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Published in:
Basic & Clinical Pharmacology & Toxicology

DOI:
10.1111/bcpt.13180

Publication date:
2019

Document version
Accepted manuscript

Citation for published version (APA):

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Download date: 14. May. 2021
Article Type: Short Communication

Bisphosphonate use and risk of renal cell carcinoma: a population-based case-control study

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(Received 14 September 2018; Accepted 20 November 2018)

Running title: Bisphosphonates and renal cell carcinoma

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Funding: This study was funded by the Program for Clinical Research Infrastructure (PROCRIN) established by the Lundbeck Foundation and the Novo Nordisk Foundation and administered by the Danish Regions. This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcpt.13180
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Keywords: Epidemiology, renal cell carcinoma, bisphosphonates, cigarette smoking, osteoporosis

ABSTRACT

The purpose of this study was to evaluate the association between the use of bisphosphonates and the risk of developing renal cell carcinoma (RCC). We conducted a case-control study in Denmark, using data linked from population-based health and administrative registries. We identified all cases of RCC from 1996 to 2013 and sampled population controls in a 10:1 ratio from the underlying population free of RCC, while matching on sex, birth year and calendar time. Bisphosphonate use before RCC diagnosis, excluding the year leading up to the diagnosis, was measured using outpatient prescription dispensations. We used conditional logistic regression to compute crude and adjusted odds ratios (ORs) comparing ever vs. never bisphosphonate use in doses indicated for treatment of osteoporosis, overall and stratified by sex, with the OR estimating the incidence rate ratio. We also examined the effects by cumulative dose and specific agent. There were 2748 RCC cases and 27,480 controls. The adjusted ORs for ever vs. never bisphosphonate use were 1.07 (95% confidence interval: 0.94-1.22) overall; 1.15 (1.00-1.32) for women; and 0.78 (0.54-1.12) for men. Smoking could not be directly controlled for in the analysis. We found a weak association between use of oral bisphosphonates and risk of renal cell carcinoma in females. The observed association could be due to confounding by cigarette smoking, and future studies are required to assess this association further.

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INTRODUCTION

Renal cell carcinoma (RCC) creates a significant impact worldwide. Further, as the incidence rate of RCC is continuing to rise\textsuperscript{1} for unknown reasons, putative aetiologies for RCC development, such as pharmacological agents and environmental stressors, warrant further investigation.

Recently, a potential association between use of non-steroidal anti-inflammatory drugs and increased risk of RCC was reported\textsuperscript{2}. The proposed mechanism was carcinogenesis secondary to drug-induced renal injury. Bisphosphonates can cause nephrotoxicity upon the renal tubules,\textsuperscript{3} from which RCC arises\textsuperscript{4}. Specifically, bisphosphate drug overload in the renal tubules can lead to renal sequelae, including acute tubular necrosis, focal segmental glomerulosclerosis and proteinuria.\textsuperscript{3}

The use of bisphosphonates in osteoporosis is extensive and expected to increase further as the population ages\textsuperscript{5}. To ensure rational prescribing of bisphosphonates, it is important to uncover their serious unintended effects, such as cancer. However, despite the accumulated epidemiological evidence for other cancers, previous studies examining the long-term cancer risk of RCC associated with bisphosphonates use are very limited.\textsuperscript{6,7} In light of recent evidence concerning NSAID use and RCC risk\textsuperscript{2}, a potential association between bisphosphate use and RCC is worth addressing. Therefore, we conducted a comprehensive population-based case-control study using data from Danish health care registries to assess whether bisphosphonate use is associated with an increased risk of RCC.

METHODS

We conducted a nested population-based case-control study in northern Denmark, in 1996-2013. Northern Denmark has approximately 2.2 million inhabitants, comprising approximately one third of the overall Danish population. In Denmark, a unique
10-digit identifier is assigned to all Danish residents at birth or at immigration, enabling linkage across all registries and complete follow-up from birth to death through the Danish national health system\textsuperscript{8}.

The present study linked data from four Danish health registries: the Danish Cancer Registry ("Cancer Registry")\textsuperscript{8}, the Danish National Patient Registry ("Patient Registry")\textsuperscript{9}, the Aarhus University Prescription Database ("Prescription Registry")\textsuperscript{9}, and the Danish Civil Registration System\textsuperscript{10}.

We identified incident cases of RCC in the Cancer Registry by searching for individuals with first ever registrations of the ICD-10 code C64. The case index date was the date of the registration of RCC in the Cancer Registry. For each case, ten population controls with no record of RCC on the case index date were matched to cases by sex and birth year. Using risk-set sampling, controls were selected from the Danish Civil Registration System among persons who were alive and resident in northern Denmark on the index date. We excluded from the study population persons who had been resident in Denmark for less than 2 years before the start of the study period, and persons with any cancer history (except non-melanoma skin cancer) prior to the index date. All codes used to identify disease and drug history of cases and controls are listed in the Appendix.

Use of bisphosphonates was identified as redeemed prescriptions in the Prescription Registry. To reduce the risk of reverse causation, we only considered dispensations from >1 year before the index date\textsuperscript{11}. To reduce the potential for misclassification of bisphosphonates exposure status, we only considered individuals with two or more redeemed bisphosphonates prescriptions as ever users of bisphosphonates. All others were classified as never users. We included all orally administered bisphosphonates marketed in Denmark through the study period (alendronate, etidronate, ibandronate, risedronate, clodronate) as well as intravenously administered bisphosphonates (ibandronate and zoledronate) in the strengths used in the treatment of osteoporosis.

Characteristics potentially associated with a risk of RCC\textsuperscript{12-16} were identified using data registered in the available registries and included sex, age on index date (in categories 0-39, 40-59, 60-79, 80+ years), comorbidity (diabetes, obesity, hypertension, chronic
obstructive pulmonary disease [COPD, as a proxy for smoking], renal failure and alcohol-related disease) and calendar period of the index date (1996-2000, 2001-2004, 2005-2009, 2010-2013); any history of use of non-steroidal antiinflammatory drugs (NSAIDs) or aspirin (ASA). The covariates were measured any time prior to the index date since 1977 in the Patient Registry and since 1992 in the Prescription Database.

We tabulated distributions of the covariates among the cases and controls, including history of pre-index date use of different bisphosphonate agents. We computed odds ratios (ORs) adjusted for the matching variables as estimates of the corresponding incidence rate ratios, contrasting ever use of any bisphosphonate with never use (reference) using conditional logistic regression. Further, adjusted OR (controlling for the other covariates) were calculated. All analyses were stratified by sex.

To assess the effect of the cumulative dose of any bisphosphonate received up to one year before the index date, the dose of all bisphosphonate was standardized to the alendronate dose and crude and adjusted odds ratios were calculated for cumulative bisphosphonate dose in the categories: less than 840 mg, 840-3360 mg and greater than 3360 mg by comparing with never users. The categories correspond to ≤3 months, 3-12 months, >12 months of use, respectively. Finally, we calculated crude and adjusted OR for RCC for specific bisphosphonates each compared with never users, and crude and adjusted OR for RCC for route of administration (intravenous (IV), oral, oral and IV or none (reference)).
RESULTS

We identified 2,748 RCC cases and 27,480 matched population controls during the study period. Sixty-two percent of the included persons were male, 55% were between the ages of 60-79 years at RCC date, and a majority had been diagnosed in the period of 2005-2009. Cases had higher prevalence of all measured comorbid conditions than the controls, such as obesity (5.1% vs. 2.4%), diabetes (12.6% vs. 7.8%), hypertension (62.8% vs. 48.1%), COPD (7.5% vs. 4.3%), renal failure (2.2% vs. 0.8%), and alcohol-related diseases (4.4% vs. 2.9). Also, the cases were more likely than controls to have a history of NSAID and ASA use (Table 1).

Prevalence of ever use of bisphosphonates was 2.6% among cases (n=72) and 2.1% among controls (n=579), and oral alendronate was the most commonly used agent (72.2% and 76.6%, for cases and controls). Distribution of overall and agent-specific cumulative dose is shown in Supplemental Table 1.

The OR for RCC when comparing ever vs never bisphosphonate use was 1.1 (95% CI 0.99-1.28), and the OR adjusted for all covariates was 1.07 (95% CI 0.94-1.22). Stratification revealed an association among female ever users (OR 1.15, 95% CI 1.00-1.32) which was strongest among females with cumulative doses above 840 mg (Fig. 1). The association appeared consistent across agents examined.

Due to the possibility of confounding by cigarette smoking, a post-hoc sensitivity analysis was performed, informed by earlier evidence\textsuperscript{12} regarding the association between smoking and RCC. When assuming an equal or higher prevalence of smoking among bisphosphonate users in the present study, the OR point estimate was attenuated.
DISCUSSION

This nationwide, population-based case-control study indicated a weak association between use of oral bisphosphonates and an increased risk of RCC in females. The study represents the most comprehensive and detailed analysis of bisphosphonates and RCC to date and our findings run counter to those of previous analyses.\textsuperscript{6,7} The earlier studies, however, did not have the level of granularity that our study provides. In our study, set in Denmark, data come from a population with universal health care access, complete registration of outpatient prescription dispensations and all hospital-based diagnoses (including cancers), and complete life-long follow-up, essentially ruling out selection bias.\textsuperscript{9} Also, through linkage to other relevant patient level data, we were able to adjust the analyses for several important confounders.

Both cigarette smoking and obesity are well-established risk factors for the development of RCC\textsuperscript{16} as well as associated with bisphosphonate use\textsuperscript{17}. Capture of these covariates by our data sources is likely incomplete, and our findings are therefore limited by our inability to control fully for cigarette smoking and obesity. Confounding by smoking could potentially explain away the observed association, as suggested by the sensitivity analysis in our study. In a meta-analysis examining the correlation between smoking and RCC, for females, there was a pooled OR point estimate of 1.27 (1.14-1.40)\textsuperscript{12}, which was similar to the observed bisphosphonate-cancer OR of 1.15. In contrast, as obesity is inversely associated with bisphosphonate use\textsuperscript{17}, unmeasured confounding by body weight would likely lead to an underestimation of the potential association, which could explain the overall null result of our study.

There are some additional limitations to our study. Low precision of some point estimates is a limitation of this analysis, especially among the long-term bisphosphonate users. Although dispensation is a valid marker of medication intake, misclassification of
medication exposure could theoretically produce the null result observed in this study; however, the consistency of the association in the all analyses argues against this. Lastly, as the majority of the patients prescribed bisphosphonates in our population were older, female patients, this could potentially limit the generalizability of our findings. However, as this likely reflects the actual user characteristics of this medication, we believe that this is appropriately representative.

In this study, we found a weak association between bisphosphonates use and RCC in females. However, the observed association may be explained by confounding by smoking. Future studies are needed to clarify whether the observed association is true or due to confounding. Further, due to the high societal cost of RCC and rising incidence rates, future endeavors should be undertaken to discover potential modifiable risk factors to decrease incidence rates.

REFERENCES


Figure 1: Adjusted odds ratios

<table>
<thead>
<tr>
<th>Bisphosphonates and renal cell carcinoma</th>
<th>Adjusted odds ratios and 95% CI</th>
<th>OR</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td>1.27</td>
<td>0.94 to 1.62</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>_ Men</td>
<td></td>
<td>0.78</td>
<td>0.54 to 1.12</td>
</tr>
<tr>
<td>_ Women</td>
<td></td>
<td>1.75</td>
<td>1.30 to 2.32</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>_ &lt;844 mg</td>
<td></td>
<td>0.92</td>
<td>0.68 to 1.24</td>
</tr>
<tr>
<td>_ 840-3,360 mg</td>
<td></td>
<td>1.17</td>
<td>0.78 to 1.78</td>
</tr>
<tr>
<td>_ &gt;3,360 mg</td>
<td></td>
<td>1.10</td>
<td>0.78 to 1.56</td>
</tr>
<tr>
<td>Women only*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>_ Cumulative dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>_ &lt;844 mg</td>
<td></td>
<td>0.90</td>
<td>0.67 to 1.23</td>
</tr>
<tr>
<td>_ 840-3,360 mg</td>
<td></td>
<td>1.21</td>
<td>0.81 to 1.82</td>
</tr>
<tr>
<td>_ &gt;3,360 mg</td>
<td></td>
<td>1.11</td>
<td>0.77 to 1.61</td>
</tr>
<tr>
<td>_ Agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>_ Alendronate</td>
<td></td>
<td>1.17</td>
<td>0.89 to 1.52</td>
</tr>
<tr>
<td>_ Etidronate</td>
<td></td>
<td>1.18</td>
<td>0.95 to 1.48</td>
</tr>
<tr>
<td>_ Ibandronate</td>
<td></td>
<td>1.01</td>
<td>0.77 to 1.34</td>
</tr>
</tbody>
</table>

*Data too sparse on men

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Table 1: Comparison of baseline and comorbidity characteristics between cases and controls

<table>
<thead>
<tr>
<th>Characteristics, n (%)</th>
<th>Cases n=2,748</th>
<th>Controls n=27,480</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females _</td>
<td>1,029 (37.4)</td>
<td>10,290 (37.4)</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-18</td>
<td>28 (1.0)</td>
<td>280 (1.0)</td>
</tr>
<tr>
<td>18-39</td>
<td>47 (1.7)</td>
<td>471 (1.7)</td>
</tr>
<tr>
<td>40-59</td>
<td>794 (28.9)</td>
<td>7,933 (28.9)</td>
</tr>
<tr>
<td>60-79</td>
<td>1,512 (55.0)</td>
<td>15,087 (54.9)</td>
</tr>
<tr>
<td>80+</td>
<td>367 (13.4)</td>
<td>3,709 (13.5)</td>
</tr>
<tr>
<td>Year of RCC diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996-2000</td>
<td>430 (15.6)</td>
<td>4,300 (15.6)</td>
</tr>
<tr>
<td>2001-2004</td>
<td>587 (21.4)</td>
<td>5,870 (21.4)</td>
</tr>
<tr>
<td>2005-2009</td>
<td>879 (32.0)</td>
<td>8,790 (32.0)</td>
</tr>
<tr>
<td>2010-2013</td>
<td>852 (31.0)</td>
<td>8,520 (31.0)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>347 (12.6)</td>
<td>2,157 (7.8)</td>
</tr>
<tr>
<td>Obesity</td>
<td>141 (5.1)</td>
<td>647 (2.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,726 (62.8)</td>
<td>13,215 (48.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>207 (7.5)</td>
<td>1,192 (4.3)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>61 (2.2)</td>
<td>220 (0.8)</td>
</tr>
<tr>
<td>Alcohol-related diseases</td>
<td>121 (4.4)</td>
<td>810 (2.9)</td>
</tr>
<tr>
<td>NSAIDs and ASA use</td>
<td>2,001 (72.8)</td>
<td>17,888 (65.1)</td>
</tr>
<tr>
<td>Bisphosphonate use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>2,676 (97.4)</td>
<td>26,901 (97.9)</td>
</tr>
<tr>
<td>Ever</td>
<td>72 (2.6)</td>
<td>579 (2.1)</td>
</tr>
</tbody>
</table>
Appendix

ICD-10 codes

Renal cell carcinoma : ICD-10 : C64


Obesity: ICD-10: DE66

Hypertension: ICD-10: DI10-DI15

COPD: ICD-10: DJ41, DJ42, DJ43, DJ44.

Renal failure: ICD-10: DN17-DN19

Alcohol-related diseases (as a by proxy for alcoholism): ICD-10: F10 (beside DF10.0), DG31.2, DG62.1, DG72.1, DI42.6, DK29.2, DK86.0, DZ72.1

ATC codes for bisphophonates

M05BA01  Etidronic acid
M05BA02  Clodronic acid
M05BA03  Pamidronic acid
M05BA04  Alendronic acid
M05BA05  Tiludronic acid
M05BA06  Ibandronic acid
M05BA07  Risedronic acid
M05BA08  Zoledronic acid