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

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ABSTRACT

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].

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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 sulfonylurea 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 record. 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 illed patients, who had image diagnoses or/and 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 ones 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 excluded individuals with 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/rasagiline 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, promipexole, 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 selegiline and rasagiline, 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 co-morbid 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 (18.8%) ($p \leq 0.0001$). However, MAO-B inhibitors did not exert significant influence on cancer association ($p = 0.0573$).

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 1
Demographic status and comorbidity among the PD subjects.

Variable	Non-cancer group $N = 5545$ (%)	Cancer group $N = 329$ (%)	*p*
Age, years (SD)[a]	73.3 (14.3)	76.5 (8.9)	<0.0001
DuP, years (SD)[a]	3.6 (2.4)	3.0 (2.5)	<0.0001
Sex			0.0004
Female	2744 (49.5)	130 (39.5)	
Male	2801 (50.5)	199 (60.5)	
Urbanization level			0.0796
1	1343 (24.2)	91 (27.7)	
2	1496 (27.0)	76 (23.1)	
3	925 (16.7)	67 (20.4)	
4–8	1781 (32.1)	95 (28.9)	
DAs use			<0.0001
None	4499 (81.1)	247 (75.1)	
ED	443 (8.0)	50 (15.2)	
ND	462 (8.3)	26 (7.9)	
Both	141 (2.5)	6 (1.8)	
MAO-B inhibitor use	664 (12.0)	51 (15.5)	0.0573
Disease history			
Hypertension	4170 (75.2)	273 (83.0)	0.0014
Diabetes	1702 (30.7)	107 (32.5)	0.4852
CAD	2635 (47.5)	167 (50.8)	0.2530

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

[a] *t*-test; SD, standard deviation.