Original Investigation

Higher Frequency of Certain Cancers in *LRRK2* G2019S Mutation Carriers With Parkinson Disease
A Pooled Analysis

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IMPORTANCE Patients with Parkinson disease (PD) who harbor *LRRK2* G2019S mutations may have increased risks of nonskin cancers. However, the results have been inconsistent across studies.

OBJECTIVES To analyze pooled data from 5 centers to further examine the association between *LRRK2* G2019S mutation and cancer among patients with PD and to explore factors that could explain discrepancies.

DESIGN, SETTING, AND PARTICIPANTS Clinical, demographic, and genotyping data as well as cancer outcomes were pooled from 1549 patients with PD recruited across 5 movement disorders clinics located in Europe, Israel, and the United States. Associations between *LRRK2* G2019S mutation and the outcomes were examined using mixed-effects logistic regression models to estimate odds ratios (ORs) and 95% CIs. Models were adjusted for age and ethnicity (Ashkenazi Jewish vs others) as fixed effects and study center as a random effect.

MAIN OUTCOMES AND MEASURES All cancers combined, nonskin cancers, smoking-related cancers, hormone-related cancers, and other types of cancer.

RESULTS The overall prevalence of the *LRRK2* G2019S mutation was 11.4% among all patients with PD. Mutation carriers were younger at PD diagnosis and more likely to be women (53.1%) and of Ashkenazi Jewish descent (76.8%) in comparison with individuals who were not mutation carriers. The *LRRK2* G2019S mutation carriers had statistically significant increased risks for nonskin cancers (OR, 1.62; 95% 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) in comparison with noncarriers. There were no associations with other cancers. There were no major statistically significant differences in the results when the data were stratified by Ashkenazi Jewish ethnicity; however, there was some evidence of heterogeneity across centers.

CONCLUSIONS AND RELEVANCE This multinational study from 5 centers demonstrates that *LRRK2* G2019S mutation carriers have an overall increased risk of cancer, especially for hormone-related cancer and breast cancer in women. Larger prospective cohorts or family-based studies investigating associations between *LRRK2* mutations and cancer among patients with PD are warranted to better understand the underlying genetic susceptibility between PD and hormone-related cancers.

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Parkinson disease (PD) and cancer have opposite biological mechanisms: PD is characterized by apoptosis and premature neuronal degeneration, and the hallmark of cancer is uncontrolled cell proliferation.[1] However, a link between PD and cancer was suspected when higher incidence rates of melanoma were observed among patients with PD.[2] The excess melanoma risk might be the result of a shared relationship between tyrosinase and melanin, but not levodopa treatment.[3-6] The overexpression of α-synuclein leads to cell degeneration in the brain. In the skin the overexpression may inhibit tyrosinase and tyrosine hydroxylase and thus decrease the levels of protective melanin.[3] In turn, the lower melanin levels could increase a person's susceptibility to the deleterious effects of ionizing radiation and environmental toxins leading to melanoma.[3] Family members of patients with PD are more likely to develop melanoma, and patients with melanoma and their family members have an increased risk of PD.[7-9]

Patients with PD have lower risks for nonskin cancers.[5,6,10,11] A meta-analysis[10] of 29 studies reported relative risks (RRs) of 0.61 (95% CI, 0.58-0.65) and 0.76 (95% CI, 0.65-0.89) for smoking-related and other cancers, respectively, among participants with PD. However, the results have been inconsistent, with some studies indicating increased risks for breast cancer[5,6,12] and prostate cancer.[8] A potential explanation for lower rates of nonskin cancers could be that the prevalence of smoking and other lifestyle risk factors are usually low in patients with PD, although differences in genetic susceptibility could play a role.[6,13]

A promising approach to disentangle the shared genetic component between cancer and PD is to hone the analysis using identified genetic forms of parkinsonism. Four PD susceptibility genes (*SYN*, *Parkin*, *DJ-1*, and *LRRK2*) could potentially link cancer and PD, since they all encode proteins with biological mechanisms that increase cell growth or decrease cell death.[1,14] The *LRRK2* (leucine-rich repeat kinase 2) gene (OMIM, 609007; chromosomal location, 12q12) encodes multiple domains, including a kinase domain and a *ras*-oncogene–like guanosine triphosphatase domain, which has similar structural position as the B-RAF kinase associated with melanoma.[15,16] The most common *LRRK2* mutation, G2019S,[17,18] has been associated with increased risk of nonskin cancers[19,20] and breast cancer,[19] whereas the R1441G/C mutation was associated with colon cancer.[21] However, results across the studies are inconsistent. Among 732 patients with PD in Spain, there was no association between R1441G/C or G2019S mutations and cancer outcomes.[22]

Because knowledge of a possible link with cancer may guide screening and counseling practices for both *LRRK2* mutation carriers with PD and asymptomatic carriers, it is important to examine the associations between such mutations and cancer in a larger sample of patients with PD, as well as to evaluate whether study differences may account for the discrepancy in the findings. Therefore, we conducted a pooled analysis examining the relationship between *LRRK2* G2019S mutation and cancer outcomes among patients with PD recruited in 5 centers located in Europe, Israel, and the United States.

Methods

Study Participants and Data Collection

The study was approved by the institutional review boards of each participating institution, and written informed consent was obtained from all patients. The participants did not receive financial compensation. Patients with PD (N = 1549) were recruited from 5 movement disorders clinics located in Israel (Sheba Medical Center and Sourasky Medical Center, Tel Aviv), Norway (St Olav's Hospital, Trondheim), Spain (University Hospital Donostia, San Sebastian), and the United States (Mt Sinai Beth Israel Medical Center, New York). Detailed descriptions about study participants, data collection, *LRRK2* genotyping, and cancer outcomes for 3 of the centers have been published[19,20,22,23] and are summarized for all 5 centers in the eTable in the Supplement. Briefly, at all centers, patients with PD were queried regarding demographic and lifestyle factors, as well as personal and family history of PD and other diseases, including self-reported cancer, type of cancer, and age at diagnosis. The confirmation of self-reported cancer outcomes varied slightly by study site. In Israel and New York, cancer outcomes were confirmed by reviewing the medical records of oncologists and surgeons[19,20]; in Spain and Norway, cancer outcomes were confirmed with medical records and tumor registry databases.[22] All patients with PD included in the present analysis were genotyped for the *LRRK2* G2019S mutation. Genotyping of the *LRRK2* R1441G/C mutation was done only in one center[22]; thus, we did not include that mutation in the present analysis. Other differences across centers included matching of patients with *LRRK2* PD and controls, the burden of data collection, and whether carriers of *GBA1*[24] or *BRCA1/2* mutations were excluded (eTable in the Supplement).

Statistical Analysis

We compared the characteristics of *LRRK2* G2019S mutation carriers with those of noncarriers using unpaired, 2-tailed *t* tests (for continuous, normally distributed variables) and χ^2 tests (for categorical variables). The significance level was set at $\alpha = .05$. Logistic regression models were used to examine the associations between G2019S mutation and several outcomes: all cancers combined, nonskin cancers (all cancers, excluding nonmelanoma skin cancer and melanoma), smoking-related cancers, hormone-related cancers, and other cancers to estimate odds ratios (ORs) and 95% CIs.[25] Smoking-related cancers included lung and bladder cancers; there was only one patient with oropharyngeal cancer, which was not included in this group owing to potential confounding by human papillomavirus infection. Hormone-related cancers included breast and ovarian cancers in women (there were no endometrial cancers) and prostate cancer in men. In addition, we separately assessed the association of G2019S mutation and each type of cancer.

We initially examined the unadjusted association between *LRRK2* G2019S mutation and cancer outcomes, and then we adjusted the analyses using different statistical models. In the first model, the association between G2019S mutation and cancer outcomes were adjusted for age at the time of the first

cancer diagnosis for patients with available data (n = 131) or age at the last clinic visit for all other patients with PD. Because of the heterogeneity across the 5 centers, the associations between G2019S mutation and cancer outcomes were estimated using mixed-effects logistic models, adjusting for age as a fixed effect and study center as a random effect (model 2). In model 3, the associations were adjusted for age and ethnicity (Ashkenazi Jew [AJ] vs non-AJ) as fixed effects and study center was modeled as a random effect. For hormone-related cancers, all analyses were carried out in sex-specific strata.

We also investigated whether associations between *LRRK2* G2019S mutation and cancer varied by ethnicity (AJ vs others). We conducted these analyses for all cancers combined, nonskin cancers, and hormone-related cancers. To test effect modification, interaction terms between G2019S mutation and ethnicity were included in models containing the main effects in separate logistic regression models. The log likelihood of models with main effects were compared with the log likelihood of models that contained main effects and the interaction terms, using a likelihood ratio test to determine the statistical significance of interactions.[25,26]

Finally, we conducted a sensitivity analysis to determine the influence of the study center on the associations between *LRRK2* G2019S mutation and cancer outcomes. The associations between G2019S mutation and cancer outcomes were estimated using model 2 (adjusted for age and study center) for all 5 centers and then by excluding each center, one at a time, to determine the change in OR and 95% CI. All statistical analyses were performed using Stata, version 12 (StataCorp).

Results

The overall prevalence of the *LRRK2* G2019S mutation was 11.4% among all patients with PD. Demographic characteristics, clinical characteristics, and cancer outcomes for 1549 patients with PD from 5 centers are presented in **Table 1**, stratified also by *LRRK2* G2019S mutation status. Mutation carriers were slightly younger at PD diagnosis (mean [SD] age, 57.8 [11.8] vs 62.4 [11.6] years; $P < .001$) and more likely to be women (53.1%) and of AJ descent (76.8%) in comparison with noncarriers. Almost half (49.2%) of the patients with PD were from Spain, 38.7% were from Israel, 10.5% were from the United States, and 1.6% were from Norway. There was large variability in the percentages of G2019S mutation carriers by study center owing to differences in geographic location, ethnicity, and data collection procedures (eTable in the Supplement). Information on smoking was collected only for a subset of patients with PD (n = 304) in 2 centers (Israel and the United States); however, *LRRK2* mutation carriers were similar to noncarriers with respect to smoking status ($P = .97$).

A total of 250 cancer outcomes (16.1%) were reported from all patients with PD; of these, 201 were nonskin cancers. The proportions of all cancers and nonskin cancers were higher among *LRRK2* G2019S mutation carriers vs noncarriers: 22.6% vs 15.3% for all cancers ($P = .01$), and 18.1% vs 12.3% for nonskin cancer ($P = .03$). In comparison with noncarriers, G2019S mutation carriers were 3 times more likely to report 2 or more cancers (4.5% vs 1.4%; $P = .04$) and younger age at the time of the first cancer diagnosis (62.5 [10.8] vs 68.3 [9.4] years; $P = .02$).

Table 2 provides associations of *LRRK2* G2019S mutation with overall cancer and various cancer outcomes among patients with PD, using 3 different statistical models. Although we did not observe any statistically significant association between *LRRK2* G2019S mutation and all cancers combined, there was a 57% increased risk (95% CI, 1.04-2.38) for nonskin cancers among *LRRK2* G2019S mutation carriers in comparison with noncarriers in models adjusted for age and study center. The association increased slightly (OR, 1.62; 95% CI, 1.04-2.52) when the analysis was also adjusted for ethnicity (AJ vs other). There was a statistically significant positive association between *LRRK2* G2019S mutation and hormone-related cancers, which was driven mostly by breast cancer in women. In models adjusted for age and study center, the OR was 2.06 (95% CI, 1.22-3.47) for hormone-related cancers in all patients and 2.88 (95% CI, 1.39-5.98) for breast cancer in women among G2019S mutation carriers vs noncarriers. The ORs for these outcomes were slightly attenuated to 1.87 ($P = .03$) and 2.34 ($P = .04$), respectively, when the models were also adjusted for AJ ethnicity. There was an OR of 2.21 ($P = .07$) for prostate cancer among male G2019S mutation carriers. There were no associations between *LRRK2* G2019S mutations and smoking-related cancers or other types of cancer.

We examined whether the associations between *LRRK2* G2019S mutation and cancer outcomes were different between AJ patients vs those of other ethnicities (**Table 3**). There were similar ORs for G2019S mutation and nonskin cancers between AJ (OR, 1.59) and the others (OR, 1.74; $P = .84$ for interaction). For breast cancer, although there was a suggestion that the risk associated with G2019S mutation was lower among AJ women (OR, 1.77; 95% CI, 0.70-4.48) in comparison with women of other ethnicities (OR, 4.65; 95% CI, 1.21-17.93), the *P* value for interaction was not statistically significant ($P = .26$). Finally, for prostate cancer there were similar ORs for AJ men (OR, 2.12) and men of other ethnic groups (OR, 2.47; $P = .85$ for interaction).

Because there were differences across the 5 centers with respect to study population, prevalence of G2019S mutation, and data collection procedures, we conducted a sensitivity analysis by excluding each center, one at a time, to determine the influence of study center on the associations between G2019S mutation and cancer outcomes (**Table 4**). The Sourasky Medical Center had the highest influence on the associations between *LRRK2* mutation and cancer outcomes. When this center was excluded from analyses, the ORs increased and became statistically significant for all cancers combined (OR, 1.84; 95% CI, 1.15-2.94) and prostate cancer (OR, 3.06; 95% CI, 1.29-7.28) in comparison with models that included all 5 centers or those that excluded the other 4 centers individually. For hormone-related cancers and breast cancers, although the ORs of different sensitivity analyses varied from 1.74 to 2.31 and from 2.37 to 3.39, respectively, all of the results were robust and statistically significant on each replication ($P < .05$).

Table 1. Characteristics and Cancer Outcomes for Patients With PD From 5 Centers

Characteristic	No. (%)			*P* Value[a]
	Total (N = 1549)	*LRRK2* Mutation		
		Carriers (n = 177)	Noncarriers (n = 1372)	
Age, mean (SD), y				
At examination	70.9 (10.8)	69.9 (11.1)	71.0 (10.8)	.21
At PD diagnosis	61.9 (11.7)	57.8 (11.8)	62.4 (11.6)	<.001
Duration of PD, mean (SD), y	9.8 (7.0)	11.2 (8.7)	9.5 (6.7)	.05
Study center				
Israel (Tel Aviv, Sheba)	**459** (29.6)	49 (27.7)	410 (29.9)	<.001
Israel (Tel Aviv, Sourasky)	**140** (9.0)	68 (38.4)	72 (5.2)	
Norway (Trondheim)	**25** (1.6)	4 (2.3)	21 (1.5)	
Spain (San Sebastian)	**762** (49.2)	25 (14.1)	737 (53.7)	
United States (Mt Sinai Beth Israel Medical Center, New York City)	**163** (10.5)	31 (17.5)	132 (9.6)	
Sex				
Male	**869** (56.1)	83 (46.9)	786 (57.3)	.009
Female	**680** (43.9)	94 (53.1)	586 (42.7)	
Ethnicity				
Ashkenazi Jews (both parents)	**589** (38.0)	136 (76.8)	453 (33.0)	<.001
Sephardic Jews (both parents)	**136** (8.8)	7 (4.0)	129 (9.4)	
Other, white	**824** (53.2)	34 (19.2)	790 (57.6)	
Smoking status ascertained, No.[b]	**304** (19.6)	100 (56.5)	204 (14.9)	
Smoker				
Never	**187** (61.5)	61 (61.0)	126 (61.8)	.97
Former	**103** (33.9)	34 (34.0)	69 (33.8)	
Current	**14** (4.6)	5 (5.0)	9 (4.4)	
Cancer outcomes				
All cancers combined	**250** (16.1)	40 (22.6)	210 (15.3)	.01
No. of cancers reported				
1	**223** (14.4)	32 (18.1)	191 (13.9)	.04
2 or 3	**27** (1.7)	8 (4.5)	19 (1.4)	
Age at diagnosis of first cancer, mean (SD), y[c]	67.5 (9.8)	62.5 (10.8)	68.3 (9.4)	.02
Skin cancer (any)	**49** (3.2)	10 (5.7)	39 (2.8)	.05
Melanoma	**22** (1.4)	5 (2.8)	17 (1.2)	.09
All nonskin cancers	**201** (13.0)	32 (18.1)	169 (12.3)	.03
Smoking-related cancers[d]	**20** (1.3)	2 (1.1)	18 (1.3)	.84
Lung cancer	**9** (0.6)	2 (1.1)	7 (0.5)	.31
Bladder cancer	**11** (0.7)	0	11 (0.8)	.23
Hormone-related cancer[e]	**97** (6.3)	20 (11.3)	77 (5.6)	.003
Breast				
Men	**2** (0.2)	1 (1.2)	1 (0.13)	.05
Women	**39** (5.7)	12 (12.8)	27 (4.6)	.002
Ovarian	**10** (1.5)	0	10 (1.7)	.20
Prostate	**48** (5.5)	8 (9.6)	40 (5.1)	.08
Colon cancer	**35** (2.3)	6 (3.4)	29 (2.1)	.28
Kidney cancer	**10** (0.7)	2 (1.1)	8 (0.6)	.39
Hematologic cancer/lymphoma	**17** (1.1)	1 (0.6)	16 (1.2)	.47
Meningioma	**13** (0.8)	3 (1.7)	10 (0.7)	.19

Abbreviation: PD, Parkinson disease.

[a] *P* values were determined using *t* tests (continuous variables) and χ^2 tests (categorical variables) comparing *LRRK2* mutation carriers with noncarriers.

[b] Smoking status data were obtained at only 2 centers (Israel and the United States).

[c] Age at diagnosis of first cancer was available only for a subset of patients with PD (n = 131); only one patient with PD reported 3 cancers.

[d] Smoking-related cancers included lung and bladder cancers. Only one patient reported cancer of the oropharynx, which was not included owing to the lack of human papilloma virus status and thus potential confounding by the virus.

[e] Hormone-related cancers included prostate cancer in men and breast and ovarian cancers in women (there were no endometrial/gynecologic cancers reported); the percentages of sex-specific hormonal cancers were based on the number of men and women.

Discussion

In this pooled analysis we observed a 62% increased risk (95% CI, 1.04-2.52) for all nonskin cancers among *LRRK2* G2019S mutation carriers in comparison with noncarriers in a large sample (N = 1549) of patients with PD from 5 multinational centers. There was a statistically significant positive association for hormone-related cancers (OR, 1.87; *P* = .03), which was driven mostly by breast cancer in women (OR, 2.34; *P* = .04). How-

Table 2. Associations of *LRRK2* G2019S Mutation With Overall Cancer and Various Cancer Types Among Patients With PD

Cancer Outcome	*LRRK2* Mutation, No. (%)[a]		OR (95% CI)[b]					
	Noncarriers (n = 1372)	Carriers (n = 177)	Model 1[c]	*P* Value	Model 2[d]	*P* Value	Model 3[e]	*P* Value
No cancer	1162 (89.5)	137 (10.5)	1 [Reference]		1 [Reference]		1 [Reference]	
All cancers combined	210 (84.0)	40 (16.0)	1.49 (0.99-2.24)	.057	1.49 (0.99-2.24)	.06	1.37 (0.92-2.04)	.13
Skin cancer	39 (79.6)	10 (2.4)	2.11 (1.03-4.31)	.04	1.11 (0.51-2.40)	.80	1.03 (0.48-2.22)	.93
Melanoma	17 (77.3)	5 (22.7)	2.36 (0.86-6.50)	.10	1.95 (0.67-5.72)	.22	1.62 (0.56-4.67)	.37
No nonskin cancer	1203 (89.2)	145 (1.8)	1 [Reference]		1 [Reference]		1 [Reference]	
All nonskin cancers	169 (84.1)	32 (15.9)	1.57 (1.04-2.38)	.03	1.57 (1.04-2.38)	.03	1.62 (1.04-2.52)	.03
Smoking-related cancers								
No	1354 (88.5)	175 (11.5)	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	18 (90.0)	2 (1.0)	0.84 (0.19-3.64)	.81	1.04 (0.22-4.94)	.96	1.20 (0.25-5.76)	.82
Lung cancer	7 (77.8)	2 (22.2)	2.15 (0.44-10.46)	.34	2.40 (0.43-13.45)	.32	2.40 (0.42-13.82)	.33
Bladder cancer	11 (100)	0						
Hormone-related cancers[f]								
No	1295 (89.2)	157 (1.8)	1 [Reference]		1 [Reference]		1 [Reference]	
Yes	77 (79.4)	20 (2.6)	2.06 (1.22-3.47)	.007	2.06 (1.22-3.47)	.007	1.87 (1.07-3.26)	.03
Breast cancer, women	27 (69.2)	12 (3.8)	2.88 (1.39-5.97)	.004	2.88 (1.39-5.98)	.004	2.34 (1.05-5.22)	.04
Ovarian cancer	10 (100)	0						
Prostate cancer, men	40 (83.3)	8 (16.7)	2.05 (0.92-4.55)	.08	2.05 (0.92-4.55)	.08	2.21 (0.95-5.18)	.07
Other cancer types								
Colon cancer	29 (82.9)	6 (17.1)	1.68 (0.69-4.11)	.26	1.68 (0.69-4.11)	.26	1.92 (0.74-5.00)	.18
Kidney/renal cancer	8 (80.0)	2 (2.0)	1.93 (0.41-9.17)	.41	1.93 (0.40-9.17)	.41	1.93 (0.40-9.17)	.41
Hematologic cancer/lymphoma	16 (94.1)	1 (5.9)	0.48 (0.06-3.68)	.48	0.48 (0.06-3.68)	.48	0.48 (0.06-3.68)	.48
Meningioma	10 (76.9)	3 (23.1)	2.40 (0.65-8.78)	.19	2.38 (0.61-9.21)	.21	2.38 (0.61-9.21)	.21

Abbreviations: OR, odds ratio; PD, Parkinson disease.

[a] Percentages are determined within each row.

[b] Results were considered statistically significant at $P < .05$.

[c] The OR and 95% CI for model 1 were adjusted for age at cancer diagnosis (for patients with PD who were diagnosed with cancer) and age at examination (for other patients with PD).

[d] The OR and 95% CI for model 2 were estimated using mixed-effects models, adjusting for age at cancer diagnosis (for patients with PD and cancer) and age at examination (for other patients with PD) as fixed effects and study center as a random effect.

[e] The OR and 95% CI for model 3 were estimated using mixed-effects models, adjusting for age at cancer diagnosis (for patients with PD and cancer) and age at examination (for other patients with PD) and ethnicity (Ashkenazi Jews vs other) as fixed effects and study center as a random effect.

[f] Analyses for hormone-related cancers were carried out in strata by sex.

ever, there were no associations between G2019S mutations and smoking-related cancers or other types of cancer.

The underlying biological mechanism that links *LRRK2* G2019S mutation and cancer, especially hormone-related cancers (eg, breast and prostate) remains largely unknown. The LRRK2 is a large protein that encodes 2 enzymatic functions, a protein kinase and a *ras*-oncogene–like guanosine triphosphatase domain, as well as multiple protein interaction domains.[14,16,27] The G2019S mutation has been shown[15] to directly increase kinase activity resulting in a gain of function. Experimental studies[27,28] have demonstrated that several mitogen-activated protein kinase kinases, which are known to reside alongside LRRK2 in the tyrosine kinase–like branch of the kinome, might be acting as LRRK2 substrates. Thus, it is possible that LRRK2 targets in vivo substrates through these mitogen-activated protein kinase docking sites and therefore may activate breast and prostate carcinogenesis through a mitogen-activated protein kinase signaling pathway.[27,28] In addition, amplification and overexpression of the *LRRK2* gene has been reported[29] in other cancers, including papillary renal and thyroid carcinomas.

It is unclear whether the increased breast cancer risk associated with *LRRK2* G2019S mutation is limited to patients with PD. To address this issue, a large study[30] in the United Kingdom genotyped 1014 breast cancer cases and 1033 controls without PD for G2019S mutations and found none. However, the prevalence of *LRRK2* G2019S varies widely by population,[17,18,23] and in the United Kingdom the frequency of this mutation is very low. Another investigation[31] of 188 breast cancer–associated single-nucleotide polymorphisms from genome-wide association studies also did not find cosegregation with PD susceptibility loci, including *LRRK2*. By contrast, colon cancer appeared to be increased in *LRRK2* R1441G/C mutation carriers without PD.[21] Therefore, evaluation of asymptomatic *LRRK2* carriers is needed to directly assess whether cancer segregates with *LRRK2* mutations independent of PD.

Breast cancer and PD have been linked in several studies.[5,6,12] Among 426 Japanese patients with PD, there was an RR of 5.5 (95% CI, 1.1-16.03) for breast cancer in comparison with the general population; however, this finding was based on only 3 cases of breast cancer.[12] In a Danish cohort of 14 088 patients with PD, there was an RR of 1.24 (95% CI, 1.0-

Table 3. Associations of *LRRK2* G2019S Mutation With Overall Cancer and Hormonal Cancers, Stratified by Ashkenazi Jewish Ethnicity

Cancer Outcome	*LRRK2* Mutation, No. (%)[a]		Model Adjusted for Age and Study Center, OR (95% CI)[b]	*P* Value
	Noncarriers	Carriers		
Ashkenazi Jewish (n = 589)				
No. of patients	453	136		
No cancer	364 (77.5)	106 (22.5)	1 [Reference]	
All cancers combined	89 (74.8)	30 (25.2)	1.20 (0.74-1.94)	.46
No nonskin cancer	399 (78.1)	112 (21.9)	1 [Reference]	
All nonskin cancers	54 (69.2)	24 (30.8)	1.59 (0.94-2.70)	.08
Hormone-related cancers[c]				
No	423 (77.8)	121 (22.2)	1 [Reference]	
Yes	30 (66.7)	15 (33.3)	1.60 (0.80-3.18)	.18
Cancer site				
Breast, women	12 (57.1)	9 (42.9)	1.77 (0.70-4.48)	.23
Prostate, men	13 (68.4)	6 (31.6)	2.12 (0.77-5.81)	.15
Non-Ashkenazi Jewish (n = 960)				
No. of patients	919	41		
No cancer	798 (96.3)	31 (3.7)	1 [Reference]	
All cancers combined	121 (92.4)	10 (7.6)	2.20 (1.05-4.61)	.04
No nonskin cancer	804 (96.1)	33 (3.9)	1 [Reference]	
All nonskin cancers	115 (93.5)	8 (6.5)	1.74 (0.78-3.88)	.17
Hormone-related cancers[c]				
No	872 (96.0)	36 (4.0)	1 [Reference]	
Yes	47 (90.4)	5 (9.6)	2.67 (0.99-7.15)	.05
Cancer site				
Breast (women)	15 (83.3)	3 (16.7)	4.65 (1.21-17.93)	.03
Prostate (men)	27 (93.1)	2 (6.9)	2.47 (0.53-11.43)	.25

Abbreviation: OR, odds ratio.

[a] Percentages are determined within each row.

[b] The OR and 95% CI were adjusted for age as a fixed effect and study center as a random effect. Results were considered statistically significant at $P \leq .05$.

[c] Analyses for hormonal cancers were carried out in strata by sex.

Table 4. Sensitivity Analysis of the Influence of Study Center on the Association Between *LRRK2* G2019S Mutation and Cancer Outcomes

Sensitivity Analysis	OR (95% CI)[a]				
	All Cancers Combined	All Nonskin Cancers	Hormone-Related Cancers	Cancer	
				Breast (Women)	Prostate (Men)
All study centers	1.49 (0.99-2.24)	1.57 (1.04-2.38)	2.06 (1.22-3.47)	2.88 (1.39-5.98)	2.05 (0.92-4.55)
P value	.06	.03	.007	.004	.08
Excluding Sheba, Israel	1.59 (0.97-2.60)	1.51 (0.92-2.47)	2.27 (1.20-4.28)	3.39 (1.49-7.74)	2.08 (0.82-5.27)
P Value	.06	.10	.01	.004	.12
Excluding Sourasky, Israel	1.84 (1.15-2.94)	2.13 (1.32-3.43)	2.31 (1.25-4.26)	2.54 (1.03-6.26)	3.06 (1.29-7.28)
P value	.01	.002	.008	.04	.01
Excluding Norway	1.35 (0.88-2.06)	1.44 (0.94-2.22)	1.74 (1.00-3.04)	2.37 (1.09-5.12)	1.84 (0.79-4.27)
P value	.17	.09	.05	.03	.16
Excluding Spain	1.40 (0.89-2.21)	1.65 (1.03-2.65)	2.21 (1.15-3.92)	2.84 (1.24-6.46)	1.97 (0.80-4.86)
P value	.14	.04	.02	.01	.14
Excluding the United States	1.48 (0.95-2.28)	1.33 (0.83-2.14)	1.88 (1.02-3.45)	3.19 (1.40-7.27)	1.56 (0.60-4.22)
P value	.08	.24	.04	.006	.35

Abbreviation: OR, odds ratio.

[a] The ORs and 95% CIs presented for this analysis were estimated using mixed-effects models, adjusting for age as a fixed effect and study center as a random effect. Results were considered statistically significant at $P < .05$.

1.5) for breast cancer,[5] which was maintained in an updated analysis[6] that included 224 incident cases (RR, 1.17; 95% CI, 1.02-1.34). Some studies[32,33] have suggested that an association between PD and breast cancer could be attributable to estrogens; however, the relationship between endogenous estrogens and PD is controversial.[34]

Glucocerebrosidase (*GBA1*) mutations in the biallelic forms are associated with an increased risk of cancer, especially hematologic cancers.[35] Because *GBA1* mutations have a founder effect in AJs and Spaniards,[35,36] the inclusion of *GBA1* mutation carriers in the group of patients with PD who were not *LRRK2* G2019S mutation carriers could potentially attenuate

the difference in cancer rates between G2019S mutation carriers and noncarriers. Although we did not include *GBA1* mutation carriers in the present analysis, it is likely that any effect is nondifferential, since *GBA1* mutations do not modify the risk between *LRRK2* mutations and PD.[36]

Advantages of our study include the large sample size of 1549 patients with PD, as well as a detailed collection of demographic characteristics, clinical characteristics, and cancer outcomes. Most nonskin cancers were verified and confirmed by medical records and tumor registry databases. One limitation of the study is that it was not a prospective cohort, but rather a cross-sectional analysis of data collected through 5 medical centers with some heterogeneity regarding data collection protocols as well as a potential for referral bias. In addition, the small number of some cancers (eg, kidney, hematologic/lymphoma, and bladder) limited the statistical power to investigate associations between *LRRK2* mutations and rare cancers. Finally, we did not have information on hormonal and reproductive factors that could confound the association between *LRRK2* mutations and breast cancer. Although we did not have complete information on the *BRCA1/BRCA2* mutation status of all women with PD, investigators at Sheba Medical Center[19] evaluated mutations in their breast cancer cases and found only a single *BRCA1* mutation that cosegregated with the *LRRK2* G2019S mutation. They separately analyzed genome-wide association study data evaluating breast cancer single-nucleotide polymorphisms in relationship to PD genes and found no suggestion of simple cosegregation or shared genetic loci.[30] Thus, the association between *LRRK2* G2019S mutation and breast cancer is unlikely to be the result of confounding by *BRCA1/BRCA2* mutation-carrier status, but this cannot be fully ruled out without genotyping all patients with breast cancer.

Although our sensitivity analyses demonstrated that the results were overall robust with removal of each center, we could not explain the lack of an association between nonskin cancers and G2019S mutations in 2 centers. One of the reasons could be the relatively small number of breast cancer cases in each center, and therefore center-specific analyses were underpowered. We observed variability in *LRRK2* G2019S mutation carriers by center, which was not entirely explained by differences in geography and ethnic backgrounds but could be the result of ascertainment of patients with PD or differences in data collection protocols. Therefore, to be more certain of the positive association between *LRRK2* G2019S mutation and risks of nonskin cancers and breast cancer, larger prospective studies using the same instruments and protocols across sites are warranted. The limited evidence that breast cancer risk appears to be increased only among patients with PD is enigmatic and requires rigorous investigation through family-based studies. Moreover, an investigation of the association between other *LRRK2* mutations in relationship to cancer among patients with PD is needed to understand the underlying genetic susceptibility.

Conclusions

This multinational study from 5 centers demonstrates that *LRRK2* G2019S mutation carriers have an overall increased risk of cancer, especially hormone-related cancer and breast cancer in women. Larger, prospective cohorts or family-based studies investigating associations between *LRRK2* mutations and cancer among patients with PD are warranted to better understand the underlying genetic susceptibility between PD and hormone-related cancers.

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