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Cancer Outcomes Among Parkinson's Disease Patients with Leucine Rich Repeat Kinase 2 Mutations, Idiopathic Parkinson's Disease Patients, and Nonaffected Controls

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Supporting Data

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Abstract

Background: Increased cancer risk has been reported in Parkinson's disease (PD) patients carrying the leucine rich repeat kinase 2 (*LRRK2*) G2019S mutation (*LRRK2-PD*) in comparison with idiopathic PD (IPD). It is unclear whether the elevated risk would be maintained when compared with unaffected controls.

Methods: Cancer outcomes were compared among 257 *LRRK2-PD* patients, 712 IPD patients, and 218 controls recruited from 7 *LRRK2* consortium centers using mixed-effects logistic regression. Data were then pooled with a previous study to examine cancer risk between 401 *LRRK2-PD* and 1946 IPD patients.

Results: Although cancer prevalence was similar among LRRK2-PD patients (32.3%), IPD patients (27.5%), and controls (27.5%; $P = 0.33$), *LRRK2-PD* had increased risks of leukemia (odds ratio [OR] = 4.55; 95% confidence interval [CI], 1.46–10.61) and skin cancer (OR = 1.61; 95% CI, 1.09–2.37). In the pooled analysis, *LRRK2-PD* patients had also elevated risks of leukemia (OR = 9.84; 95% CI, 2.15–44.94) and colon cancer (OR = 2.34; 95% CI, 1.15–4.74) when compared with IPD patients.

Conclusions: The increased risks of leukemia as well as skin and colon cancers among *LRRK2-PD* patients suggest that *LRRK2* mutations heighten risks of certain cancers.

Keywords

LRRK2 gene; G2019S mutation; Parkinson's disease; leukemia; colon cancer; pooled analysis

Although Parkinson's disease (PD) and cancer have seemingly opposite biological mechanisms, recent studies indicate a potential link.[1–3] Epidemiological and family-based studies have reported that PD patients have increased risk of melanoma[4–7]; however, they have 40% and 25% lower relative risks for smoking-related and other cancers,[8,9] respectively, when compared with the general population. Recent studies have reported

increased risks of various cancers among PD patients carrying leucine rich repeat kinase 2 (*LRRK2*) mutations.[10–15] The *LRRK2* G2019S mutation, with a prevalence ranging from 1% to 40% depending on ethnicity and age at PD onset,[16] has been associated with increased risks of nonskin cancers[11,14,15] and breast cancer,[11,14,15] whereas the *R1441C/G* mutation, which has a higher prevalence in the Basque population,[17] has been associated with colon cancer[13] and hematologic cancers.[10]

We recently performed a pooled meta-analysis among 1549 PD patients (11.4% were *LRRK2* G2019S carriers) and reported statistically significant increased risks of nonskin cancer (odds ratio [OR] = 1.62; 95% confidence interval [CI], 1.04–2.52), hormone-related cancers (OR = 1.87; 95% CI, 1.07–3.26), and breast cancer (OR = 2.34; 95% CI, 1.05–5.22) among *LRRK2-PD* in comparison with idiopathic PD (IPD).[15] However, it is unclear whether the increased risk among *LRRK2*-PD patients would be observed when compared with unaffected controls who are noncarriers of the G2019S mutation.

Therefore, the goal of this analysis was to compare the prevalence of cancer outcomes among *LRRK2*-PD patients, IPD patients, and controls using a standardized questionnaire across several international *LRRK2*-PD research centers. Furthermore, we also combined data collected in this study with previously published data from our meta-analysis[15] and examined the associations of *LRRK2* G2019S mutation with various cancers among 2365 PD patients.

Materials and Methods

Participants included in this analysis were 969 PD patients (257 *LRRK2-PD* and 712 IPD) and 218 genetically unrelated controls aged 35 years or older who were recruited from 7 Michael J. Fox Foundation *LRRK2* sites in Europe, Israel, and the United States. All of the participants completed a detailed health questionnaire, which collected information on demographic, lifestyle, and reproductive factors; self-reported cancer history; personal health-related histories; and family histories of PD and cancer. (Details about participants' recruitment and data collection methodology are provided in the supporting information materials.) Genetic testing for *LRRK2* G2019S mutation was performed in all PD patients and controls. Genotyping for other *LRRK2 mutations: R1441G/C* and *I2020T* was performed only in 2 centers in Germany and Spain. Therefore, the focus of this analysis is only on G2019S mutations (carriers vs. noncarriers). The study was approved by the respective institution review boards of all participating sites, and all participants provided written informed consent.

We compared demographic and lifestyle characteristics as well as prevalence of various cancers among *LRRK2-PD* patients, IPD patients, and controls using one-way analysis of variance models (for continuous normally distributed variables) and χ^2 tests (for categorical variables); all tests were 2-sided ($P < 0.05$). The associations of various cancer outcomes among *LRRK2*-PD patients, IPD patients, and controls were examined using mixed-effect logistic regression to estimate ORs and 95% CIs adjusting for age, sex, and Ashkenazi Jewish (AJ) ethnicity as fixed effects and study center as the random effect.[18] Multivariate models for all cancers combined, smoking-related cancers, and colon and kidney cancers

were additionally adjusted for smoking status and body mass index, whereas body mass index and reproductive factors were included in multivariate models for hormone-related cancers and breast cancer. We also investigated whether the associations between *LRRK2* G2019S mutation and cancer outcomes varied by ethnicity (AJ vs. others) in stratified analyses.[19]

Finally, we pooled data collected in this study with our previously published data[15] and compared the risk of various cancers between 401 *LRRK2-PD* and 1964 IPD patients using mixed-effect logistic regression models adjusted for age, sex, and AJ ethnicity as fixed effects and study center (random effect). For 83 over-lapping PD patients between the 2 datasets, the most recent data were used. We excluded 70 *LRRK2-PD* patients from this analysis who carried only the *R1441G/C* mutation as screening for this mutation was not performed in all participating centers. All statistical analyses were performed using STATA version 15 (College Station, TX).

Results

A total of 257 *LRRK2*-PD patients, 712 IPD patients, and 218 genetically unrelated controls aged 35 years or older were included in this analysis (Table 1). The controls were on average younger, more likely to be women, and less likely to be of AJ ethnicity in comparison with both *LRRK2*-PD and IPD patients. With regard to lifestyle factors, when compared with controls, both the *LRRK2*-PD and IPD patients were significantly less likely to be cigarette smokers and alcohol drinkers, but there was no difference in body mass index among the 3 groups (Table 1). In comparison with female patients with *LRRK2*-PD or IPD, unaffected female controls had on average a fewer number of pregnancies (1.4 vs. 2.1 and 2.6; $P < 0.0001$), and a slightly higher proportion were in menopause (94% vs. 90% and 83%; $P = 0.004$).

Overall self-reported cancer prevalence was similar among *LRRK2-PD* patients (32.3%), IPD patients (27.5%), and controls (27.5%; $P = 0.22$; Table 1). However, the *LRRK2*-PD patients reported a higher prevalence of leukemia (1.9%) in comparison with both IPD patients and controls, where no leukemia was reported ($P < 0.0001$). Interestingly, when compared with IPD patients and controls, the *LRRK2*-PD patients also reported a higher proportion of multiple cancers: 8.6% vs. 6.6% and 3.7%, respectively. However, these differences were not statistically significant (Table 1).

Although cancer prevalence was similar among the 3 groups, the IPD patients had an overall lower cancer risk (OR = 0.68; 95% CI, 0.45–1.01) in comparison to controls in multivariate-adjusted models (Table 2). With regard to specific cancers, there was a significant increased risk of leukemia (OR = 4.55; 95% CI, 1.46–10.61) when comparing *LRRK2*-PD patients to either the IPD patients or controls. Skin cancer was also significantly higher among the *LRRK2*-PD patients when compared with IPD patients (OR = 1.61; 95% CI, 1.09–2.37), but there was no difference when compared with controls (OR = 0.99; 95% CI, 0.57–1.71; Table 2). There was also suggestive evidence of increased risks of colon and kidney cancers among *LRRK2*-PD patients; however, these associations were not statistically significant. Because 77% of all participants were of AJ ethnicity, we carried out a separate analysis in

this group; the overall results were similar to the main analysis (see Supporting Information Table S1).

Finally, the results of the pooled analysis (Table 3), which combined the data from this study with our previously published paper[15] and included 401 *LRRK2*-PD and 1964 IPD patients, showed statistically significantly increased risks of leukemia (OR = 9.84; 95% CI, 2.15–44.94) and colon cancer (OR = 2.34; 95% CI, 1.15–4.72) when comparing the *LRRK2*-PD with IPD patients.

Discussion

We report the findings from a primary analysis of cancer outcomes among 257 *LRRK2*-PD patients, 712 IPD patients, and 218 unaffected controls, which used a standardized questionnaire to collect demographic and lifestyle factors as well as cancer outcomes across 7 participating sites from the largest international *LRRK2*-PD consortium. The results showed that the *LRRK2*-PD patients had a statistically significant 4.6-fold increased risk of leukemia in comparison with the IPD patients and controls. In additional support, the findings from the pooled analysis demonstrated a stronger risk of leukemia (OR = 9.84; 95% CI, 2.15–44.94) when comparing *LRRK2* G2019S mutation carriers with IPD patients, although this was based on a small number (n = 5) of leukemia reports. The observed positive association with leukemia in this study also supports the finding of Ruiz-Martinez and colleagues,[10] who reported an OR = 7.1 for myeloproliferative cancers among their PD patients carrying the *R1441G* mutation. Both studies also show that IPD patients have a lower frequency of hematologic cancers, which has been previously reported.[20,21]

In our primary analysis, we also observed a 61% increased risk of nonmelanoma skin cancer when comparing *LRRK2*-PD patients with IPD patients, although in the pooled analysis the strength of this association was attenuated (OR = 1.36) and was no longer statistically significant. These findings need to be interpreted with caution as nonmelanoma skin cancers tend to be misreported by participants.[22,23] Although *LRRK2*-PD patients had also suggestive evidence of an increased risk of colon cancer in the primary analysis (albeit not statistically significant because of the small numbers), in the pooled analysis we observed a significant 2.34-fold increased risk of colon cancer (95% CI, 1.15–4.72) when comparing *LRRK2*-PD with IPD patients. The increased risk of colon cancer has also been reported among PD patients with *LRRK2 R1441C* mutations from a large pedigree of 190 individuals in western Nebraska.[13]

Despite the associations with the specific cancers mentioned previously, we did not observe increased risks of hormone-related cancers and breast cancer, as reported in our previous study.[15] Two other studies[14,24] also reported increased risks of breast cancer among *LRKK2*-PD patients, and these populations were in part included in the pooled analysis. One of the differences is that the numbers of self-reported cancers were much lower in the international *LRRK2*-PD consortium. Moreover, the effect of *LRRK2* mutations on cancer might vary among different populations, and other studies from Italy[25] or the United Kingdom[26] did not observe an overall increase in hormone-related cancers with *LRRK2* mutations.

Our study has strengths and limitations that should be carefully considered. A strength is the use of a detailed questionnaire that collected demographic, lifestyle, and reproductive factors and cancer outcomes in a standardized manner, which minimized biases as a result of data acquisition across international *LRRK2*-PD centers. In addition, the pooled analysis included 2365 PD patients with 502 cancer outcomes collected across several sites, which represent the largest cohort of PD patients with genetic screening for *LRRK2* mutations. Although self-reports of major cancers (eg, breast, prostate, colon, lung, etc.) have been shown to be valid and reliable,[22,23,27] a limitation is that self-reported cancers from PD patients and controls were not validated systematically with medical records or cancer registry reports in participating centers. Another limitation is the relatively small sample size for comparisons of rare cancers among *LRRK2*-PD patients, IPD patients, and controls. We also did not have information on the tumor grades or stages for various cancers in this study, and because genetic associations might vary by cancer clinical phenotypes, the inclusion of cancer survivors might have affected the results. Finally, the potential for selection bias in using spouse controls and recall bias particularly among elderly PD patients as a result of the increased risk of dementia might have affected the results of this study. Nevertheless, the advantages of using spouse controls are time-and cost-efficiency and their ability to provide proxy lifestyle or health-related data for their affected relatives.[28]

In conclusion, the results of this study showed significantly increased risks of leukemia and colon cancer among the *LRRK2*-PD patients when compared with the IPD patients, which suggest that *LRRK2* mutations can lead to multiple cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1.

Demographic and lifestyle factors and cancer outcomes among Parkinson's Disease patients with *LRRK2* G2019S mutation (*LRRK2*-PD), idiopathic PD patients (IPD) and genetically unrelated controls

Characteristic	Controls, N = 218		*LRRK2*-PD, N = 257		IPD, N = 712		*P**
Age, y; mean (SD)	64.0	(11.8)	68.6	(10.3)	67.8	(10.5)	<0.0001
Age at PD Diagnosis, y; mean (SD)	–	–	57.6	(11.0)	60.1	(11.1)	0.002
Duration of PD, y; mean (SD)	–	–	11.1	(7.5)	7.8	(6.1)	<0.0001
Sex, n (%)							<0.0001
Male	70	(32.1)	123	(47.9)	441	(61.9)	
Female	148	(67.9)	134	(52.1)	271	(38.1)	
Race/ethnicity, n (%)							<0.0001
Caucasian/Ashkenazi Jews	110	(50.5)	205	(79.8)	603	(84.7)	
Caucasian/non-Ashkenazi Jews	82	(37.6)	40	(15.6)	88	(12.3)	
Hispanic or mixed/other	26	(11.9)	12	(4.7)	21	(3.0)	
Study center, n (%)							<0.0001
Beth Israel/Mount Sinai	85	(39.0)	72	(28.0)	220	(30.9)	
CUMC/New York	22	(10.1)	50	(19.5)	131	(18.4)	
TA Sourasky/Israel	3	(1.4)	80	(31.1)	248	(34.8)	
Barcelona/Spain	39	(17.9)	36	(14.0)	44	(6.2)	
Norway	20	(9.2)	3	(1.2)	28	(3.9)	
Germany	45	(20.6)	6	(2.3)	28	(3.9)	
PROGENI	4	(1.8)	10	(3.9)	13	(1.8)	
BMI, kg/m^2; mean (SD)	25.70	(4.38)	25.58	(4.10)	25.70	(4.05)	0.92
Smoking status, n (%)	N = 215		N = 241		N = 574		0.005
Never	111	(51.6)	132	(54.8)	355	(61.9)	
Former	89	(41.4)	92	(38.2)	203	(35.4)	
Current	15	(7.0)	17	(7.1)	16	(2.3)	
Drinking habits, n (%)	N = 200		N = 186		N = 348		<0.0001
Never	56	(28.0)	90	(48.4)	132	(37.9)	
Former	11	(5.5)	20	(10.8)	42	(12.1)	
Current	133	(66.5)	76	(40.9)	174	(50.0)	

Characteristic	Controls, N = 218		*LRRK2*-PD, N = 257		IPD, N = 712		*P**
Reproductive factors-women	N = 148		N = 134		N = 271		
Age at menarche, y; mean (SD)	12.84	(1.51)	12.85	(1.54)	12.84	(1.53)	0.99
Ever pregnant, n (%)	132	(89.2)	123	(91.8)	252	(93.0)	0.40
No of pregnancies, mean (SD)	1.43	(1.30)	2.06	(1.58)	2.63	(1.93)	<0.0001
Menopausal status, n (%)	139	(93.9)	121	(90.3)	226	(83.4)	0.004
Age at menopause, n (%)	49.4	(5.9)	50.7	(4.9)	49.5	(5.6)	0.12
Ever HRT use, n (%)	34	(23.0)	41	(30.6)	91	(33.6)	0.15

	Controls, N = 218		*LRRK2* PD, N = 257		IPD, N = 712		
Cancer outcomes	**n**	**%**	**n**	**%**	**n**	**%**	***P****
All cancers	60	27.5	83	32.3	196	27.5	0.33
Age at first cancer, mean and SD	55.3	12.6	58.9	12.9	59.3	12.9	0.22
No of all cancers							0.24
1	52	23.9	61	23.7	149	20.9	
2	8	3.7	18	7.0	42	5.9	
3 or 4	–	–	4	1.6	5	0.7	
Skin cancer	30	13.8	52	20.2	109	15.3	0.11
Melanoma	7	3.2	14	5.4	27	3.8	0.40
All nonskin cancers	35	16.1	43	16.7	115	16.2	0.97
Head and neck cancer	1	0.5	1	0.4	4	0.6	0.94
Lung cancer	–	–	2	0.8	4	0.6	0.47
Esophageal cancer	–	–	1	0.4	-	-	0.16
Colon cancer	2	0.9	6	2.3	6	0.8	0.15
Liver cancer	–	–	–	–	1	0.1	0.72
Pancreatic cancer	–	–	1	0.4	2	0.3	0.68
Thyroid cancer	1	0.5	1	0.4	7	1.0	0.55
Kidney cancer	1	0.5	4	1.6	6	0.8	0.43
Bladder cancer	1	0.5	1	0.4	3	0.4	0.99
Brain cancer	–	–	2	0.8	2	0.3	0.31
Leukemia	–	–	**5**	**1.9**	–	–	**<0.0001**

Characteristic	Controls, N = 218		*LRRK2*-PD, N = 257		IPD, N = 712		*P**
Lymphoma	8	3.7	3	1.2	5	0.7	0.41
Hormone-related cancers[a]	25	11.5	22	8.6	77	10.8	0.52
Women[b]	N = 148		N = 134		N = 271		
Breast cancer	14	9.5	11	8.2	24	8.9	0.93
Ovarian cancer	–	–	–	–	3	1.1	0.21
Endometrial cancer	4	2.7	1	0.7	3	1.1	0.31
Cervical cancer	2	1.4	–	–	2	0.7	0.41
Men[b]	N = 70		N = 123		N = 441		
Prostate cancer	6	8.6	10	8.1	46	10.4	0.70
Testicular cancer	1	1.4	0	0.0	2	0.5%	0.38

**P* values from one-way analyses of variance (continuous) and χ^2 tests (categorical variables) comparing *LRRK2*-PD mutation carriers, IPD patients, and controls. Student T-test was used to compare age at PD diagnosis and duration of PD between LRKK2-PD and IPD patients.

[a]Hormone-related cancers include prostate cancer in men and breast, endometrial and ovarian cancers in women.

[b]Percentages of gender-specific cancers are based on the number of men and women.

Abbreviations: PD, Parkinson's disease; *LRRK2*-PD,Parkinson's Disease patients with *LRRK2* G2019S mutation; IPD, idiopathic PD patients; BMI, body mass index; CUMC, Columbia University Medical Center; TA, Tel-Hashomer; PROGENI, Parkinson's Research Organized Genetics Initiative Study; HRT, hormone replacement therapy.

TABLE 2.

Comparisons of cancer outcomes among *LRRK2*-PD patients, IPD patients, and controls in newly collected data (N = 1187)

	Controls, N = 218		*LRRK2*-PD, N = 257		*LRRK2-PD* vs. Controls		IPD, N = 712		IPD vs. Controls		*LRRK2*-PD vs. IPD	
Cancer Outcomes	**N**	**%**	**N**	**%**	**OR***	**95% CI**	**N**	**%**	**OR***	**95% CI**	**OR***	**95% CI**
All cancers	60	27.5	83	32.3	0.86	0.55–1.35	196	27.5	0.68	0.45–1.01	1.29	0.91–1.81
Skin cancer	30	13.8	52	20.2	0.99	0.57–1.71	109	15.3	0.62	0.37–1.03	**1.61**	**1.09–2.37**
Melanoma	7	3.2	14	5.4	1.22	0.47–3.14	27	3.8	0.80	0.33–1.94	1.54	0.79–3.04
Nonskin cancer	35	16.1	43	16.7	0.87	0.51–1.47	115	16.2	0.88	0.55–1.40	1.00	0.66–1.50
Smoking-related cancers[a]	2	0.9	4	1.6	1.26	0.22–7.18	10	1.4	1.21	0.24–6.01	1.02	0.31–3.40
Colon cancer	2	0.9	6	2.3	2.15	0.41–11.31	6	0.8	0.75	0.14–4.09	2.71	0.85–8.61
Kidney cancer	1	0.5	4	1.6	2.59	0.28–23.91	6	0.8	1.10	0.1–9.87	2.20	0.58–8.29
Leukemia[b]	**0**	**–**	**5**	**1.9**	**4.55**	**1.46–10.61**	**0**	**–**		**–**	**4.55**	**1.46–10.61**
Lymphoma	5	2.3	3	1.2	0.44	0.1–1.97	8	1.1	0.45	0.13–1.52	0.51	0.22–1.21
Hormonal cancer, women and men[c]	25	11.5	22	8.6	0.55	0.30–1.04	77	10.8	0.74	0.43–1.24	0.76	0.46–1.27
Breast cancer, women	14	9.5	11	8.2	0.61	0.26–1.43	24	8.9	0.65	0.31–1.35	0.86	0.40–1.86
Prostate cancer, men	6	8.6	10	8.1	0.92	0.29–2.93	46	10.4	1.27	0.47–3.47	0.73	0.34–1.54

Bold font represents results that are statistically significant at $P < 0.05$.

*OR and 95% CI were estimated from mixed-effect logistic regression models adjusted for age, sex, and Ashkenazi Jews ethnicity (fixed effect) and study center (random effect). Multivariate models for all cancers, smoking-related cancers, colon cancer, kidney cancer, and hormone cancer also included smoking status and body mass index.

[a]Smoking-related cancers included lung, bladder, and head and neck cancers; these models were also adjusted for smoking status.

[b]Because there were no leukemia cases reported among IPD and controls, the OR = 4.55 and corresponding 95% CI (1.46–10.61) were calculated based on the ratio of observed cases (n = 5) versus expected cases (n = 0.8) among *LRRK2*-PD.

[c]Hormone-related cancers include prostate cancer in men and breast, endometrial, and ovarian cancers in women. For breast cancer, body mass index and reproductive factors were also included in multivariate models.

Abbreviations: PD, Parkinson's disease; *LRRK2*-PD, Parkinson's Disease patients with *LRRK2* G2019S mutation; IPD, idiopathic PD patients; OR, odds ratio; CI, confidence interval.

TABLE 3.

Comparisons of cancer outcomes between *LRRK2*-PD and IPD patients in the pooled analysis of1 newly collected and previously published data (N = 2365)*

	***LRRK2*-PD G2019S Mutation Carriers, N = 401**		**IPD, N = 1,964**		***LRRK2*-PD vs. IPD**		
Cancer Outcomes	**N**	**%**	**N**	**%**	**OR†**	**95% CI**	***P***
All cancers	113	28.2	389	19.8	1.25	0.94–1.64	0.12
Skin cancer	60	15.0	148	7.5	1.36	0.96–1.95	0.09
Melanoma	18	4.5	43	2.2	1.55	0.86–2.81	0.15
Nonskin cancers	68	17.0	270	13.7	1.12	0.81–1.55	0.49
Smoking-related cancers[a]	6	1.5	27	1.4	1.16	0.44–3.07	0.77
Lung cancer	4	1.0	11	0.6	1.75	0.49–6.27	0.39
Bladder cancer	1	0.2	13	0.7	0.53	0.1–4.37	0.55
Colon cancer	**12**	**3.0**	**32**	**1.6**	**2.34**	**1.15–4.72**	**0.018**
Kidney cancer	5	1.2	13	0.7	2.22	0.74–6.66	0.15
Leukemia	**5**	**1.2**	**3**	**0.2**	**9.84**	**2.15–44.94**	**0.003**
Lymphoma	3	0.7	12	0.6	0.82	0.22–3.10	0.77
Brain cancer	4	1.0	11	0.6	2.18	0.62–7.69	0.23
Hormonal cancer[b]	37	9.2	146	7.4	1.00	0.66–1.51	0.99
Breast cancer, women	21	10.0	51	6.4	1.22	0.69–2.14	0.46
Prostate cancer, men	16	8.4	82	7.0	0.97	0.53–1.77	0.91

Bold font represents results that are statistically significant at $P < 0.05$.

*Data from Agalliu et al.[15] *LRRK2 R1441G* mutation carriers (N = 70) were excluded from this analysis.

†OR and 95% CI were estimated from mixed-effect logistic regression models adjusted for age, sex, and Ashkenazi Jews ethnicity (fixed effect) and study center (random effect).

[a]Smoking-related cancers included lung, bladder and head and neck cancers.

[b]Hormonal cancers include prostate cancer in men and breast, endometrial, and ovarian cancers in women.

Abbreviations: PD, Parkinson's disease; *LRRK2*-PD, Parkinson's Disease patients with *LRRK2* G2019S mutation; IPD, idiopathic PD patients; OR, odds ratio; CI, confidence interval.