European Journal of Cancer 83 (2017) 203–210

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Medication use and kidney cancer risk: A population-based study

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Received 24 March 2017; received in revised form 29 June 2017; accepted 3 July 2017
Available online 24 July 2017

KEYWORDS
Carcinoma;
Renal cell;
Humans;
Adults;
Pharmacoepidemiology;
Drug utilisation

Abstract ***Background:*** Exposure to commonly prescribed medications may be associated with cancer risk. However, there is limited data in kidney cancer. Furthermore, methods of classifying cumulative medication exposure in previous studies may be prone to bias.
Methods: We conducted a population-based case–control study of 10,377 incident kidney cancer cases aged ≥66 years matched with 35,939 controls on age, sex, history of hypertension, comorbidity score, and geographic location. Cumulative exposure to commonly prescribed medications hypothesised to modulate cancer risk was obtained using prescription claims data. We modelled exposure in four different fashions: (1) as continuous exposures using (a) fractional polynomials (which allow for a non-linear relationship between an exposure and outcome) or (b) assuming linear relationships; and 2) as dichotomous exposures denoting (a) ≥3 years versus <3 years exposure; or (b) "ever" versus "never" exposure. We used conditional logistic regression to estimate the association of medication exposure on incident kidney cancer.
Results: The directions of association were relatively consistent across analyses; however, the magnitudes were sensitive to the method of analysis. When utilising fractional polynomials,

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http://dx.doi.org/10.1016/j.ejca.2017.07.001

increasing cumulative exposure to acetylsalicylic acid, selective serotonin reuptake inhibitors, and proton-pump inhibitors was associated with significantly reduced risk of kidney cancer, while increasing exposure to antihypertensive drugs was associated with significantly increased risk.
Conclusions: Our study provides impetus to further explore the effect of commonly prescribed medications on carcinogenesis to identify modifiable pharmacological interventions to reduce the risk of kidney cancer.

1. Introduction

Several commonly prescribed medications, such as acetylsalicylic acid [1,2], non-steroidal anti-inflammatory drugs (NSAIDs) [2,3], proton-pump inhibitors [4] (PPIs), statins [5], and selective serotonin-reuptake inhibitors [6] (SSRIs), have recently gained interest in the oncology community for their putative antineoplastic properties as studies have suggested that their use may be associated with a decreased risk of incident cancer. These medications are relatively inexpensive and well tolerated, making them ideal candidates for chemoprevention in cancer. While some of these medications have been thoroughly investigated in various malignancies, with randomised controlled trials underway [7,8], there are limited data on the association of exposure to these putative antineoplastic medications on the risk of incident kidney cancer [9,10]. Conversely, there is conflicting evidence on whether exposure to several antihypertensive medications is associated with increased risk of kidney cancer [11–14]. However, to date, there has been no study to evaluate these medications simultaneously, limiting the interpretation of the independent association of each medication class on kidney cancer risk. Determining the risk associated with each medication class may identify modifiable pharmacological interventions to reduce the risk of a cancer that is common, increasing in incidence, and often lethal.

2. Patients and methods

2.1. Setting and design

We conducted a population-based case–control study of Ontario, Canada, residents aged 66 years or older from 1st April 1997 to 31st December 2014. All patients had universal access to hospital care, physician services, and prescription drug coverage. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre, Toronto, Ontario.

2.2. Data sources

We identified medication use through prescription claims of the Ontario Drug Benefit Database, which contains comprehensive records of prescription drugs dispensed to all Ontario residents aged 65 years or older. We chose to include cases aged ≥66 years in order to have complete data available on at least 1 year's history of medication exposure. We used the Ontario Cancer Registry (OCR) to identify patients with incident unilateral or synchronous bilateral kidney cancer. We obtained hospitalisation data from the Canadian Institute for Health Information Discharge Abstract Database. We used the Ontario Health Insurance Plan database to identify claims for physician services and obtained basic demographic data from the Registered Persons Database. Details regarding all of the databases used and their validity have been provided elsewhere [15].

2.3. Study patients

We defined case patients as those with an incident diagnosis of kidney cancer (ICD-9: 189.0; ICD-10: C64) in the OCR. The date of first recorded diagnosis served as the index date for all analyses. For each individual identified as a case, we randomly selected up to four control patients. Control patients were matched to each case according to age (within 1 year), sex, comorbidity score (defined by the Johns Hopkins Aggregated Diagnostic Groups score [16] in the 5 years prior to index date), geographical area (defined by the first three characters of the postal code), and history of hypertension. To allow for equal durations of medication exposure among cases and matched controls with varying date of births, the index date among controls was assigned to allow identical duration of follow-up after age 65 years. To reduce selection bias, we used incidence-density sampling to select controls, thereby allowing cases to also serve as potential controls during the follow-up period that they were without cancer. Additionally, to reduce the potential for detection bias whereby those with medication use are more likely to interact with health services and receive diagnostic imaging, controls had to have had an interaction with the health care system within 2 years of the assigned index date. Finally, we excluded cases without any matches.