



## Original article

## Null association between androgen-deprivation therapy and nonprostate cancer mortality among older men with nonmetastatic prostate cancer

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## Abstract

**Background:** Androgen-deprivation therapy (ADT) has been associated with cardiovascular risk factors and the development of cardiovascular disease in men with metastatic prostate cancer. We sought to examine the effect of ADT on nonprostate cancer mortality among patients with nonmetastatic prostate cancer.

**Methods:** We performed a population-based, retrospective cohort study of men aged 66 years and older treated with surgery or radiotherapy for nonmetastatic prostate cancer in Ontario, Canada from 2002 to 2009 using administrative datasets (including the Ontario Cancer Registry, Ontario Drug Benefit, and Ontario Health Insurance Plan). Analysis was performed between September 2016 and April 2017. ADT exposure was operationalized as a time-varying binary and cumulative dose exposure. Primary and secondary outcomes were nonprostate cancer mortality and cardiovascular mortality, respectively. The Fine and Gray subdistribution method with generalized estimating equations was used to calculate subdistribution hazard ratios (sdHR), while accounting for competing risks.

**Results:** We examined 20,651 men treated for nonmetastatic prostate cancer. Median follow-up was 7.4 years and median ADT exposure was 6.4 months. ADT was not significantly associated with nonprostate cancer mortality (sdHR = 0.75, 95% CI: 0.37–1.50) or cardiovascular mortality (sdHR = 1.16, 95% CI: 0.37–3.63) when operationalized as a binary time-varying exposure. Similar results were obtained when we examined ADT cumulative dose exposure.

**Conclusions:** ADT is not associated with nonprostate cancer mortality or cardiovascular mortality in a large, population-based cohort of older men with localized prostate cancer treated by surgery or radiation therapy. © 2018 Elsevier Inc. All rights reserved.

**Keywords:** Androgen antagonists; Cardiovascular diseases; Radiotherapy; Prostatectomy; Comparative effectiveness research; Brachytherapy

## 1. Introduction

Active treatment options for patients with nonmetastatic prostate cancer include surgery and radiation with or without the use of androgen-deprivation therapy (ADT). The life expectancy of these patients is long with 10-year relative cancer specific survival for men newly diagnosed with prostate cancer of approximately 98% [1]. Thus, competing risks of death are significant. Cardiovascular disease remains the most common cause of death among

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men in general [1] and among those diagnosed with prostate cancer [2].

The association between ADT and cardiovascular disease is well-established [3]. Recent data have demonstrated that this also applies to men receiving ADT for clinically localized prostate cancer [4]. It is unclear whether the increased risk of cardiovascular events seen with ADT translates into increased mortality. Some studies have shown that the administration of ADT may increase the risk of cardiovascular mortality, particularly among men with moderate or severe comorbidity [5] and men of African American ethnicity [6], whereas others have shown no increase in risk [7].

The indications for the use of ADT among men with nonmetastatic prostate cancer are increasing [8] including neoadjuvant and adjuvant therapy for patients undergoing primary radiotherapy [9] and during salvage of biochemical recurrence following surgery [10]. Thus, it is important to examine the association between ADT administration and nonprostate cancer related mortality among a population-based cohort of patients with nonmetastatic prostate cancer. We examined men treated for nonmetastatic prostate cancer in Ontario, Canada to assess the association between ADT exposure and nonprostate cancer mortality and cardiovascular mortality.

## 2. Methods

### 2.1. Study design and setting

We conducted a population-based, retrospective cohort study of men aged 66 and older diagnosed with prostate cancer from April 1, 2002 to December 31, 2009 in Ontario, Canada using linked administrative data. In Ontario, all citizens receive health care, financed by the single government payer Ontario Health Insurance Program. Outpatient pharmaceuticals are provided to citizens aged 65 years and older through the Ontario Drug Benefit [11]. The Sunnybrook Health Sciences Centre Research Ethics Board approved this protocol.

### 2.2. Participants

We identified men aged 66 years and older diagnosed with prostate cancer (International Classification of Diseases, 9th Edition [ICD-9-CM] Diagnosis Code 185) in the Ontario Cancer Registry, a provincial registry which is more than 95% complete [12]. As prescription information is available beginning at age 65, age 66 was selected for cohort entry to confirm that patients were not exposed to ADT before study entry and to ensure accurate ascertainment of ADT exposure duration. We included patients treated with radical prostatectomy, external beam radiotherapy, or brachytherapy within 1 year of their initial diagnosis (Supplementary Table 1). We excluded patients

with metastatic disease at diagnosis (ICD-9-CM Diagnosis Code 198). Men were followed from the date of primary treatment until death or March 31, 2013.

### 2.3. Exposure

The primary exposure was treatment with ADT. We used the Ontario Drug Benefit database to identify luteinizing-hormone releasing-hormone agonists and antagonists administered from the date of diagnosis until death or the study end date (Supplementary Table 2). We modeled ADT both as a time-dependent binary exposure and a time-dependent cumulative exposure. In time-dependent binary models, patients could move from a non-exposed to an exposed status. Once exposed, patients remained exposed for the duration of follow-up. In time-dependent cumulative exposure models, we partitioned both exposure and follow-up time for each exposed man into categories. First, each exposed man contributed time and outcome status to the first category until he reached 6 months of cumulative exposure, the second from 6 to 12 months, the third from 12 to 18 months, the fourth from 18 to 24 months, the fifth from 24 to 36 months, and the sixth thereafter. We then repeated this procedure categorizing exposure into durations of 0 to 12 months, 12 to 24 months, and greater than 24 months.

### 2.4. Outcomes

The primary outcome was nonprostate cancer mortality. Oncologic causes of death have been validated in the OCR [13,14], thus, in using the inverse, the cause of death data ought to be valid. Our secondary outcome was cardiovascular mortality. This was obtained from the Ontario Register General—Death Database.

### 2.5. Covariates

We captured information on patients' age, comorbidity (Johns Hopkins Aggregate Disease Groups, ADG, score), diabetes diagnosis, hypertension diagnosis, dyslipidemia treatment, myocardial infarction in the past 5 years, cerebrovascular accident in the past 5 years, and geographic region using validated, linked administrative databases. As dyslipidemia diagnoses are unreliable, we used receipt of at least 6 months of continuous statin prescription (Supplementary Table 3) in the 2 years before index date as a proxy for dyslipidemia.

### 2.6. Statistical analysis

We used descriptive statistics to summarize the demographic characteristics of the cohort.

We identified an analytic subgroup with an equal number of patients treated with surgery and radiotherapy to

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