Meta-analysis of the relationship between Parkinson disease and melanoma

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ABSTRACT

Objective: To assess the epidemiologic evidence on melanoma in relation to Parkinson disease (PD) via systematic review and meta-analysis.

Methods: Epidemiologic studies on melanoma and PD were searched using PubMed, Web of Science, Scopus, and Embase (1965 through June 2010). Eligible studies were those that reported risk estimates of melanoma among patients with PD or vice versa. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using random-effects models.

Results: We identified 12 eligible publications on melanoma and PD: 8 had fewer than 10 cases with both PD and melanoma, and 7 provided gender-specific results. The pooled OR was 2.11 (95% CI 1.26–3.54) overall, 2.04 (1.55–2.69) for men, and 1.52 (0.85–2.75) for women. Analyses by temporal relationship found that melanoma occurrence was significantly higher after the diagnosis of PD (OR 3.61, 95% CI 1.49–8.77), but not before PD diagnosis (OR 1.07, 95% CI 0.62–1.84). Further analyses revealed that the lack of significance in the latter analysis was due to one study, which when excluded resulted in a significant association (OR 1.44, 95% CI 1.06–1.96). We also analyzed nonmelanoma skin cancers in relation to PD and found no significant relationship (OR 1.11, 95% CI 0.94–1.30).

Conclusions: Collective epidemiologic evidence supports an association of PD with melanoma. Further research is needed to examine the nature and mechanisms of this relationship. *Neurology*®

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GLOSSARY

CI = confidence interval; MeSH = medical subject heading; OR = odds ratio; PD = Parkinson disease; RR = relative risk; SIR/SER = standardized incidence/event ratio.

Accumulating epidemiologic evidence suggests a low occurrence of most cancer types in patients with Parkinson disease (PD).¹ Intriguingly, melanoma is among the few cancer types that are more likely to occur among patients with PD.^{2,3} A link between melanoma and PD was first suspected following a case report of recurrent malignant melanoma in a patient with PD treated with levodopa.⁴ Since then, a number of case reports have suggested that levodopa therapy increased the risk of melanoma. Reviews of these case reports have concluded, however, that the relationship between levodopa therapy and melanoma was “coincidental rather than causal.”⁴

Although suspicions surrounding levodopa therapy and increased risk of melanoma were largely dismissed, findings from recent clinical and epidemiologic studies increasingly suggest that PD is associated with a higher risk of melanoma and vice versa. The evidence from these studies, however, is not conclusive. Both malignant melanoma and PD are rare, and most available studies had fewer than 10 cases with both diseases occurring in the same individual, thus reducing the statistical power to adequately analyze the relationship. In addition, variations in study design, disease identification, and other methodologic limitations further weaken the ability of individual studies to draw a solid conclusion. We therefore conducted a system-

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atic review and meta-analysis of published literature to provide a quantitative assessment of current epidemiologic evidence on melanoma in relation to PD. We also evaluated whether the association varied by the temporal relationship between the 2 conditions or by gender, and the relationship between non-melanoma skin cancers and PD.

METHODS **Systematic search and study selection.** A literature search on melanoma and PD was performed by library staff at the National Institute of Environmental Health Sciences in June 2010. They searched the online databases for relevant studies published between 1965 and June 2010 in the order of PubMed, Web of Science, Scopus, and Embase. A combination of medical subject heading (MeSH) terms and text terms were used to perform the literature review. MeSH terms included PD, Melanoma, Skin Neoplasms, "Carcinoma, Basal Cell," "Carcinoma, Squamous Cell," and "Keratinosis, Actinic." Appropriate variations of MeSH terms were used as text terms including Parkinson disease, Parkinson's disease, Parkinson's disease, melanoma*, skin neoplasm*, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, skin cancer*. The search strategy was optimized for each database taking into consideration differences in search syntax. Restrictions were made to literature published in English and observational epidemiologic studies involving humans. Two of the coauthors independently evaluated the study titles and abstracts. Reference lists of pertinent publications and reviews were hand-searched to identify additional studies. Eligible studies for inclusion in the meta-analysis were original publications that reported a measure of association (i.e., an odds ratio [OR], relative risk [RR], or standardized incidence/event ratio [SIR/SER]), with 95% confidence intervals (CIs), for the association between PD and melanoma. Disagreements in the study selection were discussed among the coauthors until consensus was reached.

A total of 118 potential articles were identified: 86 from PubMed, 26 from Web of Science, and 6 from Scopus. Of these, we excluded 108 publications that failed to meet the inclusion criteria: 77 articles were excluded because of a lack of direct relevance or overlapped data, 5 were case reports, 2 were mortality data only, 7 were review articles, and 17 were meeting abstracts. Four articles⁵⁻⁸ examined the relationship between skin cancers and PD using similar data from the Danish National Hospital Register; however, we included only the two^{6,7} that provided the most comprehensive data. During the preparation of the current meta-analysis, we noted that 2 additional articles^{9,10} were published online and met our inclusion criteria. Thus, a total of 12 publications were included in the meta-analysis for melanoma and PD. Five of these 12 publications also provided data on nonmelanoma skin cancers and PD; we included them in our secondary analysis on nonmelanoma skin cancers in relation to PD, along with 2 additional publications^{11,12} that provided data only on nonmelanoma skin cancers.

Data extraction and classification. From each study included in the meta-analysis, we extracted and recorded the following information: name of first author, publication year, study design, sample size, location of the study, approach to PD case identification, source of ascertainment for melanoma and other skin cancers, risk estimates with corresponding 95% CIs, and other relevant study characteristics. Attempts were made to con-

tact authors to obtain gender-specific ORs and 95% CIs if they were not provided in the original publication.

Data extracted from selected studies were classified into 3 predefined categories according to the way they were reported in the original publications: occurrence of melanoma following PD diagnosis, occurrence of melanoma preceding PD diagnosis, or co-occurrence of PD and melanoma (cross-sectional studies). Two articles^{9,13} reported results on melanoma occurrence both before and after PD diagnosis in the same publication; the two analyses described in each of these two articles were treated as separate studies in the meta-analysis. Therefore, we extracted data from a total of 14 studies (described in 12 publications) for the analyses on melanoma and PD. The secondary analysis on nonmelanoma skin cancers and PD included data extracted from 7 publications.

Statistical analysis. Under the assumption that both melanoma and PD are rare diseases, we made no distinction between varying measures of association (SIR/SER, OR, or RR) reported in different studies and treated them equally in our pooled analyses. We report all results as OR for simplicity. Summary estimates with their corresponding 95% CIs were quantified using the inverse variance method of the DerSimonian and Laird random-effects models.¹⁴ Heterogeneity across studies was assessed using Cochran *Q* and *I*² statistics.¹⁵ Sensitivity analyses and metaregression were conducted to evaluate sources of heterogeneity both in the overall pooled estimate as well as within the subgroups. We assessed publication bias graphically using a funnel plot and quantitatively using the Begg rank correlation test and the Egger regression asymmetry test.¹⁶ All analyses were performed using STATA, version 10.1 (StataCorp, College Station, TX).

RESULTS **Study characteristics.** Characteristics of the 14 eligible studies on melanoma and PD and 2 additional studies on nonmelanoma skin cancers and PD are presented in table e-1 on the *Neurology*® Web site at www.neurology.org. Among the 14 studies on melanoma and PD, 6 were case-control studies,^{6,9,17-19} 7 were cohort studies^{7,10,13,20-22} or nested case-control studies,^{17,18} and one was a cross-sectional study.²³ Only 2^{21,23} of the 14 studies were explicitly designed to assess the relationship between melanoma and PD, whereas others assessed melanoma as part of their analyses on PD and other site-specific cancers or medical conditions of interest. In these studies, PD cases were identified from hospitalization records,^{6,7,13} computerized medical records,^{9,18,20} self-report,^{17,22} or clinical studies on PD.^{10,19,21,23} Ascertainties of melanoma and nonmelanoma skin cancers in these studies were based on cancer registry,^{6,7,9} medical records,^{17,18,20,22} self-reports,¹⁹ hospitalization records,¹³ clinical trial records,²¹ or examinations by a dermatologist.^{10,23} All studies were conducted in North America or among European populations and the number of individuals with both melanoma and PD ranged from 0 to 46 across studies; many studies had less than 10.

Overall association between melanoma and PD. Thirteen of the 14 studies that examined melanoma in

Figure 1 Association between melanoma and Parkinson disease (PD) according to temporal relationship

Subtotal = pooled odds ratios (ORs) within each subcategory. Overall = pooled OR for all studies. Squares indicate study-specific ORs; error bars indicate 95% confidence intervals (CIs); diamonds indicate ORs and 95% CIs from pooled analyses. One study¹³ that evaluated the occurrence of melanoma after PD diagnosis was excluded because no cases were observed.

relation to PD were included in the meta-analysis. We excluded one study¹³ with zero observed melanoma cases compared with an expected 3.7 cases following PD diagnosis because a risk estimate could not be calculated. Although mostly not statistically significant on their own, a consistent pattern of higher melanoma occurrence among patients with PD and vice versa was observed across all but one study (figure 1). The overall pooled OR was 2.11 (95% CI 1.26–3.54); there was, however, a significant heterogeneity across studies ($I^2 = 85.4\%$, Q statistic $p < 0.001$). A similar degree of heterogeneity was also observed when study type was included in the meta-regression ($I^2 = 83.8\%$), even though this variable had no statistically significant effect on the pooled OR ($p = 0.13$). We examined the source of this heterogeneity by excluding the study that reported the highest OR (OR 20.90).¹⁰ Excluding this study from the analysis reduced the pooled OR to 1.62 (95% CI 1.17–2.24) and the degree of heterogeneity also reduced by nearly 30% ($I^2 = 55.6\%$, Q statistic $p = 0.01$). When we further excluded the only study¹³ that reported an OR of less than 1 (OR

0.50), the pooled OR appeared significantly stronger (OR 1.80, 95% CI 1.50–2.16) and heterogeneity across studies was completely eliminated ($I^2 < 0.1\%$, Q statistic $p = 0.614$).

Occurrence of melanoma following PD diagnosis. Six studies examined the occurrence of melanoma after PD diagnosis. Compared with individuals without PD, a consistent increased risk of melanoma was observed among patients with PD across all studies (figure 1), with a summary OR of 3.61 (95% CI 1.49–8.77). We noted significant heterogeneity across the studies ($I^2 = 89.6\%$, Q statistic $p < 0.001$). Sensitivity analysis showed that most of this heterogeneity was contributed by one recent study.¹⁰ After excluding this study, the summary OR was 2.15 (95% CI 1.55–2.99), with a nonsignificant heterogeneity of 16% across the remaining studies (Q statistic $p = 0.312$).

Occurrence of melanoma preceding PD diagnosis. Six studies examined the occurrence of melanoma before PD diagnosis. A consistent increase in melanoma occurrence among patients with PD was observed across all studies with one exception.¹³ The pooled

Figure 2 Association between melanoma and Parkinson disease (PD) by gender

Subtotal = pooled odds ratios (ORs) within each gender group. Overall = pooled OR for all studies where gender-specific data were available. Squares indicate study-specific ORs; error bars indicate 95% confidence intervals (CIs); diamonds indicate ORs and 95% CIs from pooled analyses. In men, reference 9 provided data separately for melanoma before and after PD diagnosis.

OR for this subgroup was 1.07 (95% CI 0.62–1.84) with evidence of moderate heterogeneity ($I^2 = 49.3\%$, Q statistic $p = 0.079$). The heterogeneity was entirely due to a single study,¹³ which when excluded completely eliminated the heterogeneity ($I^2 = 0\%$, Q statistic $p = 0.999$) and showed melanoma occurrence was 1.44 (95% CI 1.06–1.96) times higher among patients with PD.

Co-occurrence of melanoma and PD. Only one study examined the cross-sectional relationship between melanoma and PD.²³ Compared with expected prevalence in the age- and sex-matched populations in the US Surveillance Epidemiology and End Results cancer database, the prevalence of malignant melanoma in patients with PD was 1.83-fold higher (95% CI 0.98–3.40).²³

Gender-specific analysis. Compared with men, women have a lower risk for both melanoma²⁴ and PD.²⁵ We therefore performed gender-specific meta-analysis with 8 studies where gender-specific estimates were obtained either from the original publication^{19,20} or from personal contact with the authors^{6,7,9,17,22} (figure 2). Our results showed that the association between melanoma and PD was similar in both men (OR 2.04, 95% CI 1.55–2.69) and

women (OR 1.52, 95% CI 0.85–2.75), although the result was not statistically significant in women. Results of the meta-regression analysis showed that gender had no statistically significant effect on the pooled OR ($p = 0.293$) and explained little of the heterogeneity among studies ($I^2 = 25.4\%$).

Nonmelanoma skin cancers and PD. Eight studies provided information on nonmelanoma skin cancers and PD (figure 3). One of them¹⁹ provided only gender-specific ORs. The directions of the study-specific ORs were variable, with 3^{6,7,11} showing a higher risk with PD, one¹³ showing a lower risk, and others^{12,13,18,19} reporting no statistical difference. The pooled OR for this subgroup was 1.11 (95% CI 0.94–1.30) with evidence of moderate heterogeneity ($I^2 = 69.1\%$, Q statistic $p = 0.001$).

Evaluation for publication bias. Visual inspections of the funnel plot revealed little asymmetry (figure 4), and no significant publication bias was detected from results of the statistical tests (Begg test: $p = 0.855$; Egger test: $p = 0.704$).

DISCUSSION In this meta-analysis of published studies, we confirmed an association between PD

Figure 3 Association between nonmelanoma skin cancers and Parkinson disease (PD)

Overall = pooled odds ratio (OR) for all studies that reported a risk estimate. Squares indicate study-specific ORs; error bars indicate 95% confidence intervals (CIs); diamonds indicate ORs and 95% CIs from pooled analyses. Reference 13 provided data separately for nonmelanoma skin cancers before and after PD diagnosis. Reference 19 provided data separately for men and women.

and a higher occurrence of melanoma. The association was similar in both men and women and appears to be bidirectional. We did not find a significant association between nonmelanoma skin cancers and PD.

Despite the small sample size and exploratory nature of the previous studies, all but one observed a higher occurrence of melanoma among patients with PD or vice versa. The discordant study¹³ contributed a substantial amount of the observed heterogeneity to the meta-analyses. This study evaluated multiple cancer sites simultaneously in relation to multiple neurologic outcomes (motor neuron disease, multiple sclerosis, and PD). In addition to the low occurrence of melanoma, the authors also reported lower occurrences of nearly all cancers among patients with PD, including breast cancer. Unlike most of the other studies, patients with PD in this study were compared to a reference cohort of hospital patients with selected minor illness. However, the information provided in the study was not sufficient to deduce the reasons for its inconsistency with other studies. Excluding this study from the meta-analyses enhanced the consistency of the association between melanoma and PD.

Our study aimed to explore the potential etiologic links between PD and melanoma. We did not include 2 studies^{26,27} that examined PD mortality among people previously diagnosed with melanoma. Our reasoning was that mortality was determined by both incidence and survival, which in addition to the inaccuracy of using death certificates in identifying

Figure 4 Funnel plot of studies on melanoma and Parkinson disease

The log odds ratio (OR) from each study is plotted on the horizontal axis, and standard error (SE) on the vertical axis.

patients with PD would have made our results less interpretable. Nonetheless, the higher PD mortality among patients with melanoma as reported in these 2 studies strengthens the evidence that melanoma and PD are likely to co-occur. Further, a subsequent analysis of the mortality data²⁸ suggests that melanoma chemotherapy cannot explain the higher PD mortality among patients with melanoma.

Most previous studies attempted to examine the temporal relationship between melanoma and PD in both directions. While such analysis may provide insights on how these 2 conditions are connected, these studies often estimated the date of diagnoses based on hospitalization registries or electronic medical records and therefore might be inherently inaccurate. Further, the insidious onset and presumed long latency period of both conditions make it difficult to tease out the temporal sequence. The current meta-analyses based on available literature suggest that these 2 conditions tended to co-occur without a clear temporal order.

A number of past observations from case reports have implicated levodopa use in PD treatment as a risk factor for melanoma. Biologically, such an association is plausible as exogenous levodopa may stimulate melanogenesis, leading to an accumulation of melanin and hence melanoma growth.⁴ However, recent epidemiologic studies have refuted a causal association.^{1,4} Opponents have argued that given the relative long latency between initiation and clinical manifestation of melanoma, generally thought to be greater than 10 years and in some cases as long as 40 years,²⁹ it is unlikely that levodopa stimulated the growth of melanoma in a short period of a few months or years, as was often described in earlier case reports. The possibility of higher occurrence of melanoma before a diagnosis of PD, as suggested in our subgroup analysis, further weakens the hypothesis that levodopa use may explain the observed association between melanoma and PD. In addition, preliminary data also suggested higher occurrence of melanoma among patients with PD treated with other medicines, such as rasagiline.^{3,30} Some researchers have raised the concern that the increased melanoma occurrence may be explained by increased medical surveillance of patients with PD.^{1,18,21} However, this suggestion is inconsistent with the fact that Parkinsonian patients are often at lower risk for most of the other types of cancers.¹

Several lines of evidence point to a possible biological link between melanoma and PD. One important piece of evidence is the common embryonic origin of melanocytes and neurons from neural crest cells.³¹ Further, levodopa serves as a substrate for the synthesis of dopamine and melanin,⁴ although the

catalytic enzymes are different. In addition, α -synuclein was detected in most malignant and benign melanocytic lesions but not in nonmelanocytic cutaneous carcinoma and normal skin.³² Adding to these lines of evidence are results from a large prospective study³³ indicating that people with a family history of melanoma had an approximately twofold higher risk of developing PD than those without. These observations lead to the hypothesis that melanoma and PD are biologically linked,³⁴ although the exact mechanisms are yet to be identified.

One potential explanation is that melanoma and PD have shared environmental or genetic risk factors or common pathogenic pathways. For example, smokers have lower risk for PD³⁵ and may also be at lower risk for melanoma³⁶; on the other hand, pesticide exposures have been linked to higher risk for both PD³⁷ and melanoma.³⁸ Results of a recent epidemiologic study linked a known genetic variation of melanoma to higher PD risk.³⁹ The authors of this study reported that lighter hair color was associated with a greater risk of PD. In particular, individuals with red hair or carrying the homozygous recessive melanocortin 1-receptor (MC1R) Arg151Cys variant allele had approximately twofold to threefold higher risk of developing PD compared to those without such traits. Given the important role of pigmentation gene polymorphisms in the development of melanomas, the authors suggested a potential role of pigmentation in explaining, at least partially, the co-occurrence of melanoma and PD.³⁹ Accordingly, a hypothesis was proposed linking pigmentation gene variations, as well as the gene encoding for tyrosinase, to the co-occurrence of PD with melanoma.³⁴ These preliminary genetic links should be further explored in future investigations. Based on available genetic and biochemical evidence, a recent hypothesis posits that the link between melanoma and PD may involve altered activities in the key enzymes of tyrosine metabolism and potential interactions with α -synuclein.⁴⁰ Given the consistent epidemiologic finding on PD and melanoma, the relevance of these hypotheses should be evaluated in future studies.

Several limitations should be considered when interpreting our results. The majority of these studies were not originally designed to evaluate the relationship between melanoma and PD; melanoma was mostly assessed along with other cancers or medical conditions. Further, these analyses were often based on very small numbers of cases with both melanoma and PD. This is particularly true for the gender-specific analyses. In most of the studies, PD and melanoma cases were identified from hospitalization registers, record linkage, and self-report; misdiagno-

sis and underdiagnosis were therefore likely, particularly for PD. Moreover, as discussed earlier, the ascertainment of the date of diagnoses in these studies were inherently imprecise. Finally, most of these studies collected limited data on risk factors that made it difficult to explore potential explanations.

Despite these limitations, the results from our meta-analysis support a moderate association of PD with a higher occurrence of melanoma. Further research is needed to examine the nature and mechanisms of this relationship in order to advance our understanding about the etiology of both diseases.

AUTHOR CONTRIBUTIONS

R.L.: study conceptualization and design, data analysis, interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. X.G.: critical revision of the manuscript for important intellectual content, data interpretation, providing statistical expertise, and final approval of the version to be published. Y.L.: organizing the data, drafting of the table, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. H.C.: study conceptualization and design, study supervision, acquisition of additional data needed, critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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Historical Abstract: May 23, 2006

REVISED DIAGNOSTIC CRITERIA FOR NEUROMYELITIS OPTICA

D. M. Wingerchuk, V. A. Lennon, S. J. Pittock, C. F. Lucchinetti, and B. G. Weinshenker

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Background: The authors previously proposed diagnostic criteria for neuromyelitis optica (NMO) that facilitate its distinction from prototypic multiple sclerosis (MS). However, some patients with otherwise typical NMO have additional symptoms not attributable to optic nerve or spinal cord inflammation or have MS-like brain MRI lesions. Furthermore, some patients are misclassified as NMO by the authors' earlier proposed criteria despite having a subsequent course indistinguishable from prototypic MS. A serum autoantibody marker, NMO-IgG, is highly specific for NMO. The authors propose revised NMO diagnostic criteria that incorporate NMO-IgG status. **Methods:** Using final clinical diagnosis (NMO or MS) as the reference standard, the authors calculated sensitivity and specificity for each criterion and various combinations using a sample of 96 patients with NMO and 33 with MS. The authors used likelihood ratios and logistic regression analysis to develop the most practical and informative diagnostic model. **Results:** Fourteen patients with NMO (14.6%) had extra-optic-spinal CNS symptoms. NMO-IgG seropositivity was 76% sensitive and 94% specific for NMO. The best diagnostic combination was 99% sensitive and 90% specific for NMO and consisted of at least two of three elements: longitudinally extensive cord lesion, onset brain MRI nondiagnostic for MS, or NMO-IgG seropositivity. **Conclusions:** The authors propose revised diagnostic criteria for definite neuromyelitis optica (NMO) that require optic neuritis, myelitis, and at least two of three supportive criteria: MRI evidence of a contiguous spinal cord lesion 3 or more segments in length, onset brain MRI nondiagnostic for multiple sclerosis, or NMO-IgG seropositivity. CNS involvement beyond the optic nerves and spinal cord is compatible with NMO.

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Comment from Richard M. Ransohoff, MD, Associate Editor: This report crystallized the recognition that NMO and MS were pathogenetically distinct, by incorporating a new serum biomarker NMO-IgG in the diagnostic criteria.