

*Short Communication*Aspirin Use in Relation to Risk of Prostate Cancer¹

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Abstract

Experimental studies have shown inhibitory effects of nonsteroidal anti-inflammatory drugs on prostate cancer cell proliferation and reduction of prostate cancer metastasis, suggesting their possible preventive role for prostate cancer. We examined the association between regular aspirin use and the risk of prostate cancer among participants in the Health Professionals Follow-up Study, a prospective cohort of 47,882 United States men who were 40–75 years of age and without a history of prostate cancer in 1986. Biennial self-administered questionnaires were used to assess regular aspirin use from 1986 to 1996. We confirmed and staged incident cases of prostate cancer according to medical records and pathology reports. During 518,072 person-years of follow-up, 2,479 new cases of prostate cancer were ascertained. Of these, 608 were diagnosed as advanced (extraprostatic) prostate cancer and 258 as metastatic prostate cancer. We found no association between aspirin use and total prostate cancer. After accounting for prostate-specific antigen examinations and other potentially confounding variables, the relative risk of total prostate cancer for aspirin users compared with nonusers was 1.05 (95% confidence interval, 0.96–1.14). For metastatic prostate cancer, we observed a suggestive decrease in risk among men

reporting greater frequency of aspirin use. The multivariate relative risk of metastatic prostate cancer among men using aspirin 22 or more days/month was 0.73 (95% confidence interval, 0.39–1.38) compared with nonusers. We noted no evidence of a linear dose-response relationship (*P* for trend = 0.40). The results from this cohort indicate that regular aspirin use is not likely to prevent the incidence of total prostate cancer, but we cannot exclude a possible benefit of frequent aspirin use on risk of developing metastatic prostate cancer.

Introduction

Aspirin and other NSAIDs⁶ are hypothesized to play a role in the chemoprevention of prostate carcinogenesis by inhibiting the activity of COXs, key enzymes that catalyze the formation of prostaglandins from arachidonic acid (1). Evidence shows that COX-2 is up-regulated in human prostate cancer, and that COX-2 levels correlate positively with prostate tumor grade (2). Enhanced levels of prostaglandin E₂ (3) and its precursor arachidonic acid (4) stimulate prostate tumor growth, and COX-2 inhibitors suppress prostate tumor growth in rats (5) as well as in human prostate tumor-derived cell lines (6). Animal studies suggest that aspirin may reduce metastasis of prostate cancer but has less influence on prostate tumor volume (7), suggesting that aspirin may more strongly suppress cellular growth for aggressive prostate cancer than for slowly growing prostate tumors.

Despite fairly consistent laboratory evidence in support of the hypothesis that NSAIDs inhibit the development of prostate cancer, epidemiological data concerning the relationship between NSAID use and risk of prostate cancer are inconclusive. Five cohort studies (8–12) and two case-control studies (13, 14) found inverse associations between NSAID use and prostate cancer risk. Two of these studies (12, 13) suggest a benefit of aspirin use on fatal or advanced prostate cancer. In contrast, three case-control studies (15–17) reported moderate positive relationships between NSAID use and prostate cancer risk. Overall, the epidemiological data suggest both an increased likelihood of aspirin users being diagnosed with early-stage prostate cancer as well as a benefit of long-term aspirin use on risk of developing advanced prostate cancer.

Because the relationship between NSAID use and prostate cancer remains unresolved, we examined prospectively the association between regular use of aspirin and subsequent risk of prostate cancer in the Health Professionals Follow-up Study, a large cohort of United States men with detailed data on aspirin use, screening behaviors, and clinical staging of cancer outcomes.

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⁶ The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; RR, relative risk; CI, confidence interval; PSA, prostate-specific antigen; OR, odds ratio.

Table 1 RR of prostate cancer in relation to aspirin use in the Health Professionals Follow-up Study

	Aspirin use ^a			
	1986	1986 + 1988	1986 + 1988 + 1990	1986 + 1988 + 1990 + 1992
Follow-up period	1986–1998	1988–1998	1990–1998	1992–1998
Total cases (non-stage A1) ^b				
Nonusers, cases/person-years	1604/368,077	880/169,448	606/100,992	222/32,510
Users, cases/person-years	875/149,995	557/79,276	375/42,877	248/28,332
Age-adjusted RR ^c (95% CI)	1.08 (1.00–1.17)	1.05 (0.94–1.17)	1.11 (0.98–1.26)	1.05 (0.88–1.26)
Multivariate RR ^d (95% CI)	1.10 (1.01–1.19)	1.06 (0.95–1.19)	1.11 (0.97–1.27)	1.04 (0.86–1.26)
Advanced cases (stages C and D) ^b				
Nonusers, cases/person-years	404/372,687	225/171,846	142/102,566	42/32,999
Users, cases/person-years	204/152,812	120/80,967	75/43,942	45/28,882
Age-adjusted RR ^c (95% CI)	1.00 (0.85–1.19)	0.89 (0.71–1.11)	0.96 (0.72–1.27)	1.03 (0.68–1.58)
Multivariate RR ^d (95% CI)	0.98 (0.82–1.16)	0.88 (0.70–1.10)	0.90 (0.67–1.21)	1.01 (0.65–1.56)
Metastatic cases (stage D) ^b				
Nonusers, cases/person-years	172/373,814	87/172,479	52/102,917	16/33,076
Users, cases/person-years	86/153,388	46/81,308	27/44,141	11/29,015
Age-adjusted RR ^c (95% CI)	0.97 (0.75–1.26)	0.85 (0.59–1.23)	0.91 (0.57–1.47)	0.63 (0.28–1.38)
Multivariate RR ^d (95% CI)	0.94 (0.72–1.23)	0.86 (0.59–1.24)	0.84 (0.52–1.36)	0.71 (0.31–1.62)

^a Aspirin use was defined as aspirin use two or more times/week. Users are participants who reported consistent aspirin use (1986; 1986 and 1988; 1986, 1988, and 1990; 1986, 1988, 1990, and 1992); nonusers are participants who consistently reported no aspirin use during the specified time periods.

^b Non-stage A1, confined to prostate gland; Stages C & D, extraprostatic extension localized to periprostatic area or metastatic disease involving lymph nodes or other organs. Stage D, metastatic disease involving lymph nodes or other organs, or fatal prostate cancer. Because stage A1 lesions are typically indolent and are especially prone to detection bias, we excluded these (3% of the total) from our analyses.

^c RR, relative risk adjusted for current age.

^d RR, relative risk adjusted for current age, time period, body mass index at age 21, height, pack-years of smoking in the previous decade, family history of prostate cancer, vigorous physical activity, intake of total energy, calcium, fructose, tomato-based foods, red meat, fish, supplemental vitamin E, linoleic acid, and α -linolenic acid.

Patients and Methods

Study Population. The Health Professionals Follow-up Study was established in 1986 when 51,529 United States male health professionals between the ages of 40 and 65 years returned a detailed mailed questionnaire concerning their history of medical conditions, medication use, diet, and lifestyle factors. Since then, follow-up questionnaires have been mailed biennially to update information on potential risk factors and to identify newly diagnosed illnesses.

Assessment of Aspirin Use. Regular use of aspirin was assessed in 1986 and every 2 years thereafter by asking participants to report whether they currently took “any of the following medications two or more times per week” and listed “aspirin (*e.g.*, Anacin, Bufferin, Alka-Seltzer),” among other drugs. Starting in 1992, the questionnaire included a more detailed assessment of aspirin use. Respondents were asked to report the average number of days each month aspirin was taken (none, 1–4, 5–14, 15–21, or 22 or more).

Identification of Cases of Prostate Cancer. On each biennial questionnaire, participants were asked whether they had been diagnosed with prostate cancer during the prior 2 years. For those who reported prostate cancer, we requested permission to obtain hospital records and pathology reports. For deceased men, we contacted next of kin for this approval. A study physician reviewed all medical records and staged prostate cancers according to information received from medical reports.

Data Analysis. We calculated person-time of follow-up for each participant from the date of return of the 1986 questionnaire to the date of prostate cancer diagnosis, death, or the end of the study period in 1998, whichever came first. The age-adjusted RR was calculated using the Mantel-Haenszel method. Multivariate RRs were computed using Cox proportional hazards regression modeling.

Results

We examined three different prostate cancer outcomes (total, advanced, and metastatic). For total prostate cancer, a weak positive relation was observed among men reporting regular aspirin use at baseline in 1986 compared with nonusers (multivariate RR, 1.10; 95% CI, 1.01–1.19; Table 1). For advanced and metastatic prostate cancer, no significant relationships were evident for aspirin use *versus* nonuse, although for metastatic cancer a suggestive but nonsignificant inverse association was found when we compared men reporting consistent aspirin use with men consistently not using aspirin (multivariate RR, 0.71; 95% CI, 0.31–1.62).

Because enhanced medical surveillance among aspirin users may decrease their likelihood of being diagnosed with metastatic prostate cancer, we repeated the analyses after excluding noncases who had not had an examination including PSA values by 1994 (52% of person-time excluded). Using consistent nonusers of aspirin as the reference group, the multivariate RRs of total, advanced, and metastatic prostate cancer associated with consistent aspirin use were 0.91 (95% CI, 0.76–1.11), 0.89 (95% CI, 0.57–1.39), and 0.63 (95% CI, 0.27–1.46), respectively.

We addressed the dose-response relation by evaluating the association between increasing frequency of aspirin use, which was first assessed in 1992, and prostate cancer risk (Table 2). For total and advanced prostate cancer, essentially null associations were found for any given level of aspirin use when compared with nonuse of aspirin. For metastatic prostate cancer, a statistically nonsignificant lower risk was seen when we compared extreme categories of frequency of aspirin use (multivariate RR comparing men using aspirin on 22+ days/month with nonusers, 0.73; 95% CI, 0.39–1.38). No evidence of a linear trend was noted (P for trend = 0.40).

After excluding noncases who had not had a PSA examination by 1994, the multivariate RRs of metastatic prostate

Table 2 RR of prostate cancer in relation to frequency of aspirin use (days/month) in the Health Professionals Follow-up Study, 1992–1998

	Frequency of aspirin use (days/month)				<i>P</i> Trend
	0–4 ^a	5–14	15–21	≥22	
Total cases (non-stage A1) ^b					
Cases/person-years	683/113,810	158/25,640	121/17,280	349/42,141	
Age-adjusted RR ^c (95% CI)	1.0	0.98 (0.82–1.16)	0.98 (0.80–1.18)	1.01 (0.89–1.15)	0.90
Multivariate RR ^d (95% CI)	1.0	0.96 (0.80–1.14)	0.97 (0.79–1.18)	1.02 (0.89–1.17)	0.83
Advanced cases (stages C & D) ^b					
Cases/person-years	126/115,313	27/25,991	26/17,553	65/42,912	
Age-adjusted RR ^c (95% CI)	1.0	0.90 (0.60–1.37)	1.15 (0.75–1.75)	1.03 (0.76–1.39)	0.70
Multivariate RR ^d (95% CI)	1.0	0.89 (0.59–1.36)	1.11 (0.72–1.70)	1.01 (0.74–1.37)	0.87
Metastatic cases (stage D) ^b					
Cases/person-years	38/115,563	9/26,048	7/17,624	14/43,100	
Age-adjusted RR ^c (95% CI)	1.0	1.01 (0.49–2.09)	1.02 (0.45–2.31)	0.72 (0.38–1.35)	0.29
Multivariate RR ^d (95% CI)	1.0	1.00 (0.47–2.14)	1.05 (0.46–2.42)	0.73 (0.39–1.38)	0.40
Fatal cases ^b					
Cases/person-years	6/115,680	2/26,063	0/17,643	3/43,138	
Age-adjusted RR ^c (95% CI)	1.0	1.38 (0.28–6.84)		0.86 (0.22–3.47)	0.65
Multivariate RR ^d (95% CI)	1.0	1.19 (0.28–6.84)		0.56 (0.12–2.71)	0.37

^a Nonuse of aspirin was defined as aspirin use on less than or equal to four days/month. In the current analyses, we began follow-up in 1992 and excluded men who had prostate cancer diagnosed before return of the 1992 questionnaire.

^b Non-stage A1, confined to prostate gland; Stages C & D, extraprostatic extension localized to periprostatic area or metastatic disease involving lymph nodes or other organs. Stage D, metastatic disease involving lymph nodes or other organs, or fatal prostate cancer. Because stage A1 lesions are typically indolent and are especially prone to detection bias, we excluded these (3% of the total) from our analyses.

^c RR, relative risks are adjusted for current age.

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cancer across increasing days/month of aspirin use (0–4, 5–14, 15–21, and 22+) were 1.00, 0.87, 1.07, and 0.64 (95% CI, 0.33–1.22), respectively (*P* for trend = 0.22).

Discussion

In this prospective study, we observed no association between aspirin use and overall prostate cancer incidence. Because of the possibility that aspirin more strongly suppresses cellular growth for aggressive tumors than for slowly growing tumors, we specifically addressed the relation of aspirin use to risk of metastatic prostate cancer. We observed a statistically nonsignificant inverse relation of consistent aspirin use on 22+ days/month, as reported on consecutive questionnaires, with metastatic prostate cancer risk.

A possible explanation of this finding is that aspirin users undergo screening more frequently, leading to diagnosis of prostate cancer at an earlier stage. However, the inverse relation with metastatic prostate cancer persisted when examinations including PSA values were taken into account. Of note, our group has observed the same pattern for genetic and constitutional features, such as a polymorphism in the androgen receptor gene, plasma insulin-like growth factor I levels, and height, which are nonbehavioral factors that are unlikely to be prone to detection bias.

Our findings are consistent with most previous cohort studies (8–10, 12) examining the association between NSAID use and prostate cancer, which found weak inverse and statistically nonsignificant associations (RRs between 0.82 and 0.95) between aspirin or NSAID use and risk of total prostate cancer. Our results are also compatible with those from one case-control study examining regular use of low-dose aspirin (13), which reported an OR of 0.84 for total prostate cancer and an OR of 0.69 for advanced prostate cancer, suggestive of a stronger benefit of aspirin use on advanced prostate cancer.

One cohort study (11) and one case-control study (14) reported strong inverse associations (ORs between 0.34 and

0.45) between regular daily NSAID intake and risk of total prostate cancer. The former study (11) comprised men with a high level of surveillance for prostate cancer and found a stronger apparent protective effect of NSAIDs among older men (OR, 0.17), suggesting that NSAIDs may prevent the progression of preclinical disease to clinically detectable cancer. In the latter study (14), controls were healthy men who underwent prostate screening, possibly a group enriched with health-seeking behaviors, thereby biasing the results in favor of a protective effect of NSAIDs. The results for total prostate cancer in these two studies (11, 14) were markedly different from all other available data (8–10, 12, 13, 15–17).

Three case-control studies (15–17) found increased risks of total prostate cancer (ORs between 1.28 and 1.60) with greater number of NSAID prescriptions. However, the positive relationships in these studies may have been attributable to detection bias, because men needed to see a doctor to receive a NSAID prescription. Moreover, use of over-the-counter NSAIDs were not taken into consideration (15–17), and the exposure definition may have included NSAIDs with little anti-inflammatory activity (16, 17).

An inverse association between aspirin use and metastatic prostate cancer is supported by laboratory studies showing that NSAIDs suppress prostate cancer cell growth, apparently through an induction of apoptosis (18). The inhibition of prostate cancer metastasis by NSAIDs may involve several pathways, including inhibition of enzymatic degradative processes of prostate tumor cell invasiveness (19), down-regulation of vascular endothelial growth factor expression (20) and decreased angiogenesis in prostate cancer cells (21), activation of transcription factors such as peroxisome proliferator-activated receptor γ (22), potentially resulting in antiproliferative effects in PC-3 cell lines (23), and inhibition of androgen receptor transcriptional activity in LNCaP cells (24).

In summary, our results among United States men do not support the hypothesis that regular aspirin use prevents the

incidence of total prostate cancer. However, the suggestion of a potential decrease in the risk of metastatic prostate cancer among frequent users of aspirin warrants further study.

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