The Use of Aspirin and the Risk of Mortality in Patients with Prostate Cancer

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

CPRD = Clinical Practice Research Datalink

NCDR = National Cancer Data Repository

PSA = prostate specific antigen

Purpose: The association between the use of aspirin and mortality in patients with prostate cancer remains uncertain. We determine whether the use of aspirin in patients with prostate cancer is associated with a decreased risk of prostate cancer mortality and all cause mortality.

Materials and Methods: Using the United Kingdom National Cancer Data Repository, Clinical Practice Research Datalink and associated databases, we identified a cohort of men with nonmetastatic prostate cancer between 1998 and 2009, followed until 2012. Cox proportional hazards models were used to estimate adjusted HRs with 95% CIs of mortality outcomes associated with post-diagnostic use of aspirin defined as a time-varying exposure. Effect modification by pre-diagnostic aspirin use was also assessed.

Results: The cohort included 11,779 men followed for 5.4 years (SD 2.9). Post-diagnostic aspirin use was associated with an increased risk of prostate cancer mortality (HR 1.46, 95% CI 1.29–1.65) and all cause mortality (HR 1.37, 95% CI 1.26–1.50). These increased risks were restricted to patients initiating aspirin after the prostate cancer diagnosis (HR 1.84, 95% CI 1.59–2.12, and HR 1.70, 95% CI 1.53–1.88, respectively), and not in patients who were already exposed to aspirin before the diagnosis (HR 0.97, 95% CI 0.81–1.16 and HR 0.98, 95% CI 0.87–1.18, respectively).

Conclusions: The post-diagnostic use of aspirin is not associated with a decreased risk of prostate cancer outcomes. Increased risks were restricted to patients initiating these drugs after their diagnosis, suggesting a noncausal association.

Key Words: aspirin, prostatic neoplasms, mortality, prognosis

Aspirin has been shown to have anti-inflammatory properties that may confer a positive effect in preventing and limiting the progression of cancer.[1] To date, several observational studies have investigated the association between aspirin and prostate cancer outcomes, although with conflicting findings.[2–9] Indeed, in some studies the use of aspirin was associated with strong risk reductions in prostate cancer mortality ranging between 39% to 57%,[3,5,6,8] while others reported null findings.[2,7,9] Despite these inconsistent results, several have advocated the launch of aspirin randomized controlled trials in patients with prostate cancer.[3,6] However, several of the aforementioned studies had important methodological shortcomings.[3,5,10]

Thus, given the contradictory findings of previous observational studies,[2–9] we conducted a large population

based study to determine whether the post-diagnostic use of aspirin is associated with a decreased risk of cancer related and all cause mortality in men newly diagnosed with prostate cancer.

MATERIALS AND METHODS

Data Sources

This study was conducted by linking 4 large electronic databases from the United Kingdom including the NCDR, CPRD, HES (Hospital Episode Statistics) database and the ONS (Office for National Statistics) database. The NCDR contains tumor information, including site of primary growth (coded using ICD-10) and tumor characteristics (grade, stage and treatments). The CPRD contains information on drug exposures and diagnoses that have been shown to be of high quality.[11–15] The HES database contains dates of hospital admissions, diagnoses and procedures. Finally, the ONS contains the death certificates of UK citizens and was used to identify the cause of death (ICD-10) for all patients who died during followup. The study protocol (13_011) was approved by the Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study Cohort

A population based cohort study was conducted within the aforementioned databases. The NCDR was used to identify patients newly diagnosed with prostate cancer (ICD-10: C61) between April 1, 1998 and December 31, 2009. We excluded patients with less than 1 year of baseline medical history in the CPRD as well as those diagnosed with metastases. Furthermore, all patients were required to have at least 1 year of followup, which was necessary for latency considerations. Thus, cohort entry was set to the year after the prostate cancer diagnosis, and all patients were observed until death, end of registration with the general practice or end of study period (October 1, 2012), whichever came first.

Aspirin Exposure

The use of aspirin after the prostate cancer diagnosis (ie post-diagnostic use) was entered as a time-dependent variable in the models. Thus, patients were able to move from a period of nonexposure to a period of exposure. Furthermore, aspirin exposure was lagged by 1 year to take into account a latency time window as short drug exposures are unlikely to have any biological effect. Thus, patients were considered unexposed to aspirin up until 1 year after their first prescription and then considered exposed for the remainder of followup.

The use of aspirin was expressed in post-diagnostic use and cumulative duration of use. For the first approach the post-diagnostic use of aspirin was compared with nonuse up until the time of the event (ie risk set). For the second approach, it was of interest to assess the association between post-diagnostic aspirin cumulative duration of use and mortality outcomes. Therefore, cumulative duration of use was defined, in a time-dependent fashion, as the total number of months of aspirin use. This variable was calculated by summing the durations of all prescriptions received between prostate cancer diagnosis and the time of the risk set. This variable was then classified into 1 of the 4 categories of less than 12 months, 12 to 23 months, 24 to 35 months and 36 months or more of use. A secondary analysis also examined whether pre-diagnostic use (ie use of aspirin at any time before diagnosis) modified the association between post-diagnostic use of aspirin and the mortality outcomes.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the cohort. Time-dependent Cox proportional hazards models were used to estimate HRs with 95% CIs of cancer related and all cause mortality. For the primary analysis we assessed whether the use of aspirin after prostate cancer diagnosis was associated with a decreased risk of the study outcomes. All models were adjusted for potential confounders measured at the time of the prostate cancer diagnosis including age, year of diagnosis, ethnicity, obesity (30 kg/m^2 or greater), smoking status and socioeconomic status using the Townsend Material Deprivation Score.[16] The models also adjusted for cardiovascular comorbidities (hypertension, heart failure, coronary heart disease, rhythmic disorders, valvular disorders, peripheral artery disease, myocardial infarction, ischemic stroke) and use of antihypertensive drugs, statins, pre-diagnostic use of aspirin, nonsteroidal anti-inflammatory drugs, antiplatelet drugs, 5-alpha reductase inhibitors and antidiabetic drugs all measured in the year before diagnosis. The models also considered the prostate cancer related variables of PSA before diagnosis, Gleason score, as well as prostate cancer related treatments (prostatectomy, radiation therapy, ADT and chemotherapy), all measured in the year between the prostate cancer diagnosis and cohort entry. Variables with missing information were coded with an unknown category.

Secondary and Sensitivity Analyses

We conducted 3 secondary analyses. The first assessed whether there was a duration-response relationship between post-diagnostic use of aspirin and mortality outcomes in terms of cumulative duration of use. In the second we determined whether pre-diagnostic use of aspirin modified the association between post-diagnostic use of aspirin and the study outcomes. For this analysis, effect modification was assessed by including interactions in the models between pre-diagnostic and post-diagnostic use of aspirin. Finally, in keeping with a recent study,[9] we examined the relationship between post-diagnostic aspirin use and prostate cancer mortality among patients with Gleason score 7 or greater disease.

We conducted 2 sensitivity analyses. The first additionally adjusted for time-dependent cancer related variables. The second used an alternate exposure lag period of 2 years. All analyses were conducted with SAS® version 9.3.

RESULTS

Of the 15,940 patients diagnosed with prostate cancer during the study period 11,779 met the study

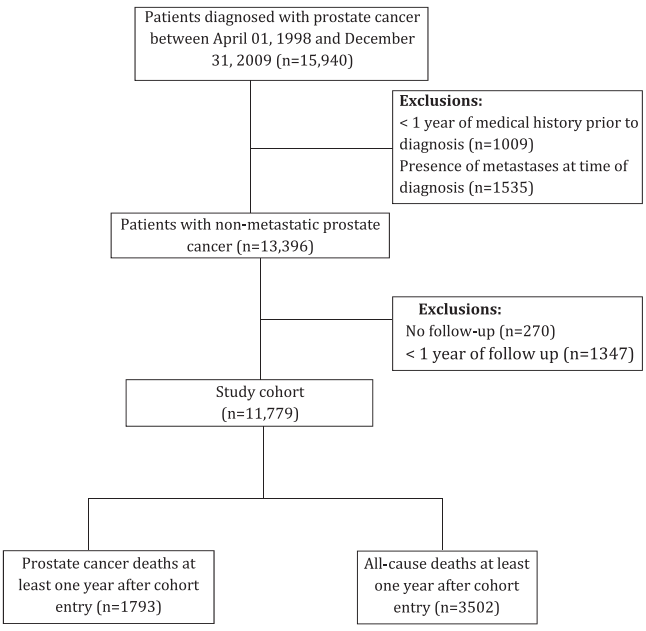
inclusion criteria (see figure). Mean age (SD) at diagnosis was 71.3 (8.8) years and mean followup was 5.4 (2.9) years. During followup there were 1,793 cases of prostate cancer mortality (crude incidence rate 28.2 per 1,000 per year, 95% CI 26.9–29.5) and 3,502 cases of death from any cause (55.1 per 1,000 per year, 95% CI 53.3–56.9).

Supplementary table 1 (http://jurology.com/) presents the baseline characteristics of the cohort. Overall most of the patients were of white ethnicity and ever smokers. The most prevalent drugs in the year before diagnosis were aspirin use (35.2%), statins (26.8%) and other non-anti-inflammatory drugs (25.8%). As for cardiovascular comorbidities the most prevalent diseases were hypertension (54.8%) and coronary heart disease (25.3%). Finally, in the year following the diagnosis the majority of patients received radiation therapy and ADT, with a smaller proportion undergoing radical prostatectomy. Pre-diagnostic users of aspirin were more likely to be on antihypertensive drugs and have cardiovascular comorbidities.

Table 1 presents the results for prostate cancer mortality. Overall the use of aspirin after diagnosis was associated with a 46% increased risk of prostate cancer mortality (HR 1.46, 95% CI 1.29–1.65). Overall there was no evidence of a duration-response relationship between the use of aspirin and the risk of prostate cancer mortality, although the highest risk was observed with use of less than 12 months (HR 1.61, 95% CI 1.40–1.84).

The results of the all cause mortality are presented in table 2. The use of aspirin was associated with an increased risk of all cause mortality (HR 1.37, 95% CI 1.26–1.50). There was no evidence of a duration-response relationship, which followed a similar pattern as the one observed with prostate cancer mortality (table 3).

As shown in table 3, there was evidence of effect modification by pre-diagnostic use of aspirin. The initiation of aspirin after prostate cancer diagnosis was associated with increased risks of prostate cancer mortality and all cause mortality (HR 1.84, 95% CI 1.59–2.12 and HR 1.69, 95% CI 1.53–1.88, respectively). In contrast, the HRs were closer to the null for patients previously exposed to aspirin before diagnosis (HR 0.97, 95% CI 0.81–1.16 and HR 0.99, 95% CI 0.87–1.18, respectively). Finally, a similar increased risk was observed among men with Gleason score 7 or greater disease (HR 1.85, 95% CI 1.51–2.30).



Study flow chart

Table 1. *Crude and adjusted HRs for the association between post-diagnostic aspirin and the risk of prostate cancer mortality*

	No. Events	Person -Yrs	Crude Rate (per 1,000/yr)	Crude HR	Adjusted HR (95% CI)*
Nonuse	992	33,500	29.6	1.00	1.00 (Reference)
Use	801	18,044	44.4	1.59	1.46 (1.29–1.65)
Cumulative mos of use:					
Less than 12	390	7,207	54.1	1.80	1.61 (1.40–1.84)
12–23	175	4,073	43.0	1.47	1.33 (1.10–1.60)
24–35	84	2,615	32.1	1.20	1.06 (0.83–1.37)
36 or Greater	152	4,149	36.6	1.48	1.32 (1.06–1.64)

*Adjusted for age, year of cohort entry, race, obesity (30 kg/m^2 or greater), smoking status, alcohol use, socioeconomic status, antihypertensive drug use, cardiovascular comorbidities, use of statins, aspirin, other antiplatelet drugs, nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors (finasteride and dutasteride), metformin, sulfonylureas, insulin and other antidiabetic drugs. Prostate cancer related variables include PSA, Gleason score and cancer treatments during first year after diagnosis (chemotherapy, androgen deprivation therapy, prostatectomy and radiation therapy).

Table 2. *Crude and adjusted HRs for the association between post-diagnostic aspirin and the risk of all cause mortality*

	No. Events	Person -Yrs	Crude Rate (per 1,000/yr)	Crude HR	Adjusted HR (95% CI)*
Nonuse	1,816	33,500	54.2	1.00	1.00 (Reference)
Use	1,686	18,044	93.4	1.76	1.37 (1.26–1.50)
Cumulative mos of use:					
Less than 12	733	7,207	101.7	1.87	1.49 (1.35–1.64)
12–23	369	4,073	90.6	1.69	1.29 (1.13–1.47)
24–35	216	2,615	82.6	1.60	1.17 (1.00–1.38)
36 or Greater	368	4,149	88.7	1.67	1.23 (1.07–1.43)

*Adjusted for age, year of cohort entry, race, obesity (30 kg/m^2 or greater), smoking status, alcohol use, socioeconomic status, antihypertensive drug use, cardiovascular comorbidities, use of statins, aspirin, other antiplatelet drugs, nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors (finasteride and dutasteride), metformin, sulfonylureas, insulin and other antidiabetic drugs. Prostate cancer related variables include PSA, Gleason score and cancer treatments during first year after diagnosis (chemotherapy, androgen deprivation therapy, prostatectomy and radiation therapy).

Table 3. *Effect modification by pre-diagnostic use of aspirin on the association between post-diagnostic use of aspirin and mortality outcomes*

	Adjusted RR (95% CI)*	
	Aspirin use before diagnosis	No aspirin use before diagnosis
Prostate Ca	0.97 (0.81–1.16)	1.84 (1.59–2.12)
All cause mortality	0.99 (0.87–1.18)	1.69 (1.53–1.88)

All values $p < 0.001$.

* Adjusted for age, year of cohort entry, race, obesity (30 kg/m^2 or greater), smoking status, socioeconomic status, antihypertensive drug use, cardiovascular comorbidities, use of statins, aspirin, other antiplatelet drugs, nonsteroidal anti-inflammatory drugs, 5α-reductase inhibitors (finasteride, dutasteride), metformin, sulfonylureas, insulin and other antidiabetic drugs. Prostate cancer related variables include PSA, Gleason score and cancer treatments during first year after diagnosis (chemotherapy, androgen deprivation therapy, prostatectomy and radiation therapy).

Sensitivity Analyses

In sensitivity analyses the addition of cancer treatments as time-dependent covariates did not materially change the results of the primary analyses (prostate cancer mortality HR 1.46, 95% CI 1.28–1.63 and all cause mortality HR 1.36, 95% CI 1.25–1.49). Increasing the lag period to 2 years led to a decrease in the HRs for prostate cancer and all cause mortality outcomes (HR 1.23, 95% CI 1.06–1.42 and HR 1.23, 95% CI 1.12–1.37, respectively, supplementary table 2, http://jurology.com/).

DISCUSSION

In this large population based cohort of men newly diagnosed with nonmetastatic prostate cancer, the use of aspirin after diagnosis was associated with a 46% increased risk of prostate cancer mortality with no clear duration-response relationship. Similar results were observed among high risk patients and when the outcome was all cause mortality. In a secondary analysis these increased risks were restricted to patients who initiated aspirin after diagnosis, while null effects were observed in patients who also used aspirin before diagnosis.

To date, several observational studies have examined the association between the use of aspirin and the incidence of mortality with mixed findings.[2,3,5–9] These studies measured aspirin exposure in different time windows. Three studies assessed the pre-diagnostic use of aspirin[6,7,9] while 6 assessed the post-diagnostic use of aspirin.[2,3,5,7–9] In the pre-diagnostic use studies aspirin use was not associated with a decreased risk of prostate cancer mortality overall,[6,7] although 1 study reported a risk reduction with higher doses (greater than 75 mg, HR 0.61, 95% CI 0.37–0.99).[6] As for the post-diagnostic studies, 4 studies reported decreased risks of prostate cancer mortality such as in high risk groups[5,8,9] and in patients treated with radical prostatectomy or radiation therapy (0.43, 95% CI 0.21–0.81).[3] In contrast, the 2 other post-diagnostic studies reported null associations with point estimates close to the null value.[2,7]

Several of the aforementioned observational studies had methodological shortcomings which may explain their discrepant results. Specifically, immortal time bias was present in 3 studies,[2,3,10] a bias that is the result of misclassifying unexposed person-time as exposed person-time in cohort studies.[17] Indeed, in some of the studies aspirin use was defined as exposure at diagnosis or at any time during followup. This definition is problematic as it will invariably create a period of immortality between baseline and the first prescription during followup where it was impossible, by design, for the outcome to occur. This bias can be avoided using statistical analyses that consider exposure as a time-varying variable,[18] as was done in this study. Other studies had small sample sizes[8] and did not consider latency time windows.[2,19]

Overall the results of the present study contrast with those of the previous observational studies assessing the post-diagnostic use of aspirin on prostate cancer outcomes.[2,3,5,6,8] While the use of aspirin was associated with an increased risk of prostate cancer mortality and all cause mortality in the present study, there was no clear evidence of duration-response relationships. Moreover, in sensitivity analyses increasing the lag period to 2 years diluted the HRs towards the null. Furthermore, including cancer treatments as time-dependent covariates did not materially change the estimates. Finally, there was effect modification by pre-diagnostic use of aspirin, where the increased risks were restricted to patients who initiated aspirin after prostate cancer diagnosis with null associations with use initiated before diagnosis. The latter findings are consistent with those of 3 observational studies that reported null associations with pre-diagnostic use of aspirin on prostate cancer mortality.[6,7,9] Taken together, these results argue against a protective association between the use of aspirin and the risk of prostate cancer mortality and all cause mortality. In light of a recent study reporting decreased prostate cancer mortality among high risk patients (HR 0.60 95% CI 0.37–0.99),[9] we performed a similar analysis but were not able to replicate these findings (HR 1.85 95% CI 1.51–2.30).

As for our findings of an increased risk, it is possible that the use of aspirin after prostate cancer diagnosis is related to prostate cancer disease progression. Indeed, certain prostate cancer treatments such as ADT have been associated with an increased risk of cardiovascular events[20,21] and, thus, it is possible that the prescribing of aspirin

was the result of treatment related adverse events which themselves are associated with worse disease progression.

This population based study has a number of strengths and some potential limitations. We assembled a large cohort of patients with prostate cancer followed for up to 15 years. In addition, because the CPRD contains prerecorded prescriptions, the possibility of recall bias was eliminated. However, it is unknown whether prescriptions were actually filled and if patients fully complied with the treatment regimen. Such misclassification of exposure would have biased the results towards the null. Furthermore, aspirin is available over-the-counter, it is possible that users were misclassified as nonusers. However, it is reasonable to assume that patients with chronic cardiovascular conditions are likely those to be the long-term users of aspirin. Moreover, although we adjusted for more than 30 potential confounders, residual confounding remains a possibility. Furthermore, we were not able to adjust for tumor stage as it was missing in 90% of the patients, and many patients had missing Gleason scores and PSA values. However, the models were adjusted for cancer related treatments which are closely related to stage, Gleason score and PSA.[22] Furthermore, including these treatments as time-dependent covariates did not materially change the results, although residual confounding may not be ruled out.

Another limitation is the relatively short followup (5.4 years), although this may be related, at least in part, to the high mean age at cohort entry (71.3, SD 8.8 years). It is also important to consider possible outcome misclassifications related to the primary outcome of prostate cancer mortality. While this is a possibility, prostate cancer mortality has been shown to be generally well coded in death certificates.[23] Moreover, our secondary outcome of all cause mortality is more likely to be subject to confounding by indication. Furthermore, given that screening was never implemented in the UK, caution should be exercised when generalizing our results to other populations. Finally, the CPRD database contains information on important confounders such as body mass index and smoking. Therefore, we were able to adjust for a number of important variables often absent in administrative databases.

In summary, the use of aspirin after prostate cancer diagnosis is not associated with a decreased risk of mortality outcomes in patients with prostate cancer. While an increased risk was observed in this study, the associations were driven by patients who initiated aspirin after diagnosis. Additional observational studies are needed to confirm these findings.

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