may be associated with a small reduction in prostate cancer incidence. Four large prospective studies (each including approximately 2500 cases of prostate cancer) have examined aspirin use in relation to prostate cancer incidence *(8–11)*. Three of these studies found statistically significant, 20%–30% reductions in prostate cancer risk in regular users of aspirin *(8,10,11)*. In an analysis of prescription records from the United Kingdom General Practice Research Database, having a current aspirin prescription was associated with an approximately 30% reduction in risk, but no trend with duration of use was observed *(11)*. In an analysis of a pharmacy database in Quebec, aspirin use for 5 or more years was associated with approximately 30% lower prostate cancer risk *(10)*. In a cohort of California Kaiser Permanente health plan members, use of six or more presumably regular strength aspirin tablets per day at baseline was associated with an approximately 20% reduction in prostate cancer risk compared with use of less than six tablets per day *(8)*. However,

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in the Health Professionals Follow-up Study, men who had reported taking two or more aspirin tablets a week on four consecutive biennial questionnaires, and were therefore presumably long-duration users, were not at reduced risk, nor were men who reported frequent aspirin use (22 or more days per month) *(9)*.

Results from large epidemiologic studies of the use of non-aspirin NSAIDs or NSAIDs overall (i.e., including aspirin) have not suggested any reduction in prostate cancer risk. Use of non-aspirin NSAIDs was not associated with prostate cancer risk in two large prospective studies *(10,11)*. Overall NSAID use was associated with slightly increased risk in an analysis of the U.K. General Practice Research Database *(12)*. However, that study examined only prescriptions during an interval of 13–36 months before diagnosis date, and it is possible that the observed increase in risk was due to the prescription of NSAIDs to relieve pain from undiagnosed cancer.

Several much smaller studies have also examined the association between various measures of NSAID use and prostate cancer incidence, with mixed results *(13–21)*. Six studies found no clear association *(13–18)*, two found a substantially reduced risk *(19,20)*, and one found an increased risk *(21)*. However, these studies had limited statistical power to detect small reductions in risk, and none of them examined duration of NSAID use.

It therefore remains unclear whether NSAIDs are associated with reduced risk of prostate cancer, and if so, whether this association differs by frequency or duration of use. We examined the association between NSAID use and prostate cancer incidence in a large cohort of U.S. men, using relatively detailed information collected at several time points, to examine NSAID use by current frequency of use and duration of regular use.

Patients and Methods

Study Cohort

Men in this analysis were drawn from the 86 404 male participants in the Cancer Prevention Study II Nutrition Cohort (hereafter called the Nutrition Cohort), a prospective study of cancer incidence and mortality among U.S. men and women established in 1992–1993 and described in detail elsewhere *(22)*. The Nutrition Cohort is a subgroup of the approximately 1.2 million participants in the Cancer Prevention Study II (CPS-II), a prospective study of cancer mortality that was established by the American Cancer Society in 1982. The Emory University Institutional Review Board approves all aspects of the Nutrition Cohort. At enrollment in 1992–1993, Nutrition Cohort participants completed a mailed self-administered questionnaire that included information on demographic, medical, and lifestyle factors. Follow-up questionnaires to update exposure information and to ascertain newly diagnosed cancers were sent in 1997, 1999, and 2001. The response rate for each of these follow-up questionnaires was at least 90%. We excluded from this analysis 3489 men who were lost to follow-up (i.e., they were alive at the time of the first follow-up questionnaire in 1997 but did not return the 1997 follow-up questionnaire or any subsequent questionnaire). We also excluded men with a history of cancer, other than nonmelanoma skin cancer, at enrollment in 1992–1993 (n = 9740). In addition, we excluded men with missing or incomplete information on NSAID use on the 1992–1993 enrollment questionnaire (n = 2817) or who had missing information on year of prostate cancer diagnosis (n = 14). A total of 698 men reported a prostate cancer diagnosis that could not be verified and therefore were not counted as case patients. Of these 698 men, we excluded those who reported a prostate cancer diagnosis during the first follow-up interval (n = 200) but allowed the 498 men who reported a prostate cancer during later follow-up intervals to contribute person-time until the start of the follow-up interval in which they reported a prostate cancer diagnosis. A total of 70 144 participants therefore remained for analysis.

Case Ascertainment

We documented 4853 incident cases of prostate cancer between enrollment in 1992–1993 and August 31, 2001. Of these, 4694 were initially identified by self-report on the 1997, 1999, or 2001 follow-up questionnaires and subsequently verified by obtaining medical records or, when complete medical records could not be obtained, through linkage with state registries *(22)*. A comparison of self-reports with information from state cancer registries has demonstrated that participants in the Nutrition Cohort can accurately self-report a cancer diagnosis (sensitivity = 0.93) *(23)*. An additional 97 men who did not self-report prostate cancer were identified as prostate cancer cases through linkage of the cohort with the National Death Index *(24)*. For these 97 case patients, the death certificate listed prostate cancer as the primary cause of death between the date of enrollment and August 31, 2001. Seventy of the 97 deaths were subsequently verified by linkage with state registries. Finally, 62 men who did not self-report prostate cancer were identified as prostate cancer case patients during the process of verifying a different cancer. We classified prostate cancer cases as advanced if they were stage III or IV at diagnosis (n = 611) *(25)* or if prostate cancer was listed as the underlying cause of death on the death certificate and no information on stage at diagnosis was available from medical records or registry linkage (n = 27).

Ascertainment of NSAID Use

NSAID use was reported on questionnaires in 1982 (at the time of enrollment into the larger CPS-II mortality cohort), 1992–1993 (at enrollment into the Nutrition Cohort), 1997, and 1999. The 1982 questionnaire asked for "times per month" aspirin was used in the last month but did not include information about aspirin dose or about use of use of NSAIDs other than aspirin, the only NSAID available over the counter at that time. The questionnaire completed at enrollment in 1992–1993 (hereafter referred to as the 1992 questionnaire) asked about use during the past year of three types of NSAIDs: aspirin, ibuprofen, and "other nonsteroidal analgesics." For each type of NSAID, participants were asked if they used the medication regularly, and if so, the average days per month of use, the average number of pills taken on days used, and the number of years used. Follow-up questionnaires in 1997 and 1999 asked similar questions about days per month and pills per day and asked separately about use of low-dose (or "baby") aspirin and regular dose aspirin.

Statistical Analysis

For each type of NSAID, we calculated the number of pills used per month by multiplying days used per month by average number of pills used per day. We counted each low-dose aspirin pill (typically 80 mg) as one-quarter of a regular-dose aspirin

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pill (typically 325 mg). Participants who reported days per month they used a particular NSAID but did not report pills per day for that NSAID were assigned a value of one pill per day. Total NSAID pills per month was calculated by summing pills per month of aspirin, ibuprofen, and other NSAIDs.

We used Cox proportional hazards modeling *(26)* to calculate rate ratios for prostate cancer incidence associated with NSAID use after adjusting for age and potential prostate cancer risk factors. The time axis used was follow-up time since enrollment in 1992–1993. The proportional hazards assumption was verified by modeling interactions between NSAID exposure and a linear time variable.

We examined two measures of NSAID use, current frequency of NSAID use, and duration of regular NSAID use, in which regular use was defined as taking 30 or more NSAID pills per month. Cutpoints for all NSAID variables were consistent with those used in a previous NSAID analysis in this cohort *(27)*. Current frequency of NSAID use was examined using a time-dependent variable defined by pills per month reported at enrollment and was then updated by pills per month reported on each follow-up questionnaire. Two-sided P_{trend} values were calculated using a continuous variable for pills per month and the likelihood ratio statistic.

Analyses of duration of regular NSAID use were designed specifically to examine risk among men who we hypothesized would be at the lowest risk: current regular NSAID users who had used NSAIDs regularly over several years. Although years of NSAID use was reported at enrollment, participants could have reported years when NSAIDs were used only occasionally, rather than regularly. We therefore defined duration of regular use based on whether or not regular NSAID use had been reported on previous questionnaires.

We created a time-dependent variable for duration of regular NSAID use with four categories: 1) never use, 2) past or less than regular use only, 3) current regular use of less than 5 years, and 4) current regular use of 5 or more years. During the follow-up interval between completion of the 1992 and 1997 questionnaires, participants were categorized as having 5 or more years' regular use if they reported at least 5 years of NSAID use on their 1992 questionnaire and also reported regular NSAID use on both the 1982 and 1992 questionnaires. During the 1997–1999 follow-up interval, participants were categorized as having 5 or more years of regular NSAID use if they reported regular NSAID use on both the 1992 and 1997 questionnaires. During the 1999–2001 follow-up interval, participants were categorized as having 5 or more years of regular NSAID use if they reported regular aspirin use on the 1992, 1997, and 1999 questionnaires. During each follow-up interval, participants who had not reported NSAID use on either the questionnaire at the start of that follow-up interval or on any previous questionnaire were categorized as never users. All participants who were neither never users nor current regular users were categorized as past or less than regular users only.

When examining each individual type of NSAID (aspirin, ibuprofen, or "other NSAIDs") we calculated current frequency of use and duration of regular use as described above. However, duration of regular use of ibuprofen or other NSAIDs could not be calculated for the 1992–1997 interval because the 1982 questionnaire asked about aspirin use only.

Analyses of each type of NSAID were adjusted for use of other types of NSAID. Specifically, current frequency of use of each NSAID type was adjusted for current frequency of use of each of the other NSAIDs, and duration of regular use of each NSAID type was adjusted for duration of regular use of each of the other NSAIDs. However, for the 1992–1997 interval, we adjusted duration of regular aspirin use for current frequency of ibuprofen and "other NSAIDs" because duration of use of NSAIDs other than aspirin could not be calculated.

Potential confounders that were included in all multivariable models were age, race, diabetes, history of heart attack, history of prostate-specific antigen (PSA) testing, education, and family history of prostate cancer in a brother or father. Although history of heart attack is not an established risk factor for prostate cancer, we adjusted for it because history of heart attack was associated with a slightly reduced risk of prostate cancer diagnosis in this cohort, as well as with a higher prevalence of regular aspirin use. We adjusted for age using the stratified Cox procedure with 1-year age strata *(28)*. Follow-up after 1997 (when information about PSA testing was first collected) was adjusted for history of PSA testing using a time-dependent variable defined by whether or not a participant had reported PSA testing during the previous follow-up interval. All other covariates were based on information reported at enrollment and were modeled using the categories shown in Table 1. Categories for each covariate were similar to those used in previous analyses of prostate cancer in this cohort.

Table 1. Prostate cancer risk factors by use of nonsteroidal anti-inflammatory drugs (NSAIDs) at enrollment of the Cancer Prevention Study II Nutrition Cohort in 1992–93*

	Percentage of participants using NSAIDs (pills per month)		
	None (N = 29 050)	1–29 (N = 17 078)	≥30 (N = 24 016)
Age, y			
<60	26.8	29.4	21.4
60–69	57.6	57.1	59.1
70–79	15.0	13.0	18.8
≥80	0.7	0.6	0.8
Race			
White	96.9	97.5	98.2
Black	1.5	1.1	0.9
Other/Missing	1.7	1.5	1.0
Diabetes			
No	91.5	92.3	89.0
Yes	8.1	7.4	10.6
Missing	0.3	0.3	0.3
History of Heart Attack			
No	94.1	93.4	79.2
Yes	5.9	6.6	20.8
PSA Testing†			
No	14.4	11.9	12.4
Yes	85.6	88.1	87.6
Education			
Less than high school	8.2	7.3	8.2
High school graduate	19.6	17.4	19.2
Some college	25.3	25.7	26.4
College graduate	21.5	22.7	21.3
Graduate school	24.6	26.4	24.4
Missing	0.7	0.5	0.6
Family History of Prostate Cancer			
No	87.9	87.5	88.4
Yes	12.1	12.5	11.6

*Percentages adjusted to the age distribution of the entire study population.

†Ever reported prostate specific antigen (PSA) testing during study follow-up, excluding testing reported after prostate cancer diagnosis.

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Results

At enrollment in 1992–1993, 34% of participants (n = 24 016) reported use of 30 or more NSAID pills per month. Aspirin was the most commonly used NSAID, with 28% (n = 19 534) of participants reporting use of 30 or more aspirin per month.

Compared with nonusers, regular NSAID users (≥30 pills per month) at enrollment were on average older and slightly more likely to be white (Table 1). However, nearly all participants, regardless of NSAID use, were white. Regular NSAID users were considerably more likely to have reported a history of heart attack, likely due to the use of aspirin for secondary prevention of heart disease. Nearly all participants reported having received a PSA test during the study follow-up period, although both regular and occasional NSAID users were slightly more likely than nonusers to have received a PSA test during the study follow-up period.

Current frequency of total NSAID use was not associated with overall prostate cancer incidence (Table 2), even at relatively high levels of use (for ≥60 total NSAID pills per month, multivariable RR = 0.95, 95% CI = 0.86 to 1.05). This association was similar when adjusted only for age and race rather than for all covariates (age and race–adjusted RR = 0.94, 95% CI = 0.85 to 1.04). However, for advanced prostate cancer there was a suggestion of reduced risk with high levels of total NSAID use (for ≥60 pills per month, RR = 0.77, 95% CI = 0.57 to 1.04). In analyses by type of NSAID used, risk decreased with increasing frequency of ibuprofen use (P_{trend} = .03), although no specific level of use was associated with a statistically significant reduction in risk.

Long-duration regular NSAID use (defined as use of 30 or more pills a month for 5 or more years) was associated with slightly reduced overall prostate cancer incidence (multivariable RR = 0.82, 95% CI = 0.71 to 0.94) (Table 3). This association was similar when adjusted only for age and race (age and race–adjusted RR = 0.80, 95% CI = 0.70 to 0.92). The rate ratio associated with long duration regular NSAID use was slightly lower for advanced prostate cancer (RR = 0.67, 95% CI = 0.44 to 1.03) than for overall prostate cancer, although statistical precision was limited for analyses of advanced prostate cancer.

The absolute rate of prostate cancer (standardized to the approximate age distribution of person-years included in this analysis using 5-year age categories) was 1013 per 100 000 person-years among men who had never reported NSAID use, and 847 per 100 000 person-years among long-duration regular NSAID users.

As noted in the methods section, information about PSA testing was first collected in 1997, and therefore only follow-up from 1997 onward could be adjusted for history of PSA testing. However, in analyses restricted to the 1997–2001 follow-up interval, adjustment for history of PSA testing did not substantially change the results. For overall prostate cancer, the multivariable rate ratio for long-term regular NSAID use during the 1997–2001 interval was 0.87 (95% CI = 0.72 to 1.05) without adjustment for history of PSA testing and 0.84 (95% CI = 0.69 to 1.02) with adjustment for history of PSA testing. For advanced prostate cancer, the corresponding rate ratio was

Table 2. Prostate cancer incidence by current frequency of NSAID use, Cancer Prevention Study II Nutrition Cohort, 1992–2001*

		All Prostate Cancer		Advanced Prostate Cancer†	
Pills per month	Person-Years	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
Total NSAIDs					
None	184 818	1852	1.00 (referent)	269	1.00 (referent)
1–14	88 725	967	1.03 (0.96 to 1.12)	123	0.97 (0.78 to1.21)
15–29	48 234	526	1.07 (0.97 to 1.18)	53	0.76 (0.57 to 1.02)
30–59	107 158	1069	0.99 (0.91 to 1.06)	143	0.97 (0.79 to 1.19)
≥60	45 790	439	0.95 (0.86 to 1.05)	50	0.77 (0.57 to 1.04)
P_{trend}			.16		.42
Aspirin‡					
None	226 548	2274	1.00 (referent)	332	1.00 (referent)
1–14	86 137	953	1.04 (0.96 to 1.12)	110	0.90 (0.72 to 1.13)
15–29	42 527	455	1.06 (0.96 to 1.17)	46	0.75 (0.55 to 1.02)
30–59	98 936	981	0.99 (0.91 to 1.07)	127	0.94 (0.76 to 1.15)
≥60	20 577	190	0.95 (0.82–1.11)	23	0.79 (0.51 to 1.20)
P_{trend}			.75		.90
Ibuprofen‡					
None	393 020	4038	1.00 (referent)	534	1.00 (referent)
1–14	45 642	476	1.02 (0.93 to 1.13)	54	0.91 (0.69 to 1.21)
15–29	11 878	115	0.95 (0.79 to 1.14)	14	0.91 (0.54 to 1.55)
30–59	11 075	99	0.88 (0.72 to 1.07)	17	1.17 (0.72 to 1.89)
≥60	13 109	125	0.92 (0.77 to 1.10)	19	1.06 (0.67 to 1.68)
P_{trend}			.03		.56
Other NSAIDs‡					
None	445 226	4525	1.00 (referent)	610	1.00 (referent)
1–14	9977	118	1.08 (0.90 to 1.30)	11	0.81 (0.45 to 1.48)
15–29	2987	37	1.21 (0.87 to 1.67)	3	0.75 (0.24 to 2.32)
30–59	8141	86	0.98 (0.79 to 1.21)	5	0.42 (0.18 to 1.02)
≥60	8394	87	0.98 (0.79 to 1.21)	9	0.76 (0.39 to 1.47)
P_{trend}			.69		.09

*NSAID = Nonsteroidal anti-inflammatory drug. Rate ratios (RRs) adjusted for age, race, diabetes, history of heart attack, history of PSA testing, education, and family history of prostate cancer. P_{trend} (two-sided) values calculated using a continuous variable for pills per month and the likelihood ratio statistic. CI = confidence interval.

†Stage III or IV at diagnosis or fatal prostate cancer of unknown stage at diagnosis.

‡Also adjusted for use of other types of NSAIDs.

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Table 3. Prostate cancer incidence by duration of regular NSAID use, Cancer Prevention Study II Nutrition Cohort, 1992–2001*

NSAID type and duration of use	Person-Years	All Prostate Cancer		Advanced Prostate Cancer†	
		No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
Total NSAIDs					
No reported use	84250	839	1.00 (referent)	115	1.00 (referent)
Past or less than regular use only	237527	2,506	1.03 (0.95 to 1.12)	330	1.04 (0.84 to 1.29)
Current regular use, <5 years duration	122095	1,216	1.03 (0.94 to 1.12)	166	1.05 (0.82 to 1.33)
Current regular use, ≥5 years duration	30853	292	0.82 (0.71 to 0.94)	27	0.67 (0.44 to 1.03)
Aspirin‡					
No reported use	99246	977	1.00 (referent)	135	1.00 (referent)
Past or less than regular use only	255966	2,705	1.05 (0.97 to 1.13)	353	1.05 (0.85 to 1.28)
Current regular use, <5 years duration	96750	957	1.04 (0.95 to 1.14)	132	1.08 (0.84 to 1.37)
Current regular use, ≥5 years duration	22763	214	0.85 (0.73 to 0.99)	18	0.64 (0.39 to 1.05)

*Regular use defined as ≥30 pills per month. NSAID = Nonsteroidal anti-inflammatory drug. Rate ratios (RRs) adjusted for age, race, diabetes, history of heart attack, history of PSA testing, education, and family history of prostate cancer. CI = confidence interval.

†Stage III or IV at diagnosis or fatal prostate cancer of unknown stage at diagnosis.

‡Also adjusted for use of other types of NSAIDs.

0.70 (95% CI = 0.38 to 1.28) both with and without adjustment for history of PSA testing.

The association between long-duration regular NSAID use and prostate cancer incidence appeared similar when examined by attained age. The rate ratio for long-duration regular NSAID use was 0.84 (95% CI = 0.69 to 1.03) among men under age 70 years and 0.79 (95% CI = 0.66 to 0.96) among men over age 70 years.

In analyses by NSAID type, long-duration regular aspirin use was associated with a small reduction in overall prostate cancer incidence (RR = 0.85, 95% CI = 0.73 to 0.99). The rate ratio for long-duration regular ibuprofen use was 0.63 (95% CI = 0.38 to 1.04) for overall prostate cancer incidence. There was no apparent reduction in risk with long-duration regular use of NSAIDs other than aspirin or ibuprofen (RR = 0.89, 95% CI = 0.56 to 1.41).

Discussion

In this study, 5 or more years of regular use of aspirin or total NSAIDs was associated with a modest reduction in prostate cancer incidence. With respect to aspirin use, this finding is consistent with that seen in three *(8,10,11)* of four previous large prospective studies *(8–11)*. We had limited statistical power to examine the effects of long-duration regular use of individual NSAID types other than aspirin. Ibuprofen accounted for most nonaspirin NSAID use in this cohort. Long-duration regular ibuprofen use was associated with a reduction in risk similar in magnitude to that associated with aspirin use, although this association was not statistically significant. In contrast, there was no suggestion of any association between nonaspirin NSAID prescriptions and prostate cancer risk in two previous studies *(10,11)*. It is possible that this apparent difference in results is due to differences in the types of NSAIDs commonly used. Ibuprofen accounted for only a small proportion of nonaspirin NSAID prescriptions in one of these studies *(10)*, and it is unclear what types of NSAIDs were commonly prescribed in the second study *(11)*.

It is noteworthy that long-duration regular use of aspirin or of total NSAIDs was associated with reduced prostate cancer incidence in this study, whereas no association was observed with shorter-duration use. Few previous studies have examined duration of NSAID use. With respect to aspirin use, our results are similar to those from the Quebec pharmacy database analysis, in which aspirin use for at least 5 years was associated with reduced prostate cancer incidence, whereas no association was observed with shorter-duration use *(10)*. In the U.K. General Practice Research Database, current aspirin use was associated with reduced prostate cancer incidence regardless of duration of use *(11)*. In the Health Professionals Follow-up Study, long-duration aspirin use was not associated with prostate cancer incidence *(9)*. However, long duration aspirin use included use of as few as two aspirin tablets per week. No apparent association was observed with long-duration use of nonaspirin NSAIDs in two previous studies *(10,11)*. Results from our study highlight the potential importance of accounting for duration in studies of NSAIDs and prostate cancer incidence, including both observational studies and randomized trials.

A limitation of our study, and of all observational studies on NSAID use and prostate cancer risk, is that confounding by factors associated with both NSAID use and prostate cancer risk cannot be ruled out. In particular, PSA testing is an important potential confounder to consider because it may increase the probability of a prostate cancer diagnosis by detecting tumors that would never have become clinically apparent. However, PSA testing is unlikely to account for the reduction in risk associated with NSAID use because the prevalence of PSA testing was slightly higher among men who used NSAIDs regularly than among those who did not. An additional limitation of this study is that information on use of low-dose aspirin was not collected until 1997; therefore, we were able to examine duration of use only for standard-dose aspirin.

Strengths of this study include its prospective design and large size. In addition, detailed information on NSAID use was collected at several different time points. This information allowed us to examine prostate cancer risk among long-duration regular users, that is, men who were both current regular NSAID users and had been regular users for several years. In addition, our measure of total NSAID use included both NSAIDs obtained by prescription and those obtained over the counter. Previous large studies measured only use of NSAIDs obtained by prescription *(10,11)* or only aspirin use *(8,9)*.

In this large prospective study, long-duration regular NSAID use was associated with a modest reduction in prostate cancer risk. In our view, it would be premature to consider reduced risk of prostate cancer a benefit of using aspirin or other NSAIDs because to date there are relatively few large observational studies and no randomized trials addressing this question. However,

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because prostate cancer is a common cause of morbidity and mortality in older men, any true protective effect could be of some importance in assessing the risks and benefits of using aspirin or other NSAIDs.

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Note

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