A Large Cohort Study of Long-term Acetaminophen Use and Prostate Cancer Incidence

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RUNNING HEAD: Acetaminophen and prostate cancer

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Abstract

Background: Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), particularly long-term use, has been associated with modestly reduced risk of prostate cancer in previous epidemiologic studies. Acetaminophen, a commonly used pain-reliever, is not traditionally considered an NSAID but can have anti-inflammatory effects. Few studies have examined the association between long-term acetaminophen use and prostate cancer incidence.

Methods: We examined the association between acetaminophen use and prostate cancer incidence among 78,485 men in the Cancer Prevention Study II Nutrition Cohort. Information on acetaminophen use was obtained from a questionnaire completed at study enrollment in 1992 and updated using follow-up questionnaires in 1997 and every two years thereafter. Relative risks were estimated using proportional hazards regression models. All models were adjusted for age, race, education, body mass index, diabetes, NSAID use, and history of prostate-specific antigen (PSA) testing.

Results: During follow-up from 1992 through 2007, 8,092 incident prostate cancer cases were identified. Current regular use of acetaminophen (≥ 30 pills per month) for ≥ 5 years was associated with lower risk of overall prostate cancer (RR = 0.62, 95% CI 0.44-0.87) and aggressive prostate cancer (RR = 0.49, 95% CI 0.27-0.88). Current regular use of < 5 years duration was not associated with prostate cancer risk.

Conclusion: These results suggest that long-term regular acetaminophen use may be associated with lower prostate cancer risk.

Impact: If the association between acetaminophen use and lower risk of prostate cancer is confirmed, it could provide clues about biological mechanisms that are important in prostate carcinogenesis.
Introduction

Both acetaminophen and NSAIDs (nonsteroidal anti-inflammatory drugs) are commonly used to relieve pain and lower fever, but acetaminophen does not relieve inflammation due to rheumatoid arthritis (1) and is not traditionally considered an NSAID. However, both studies of osteoarthritis and dental surgery, and studies using rodent models indicate that acetaminophen can have anti-inflammatory effects (2).

Use of NSAIDs, particularly aspirin, has been associated with slightly lower risk of prostate cancer in epidemiologic studies. A recent meta-analysis included 17 studies of aspirin use with a pooled OR of 0.83 (95% CI 0.77-0.89) and 12 studies of non-aspirin NSAIDs with a pooled OR of 0.90 (95% CI 0.80-1.01) (3). In a previous analysis of the Cancer Prevention Study II (CPS-II) Nutrition Cohort, use of > 30 NSAID pills per month for > 5 years was associated with lower risk of prostate cancer (RR = 0.82, 95% CI 0.71-0.94), whereas no association was seen with shorter term use (4).

In contrast to the large number of studies of NSAID use and prostate cancer, relatively few studies have examined acetaminophen use (5-9). In the largest study to date, an analysis of a prescription database from the United Kingdom including 2,182 prostate cancer cases, overall use of acetaminophen was not associated with risk of prostate cancer, but long-term use ( ≥ 4 years) was associated with substantially lower risk (OR = 0.50, 95% CI 0.38-0.65) (6). Four other studies reported no association between acetaminophen use and risk of prostate cancer (5, 7-9). However, only two of these examined long-term use (7, 9), and neither specifically examined use that was both long-term and regular.

We examined the association between acetaminophen use and risk of prostate cancer among men in the Cancer Prevention Study-II (CPS-II) Nutrition Cohort, focusing specifically on long-term regular use. The CPS-II Nutrition Cohort is well-suited to examine this association due to the availability of a large number of prostate cancer cases and regularly updated information on acetaminophen use.
Methods

Study Cohort

Men in this analysis were drawn from the 86,402 male participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence in the United States established in 1992 and described in detail elsewhere (10). 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 established by the American Cancer Society in 1982. The Emory University Institutional Review Board approves all aspects of the CPS-II Nutrition Cohort. At enrollment in 1992 or 1993, participants completed a mailed self-administered questionnaire including information on demographic, medical, and lifestyle factors. Follow-up questionnaires to update exposure information and to ascertain newly diagnosed cancers were sent in 1997 and every two years thereafter. The response rate for each follow-up questionnaire was at least 86%.

This analysis excluded men with a history of prostate cancer at enrollment (N=3,729), with missing or incomplete information on acetaminophen use at enrollment (N=994), who were lost to follow-up (alive at the time of the first follow-up questionnaire in 1997, but did not complete the 1997 or any subsequent follow-up questionnaire, N=2,958), or who had missing information on year of prostate cancer diagnosis (N=19). A total of 889 men reported a prostate cancer diagnosis that could not be verified and therefore were not counted as cases. Of these, we excluded men who reported a prostate cancer diagnosis during the first follow-up interval (N=217), but allowed the remaining 672 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 78,485 men remained for analysis.

Ascertainment of Cancer Cases

Of the 8,092 prostate cancer cases included in this analysis, 7,854 were initially identified by self-report on the follow-up questionnaires and were subsequently verified by obtaining medical records, or through linkage with state cancer registries when complete medical records could not be obtained (10). Ascertainment of cancer by self-report is estimated to have a sensitivity of 93% in the Nutrition Cohort (11). An additional 238 cases of cancer were identified through linkage with the National Death Index (12), of which 193 were verified through subsequent linkage with state cancer registries. Sixty-three men diagnosed with T1a prostate cancers were censored at their diagnosis date rather than being counted as cases because
these tumors are incidentally detected and tend to be relatively innocuous. We classified prostate cancers as "aggressive" if they were AJCC stages III or IV at diagnosis (13) (N = 942) or if Gleason score was \( \geq 7 \) (or histologic grade was 3 or more if no Gleason score was available) \( (N = 2,295) \), or if prostate cancer was listed as the underlying cause of death on the death certificate and no information on stage, Gleason score, or grade was available from medical records or registry linkage \( (N = 45) \). We classified prostate cancers as "non-aggressive" if they were localized (AJCC stage II) and Gleason score was \( < 7 \) (or histological grade was lower than 3 if no Gleason score was available) \( (N=4,467) \). Cancers which we could not classify as either aggressive or non-aggressive due to insufficient information on stage, Gleason score, and/or histologic grade \( (N=343) \) were censored from analyses of aggressive and non-aggressive cancer, but were included as cases in analyses of overall prostate cancer.

**Assessment of Acetaminophen Use**

Acetaminophen use was reported on questionnaires in 1982 (at the time of enrollment into the larger CPS-II mortality cohort), 1992-93 (at enrollment into the Nutrition Cohort), 1997, and every two years thereafter. The 1982 questionnaire asked for “times per month” acetaminophen was used in the last month. The questionnaire completed at enrollment in 1992-93 (hereafter referred to as the 1992 questionnaire) asked if acetaminophen was used regularly, and if so, the average days per month used and the average number of pills taken on days used. Similar questions were asked about acetaminophen use in 1997, 1999, 2001, 2003 and 2005.

**Statistical Analysis**

We calculated acetaminophen pills per month by multiplying days used per month by average pills used per day. Participants who reported days per month but did not report pills per day were assigned a value of one pill per day. Regular acetaminophen use was defined as \( \geq 30 \) pills per month. Current regular use was initially defined by use in 1992 and was updated by use reported in 1997, 1999, 2001, 2003, and 2005. Use reported in 1982 contributed to calculation of duration of use as described below.

Consistent with our previous analysis of NSAID use and prostate cancer (4), we created a time-dependent variable for acetaminophen use based on current use status, frequency, and duration of use. This variable had four categories: 1) never reported use, 2) past or less than regular use, 3) current regular use of less than five years, and 4) current regular use of five or
more years. During the follow-up interval between completion of the 1992 and 1997 questionnaires, current users were categorized as having five or more years’ regular use if they reported at least five years of acetaminophen use on their 1992 questionnaire and also reported regular acetaminophen use on both the 1982 and 1992 questionnaires. During the 1997-1999 follow-up interval, current users were categorized as having five or more years of regular use if they reported regular acetaminophen use on both the 1992 and 1997 questionnaires. During the 1999-2001 and subsequent follow-up intervals, current users were categorized as having five or more years of regular acetaminophen use if they reported regular acetaminophen use on the three immediately preceding questionnaires. All participants who were neither never users nor current regular users were categorized as past or less than regular users. Participants with missing data on acetaminophen use on any follow-up questionnaire were censored from further follow-up.

We conducted a subanalysis to determine if intermediate duration acetaminophen use (2 - < 5 years) was associated with risk of prostate cancer. In this subanalysis, we categorized men as having 2 - < 5 years of regular use if they reported regular acetaminophen use on two consecutive biennial questionnaires but did not meet the definition of having used for 5 or more years. This subanalysis did not include follow-up before 1999 because information from two consecutive biennial questionnaires was not available before 1999.

Cox proportional hazards regression models (14) were used to estimate relative risks (RR) and 95% confidence intervals (CI) for incident prostate cancer. Follow-up time for Cox models began on the date of completion of the 1992 questionnaire. All models were adjusted for age, race, education, body mass index (BMI), diabetes, use of nonsteroidal anti-inflammatory drugs (NSAIDs, including aspirin), and history of PSA testing. Age was adjusted for using the stratified Cox procedure (15) with one year strata. All other covariates were modeled using the categories shown in Table 1. History of PSA testing, NSAID use, and diabetes were modeled as time-dependent variables, using updated information from follow-up questionnaires. All other covariates were modeled based on status in 1992.

Because acetaminophen may inhibit inflammation, we examined if the association between long-term regular acetaminophen use and prostate cancer was modified by use of NSAIDs and BMI (which is associated with systemic inflammation (16, 17)). Specifically, we modeled multiplicative interaction terms between a dichotomous variable for current regular
acetaminophen use for > 5 years, and NSAID use (time-dependent continuous variable for pills per month) and BMI (continuous).

Results

Table 1 shows selected characteristics by duration of acetaminophen use in 1997. Results are shown at the time of the 1997 follow-up questionnaire, rather than at enrollment in 1992. Data from 1992 was of limited use for characterizing the correlates of acetaminophen use in this study population because few men (N = 123) met the conservative criteria for categorization as long-term regular acetaminophen users in 1992 (which included regular use in 1982). In 1997, about 62% of participants had never reported acetaminophen use, 4% reported current regular use, and 1% were current regular users who had used regularly for 5 or more years. The proportion of men categorized as long-term regular users remained similar later during follow-up. Compared to nonusers, regular long-term users were on average older, less educated, and slightly more likely to be obese, diabetic, and to use NSAIDs regularly. History of PSA testing in 1997 did not differ by acetaminophen use. Questions about osteoarthritis and rheumatoid arthritis were not asked until 2001. Since arthritis is a major indication for acetaminophen use, the prevalence of osteoarthritis and/or rheumatoid arthritis in 2001 was substantially higher among long-term acetaminophen users (40%) than among nonusers (12%). Specific information on dose of acetaminophen was not available. However, among long-term regular users in 1997, the median number of pills per day was 2.0. Only 14% of long-term regular users in 1997 reported use of more than 4 pills per day. Given that an extra-strength tablet available in the United States typically contains 500 mg of acetaminophen, few long-term regular users in this study are likely to have regularly used more than 2,000 mg/day (half of the maximum recommended daily dose of 4,000 mg).

Current regular use for < 5 years was not associated with prostate cancer risk (Table 2). However, current regular acetaminophen use for > 5 years was associated with lower risk of both total and aggressive prostate cancer. The association between current regular acetaminophen use for > 5 years (hereafter referred to as long-term regular use) and prostate cancer was similar when adjusted only for age and race (RR = 0.61, 95% CI 0.43-0.86), rather than being multivariable adjusted. Current regular use regardless of duration (combining the < 5 year and > 5 year categories) was not associated with prostate cancer risk (RR = 0.94, 95% CI 0.84-1.05). Neither rheumatoid arthritis nor osteoarthritis was associated with prostate...
cancer risk and adjustment for these factors (during follow-up from 2001 onwards) had a negligible effect on results. There was no evidence of interaction between long-term regular acetaminophen use and either BMI or NSAID use, although statistical power to examine these interactions was limited.

In a subanalysis using follow-up from 1999 forward, when duration of use could be more precisely measured (see methods), intermediate duration regular acetaminophen use (2 - < 5 years) was not associated with risk of prostate cancer (RR = 1.09, 95% CI 0.79-1.51). We also conducted an analysis redefining regular use as ≥ 60 pills per month, instead of ≥ 30 pills per month, in order to determine if long-term use at higher doses might be associated with a larger reduction in risk. The RR for long-term regular use, compared to never reported use, was similar using this definition (RR = 0.64, 95% CI 0.39-1.04), although numbers were limited.

Discussion

In this large prospective study, regular use of acetaminophen (≥ 30 pills/month) for 5 or more years was associated with considerably lower risk of both aggressive and overall prostate cancer. Shorter-term use of acetaminophen was not associated with risk of prostate cancer.

To our knowledge, five other epidemiologic studies have examined the association between acetaminophen use and risk of prostate cancer (5-9). Our results are consistent with those of the largest of these studies, an analysis of computerized prescription data from the United Kingdom (UK) that included 2,182 prostate cancer cases (6). In that analysis, total duration of acetaminophen use during a study period of up to 7 years was calculated by summing the intended duration of all prescriptions; use for < 1 year was associated with slightly higher risk (OR = 1.14, 95% CI 1.00-1.31), attributed to reverse causation, use for 1-2 years was associated with lower risk (OR = 0.67, 95% CI 0.49-0.92), no clear association was seen with use of 2-4 years (OR = 0.87, 95% CI 0.66-1.15) and use for > 4 years was associated with considerably lower risk (OR = 0.50, 95% CI 0.38-0.65). Four other studies reported no association between acetaminophen use and prostate cancer risk (5, 7-9). However, none of these studies examined acetaminophen use that was both long-term and regular. In a U.S. case-control study including 1,001 cases (9), acetaminophen use for ≥ 5 years was not associated with prostate cancer risk (OR = 1.15, 95% CI 0.71-1.148), but this category of long-term use included use as infrequent as once a week. In a small U.S. cohort including 141
prostate cancer cases (7), there was no apparent association between acetaminophen use for ≥
5 years and prostate cancer risk (OR = 0.88, 95% CI 0.34-2.33) but statistical power was
limited. Two additional studies, a Danish pharmacy database analysis (5), and a case-control
study in the UK (8), did not examine either long-term or regular use. In the Danish analysis (5),
acetaminophen use was defined as having received at least one prescription for
acetaminophen. In the UK case-control study, acetaminophen use was defined as any reported
current use (8). Overall, results of our study, together with those of other studies, suggest that if
there is any association between acetaminophen use and prostate cancer it is likely to be
limited to long-term regular use.

While epidemiologic evidence remains limited, it is biologically plausible that
acetaminophen use could reduce prostate cancer risk by inhibiting chronic inflammation, which
is hypothesized to increase risk of prostate cancer (18). Acetaminophen, like NSAIDs, may act
by inhibiting the cyclooxygenase-2 (COX-2) enzyme, an important mediator of inflammation (1,
19, 20). One recent study reported that a standard clinical dose of acetaminophen reduced
COX-2 activity in whole blood as much as a standard clinical dose of the selective COX-2
inhibitor celecoxib (21). In addition, three recent studies reported an inverse association
between acetaminophen use and serum prostate specific antigen (PSA) levels among men
without prostate cancer (7, 8, 22). The largest of these studies included 263 acetaminophen
users and found acetaminophen use to be associated with a statistically significant 9%
reduction in mean serum PSA level (8). In each study, acetaminophen use was associated with
a larger reduction in PSA level than was NSAID use. Because serum PSA levels can reflect
prostatic inflammation (23, 24), these studies provide indirect evidence that acetaminophen may
inhibit inflammation in the prostate.

It is important to consider the possible effect of acetaminophen on serum PSA levels
when interpreting our results. If long-term regular acetaminophen use reduced serum PSA
levels in our study population, there are at least two possible interpretations of our results. First,
acetaminophen use might have had biological effects on the prostate (e.g. reduced
inflammation) that both reduced serum PSA and inhibited prostate carcinogenesis.
Alternatively, acetaminophen use might have reduced serum PSA but had no biological effect
on prostate carcinogenesis. In this case, the lower risk of prostate cancer diagnosis among
long-term acetaminophen users in our study could have been due solely to a reduction in the
sensitivity of PSA testing. However, a reduction in PSA sensitivity due to acetaminophen use
would be expected to delay prostate cancer diagnosis, and therefore result in a lower risk of non-aggressive prostate cancer, but not necessarily in a lower risk of aggressive prostate cancer. In our study, the lower risk associated with long-term regular acetaminophen use was, if anything, more apparent for aggressive prostate cancer than for non-aggressive prostate cancer.

A limitation of our study is that the prevalence of long-term regular acetaminophen use was low, resulting in relatively few cases with this exposure and limiting the precision of our risk estimate. Also, no information was available on dose per tablet of acetaminophen. In addition, as in all observational studies of this topic, confounding by factors associated with both acetaminophen use and prostate cancer risk cannot be ruled out. However, adjustment for measured prostate cancer risk factors had negligible influence on results. We are not aware of unmeasured factors that are strongly associated with both acetaminophen use and prostate cancer risk. Finally, the validity of self-reported acetaminophen use is unknown and there was undoubtedly some error in reporting. However, errors in reporting of acetaminophen use are unlikely to differ based on outcome, and therefore are unlikely to explain the association between long-term regular acetaminophen use and lower risk of prostate cancer.

Important strengths of our study include its large size and prospective design and the ability to identify long-term regular users of acetaminophen based on repeated questionnaires. With the exception of the pharmacy database analysis from the UK (6) previous studies have not specifically examined the association between long-term regular use of acetaminophen and risk of prostate cancer.

In summary, long-term regular acetaminophen use was associated with approximately 38% lower risk of prostate cancer in this large prospective study. While this result is intriguing, it should be noted that acetaminophen use can have adverse effects including liver damage, although it is considered relatively safe at recommended doses (25-27). Further research is needed both to clarify the association between long-term regular acetaminophen use and prostate cancer and to investigate potential biological mechanisms through which acetaminophen may inhibit prostate carcinogenesis.
<table>
<thead>
<tr>
<th>Acetaminophen Use</th>
<th>Never reported use (N=34,243)</th>
<th>Past or occasional use (N=18,863)</th>
<th>Current Regular Use,2 &lt; 5 yrs (N=1,553)</th>
<th>Current Regular Use,2 ≥ 5 yrs (N=596)</th>
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<td>22.5 - &lt; 25.0</td>
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<td>12.5</td>
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<td><strong>NSAID use (pills/mo)</strong></td>
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<td>36.6</td>
<td>35.7</td>
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<td>1 - &lt; 15</td>
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<td>26.0</td>
<td>16.4</td>
<td>17.5</td>
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<td>8.8</td>
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<tr>
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<td>10.9</td>
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<td>67.3</td>
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<td>8.4</td>
<td>9.8</td>
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</table>

1 - Percentages adjusted to the age distribution of the entire study population.
2 - Regular use defined as ≥ 30 pills per month.
Table 2.
Prostate cancer incidence by duration of regular acetaminophen use,\textsuperscript{1}
Cancer Prevention Study II Nutrition Cohort, 1992-2007

<table>
<thead>
<tr>
<th>Acetaminophen Use</th>
<th>Person years</th>
<th>Aggressive Prostate Cancer\textsuperscript{2}</th>
<th>Non-Aggressive Prostate Cancer\textsuperscript{3}</th>
<th>All Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cases       RR (95% CI)</td>
<td>Cases       RR (95% CI)</td>
<td>Cases       RR (95% CI)</td>
</tr>
<tr>
<td>Never reported use</td>
<td>465,529</td>
<td>2,034       1.00 (referent)</td>
<td>2,832       1.00 (referent)</td>
<td>5,092       1.00 (referent)</td>
</tr>
<tr>
<td>Past or less than regular use only</td>
<td>250,865</td>
<td>1,108       0.97 (0.90-1.04)</td>
<td>1,449       0.95 (0.89-1.01)</td>
<td>2,664       0.96 (0.92-1.01)</td>
</tr>
<tr>
<td>Current regular use, &lt; 5 years</td>
<td>28,167</td>
<td>129        1.03 (0.86-1.23)</td>
<td>165         1.00 (0.85-1.17)</td>
<td>304         1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>Current regular use, ≥ 5 years</td>
<td>4,400</td>
<td>11         0.49 (0.27-0.88)</td>
<td>21          0.75 (0.49-1.15)</td>
<td>32          0.62 (0.44-0.87)</td>
</tr>
</tbody>
</table>

1 - Regular use defined as ≥ 30 pills per month. Relative Risks (RRs) adjusted for age, race, education, BMI, diabetes, NSAID use, and history of PSA testing. CI = confidence interval.
2 - Stage III or IV, or Gleason score ≥ 7, or fatal prostate cancer if unknown stage at diagnosis.
3 - Stage II and Gleason score < 7.
References:
