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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

were not confirmed by a neurologist. We excluded patients with parkinsonism if such cases never met the neurologist criteria for PD or LBD.

Controls. Each case was individually matched by age (±1 year) and sex to 3 referent participants residing in Olmsted County. Controls were free of PD, LBD, parkinsonism, tremor, or any of the H-ICDA and *ICD-9* codes that were used to find potential cases at the index date (date of PD diagnosis in the matched PD case). Controls were selected from a list of all Olmsted County residents provided by the REP database who had recorded contact with a REP-participating provider at least once in the index year or 3 years thereafter.[25]

Controls were selected randomly from the complete list of REP participants meeting criteria. Controls were excluded if they carried any of the 33 unique H-ICDA codes or 3 unique *ICD-9* codes used to generate the case list at any time in their history of follow-up with REP-participating providers. Thus, patients who were free of PD at the index date but later developed PD that was recorded by a REP-participating provider were excluded from the control list. The presence of Alzheimer disease or vascular dementia was not an exclusion criterion. On manual review of the control list, 1 duplicate was discovered; the duplicate was removed and replaced with the next random control that met criteria.

Follow-Up and Ascertainment of Melanoma. The medical records of participants were examined both before and after the index date for cases of melanoma with the aid of the REP system and manual record review. To ascertain cases of melanoma, we searched the REP database for H-ICDA and *ICD-9* codes for melanoma and personal history of melanoma. All potential identified cases underwent manual chart review by a single physician to identify true melanoma cases. Cutaneous melanomas were considered true only if confirmatory pathology records were available, and cases of atypical cutaneous nevi without confirmed melanoma diagnosis by pathology were considered negative for melanoma. Uveal melanomas were considered true only if ophthalmology records confirmed the diagnosis. There were no cases of atypical choroidal nevi or conjunctival melanoma discovered.

Statistical Analyses. Logistic regression analysis was used to determine whether patients with PD were more likely to have a history of melanoma than did controls. Patients who developed melanoma after the index date or after PD diagnosis were censored in this analysis. Average age at melanoma diagnosis and average years of pre- and postindex date follow-up were calculated as mean ± SD for both PD cases and controls.

Melanoma Cohort

Cases. The results from the PD cohort study caused us to alter our hypothesis about the relationship between PD and melanoma. We hypothesized that patients with a history of melanoma would be more likely to develop PD after their melanoma diagnosis than would age- and sex-matched controls with similar environmental exposures. To test this new hypothesis, we found all potential cases of melanoma between January 1, 1976, and December 31, 2014, by searching the REP database for 61 unique H-ICDA codes and 32 unique *ICD-9* codes. All potential identified cases underwent manual chart review by a single physician to identify true melanoma cases. Cutaneous and conjunctival melanomas were confirmed by pathology records. Uveal melanomas required confirmatory ophthalmology records. No cases of atypical choroidal nevi were encountered on review, and cases of atypical cutaneous nevi without confirmed melanoma diagnosis by pathology were considered negative for melanoma.

Controls. Each case was individually matched by age (±1 year) and sex to 1 referent participant residing in Olmsted County selected randomly from the REP database in the same fashion as for the PD cohort. Controls were free of melanoma, atypical nevi, or any of the H-ICDA and *ICD-9* codes that were used to find potential cases at the index date (date of melanoma diagnosis in the matched melanoma case) or at any time in their history of follow-up with REP-participating providers.

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Follow-Up and Ascertainment of PD. The medical records of participants were examined both before and after the index date for cases of PD with the aid of the REP system and manual record review. To ascertain cases of PD, we searched the REP database for H-ICDA and *ICD-9* codes for PD and LBD. All potential identified cases underwent manual chart review by a single physician to identify only those PD and LBD cases with a neurologist-confirmed diagnosis. Finally, smoking status was recorded when available for patients in the melanoma cohort and their corresponding controls; the number of patients deceased in each group was recorded; and cause of death was recorded when applicable for patients in the melanoma cohort.

Statistical Analyses. Average age at PD diagnosis and average years of pre- and postindex date follow-up were calculated as mean ± SD for both melanoma cases and controls. In patients with available information, the percentage of patients who had ever smoked was determined for patients in the melanoma cohort and their corresponding controls. A 2-tailed *t* test was used to determine whether any considerable difference existed in the percentage of ever-smokers in the melanoma cohort compared with controls.

A Cox proportional hazards model was used to determine the risk of postindex date PD in patients with melanoma compared with controls. A Kaplan-Meier analysis and a log-rank test were performed to determine whether there was a difference in the 35-year cumulative risk of developing PD in the melanoma cohort compared with controls. Patients who developed PD before melanoma diagnosis in the melanoma cohort or before the index date in the control group were censored in these analyses; and for the Kaplan-Meier analysis, the remaining patients were censored if and when their time of most recent follow-up was reached. A Cox proportional hazards model was used to assess the risk of death from metastatic melanoma in patients with melanoma with and without PD.

The results of this phase of the study were expected to be consistent with and complementary to the results of PD cohort analysis, as there was significant overlap with inclusion of patients of interest (those with both melanoma and PD).

Qualitative Case Review

A further qualitative case review was undertaken to specifically target patients relevant to the ophthalmologist. The Mayo Clinic electronic medical record system was reviewed from January 1, 1996, through August 31, 2014, for patients carrying diagnoses for both PD and uveal or conjunctival melanoma using *ICD-9* codes. All cases found were manually reviewed for neurologist-confirmed PD and ophthalmologist-confirmed uveal melanoma or pathologist-confirmed conjunctival melanoma.

RESULTS

Parkinson Disease Cohort

Patient Demographic Characteristics. There were 974 patients diagnosed with PD between January 1, 1976, and December 31, 2013, in the REP database, all of whom were white. Of the 974, 58% (561) were men. The average age of PD diagnosis was 75±10 years and ranged from 42 to 98 years. All patients with PD were treated with carbidopa-levodopa beginning in the index year, and treatment continued until most recent follow-up or death. A referent cohort of 2922 white patients ranged from ages 42 to 98 years at the index date (date of matched PD diagnosis).

The average number of years for which records were available before the index date was 42±18 years for patients with PD and 36±18 years for referent participants. The average follow-up after the index date was 5±5 years for patients with PD and 12±8 years for referent participants.

Risk of Melanoma. There were 32 total cases of confirmed melanoma in the PD cohort. Of these, 3 were choroidal melanomas and 29 were cutaneous melanomas. There were 63 total cases of confirmed melanoma in the group of referent participants; one of these was choroidal melanoma, whereas the remainder were cutaneous. There were no cases of ciliary body, iris, or conjunctival melanoma in either group. There were no cases of melanoma involving the eyelid. All cases of choroidal

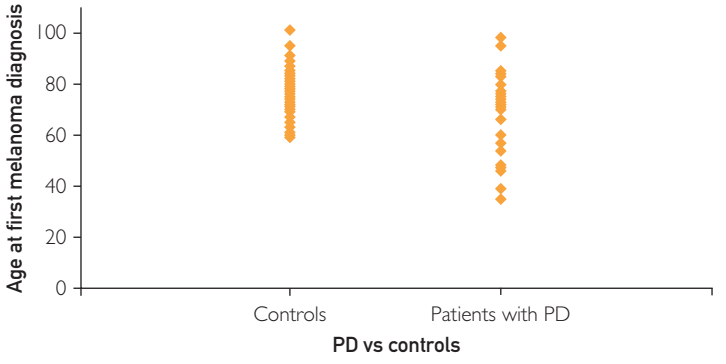

FIGURE 1. Age of melanoma diagnosis in patients with Parkinson disease (PD) compared with controls. A scatterplot of the age at first melanoma diagnosis is shown for both controls and patients with PD. Patients with PD who developed melanoma was found to be 7 years younger (70±15 years) than those in the control group (77±8 years). This was statistically significant (*P*=.004).

melanoma in both PD and control groups were diagnosed before the index date, and all these cases were in male patients.

In the PD group, only 6 melanomas (all cutaneous) were diagnosed after PD diagnosis. The remainder were diagnosed before patients received any PD treatment, leaving 26 total preindex date melanomas (2.7% of the total PD cohort). In the control group, 21 (33%) of the total 63 melanomas were diagnosed before the index date, corresponding to only 0.7% of the control group. Examining preindex date melanomas alone, logistic regression analysis revealed a 3.8-fold increased likelihood of patients with PD having a history of melanoma compared with controls (95% CI, 2.1-6.8; *P*<.001). Because there were only 6 postindex date melanomas in the PD group, the data did not lend itself to Kaplan-Meier analysis with good reliability.

Before proceeding with *t* test comparisons, Shapiro-Wilk tests were performed on subset data for age of melanoma diagnosis in both case and control groups to test normality (*P*=.12 and *P*=.29, respectively). Patients with PD who developed melanoma were found to be an average of 7 years younger (70±15 years) than those in the control group (77±8 years). This was statistically significant (*P*=.004) (Figure 1).

Melanoma Cohort

Patient Demographic Characteristics. There were 1544 patients diagnosed with melanoma between January 1, 1976, and December 31, 2014, in the REP database: 1540 whites, 2 Asians, 1 Pacific Islander, and 1 American Indian. Of the 1544, 52% (810) were male patients. The average age at melanoma diagnosis was 57±18 years and ranged from 10 to 101 years. Of the 1544 patients with melanoma, 1497 had cutaneous melanoma. Four of these cases involved the eyelid, and all but 1 patient who refused treatment underwent primary surgical excision. Of the remaining 47 patients, 40 had choroidal melanoma. Documentation of treatment was not found for all patients; but of the available information, 16 patients with choroidal melanoma underwent plaque brachytherapy, 10 had enucleation, 2 had transpupillary thermotherapy alone, 1 had cryotherapy alone, and 1 underwent exenteration for extrascleral extension. Finally, there were 4 patients with conjunctival melanoma who underwent surgical excision, 2 patients with ciliochoroidal melanoma for whom documentation of treatment was not found, and 1 patient with iris melanoma who underwent plaque brachytherapy.

A referent cohort of 1544 patients (of whom 1542 were white and 2 were Asian) ranged from ages 10 to 101 years at the index date (date of matched melanoma diagnosis). The average number of years for which records were available before the index date was 31±19 years for patients with melanoma and 44±13 years for referent participants. The average years of postindex date follow-up was 7±8 for patients with melanoma and 8±10 for referent participants.

Information on smoking status was available for 88% of the patients in the melanoma cohort and 85% of the controls. Of the patients with available data, 36% of the patients with melanoma were prior or current smokers and 40% of the controls were ever-smokers. This difference was not statistically significant (*P*=.67).

Risk of PD. There were 43 total cases of confirmed PD in the melanoma cohort, all of whom were white. Of these, 3 were in patients with choroidal melanomas and 40 were in patients with cutaneous melanomas, none of

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which involved the eyelid. The 3 choroidal patients with melanoma were men, and 28 of the cutaneous patients with melanoma were men. There were 14 total cases of confirmed PD in the group of referent participants, all of whom were white and 9 of whom were male patients.

Before *t* test comparisons, Shapiro-Wilk tests were performed on subset data for age of PD diagnosis in both case and control groups to test normality (P=.08 and P=.09, respectively). Patients with melanoma were found to develop PD at about the same age (77±11 years) as patients without melanoma (78±11 years) (P=.78).

All 3 cases of choroidal melanoma developed PD after the index date, and these were the same 3 male cases found in the original PD cohort analysis. Melanoma treatment information was available for only 1 of the 3 cases, and he was reported to have had plaque brachytherapy. In the melanoma cohort, only 6 cases of PD were diagnosed before melanoma diagnosis (0.4%), and these were the same 6 patients with cutaneous melanoma described in the PD cohort. The remaining cases of PD were diagnosed after the initial diagnosis and treatment of melanoma; these patients, on average, developed PD 11±12 years after the diagnosis of melanoma. However, PD was found to develop as late as 51 years after melanoma diagnosis in this study. In the control group, 5 of the total 14 cases of PD were diagnosed before the index date (0.3%) and the remaining 9 cases developed PD an average of 11±7 years after the index date. The percentage of preindex date PD diagnoses was not statistically significant between the case and control groups (P=.76), and these patients were censored from further analysis.

Using a Cox proportional hazards model, the melanoma cohort was found to have a 4.2-fold increased risk of developing PD after the index date compared with controls (95% CI, 2.0-8.8; P<.001). A Kaplan-Meier analysis and a log-rank test were performed to further examine the risk of developing PD after melanoma diagnosis compared with controls without melanoma. Patients in the melanoma cohort were found to have an 11.8% (95% CI, 4.0%-19.6%) 35-year cumulative risk of developing PD compared with a 2.6% (95% CI, 0.4%-4.8%) 35-year cumulative risk in controls, and this difference was statistically significant (P< .001) (Figure 2).

Deceased Patients. At the time of record review, there were 345 deceased patients (22%) in the melanoma cohort, 316 without PD and 29 with PD; there were 322 deceased patients (21%) in the control group, 313 without PD and 9 with PD. On further examination of the 345 deceased patients in the melanoma cohort, it was found that the cause of death for 115 of the 345 (33%) was metastatic melanoma and only 1 of those 115 had PD; that patient received a diagnosis of cutaneous melanoma of the leg. Thus, in the melanoma cohort, patients without PD had a 10.5-fold increased risk of death from metastatic melanoma compared with patients with PD (95% CI, 1.5-72.2; P=.02).

Qualitative Case Review

An additional 10 patients (5 female patients) with PD were found to have choroidal

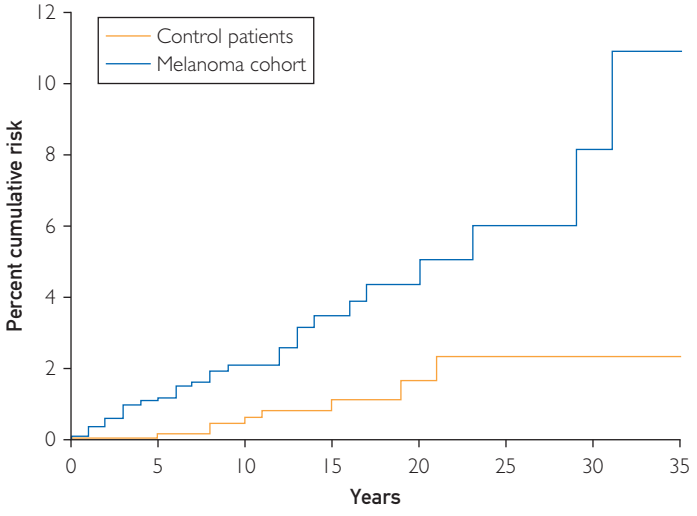

FIGURE 2. Cumulative risk of developing Parkinson disease (PD) in patients with melanoma compared with age- and sex-matched controls. A failure plot derived using Kaplan-Meier analysis is shown for both patients with melanoma and their corresponding controls. Patients were censored in the analysis if they carried a diagnosis of PD before melanoma diagnosis or before the index date. Patients were censored throughout the analysis if and when their time of last follow-up was reached. The 35-year cumulative risk of developing PD was approximately 11.8% in patients with a history of melanoma compared with only 2.6% in controls. This difference was found to be statistically significant using the log-rank test (P<.001).

melanoma (1 ciliochoroidal) on review of the Mayo Clinic electronic records. There was also 1 case of ciliary body melanoma and 1 case of conjunctival melanoma found in male patients with PD on chart review. Three of the patients with choroidal melanoma were diagnosed after PD diagnosis and after treatment with carbidopa-levodopa had begun. However, the remainder were diagnosed before PD diagnosis and before any PD treatment.

DISCUSSION

This retrospective cohort study provides supportive evidence for an association between PD and melanoma, and the REP database provides an ideal platform for the study, ensuring that all participants reside in the same geographic environment.

Parkinson Disease Cohort

A review of the PD cohort reported an increased risk of preexisting melanoma in patients with PD. The 3.8-fold increased risk has important clinical implications. Melanoma is a curable disease if detected and treated early. Thus, a compelling argument can be made for more aggressive melanoma-screening protocols in patients with PD.

Interestingly, most melanomas diagnosed in the PD group were diagnosed before the diagnosis or treatment of PD. Only 6 melanomas were diagnosed after PD treatment had begun, and those were all cutaneous melanomas. This is in contrast to the control group in which most (42 of 63 [67%]) melanomas were diagnosed after the index date. This makes a compelling case for a genetic association between melanoma and PD and argues against any role of levodopa in increasing melanoma risk, which is consistent with results previously found by Olsen et al.[19] However, it is important to take into consideration that the control group had a longer duration of follow-up than did patients with PD by an average of 7 years. It is possible that this accounts for some of the difference in the number of postindex date melanoma cases between the PD and control groups. If patients with PD had longer follow-up, it is likely that more cases of melanoma would have been found.

In this study, patients with PD who developed melanoma were found to be 7 years younger at first melanoma diagnosis than those in the control group. Combining this knowledge with the fact that most melanomas in patients with PD were diagnosed before PD diagnosis in this study, it is clear that waiting for a PD diagnosis to begin aggressive screening measures for most of these patients would be too late. Thus, a combination of family history of PD and/or melanoma along with environmental risk factors may help guide screening. Additional risk factors associated with PD include rural living, pesticide use (controversial), head trauma, depression, and family history of tremor.[31,32] Certain genetic variations, including alpha-synuclein, parkin, and leucine rich repeat kinase 2 sequence variations, are also associated with development of PD and PD-associated dementia.[33,34] It could be that some of the environmental or genetic risk factors for PD are also risk factors for melanoma; and as it stands, fair skin color and male sex are known risk factors for both diseases.[35-38] Moreover, a recent study has documented an increase in the incidence of PD between 1976 and 2005, presumably related to a change in environmental risk factors,[39] and there has been an increasing incidence of melanoma[40,41] as well. Still, it remains unclear exactly how we might use these other risk factors to determine the necessity of melanoma screening for any given patient. Notably, smoking is not a risk factor for melanoma and was, therefore, not examined in this portion of the study.[42,43]

Melanoma Cohort

The melanoma cohort was collected and reviewed about a year after the original study of the PD cohort. This allowed time for an additional 11 patients with previous melanoma diagnoses to develop PD. These 11, who all had an existing diagnosis of cutaneous melanoma at the time of their PD diagnosis, were added to the 32 examined in the original PD cohort.

Because all but 6 patients developed PD after a preexisting melanoma diagnosis, the melanoma cohort lent itself to Kaplan-Meier analysis, which revealed a statistically significant difference in the 35-year cumulative risk of developing PD in patients with melanoma (11.8%) compared with controls (2.6%). This was complementary to the 4.2-fold

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increased risk of postindex date PD found in the melanoma cohort using a Cox proportional hazards model. Given this information, it actually brings up an interesting thought that the physicians diagnosing patients with melanoma may need to consider counseling their patients about an increased risk of developing PD an average of 11 years down the road.

Smoking status was examined in the melanoma cohort and their corresponding controls because patients who have ever smoked have a known 2-fold decreased risk of developing PD.[44] There was no marked difference in the number of ever-smokers in the melanoma cohort compared with controls, so we do not suspect that this was a confounding factor.

As a point of interest, the cause of death of patients in the melanoma cohort was also examined. Of patients who were deceased at the time of record review, only 1 of the 29 patients with PD died of metastatic melanoma compared with 114 deaths from metastatic melanoma in the 316 patients without PD. This translated to a 10.5-fold increased risk of death from metastatic melanoma in patients without PD in the setting of a known melanoma diagnosis. This suggests that somehow PD may be a protective factor when considering the risk of metastatic melanoma, but it is also possible that there is an underlying immune reaction that both suppresses development of metastatic melanoma and causes PD. It is known that patients with PD have inadequate innate immune responses, increased markers of adaptive immunity, and disruption of the blood-brain barrier.[45] This makes a common underlying immunologic association between PD and melanoma plausible.

Qualitative Case Review

The additional 11 cases of uveal melanoma and 1 case of conjunctival melanoma found in patients with PD on qualitative review of the Mayo Clinic electronic records further compel the ophthalmologist to be on heightened alert in terms of both screening patients with PD for melanoma and potentially counseling patients diagnosed with uveal and conjunctival melanoma that they may be at increased risk of PD. Furthermore, half (5 of 10) the choroidal melanoma cases were female patients in the qualitative case review, which suggests that a relationship between PD and uveal melanoma is not unique to male patients despite the fact that all 3 patients with concomitant PD and uveal melanoma diagnoses from the REP database were male patients.

Study Limitations

As with all retrospective reviews, this study has its limitations. Detailed information was not available on a large enough proportion of participants to adequately assess differences in environmental risk factors between the case and control groups. However, all patients were taken from the REP database, meaning that all were residents of Olmsted County. This allows some degree of uniformity with regard to environmental exposures. Moreover, use of the REP database limits referral bias that can often be found with studies performed at large academic institutions while ensuring good capture of all patients with PD and melanoma diagnoses residing in Olmsted County. However, one must still consider that patients diagnosed with cancer are more likely to have regular physician contact, which could possibly lead to an increased rate or earlier diagnosis of PD in patients with a cancer history. Finally, there were limitations on the number of participants available for review in this study because of the relatively small geographic region that was chosen. Thus, it was not possible to perform reliable statistical analysis of subgroups, such as cutaneous or choroidal melanomas alone, nor was it possible to reliably perform Kaplan-Meier analysis in phase I of this study.

Recommendations and Future Directions

The results of this study provide supportive evidence for an association between PD and melanoma and discourage acceptance of previous suggestions that levodopa is the root cause of this link. It is more likely that there are common environmental, genetic, or immunologic abnormalities underlying both conditions in these patients, but future research is necessary to confirm and better characterize the underlying cause of this relationship. After the underlying cause of the relationship between melanoma and PD is better understood, more definitive recommendations can be made about the level of rigor and frequency of melanoma screening required in patients

with PD as well as the likelihood that a given patient with melanoma will develop PD in the future. For now, because of the apparent increase in incidence of both diseases and their reciprocal relationships, it is important for physicians to be vigilant for 1 disease in the context of the other.[39-41]

CONCLUSION

The association between PD and melanoma holds importance to a wide array of health care providers, including general practitioners, dermatologists, neurologists, ophthalmologists, and oncologists. Future research will provide further insight into the cause of this relationship as well as necessary screening or patient counseling measures that should be implemented.

Abbreviations and Acronyms: **H-ICDA** = *Hospital-International Classification of Diseases Adapted*; ***ICD-9*** = *International Classification of Diseases, Ninth Revision*; **LBD** = Lewy body dementia; **PD** = Parkinson disease; **REP** = Rochester Epidemiology Project

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