Title

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

Journal

JAMA Neurology, 72(1)

ISSN

2168-6149

Authors

Agalliu, Ilir
San Luciano, Marta
Mirelman, Anat
et al.

Publication Date

2015

DOI

10.1001/jamaneurol.2014.1973

Peer reviewed

Published in final edited form as:

JAMA Neurol. 2015 January ; 72(1): 58–65. doi:10.1001/jamaneurol.2014.1973.

Higher frequency of certain cancers in *LRRK2* G2019S mutation carriers with Parkinson's disease: A pooled analysis

Ilir Agalliu, MD[1], **Marta San Luciano, MD**[2], **Anat Mirelman, MD**[3], **Nir Giladi, MD**[3,8], **Bjorg Waro, MD**[4], **Jan Aasly, MD, PhD**[4], **Rivka Inzelberg, MD**[5,7], **Sharon Hassin-Baer, MD**[5,8], **Eitan Friedman, MD**[5,8], **Javier Ruiz-Martinez, MD**[6], **Jose Felix Marti-Masso, MD**[6], **Avi Orr-Urtreger, MD**[8,9], **Susan Bressman, MD**[10], and **Rachel Saunders-Pullman, MD**[10]

[1]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx NY

[2]Department of Neurology, University of California San Francisco, San Francisco, CA

[3]Movement Disorders Unit, Department of Neurology, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel

[4]Department of Neurology, St. Olavs Hospital, and Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

[5]Parkinson's Disease and Movement Disorders Clinic and Department of Neurology, Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel

[6]Biodonostia Research Institute, Neurosciences Area - University of the Basque Country, (EHU-UPV) Neurology Department, University Hospital Donostia, Center for Biomedical Research in Neurodegenerative Diseases Network (CIBERNED), San Sebastian, Spain,

[7]Department of Neurology, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel

[8]Department of Human Genetics, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

[9]Genetic Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[10]Departments of Neurology, Mount Sinai Beth Israel Medical Center, and Albert Einstein College of Medicine, Bronx NY, and Icahn School of Medicine at Mount Sinai

Abstract

Importance—Parkinson disease (PD) patients who harbor *LRRK2* G2019S mutations may have increased risks of non-skin cancers. However, the results have been inconsistent across studies.

Objective—To analyze pooled data from five centers to further examine the association between *LRRK2* G2019S mutation and cancer among PD patients 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 1,549 PD patients recruited across five movement disorders clinics located in Europe, Israel, and the United States. Associations between *LRRK2* G2019S

Declaration on Interests: None

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, non-skin 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 PD patients. 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 non-skin 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 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 five 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 PD patients are warranted to better understand the underlying genetic susceptibility between PD and hormone-related cancers.

Keywords

LRRK2 gene; G2019S mutation; Parkinson Disease; cancer; non-skin cancer; hormone-related cancers; breast cancer; pooled analysis

Introduction

Parkinson disease (PD) and cancer have opposite biological mechanisms: PD is characterized by apoptosis and premature neuronal degeneration, 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 PD patients[2]. The excess melanoma risk might be the result of a shared relationship between tyrosinase and melanin, but not L-dopa treatment[3–6]. The overexpression of alpha-synuclein leads to cell degeneration in the brain. In the skin, the overexpression may inhibit tyrosinase and tryrosine 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 PD patients are more likely to develop melanoma, and patients with melanoma and their family members have an increased PD risk[7–9].

PD patients have lower risks for non-skin cancers [5,6,10,11]. A meta-analysis 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 others cancers, respectively, among PD participants[10]. 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 non-skin cancers could be that the prevalence of smoking and other lifestyle risk factors are usually low in PD patients; 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 non-skin 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 PD patients 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 associations between such mutations and cancer in a larger sample of PD patients, as well as to evaluate whether study differences may account for the discrepancy in findings. Therefore, we conducted a pooled analysis examining the relationship between *LRRK2* G2019S mutation and cancer outcomes among PD patients recruited in five 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. PD patients (n=1,549) were recruited from five 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 three of the centers have been published [19,20,22,23] and are summarized for all five centers in the eTable in the Supplement. Briefly, at all centers, PD patients 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]; whereas in Spain and Norway, cancer outcomes were confirmed with medical records and tumor registry databases [22]. All PD patients included in the present analysis were genotyped for *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 patients 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 characteristics of *LRRK2* G2019S mutation carriers with those of non-carriers using unpaired, two-tailed t tests (for continuous, normally distributed variables), and chi-square tests (for categorical variables). The significance level was set at α=.05. Logistic regression models were used to examine the associations between G2019S mutation and several outcomes: all cancers combined, non-skin cancers (all cancers, excluding non-melanoma 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, 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 PD patients. Because of the heterogeneity across the five centers, the associations between G2019S mutation and cancer outcomes were estimated using mixed-effect, logistic models, adjusting for age as fixed effect and study center as a random effect (model 2). In model 3, the associations were adjusted for age and ethnicity (Ashkenazi Jewish [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 cancer combined, non-skin 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 statistical significance of interactions [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 five 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 PD patients. Demographic characteristics, clinical characteristics, and cancer outcomes for 1,549 PD patients from five centers are presented in Table 1, stratified also by *LRRK2* G2019S mutation status. Mutation carriers were slightly younger at PD diagnosis (57.8±11.8 vs. 62.4±11.6 years, p<0.0001) and more likely to be women (53.1%) and of AJ descent (76.8%) in comparison with non-carriers. Almost half (49.2%) of PD patients 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 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 PD patients (n=304) in two centers (Israel and United States); however, *LRRK2* mutation carriers were similar to non-carriers with respect to smoking status (p=0.97).

A total of 250 cancer outcomes (16.1%) were reported from all PD patients; of these, 201 were non-skin cancers. The proportions of all cancers and non-skin cancers were higher among *LRRK2* G2019S mutation carriers vs. non-carriers: 22.6% vs. 15.3% for all cancers (p=0.01), and 18.1% vs. 12.3%, respectively for non-skin cancer (p=0.03). In comparison with non-carriers, G2019S mutation carriers were three times more likely to report two or more cancers (4.5% vs. 1.4%; p=0.04) and younger age at the time of the first cancer diagnosis (62.5±10.8 vs. 68.3±9.4 years; p=0.02).

Table 2 provides associations of *LRRK2* G2019S mutation with overall cancer and various cancer outcomes among PD patients, using three 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 non-skin cancers among *LRRK2* G2019S mutation carriers in comparison with non-carriers 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, 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 carries vs. non-carriers. The ORs for these outcomes were slightly attenuated to 1.87 (p=0.03) and 2.34 (p=0.04) respectively, when the models were also adjusted for AJ ethnicity. There was an OR of 2.21 (p=0.07) 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 non-skin cancers between AJ (OR, 1.59) and others (OR, 1.74; p= 0.84 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=0.26). Finally, for prostate cancer there were similar ORs for AJ men (OR, 2.12) and men of other ethnic groups (OR, 2.47; p=0.85 for interaction).

Because there were differences across the five 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 cancers 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 five centers or those that excluded the other four 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 ($p<0.05$).

Discussion

In this pooled analysis we observed a 62% increased risk (95% CI, 1.04 – 2.52) for all non-skin cancers among *LRRK2* G2019S mutation carriers in comparison with non-carriers in a large sample (N=1,549) of PD patients from five multinational centers. There was a statistically significant positive association for hormone-related cancers (OR, 1.87; p=0.03), which was driven mostly by breast cancer in women (OR, 2.34; p=0.04). However, there were no associations between G2019S mutations and smoking-related cancers or other types of cancer.

The underlying biological mechanism that links *LRRK2* G2919S mutation and cancer, especially hormone–related cancers (eg, breast and prostate) remains largely unknown. The LRRK2 is a large protein that encodes two 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 [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 PD patients. To address this issue, a large study[30] in the United Kingdom genotyped 1,014 breast cancer cases and 1,033 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 PD patients 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 three cases of breast cancer [12]. In a Danish cohort of 14,088 PD patients, there was an RR of 1.24 (95%CI, 1.0–1.5) 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 malignancy [35]. Because *GBA1* mutations have a founder effect in AJs and Spaniards[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 non-carriers. 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 [24].

Advantages of our study include the large sample size of 1,549 PD patients, as well as detailed collection of demographic characteristics, clinical characteristics, and cancer outcomes. Most non-skin 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 five 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 [31]. 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 breast cancer patients.

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 non-skin cancers and G2019S mutations in two centers. One of the reasons could be the relative 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 also be the result of ascertainment of PD patients or differences in data collection protocols. Therefore, to be more certain of the positive association between *LRRK2* G2019S mutation and risks of non-skin 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 PD patients 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 PD patients is needed to understand the underlying genetic susceptibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank Dr. Chris Coffey for his advice on statistical analysis methods, and Robert Ortega for data analysis at Mount Sinai Beth Israel Medical Center. Drs. Ilir Agalliu and Rachel Saunders-Pullman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This work was supported by the Michael J. Fox Foundation, and the National Institutes of Health (NIH) grant K02-NS073836 (to RSP). The funding agencies had no role in the design and conduct of the study; data collection, management, analysis, and interpretation of the data; as well as in preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Devine MJ, Plun-Favreau H, Wood NW. Parkinson's disease and cancer: two wars, one front. Nature reviews. Cancer. 2011 Nov; 11(11):812–823.
2. Skibba JL, Pinckley J, Gilbert EF, Johnson RO. Multiple primary melanoma following administration of levodopa. Archives of pathology. 1972 Jun; 93(6):556–561. [PubMed: 5025039]
3. Pan T, Zhu J, Hwu WJ, Jankovic J. The role of alpha-synuclein in melanin synthesis in melanoma and dopaminergic neuronal cells. PloS one. 2012; 7(9):e45183. [PubMed: 23028833]
4. Inzelberg R, Rabey JM, Melamed E, et al. High prevalence of malignant melanoma in Israeli patients with Parkinson's disease. Journal of neural transmission. 2011 Aug; 118(8):1199–1207. [PubMed: 21298300]
5. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellemkjaer L, Moller H. Atypical cancer pattern in patients with Parkinson's disease. British journal of cancer. 2005 Jan 17; 92(1):201–205. [PubMed: 15583688]
6. Rugbjerg K, Friis S, Lassen CF, Ritz B, Olsen JH. Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease. International journal of cancer. Journal international du cancer. 2012 Oct 15; 131(8):1904–1911. [PubMed: 22278152]
7. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Family history of melanoma and Parkinson disease risk. Neurology. 2009 Oct 20; 73(16):1286–1291. [PubMed: 19841380]
8. Kareus SA, Figueroa KP, Cannon-Albright LA, Pulst SM. Shared predispositions of parkinsonism and cancer: a population-based pedigree-linked study. Archives of neurology. 2012 Dec; 69(12): 1572–1577. [PubMed: 22945795]

9. Liu R, Gao X, Lu Y, Chen HL. Meta-analysis of the relationship between Parkinson disease and melanoma. Neurology. 2011 Jun; 76(23):2002–2009. [PubMed: 21646627]
10. Bajaj A, Driver JA, Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. Cancer causes & control : CCC. 2010 May; 21(5):697–707. [PubMed: 20054708]
11. Inzelberg R, Jankovic J. Are Parkinson disease patients protected from some but not all cancers? Neurology. 2007 Oct 9; 69(15):1542–1550. [PubMed: 17699801]
12. Minami Y, Yamamoto R, Nishikouri M, Fukao A, Hisamichi S. Mortality and cancer incidence in patients with Parkinson's disease. J Neurol. 2000 Jun; 247(6):429–434. [PubMed: 10929271]
13. Hernan MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Annals of neurology. 2002 Sep; 52(3):276–284. [PubMed: 12205639]
14. Garber K. Parkinson's disease and cancer: the unexplored connection. Journal of the National Cancer Institute. 2010 Mar 17; 102(6):371–374. [PubMed: 20215596]
15. West AB, Moore DJ, Biskup S, et al. Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. Proc Natl Acad Sci USA. 2005 Nov 15; 102(46):16842–16847. [PubMed: 16269541]
16. Zheng B, Jeong JH, Asara JM, et al. Oncogenic B-RAF negatively regulates the tumor suppressor LKB1 to promote melanoma cell proliferation. Molecular cell. 2009 Jan 30; 33(2):237–247. [PubMed: 19187764]
17. Clark LN, Wang Y, Karlins E, et al. Frequency of LRRK2 mutations in early- and late-onset Parkinson disease. Neurology. 2006 Nov 28; 67(10):1786–1791. [PubMed: 17050822]
18. Sierra M, Gonzalez-Aramburu I, Sanchez-Juan P, et al. High frequency and reduced penetrance of LRRK2 G2019S mutation among Parkinson's disease patients in Cantabria (Spain). Movement disorders : official journal of the Movement Disorder Society. 2011 Nov; 26(13):2343–2346. [PubMed: 21954089]
19. Inzelberg R, Cohen OS, Aharon-Peretz J, et al. The LRRK2 G2019S mutation is associated with Parkinson disease and concomitant non-skin cancers. Neurology. 2012 Mar; 78(11):781–786. [PubMed: 22323743]
20. Saunders-Pullman R, Barrett MJ, Stanley KM, et al. LRRK2 G2019S mutations are associated with an increased cancer risk in Parkinson disease. Movement disorders : official journal of the Movement Disorder Society. 2010 Nov 15; 25(15):2536–2541. [PubMed: 20818610]
21. Strongosky AJ, Farrer M, Wszolek ZK. Are Parkinson disease patients protected from some but not all cancers? Neurology. 2008 Nov 11; 71(20):1650–1650. [PubMed: 19001259]
22. Ruiz-Martinez J, de la Riva P, Rodriguez-Oroz MC, et al. Prevalence of cancer in Parkinson’s disease related to R1441G and G2019S mutations in LRRK2. Movement disorders : official journal of the Movement Disorder Society. 2014; 29(6):750–755. [PubMed: 24357540]
23. Orr-Urtreger A, Shifrin C, Rozovski U, et al. The LRRK2 G2019S mutation in Ashkenazi Jews with Parkinson disease: is there a gender effect? Neurology. 2007 Oct 16; 69(16):1595–1602. [PubMed: 17938369]
24. Gan-Or Z, Bar-Shira A, Mirelman A, et al. LRRK2 and GBA mutations differentially affect the initial presentation of Parkinson disease. Neurogenetics. 2010 Feb; 11(1):121–125. [PubMed: 19458969]
25. Breslow, NE.; Day, NE. The Analysis of Case-Control Studies. Lyon: International Agency for Research on Cancer; 1980.
26. Kleinbaum, DG.; Kupper, LK.; Nizam, A.; Muller, KE. Applied Regression Analysis and Other Multivariable Methods. 4 ed. Belmont, CA: Thompson; 2007.
27. Smith WW, Pei Z, Jiang H, Dawson VL, Dawson TM, Ross CA. Kinase activity of mutant LRRK2 mediates neuronal toxicity. Nature neuroscience. 2006 Oct; 9(10):1231–1233.
28. Liou GY, Gallo KA. New biochemical approaches towards understanding the Parkinson's disease-associated kinase, LRRK2. The Biochemical journal. 2009 Nov 15; 424(1):e1–e3. [PubMed: 19839940]

29. Looyenga BD, Furge KA, Dykema KJ, et al. Chromosomal amplification of leucine-rich repeat kinase-2 (LRRK2) is required for oncogenic MET signaling in papillary renal and thyroid carcinomas. Proc Natl Acad Sci USA. 2011 Jan 25; 108(4):1439–1444. [PubMed: 21220347]

30. Mortiboys H, Cox A, Brock IW, Bandmann O. The common PARK8 mutation LRRK2G^{2090}S is not a risk factor for breast cancer in the absence of Parkinson's disease. J Neurol. 2013; 260(8): 2177–2178. [PubMed: 23824357]

31. Kravitz E, Laitman Y, Hassin-Baer S, Inzelberg R, Friedman E. Parkinson's disease genes do not segregate with breast cancer genes' loci. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2013 Aug; 22(8):1464–1472.

32. Ragonese P, D'Amelio M, Callari G, Salemi G, Morgante L, Savettieri G. Age at menopause predicts age at onset of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2006 Dec; 21(12):2211–2214. [PubMed: 17029261]

33. Ragonese P, D'Amelio M, Salemi G, et al. Risk of Parkinson disease in women: effect of reproductive characteristics. Neurology. 2004 Jun 8; 62(11):2010–2014. [PubMed: 15184606]

34. Ragonese P, D'Amelio M, Savettieri G. Implications for estrogens in Parkinson's disease: an epidemiological approach. Annals of the New York Academy of Sciences. 2006 Nov.1089:373–382. [PubMed: 17261781]

35. Mistry PK, Taddei T, vom Dahl S, Rosenbloom BE. Gaucher disease and malignancy: a model for cancer pathogenesis in an inborn error of metabolism. Critical reviews in oncogenesis. 2013; 18(3):235–246. [PubMed: 23510066]

36. Cormand B, Grinberg D, Gort L, Chabas A, Vilageliu L. Molecular analysis and clinical findings in the Spanish Gaucher disease population: putative haplotype of the N370S ancestral chromosome. Human mutation. 1998; 11(4):295–305. [PubMed: 9554746]

Table 1

Characteristics and cancer outcomes for all Parkinson disease (PD) patients, as well as stratified by LRRK2 G2019S mutation carrier status

Characteristics	Total (N=1,549)		LRRK2 Mutation Carriers (N=177)		LRRK2 Mutation Non-Carriers (N=1,372)		P-value*
Age at exam (y); mean SD	70.9	10.8	69.9	11.1	71.0	10.8	0.21
Age at PD diagnosis (y); mean SD	61.9	11.7	57.8	11.8	62.4	11.6	<0.0001
Duration of PD (y); mean SD	9.8	7.0	11.2	8.7	9.5	6.7	0.05
Study Center; n %							<0.0001
Israel (Tel Aviv, Sheba)	459	29.6	49	27.7	410	29.9	
Israel (Tel Aviv, Sourasky)	140	9.0	68	38.4	72	5.3	
Norway	25	1.6	4	2.3	21	1.5	
Spain (San Sebastian)	762	49.2	25	14.1	737	53.7	
US (Beth Israel, New York City)	163	10.5	31	17.5	132	9.6	
Sex; n %							0.009
Male	869	56.1	83	46.9	786	57.3	
Female	680	43.9	94	53.1	586	42.7	
Ethnicity; n %							<0.0001
Ashkenazi Jews (both parents)	589	38.0	136	76.8	453	33.0	
Sephardic Jews (both parents)	136	8.8	7	3.4	129	9.4	
Other Ethnicity, Caucasian	824	53.2	34	19.2	790	57.6	
Smoking status ascertained; N	304		100		204		0.97
Never smoker; n %	187	61.5	61	61.0	126	61.8	
Former smoker; n %	103	33.9	34	34.0	69	33.8	
Current smoker; n %	14	4.6	5	5.0	9	4.4	
Cancer Outcomes							
All Cancers Combined; n %	250	16.1	40	22.6	210	15.3	0.013

Characteristics	Total (N=1,549)		LRRK2 Mutation Carriers (N=177)		LRRK2 Mutation Non-Carriers (N=1,372)		P-value*
Number of Cancers Reported; n %							0.04
1	223	14.4	32	18.1	191	13.9	
2 or 3	27	1.7	8	4.5	19	1.4	
Age at diagnosis of first cancer§ (y); mean SD	67.5	9.8	62.5	10.8	68.3	9.4	0.023
Skin Cancer (any); n %	49	3.2	10	5.7	39	2.8	0.05
Melanoma; n %	22	1.4	5	2.8	17	1.2	0.09
All Non-Skin Cancers (excluding skin & melanoma)	201	13.0	32	18.1	169	12.3	0.032
Smoking-related cancers †; n %	20	1.3	2	1.1	18	1.3	0.84
Lung cancer; n %	9	0.6	2	1.1	7	0.5	0.31
Bladder cancer; n %	11	0.7	0	-	11	0.8	0.23
Hormone-related cancer‡; n %	97	6.3	20	11.3	77	5.6	0.003
Breast Cancer; n %							
Breast Cancer (women)	39	5.7	12	12.8	27	4.6	0.002
Breast Cancer (men)	2	0.2	1	1.2	1	0.13	0.05
Ovarian Cancer; n %	10	1.5	0	-	10	1.7	0.2
Prostate Cancer; n %	48	5.5	8	9.6	40	5.1	0.08
Colon Cancer; n %	35	2.3	6	3.4	29	2.1	0.28
Kidney Cancer; N %	10	0.7	2	1.1	8	0.6	0.39
Hematologic/Lymphoma; n %	17	1.1	1	0.6	16	1.2	0.47
Meningioma; n %	13	0.8	3	1.7	10	0.7	0.19

* P-values from t-tests (continuous) and chi-square tests (categorical variables) comparing LRRK2 mutation carriers vs. non-carriers

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

† Smoking-related cancers include lung and bladder cancers. Only one patient reported a cancer of the oropharynx, which was not included due to lack of HPV-status and thus potential confounding by HPV

‡ Hormone-related cancers include prostate cancer in men and breast and ovarian cancers in women (there were no endometrial/gynecologic cancers reported); percentages of gender-specific hormonal cancers are based on the number of men and women

Table 2

Associations of LRRK2 G2019S mutation with overall cancer and various cancer types among Parkinson patients

Cancer Outcomes	Non-Carriers (n=1,372)		Carriers (n=177)		Model 1*			Model 2†			Model 3‡		
	N	%	N	%	OR*	95% CI	p	OR†	95% CI	p	OR‡	95% CI	p
No	1,162	89.5	137	10.5	1	-		1	-		1	-	
All Cancers combined	210	84.0	40	16.0	1.49	0.99 – 2.24	0.057	1.49	0.99 – 2.24	0.057	1.37	0.92 – 2.04	0.13
Skin Cancer	39	79.6	10	20.4	**2.11**	**1.03 – 4.31**	**0.04**	1.11	0.51 – 2.40	0.80	1.03	0.48 – 2.22	0.93
Melanoma	17	77.3	5	22.7	2.36	0.86 – 6.50	0.10	1.95	0.67 – 5.72	0.22	1.62	0.56 – 4.67	0.37
No	1,203	89.2	145	10.8	1	-		1	-		1	-	
All Non-Skin Cancers	169	84.1	32	15.9	**1.57**	**1.04 – 2.38**	**0.034**	**1.57**	**1.04 – 2.38**	**0.034**	**1.62**	**1.04 – 2.52**	**0.031**
Smoking-related cancers													
No	1,354	88.5	175	11.5	1	-		1	-		1		
Yes	18	90.0	2	10.0	0.84	0.19 – 3.64	0.81	1.04	0.22 – 4.94	0.96	1.20	0.25 – 5.76	0.82
Lung Cancer	7	77.8	2	22.2	2.15	0.44 – 10.46	0.34	2.40	0.43 – 13.45	0.32	2.40	0.42 – 13.82	0.33
Bladder Cancer	11	100	0	-	-	-	-	-	-	-	-	-	-
Hormone-related cancers§													
No	1,295	89.2	157	10.8	1	-		1	-		1	-	
Yes	77	79.4	20	20.6	**2.06**	**1.22 – 3.47**	**0.007**	**2.06**	**1.22 – 3.47**	**0.007**	**1.87**	**1.07 – 3.26**	**0.03**
Breast Cancer, women	27	69.2	12	30.8	**2.88**	**1.39 – 5.97**	**0.004**	**2.88**	**1.39 – 5.98**	**0.004**	**2.34**	**1.05 – 5.22**	**0.04**
Ovarian Cancer	10	100	-	-	-	-	-	-	-	-	-	-	-
Prostate Cancer, men	40	83.3	8	16.7	2.05	0.92 – 4.55	0.08	2.05	0.92 – 4.55	0.08	2.21	0.95 – 5.18	0.07
Other Cancer Types													
Colon Cancer	29	82.9	6	17.1	1.68	0.69 – 4.11	0.26	1.68	0.69 – 4.11	0.26	1.92	0.74 – 5.00	0.18

Cancer Outcomes	Non-Carriers (n=1,372)		Carriers (n=177)		Model 1*			Model 2†			Model 3‡		
	N	%	N	%	OR*	95% CI	p	OR†	95% CI	p	OR‡	95% CI	p
Kidney/Renal Cancer	8	80.0	2	20.0	1.93	0.41 – 9.17	0.41	1.93	0.40 – 9.17	0.41	1.93	0.40 – 9.17	0.41
Hematologic/Lymphoma	16	94.1	1	5.9	0.48	0.06 – 3.68	0.48	0.48	0.06 – 3.68	0.48	0.48	0.06 – 3.68	0.48
Meningioma	10	76.9	3	23.1	2.40	0.65 – 8.78	0.19	2.38	0.61 – 9.21	0.21	2.38	0.61 – 9.21	0.21

Percentages represent row percent

*OR and 95% CI for model 1 were adjusted for age at cancer diagnosis (for PD patients diagnosed with cancer) and age at exam (for other PD patients)

†OR and 95% CI for model 2 were estimated using mixed effect models adjusting for age at cancer diagnosis (for PD patients diagnosed with cancer) and age at exam (for other PD patients) as fixed effect, and study center as random effects

‡OR and 95% CI for model 3 were estimated using mixed effect models adjusting for age at cancer diagnosis (for PD patients diagnosed with cancer) and age at exam (for other PD patients) and ethnicity (Ashkenazi Jews vs. other) as fixed effect, and study center as random effect

§Analyses for hormonal cancers were carried out in strata by gender. Bold font represents results that are statistically significant at p<0.05

Table 3

Associations of *LRRK2* G2019S mutation with overall cancer and hormonal cancers, stratified by Ashkenazi Jewish ethnicity

Ashkenazi Jewish (n=589)							
Cancer Outcomes	**Non-Carriers (n=453)**		**Carriers (n=136)**		**Model adjusted for age and study center***		
	N	**%**	**N**	**%**	**OR***	**95% CI**	**p**
No	364	77.5	106	22.5	1	-	
All Cancers combined	89	74.8	30	25.2	1.20	0.74 – 1.94	0.46
No	399	78.1	112	21.9	1	-	
All Non-Skin Cancers	54	69.2	24	30.8	1.59	0.94 – 2.70	0.08
Hormone-related cancers§							
No	423	77.8	121	22.2	1	-	
Yes	30	66.7	15	33.3	1.60	0.80 – 3.18	0.18
Breast Cancer, women	12	57.1	9	42.9	1.77	0.70 – 4.48	0.23
Prostate Cancer, men	13	68.4	6	31.6	2.12	0.77 – 5.81	0.15
Non-Ashkenazi Jewish (n=960)							
Cancer Outcomes	Non-Carriers (n=919)		Carriers (n=41)		Model adjusted for age and study center*		
	N	%	N	%	OR*	95% CI	p
No	798	96.3	31	3.7	1		
All Cancers combined	121	92.4	10	7.6	**2.20**	**1.05 – 4.61**	**0.04**
No	804	96.1	33	3.9	1		
All Non-Skin Cancers	115	93.5	8	6.5	1.74	0.78 – 3.88	0.17
Hormone-related cancers§							

Ashkenazi Jewish (n=589)							
Cancer Outcomes	**Non-Carriers (n=453)**		**Carriers (n=136)**		**Model adjusted for age and study center***		
	N	**%**	**N**	**%**	**OR***	**95% CI**	**p**
No	872	96.0	36	4.0	1	-	
Yes	47	90.4	5	9.6	**2.67**	**0.99 – 7.15**	**0.051**
Breast Cancer, women	15	83.3	3	16.7	**4.65**	**1.21 – 17.93**	**0.03**
Prostate Cancer, men	27	93.1	2	6.9	2.47	0.53 – 11.43	0.25

Percentages represent row percent

*OR and 95% CI were adjusted for age as fixed effect, and study center as random effects

§Analyses for hormonal cancers were carried out in strata by gender. Bold font represents results that are statistically significant at p≤0.05

Table 4

Sensitivity analysis of the influence of study center on association between LRRK2 G2019S mutation and cancer outcomes

Sensitivity Analysis	All Cancers Combined	All Non-Skin Cancers	Hormone-Related Cancers	Breast Cancer (women)	Prostate Cancer (men)
All Study Centers					
OR*	1.49	**1.57**	**2.06**	**2.88**	2.05
95% CI	0.99 – 2.24	**1.04 – 2.38**	**1.22 – 3.47**	**1.39 – 5.98**	0.92 – 4.55
p-value	0.057	**0.034**	**0.007**	**0.004**	0.08
Excluding Sheba / Israel					
OR*	1.59	1.51	**2.27**	**3.39**	2.08
95% CI	0.97 – 2.60	0.92 – 2.47	**1.20 – 4.28**	**1.49 – 7.74**	0.82 – 5.27
p-value	0.06	0.1	**0.012**	**0.004**	0.12
Excluding Sourasky / Israel					
OR*	**1.84**	**2.13**	**2.31**	**2.54**	**3.06**
95% CI	**1.15 – 2.94**	**1.32 – 3.43**	**1.25 – 4.26**	**1.03 – 6.26**	**1.29 – 7.28**
p-value	**0.011**	**0.002**	**0.008**	**0.04**	**0.011**
Excluding Norway					
OR*	1.35	1.44	**1.74**	**2.37**	1.84
95% CI	0.88 – 2.06	0.94 – 2.22	**1.00 – 3.04**	**1.09 – 5.12**	0.79 – 4.27
p-value	0.17	0.09	**0.05**	**0.03**	0.16
Excluding Spain					
OR*	1.4	**1.65**	**2.21**	**2.84**	1.97
95% CI	0.89 – 2.21	**1.03 – 2.65**	**1.15 – 3.92**	**1.24 – 6.46**	0.80 – 4.86
p-value	0.14	**0.04**	**0.016**	**0.013**	0.14
Excluding US (NYC)					
OR*	1.48	1.33	**1.88**	**3.19**	1.56
95% CI	0.95 – 2.28	0.83 – 2.14	**1.02 – 3.45**	**1.40 – 7.27**	0.60 – 4.22
p-value	0.08	0.24	**0.04**	**0.006**	0.35

* ORs and 95% CI presented for this analysis were estimated using mixed effect models adjusting for age as fixed effect, and study center as random effects.

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