MAYO CLINIC

# Parkinson Disease and Melanoma: Confirming and Reexamining an Association

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## Abstract

**Objective:** To examine an association between melanoma and Parkinson disease (PD).

**Patients and Methods:** Phase I: Rochester Epidemiology Project records were used to identify (between January 1, 1976, and December 31, 2013) patients with PD in Olmsted County, Minnesota, with 3 matched controls per case. After review, JMP statistical software with logistic regression analysis was used to assess the risk of preexisting melanoma in patients with PD vs controls. Phase II: All Rochester Epidemiology Project cases of melanoma were identified (between January 1, 1976, and December 31, 2014), with 1 control per case. A Cox proportional hazards model was used to assess the risk of developing PD after the index date in cases vs controls, and Kaplan-Meier analysis was performed to determine the 35-year cumulative risk of PD. A Cox proportional hazards model was used to assess the risk of death from metastatic melanoma in patients with melanoma without PD compared with those with PD.

**Results:** Phase I: Patients with PD had a 3.8-fold increased likelihood of having preexisting melanoma as compared with controls (95% CI, 2.1-6.8; $P<.001$). Phase II: Patients with melanoma had a 4.2-fold increased risk of developing PD (95% CI, 2.0-8.8; $P<.001$). Kaplan-Meier analysis revealed an increased 35-year cumulative risk of PD in patients with melanoma (11.8%) compared with controls (2.6%) ($P<.001$). Patients with melanoma without PD had a 10.5-fold increased relative risk of death from metastatic melanoma compared with patients with melanoma with PD (95% CI, 1.5-72.2) ($P=.02$).

**Conclusion:** There appears to be an association between melanoma and PD. Further study is warranted; but on the basis of these results, physicians may consider counseling patients with melanoma about PD risk and implementing cutaneous and ocular melanoma surveillance in patients with PD.

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There has been much speculation on the relationship between Parkinson disease (PD) and melanoma.[1] Dating back to 1972, there have been numerous reports suggesting that levodopa therapy may be implicated in malignant melanoma.[2-5] This association is plausible because levodopa is an intermediary product involved in melanin synthesis, and it has been shown to increase melanin and melanoma cell growth in plant and human cell studies, respectively.[6-8] Moreover, levodopa has been speculated to accelerate the growth of preexisting malignant melanomas in humans.[9] However, randomized controlled trials and prospective studies have not substantiated these claims, begging the question of whether medical treatment of PD increases the risk of melanoma or if it is mere coincidence.[10-13]

Some have hypothesized that there is an association between melanoma and PD itself, regardless of PD treatment. Indeed, several publications indicate an increased risk of melanoma in patients with PD, ranging from a 2-fold increased risk up to a reported 7-fold increased risk in a recent prospective North American study.[10,14-19] In 1 study, there was actually an increase in the prodromal markers for PD in patients with a history of melanoma.[20] Nevertheless, other work suggests that there is not a strong association between melanoma and PD before treatment with levodopa.[21] Overall, this is a highly controversial and compelling subject that has given much consideration to the need for more rigorous melanoma screening measures in this patient population.

Most of the large studies performed in this area have been done in regard to cutaneous melanoma, with no large studies dedicated to uveal melanoma available on extensive chart review. With regard to the ophthalmologist, there have been a few case reports of choroidal melanoma in patients with PD treated with levodopa as well as 1 case of an eyelid margin melanoma.[4,22,23] Because of the curable nature of melanoma if detected early, this is an important topic about which ophthalmologists, dermatologists, neurologists, oncologists, and general practitioners should all be aware, and there is a need for further investigation in this area.

Furthermore, most previous studies have examined the risk of melanoma in PD cohorts rather than examining the risk of developing PD in melanoma cohorts. However, there have been previous reports that there is an increased occurrence of melanoma before the development of PD.[5] If there is an increased risk of developing PD after melanoma diagnosis, this could be important information with regard to counseling patients in the setting of a melanoma diagnosis and, therefore, also warrants additional study.

The Rochester Epidemiology Project (REP) medical records linkage system provides a large cohort of patients who are all residents of Olmsted County, Minnesota, which allows further investigation of these underaddressed issues. To test our hypothesis that patients with PD have an increased risk of developing cutaneous and choroidal melanoma after PD diagnosis, we reviewed the charts of all available PD cases in the REP database, intending to compare the prevalence of melanoma with that of age- and sex-matched controls. The results from our initial study led to a new hypothesis and review of all available melanoma cases to evaluate the risk of subsequently developing PD in these patients. Finally, we reviewed all Mayo Clinic records for additional cases of concomitant PD and conjunctival or uveal melanoma. The findings of the review of both the PD and melanoma cohorts as well as additional relevant cases from the review of Mayo Clinic records are reported here.

## PATIENTS AND METHODS

This study adheres to the Health Insurance Portability and Accountability Act. This study received institutional review board approval and adhered to the tenets of the Declaration of Helsinki.

This study was designed as a retrospective cohort study using the REP medical records linkage system. The database consists only of residents of Olmsted County and queries yield only those participants who have provided informed consent for research. Medical care of this population is provided primarily by Mayo Clinic and Olmsted Medical Center, but additional small independent clinics also participate in the REP, resulting in the capture of nearly all Olmsted County residents.[24-26] Previous work has shown that this database is not biased toward patients with health conditions that require more frequent monitoring.[27,28]

Previous studies have shown that the REP medical records database has excellent agreement for patient status at last contact, date of last contact, and date of death as compared with manual record abstraction.[29] The REP database was used when possible for these elements of the chart review.

Statistical analysis was carried out using JMP statistical software from SAS Institute (JMP Pro 10.0.0). *P* values of .05 or less were considered statistically significant. When applicable, Shapiro-Wilk tests were used for normality and, when appropriate, means were compared using a 2-tailed *t* test.

### Parkinson Disease Cohort

**Cases.** We hypothesized that there would be a considerably higher incidence of melanoma diagnosed in patients with PD compared with an age- and sex-matched cohort with similar environmental exposures. We suspected that most melanomas in patients with PD would be diagnosed after the PD diagnosis. To test this hypothesis, we found all potential cases of PD between January 1, 1976, and December 31, 2013, by searching the REP database for 33 unique H-ICDA codes and 3 unique *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes. We then narrowed these to only those cases of PD that were diagnosed or confirmed by a neurologist. We included cases of Lewy body dementia (LBD) because it is considered to be a subdivision of the same underlying condition as PD with dementia.[30] We excluded any cases that

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