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

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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

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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