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Original Research

Cancer risk in patients with Parkinson's disease in South Korea: A nationwide, population-based cohort study

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Abstract ***Introduction:*** The association between Parkinson's disease (PD) and cancer development is controversial, especially in Asia. Therefore, we conducted a nationwide population-based cohort study to assess the overall cancer risk and risk for specific cancers in patients with PD in Korea.

Methods: Using data from the Korean National Health Insurance Database, we analysed 52,009 patients diagnosed with PD between 2010 and 2015 and 260,045 individuals without PD. Patients previously diagnosed with cancer were excluded. The age- and sex-matched cohorts were followed up until 2016 for cancer development. Cox proportional hazards regression models were used to evaluate the relationship between PD and cancer.

Results: Patients with PD had a lower overall cancer risk (hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.74–0.82) after adjustment for multiple covariates during 2,022,852.6 person-years of follow-up. Patients with PD showed significantly lower risk of laryngeal cancer (HR, 0.45; 95% CI, 0.21–0.84), gastric cancer (HR, 0.72; 95% CI, 0.63–0.82), colorectal cancer (HR, 0.675; 95% CI, 0.60–0.76), liver cancer (HR, 0.80; 95% CI, 0.67–0.95), pancreatic

Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; ICD-10-CM, International Classification of Diseases; 10th Revision, Clinical Modification; NHIS, National Health Insurance Service; PD, Parkinson's disease; RIDs, rare intractable diseases.

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cancer (HR, 0.75; 95% CI, 0.62–0.91), lung cancer (HR, 0.73; 95% CI, 0.63–0.84), leukaemia (HR, 0.49; 95% CI, 0.24–0.89), uterine cervical cancer (HR, 0.64; 95% CI, 0.40–0.99) and prostate cancer (HR, 0.78; 95% CI, 0.66–0.91).

Conclusion: This nationwide population-based cohort study revealed that patients with PD had lower overall cancer risk and lower risk of specific cancers. Contrary to the results of the recent Asian study, this large cohort study revealed that patients with PD were less likely to develop cancer than those without PD in Korea. Our results were consistent with those of previous Western studies, despite differences in ethnicity and environment.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 2–3% of the population aged >65 years [1]. Neuronal loss in the substantia nigra and the resultant dopamine deficiency within the basal ganglia lead to the classical motor symptoms of PD [2].Although the prevalence of PD has been reported to increase gradually [3], this slowly debilitating disease remains incurable and irreversible [2]. Another chronic disease that devastates human health and has considerable research focus is cancer. Recent growing evidence has revealed a significant association between PD and cancer [4–9]. Cancer, the leading cause of death worldwide [10], is a disease characterised by infinite cellular proliferation and lack of apoptosis. In patients with PD, an increased tendency for cells to undergo apoptosis can be expected to reduce the risk of developing cancer. Furthermore, research studies showing that cancer and PD share the same genes and biological pathways give credence to the proposition that people who develop PD may have some biological protection against cancer [11,12].

Several studies investigating cancer development in patients with PD showed inconsistent results, especially in Asia. Several studies have reported low incidence of cancer in patients with PD [4–6,8,9], or no association [13]. In a meta-analysis of 29 observational studies, although all were Western studies, patients with PD had a decreased risk of developing cancer compared with controls [6]. On the contrary, one recent Asian study reported that cancer incidence in patients with PD was increased [7].

Most of these studies were conducted in the United States or Europe, where genetic factors or socioeconomic status differs from those of Asia. Globally, lung, breast and colorectal cancers were the most common cancers in order in 2018. The most common cancers in men were the lung, prostate and colorectal cancers, and in women, the order is breast, colon and lung cancers [10]. In Korea, the most common cancer was gastric cancer, followed by colorectal cancer and thyroid cancer. The most common cancers in men in Korea were gastric, lung and colorectal cancer, and those in women are breast, thyroid and colorectal cancer [14].Because of the differences between Asia and the West, it is of interest to determine whether the association of PD and cancer is indeed different between Asians and Westerners. Asian studies are rare and need more research. In addition, most of the previous studies were small, or the diagnosis of PD was not clear [6,15].

Therefore, we conducted this nationwide population-based, age- and sex-matched cohort study to investigate cancer incidence in patients with PD, using National Health Insurance Service (NHIS) data and national disease registration data for the entire Korean population.

2. Data sources and methods

2.1. Data source

Data used in this study were obtained from the Health Insurance Review and Assessment Service of Korea. South Korea has a compulsory national health insurance system, the NHIS, which covers approximately 97% of their population and provides universal health coverage. The Korean NHIS database includes almost all medical data, including diagnostic codes, procedures, prescription drugs, personal information and a registry of cancer and rare intractable diseases. The NHIS also has a registration programme for cancer and some intractable diseases to enhance benefit coverage, and PD is one of these intractable diseases. All patients with these intractable diseases are required to have their diagnosis certified by physicians through uniform diagnostic criteria distributed by the NHIS. After the physician's assessment, the institution also reviews the diagnosis before submission to the NHIS. This systematic process ensures that the registration data are reliable.

In this study, all personal identification numbers were encrypted into scrambled numbers before data processing to comply with the privacy guidelines of the Health Insurance Portability and Accountability Act. The need for written informed consent was waived as the study used deidentified data, and none of the patients were contacted. The study was conducted according to the ethical principles outlined in the Declaration of Helsinki. All study procedures and ethical aspects were approved by the Institutional

Review Board (IRB) of Korea University Ansan Hospital (IRB no. 2018AS0098).

2.2. Study population and design

We used a cohort study design to investigate the association of PD with cancer development. The study population included the PD group and non-PD group, aged ≥40 years. Newly diagnosed PD was identified on the basis of the ICD-10-CM (International Classification of Diseases, 10th Revision, Clinical Modification) code for PD (G20) and the PD registration code (V124) in the registry of intractable diseases between January 2010 and December 2015. Patients with a history of PD or cancer during a washout period from 2007 to 2009 were excluded.

The gold standard for diagnosis of PD is the neuropathological assessment [16]. However, in general, PD is diagnosed based on the presence of clinical features, and the United Kingdom (UK) Parkinson's Disease Society Brain Bank criteria 2 are used in the clinic and in clinical research to make a diagnosis of PD [2].The PD registration code (V124) is almost identical to the UK Parkinson's Disease Society Brain Bank diagnostic criteria. The criteria for the V124 code are as follows: (1) The criteria for the diagnosis of parkinsonian syndrome (parkinsonism) include mild or worse bradykinesia and at least one of the following: muscular rigidity, rest tremor and postural instability. (2) The exclusion criteria for PD are as follows: history of strokes, head injury, definite encephalitis, drug side-effects and hypoxia. (3) The supportive prospective positive criteria for PD include three or more of the following conditions in combination with those from (1), which are required for the diagnosis of definite PD: unilateral onset, presence of rest tremor, progressive disorder, persistent asymmetry affecting the side of onset the most, excellent response (70–100%) to Levodopa, severe Levodopa-induced chorea, Levodopa response for ≥5 years and clinical course of ≥10 years.

For the comparison cohort, an age- and sex-matched population without PD was randomly extracted, assigning 5 patients for every patient with PD. Randomisation was performed using an algorithm within the SAS software programme (version 9.4, SAS Institute, Cary, NC, USA).

Finally, a total of 52,009 subjects were identified in the PD group and 260,045 subjects in the non-PD group. Each person in these retrospective cohorts was followed up for cancer development until 2016. Those who had no events and were alive until 31st December 2016 were censored after this time point.

2.3. Predictor and outcome variables

Details of patients' age, sex, household income and comorbidities were obtained from the NHIS database. We assessed the effects of household income at the index date according to two income groups (lowest quartile and the remaining quartiles). Moreover, we analysed comorbidities including hypertension (ICD-10-CM codes I10–13 and I15 and claims for antihypertensive agents), diabetes mellitus (DM; ICD-10-CM codes E11–E14 and claims for oral antidiabetic agents or insulin) and dyslipidemia (ICD-10-CM code E78 and claims for agents for dyslipidemia). We also defined the presence of comorbidities as any diagnoses of the aforementioned codes within 3 years before the index date. The operational definitions of the study end-points were incidences of cancer.

2.4. Statistical analysis

To compare the characteristics between cohorts, Student's *t*-test was used for continuous variables, and the chi-square test, for binary and categorical variables. Cancer incidence rates were calculated per 1000 person-years. The cumulative cancer incidence for each group was plotted using Kaplan–Meier curves and compared using the log-rank test. Multivariate Cox proportional hazards regression models were used to assess hazard ratios (HRs) and 95% confidence intervals (CI) to investigate the association between PD and cancer development.

Two-sided P-values <0.05 were considered to be statistically significant. All statistical analyses were performed using SAS software.

3. Results

Table 1 shows the general characteristics of the patient population and control cohorts. Because the cohorts were age and sex matched, the mean age ± standard deviation (44 ± 13 years) and the proportion of males (32%) were the same between the two groups. Meanwhile, DM, hypertension and dyslipidemia were found

Table 1
Population characteristics between patients with Parkinson's disease and controls.

	PD group (n = 52,009)	Non-PD group (n = 260,045)	P-value
Age, years	71 ± 10	71 ± 10	1
Age of ≥65 years	40,624 (78)	203,120 (78)	1
Male sex	21,213 (41)	106,065 (41)	1
Household income (lower 25%)	13,311 (26)	67,002 (26)	0.41
Comorbidities			
Diabetes mellitus	12,666 (24)	45,626 (18)	<0.0001
Hypertension	27,539 (53)	124,208 (48)	<0.0001
Dyslipidemia	17,432 (34)	64,310 (25)	<0.0001
Chronic obstructive pulmonary disease	15,626 (30)	62,772 (24)	<0.0001
Chronic kidney disease	639 (1.2)	1003 (0.4)	<0.0001

PD, Parkinson's disease.
Data are presented as mean ± standard deviation or n (%).

Table 2
Cancer incidence rates between patients with Parkinson's disease and controls.

Cancer type		PD group (n = 52,009)		Non-PD group (n = 260,045)	
	ICD-10 code	Event	%	Event	%
Overall	C	1572	3.0	9833	3.8
Oral cavity and pharyngeal cancer[a]	C00, C01-14	24	0.05	160	0.06
Laryngeal cancer[a]	C32	9	0.02	100	0.04
Oesophageal cancer[a]	C15	24	0.05	158	0.06
Gastric cancer[a]	C16	264	0.51	1801	0.69
Colorectal cancer[a]	C18-21	310	0.60	2227	0.86
Liver cancer[a]	C22	151	0.29	927	0.36
Pancreatic cancer[a]	C25	116	0.22	744	0.29
Biliary cancer	C23, C24	78	0.15	425	0.16
Lung cancer[a]	C33, C34	207	0.40	1383	0.53
Renal cancer[a]	C64	38	0.07	207	0.08
Bladder cancer[a]	C67	79	0.15	462	0.18
Thyroid cancer	C73	88	0.17	520	0.20
Leukaemia	C91-95	10	0.02	99	0.04
Lymphoma	C81-86	34	0.07	188	0.07
Multiple myeloma	C90	18	0.03	105	0.04
Skin cancer	C43	13	0.03	45	0.02
Breast cancer (women)	C50	72	0.14	423	0.16
Uterine cervical cancer (women) [a]	C53	21	0.04	162	0.06
Uterine corpus cancer (women)	C54, C55	15	0.03	80	0.03
Ovarian cancer (women)	C56	22	0.04	142	0.05
Prostate cancer (men)	C61	185	0.36	1152	0.44
Testicular cancer (men)	C62	1	0.002	15	0.01

PD, Parkinson's disease; ICD-10, International Classification of Diseases, 10th Revision.
[a] Smoking-related cancers [30].

to be more common in patients with PD than in normal controls (all $P < 0.0001$).

Cancers were diagnosed in 1572 patients (3.0%) in the PD group and in 9833 patients (3.8%) in the non-PD group. Table 2 shows the incidence of each cancer in both groups and the cancer codes (ICD-10 codes) used in the study.

The Kaplan–Meier survival curves and log-rank tests over the 6-year follow-up period are presented in Fig. 1. Patients with PD developed fewer cancers than those without PD (log-rank $P < 0.05$). However, there were no significant results with lymphoma ($P = 0.06$), ovarian cancer ($P = 0.06$), renal cancer ($P = 0.28$), uterine corpus cancer ($P = 0.93$), testicular cancer ($P = 0.23$) and skin cancer ($P = 0.19$).

The crude incidence rates of cancer per 1000 individuals in the PD group and control group were 9.1 and 11.4, respectively. After adjustment for age, sex, hypertension, DM, hyperlipidaemia and income, the overall HR for cancer in patients with PD compared with that in controls was 0.78 (95% CI, 0.74–0.82; Table 3). Patients with PD were at lower risk for laryngeal cancer (HR, 0.45; 95% CI, 0.21–0.84) and lung cancer (HR, 0.73; 95% CI, 0.63–0.84) than patients without PD. Regarding digestive system cancers, patients with PD were less likely to develop gastric, colorectal, liver and pancreatic cancer than those without PD. Among the haematologic malignancies, patients with PD were also at lower risk for developing leukaemia (HR, 0.49; 95% CI, 0.24–0.89), but there were no significant differences for lymphoma and multiple myeloma. Interestingly, the risk of skin cancer was increased in patients with PD, but it was not statistically significant (HR, 1.5; 95% CI, 0.75–2.6). Meanwhile, men with PD had a lower risk for prostate cancer (HR, 0.78; 95% CI, 0.66–0.91) than men without PD. In women, those with PD were less likely to develop cervical cancer (HR, 0.64; 95% CI, 0.40–0.99).

4. Discussion

In this study, we examined the association between PD and cancer development in 312,054 age- and sex-matched individuals from a nationwide longitudinal cohort database. Interestingly, we found that patients with PD had a significant lower risk for overall cancer incidence than those without PD after adjustment for sociodemographic factors and comorbidities.

Our findings are consistent with the results of some previous studies [4–6,8,9].In a meta-analysis of 29 observational studies, patients with PD had a 27% decreased risk of developing cancer compared with controls [6]. The 29 studies included a total of 107,598 patients with PD, and the aggregate risk for cancer in these patients was 0.73 (95% CI, 0.63–0.83) compared with that of controls. However, all the studies included in this meta-analysis were conducted in the West.

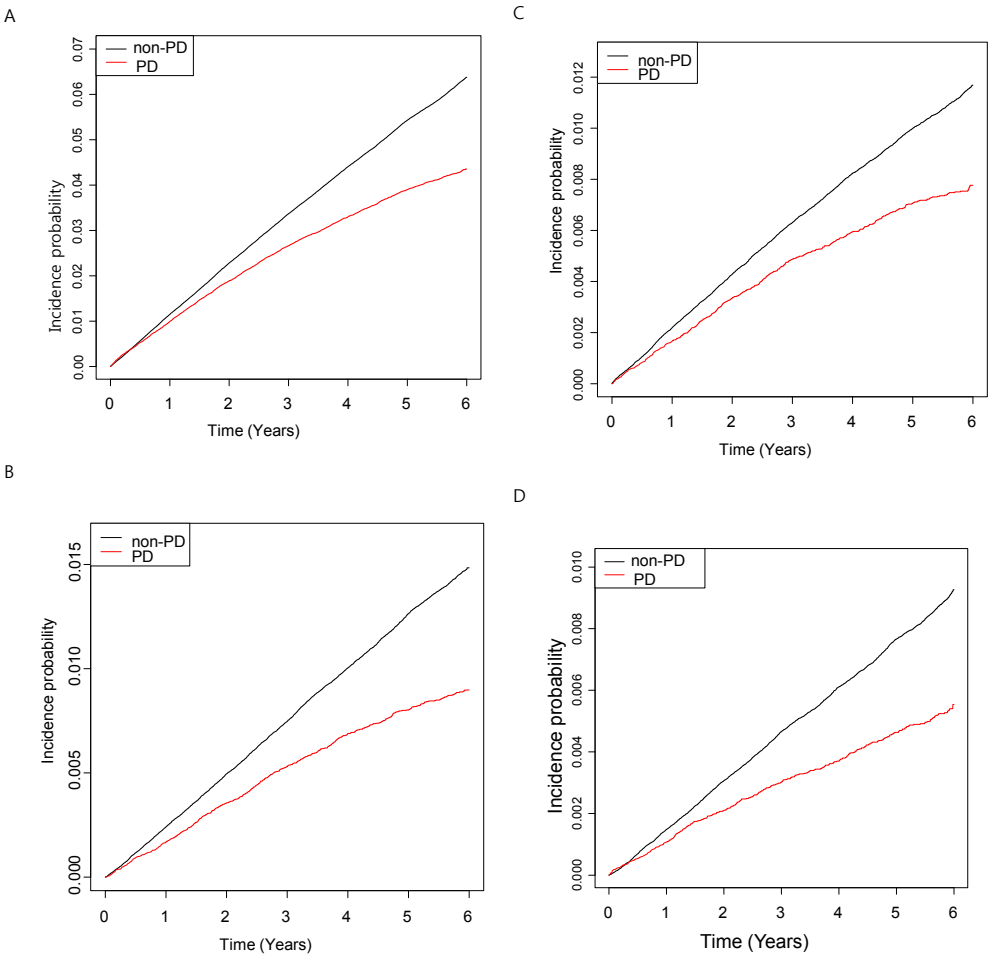

Fig. 1. Kaplan–Meier survival curves for development of overall and the three most common cancers in the Parkinson's disease (PD) group (red line) and the non-PD group (black line) during the study period. (A) Overall cancer incidence (B) Colorectal cancer (C) Gastric cancer (D) Lung cancer. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

One Taiwan study reported that PD was, overall, a risk factor for cancer in Taiwan. These discrepancies in results between the Western and Taiwan study could be attributed to different genetic factors but may be a matter of accuracy in the diagnosis of PD. Because PD is a very complex disease, diagnosing PD with only the diagnostic code may not be accurate. Therefore, we used not only diagnostic codes but also patients who met the uniform diagnostic criteria set by the government. Patients with PD included in our study met nearly the same criteria as the UK Parkinson's Disease Society Brain Bank clinical diagnosis [17]. Therefore, the diagnosis accuracy in our study was very high. Contrary to the results of the Taiwan study, this large cohort study revealed that patients with PD were less likely to develop cancer than those without PD in Asia.

Our findings revealed that the risk of laryngeal cancer, gastric cancer, colorectal cancer, liver cancer, pancreatic cancer, lung cancer, leukaemia, uterine cervical cancer and prostate cancer was reduced in patients with PD. These results are also consistent with the results of most previous studies.

Some studies showed that patients with PD had a lower risk of lung and colon cancer [4,6,18]. A meta-analysis reported a low risk of prostate cancer and leukaemia in patients with PD [6], while a UK study found that the risk of laryngeal cancer and gastric cancer was also low in patients with PD [4]. A large-scale cohort study also reported that the risk of pancreatic cancer was low in men with PD [18]. To our knowledge, our study is the first to report a lower risk of liver cancer and uterine cervical cancer in patients with PD.

Our results showed that the risk of skin cancer was increased in patients with PD but was not statistically significant (HR 1.5; 95% CI, 0.75–2.6). Skin cancer is commonly diagnosed in the West, but it is rare in Asian countries including Korea [19–22]. Some Western studies reported increased risk of skin cancer, especially melanoma, in patients with PD [8,23–25]. We could not analyse the risk by the detailed type of skin cancer in this study.

There are several potential biological explanations for the low cancer incidence in patients with PD observed in our cohort. The reason for this association is not well known yet.

Table 3
Crude incidence rates and hazard ratios for overall and specific cancers between patients with Parkinson's disease and controls.

Cancer type	Crude IR per 1000 patients			
	PD group (n = 52,009)	Non-PD group (n = 260,045)	HR (95% CI) without adjustment	HR (95% CI) with adjustment[a]
Overall	9.1	11.4	0.8 (0.76–0.84)	0.78 (0.74–0.82)
Oral cavity and pharyngeal cancer[b]	0.14	0.18	0.75 (0.48, 1.1)	0.75 (0.48, 1.1)
Laryngeal cancer[b]	0.05	0.11	0.45 (0.21, 0.84)	0.45 (0.21, 0.84)
Oesophageal cancer[b]	0.14	0.18	0.76 (0.48, 1.1)	0.76 (0.48, 1.1)
Gastric cancer[b]	1.5	2.0	0.73 (0.64, 0.83)	0.72 (0.63, 0.82)
Colorectal cancer[b]	1.8	2.5	0.7 (0.62, 0.78)	0.68 (0.6, 0.76)
Liver cancer[b]	0.85	1.05	0.81 (0.68, 0.96)	0.8 (0.67, 0.95)
Pancreatic cancer[b]	0.66	0.84	0.78 (0.64, 0.94)	0.75 (0.62, 0.91)
Biliary cancer	0.44	0.48	0.92 (0.72, 1.2)	0.89 (0.7, 1.1)
Lung cancer[b]	1.2	1.6	0.75 (0.65, 0.86)	0.73 (0.63, 0.84)
Renal cancer[b]	0.21	0.23	0.92 (0.64, 1.3)	0.86 (0.60, 1.2)
Bladder cancer[b]	0.45	0.52	0.86 (0.67, 1.1)	0.82 (0.64, 1.04)
Thyroid cancer	0.5	0.59	0.85 (0.67, 1.1)	0.83 (0.65, 1.03)
Leukaemia	0.06	0.11	0.51 (0.25, 0.92)	0.49 (0.24, 0.89)
Lymphoma	0.19	0.21	0.9 (0.62, 1.3)	0.87 (0.59, 1.2)
Multiple myeloma	0.1	0.12	0.86 (0.50, 1.4)	0.85 (0.5, 1.4)
Skin cancer	0.07	0.05	1.5 (0.75, 2.6)	1.5 (0.75, 2.6)
Breast cancer (women)	0.68	0.8	0.85 (0.66, 1.1)	0.82 (0.63, 1.04)
Uterine cervical cancer (women)[b]	0.2	0.31	0.65 (0.4, 1.0)	0.64 (0.4, 0.99)
Uterine corpus cancer (women)	0.14	0.15	0.94 (0.52, 1.6)	0.9 (0.49, 1.5)
Ovarian cancer (women)	0.21	0.27	0.78 (0.48, 1.2)	0.75 (0.46, 1.2)
Prostate cancer (men)	2.6	3.3	0.8 (0.69, 0.94)	0.78 (0.66, 0.91)
Testicular cancer (men)	0.01	0.04	0.33 (0.02, 1.6)	0.33 (0.02, 1.6)

IR, incidence rate; PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval.
[a] Adjustment for diabetes mellitus, hypertension, dyslipidemia and income status.
[b] Smoking-related cancers [30].

Smoking has been the most proposed related factors of both PD and cancers. There is strong evidence that smoking is protective for PD [26]. In 1976, the British Doctors' study on smoking and cancer reported a negative relation between parkinsonism and smoking and that patients with parkinsonism also had higher mortality in non-smokers than ever-smokers [27]. In addition, similar results have been obtained in large-scale retrospective studies [28]. Previous studies reported a reduced risk of smoking-related cancers in patients with PD [4,9,29] Decreased smoking rates in patients with PD may explain the risk of developing smoking-related cancers such as cancers of the lungs, larynx, stomach, colorectum, liver, pancreas and cervix [30]. In addition, the risk of cancer was more pronounced in patients with PD older than 65 years (data not shown). Because the relative benefit of non-smoking in patients with PD may be greater in older people, the risk of cancer may be reduced. In Korea, as of 2017, the smoking rate was 22% in the overall adult population, 38% in men and 6% in women [31]. Despite the differences in the smoking rate between men and women, both men and women with PD had a reduced risk of developing cancer (data not shown).

On the other hand, the incidence of smoking-related cancers such as oral cavity and pharyngeal cancer, oesophageal cancer, renal cancer and bladder cancer, was not significantly different between patients with PD and controls in our study. In addition, as in our study, several studies reported the risk reduction of malignancies not thought to be associated with smoking, such as prostate cancer [4,8,9]. These results cannot be explained by smoking alone.

Thus, several other hypotheses have been proposed to explain these reduced risks. The essential characteristics of these two diseases are related to cell proliferation abnormalities. PD is a neurodegenerative disorder characterised by dopaminergic neuronal death, whereas cancer is a disease characterised by infinite cellular proliferation and lack of apoptosis. In patients with PD, the tendency of cells to undergo apoptosis is increased, thereby reducing the risk of developing cancer. Several studies have reported cell death and neurological changes outside the substantia nigra in patients with PD [32–34]. Other neurodegenerative diseases such as Alzheimer disease have also been associated with reduced cancer risk [35].

Patients with PD may develop non-specific non-motor symptoms before diagnosis [2]. These symptoms may have reduced the risk of cancer in patients with PD by changing health behaviours to a healthy direction. Patients with PD may develop gastrointestinal

symptoms, which can lead to endoscopy. It may be that the incidence of gastrointestinal cancer was low because it was found and treated in the precancer stage.

In addition, there is growing evidence to support common genetic mechanisms in PD and cancer. Mutations in a variety of genes involved in the dysregulation of the cell cycle and protein turnover have been implicated in both PD and cancer [36]. It was reported that Parkin mutations caused juvenile PD, and it has since then emerged as the most frequent cause of early-onset disease. Recently, some studies have investigated about cancers in patients with hereditary PD, such as those caused by mutations in PARK1 (SNCA), PARK2 (PARK), PARK6 (PINK1), PARK7 (DJ-1) and PARK8 (LRRK2) [36]. Lung cancer and prostate cancer have been most frequently reported to be associated with mutations in these genes [36]. In cancer, Parkin was already a suspected tumour suppressor gene because it resides on the long arm of chromosome 6, a segment of which has long been known to be altered or deleted in a wide variety of human cancers [37,38].In addition, in a large family with the LRRK2 p.R1441C mutation identified in 23 affected members, eight different types of cancer were diagnosed, including lung, testicular, colon, bladder, pancreatic and gall bladder cancer [39,40]. Colon cancer was found in four members, suggesting a potential link between the LRRK2 p.R1441C mutation and colon cancer.

Although familial PD is rare, it could be speculated that mutations that predispose the cell towards apoptosis might lead to the expression of PD and a decrease in cancer risk, whereas those that favour cell growth would lead to increased cancer risk and decreased PD incidence [12,41]. Dysregulation of the ubiquitin–proteasome pathway, which is responsible for protein degradation and cell cycle control, is also common in PD and many cancers. PD has been associated with the inhibition of proteasome function [42], whereas cancer has been associated with its overexpression [43]. A study on possible links between PD and cancer risk hypothesised that elevated circulating melatonin levels in patients with PD contribute to their lower cancer risk [44]. There are also some evidence of the role of melatonin in carcinogenesis [45]. The findings of higher morning melatonin levels in patients with PD than in healthy controls could support this hypothesis, although evidence regarding the role of melatonin in neurodegenerative diseases is not conclusive [6].

This cohort study has many strengths. First, it was conducted using data from a nationwide population-based database that allowed an accurate evaluation of the associations between specific diseases, age and sex. Particularly, the accuracy of PD diagnosis was high because we used not only the diagnostic code but also uniform diagnostic criteria, which are almost identical to the UK Parkinson's Disease Society Brain Bank diagnostic criteria. Second, a cohort study would be the method of choice in exploring the association between PD and cancers. Randomised clinical trials are not feasible in this regard, and survival effects are considerable in case–control studies in that if PD-related mortalities developed before the onset of cancer, exposures to cancer would be underestimated in the case group. Finally, the health insurance programme in Korea has a coverage rate exceeding 97% of the entire population, and all medical records could be accurately traced in the NHIS. Therefore, patients with PD with or without cancers could hardly be lost to follow-up under the NHIS programme. Furthermore, the reference cohort was matched by the most important confounding factors—age and sex.

Our study has some limitations. First, information concerning cancer-associated covariates, including smoking habits, alcohol consumption, body mass index and family history of malignancy, was not available in the NHIS database and thus was not included in our analysis. Second, data on treatment or severity of disease in each individual could not be obtained. Third, although we selected the reference cohort by matching the most important confounding factors, age and sex, and the robust estimation of HRs was obtained by multivariate analyses, there were still some other factors not considered.

In conclusion, this nationwide population-based cohort study revealed that patients with PD had lower overall cancer risk and lower risk of specific cancers. Contrary to the result of the recent Asian study, this large cohort study revealed that patients with PD were less likely to develop cancer than those without PD in Korea. Our results were consistent with those of previous Western studies, despite differences in ethnicity and environment among the patients. Further studies are required to elucidate the underlying mechanism and possible genetic correlations between PD and cancers.

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Conflict of interest statement

None declared.

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