Original Investigation

Association Between Parkinson Disease and Risk of Cancer in Taiwan

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IMPORTANCE Parkinson disease (PD) has been reported to be associated with a general reduced risk of cancer. These studies were mainly carried out in Western populations and little was known about associations in East Asians.

OBJECTIVE To analyze the association between PD and risk of cancer.

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, the data were obtained from the Taiwan National Health Insurance Research Database, which contained information on approximately 24.7 million insured individuals. The cohort included individuals with newly diagnosed as having PD between 2004 and 2010. An age- and sex-matched systematic random-sampling method was used for subject selection in the reference non-PD cohort. Multivariate Cox proportional hazard regression analysis was used to determine the effects of PD on the risks of cancer, as shown by hazard ratios (HRs) with 95% CIs.

MAIN OUTCOMES AND MEASURES The Taiwan Population Census and National Cancer Registry Databases were used to identify patients with cancer. The last follow-up date was December 31, 2012.

RESULTS In 62 023 patients with PD, the HR for all subsequent cancers combined was 1.58 (95% CI, 1.50-1.65). Of the 19 types of cancer, Parkinson disease was not associated with breast, ovarian, or thyroid cancers. Increased HRs were found in the remaining 16 cancers, including malignant brain tumors (HR, 3.42; 95% CI, 1.84-6.38), gastrointestinal tract cancers (esophageal [HR, 1.81; 95% CI, 1.28-2.57], stomach [HR, 1.59; 95% CI, 1.30-1.94], colorectal [HR, 1.47; 95% CI, 1.31-1.65], liver [HR, 1.89; 95% CI, 1.67-2.14]; gallbladder [HR, 1.73; 95% CI, 1.16-2.57], and pancreas [HR, 1.48; 95% CI, 1.09-2.02]) ($P < .05$ for all comparisons), lung cancers (HR, 1.56; 95% CI, 1.38-1.76), some hormone-related cancers (uterine [HR, 1.83; 95% CI, 1.12-3.01], cervical [HR, 1.36; 95% CI, 1.05-1.76], and prostate [HR, 1.80; 95% CI, 1.52-2.13; $P < .05$ for all comparisons), urinary tract cancers (kidney and bladder cancers; HRs, 1.59 and 1.99, respectively; $P < .001$ for both comparisons), lymphoma and/or leukemia (HR, 1.62; 95% CI, 1.31-2.01), melanoma (HR, 2.75; 95% CI, 1.35-5.59), and other skin cancers (HR, 1.81; 95% CI, 1.46-2.23). For hepatocellular carcinoma, the highest HR resided in the 50- to 59-year-old group (HR, 2.57; 95% CI, 1.7-3.89).

CONCLUSIONS AND RELEVANCE Our study concludes that PD is is associated with most cancers in Taiwan. Further studies are needed to clarify whether our findings can be applied to other East Asian populations. The differences between our study and most previous cohorts suggest the importance of ethnicity and environmental exposures in disease pathogenesis.

Invited Commentary

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Parkinson disease (PD) is the most common neurodegenerative movement disorder and is caused by premature death of dopamine-containing neurons in the substantia nigra. It affects 1% of the population older than 60 years.[1] Although most PD cases are sporadic forms that result from a combination of polygenic inheritance and gene-environment interactions, a familial history of PD can be disclosed in approximately 10% of the cases.[2] Studies in families with PD led to the identification of 15 PD loci (*PARK1-15*).[3] Several of these *PARK* genes, such as *SNCA*,[4,5] *PARKIN*,[6-9] *PINK1*,[10,11] *DJ-1*,[12,13] *LRRK2*,[14-16] and *FBOX7*,[17] were found to play roles in both PD and cancers.

During the past 50 years, more than 25 epidemiological studies were done on the association between PD and cancers.[18] On the one hand, most of these studies showed that people with PD had a decreased risk of cancer compared with those without.[19,20] The exception was a Swedish cohort[21] including 11 786 patients with PD (hereinafter, PD patients) from 1954 to 2009 that showed a marginally increased risk of cancer in PD patients vs PD-free individuals. On the other hand, PD was variably disclosed to be associated with high rates of certain cancers in recent studies, although the results have been inconsistent to date. These cancers included melanoma, brain, breast, uterus, kidney, and prostate cancers.[16,21-24] Moreover, these studies were mostly done in Western populations, and little was known about associations in East Asians.

It is becoming clear that genetic backgrounds play important roles in a diverse array of disease pathogenesis.[3,25-27] Parkinson disease and lung cancer are 2 examples that demonstrate the importance of ethnicity in disease pathogenesis. *LRRK2* G2019S mutation causes typical PD. The mutation occurs in approximately 40% of Arab Berbers with PD,[28] 20% of Ashkenazi Jewish patients,[29] but only 1% to 7% of PD patients who are of European origin.[30,31] *EGFR* tyrosine kinase domain-activating mutations convert it into a driver oncogene in lung adenocarcinoma.[32-34] The percentage of *EGFR*-activating mutations approaches 50% in East Asian patients with lung adenocarcinoma but only 10% in white patients.[35,36] We therefore aimed to investigate whether the association between PD and cancers differs between East Asians and those of European origin. Because East Asians share similar genetic backgrounds,[37] we conducted the study using the Taiwan National Health Insurance (NHI) Research Database (NHIRD). This nationwide population-based follow-up cohort study examined whether PD is a risk or a protective factor among different cancer types.

At a Glance

- Parkinson disease (PD) has been reported to be associated with a reduced risk of cancer but has not been studied in East Asian populations.
- A total of 62 023 East Asian patients with PD diagnosed from 2004 to 2010 were studied.
- A diagnosis of PD was not associated with an increased risk of breast, ovarian, or thyroid cancers.
- Increased hazard ratios (HRs) were found in many other cancers.
- Parkinson disease was associated with an increased risk of malignant brain tumor (HR, 3.42; 95% CI, 1.84-6.38).

Methods

Data Source

The NHI is a single-payer universal health insurance program that has been operating since 1995, and more than 99% of the population are enrolled. The National Health Research Institute compiles all medical claims in the NHI program and releases the database for research purpose. Data for our cohort study were obtained from the NHIRD, which comprises comprehensive information of clinical visits for each insurant, such as demographic data, date of visits, diagnostic codes according to the *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)*, and prescriptions. The details of the NHIRD were described in the previous studies.[38] This study was approved by the ethical review board of the Taichung Veterans General Hospital.

Study Cohort

The cohort included 133 322 individuals with PD newly diagnosed (*ICD-9-CM* code 332) between 2004 and 2010. The date of initial diagnosis was set as the index date for each person. A total of 66 385 patients with secondary parkinsonism (*ICD-9-CM* code 332.1), 350 with missing information on sex and age, and 4564 with malignant neoplasms before the index date were excluded. For the reference non-PD cohort, 2 subjects were selected using a systematic random-sampling method for each corresponding PD patient. The individuals in the PD and non-PD cohorts were matched for age, sex, and index year under the same exclusion criteria. Finally, a total of 62 023 PD patients and 124 046 without PD were included in this study (**Figure 1**).

Outcome Measurement

We used the Taiwan Population Census and National Cancer Registry Databases[39] to identify patients with cancer in this study. The National Cancer Registry Database recorded information of cancer diagnostic date and histological types. Each study patient was followed until a diagnosis of malignant disease (*ICD-9-CM* code 140-208) was made, or until the patient was censored for death, lost to follow-up, withdrew from the database, or until the date of December 31, 2012, whichever came first.

Statistical Analysis

The follow-up in person-years for an event was used for estimating the incidence density of cancer. Multivariate Cox proportional hazard regression models were used to determine the effects of PD on the risk of cancer, as shown by hazard ratio (HR) with 95% CIs. Furthermore, this study also estimated the effects of PD on the risk of specific cancer type and histological type. All analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc), and results were considered statistically significant for 2-tailed $P < .05$.

Figure 1. Flowchart Showing the Inclusion and Exclusion Results of the Parkinson Disease (PD) Cohort and the Non-PD Reference Cohort Used in the Present Study of the Association Between PD and Cancer

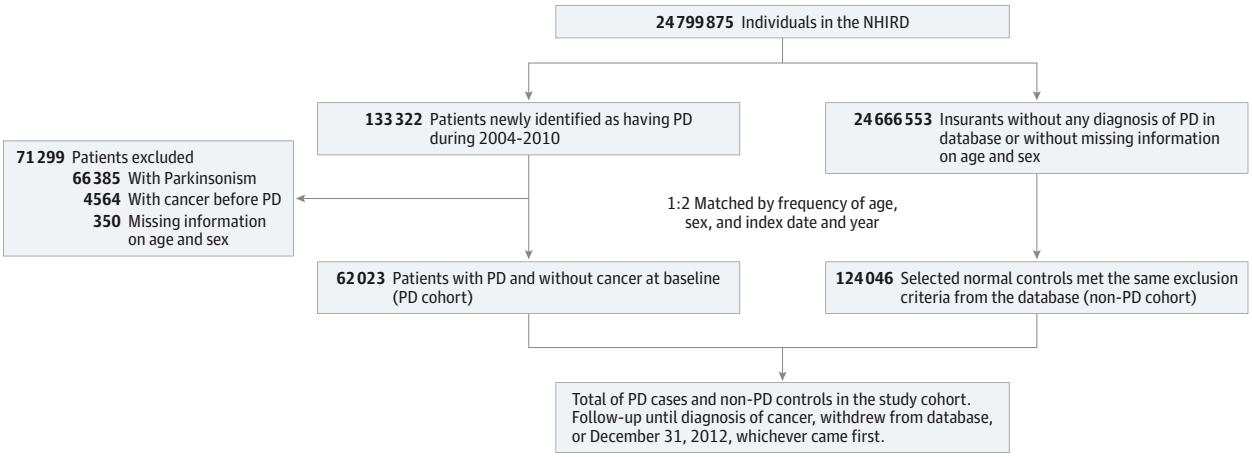
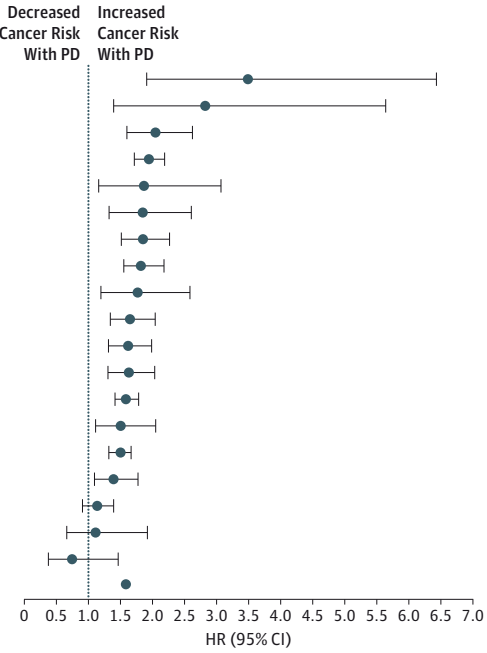


Figure 2. Comparisons of Incidence Density of Cancers Between the Parkinson Disease (PD) Group and Non-PD Group

Cancer Type	*ICD-9-CM* Code	HR[a] (95% CI)	*P* Value
Brain	191	3.42 (1.84-6.38)	<.001
Melanoma		2.75 (1.35-5.59)	.005
Kidney	189	1.99 (1.54-2.57)	<.001
Liver	155	1.89 (1.67-2.14)	<.001
Uterus (women)	179, 182	1.83 (1.12-3.01)	.02
Esophagus	150	1.81 (1.28-2.57)	<.001
Skin	173	1.81 (1.46-2.23)	<.001
Prostate (men)	185	1.80 (1.52-2.13)	<.001
Gallbladder	156	1.73 (1.16-2.57)	.007
Lymphoma/leukemia		1.62 (1.31-2.01)	<.001
Stomach	151	1.59 (1.30-1.94)	<.001
Bladder	188	1.59 (1.25-2.01)	<.001
Lung	162	1.56 (1.38-1.76)	<.001
Pancreas	157	1.48 (1.09-2.02)	.01
Colorectal	153, 154	1.47 (1.31-1.65)	<.001
Cervical (women)	180	1.36 (1.05-1.76)	.02
Breast (women)	174, 175	1.11 (0.90-1.37)	.33
Thyroid	193	1.10 (0.63-1.91)	.75
Ovary (women)	183	0.73 (0.73-1.44)	.36
All cancer	140-171, 173-194	1.58 (1.50-1.65)	<.001



HR indicates hazard ratio (bold HRs indicate statistical significances; $P < .05$); *ICD-9-CM*, *International Classification of Disease, Ninth Revision, Clinical Modification*.

[a] Adjusted for sex and age.

Results

Figure 2 shows the comparison of incidence density of cancers between the PD cohort and the non-PD reference cohort. The HR comparing the PD and the non-PD cohorts in association with all cancer outcomes combined was 1.58 (95% CI, 1.50-1.65; $P < .001$). The data showed that PD was not significantly associated with 3 of 19 cancers studied, including breast cancer (HR, 1.11; 95% CI, 0.90-1.37; $P = .33$), ovarian cancer (HR, 0.73; 95% CI, 0.37-1.44; $P = .36$), and thyroid cancer (HR, 1.10; 95% CI, 0.63-1.91; $P = .75$). For the other 16 cancers studied, PD was associated with an increased cancer incidence density. These included malignant brain tumors (HR, 3.42; 95% CI, 1.84-6.38; $P < .001$), gastrointestinal tract cancers (esophageal [HR, 1.81; 95% CI, 1.28-2.57], stomach [HR, 1.59; 95% CI, 1.30-1.94], colorectal [HR, 1.47; 95% CI, 1.31-1.65], liver [HR, 1.89; 95% CI, 1.67-2.14]; gallbladder [HR, 1.73; 95% CI, 1.16-2.57], and pancreas [HR, 1.48; 95% CI, 1.09-2.02]); $P < .05$ for all comparisons), lung cancers (HR, 1.56; 95% CI, 1.38-1.76; $P < .001$), hormone-related cancers (uterine [HR, 1.83; 95% CI, 1.12-3.01], cervical [HR, 1.36; 95% CI, 1.05-1.76], and prostate [HR, 1.80; 95% CI, 1.52-2.13]); $P < .05$ for all comparisons), urinary tract (kidney and bladder cancers; HR, 1.59 and 1.99, respectively;

Table 1. Comparisons of Incidence Density of Liver Cancer and Malignant Brain Tumors Between PD Group and Non-PD Group by Characteristics

	Non-PD Group				PD Group					
Variables	No.	Events	FT	Rate[a]	No.	Events	FT	Rate[a]	HR (95% CI)[b]	*P* Value
Liver Cancer										
Sex										
Men	61 074	327	214 633	15.24	30 537	270	97 857	27.59	1.85 (1.57-2.17)	<.001
Women	62 972	213	222 973	9.55	31 486	191	105 388	18.12	1.97 (1.62-2.40)	<.001
Age, y										
<50	20 722	13	78 606	1.65	10 361	14	38 315	3.65	1.77 (0.83-3.77)	.14
50-59	13 588	40	46 626	8.58	6794	51	22 567	22.60	2.57 (1.7-3.89)	<.001
60-69	24 788	149	87 786	16.97	12 394	115	42 098	27.32	1.59 (1.25-2.03)	<.001
≥70	64 948	338	224 589	15.05	32 474	281	100 264	28.03	1.74 (1.49-2.04)	<.001
Overall	124 046	540	437 606	12.34	62 023	461	203 245	22.68	1.89 (1.67-2.14)	<.001
Hepatocellular carcinoma	124 046	478	437 606	10.92	62 023	416	203 245	20.47	1.93 (1.69-2.20)	<.001
Cholangiocarcinoma	124 046	43	437 606	0.98	62 023	26	203 245	1.28	1.34 (0.82-2.18)	.24
Others	124 046	19	437 606	0.43	62 023	19	203 245	0.93	2.34 (1.23-4.44)	.01
Malignant Brain Tumors										
Sex										
Women	62 972	5	222 970	0.22	31 486	9	105 385	0.85	3.75 (1.25-11.2)	.02
Men	61 074	11	214 626	0.51	30 537	17	97 850	1.74	3.32 (1.56-7.10)	.002
Age, y										
<60	13 588	3	125 231	0.24	6794	6	60 881	0.99	4.07 (0.20-2.73)	.64
60-69	24 788	6	87 784	0.68	12 394	4	42 094	0.95	1.51 (0.42-5.37)	.52
≥70	64 948	7	224 580	0.31	32 474	16	100 260	1.60	4.71 (1.93-11.5)	<.001
Overall	124 046	16	437 595	0.37	62 023	26	203 235	1.28	3.42 (1.84-6.38)	<.001
Glioblastoma	124 046	10	437 595	0.23	62 023	14	203 235	0.69	3.07 (1.36-6.93)	.007
Astrocytoma and others	124 046	6	437 595	0.14	62 023	12	203 235	0.59	4.34 (1.62-11.6)	.003

Abbreviations: FT, follow-up time in person-years; HR, hazard ratio; PD, Parkinson disease.

[a] Per 10 000 person-years.

[b] Adjusted for sex and age.

P < .001 for both comparisons), lymphoma and/or leukemia (HR, 1.62; 95% CI, 1.31-2.01; *P* < .001), melanoma (HR, 2.75; 95% CI, 1.35-5.59; *P* = .005) and other skin cancers (HR, 1.81; 95% CI, 1.46-2.23; *P* < .001).

We further analyzed liver cancers and malignant brain tumors by sex and age stratifications (**Table 1**). In both men and women, PD was a significant risk factor for liver cancers (HR, 1.97 and 1.85, respectively; *P* < .001 for both comparisons). When stratified by age, the highest HR resided in the group aged 50 to 59 years (HR, 2.57; 95% CI, 1.7-3.89; *P* < .001). Hepatocellular carcinoma (HCC) comprised most liver cancers in our study population, and the association between PD and intrahepatic cholangiocarcinoma was not significant (HR, 1.34; 95% CI, 0.82-2.18; *P* = .24). As to the malignant brain tumors, we showed that PD was a risk factor in both women and men (HR, 3.75 and 3.32, respectively; *P* = .02 and .002) and in both glioblastoma (HR, 3.07; 95% CI, 1.36-6.93; *P* = .007) and non-glioblastoma brain malignant neoplasms (HR, 4.34; 95% CI, 1.62-11.6; *P* = .003). When stratified by age, PD was associated with an increased risk only in patients 70 years or older (HR, 4.71; 95% CI, 1.93-11.5; *P* < .001).

To investigate the association between PD and lung cancers of different cell types, we further stratified lung cancers by sex, age, and histologic characteristics (**Table 2**). We showed that PD was a significant risk factor for lung cancers in both sexes (HR, 1.56 and *P* < .001 for both comparisons). The risk could not be observed in patients younger than 60 years, and the HRs increased with aging. The HR was 1.02 (95% CI, 0.24-4.29; *P* = .98) in the group younger than 50 years, 1.09 (95% CI, 0.63-1.91; *P* = .75) in the group aged 50 to 59 years, 1.44 (95% CI, 1.08-1.92; *P* = .01) in the group aged 60 to 69 years, and 1.47 (95% CI, 1.28-1.68; *P* < .001) in the group that was 70 years or older. When analyzing different histological types, PD was a risk factor for adenocarcinoma (HR, 1.61; 95% CI, 1.35-1.92; *P* < .001) and small cell carcinoma (HR, 1.79; 95% CI, 1.17-2.74; *P* = .007), but not squamous cell carcinoma (HR, 1.30; 95% CI, 0.99-1.72; *P* = .06) or other types of non-small cell lung cancers (HR, 1.10; 95% CI, 0.68-1.77; *P* = .71).

To determine if the factor of age contributed to the non-significant results between PD and breast cancers, PD and ovarian cancers, and PD and thyroid cancers, we further examined the hormone-related cancers by age stratification. As shown in **Table 3** and **Table 4**, PD remained an insignificant factor with regard to thyroid cancers in both sexes and in each individual age group. Similarly, PD was not associ-

Table 2. Comparisons of Incidence Density of Lung Cancer Between the PD Group and Non-PD Group by Characteristics

	Non-PD Group				PD Group					
Variables	No.	Events	FT	Rate[a]	No.	Events	FT	Rate[a]	HR (95% CI)[b]	*P* Value
Sex										
Women	62 972	223	222 976	10.00	31 486	157	105 393	14.90	1.56 (1.27-1.92)	<.001
Men	61 074	442	214 651	20.59	30 537	293	97 864	29.94	1.56 (1.35-1.81)	<.001
Age, y										
<50	20 722	5	78 606	0.64	10 361	3	38 315	0.78	1.02 (0.24-4.29)	.98
50-59	13 588	36	46 626	7.72	6794	19	22 567	8.42	1.09 (0.63-1.91)	.75
60-69	24 788	113	87 792	12.87	12 394	79	42 094	18.77	1.44 (1.08-1.92)	.01
≥70	64 948	511	224 603	22.75	32 4 74	349	100 281	34.80	1.47 (1.28-1.68)	<.001
Overall	124 046	665	437 626	15.20	62 023	450	203 257	22.14	1.56 (1.38-1.76)	<.001
Adenocarcinoma	124 046	299	437 626	6.83	62 023	211	203 257	10.38	1.61 (1.35-1.92)	<.001
Squamous cell carcinoma	124 046	142	437 626	3.24	62 023	79	203 257	3.89	1.30 (0.99-1.72)	.06
Small cell carcinoma	124 046	50	437 626	1.14	62 023	38	203 257	1.87	1.79 (1.17-2.74)	.007
Non-small cell carcinoma	124 046	52	437 626	1.19	62 023	25	203 257	1.23	1.10 (0.68-1.77)	.71
Others	124 046	122	437 626	2.79	62 023	97	203 257	4.77	1.85 (1.41-2.42)	<.001

Abbreviations: FT, follow-up time in person-years; HR, hazard ratio; PD, Parkinson disease.

[a] Per 10 000 person-years.

[b] Adjusted for sex and age.

Table 3. Comparisons of Risk of Hormone-Related Cancers in Women Between PD Group and Non-PD Group, Adjusted for Age

	Breast		Uterus		Cervical		Ovary		Thyroid	
Age, y	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall	1.11 (0.90-1.37)	.33	**1.83 (1.12-3.01)**	**.02**	**1.36 (1.05-1.76)**	**.02**	0.73 (0.37-1.44)	.36	1.14 (0.61-2.13)	.69
<50	1.23 (0.68-2.24)	.49	1.63 (0.47-5.63)	.44	1.28 (0.65-2.52)	.48	0.20 (0.03-1.60)	.13	6.61 (0.74-59.2)	.09
50-59	0.69 (0.42-1.15)	.16	1.85 (0.67-5.11)	.24	0.77 (0.33-1.83)	.56	0.77 (0.08-7.48)	.83	0.71 (0.14-3.53)	.68
60-69	1.12 (0.77-1.64)	.55	2.16 (0.90-5.20)	.09	1.19 (0.72-1.94)	.50	0.21 (0.03-1.67)	.14	1.32 (0.43-4.05)	.63
≥70	1.14 (0.81-1.61)	.46	1.30 (0.50-3.35)	.59	**1.50 (1.03-2.20)**	**.04**	1.38 (0.56-3.38)	.49	0.62 (0.20-1.90)	.40

Abbreviations: HR, hazard ratio; PD, Parkinson disease; bold indicates statistical significance.

Table 4. Comparisons of Risk of Hormone-Related Cancers in Men Between PD Group and Non-PD Group, Adjusted for Age

	Prostate		Thyroid	
Age, y	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Overall	**1.80 (1.52-2.13)**	**<.001**	0.99 (0.31-3.23)	.99
<50	NA	NA	NA	NA
50-59	1.58 (0.62-4.00)	.34	1.91 (0.12-30.6)	.65
60-69	1.30 (0.83-2.02)	.25	NA	NA
≥70	**1.70 (1.42-2.05)**	**<.001**	1.41 (0.33-6.00)	.65

Abbreviations: HR, hazard ratio; PD, Parkinson disease; bold indicates statistical significance.

ated with the risk of breast or ovarian cancers in each individual age group. For uterine cancers, the risk effect of PD (overall HR, 1.83; 95% CI, 1.12-3.01; $P = .02$) was not observed when patients were stratified by age. For cervical cancers, the risk effect of PD (overall HR, 1.36; 95% CI, 1.05-1.76; $P = .002$) remained only in the patients who were 70 years or older (HR, 1.50; 95% CI, 1.03-2.20; $P = .04$). For prostate cancers, PD was associated with an increased cancer risk in all patients (HR, 1.80; 95% CI, 1.52-2.13; $P < .001$) and in patients 70 years or older (HR, 1.70; 95% CI, 1.42-2.05; $P < .001$).

Discussion

To our knowledge, this is the first nationwide large-scale study that has investigated the association between PD and cancers in East Asians. Our study concludes that PD is overall a risk factor for cancer in Taiwan. There were only 3 types of cancers that were not associated with PD in our cohort: breast, ovarian, and thyroid cancers. Increased melanoma risk in PD patients was consistently reported in previous trials.[40-42] In line with these findings, our study also revealed an increase of mela-

noma risk in the PD cohort despite the fact that melanoma incidence was relatively low among Asians.[43] The excess melanoma risk might be the result of shared biosynthetic pathways between tyrosine and L-dopa.[44] Family members of PD patients were more likely to develop melanoma, and patients with melanoma and their family had an increased risk of PD.[45] Increased incidences of malignant brain tumors, prostate, uterine, and renal cancers in PD patients were variably reported in the previous studies, and these results were validated in our cohort.[23,24]

Previous studies in Western populations described a reduced risk of smoking-related cancers in the PD patients.[21,22,24] In contrast, our study disclosed that PD was associated with increased cancer risks in 16 out of 19 cancers studied, including those categorized as smoking-related: esophageal, lung, and bladder cancers. In addition, PD was not associated with breast cancer risk in our cohort, whereas it was reported to be associated with increased breast cancer risks in a Danish cohort,[22] an English cohort,[24] and a pooled analysis[16] done in *LRRK2*-mutated PD patients (patients' ethnicities included Ashkenazi and Sephardic Jews and whites). These discrepancies could be attributed to a combination of different genetic backgrounds and habitual and/or environmental exposures.

Smoking was the most discussed habitual exposure related to both PD and cancers. In Taiwan, the smoking percentage was 16.4% in the overall adult population, 29.2% in men, and 3.5% in women.[46] Despite the differences in smoking percentage between men and women, PD remained a risk factor for most cancers examined in our study with or without sex stratification.

Pesticide exposure was reported to be one of the etiologies of PD. The diverse associations between pesticide exposures and PD onset in different geographic areas were attributed to gene-environment interactions in several studies.[47,48] Although precise data on the differences of pesticide exposures between Taiwan and Western countries were unavailable, it was reasonable to speculate that this discrepancy contributed partly to the nearly opposite results between our study and the previous cohorts in view of PD and risk of cancer.

Esophageal cancers demonstrate how different habitual and/or environmental exposures lead to diverse processes of carcinogenesis. Adenocarcinoma is currently the most predominant cell type of esophageal cancers in several Western countries,[49] whereas most esophageal cancers in our cohort remain squamous cell carcinoma. Use of the combination of tobacco, alcohol, and areca nuts leads to a multiplicative carcinogenic effects for esophageal squamous cell carcinoma.[50] A high percentage of patients in Taiwan are users of this combination.[50] This may partly explain the disparate cancer types observed and the distinct associations between PD and risk of esophageal cancers found in different geographic areas.

Lung adenocarcinoma is a well-understood model that illustrates the importance of ethnicity in disease pathogenesis. The percentage of *EGFR*-activating mutations is unexpectedly high among East Asians with lung adenocarcinoma.[35,36] Similar stories were surprisingly found in triple-negative breast cancers (TNBCs). It was reported that *EGFR*-activating mutations were found in 11.4% of TNBCs in a Chinese cohort, whereas none were found in white cohorts.[51-53] No direct evidence to date links *EGFR* mutations to cancer risk in PD patients. Nevertheless, the opposite associations between lung and/or breast cancers and PD in our cohort vs white cohorts and the strikingly different *EGFR*-activating mutation rates between East Asians and whites provide a hint of possible linkage. Indeed, *EGFR* was reported to interact with several *PARK* genes, such as *PARK2*, *LRRK2*, and *DJ-1*.[54-56] *PARK2* mutation has been shown to be associated with familial lung cancer,[9] and *DJ-1* has been reported to play roles in breast cancer.[12,13] Further studies are needed to elucidate the role of *EGFR* in respect of cancer development among PD patients.

We also showed in our study an increased risk of HCC in the PD cohort, with the highest HR resided in the group aged 50 to 59 years. It is not clear why the highest risk occurs in the fifth decade, but the possible contribution by genetic alteration is worth considering. The association between *PARK2* mutation and early-onset PD has been well established.[3] Furthermore, somatic mutations of *PARK2* were associated with multiple types of cancers.[6] It has been revealed that HCC developed spontaneously in a *Park2* knockout mouse model, and *PARK2* has been suggested to be a tumor suppressor for HCC.[7] There is a diverse heterogeneity in the rate of progression from a steady hepatitis carrier state to HCC development. The HCC risk distribution pattern among our PD cohort suggests a possible association between *PARK* genes and HCC. The results provide a new way of thinking in regard to the variable HCC onset age.

Our study revealed PD as a risk factor for most cancers examined. In breast, ovarian, and thyroid cancers, no association with PD was found. We could not identify PD's protective role in any single cancer in our study. The finding was nearly opposite of those in most cohort studies or meta-analyses derived from Western populations.[57] There were, however, nationwide Swedish[21] and English[24] cohort studies that partly supported our findings. In other words, the associations between PD and cancers were still nonconclusive, and the results derived from Western populations could not be applied to East Asians. Our findings suggested that different genetic backgrounds and habitual and/or environmental exposures combined resulted in the disparate outcomes. It is, therefore, reasonable to speculate that different alterations of *PARK* genes may contribute to distinct interactions with specific tumor-associated genes that end up in a diverse outcome of cancer development in different ethnic groups. The study highlights the fact that ethnicity matters in disease pathogenesis.

The study has a number of strengths. First, this cohort study was conducted from a nationwide population-based database containing more than 24 million subjects that allowed an accurate evaluation of the associations between specific diseases (eg, PD and cancers), age, and sex. Second, a cohort study would be the method of choice in the exploration of the association between PD and cancers. Randomized clinical trials were not feasible in this regard, and survival effects were 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 program in Taiwan has a coverage rate exceeding 99% of the entire population, including patients with cancers, and all the medical records could be accurately traced in the NHIRD. Therefore, PD patients with or without cancers could hardly be lost to follow-up under our NHIRD program, and vice versa. In addition, the reference cohort was matched by the most important confounding factors—age and sex.

However, there were still limitations in this study. First of all, PD was defined according to the medical records in our study, and underascertainment of PD cases in the reference cohort was very likely. Either service-based studies or studies by record linkage system underestimated the incidence of PD because they exclude patients who do not seek medical advice.[58] This would make the HRs underestimated, indicating that PD patients would have an even higher risk for cancer than the current measurement. Second, smoking status was not available in the NHIRD record and was thus not included in our analysis. 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 others not considered. Finally, the hypothesis of this study was generated from a genetic point of view. Nevertheless, we have not yet investigated the *PARK* gene alterations of the PD patients who developed subsequent cancers in our cohort. Further studies are needed to elucidate the possible genetic correlations between these 2 disease entities.

Conclusions

Based on this nationwide study on the association between PD and cancer risk, we conclude that PD is a risk factor for most cancers in Taiwan. In our cohort, only breast, ovarian, and thyroid cancers show no association with PD. Further studies are needed to clarify whether our findings can be applied to other East Asian populations. The striking differences between our study and the previous studies in Western cohorts suggest the importance of ethnicity and environmental exposures in disease pathogenesis.

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