Cancer risks among the users of ergot-derived dopamine agonists for Parkinson's disease, a nationwide population-based survey

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A B S T R A C T

Background: Factors of cancer occurrence among Parkinson disease patients are still not well known, although genetic predilection has been investigated. The aim of this study is to evaluate the medication effect of dopamine agonists of Parkinson disease on incidence of cancers from the Taiwan National Health Insurance Research Database.

Methods: We conducted a population-based nested case–control study by using the resources of the Taiwanese National Health Insurance from 1996 to 2000 and analyzed the prevalence of cancer among patients with Parkinson disease. A nested analysis was then implemented among those patients with both Parkinson disease and cancer, focusing separately on the use of ergot- and nonergot-derived-dopamine agonists.

Results: We reviewed 6211 patients with Parkinson’s disease and found 329 patients with cancer. The ergot-derived dopamine agonists users were associated with an increased odds ratio for cancer, compared with nonergot-derived dopamine agonist users, with an adjusted odds ratio of 2.16 (95% confidence interval, 1.55–2.99). Among all the cancer types, we observed the higher occurrence of liver cancer among the ergot-derived dopamine agonist users.

Conclusion: The association of ergot-derived-dopamine agonist use and cancers, especially the liver cancers, has provided us the information to further understand the drug–cancer interaction. We hope this result would prompt further investigations on the risk and benefit of the dopamine agonists use among the Parkinson’s disease patients.

1. Introduction

Parkinson’s disease (PD) has the clinical manifestations of bradykinesia, tremors, rigidity, and postural instability, with an annual estimated incidence ranging from 10.2 to 16.6 individuals per 100,000 people [1]. Pathological examination revealed a caudo-rostral progression of cytoplasmic Lewy bodies in the brainstem [2], as well as a loss in dopaminergic neurons in the striatum and substantia nigra. Furthermore, studies have suggested that the nonmotor symptoms in PD patients have a substantial impact on their quality of life [3]. The work tiers from clinical, pathological to genetic and molecular efforts were intended to improve the accuracy of diagnosis for PD, especially for those with probable PD [4]. Although dopamine-replacing agents such as levodopa and dopamine agonists (DAs) improve motor function [5], they also have certain undesired side effects, such as neuropsychiatric symptoms [6] and valvular heart disease [7]. Epidemiologic discussions of this neurodegenerative disease have suggested that tea [8], caffeine and smoking [9] may exert protection against PD, whereas exposure to pesticides may contribute to it [10]. A comorbid association reports with diabetes mellitus among patients with PD [11,12] gave hints about neurovascular insults to get PD, and similar concept raised as the statin users with lower incidence of PD [13,14].
Recently cancer risk among the PD patients gained much attention, especially for those with a genetic linkage [15,16], and the role of parkin, the E3 ubiquitin ligase, in cancers [17]. Therefore it is nothing to be surprised at the possibility of cross-talking between neurodegeneration and neoplasms. However, we wonder the exogenous factors, especially our prescribed medicines, attributed to the cancer occurrence for the vast population with idiopathic PD. A mirror is the higher cancer incidence among the users of sulfonpyrazone for diabetes mellitus [18,19], thus we speculate anti-PD medications, particularly DAs, as the possible contributor to the cancer occurrence. Thus, the purpose of this nationwide study of PD patients was to clarify the association between the use of DAs and clinical cancer.

2. Methods

2.1. Data source

In Taiwan the National Health Insurance (NHI) program is a health insurance system available to all the Taiwanese citizens. Established in 1996, the NHI has provided more than 99% of the Taiwan population with basic health care needs. The National Health Research Institute (NHRI) built up and managed the National Health Insurance Research Database (NHIRD) which involved reimbursement claim data from the NHI program.

The nested case–control study population was established from the Longitudinal Health Insurance Database (LHID). The LHID, a subset of NHIRD, randomly enrolled one million insured individuals through 1996 to 2000 and the stratification structure of age and sex was similar to NHIRD. LHID contain all the annual reimbursement claim data, including sex, occupation, income and medical services records. To ensure the confidentiality of the insured population, NHRI created a scrambled and random identification number to link each insured individual’s reimbursement claim data before releasing them for research purposes. In this research, the disease diagnosis was defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) form outpatient and inpatient data. The cancer records were obtained from the sub-registry of NHIRD for catastrophically ill patients, who had image diagnoses or/pathological confirmations. For this study we got the approval from the Research Ethics Committee of China Medical University and Hospital, Taichung, Taiwan (Certification ID, CMU-REC-11-012, issued on Apr 18, 2012) and by the Ethics Committee of the Cardinal Tien Hospital, New Taipei City, Taiwan (IRB No. CTH-101-3-5-059, issued on Jun 14, 2013).

2.2. Study population

In this nationwide study, we enrolled PD one from the discharge patients and the outpatients with coding International Classification of Diseases 9th Revision-Clinical Modification, ICD-9-CM 332, during 2000–2009 as the patient population. We also included in individual to cancer history prior to the PD diagnosis as well as those who were younger than 18 years of age to avoid possible genetic confounding to analysis. Those with histories of dementia or cerebrovascular disease, who might have parkinsonism features, were also excluded in this study. We checked the medications for PD among these enrolled cases, i.e., levodopa/carbidopa, amantadine, selegiline/raagainle and the DAs, and the ones with long-term prescription were regarded as the high probability of a PD subject with less false-positive possibility. Then we identified the PD subjects with newly diagnosed cancers (ICD-9-CM 140-208) as the cancer group, and set the day of cancer diagnosis as the index date. The other PD patients without cancers were grouped as controls, and the index dates in non-cancer patients were defined as a day by simple randomization method before end of LHID, or Dec 31, 2010. And we defined the duration between the time of PD diagnosis and the index date as the “duration of Parkinson’s disease” (DuP). We cast the interest on the anti-PD drugs used before index date as the exposure factor.

The DAs drugs used classified into three groups: ergot-derived DAs (ED, bromocriptine, pergolide, and cabergoline), nonergot-derived DAs (ND, ropinirole, pramipexole, apomorphine, and rotigotine), and both used. Levodopa-only users were classified into the non-DA group. We also analyzed the monotherapy of monoamine-oxidase B (MAO-B) inhibitors before the index dates, including the selegline and rasagline, the non-levodopa medicines as compared with DAs on cancer formation while PD therapy. We also took the possible urbanization difference into consideration, for the sake of the higher risk of PD on exposure of pesticides in the rural farming districts [20]. The data will be also stratified according to the levels of urbanization. The Level 1 represented the highest urbanization and the level 8, the lowest [21].

The cohort disease histories were considered as confounding factors in this research. The disease histories including hypertension (ICD-9-CM 401-405), diabetes (ICD-9-CM 250) and coronary artery disease (CAD; ICD-9-CM 410-414) were obtained from inpatient and outpatient files. The cancers were classified as: liver cancer (ICD-9-CM 155), lung cancer (ICD-9-CM 162), colorectal cancer (CRC, ICD-9-CM 153 and 154), head and neck cancer (HNC, ICD-9-CM 140-149), pancreatic cancer (ICD-9-CM 157), skin cancer (ICD-9-CM 172 and 173), stomach cancer (ICD-9-CM 151), urinary tract cancer (ICD-9-CM 188 and 189), breast cancer (ICD-9-CM 174, female only), prostate cancer (ICD-9-CM 185, male only) and others.

2.3. Statistical analysis

We calculated the mean and standard deviation (SD) for age and DuP, and demonstrated the number and proportion for sex and comorbidities between cancer and non-cancer groups. The t test for continuous variables and chi-square test for category variables were applied to investigate the difference between these two groups. The adjusted logistic regression was used to measure the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the effect of DAs drugs on cancer risk. All statistical analyses were performed by SAS 9.3 software (SAS Institute, Cary, NC, USA). The significance was set at the level less than 0.05 for two-side testing of p-values.

3. Results

We enrolled 329 cancer patients from 6211 patients with PD (Table 1, and the Figure in supplementary information). Among the 329 patients only 5 patients were younger than 50 years. In addition, from our database there were 23 PD patients younger than 18 years, who all were without cancers and not taken into our analysis. The mean age in the cancer group was slightly elder than that in non-cancer group (76.5 and 73.3 years respectively). The DuP in the noncancer group was half a year longer than that in the cancer group (3.6 y vs 3.0 y; p < 0.0001). There was no significant differences of the population distribution according to the urbanization level (p = 0.0796). The prevalence of DA exposure in the cancer group (25.0%) was higher than that in the non-cancer group (18.3%) (p < 0.0001). However, MAO-B inhibitors did not exert significant influence on cancer association (p = 0.5073).

Whether the DAs affected the cancer occurrence among PD patients is our prime interest to explore in this study. Table 2 shows the odds ratios for cancer in individuals with DA use or not. Common diseases such as hypertension, diabetes mellitus, and coronary arterial disease did not have evident associations with cancer among the patients with PD. Neither did the significant differences exist on adjustment by the MAO-B inhibitor use. The elderly patients with age ranging from 70 to 79 years, and the men with PD had higher odds ratios. After adjustment for age, sex, DuP, comorbidities and MAO-B inhibitor use, individuals who had used ED.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-cancer group</th>
<th>Cancer group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>73.3 (14.3)</td>
<td>76.5 (8.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DuP, years (SD)</td>
<td>3.6 (2.4)</td>
<td>3.0 (2.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.0044</td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>2744 (49.5)</td>
<td>130 (39.5)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2801 (50.5)</td>
<td>199 (60.5)</td>
<td></td>
</tr>
<tr>
<td>Urbanization level</td>
<td>0.0796</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1343 (24.2)</td>
<td>91 (27.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1496 (27.0)</td>
<td>76 (23.1)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>925 (16.7)</td>
<td>67 (20.4)</td>
<td></td>
</tr>
<tr>
<td>4–8</td>
<td>1781 (32.1)</td>
<td>95 (28.9)</td>
<td></td>
</tr>
<tr>
<td>DAs use</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4499 (81.1)</td>
<td>247 (75.1)</td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>443 (8.0)</td>
<td>50 (15.2)</td>
<td></td>
</tr>
<tr>
<td>ND</td>
<td>462 (8.3)</td>
<td>26 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>141 (2.5)</td>
<td>6 (1.8)</td>
<td></td>
</tr>
<tr>
<td>MAO-B inhibitor use</td>
<td>0.0573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease history</td>
<td>664 (12.0)</td>
<td>51 (15.5)</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>4170 (75.2)</td>
<td>273 (83.0)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1702 (30.7)</td>
<td>107 (32.5)</td>
<td>0.4852</td>
</tr>
<tr>
<td>CAD</td>
<td>2635 (47.5)</td>
<td>167 (50.8)</td>
<td>0.2530</td>
</tr>
</tbody>
</table>

DuP: duration of Parkinson’s disease; ED: ergot-derived dopamine agonists; ND: non-ergot-derived dopamine agonists; MAO-B inhibitor: monoamine oxidase B inhibitor.

Table 1: Demographic status and comorbidity among the PD subjects.
exhibited a 2.16-fold higher risk for cancer (OR = 2.16, 95% CI = 1.55–2.99). However, there was no difference for cancer risk in patients who had used ND (OR = 0.99, 95% CI = 0.65–1.51) and in patients who had used both (OR = 0.96, 95% CI = 0.41–2.24). Among the 5 cancer patients younger than 50 years, only one had ED use and the other 4 without ever DA exposure.

We did not observe a significant difference in the cancer distribution among our patients based on the urbanization level of their residences. The female ED users exhibited a 2.56-fold higher cancer risk (OR = 2.56, 95% CI = 1.54–4.26), and the risk among the male ED users was 1.93-fold higher (OR = 1.93, 95% CI = 1.26–2.97) (Table 3). While calculating the cancer risks of the ED/ND use, the female ED users had a higher risk by 2.47 folds than the ND users did, and that the male ED users exhibited a 1.76-fold higher risk than the ND users did.

Table 4 shows the case numbers and the risks of various types of cancer based on DA exposure. Although we examined a limited number of cases, the majority of the cases exhibited a higher percentage of ED use for all types of cancer, except for prostatic and colorectal cancers in the ED group, compared with the percentage of ND use. The analysis results indicated that the ED users had a higher risk for liver cancer (OR = 4.06, 95% CI, 1.98–8.35; p < 0.01) and HNC (OR = 4.45; 95% CI, 1.14–17.43; p < 0.05) compared with non-DA users.

### 4. Discussion

Cancers had ranked as the most common cause of death in Taiwan for decades, with increased incidences of breast, colorectal, hepatic, lung and prostate cancers in recent years [22]. Because the growing cost of cancer treatment may impact the health insurance system, the risk of drug-precipitated cancers should be evaluated, not only for the sake of the revision of the public health policy but also weighing the beneficial of therapeutic agents on the treatment of the neurodegenerative diseases.

Cancer association has been well known with the anti-diabetic agents, no matter the observations in or outside Taiwan [18,19,23,24]. Although indirect or controversial reports about the association of PD and cancer [15,16,25,26], diabetes mellitus patients still have a potential risk for PD [11,12], and the cancer risk among PD patients may be also attributed to the prescribing medicines for PD, as the story in diabetes mellitus. This gave hint us to think of the relation of DAs to cancer, in addition to their adverse effects on treatment of PD.

In this study, the prevalence of cancers among our PD patients was 5.2%. We did not find any hematologic malignancies. We observed a higher risk of cancer among the ED users on PD treatment. Among the ED users, there were more cases of liver, HNC, skin and stomach cancers, but significant difference existed for liver and HNC cancers. Another our interesting finding is skin cancer, although the report of the risk of skin cancers including the melanoma in PD [27]. There were only 12 cases with skin cancer in our analysis: no one on ND use, 9 non-DA users and 3 ED users, and we did find the significance while analyzing the risk of skin cancer. The result may be attributed to the ethic difference of the skin cancers among Asians, especially melanoma. Prostate cancer had higher odds ratio among the ND users, but without significance (OR 1.82, 95% CI 0.23–14.62). Our finding is not consistent with the prior finding of predisposition of prostatic cancer among PD subjects [16]. Among the 5 cancer patients younger than 50 years there were 2 with liver cancers, one with HNC, and 2 with breast cancers. From our data bank there was lack of the genetic information related to PD, and from the limited case number we did not confirm any genetic contribution to or pharmacologic effect on the cancers for the juvenile PD group.

There was still little information about exact mechanism that links ED with cancers. However, ED exerted its agonist effect on 5-HT2B receptor which results in fibrotic change of the cardiac valves [28]. Therefore, people may speculate that ED may induce or modulate cancer occurrence through some aberrant signal pathway or chemical isomerization [29] for solid tumors. The serotonin-5-HT2B receptor-FOXO3a signal pathway has been known to promote the cell proliferation of the hepatocellular carcinoma, even in the serum-free condition [30]. This may explain our finding of higher percentage of liver cancers among our ED users.

This study still had certain limitations. The first is the possible misdiagnosis of PD, resulting from the discrepancy between the clinical impression and the neuropathological findings [31]. Problems of diagnoses occurred while cases of atypical parkinsonism coding ICD 332.0/332.1 enrolled into this analysis, and we could not recheck our sampled cases by the neuroimage information such as brain MRI or TRODAT-1 from the LHID. Thus we explored the registered medicine files, including the levodopa and DA, to reduce the sampling error, presuming the continuously refilled medications for these PD patients with satisfied response. The second limitation is poor information source to analyze other risk factors causing cancers from the LHID database, such as environmental information about the carcinogen exposure, residential district or occupation. The presence of this confounding factor may affect the outcome of our study. We had tried the analyses about the
urbanization levels of our study patients, and found no difference (Tables 1 and 2). The third limitation is the absence of information regarding the exposing durations and dosages of each DA, regardless of ED or ND, among our PD patients. However, we found the shorter DuP in the cancer group (Table 1), implying the possibility of the earlier or/and longer use of DAs in this group. The exposing duration and dosing effects to suspected carcinogenic medication may be indeed important pieces of information to establish the association. Fourth, clinical difficulty is always present from our database on evaluating the interaction(s) of DA with other drugs and the modifying factors of ED- or ND-related cancers, due to lack of information on outcome, the longevity of the patients with cancer among the DA users, and the responses of the cancer therapies or managements.

Even though the study limitations stated above, our survey is the first report linking DA use and the risk of cancers by the Taiwanese nationwide database. We worried about the ED safety for this long-lasting neurodegenerative disorder. ED users, not only among the PD patients but also those with the prolactin-secreting pituitary gland tumors, may require regular checkups to detect the dormant cancers, in addition to the valvular heart disease. Additional pharmacological studies are also required to identify the possible DA-related up- or downregulation mechanisms of cancer formation.

Author contribution

The contributions of each author are as follows: Concept and design: Vinchi Wang, Chia-Hung Kao; administrative support: Tzu-Hao Chao, Chung-Chih Hsieh; data collection and organization: Vinchi Wang, Che-Chen Lin, Chia-Hung Kao; data analysis and interpretation: Vinchi Wang, Che-Chen Lin, Chia-Hung Kao; manuscript writing: all authors; and final approval of manuscript: all authors.

Competing interests

All authors state that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.10.015.

References


