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Original article

New-onset diabetes after androgen-deprivation therapy for prostate cancer: A nationwide propensity score-matched four-year longitudinal cohort study

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ABSTRACT

Introduction: Androgen-deprivation therapy (ADT) is important in the treatment of prostate cancer. However, the relationship between ADT and the risk of diabetes remains unclear, and the association between duration and types of ADT has not been fully investigated.
Aim: To examine the risk of developing type 2 diabetes mellitus (T2DM) in men who underwent ADT for prostate cancer.
Methods: Data were collected retrospectively from the Longitudinal Health Insurance Database of Taiwan. In total, 4604 prostate cancer patients ≥40 years old who underwent ADT were included in the study cohort, and 4604 prostate cancer patients without ADT were included as controls, after adjusting for age and other comorbidities.
Results: During the four-year follow-up period, the incidence of new-onset T2DM was 27.49 and 11.13 per 1000 person-years in the ADT and ADT-never cohorts, respectively. The ADT cohort was 2.19 times more likely to develop T2DM than the control group (95% CI 1.90–2.53, $P < 0.001$). Furthermore, the association was particularly striking in the subgroup of patients receiving complete androgen blockade (adjusted HR 2.33, 95% CI 1.96–2.78, $P < 0.001$).
Conclusions: Men with prostate cancer who received ADT are at risk for developing diabetes.

1. Introduction

Prostate cancer is the most common solid organ malignancy and the second leading cause of cancer-related deaths in men worldwide.[1] Androgen-deprivation therapy (ADT) has been recognized to be effective and the preferred first-line treatment for metastatic prostate cancer. During the past decade, the use of ADT has been rapidly increasing, both as the primary treatment for non-localized prostate cancer and adjuvant therapy or in conjunction with radiotherapy for locally advanced prostate cancer. Moreover, ADT is also used as a salvage therapy for patients with elevating prostate-specific antigen levels after adjuvant treatment, such as radical prostatectomy or radiation therapy.[2]

The growth of prostate cancer cells is dependent on androgen. The goal of ADT is to reduce the secretion of testicular androgens or to inhibit the androgen receptors, thereby resulting in a castration status. Except for orchiectomy (surgical castration), there are two major forms of ADT: gonadotropin-releasing hormone (GnRH) agonist and oral anti-androgen. GnRH agonists are synthetic analogs of GnRH that can lower the amount of testosterone secreted by the testicles. By the modality of regular administrations of GnRH agonist every 4 weeks, the patient's GnRH-receptors are down-regulated, the secretion of luteinizing hormone is suppressed, and thereafter the production of testosterone subsequently decreases. Oral anti-androgens, on the other hand, can directly compete with androgens at the receptor level, and reach the castrated effect. Physicians may choose to treat patients by combining these two kinds of medications, called a complete androgen blockade (CAB).

Although studies have shown the therapeutic benefit of ADT regarding prostate cancer control, the hypogonadism produced by ADT leads to numerous adverse effects, including insulin resistance,[3,4]

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cardiovascular disease,[5] cognitive declines,[6] anemia,[7] sexual dysfunction,[8] and diminished quality-of-life.[9] Most of these adverse effects are related to low testosterone levels in the serum and these complications may result in a high risk/benefit ratio and require more careful consideration when using ADT. In addition, most patients with prostate cancer die of conditions other than their primary cancer, including complications of ADT. Therefore, the awareness and management of adverse effects of ADT becomes a crucial concern.

Diabetes mellitus (DM) and metabolic syndrome are the main public health issues in the 21st century because of their increasing global prevalence and mortality. An estimated 415 million people worldwide and approximately 10% of the population in the United State are affected by diabetes, and the trends suggested that the rate would continue to rise.[10] The World Health Organization (WHO) estimates that diabetes resulted in 1.5 million deaths globally in 2012. Moreover, diabetes may be attributable to another 2.2 million deaths yearly because of its associated complications. Type 2 diabetes (T2DM), characterized by insulin resistance and relative lack of insulin, accounts for 90% of diabetes cases. The major complications of T2DM are related to blood vessel damage, either small blood vessel diseases, including retinopathy, nephropathy, and neuropathy, or macrovascular diseases, including stroke, coronary artery disease and peripheral vascular disease.

A number of previous cross-sectional studies have suggested that long-term ADT may increase the risk of developing insulin resistance and hyperglycemia in men with prostate cancer.[3,4] However, the longitudinal presence of new-onset T2DM in men with prostate cancer undergoing ADT has not been completely evaluated, and the association between types and duration of ADT have also not been fully examined. As this issue has never been addressed in the Asian population, we collected data from the Taiwan National Health Insurance (NHI) database on a cohort of patients with prostate cancer who were treated with ADT and assessed the association between ADT and new-onset T2DM.

2. Material and methods

2.1. Design

This was a retrospective population-based longitudinal cohort study in men 40 years or older with documentation of prostate cancer. The primary comparison was between patients with similar characteristics who ever and never received ADT.

2.2. Database

We obtained data for patients with illness from the registry of the Taiwan National Health Insurance (NHI) database. This health insurance program is a national healthcare system that aims to provide healthcare for all residents in Taiwan. The program started in 1995 and eventually covered 98% (in 2009) of this country's population of 23.3 million people, making it one of the largest of such databases worldwide. The database contains complete registration files and medical documentations of patients in the NHI program who were diagnosed with cancer. Prior studies have validated the data in this database. Our data source was a randomly sampled cohort of 1 million people. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (IRB number: KMUHIRB-EXEMPT(II)-20150017). The database consisted of de-identified secondary data released to the public for study purposes. This study was conducted in accordance with the Declaration of Helsinki.

2.3. Patients

The study consisted of a study cohort and a propensity score-matched control cohort for comparison. Patients who were diagnosed with prostate cancer [Clinical Modification (ICD-9-CM) code 185] in Taiwan from January 1, 2000 to December 31, 2005 were eligible for inclusion in the study cohort. Patients with new-onset T2DM were identified using ICD-9-CM diagnostic codes 250 as well as diagnoses made by clinical physicians and endocrinologists. Patients were excluded from the study if they met any of the following criteria: (1) age younger than 40 years; (2) diabetes was diagnosed before the index date; (3) incomplete demographic data; (4) diabetes was diagnosed within 90 days of the index date or follow-up duration was <90 days. Patients' demographic data, including age and follow-up duration, were recorded. The baseline comorbidities that may have affected our result were examined. This included stroke (ICD-9-CM code: 430–438), depression (ICD-9-CM code: 296.2–296.3, 300.4, 311), hypertension (ICD-9-CM code: 401–415), coronary artery disease (ICD-9-CM code: 411, 412, 414, 428), chronic kidney disease (ICD-9-CM code: 581, 582, 583, 585, 586, 587), and hyperlipidemia (ICD-9-CM code: 274).

2.4. Statistical analysis

Propensity score-matched Cox proportional hazards regression models were applied to match age, index year and all comorbidities to define the ADT-never cohort of prostate cancer as a control group. The average follow-up duration and the average duration of developing T2DM in the ADT and ADT-never cohorts were presented as mean ± SD years. Pearson's chi-squared tests and Fisher's exact tests were used to estimate the comparison in the new-onset T2DM events and follow-up durations between the ADT and ADT-never cohorts. We subsequently used Kaplan–Meier survival analysis to investigate the difference in diabetes-free survival rates between the cohorts. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) were obtained to examine the risk of new onset diabetes among the different treatment groups after adjusting for possible confounding factors. A two-sided $P < 0.05$ was considered as statistically significant. All statistical analyses were conducted using SAS version 9.3.1 Statistical Package (SAS Institute Inc., Cary, NC).

3. Results

Between January 1, 2000 and December 31, 2005, a total of 17,070 men were identified to have prostate cancer (Fig. 1). First, patients who were <40 years of age (n = 419) were excluded as type 2 diabetes is uncommonly diagnosed before age 40. Second, patients diagnosed with diabetes before the index date (n = 129) and diagnosed as diabetes within 90 days after the index date or follow-up duration <90 days (n = 900) were excluded to ensure that none of the enrolled participants had diabetes at the start of study. We further excluded 1261 patients because of incomplete demographic data. Thereafter, a cohort group of 4604 men who underwent ADT was developed. Propensity score matching of the ADT group to the control group (ADT-never) was performed at a ratio of 1 to 1. The breakdown of patients' disposition by inclusion and exclusion criteria is shown in Fig. 1.

Table 1 presents the baseline characteristics of the ADT and ADT-never cohorts. There were no significant differences in age and all comorbidities between the study cohort and control cohort. The mean age of the patients in ADT cohort was 73.05 years and ADT-never was 72.80 years. Table 2 presents the follow-up duration and the duration of developing T2DM between the ADT and ADT-never cohorts. The average follow-up duration in the ADT and ADT-never cohorts were 4.04 ± 2.88 and 5.80 ± 2.98 years, respectively. The average duration of developing T2DM in the ADT and ADT-never cohorts were 2.23 ± 1.92 and 2.46 ± 2.01 years, respectively. There was no significant difference in the duration of developing T2DM between the study and control cohorts.

Table 3 presents the risk of new-onset T2DM between ADT and ADT-never cohorts. The incidence of diabetes during the follow-up period was 11.13 per 1000 person-years in the ADT-never cohort and 27.49 per 1000 person-years in the ADT cohort. The adjusted hazard ratio for diabetes in the ADT cohort was 2.19 (95% CI 1.90–2.53, $P < 0.001$).

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