

## Parkinson's disease and risk of colorectal cancer: A population-based case-control study in Taiwan

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### Abstract

**Objective:** The aim of this study was to evaluate whether there is an association between Parkinson's disease (PD) and colorectal cancer in Taiwan. **Methods:** This was a case-control study using claim data of the Taiwan National Health Insurance Program. There were 64,619 subjects aged 20-84 with newly diagnosed colorectal cancer as cases and 64,619 randomly selected subjects without colorectal cancer as controls from 2005 to 2011. Both cases and controls were matched by sex, age, comorbidities, and index year of diagnosing colorectal cancer. Subjects who were diagnosed with PD within 5 years of diagnosing colorectal cancer were excluded. The multivariable logistic regression model was used to estimate the adjusted odds ratio (OR) and 95% confidence interval (95% CI) for risk of colorectal cancer associated with PD. **Results:** After adjusting for confounding factors, the multivariable logistic regression analysis revealed that the adjusted OR of colorectal cancer was 0.69 for subjects with PD more than 5 years before index date (95% CI 0.59, 0.81), as compared with subjects without PD. **Conclusion:** PD is associated with reduced odds of colorectal cancer. Further research is needed to elucidate the mechanisms underlying our findings.

**Key words:** Colorectal cancer; Parkinson's disease

### INTRODUCTION

Parkinson's disease (PD) is known as the *second most common* neurodegenerative disorder after Alzheimer's disease in the world. Recent evidence has suggested that people with PD are associated with reduced risk of many common cancers, but associated with increased risk of melanoma and breast cancer.<sup>1-6</sup> Although not well established, a *hypothesis is proposed* that regulation of potential specific genes and pathways could increase the incidence of some neurodegenerative disorders including PD, and simultaneously lower the incidence of some cancers, and vice versa.<sup>7-9</sup> These two opposite directions could partially explain why inverse association is found between PD and some cancers.

In our previous studies, after controlling for potential confounding factors, PD is found to be associated with decreased odds of lung cancer (adjusted OR 0.85), hepatocellular carcinoma (adjusted OR 0.95), and pancreatic cancer (adjusted OR 0.82, 95% CI 0.55, 1.21) in Taiwan, but without statistical significance.<sup>10-12</sup> Moreover,

colorectal cancer ranked the third leading cause of cancer deaths after lung cancer and hepatocellular carcinoma in Taiwan in 2014 (5603 deaths, crude death rate 23.9 per 100,000 populations).<sup>13</sup> Till now, no conclusive information on the association between PD and colorectal cancer can be found in Taiwan. If the association really exists, it would add updated evidence on this issue. Hence, we conducted a case-control study using the database from the Taiwan National Health Insurance Program to explore whether there is an association between PD and colorectal cancer in Taiwan.

### METHODS

#### *Study design and data sources*

Taiwan is an independent country with more than 23 million people. We conducted a population-based case-control study using insurance claim data from the Taiwan National Health Insurance Program which covers 99% of Taiwan population since 1995.<sup>14</sup> This insurance program also includes a catastrophic illness program to protect vulnerable

beneficiaries (including colorectal cancer patients) by exempting them from co-payments for the corresponding medical services. The details of this insurance program have been well written down in previous studies.<sup>15-19</sup> The study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

#### *Inclusion and exclusion criteria*

Subjects aged 20-84 with new diagnosis of colorectal cancer between 2005 and 2011 were selected as the cases (based on International Classification of Disease, 9th Revision of Clinical Modification, ICD-9 codes 153 and 154). Cases with colorectal cancer were identified from the Registry of Catastrophic Illnesses Patient Database, a dataset containing health claims data for treatment of catastrophic illness, which consists of thirty categories of diseases that require long-term care. Subjects without colorectal cancer were randomly selected from the same database as the controls. The index date was defined as the date of cases being diagnosed with colorectal cancer. Both cases and controls were matched by sex, age (every 5 year), comorbidities, and index year of diagnosing colorectal cancer. Comorbidities potentially related to colorectal cancer were included as follows: PD (ICD-9 code 332.0), alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 571.0-571.3, 790.3, and V11.3), chronic obstructive pulmonary disease (ICD-9 codes 491, 492, 493, and 496), colorectal adenoma (ICD-9 codes 211.3 and 211.4), diabetes mellitus (ICD-9 code 250), hyperlipidemia (ICD-9 codes 272.0, 272.1, 272.2, 272.3, and 272.4), and inflammatory bowel disease (ICD-9 codes 555.X and 556.X).

To reduce biased results, subjects who were diagnosed with PD only within 5 years of diagnosing colorectal cancer were excluded from the study. That is, only subjects with the interval between colorectal cancer and PD more than 5 years could be included in the study. In addition, subjects who had any other cancer (ICD-9 codes 140-208) or secondary Parkinsonism (ICD-9 code 332.1) before index date were excluded from the study.

#### *Statistical analysis*

The standardized difference was used to quantify differences in mean or prevalence between patients with and without colorectal cancer for continuous and categorical matching variables. A

value of standardized mean difference equals 0.01 or less, which indicates a negligible difference in mean or prevalence between patients with and without colorectal cancer.<sup>20</sup> Initially, all covariables were examined by the univariable unconditional logistic regression model. Only those found to be statistically significant in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model to estimate the adjusted odds ratio (OR) and 95% confidence interval (95% CI) for the risk of colorectal cancer associated with PD and other comorbidities. Analyses were performed using the SAS 9.2 (SAS Institute Inc., Carey, North Carolina, USA), with  $P < 0.05$  as statistically significant.

## RESULTS

#### *Characteristics of the study population*

Table 1 reveals the characteristics between the cases and controls. The cases had 64619 subjects with new diagnosis of colorectal cancer and the controls had 64619 subjects without colorectal cancer. The mean ages (standard deviation) were 64.0 (12.8) years in cases and 64.7 (12.8) years in controls. The controls had a higher proportion of PD than the cases (0.60% vs. 0.39%). The cases had higher proportions of alcohol-related disease (5.69% vs. 4.79%), chronic obstructive pulmonary disease (17.9% vs. 17.3%), colorectal adenoma (7.29% vs. 5.39%), diabetes mellitus (20.1% vs. 19.6%), hyperlipidemia (30.9% vs. 30.5%), and inflammatory bowel disease (2.09% vs. 1.86%) than the controls. In further analysis, among 255 subjects with PD in cases, 0 subject was aged 20-39 (0%), 17 subjects were aged 40-64 (6.7%), and 238 subjects were aged 65-84 (93.3%). Among 386 subjects with PD in controls, 1 subject was aged 20-39 (0.3%), 26 subjects were aged 40-64 (6.7%) and 359 subjects were aged 65-84 (93%).

#### *Colorectal cancer associated with Parkinson's disease and comorbidities*

Table 2 reveals the odds ratio of colorectal cancer associated with PD and comorbidities. After adjusting for potential confounding factors, the multivariable unconditional logistic regression model revealed that the adjusted OR of colorectal cancer was 0.69 for subjects with PD more than 5 years before index date (95% CI 0.59, 0.81), as compared with subjects without PD. In addition, male (adjusted OR 1.04, 95% CI 1.01, 1.06), age

**Table 1. Comparison of sociodemographic factors, Parkinson's disease and other comorbidities between colorectal cancer cases and controls**

Characteristic	Colorectal cancer				Standard difference*
	No N= 64619		Yes N= 64619		
	n	(%)	n	(%)	
Sex					
Female	28350	(43.9)	27583	(42.7)	0.02
Male	36269	(56.1)	37036	(57.3)	0.02
Age group (years)					
20-39	2596	(4.0)	2765	(4.3)	0.01
40-64	27705	(42.9)	29055	(44.9)	0.04
65-84	34318	(53.1)	32799	(50.8)	0.05
Age (years), mean (standard deviation)	64.7	(12.8)	64.0	(12.8)	0.04
Comorbidities					
Parkinson's disease	386	(0.60)	255	(0.39)	0.03
Alcohol-related disease	3096	(4.79)	3678	(5.69)	0.04
Chronic obstructive pulmonary disease	11177	(17.3)	11541	(17.9)	0.02
Colorectal adenoma	3485	(5.39)	4711	(7.29)	0.08
Diabetes mellitus	12642	(19.6)	12962	(20.1)	0.01
Hyperlipidemia	19677	(30.5)	19967	(30.9)	0.01
Inflammatory bowel disease	1199	(1.86)	1348	(2.09)	0.02

Data are presented as the number of subjects in each group with percentages given in parentheses, or mean with standard deviation given in parentheses.

\*A value of standardized mean difference equals 0.01 or less, which indicates a negligible difference in means or prevalence between patients with and without colorectal cancer (reference 20).

(per one year, adjusted OR 1.00, 95% CI 1.00, 1.00), alcohol-related disease (adjusted OR 1.16, 95% CI 1.10, 1.22), chronic obstructive pulmonary disease (adjusted OR 1.07, 95% CI 1.04, 1.10), colorectal adenoma (adjusted OR 1.36, 95% CI 1.30, 1.42), diabetes mellitus (adjusted OR 1.05, 95% CI 1.03, 1.08), and inflammatory bowel disease (adjusted OR 1.12, 95% CI 1.04, 1.21) were other factors significantly associated with colorectal cancer.

**Table 2. Crude and adjusted odds ratios and 95% confidence intervals of colorectal cancer associated with Parkinson's disease and comorbidities**

Variable	Crude odds ratio	(95% CI)	Adjusted odds ratio†	(95% CI)
Sex (male vs. female)	1.05	(1.03, 1.07)	1.04	(1.01, 1.06)
Age (per one year)	1.00	(1.00, 1.00)	1.00	(1.00, 1.00)
Parkinson's disease	0.66	(0.56, 0.77)	0.69	(0.59, 0.81)
Comorbidities (yes vs. no)				
Alcohol-related disease	1.20	(1.14, 1.26)	1.16	(1.10, 1.22)
Chronic obstructive pulmonary disease	1.04	(1.01, 1.07)	1.07	(1.04, 1.10)
Colorectal adenoma	1.38	(1.32, 1.44)	1.36	(1.30, 1.42)
Diabetes mellitus	1.03	(1.00, 1.06)	1.05	(1.03, 1.08)
Hyperlipidemia	1.02	(0.99, 1.05)	-	-
Inflammatory bowel disease	1.13	(1.04, 1.22)	1.12	(1.04, 1.21)

†Variables found to be statistically significant in the univariable unconditional logistic regression model were further examined by the multivariable unconditional logistic regression model. Adjusted for sex, age, alcohol-related disease, chronic obstructive pulmonary disease, colorectal adenoma, diabetes mellitus, and inflammatory bowel disease.

## DISCUSSION

In this population-based case-control study, we found that patients with PD more than 5 years before index date were associated with reduced odds of colorectal cancer (adjusted OR 0.69, 95% CI 0.59, 0.81, Table 2). This finding is compatible with Boursi *et al.*'s study<sup>21</sup>, in which cases with PD more than 1 year before the date of colorectal cancer diagnosis were associated with lower odds of colorectal cancer (adjusted OR 0.74, 95%CI 0.59-0.94), compared with the matched controls. As mentioned in our previous study<sup>12</sup>, during the period before diagnosing colorectal cancer, the cancer could be little symptomatic, which could cause an critical issue of potential reverse causality or follow-up bias. Therefore, it would be important that the diagnosis of PD should exist before diagnosing colorectal cancer. In our study, we used the relatively rigorous inclusion criteria to reduce the biased results. That is, only those with the interval between colorectal cancer and PD more than 5 years could be included in the study. That is why the prevalence of PD is low in the present study (0.39% in cases and 0.60% in controls, Table 1). Moreover, there is no idea what cut-point is appropriate, but any shown association should be highly convincing if Parkinson's disease exists for a longer time before diagnosing colorectal cancer. In addition, based on the high quality of medical care in Taiwan, it does not need to take 5 years to diagnose colorectal cancer since the onset of colorectal cancer-related symptoms/signs. Therefore, we think the clinical diagnosis of PD really proceeds to the detection of colorectal cancer in the present study. Potential reverse causality or follow-up bias could be excluded.

However, in Lin *et al.*'s study using the same database of the Taiwan National Health Insurance Program<sup>22</sup>, the authors found that patients with PD had a higher hazard of colorectal cancer (HR 1.47, 95% CI 1.31,1.65). We think that Lin *et al.*'s study did not control for confounding factors potentially related to colorectal cancer. It would overestimate the effect of PD on colorectal cancer.

Although no definite evidence is available, different hypotheses have been proposed to explain the biological mechanisms underlying the association between PD and cancer risk. To date, no unique hypothesis can completely explain the mechanisms. We summarize the literature as follows. Common genetic components might play a pivotal role on this association. For example, phosphatase and tensin homologue-induced kinase 1 (PINK1) and Parkin are found to be

associated with regulation of cell division, cell growth, and cell cycle.<sup>23-26</sup> Mutation of PINK1 or Parkin gene could cause major defects in cell division, cell growth, and cell cycle.<sup>23-26</sup> If these defects occur in central nerve system, neuron cells could progressively degenerate and die. Consequently PD develops. If these defects occur in *precancerous* cells, cell division, cell growth, and cell cycle could be damaged. Consequently *precancerous* cells cannot survive and cancers do not develop. That is, mutation or deletion of common genetic components could increase the incidence of some neurodegenerative disorders, and simultaneously lower the incidence of some cancers, and vice versa.<sup>7-9</sup> These two opposite directions could partially explain why inverse association is found between PD and some cancers.

The present study has some limitations. First, some risk factors for colorectal cancer, including body mass index, *cigarette smoking*, and alcohol consumption, could not be adequately addressed in this database. We used chronic obstructive pulmonary disease instead of *cigarette smoking*, diabetes mellitus and hyperlipidemia instead of *obesity*, and alcohol-related disease instead of alcohol consumption. *Second*, although the diagnosis of comorbidities included is based on ICD-9 codes, not on clinical diagnosis, the diagnosis accuracy of comorbidities based on ICD-9 codes has been well evaluated in previous studies.<sup>10-12,27-39</sup> Colorectal cancer was included based on catastrophic illness program. The accuracy can be definitely sure. *Third*, although both cases and controls were matched by sex, age (every 5 year), and comorbidities, the distributions of these variables seem to be a little different in both groups. Therefore, whether this shown association is confounded by these variables needs further research to elucidate. *Fourth*, patients with the interval between colorectal cancer and PD more than 5 years could be included in the study. If one speculates that the association relies on common genetic factors, then this timeframe doesn't seem to be justified. *Fifth*, there is likely some bias due to the increased mortality associated with PD. Patients with PD may die before they get a cancer diagnosis which would result in an apparent lower risk of cancer. *Sixth*, the reduced incidence of colorectal cancer in patients with PD could potentially be confounded by the fact that patients with PD might very often experience constipation due to the side effect of medications. As a result, clinicians might not investigate this "expected" symptom

as aggressively with colonoscopy as they would do in patients without PD. Therefore, it could underestimate the incidence of colorectal cancer in patients with PD.

In spite of the above several limitations, the present study has much strength. This is a clinically relevant issue with some scientific novelty. We conducted a population-based case-control study using a well-organized database with a big sample size to increase its statistic power. The topic is very important. The inclusion criteria are relatively rigorous to reduce the possibility of potential reverse causality and follow-up bias. Confounding factors potentially related to colorectal cancer have been well controlled to increase its unbiased results on the association between PD and colorectal cancer. In addition, subjects who had any other cancer or secondary Parkinsonism before the index date were excluded from the study. Therefore, the controls did not have any cancer. The present study was to focus on PD and colorectal cancer. The results are impressive. The present study is a worthwhile contribution to the literature on PD and cancer risk.

We conclude that PD is associated with reduced odds of colorectal cancer. In addition, male, age, alcohol-related disease, chronic obstructive pulmonary disease, colorectal adenoma, diabetes mellitus, and inflammatory bowel diseases are significantly associated with colorectal cancer. Further research is needed to elucidate the mechanisms underlying our findings.

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## DISCLOSURE

Conflict of interest: None

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