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Original Research

Post-diagnostic use of beta-blockers and the risk of death in patients with prostate cancer

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Abstract ***Background:*** Recent observational studies have produced conflicting results with respect to beta-blocker use after prostate cancer diagnosis and mortality outcomes.
Objective: To determine whether post-diagnostic use of beta-blockers is associated with prostate cancer mortality and all-cause mortality.
Patients and methods: A cohort of 6270 men newly-diagnosed with non-metastatic prostate cancer between 1st April 1998, and 31st December 2009, followed until 1st October 2012, was identified using large population-based electronic databases from the United Kingdom. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) of mortality outcomes associated with post-diagnostic use of beta-blockers. Secondary analyses were performed to examine the independent effects of non-selective beta-blockers, as well as cumulative duration of use.
Results: During a mean follow-up time of 3.8 years (standard deviation: 2.7 years), 1761 deaths occurred, including 715 from prostate cancer. Post-diagnostic use of beta-blockers was not associated with a decreased risk of prostate cancer mortality (HR: 0.97, 95% CI: 0.72–1.31) and all-cause mortality (HR: 0.97, 95% CI: 0.81–1.16). There was no statistically significant association for non-selective beta-blockers (prostate cancer mortality, HR: 1.05, 95% CI: 0.72–1.53 and all-cause mortality, HR: 0.94, 95% CI: 0.74–1.18), and no statistically significant trends of cumulative duration of use for both mortality outcomes.
Conclusion: The use of beta blockers, including those of the non-selective type, was not associated with a decreased risk of prostate cancer and all-cause mortality.

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1. Introduction

Beta-blockers have recently been under investigation for their antineoplastic effects [1,2]. Indeed, preclinical data have shown that activation of β-adrenergic receptors is involved in tumour cell proliferation, angiogenesis and tumour migration [3,4]. Moreover, laboratory models have demonstrated that catecholamines such as epinephrine and norepinephrine can induce tumour cell invasion and migration [1,5]. Thus, the inhibitory potential of beta-blockers has become the focus of several *in vitro* studies on tumour progression and metastasis, which included prostate and other tumour types [1,6,7].

To date, several observational studies have reported strong risk reductions in metastasis and cancer-specific mortality with the use of beta-blockers in patients with certain cancer types [2,8–13]. With respect to prostate cancer, observational studies have reported conflicting results [13–16]. These studies had a number of methodological limitations, including small sample sizes [16] and possible immortal time bias [13,17–19]. Furthermore, none of these studies examined the effects of the less commonly prescribed non-selective beta blockers, such as propranolol, which have been associated with decreased metastasis in animal models [1,3,4].

Thus, given the potential anti-tumour effects of beta-blockers, and recent and conflicting evidence in patients with prostate cancer, we conducted a large-population based cohort study to assess whether post-diagnostic use of these drugs is associated with a decreased risk of cancer-specific and all-cause mortality in men diagnosed with prostate cancer. Secondary objectives were to assess whether these effects varied with cumulative duration of use, and whether beta-blocker selectivity had an impact on these outcomes.

2. Patients and methods

2.1. Data sources

This study was conducted by linking the following four large electronic databases from the United Kingdom (UK): the National Cancer Data Repository (NCDR), Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) database, and the Office for National Statistics (ONS) database. The NCDR contains tumour information, including site of primary growth (coded using the International Classification of Diseases, 10th Revision [ICD-10]) and tumour characteristics (such as grade, stage and primary treatments received). The CPRD contains data on more than 13 million individuals enrolled in more than 680 general practices. Furthermore, the recorded information on drug exposures and diagnoses in the CPRD has been validated and proven to be of high quality [20–24]. The HES database contains dates of hospital admissions, primary and secondary diagnoses (coded using the ICD-10 classification), and procedures (coded using the ICD-10 classification and Office of Population Censuses and Surveys Classification of Interventions and Procedures, Fourth Version). Finally, the ONS contains the electronic death certificates of all citizens living in the United Kingdom and was used to identify the underlying cause of death (coded using the ICD-10 classification) for all patients who died during follow-up. The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD and the Research Ethics Board of the Jewish General Hospital, Montreal, Quebec, Canada.

2.2. Study population

A population-based retrospective cohort study was conducted within the databases described above. First, we used the NCDR to identify all men newly-diagnosed with prostate cancer (ICD-10 code: C61) between 1st April 1998, and 31st December 2009. These patients were then linked to the CPRD, HES and ONS databases.

We excluded patients diagnosed with metastatic disease and those with less than 1 year of up-to-standard medical history in the CPRD before the prostate cancer diagnosis. The cohort was also restricted to patients who received at least one prescription for an antihypertensive drug (consisting of beta-blockers, angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], calcium channel blockers [CCBs], alpha-blockers and others [diuretics, aldosterone antagonist and vasodilators]) in the year prior to diagnosis. Restricting the cohort to patients with a history of antihypertensive drug use was necessary to minimise potential confounding by indication, which was a major limitation of some of the previous studies [2,8,14,25]. Furthermore, all patients were required to have at least 1 year of follow-up, 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 (either from prostate cancer or from other causes), end of registration with the general practice or end of study period (1st October 2012), whichever came first.

2.3. Beta-blocker exposure assessment

The use of beta-blockers (listed in Supplemental Table 1) after the prostate cancer diagnosis was entered as a time-dependent variable in the models, allowing patients to move from a period of non-exposure to a period of exposure. Furthermore, beta-blocker exposure was lagged by 1 year to take into account a biologically meaningful latency time window, as short duration exposures are unlikely to have any biological effects. Thus, patients were considered unexposed to beta-blockers up until the 1 year after the time of a first