Nonsteroidal Anti-inflammatory Drugs and Risk of Prostate Cancer in the Baltimore Longitudinal Study of Aging

Elizabeth A. Platz,1,2,3 Sabine Rohrmann,1 Jay D. Pearson,2,6 Maria M. Corrada,7 Douglas J. Watson,6 Angelo M. De Marzo,2,3,4 Patricia K. Landis,2 E. Jeffrey Metter,5 and H. Ballentine Carter 2,3

1Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health; 2James Buchanan Brady Urological Institute, Sidney Kimmel Comprehensive Cancer Center, and 3Department of Pathology, Johns Hopkins Medical Institutions; 4Clinical Research Branch, Intramural Research Program, National Institute on Aging, Baltimore, Maryland; 5Department of Epidemiology, Merck & Co., Blue Bell, Pennsylvania; and 6Clinic for Aging Research

Abstract

Background: Laboratory and epidemiologic studies suggest that aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAID) reduce the risk of cancer, possibly via inhibition of the cyclooxygenase enzymes. We evaluated the association of aspirin and nonaspirin NSAIDs with subsequent prostate cancer in a prospective study. We also assessed whether use of these drugs influences serum prostate-specific antigen (PSA) concentration.

Methods: Participants were 1,244 male members of the Baltimore Longitudinal Study of Aging. Use of prescription and over-the-counter drugs was collected by questionnaire and interview at multiple study visits. One hundred forty-one prostate cancer cases diagnosed between 1980 and May 2004 were confirmed by medical record review. We used Cox proportional hazards regression to estimate the rate ratio (RR) of prostate cancer updating drug use over time and taking into account age and year. We used generalized estimating equations to calculate age-adjusted geometric mean PSA concentration by aspirin or nonaspirin NSAIDs use among 933 of the men without prostate cancer, for whom 3,749 PSA measurements in archived sera had been done previously.

Results: On 46.0% and 21.5% of the visits, current use of aspirin or nonaspirin NSAIDs (mostly ibuprofen) was reported, respectively. The RRs of prostate cancer comparing ever to never use were 0.76 (95% confidence interval 95% CI), 0.54-1.07 for aspirin, 0.79 (95% CI, 0.54-1.16) for nonaspirin NSAIDs, and 0.71 (95% CI, 0.49-1.02) for either medication. The association for ever use of either aspirin or nonaspirin NSAIDs was suggestively more pronounced in men <70 years (RR, 0.54; 95% CI, 0.27-1.03) than in men ≥70 years (RR, 0.78; 95% CI, 0.50-1.22; Pinteraction = 0.73). The RR for current use of either drug was attenuated relative to ever use. Mean PSA concentration did not differ between users and nonusers of either aspirin or nonaspirin NSAIDs (1.01 versus 0.98 ng/mL, P = 0.56).

Conclusion: In this prospective study, men, in particular younger men, who had ever used aspirin or nonaspirin NSAIDs had a modest nonstatistically significant lower risk of prostate cancer. The modest inverse association was unlikely due to detection bias that might have resulted if anti-inflammatory drugs had influenced serum PSA concentration.

Introduction

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) have been hypothesized to decrease prostate cancer risk by inhibiting cyclooxygenase (COX) enzymes (1), which catalyze the conversion of arachidonic acid to proinflammatory prostaglandins (2). Although only a few studies have been published on COX-1 expression in the prostate, it has been reported to be expressed in normal prostate basal cells in benign prostatic hyperplasia (3) and in prostate smooth muscle (3, 4) and to be expressed at elevated levels in prostate cancer (3). Whereas a number of reports (3-10) have examined COX-2 expression in prostate cancer, the results remain controversial; several indicate that COX-2 is highly expressed in prostate cancer, whereas others found that COX-2 expression is absent in the majority of adenocarcinomas but is overexpressed in some proliferative inflammatory atrophy lesions, especially in associated macrophages (9). More recently Yegnasubramanian et al. reported that the CpG islands in the promoter region of the gene encoding COX-2, PTGS2, is selectively hypermethylated in prostate cancer tissue compared with benign prostate, suggesting a mechanism for the lack of expression of COX-2 in prostate cancer (11).

Inflammation is commonly found in or surrounding regions of focal atrophy (12) and in diagnostic or resected prostate specimens (13-16). Whether intraprostatic inflammation is an etiologic contributor to the development of prostate cancer is unknown, although it is postulated that inflammation may serve as both an initiator and a promoter of carcinogenesis through its effects on DNA damage and cell killing (17). Because the determinants of the inflammatory response and its byproducts are targets for prevention and intervention by the administration of drugs that inhibit the inflammatory response, detailed evaluation in epidemiologic studies of the influence of use of such drugs on the risk of prostate cancer, as well as, careful consideration of possible sources of bias in these studies is warranted.

When taken together, prospective and case-control studies suggest a weak inverse association between regular use of aspirin or NSAIDs and risk of prostate cancer (18-20). Among the prospective studies, the relative risk of prostate cancer or prostate cancer death for regular aspirin use ranges from 0.45 [95% confidence interval (95% CI), 0.28-0.73] for daily use (21) to 0.76 (95% CI, 0.60-0.98) for use of more than six aspirin tablets almost every day versus none (22) to 1.05 (95% CI, 0.96-1.14) for twice or more per week (23). Although null for total prostate cancer, in the latter study, the relative risk of...
metastatic or fatal prostate cancer for use ≥22 days per month
versus fewer than 4 days per month was 0.73 (95% CI, 0.39-
1.38; ref. 23). Among the case-control studies, one reported
strong inverse associations of 0.34 (95% CI, 0.23-0.58) for daily
use of over-the-counter aspirin or ibuprofen and 0.35 (95% CI,
0.15-0.84) for daily prescription NSAIDs use in the previous
year (24). Others have reported more modest relative risk
estimates of prostate cancer for regular use of aspirin or other
NSAIDs (1, 25-27).

For all of the case-control studies, differential likelihood of
participation of cases and controls by use of aspirin and
nonaspirin NSAIDs and differential accuracy in recall of use
of aspirin and nonaspirin NSAIDs between cases and controls
are possible. However, germane to both prospective and case-
control studies is the possibility of differential sensitivity
detection of prostate cancer in the prostate-specific antigen
(PSA) era by use of aspirin and nonaspirin NSAIDs. Typically,
prostate cancer cases are identified on biopsy in men who have
an elevated serum PSA concentration. However, in men
diagnosed with organ-confined prostate cancer in the PSA range of 2 to 22 ng/mL, only 10% of the variability in PSA level may be accounted for by tumor volume in the peripheral zone (25). In men with limited
disease, prostate cancer may be serendipitously detected by
PSA screening. An elevated serum PSA may result from
enhanced leakage of PSA from damaged epithelial cells into
the circulation that occurs because of inflammation in
prostate diseases unrelated to cancer, such as benign prostatic
hyperplasia and prostatitis (28, 29). Inverse associations
between aspirin and nonaspirin NSAIDs and prostate cancer
in the PSA era, therefore, may be due to differential
ascertainment of prostate cancer status through effects of
NSAIDs on inflammation and hence the sensitivity of the
routinely used PSA test.

We evaluated the association of use of aspirin and
nonaspirin NSAIDs with subsequent prostate cancer risk in the
ongoing, prospective Baltimore Longitudinal Study of
Aging (BLSA). To assess the specificity of the associations
for these analgesics, we also evaluated the association of use of
acetaminophen, an analgesic for which the standard
consideration is that it does not influence the COX-1 and COX-2
enzymes at typically used doses, with prostate cancer.
Because inflammation may influence both the development
and the leakage of PSA into circulation, to
address the issue of detection bias we also examined
whether serum PSA concentration in men without prostate
cancer differed between users and nonusers of aspirin and
nonaspirin NSAIDs.

Materials and Methods

Study Population. Participants were members of the
BLSA, a prospective cohort study begun in 1958 by the
National Institute on Aging (Bethesda, MD). A total of 1,806
men have participated in the BLSA. Most of the men are
White (85.2% White, 11.5% Black, remainder other race/
ethnicity) and are of a relatively high socioeconomic status.
Before 1998, participants returned biennially; subsequently
older subjects were seen more frequently than younger
subjects for follow-up visits that included assessment of
medical history and medications use. History of use of
analgesics was available for 1,704 of the men. Because
NSAIDs other than aspirin, for the most part, were not
available on the market during the early years of the BLSA,
we restricted follow-up from 1980 to May 2004 and in doing
so, excluded 392 men whose visits ended before 1980. We
also excluded 30 men who were diagnosed with prostate
cancer or cancer of any other site (except nonmelanoma skin
cancer) before 1980. In addition, for men who enrolled in the
BLSA after 1980, we excluded those who had cancer before
the first visit on which they answered questions about
medication use (n = 36). After these exclusions, 1,244 men
were included in analysis.

Use of Aspirin and Nonaspirin NSAIDs. At each visit,
participants were asked about current and previous use of
prescription and over-the-counter drugs, including vitamins,
aspirin, and antacids since their last visit. From the
participants’ reports we abstracted aspirin and aspirin-
containing drugs (e.g., acetalsalicylic acid, Bayer, baby
aspirin, Alka-Seltzer, Anacin, Bufferin, Ecotrin, and Exceldrin)
and nonaspirin NSAIDs (e.g., ibuprofen [Advil and Motrin],
naproxen [Naprosyn], Anaprox, and Aleve; etodolac
[Lodine], nabumetone [Relafen], oxaprozin [Daypro], piroxic-
amic [Feldene], celecoxib [Celebrex], and rofecoxib [Vioxx]).
We also abstracted drugs that contain acetaminophen (e.g.,
Tylenol, Vicodin, and Percocet). Drugs containing both
aspirin and acetaminophen, such as Excedrin, were counted
as aspirin; this type of drug was infrequently used. We did
not separately consider use of the selective COX-2 inhibitors
Celebrex and Vioxx because their U.S. Food and Drug
Administration approval dates were late during the follow-
up period and were not widely used in this cohort. Dose
and frequency of use of medications were generally not
available in the study records before 1990, but subsequently
this information was routinely requested. To obtain an
estimate of duration of use back to 1980, we summed over
the number of years encompassed by visits in which the
participant reported use of these drugs. To characterize dose
and frequency of use, for visits since 1990, we also
calculated the current frequency of use, mean dose per
day, the length of use and the mean amount of medication
per tablet of aspirin, ibuprofen, and acetaminophen.

Case Ascertainment. Prostate cancer cases were identified
among male BLSA participants through review of medical
records and by mailed questionnaire since 1958. Starting in
1991, at each visit male participants underwent an evaluation
by a single study urologist using digital-rectal examination
and PSA testing. Men with a suspicious digital-rectal
examination or a serum PSA concentration ≥4 ng/mL were
included as cases and their person-time at risk was censored
at their date of death. Using these methods, 214 of the 1,806
men (11.8%) were diagnosed with prostate cancer since the
beginning of the BLSA. Among the 1,244 men eligible for
the analysis during the 1980 to May 2004 period, 141 of these
men were diagnosed with prostate cancer (11.3%).

Statistical Analysis. Cox proportional hazards regression
was used to estimate the rate ratio (RR) of prostate cancer
associated with ever or current use (yes/no) of aspirin,
nonaspirin NSAIDs, or acetaminophen. We set age as the
time metric and adjusted for calendar year (continuous) to
calculate for secular trends in the use of nonaspirin NSAIDs and in the
screening for elevated PSA. Men were censored at the time of
prostate cancer diagnosis, death, or loss-to-follow-up.

Ever use of the analgesic drugs since 1980 was evaluated by
entering into the model a time-dependent variable, where
before the first reported use the value for that variable was
never, whereas at the time of report of the first use and all
other times subsequently the value for that variable was ever.
Current use of the drugs was evaluated by entering into
the model a time-dependent variable with simple updating.
Duration of use was entered into the model as two
time-dependent indicator variables for <4 years of use and ≥4 years
of use versus never use. For visits with missing information on
analgesics use, the prior visit’s use was substituted. We assessed the association of aspirin, nonaspirin NSAIDs, and acetaminophen with prostate cancer after mutual statistical adjustment for race or use of vitamin E or calcium supplements did not appreciably alter these estimates, we show results only for analyses that took into account age and mutual adjustment for the analgesic drugs.

Because never users of analgesic drugs might systematically differ from ever users on baseline risk of prostate cancer due to unmeasured factors that are correlates of analgesics use, we also determined the risk of use of aspirin, nonaspirin NSAIDs, and acetaminophen after excluding men who never reported taking any of the three analgesics drugs.

We also evaluated the association of use of these drugs since 1980 with high (≥10 ng/mL) and low (<10 ng/mL) serum PSA concentration at the visit closest in time to prostate cancer diagnosis and high (≥7) and low (<7) Gleason sum. Too few men had an advanced-stage cancer (n = 10) to evaluate the association by stage. We stratified the analysis by <70 and ≥70 years of age to determine whether the association of these drugs with prostate cancer varied by age. To test for interaction, we entered a term for the cross-product of age and analgesic drug use along with the main effects terms for each. The coefficient for the cross-product term was evaluated by the Wald test.

In a separate analysis, we used previously measured concentrations of serum PSA in archived samples from male participants in the BLSA to examine whether PSA concentration varied by use of aspirin, nonaspirin NSAIDs, and acetaminophen (30). Included were 3,749 PSA determinations in blood samples collected from 933 men (mean of 4.0 determinations per man) who were never diagnosed with prostate cancer. We estimated differences in the mean PSA concentration among men who currently used aspirin, nonaspirin NSAIDs, or acetaminophen at the same visit as a given PSA determination using generalized estimating equations. This approach allowed us to take into account repeated measures of medications use and PSA concentration over time and to mutually statistically adjust for current use of the other drugs and age (continuous). Because PSA concentration is skewed, we calculated the geometric mean. We repeated the analysis excluding PSA concentrations ≥4 ng/mL and further stratified by age (<70 and ≥70 years old). All hypothesis tests were two sided. The analyses were conducted using SAS release 8.01 (SAS Institute, Cary, NC).

Results

The 1,244 men who reported on medications use since 1980 contributed 13,102 person-years of follow-up. Median follow-up time was 9 years and median age at the last visit or diagnosis of prostate cancer, whichever came first, was 70 years. Among the 1,244 men, 141 cases of prostate cancer were diagnosed, and of these 83% were diagnosed since 1990 when PSA screening became widespread. Among the 53% and 85% of the cases for which stage and grade, respectively, were available, 80% were organ-confined at diagnosis and 68% were Gleason sum <7. For the 96% of cases for which serum PSA measurements in archived sera were available, 79% had a serum PSA concentration <10 ng/mL at the visit closest in time to their diagnosis of prostate cancer.

On 46.0%, 21.5%, and 15.4% of the visits since 1980, the men reported using aspirin, nonaspirin NSAIDs, and acetaminophen, respectively. The 695 men who used aspirin on at least one visit since 1990 reported on 67.8% of the visits since 1990, and during the period during which the frequency of use and dose was routinely collected, that they currently were regular users and on 27.5% of the visits that they were occasional users. The majority of aspirin use (76.5%) was one dose per day on the days that they took it, the median dose was 325 mg, and for 47.8% of the visits the duration of use was >5 years. The 566 men who on at least one visit since 1990 used nonaspirin NSAIDs reported on 24.9% of the visits that they currently were regular users and on 48.4% of the visits that they were occasional users. On the days that they took nonaspirin NSAIDs, 46.1% of the use was one dose per day and 50.8% of the use was two or more doses per day. The most commonly used nonaspirin NSAID was ibuprofen, the median dose of which was 200 mg; 39.2% of the nonaspirin NSAIDs use was for 1 to 5 years and 22.5% was for >5 years. The 355 men who on at least one visit since 1990 used acetaminophen reported on 7.2% of the visits that they currently used it regularly and on 81.1% of the visits that they used it occasionally. The median acetaminophen dose was 325 mg, and on the days that they took it, they took one dose per day (61.5%); 28.6% of the acetaminophen use was for 1 to 5 years and 51.4% was for >5 years.

Results in the Entire Analytic Cohort. Comparing ever to never users, the RR of prostate cancer was 0.76 (P = 0.11) for aspirin, 0.79 (P = 0.23) for nonaspirin NSAIDs, 0.71 (P = 0.06) for either medication, and 0.89 (P = 0.56) for acetaminophen (Table 1). The associations comparing current users to non-users of aspirin or nonaspirin NSAIDs were attenuated relative to ever use, although for acetaminophen the association for current use was nonstatistically significantly inverse (Table 1).

Risk of prostate cancer was lower in men who had used aspirin or nonaspirin NSAIDs for up to 4 years compared with never users (Table 2). However, the risk of prostate cancer was nonsignificantly higher in men who used aspirin or nonaspirin NSAIDs for >4 years compared with never users.

We evaluated whether the associations for current use compared with nonuse of these drugs varied by prognostic indicators. In cases with a PSA concentration of <10 ng/mL at the visit closest in time to their diagnosis (n = 98 cases), the RR of prostate cancer were 0.82 (95% CI, 0.54-1.23) for aspirin, 0.99 (95% CI, 0.62-1.60) for nonaspirin NSAIDs, and 0.91 (95% CI, 0.50-1.64) for acetaminophen. For cases with a PSA concentration ≥10 ng/mL (n = 36 cases), the association for aspirin (RR, 0.80; 95% CI, 0.40-1.59) was similar to that for <10 ng/mL; the associations for nonaspirin NSAIDs (RR, 0.77; 95% CI, 0.29-2.02) and acetaminophen (RR, 0.18; 95% CI, 0.03-1.31) were dissimilar to those for <10 ng/mL, although these findings were based on small numbers. For Gleason sum <7 (n = 63 cases), the RR were 0.60 (95% CI, 0.36-1.01) for aspirin, 1.13 (95% CI, 0.63-2.01) for nonaspirin NSAIDs, and 0.63 (95% CI, 0.27-1.46) for acetaminophen. For Gleason sum ≥7 (n = 33 cases), the associations for aspirin (RR, 1.76; 95% CI, 0.84-3.69) and acetaminophen (RR, 0.22; 95% CI, 0.03-1.65) differed from those for Gleason sum <7, whereas the association for nonaspirin NSAIDs (RR, 1.04; 95% CI, 0.45-2.42) was similar to Gleason <7; these findings were based on small sample size, however.

In men <70 years old, ever use of aspirin and ever use of nonaspirin NSAIDs were inversely associated with prostate cancer; no association was present for ever use of acetaminophen (Table 3). In men ≥70 years old, there was a nonstatistically significant suggestion of a modest reduction in risk with ever use of aspirin, and possibly for ever use of acetaminophen, but not for ever use of nonaspirin NSAIDs (Table 3).

Results in Ever Users of Aspirin, Nonaspirin NSAIDs, or Acetaminophen. Because men who during follow-up never used any of the three analgesic drugs might differ on baseline risk of prostate cancer because of unmeasured factors that covary with propensity to use such medications, we repeated the analysis limiting the cohort to men who at some point during the study period used at least one of the three drugs (113 cases in 1,022 men). The RRs of prostate cancer for the period of ever use compared with the period of never use were
Table 1. Association of ever and current use of aspirin, nonaspirin NSAIDs, and acetaminophen with subsequent prostate cancer (BLSA, 1980-2004)

| Medication | Ever use | | Current use | |
|------------|----------|-------------------|-------------------|
| | No | Yes | No | Yes |
| Aspirin | | | | |
| Cases | 51 | 90 | 78 | 63 |
| Person-years | 6,049 | 7,053 | 7,933 | 5,169 |
| RR* (95% CI) | 1.00 (reference) | 0.76 (0.54-1.07) | 1.00 (reference) | 0.81 (0.58-1.15) |
| Nonaspirin NSAIDs | | | | |
| Cases | 93 | 48 | 111 | 30 |
| Person-years | 9,526 | 3,576 | 10,792 | 2,310 |
| RR* (95% CI) | 1.00 (reference) | 0.79 (0.54-1.16) | 1.00 (reference) | 0.96 (0.63-1.45) |
| Aspirin and/or nonaspirin NSAIDs | | | | |
| Cases | 39 | 102 | 62 | 79 |
| Person-years | 5,117 | 7,985 | 6,693 | 6,409 |
| RR* (95% CI) | 1.00 (reference) | 0.71 (0.49-1.02) | 1.00 (reference) | 0.81 (0.57-1.16) |
| Acetaminophen | | | | |
| Cases | 102 | 39 | 127 | 14 |
| Person-years | 9,928 | 3,174 | 11,317 | 1,785 |
| RR* (95% CI) | 1.00 (reference) | 0.89 (0.59-1.34) | 1.00 (reference) | 0.69 (0.39-1.20) |

*Calculated from a Cox proportional hazards regression model with age as the time metric, adjusted for calendar year (continuous), and mutually adjusted for use of the other types of medications. Ever use was entered into the model as a time-dependent covariate that before reporting use the variable had a value of never, but once use was reported the variable was fixed as ever. Current use was entered into the model as a time-dependent covariate with simple updating.

Aspirin, Nonaspirin NSAIDs, or Acetaminophen. Age-adjusted geometric mean PSA concentration in men without a diagnosis of prostate cancer did not differ between current users and nonusers of aspirin or current users and nonusers of nonaspirin NSAIDs overall, after excluding men with elevated PSA concentrations, or when stratifying by age, with the exception of a statistically significant higher mean in younger men with normal range PSA (Table 4). Men who used acetaminophen tended to have a lower PSA concentration than men who did not use acetaminophen, even after excluding men with a PSA concentration of 4 ng/mL or higher, although this difference was not statistically significant (Table 4).

Serum PSA Concentration in Users and Nonusers of Aspirin, Nonaspirin NSAIDs, or Acetaminophen. Age-adjusted geometric mean PSA concentration in men without a diagnosis of prostate cancer did not differ between current users and nonusers of aspirin or current users and nonusers of nonaspirin NSAIDs overall, after excluding men with elevated PSA concentrations, or when stratifying by age, with the exception of a statistically significant higher mean in current users compared with nonusers of nonaspirin NSAIDs among younger men with normal range PSA (Table 4). Men who used acetaminophen tended to have a lower PSA concentration than men who did not use acetaminophen, even after excluding men with a PSA concentration of 4 ng/mL or higher, although this difference was not statistically significant (Table 4).

Discussion

In this prospective study, men who had ever used aspirin or nonaspirin NSAIDs had a modest nonstatistically significantly lower risk of prostate cancer. The inverse association for ever use of nonaspirin NSAIDs was statistically significant in younger men. No clear differences in the patterns of association were found by serum PSA closest in time to prostate cancer diagnosis or Gleason sum. A possible modest inverse association with prostate cancer was observed for current use of acetaminophen, an analgesic which until recently was not thought to inhibit the COX-1 and COX-2 enzymes at typically used doses. Mean PSA concentration measured in archived sera collected at multiple time points from men who had never had a diagnosis of prostate cancer did not differ between current users and nonusers of aspirin or nonaspirin NSAIDs. Thus, it is unlikely that the suggestion of an inverse association of use of aspirin and nonaspirin NSAIDs with prostate cancer that we observed is due to a difference between users and nonusers in the accuracy of detection of prostate cancer by screening for elevated PSA.

Our nonstatistically significant finding for aspirin use and prostate cancer is consistent with the modest magnitude of association observed in three previously published prospective studies (20, 22, 31). The RR for death from urogenital cancers, the majority of which were likely prostate cancer, in the prospective Cancer Prevention Study was 0.82 (95% CI, 0.56-1.19) among those with baseline aspirin use of >16 times per month for at least a year compared with nonuse (31). Within a prospective study conducted among Kaiser Permanente members, the RR of prostate cancer was 0.76 (95% CI, 0.60-0.98) comparing those who used took more than six aspirin tablets almost every day with those who did not (22). Using the case-control design nested within the General Practice Research Database in the United Kingdom, the odds ratio (OR) for current use of aspirin prescribed by a physician was 0.70 (95% CI, 0.61-0.79; ref. 20). In a fourth prospective analysis conducting in the Health Professionals Follow-up Study, no association was observed for regular, consistent, or frequent aspirin use and prostate cancer, although frequent use of aspirin (≥22 days per month) was associated with a nonstatistically significant 27% lower risk of metastatic or fatal prostate cancer (23). In the BLSA, too few cases were diagnosed at advanced stage since

Table 2. Association of duration of use of aspirin, nonaspirin NSAIDs, and acetaminophen with subsequent prostate cancer (BLSA, 1980-2004)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration of use</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>&lt;4 y</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>Person-years</td>
<td>6,049</td>
<td>2,308</td>
</tr>
<tr>
<td>RR* (95% CI)</td>
<td>1.00 (Reference)</td>
<td>0.75 (0.53-1.06)</td>
</tr>
<tr>
<td>Nonaspirin NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>93</td>
<td>26</td>
</tr>
<tr>
<td>Person-years</td>
<td>9,526</td>
<td>1,742</td>
</tr>
<tr>
<td>RR* (95% CI)</td>
<td>1.00 (reference)</td>
<td>0.79 (0.53-1.16)</td>
</tr>
<tr>
<td>Aspirin and/or nonaspirin NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Person-years</td>
<td>5,117</td>
<td>2,405</td>
</tr>
<tr>
<td>RR* (95% CI)</td>
<td>1.00 (reference)</td>
<td>0.69 (0.48-0.99)</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>102</td>
<td>28</td>
</tr>
<tr>
<td>Person-years</td>
<td>9,928</td>
<td>1,582</td>
</tr>
<tr>
<td>RR* (95% CI)</td>
<td>1.00 (reference)</td>
<td>0.93 (0.61-1.44)</td>
</tr>
</tbody>
</table>

*Calculated from a Cox proportional hazards regression model with age as the time metric, adjusted for calendar year (continuous), and mutually adjusted for use of the other types of medications.
Table 3. Association of ever use of aspirin, nonaspirin NSAIDs, and acetaminophen with subsequent prostate cancer according to age (BLSA, 1980-2004)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Age &lt; 70 y</th>
<th></th>
<th></th>
<th>Age ≥ 70 y</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never</td>
<td>Ever</td>
<td></td>
<td>Never</td>
<td>Ever</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>13</td>
<td>29</td>
<td></td>
<td>31</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>4,371</td>
<td>4,554</td>
<td>0.71 (0.39-1.31)</td>
<td>1,265</td>
<td>2,932</td>
<td>0.78 (0.51-1.18)</td>
</tr>
<tr>
<td>$P_{interaction}$</td>
<td></td>
<td>0.45</td>
<td></td>
<td>1.00 (reference)</td>
<td>0.78 (0.51-1.18)</td>
<td></td>
</tr>
<tr>
<td>Nonaspirin NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>33</td>
<td>9</td>
<td></td>
<td>52</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>6,748</td>
<td>2,157</td>
<td>0.39 (0.18-0.86)</td>
<td>2,187</td>
<td>2,010</td>
<td>0.98 (0.63-1.53)</td>
</tr>
<tr>
<td>$P_{interaction}$</td>
<td></td>
<td>0.58</td>
<td></td>
<td>1.00 (reference)</td>
<td>0.98 (0.63-1.53)</td>
<td></td>
</tr>
<tr>
<td>Aspirin and/or nonaspirin NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>10</td>
<td>32</td>
<td></td>
<td>25</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>3,742</td>
<td>5,163</td>
<td>0.54 (0.27-1.03)</td>
<td>1,074</td>
<td>3,123</td>
<td>0.78 (0.50-1.22)</td>
</tr>
<tr>
<td>$P_{interaction}$</td>
<td></td>
<td>0.73</td>
<td></td>
<td>1.00 (reference)</td>
<td>0.78 (0.50-1.22)</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>29</td>
<td>13</td>
<td></td>
<td>64</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>6,772</td>
<td>2,133</td>
<td>0.98 (0.45-2.09)</td>
<td>2,611</td>
<td>1,586</td>
<td>0.87 (0.53-1.43)</td>
</tr>
<tr>
<td>$P_{interaction}$</td>
<td></td>
<td>0.74</td>
<td></td>
<td>1.00 (reference)</td>
<td>0.87 (0.53-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

*Calculated from a Cox proportional hazards regression model with age as the time metric, adjusted for calendar year (continuous), and mutually adjusted for use of the other types of medications.

†From a Wald test of the coefficient for the cross-product term for age (binary) and medications use (binary).

1980 to evaluate this association. Findings from other prospective studies that evaluated the association of aspirin with total prostate cancer were essentially null when comparing daily use versus none (32) or use in the past 30 days versus none (33). Our findings are also consistent with some of the case-control studies, which reported estimates of roughly 0.85 for aspirin and total prostate cancer (1, 26, 27).

We observed a modest and nonstatistically significant inverse association of ever, but not current use of nonaspirin NSAIDs with prostate cancer. One prospective study that investigated the relation of total NSAIDs, which included both aspirin and nonaspirin NSAIDs, with prostate cancer reported a strong inverse association (OR, 0.45; 95% CI, 0.28-0.73) for daily use (21). A similar strong effect was observed by Nelson and Harris (24) in a case-control study (OR of prostate cancer, 0.34; 95% CI, 0.20-0.58) for regular daily users of over-the-counter ibuprofen or aspirin and 0.35 (95% CI, 0.15-0.84) for those taking prescription NSAIDs. Findings from other case-control studies are more similar in magnitude to what we observed. Norrish et al. (1) reported an OR of 0.87 (95% CI, 0.49-1.55) for total prostate cancer and 0.72 (95% CI, 0.55-1.46) for advanced prostate cancer comparing nonaspirin NSAIDs users to non-users in a population-based case-control study. Irani et al. (26) observed an OR of prostate cancer of 0.84 for use of nonaspirin NSAIDs in the past 5 years in a case-control study of men undergoing prostate biopsy. However, the only other prospective study that evaluated nonaspirin NSAIDs (prescribed by a physician; ref. 20) and a very large case-control study (27) did not observe an association between use or duration of use of nonaspirin NSAIDs and prostate cancer.

Aspirin inhibits the COX-1 enzyme and, to a lesser extent, the COX-2 enzyme (34, 35). Ibuprofen and related nonaspirin NSAIDs inhibit both COX-1 and COX-2, whereas selective COX-2 inhibitors have relatively little effect on COX-1. Because the inhibition of COX enzymes by aspirin and nonaspirin NSAIDs is transient, the former by irreversible covalent binding and the latter by competitive inhibition, we investigated the relative importance of ever use, current use, and duration of use. The association for ever use of aspirin and nonaspirin NSAIDs seemed to be slightly stronger than for current use. Shorter duration of use of either aspirin or nonaspirin NSAIDs was statistically significantly inversely associated with prostate cancer, whereas longer duration of use was associated with a nonstatistically significant higher risk of prostate cancer. Further study is needed to determine whether this finding was due to chance, bias (e.g., differences in the extent of unaccounted for confounding or other sources of bias in the findings for shorter versus longer duration of use; misclassification of duration of use of anti-inflammatory medications), or biology (e.g., a greater reduction in and resolution of inflammation by use of shorter-term, but higher dose anti-inflammatory agents; or whether longer-term users of anti-inflammatory drugs are those individuals who are more susceptible to inflammation in general, and thus their use appears as a marker for prostate cancer risk).

Table 4. Geometric mean PSA concentration by current use of aspirin, nonaspirin NSAIDs, and acetaminophen (BLSA)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Geometric mean PSA concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All observations</td>
</tr>
<tr>
<td></td>
<td>Age &lt; 70 y</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.01</td>
</tr>
<tr>
<td>No</td>
<td>0.99</td>
</tr>
<tr>
<td>$P$</td>
<td>0.67</td>
</tr>
<tr>
<td>Nonaspirin NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.01</td>
</tr>
<tr>
<td>No</td>
<td>0.98</td>
</tr>
<tr>
<td>$P$</td>
<td>0.69</td>
</tr>
<tr>
<td>Aspirin and/or nonaspirin NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.01</td>
</tr>
<tr>
<td>No</td>
<td>1.01</td>
</tr>
<tr>
<td>$P$</td>
<td>0.56</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.93</td>
</tr>
<tr>
<td>No</td>
<td>1.01</td>
</tr>
<tr>
<td>$P$</td>
<td>0.09</td>
</tr>
</tbody>
</table>

NOTE: Geometric mean PSA concentrations were mutually statistically adjusted for current use of aspirin, nonaspirin NSAIDs, and acetaminophen and were adjusted for age using generalized estimating equations to take into account repeated measures of medications use and PSA concentration over time.
The inverse association with prostate cancer for ever use of nonaspirin NSAIDs, and possibly ever and current use of aspirin, was suggestively more pronounced in younger than in older men. In contrast to our findings, Roberts et al. (21) in a prospective study observed the inverse association between total NSAIDs and prostate cancer was strengthened as age increased. More work is needed to understand possible influence of age, if any, on the association of use of aspirin and nonaspirin NSAIDs with prostate cancer.

To investigate the specificity of the association for drugs taken to alleviate inflammation and pain, we also evaluated the association of acetaminophen, which until recently was not thought to inhibit the COX-1 or COX-2 enzymes at commonly used doses and therefore, was not thought to exhibit an anti-inflammatory effect, with prostate cancer. We observed a modest and nonstatistically significant inverse association for current use of acetaminophen. Two other groups have investigated the association with prostate cancer for acetaminophen. A nested case-control study reported no association for current use of acetaminophen (paracetamol) prescribed by a physician, but did note an inverse association with duration of acetaminophen use (compared >4 years to no use: OR, 0.50; 95% CI, 0.38-0.65, \( P_{\text{trend}} = 0.02 \); ref. 20). A nonstatistically significant inverse association for any acetaminophen use (combining <1 tablet per day and ≥1 tablet per day versus nonusers: OR, 0.70; 95% CI, 0.28-1.73) was reported in a U.S. case-control study (24). Whether these findings reflect chance, residual confounding by concurrent use of aspirin or nonaspirin NSAIDs, or cause is unknown; more work is needed, including on the targets of acetaminophen. For example, recent studies suggest that acetaminophen at 1 gram doses may partially inhibit COX-1 (in platelets) and COX-2 (in monocytes; ref. 36) and that the action of acetaminophen on pain relief may be mediated by its effects on COX-3, a variant of COX-1 that is expressed in the brain (37). Because of the relatively infrequent use and the low to moderate doses taken, in the present study, we were unable to address whether acetaminophen used continuously at doses of ≥1 g/d is associated with prostate cancer.

In the PSA era, detection of prostate cancer is largely dependent on screening for elevated serum PSA. Intraprostatic inflammation seems to be common in the prostates of older men. The epithelial damage caused by inflammation coupled with the increased vascular permeability that occurs during inflammation may be one mechanism by which PSA enters the circulation, independent of the presence of cancer. Given that the majority of the prostate cancer cases included in this analysis were diagnosed in the PSA era, we were concerned that differential detection of prostate cancer might have resulted between men who used aspirin and nonaspirin NSAIDs, and who thus might have had reduced intraprostatic inflammation, and those who did not use anti-inflammatory drugs. To address this question, we used repeated measures of serum PSA concentration over time and compared aspirin and nonaspirin NSAIDs use that was concurrent with the time of PSA measurement. However, we did not observe evidence for a lower serum PSA concentration in users of aspirin and nonaspirin NSAIDs. Thus, it is unlikely that the modest inverse association between these anti-inflammatory drugs and prostate cancer is due to reduced sensitivity of prostate cancer detection by use of these drugs. We did observe a tendency for men who currently used acetaminophen to have slightly lower serum PSA concentrations than nonusers, and the possible detection bias that might result could explain, in part, the inverse association for current use acetaminophen and prostate cancer in this cohort. How acetaminophen might influence serum PSA is unknown.

The BLSA is a rich resource for research on prostate cancer and other diseases and conditions because of the ongoing collection of repeated exposure, urologic, and other health measures on participants over the long term. The overall and age-specific prostate cancer incidence rates for the BLSA men included in this analysis were higher than for the United States, which is likely due to the intensive screening the men have undergone since 1991 as part of the BLSA protocol. The greatest elevation in the incidence rate above the U.S. rate was among the oldest men, who in the community setting are less likely to be screened. For this analysis, the small number of prostate cancer cases diagnosed among the BLSA men limited our ability to detect small associations as being different from the null hypothesis. The possible attenuating bias that would result from enhanced medical contact and possibly greater cancer screening in those taking aspirin or NSAIDs for diseases that require more frequent medical contact is unlikely in this study because of the BLSA screening protocol. Furthermore, we showed that among men without prostate cancer, PSA concentration did not differ between users and nonusers of aspirin and nonaspirin NSAIDs and thus, detection bias is unlikely to account for the modest inverse association of aspirin and NSAIDs use with and prostate cancer. Because of the systematic prostate cancer screening in the BLSA and because members of this cohort exhibit health-seeking behaviors, the majority of the prostate cancers with known stage and that were included in the primary analysis were early-stage disease. Thus, we cannot evaluate whether the association for aspirin and nonaspirin NSAIDs is more apparent for disease that was advanced at diagnosis. In the analysis we took into account age and calendar year as potentially confounding factors, race and use of vitamin E or calcium supplements were not confounders. Few suspected risk factors for prostate cancer have been identified and most of these are associated with advanced disease, not early disease, which comprised the majority of cases included in this study. Furthermore, the analysis excluded men who never during the period of follow-up reported using any of the three types of analgesics; these men might differ in their characteristics from users based on their propensity to not use analgesics. The findings were similar to overall, with the possible exception of a slightly stronger inverse association for nonaspirin NSAIDs, suggesting that confounding by unmeasured correlates of anti-inflammatory drugs use that are also associated with prostate cancer do not explain the modest inverse associations that we observed.

The current analysis was conducted in a cohort of men with high prevalence of use of aspirin and moderate prevalence of use of NSAIDs during the period of follow-up. At visits since 1990, the time during which a more detailed assessment of medications usage was done in the BLSA, the majority of current aspirin users took one dose of a standard over-the-counter 325 mg aspirin tablet regularly and many of the current nonaspirin NSAIDs users regularly or occasionally took one or more doses, with the most common pattern of use being a standard over-the-counter 200 mg tablet of ibuprofen. A strength of this analysis was the recurrent updating of medication records on all participants over a >20-year period and thus, reducing exposure measurement error.

Because information on frequency and dose of medications used was not systematically collected in the BLSA in the 1980s, as a surrogate for duration of use we calculated the number of years of use as the number of years encompassed by visits during which the men reported use. The extent of error in the measurement of duration of use is unlikely to have differed by whether a man was subsequently diagnosed with prostate cancer. Thus, measurement error would have tended to attenuate, not enhance the association between duration of use and prostate cancer.

In conclusion, in this prospective study, we observed a modest, nonstatistically significant inverse association between use of aspirin and nonaspirin NSAIDs and the subsequent diagnosis of prostate cancer, which was statistically significant for ever use of nonaspirin NSAIDs in younger.
men. Use of acetaminophen, which is not believed to have anti-inflammatory effects, was not consistently inversely associated with prostate cancer risk. Based on our evaluation of serum PSA concentration among men with and without a diagnosis of prostate cancer, our study is unlikely to have been biased by differential ascertainment of prostate cancer that might have resulted if aspirin and nonaspirin NSAIDs had influenced serum PSA concentration. Our findings add to the literature suggesting a modest benefit of anti-inflammatory drugs in relation to prostate cancer.

References

Nonsteroidal Anti-inflammatory Drugs and Risk of Prostate Cancer in the Baltimore Longitudinal Study of Aging


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/14/2/390

Cited articles
This article cites 36 articles, 6 of which you can access for free at:
http://cebp.aacrjournals.org/content/14/2/390.full#ref-list-1

Citing articles
This article has been cited by 4 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/14/2/390.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.