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Long term antihypertensive drug use and prostate cancer risk: A 9-year population-based cohort analysis

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ABSTRACT

Background: Recent findings from clinical trials have indicated inconsistent associations between angiotensin II receptor blockers and the risk of cancer incidence. Furthermore, the relationship between antihypertensive drugs and prostate cancer in hypertensive patients remains unclear.
Methods: From Taiwan's national health insurance database, we identified 80,299 patients diagnosed with hypertension in 2001 and matched with 321,916 subjects without hypertension by age, income, urbanization level, and index day. A total of 684 hypertensive patients without antihypertensive drug use (drug non-user subcohort) were also matched (1:4) with 2736 patients on antihypertensive medication (drug subcohort) using the same criteria. Each subject in the two study groups was followed up for a maximum of nine years, during which death was considered a competing event when performing the stratified Fine and Gray regression hazards model for the estimation of prostate cancer risk for the cohorts. Uptake of antihypertensive prescription was considered a time-dependent variable.
Results: Our findings indicate that patients with hypertension are at significantly increased risk for prostate cancer incidence when compared to their matched non-hypertensive counterparts (sHR = 6.80, 95% CI = 1.97–23.44, $p = 0.0024$). Among hypertensive patients, those with long term antihypertensive drug use are not at elevated risk of developing prostate cancer relative to non-users of antihypertensive drugs (1–5 year vs. non-user sHR = 0.99, 95% CI = 0.32–3.05; >5 year vs. non-user sHR = 0.88, 95% CI = 0.34–2.26).
Conclusions: Hypertension is considered a risk factor for prostate cancer. However, long term uptake of antihypertensive medication in male hypertensive patients should not be a concern for the development of prostate cancer.

1. Introduction

Hypertension is a highly prevalent morbidity in older adults and acts as a major risk factor for cardiovascular diseases, congestive heart failure, and coronary heart disease [1,2]. The beneficial therapeutic effect of both medical and non-pharmacological interventions on the aggressive and effective control of blood pressure has been well-established in the scientific literature. Several classes of antihypertensive drugs are currently available for initial therapy, including diuretics, alpha- and beta-blockers, aldosterone antagonists, calcium-channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARBs), and direct renin inhibitors (DRIs). Significant reductions in cardiovascular and renal morbidity and mortality through systemic and intensive use of these blood pressure-lowering medications have been previously demonstrated [3]. Patients typically require two or more drugs to effectively control their blood pressure. Nevertheless, ingestion of antihypertensive drugs over a cumulative period of time can potentially lead to adverse effects in older individuals, who tend to be accompanied

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by comorbidities such as hypercholesterolemia, diabetes mellitus, chronic renal disease, and other cardiovascular diseases [3–5].

A population-based case–control study in Finland by Kemppainen et al. [6] describes a marginally increased risk for prostate cancer (PC) in antihypertensive drug users. This positive association, however, does not significantly differ with the cumulative dose or duration of use. Concurrent health conditions that hypertensive patients already possess, in addition to the decreased blood circulation that antihypertensive agents induce, are potential promoters of carcinogenesis. Conversely, in another recent epidemiological study, Poch et al. [7] indicate a lack of association between calcium-channel blockers and PC.

The association between the use of ARBs and increased cancer risk was first identified in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) trial of candesartan in 2003 [8]. It was proposed that angiotensin type-1 (AT1) and type-2 (AT2) receptors were involved with the regulatory process of cellular proliferation, angiogenesis, and tumor progression [9]. Trials conducted investigating telmisartan, ONTARGET, and TRANSCEND also noted higher hazard for malignancies [10]. These trials commonly had an average follow-up period exceeding three years. A meta-analysis performed by Sipahi et al. [11], also revealed a modest increase in risk of cancer incidence. Conversely, the ARB Trialists Collaboration found no significant increase in overall cancer incidence with long term ARB use in the 15 clinical trials examined [12]. Overall, only a few existing studies were conducted in a cohort design, with a long term follow-up period, and a sufficiently large sample, to examine the cumulative dose effect of antihypertensive agents on the development of PC and the effect of non-drug use in the presence of hypertension. Furthermore, most studies did not study the drug switching behavior commonly seen among hypertension patients and only a few investigated the use of all drug classes which resemble more closely to pragmatic settings.

In realization of these shortcomings, we evaluate here the risk of developing PC in hypertensive patients with up to nine years of follow-up in a nationwide study. Among hypertensive individuals, we aim to also compare hazard ratios between the users and non-users of antihypertensive drugs with consideration of cumulative dose effect in a time-dependent manner.

2. Material and methods

2.1. Data source

Data used in this study is based on claims data from the compulsory National Health Insurance (NHI), which is managed and provided by The Collaboration Center of Health Information Application (CCHIA), Ministry of Health and Welfare of Taiwan. This comprehensive database contains health care data of over 99% of the nation's population including demographics, dates of clinical visits, diagnostic codes, prescription orders, and associated expenditures for which contracted facilities file their medical claims inclusive of services from laboratory tests to treatment and prescription orders. Numerous cardiovascular and cancer epidemiology studies using this database can be found in the published literature [13,14].

2.2. Ethics statement

Because the CCHIA-NHI database entirely consists of anonymous and encrypted secondary data released to the public for research purposes, this study was exempted from a full review by the ethics review committee at the China Medical University Hospital.

2.3. Subject selection

Subjects were selected from the CCHIA-NHI database: they included male patients aged 50 or above with newly diagnosed hypertension (International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnostic codes 401 to 405) in 2001. At least one of the following enrollment criteria had to be met for inclusion in the study: (1) one or more inpatient admissions with diagnosis of hypertension, or (2) three or more outpatient visits within a 6-month period, each with a diagnosis of hypertension. Subjects from the control cohort were selected in the same year from the CCHIA-NHI database on the basis that they were not diagnosed with hypertension nor had any use of antihypertensive drugs. They were individually matched at a ratio of 4:1 with the hypertension cohort by age, urbanization level, income, and index day (i.e., date of newly diagnosed hypertension) (Fig. 1).

Prescribed use of antihypertensive drugs in the follow-up period was considered: prescription records contained dates of order, dosage, route of every prescription, and number of days prescribed for each dispensed drug. Furthermore, two subcohorts were then categorized from the hypertension cohort: one with regular use of antihypertensive drugs (drug subcohort), and the other without any antihypertensive drug use (drug non-user subcohort) during the follow-up period. Regular drug use was defined as uninterrupted use for a minimum of one year. Drug non-users were matched (1:4) with drug users according to age, urbanization level, income, and index day (Fig. 1). Index day for the drug non-users was assigned as the date of incident hypertension diagnosis, and index day for the drug users was assigned as the date of new diagnosis which coincided with the prescription of antihypertensive drugs.

Patients with diagnosis of cancer prior to or within the first year following index day were excluded from the study to preclude immortal time bias. Comorbidities were classified as those existing prior to the index day and included congestive heart failure, diabetes mellitus, cardiovascular disease (CVD), and hyperlipidemia. The end of follow-up period for the two-part analysis (hypertension vs. non-hypertension cohorts, and hypertensive drug subcohort vs. hypertensive drug non-user subcohort) was marked on the day of PC diagnosis, terminated enrollment from the NHI, death, or until the end of this study [11]. Follow-up data was available up to a maximum of nine years for study subjects.

2.4. Identification of prostate cancer cases

Taiwan's NHI has established a well-utilized program to alleviate the financial burden of cancer patients following their cancer diagnoses. But because costs involved in cancer treatment can be substantial, strict guidelines are in place requiring careful examination of medical records before patients can qualify for coverage. In order to be covered by the aid program, patients have to apply for a cancer catastrophic illness certificate. Successful candidates must possess adequate evidence supporting their diagnosis of cancer such as histology or pathology reports, additional laboratory evidence, and clinical images which can include tumor marker surveys, X-ray, bone scan, computed tomography scan, or magnetic resonance imaging. Detailed inspection of patient medical records and laboratory information (including images) by a minimum of two oncologists is also required. Such medical information and data on the cancer patients are compiled in the Registry of Catastrophic Illness Patient Database. Since inclusion in the database requires close scrutiny of cancer diagnoses, we believe to have retrieved reliable information from this database for our identification of PC diagnoses (ICD-9-CM = 185x).

2.5. Antihypertensive drugs

We calculated the daily dosage for the drugs and evaluated amount of drug use with defined daily dose (DDD). DDD is the recommended daily average maintenance dose for a drug, which is needed to provide its main indication in adults. Moreover, we constructed time-varying covariates for antihypertensive drug use in the analysis. Seven major groups of antihypertensive agents were included and their Anatomical Therapeutic Chemical (ATC) classifications are listed in Supplementary Table 1.