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Regular use of aspirin and prostate cancer risk (United States)

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Abstract It has been hypothesized that aspirin and other nonsteroidal anti-inflammatory drugs can decrease the risk of developing prostate and other cancers, although observational studies have not been very conclusive. The current study examined the effects of regular aspirin use on prostate cancer risk in 1,029 patients with primary, incident cancer of the prostate and 1,029 hospital controls frequency-matched to cases by 5-year age group and period of questionnaire completion. Patients who reported use of aspirin for at least once a week for at least 6 months were classified as regular users, with others classified as non-users. Results indicate that regular aspirin use may not be associated with decreased prostate cancer risk [odds ratio (OR) 1.05, 95% confidence interval (CI) 0.89–1.25], frequency of use (OR for at least seven/week 0.91, 95% CI 0.73–1.13), duration of use (OR for at least 10 years of use 1.17 95% CI 0.93–1.46) or tablet years (defined as tablets per day *x* years of use). A similar lack of association was observed when analyses were performed examining stage of the cancer. These data suggest that aspirin use may not be associated with reduced risk of prostate cancer.

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Introduction

It is estimated that approximately 232,090 new prostate cancer cases will be diagnosed in 2005, and 30,350 deaths due to prostate cancer will occur, ranking it first and second in cancer incidence and mortality, respectively, amongst American males [1]. Few conclusive risk factors, such as age, being African American and family history of prostate cancer have been identified, none of which are modifiable [2]. Thus, the role of chemoprevention has become important in decreasing the burden of this disease.

It has been hypothesized that aspirin and othernonsteroidal anti-inflammatory drugs (NSAIDs) can decrease the risk of developing prostate and other cancers [3]. Possible mechanisms, including inhibition of angiogenesis and induction of apoptosis, are thought to be mediated via the inhibition of cyclooxygenase (COX) enzymes, which leads to a decrease in prostaglandin (PG) synthesis [4]. The COX-1 form is constitutively expressed and involved in homeostasis, while COX-2 is induced under certain conditions and involved in inflammation. Aspirin primarily inhibits COX-1, but can also affect COX-2 [3].

In 2000, Gupta et al. [5] were the first to report about COX-2 overexpression in human prostate adenocarcinoma relative to benign tissue. In the same year, Yoshimura et al. [6] reported that the expression of immunoreactive COX-2 in tumor cells was much stronger than what they detected in benign prostatic hypertrophy and normal prostate cells. Several studies have reported similar results regarding COX-2 overexpression in prostate cancer cells, while others have found that COX-2 overexpression to be present

not in prostatic tumor tissue, but in surrounding cells or lesions implicated in prostate cancer [7]. Recent reviews by Hussain et al. [8] and Pathak et al. [9] include mentions of data suggestive of a possible role of NSAIDs in the chemoprevention of prostate cancer. These include COX-2 overexpression upregulating anti-apoptotic Bcl-2 [10], promotion of prostate carcinoma cell lines through PGE2 treatment [11] and stimulation of PIN cell growth by PGE2 via activation of the IL-6 signaling pathway [12]. Additionally, inhibiting the COX pathways decreases the production of reactive oxygen species that have the potential to damage various cellular components like DNA [8].

Despite the convincing results provided by laboratory studies, results from observational studies have not been very conclusive [13–24]. In general, they suggest a weak inverse association between regular aspirin or NSAID use and prostate cancer risk, with point estimates slightly below one. The majority of previous studies employed a relatively crude classification of aspirin use and few examined more specific exposure characteristics like duration or frequency or use.

In this hospital-based case–control study, we evaluated the association between aspirin use and prostate cancer risk. In addition to performing analyses comparing regular to non-regular users, we were also able to examine the effects of frequency, duration and intensity. We performed the same analyses stratified by stage at diagnosis.

Methods

The population for this hospital-based case–control study was drawn from male patients seen at the Roswell Park Cancer Institute (RPCI) in Buffalo, New York, between 1982 and 1998. All completed the Patient Epidemiological Data System (PEDS) questionnaire, which was offered to all patients during their first RPCI visit during that time period, prior to treatment, and was filled out by approximately half. The 16-page instrument covered information on reproductive and medical histories, family history of cancer, occupational and environmental exposures, tobacco use, alcohol consumption, and diet. It also assessed aspirin and other medication use prior to the onset of any current illness. Specifically, the instrument queried: 'If you are currently ill, indicate how often you took these medications before the illness'. Participants provided information on how many times a week and for how many years they took aspirin.

Cases consisted of 1,029 men with primary incident cancer of the prostate, identified from the PEDS database and RPCI tumor registry. Controls consisted of 1,029 men who were seen at RPCI for non-neoplastic conditions. They were randomly selected from the PEDS database, and frequency matched to the cases based on five-year age groups and time period of questionnaire completion (pre versus post 1990, so that controls would be comparable to cases with respect to opportunity to receive PSA testing).

For study purposes, subjects who reported aspirin use of at least once a week for at least 6 months were classified as regular users. All others were considered non-users. Frequency of use was assessed by comparing participants who were classified as non-users to participants who reported that they had taken aspirin either one to six times per week or seven or more times per week. Duration of use was evaluated by comparing non-users to participants who took aspirin for 6 months to 10 years or more than 10 years. We also evaluated a combined measure of frequency and duration by computing tablet years (tablets per day x years of use). Reason for aspirin use was unavailable for these analyses.

Descriptive analyses included Student t-tests of means for cases and controls for continuous variables, and chi square tests for categorical variables. Covariates that were examined consisted of known and suspected risk factors for prostate cancer: age, education, family history of prostate cancer, cigarette smoking, race and body mass index. None of the covariates fit the classic definition of cofounders by being associated with both diseases status and aspirin use. However, as family history of prostate cancer is one of the better established risk factors described in the literature and, along with body mass index, was found to be a strong predictor of disease in this patient group, it was decided to include both variables in regression models, along with age. Race was excluded from further analyses, as the group was almost exclusively white.

Unconditional logistic regression analysis was used to compute odds ratios (ORs) with 95% confidence intervals (CIs). In all analyses, non-regular aspirin users represented the reference group.

Results

Table 1 summarizes the descriptive characteristics of the study population. Both cases and controls were predominantly white (98% for each). Compared with controls, cases were more likely to have a family history of prostate cancer and had a higher body mass index (BMI). Controls were slightly more likely to be ever-smokers, although the more detailed smoking characteristics did not differ much from those of cases considered ever-smokers. Results of logistic regression modeling are reported in Tables 2 and 3.

About 51% of the cases and 50% of the controls were classified as regular aspirin users (Table 2). Regular aspirin

Table 1 Characteristics of prostate cancer cases and hospital controls, Roswell Park Cancer Institute – 1982–1998

Variable	Cases (n = 1029)	Controls (n = 1029)	p-value[a]
Age[b]			
Mean (SD)	67.1 (7.8)	67.1 (7.9)	0.93
Education[a]			
Up to high school	262 (26%)	245 (24%)	0.18
High school	270 (26%)	289 (28%)	
Some college	195 (19%)	223 (22%)	
College graduate	298 (29%)	266 (26%)	
Race			
Black	20 (2%)	16 (2%)	0.42
White	1004 (98%)	1011 (98%)	
Other	5 (1%)	2 (1%)	
Family history of prostate cancer			
No	889 (86%)	947 (92%)	<0.001
Yes	140 (14%)	82 (8%)	
Smoking (packyears)[c]			
Never	355 (35%)	355 (33%)	0.60
0.2–17.5	167 (17%)	166 (16%)	
18–37	179 (18%)	168 (17%)	
37–59	172 (17%)	163 (16%)	
60+	133 (13%)	158 (18%)	
Body Mass Index (kg/m^2)[d]			
≤23.76	224 (22%)	258 (26%)	0.04
23.77–25.82	245 (24%)	245 (24%)	
25.83–27.94	300 (30%)	246 (25%)	
27.95+	235 (23%)	256 (26%)	
Stage at diagnosis			
Local	501 (49%)	–	–
Regional	281 (27%)		
Distant	232 (23%)		
Unknown	15 (1%)		

[a] Pearson χ^2 test for proportions

[b] t-test for mean values, mean (SD)

[c] Based on quartiles of control distribution after excluding never-smokers

[d] Based on quartiles of control distribution

use was not associated with cancer risk (adjusted OR 1.05, 95% CI 0.89–1.25). Respondents who reported frequency of use of 1–6 tablets per week were at a small, non-significant increase in risk of prostate cancer compared to non-regular users (adjusted OR 1.20, 95% CI 0.97–1.47), while taking at least seven tablets per week was associated with a slight decrease in risk (0.91, 95% CI 0.73–1.13). Duration of use was not associated with risk (1–10 years of

Table 2 Risk of prostate cancer in association with aspirin use Roswell Park Cancer Institute – 1982–1998

	Cases (n = 1029)	Controls (n = 1029)	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Regular use				
Non-users[b] (referent)	508 (49%)	519 (50%)	1.00	1.00
Users[c]	521 (51%)	510 (50%)	1.04 (0.88, 1.24)	1.05 (0.89, 1.25)
Aspirin frequency				
1–6/week	297 (29%)	256 (25%)	1.19 (0.96, 1.45)	1.20 (0.97, 1.47)
7+/week	224 (22%)	254 (25%)	0.90 (0.73, 1.12)	0.91 (0.73, 1.13)
Duration of use				
1–10 years	282 (27%)	300 (29%)	0.96 (0.78, 1.18)	0.97 (0.79, 1.19)
10+years	239 (23%)	210 (21%)	1.16 (0.93, 1.45)	1.17 (0.93, 1.46)
Tablet years				
1–10 tablet yrs	392 (38%)	392 (38%)	1.00 (0.84, 1.20)	1.01 (0.84, 1.22)
10+tablet years	129 (13%)	129 (13%)	1.21 (0.91, 1.60)	1.21 (0.91, 1.61)

[a] Adjusted for age, family history of prostate cancer, BMI

[b] Non-users served as reference group for all logistic regression analyses

[c] Men who reported use of these agents at least once a week for at least six months were classified as aspirin users

Table 3 Risk of prostate cancer by stage in association with aspirin use Roswell Park Cancer Institute – 1982–1998

	Controls (n = 1029)	Local (n = 501)	Adjusted OR[a] (95% CI)	Regional (n = 281)	Adjusted OR[a] (95% CI)	Distant (n = 232)	Adjusted OR[a] (95% CI)
Regular use							
Non-Users[b] (referent)	519 (50%)	249 (50%)	1.00	136 (48%)	1.00	117 (51%)	1.00
Users[c]	510 (50%)	252 (50%)	1.04 (0.84, 1.29)	145 (52%)	1.10 (0.84, 1.43)	115 (49%)	1.01 (0.75, 1.34)
Aspirin frequency							
1–6/week	256 (25%)	142 (28%)	1.16 (0.90, 1.50)	77 (27%)	1.15 (0.82, 1.54)	74 (18%)	1.34 (0.96, 1.87)
7+/week	254 (25%)	110 (22%)	0.92 (0.70, 1.21)	68 (24%)	1.04 (0.86, 1.65)	41 (17%)	0.70 (0.47, 1.03)
Duration of use							
1–10 years	300 (29%)	141 (28%)	1.00 (0.78, 1.29)	74 (26%)	0.97 (0.70, 1.33)	63 (27%)	0.92 (0.65, 1.29)
10+ years	210 (20%)	111 (22%)	1.10 (0.83, 1.45)	71 (25%)	1.28 (0.92, 1.78)	52 (22%)	1.14 (0.79, 1.65)
Tablet years							
1–10 tablet yrs	401 (39%)	194 (39%)	1.03 (0.82, 1.29)	104 (37%)	1.00 (0.75, 1.34)	87 (38%)	0.97 (0.71, 1.33)
10+ tablet years	109 (11%)	58 (12%)	1.10 (0.77, 1.57)	41 (15%)	1.44 (0.96, 2.17)	28 (12%)	1.13 (0.71, 1.80)

[a] Adjusted for age, family history of prostate cancer, BMI

[b] Non-users served as reference group for all logistic regression analyses

[c] Men who reported use of these agents at least once a week for at least six months were classified as aspirin users

use OR 0.97, 95% CI 0.79–1.19; >10 years of use OR 1.17, 95% CI 0.93–1.46). Tablet-years were created by combining frequency and duration of use. This measure was also not associated with a change in risk (≤10 tablet-years OR 1.01, 95% CI 0.84–1.22; >10 tablet-years OR 1.21, 95% CI 0.91–1.61).

No significant association between aspirin use and disease stage (local, regional, distant) was observed (Table 3). The same set of 1,029 controls was used in each of these analyses, which also adjusted for age, family history of prostate cancer, and BMI. Again, most point estimates were slightly above one, although there was a 30% reduction in the risk of distant prostate cancer associated with high frequency of use (7+tablets per week OR 0.70, 95% CI 0.47–1.03).

Discussion

In this hospital-based case–control study based on data collected via a self-administered questionnaire, we observed no association between aspirin use and prostate cancer risk. We also examined whether aspirin use was associated with tumor stage. As with the other analyses that were performed, a lack of association was observed with various subgroups. Most of the point estimates were slightly above one, although all 95% confidence intervals include unity.

While the results from this study differed from most previous studies in that our point estimates were generally not less than one, the lack of statistical significance we observed follows what has been reported by others. Of the previous studies [13–24], a majority observed weak inverse associations between aspirin use and risk, with only a few achieving statistical significance [17, 18, 21–24]. Two recent meta-analyses that examined aspirin/NSAID use and prostate cancer risk [25, 26] reached the same conclusions regarding the strength of association and statistical significance. Gonzalez-Perez et al. [25] reported a summary OR of 0.92 (95% CI 0.81–1.04). Mahmud et al. (26) reported a summary OR for aspirin use of 0.9 (95% CI 0.82–0.99), and noted that most of the studies used in their meta-analysis were limited by such factors as limited dose and duration information, exposure misclassification and either did not or were unable to adjust for detection bias. The two most recent studies published on this topic [23, 24] both reported an association between aspirin use and decreased risk. Platz et al. [24], in a prospective cohort, reported a borderline significant inverse association (RR for ever to never aspirin use = 0.76, 95% CI 0.54–1.07). They also performed a separate age-adjusted analysis in which they used measured concentrations of serum PSA to examine whether PSA varied amongst users and non-users of various analgesics. The only statistically significant differences they found were between current users and nonusers of non-aspirin NSAIDs among younger men with normal range PSA [24]. Garcia-Rodriguez et al. [23] conducted a case–control study nested within a prescription database in the United Kingdom, and reported an OR of 0.70 (95% CI 0.61–0.79) for current aspirin users versus non-users.

Our null findings may be related to the possibility that, prior to cancer diagnosis or because of associated conditions or complications, cases experienced sufficient discomfort to warrant aspirin usage. Unfortunately, reasons for aspirin use were not available. It is also possible that

men who use aspirin on a frequent and long-term basis exhibit health behaviors that differ from men who do not, such as undergoing cancer screening more frequently, potentially biasing results.

While we attempted to address the issue of PSA testing influencing screening through matching on time period, having and incorporating the PSA information into our models would have allowed for more thorough analyses. However, when we performed subgroup analyses on individuals who filled out the questionnaire from 1982–1986 and 1994–1998, the results for these two groups were similar to each other (data not shown) and to the overall group. Additionally, if frequent visits to the doctor would result in increased aspirin use, PSA testing and screening, we might expect a positive trend in risk estimates for aspirin use with increasing stage at diagnosis, which was not what occurred in our data (Table 3).

Exposure misclassification of aspirin use may have also affected the results, since the analyses were based on self-reported aspirin use and data verification was not possible. The hospital-based design, while potentially reducing recall bias, decreases the generalizability of our findings to the general population. Generalizability is also affected by having only about 50% of eligible patients complete the PEDS questionnaire. We do not have data on non-responders, and so are unable to ascertain whether or not these individuals differed from participants on aspirin use or other key factors. However, we did see that one of the strongest risk factors for prostate cancer, family history, was associated with risk in this study group. Further, previously published studies based on PEDS data faced the same issue, and several were able to replicate associations frequently reported in the epidemiology literature [27–32], including for prostate cancer [27].

Another limitation that was faced was the relative lack of non-aspirin analgesic information for some of the participants. In participants in which this information was available, however, there was no association with aspirin use or cancer risk (data not shown).

The primary strength of the study is the overall size. Data for over 2,000 individuals was analyzed, with controls randomly selected (after meeting matching criteria) from a large pool of potential participants. The aspirin questions allowed us to examine not only regular use, but also frequency, duration and intensity, variables that have not been explored in many of the previously published studies. Finally, while there was a lack of PSA information on individual patients, we matched controls to cases on the general time period in which they filled out the PEDS questionnaire. This would increase the likelihood that the two groups would be comparable on having had the opportunity to have PSA testing and likely subject to similar biases.

In conclusion, in this case–control study, we observed a lack of association between regular use of aspirin and prostate cancer risk. While overall conclusions differ from those made by several other studies, further studies are warranted that also employ frequency and duration measures.

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