# Clinicopathologic Characteristics of Melanoma in Patients with Parkinson Disease

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Patients with Parkinson disease (PD) are at high risk for developing melanoma, although current literature lacks details on the associated clinicopathologic characteristics. Our retrospective case-control study aimed to guide skin cancer surveillance recommendations for patients with PD, focusing on tumor sites. Our study included 70 adults with concurrent diagnoses of PD and melanoma from January 1, 2007 to January 1, 2020 at Duke University and 102 age-, sex-, and race-matched controls. The head/neck region accounted for 39.5% of invasive melanomas in the case group compared with 25.3% in the control group as well as 48.7% of noninvasive melanomas in the case group compared with 39.1% in the control group. Of note, 50% of metastatic melanomas in patients with PD originated on the head and neck (n = 3). Logistic regression showed 2.09 times higher odds of having a head/neck melanoma in our case group compared with that in the control group (OR = 2.09, 95% confidence interval = 1.13–3.86; $P = 0.020$). Our study is limited by small sample size, and our case cohort lacked diversity regarding race, ethnicity, sex, and geography. Validation of the reported trends could provide more robust guidance for melanoma surveillance in patients with PD.

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## INTRODUCTION

Melanoma is an increasingly common cancer in the United States, with an estimated 106,110 new diagnoses and 7,180 deaths from invasive cutaneous melanoma in 2021 (American Cancer Society, 2021). Although the overall incidence of melanoma has increased in recent years, certain populations are disproportionately affected, specifically fair-skinned individuals, those living in geographic locations closer to the equator, and patients living with Parkinson disease (PD) (Bose et al., 2018; Whiteman et al., 2016). Melanoma mortality is fortunately trending downward, with melanoma death rates between 2014 and 2018 falling by approximately 7% per year in adults aged ≤50 years and approximately 5% per year in older adults; furthermore, the 5-year relative survival rate (2010–2016) is 93% among all stages at diagnosis and 99% for local disease (American Cancer Society, 2021).

The enigmatic association between cancer and PD has been explored by numerous studies. Patients with PD have an overall lower risk of developing cancer at any primary site than those in the general population but paradoxically face a significantly higher risk for melanoma (Bose et al., 2018). One study noted that the risk of developing melanoma in patients with PD is increased two-fold (Olsen et al., 2005). A multicenter study reported that patients with PD had a 2.24-fold higher risk of developing malignant melanoma than age- and sex-matched controls, recommending that patients newly diagnosed with PD undergo preventative screening for melanoma (Bertoni et al., 2010).

Multiple theories for the pathophysiological link between melanoma and PD exist, including genetic alterations related to melanin biosynthesis, cellular detoxification mechanisms, the oxidative stress response, cellular trafficking, and disease of the substantia nigra (Bose et al., 2018; Rumpf et al., 2013). Additional factors that modulate the risk of developing melanoma in patients with PD have been explored, specifically medication therapy with levodopa and carbidopa-levodopa. The DATATOP (deprenyl and tocopherol antioxidative therapy of parkinsonism) trial suggested that the relationship between levodopa and melanoma was of coincidental rather than causal nature, although the authors admitted that the study was underpowered to assess causality; in addition, there is a paucity of studies including analysis of other medications commonly used in PD as well as studies examining the pathologic characteristics of melanoma in patients with PD (Constantinescu et al., 2007).

We identified 70 adult patients with concurrent diagnoses of PD and melanoma between the dates of January 1, 2007 and January 1, 2020 treated in the Duke University Health System as well as 102 age- (within 2 years), sex-, and race-matched control patients with melanoma but without a

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*Abbreviations: BCC, basal cell carcinoma; PD, Parkinson disease; SCC, squamous cell carcinoma*

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diagnosis of PD. Our primary aim was to characterize the clinicopathologic characteristics of melanoma in patients with PD. Secondarily, we sought to identify patient characteristics that may be associated with the development of melanoma in patients with PD such as dopaminergic drug therapy, previous personal or family history of melanoma, personal history of other skin cancers (squamous cell carcinoma [SCC] and basal cell carcinoma [BCC]), or dysplastic nevi. This study is a systematic collation of data and a description of melanoma characteristics in patients with PD that provides an essential update to existing literature regarding this enigmatic diagnostic association. We hope that our study will guide future, prospective research addressing the prevention, surveillance, and treatment of melanoma in patients with PD because previous studies have heralded the need for early detection and screening in this population (Bertoni et al., 2010; Constantinescu et al., 2007).

## RESULTS

Our case group comprised 70 patients with both melanoma and PD. Ten of these patients had more than one melanoma, including one patient with two primary melanomas diagnosed on the same day. The remaining nine patients had an initial primary melanoma followed by a later diagnosis of a subsequent primary melanoma. Our control group contained 102 patients and 102 primary melanomas with sufficiently detailed pathology reports for inclusion. Case-group patients were matched to controls for age (within 2 years), sex, and race with a similar distribution in variables after matching.

### Demographic information

The demographic information of patients included in the study is summarized in Table 1. The majority of case-group patients were male (n = 51, 72.9%) and Caucasian (n = 69, 98.6%), and the median (quartile 1–third quartile) age at biopsy was 70.9 (65.4–76.0) years. The median (quartile 1–third quartile) age at diagnosis of PD was 72.3 (67.3–80.5) years in the case group, and 43 of these patients (61.4%) had a melanoma diagnosis before PD. The median (quartile 1–third quartile) time from the first diagnosis of melanoma to the diagnosis of PD was 2.3 years (−1.4, −6.2).

### Melanoma characteristics

In total, 184 melanomas were included from the 172 patients in this study, with 82 of these originating from the case group. The treatment, staging, and characteristics of all melanomas are summarized in Table 2. The major site of primary melanoma in the case group was head/neck (n = 36, 43.9%), 68.3% (n = 56 of 82) of the melanomas were treated with wide local excision, and 23.2% (n = 19 of 82) were treated with Mohs micrographic surgery. For the control group, primary melanomas were most commonly truncal (n = 32, 31.4%), 78.4% (n = 80 of 102) were treated with wide local excision, and 15.7% (n = 16 of 102) were treated with Mohs micrographic surgery. Twenty sentinel lymph node biopsies were performed (24.4%), and seven of these (35.0%) were positive for nodal involvement in the case group; in comparison, 41 sentinel lymph node biopsies were performed (40.6%), and 24 of these (58.5%) were positive for nodal involvement in the control group. The majority of case-group patients had an American Joint Commission on Cancer, eight edition stage of stage 0 and malignant melanoma in situ

**Table 1. Demographic Information**

| Information | Case (n = 70) | Control (n = 102) | Total (n = 172) |
|---|---|---|---|
| Sex | | | |
| Male | 51 (72.9%) | 74 (72.5%) | 125 (72.7%) |
| Race | | | |
| Caucasian | 69 (98.6%) | 100 (98.0%) | 169 (98.3%) |
| Other[1] | 1 (1.4%) | 2 (2.0%) | 3 (1.7%) |
| Age at first diagnosis (years) based on ICD code | | | |
| Mean (SD) | 65.1 (8.7) | 65.2 (8.7) | 65.2 (8.6) |
| Median (Q1–Q3) | 65.8 (59.9–71.4) | 65.7 (59.9–71.6) | 65.8 (59.9–71.5) |
| Range | 40.1–81.6 | 41.1–81.3 | 40.1–81.6 |
| Age at biopsy (y) based on pathology report | | | |
| Mean (SD) | 69.7 (9.2) | 65.4 (8.8) | 67.1 (9.2) |
| Median (Q1–Q3) | 70.9 (65.4–76.0) | 65.8 (59.8–71.6) | 68.3 (62.1–73.4) |
| Range | 40.7–92.3 | 41.1–81.3 | 40.7–92.3 |
| Age at Parkinson disease diagnosis (y) | | | |
| Mean (SD) | 72.2 (10.1) | | 72.2 (10.1) |
| Median (Q1–Q3) | 72.3 (67.3–80.5) | | 72.3 (67.3–80.5) |
| Range | 44.6–92.4 | | 44.6–92.4 |
| Melanoma diagnosed before Parkinson disease | 43 (61.4%) | | 43 (61.4%) |
| Time from the initial diagnosis of melanoma to the date of diagnosis of Parkinson disease (years) | | | |
| Mean (SD) | 2.7 (6.3) | | 2.7 (6.3) |
| Median (Q1–Q3) | 2.3 (−1.4, 6.2) | | 2.3 (−1.4, 6.2) |
| Range | −12.3, −22.6 | | −12.3, −22.6 |

Abbreviations: ICD, International Classification of Diseases; Q1, first quartile; Q3, third quartile.
[1]Other includes Asian, Pacific Islander/Hawaiian, American Indian, and Hispanic/Latino.

## Table 2. Melanoma Characteristics and Treatment

| Variable | Case (n = 82) | Control (n = 102) | Total (n = 184) | Unadjusted P-Value |
|---|---|---|---|---|
| Site of primary melanoma | | | | 0.25[1] |
| Head/neck | 36 (43.9%) | 29 (28.4%) | 65 (35.3%) | |
| Upper extremity | 15 (18.3%) | 22 (21.6%) | 37 (20.1%) | |
| Lower extremity | 12 (14.6%) | 17 (16.7%) | 29 (15.8%) | |
| Trunk | 17 (20.7%) | 32 (31.4%) | 49 (26.6%) | |
| Choroidal | 2 (2.4%) | 2 (2.0%) | 4 (2.2%) | |
| SLNB | | | | 0.021[1] |
| Missing | 0 | 1 | 1 | |
| No SLNB | 62 (75.6%) | 60 (59.4%) | 122 (66.7%) | |
| Yes SLNB | 20 (24.4%) | 41 (40.6%) | 61 (33.3%) | |
| Nodal metastasis if SLNB is performed | | | | 0.08[1] |
| Not applicable | 62 | 61 | 123 | |
| Negative | 13 (65.0%) | 17 (41.5%) | 30 (49.2%) | |
| Positive | 7 (35.0%) | 24 (58.5%) | 31 (50.8%) | |
| American Joint Committee on Cancer, Eight Edition stage | | | | <0.001[1] |
| Stage 0 (melanoma in situ) | 39 (47.6%) | 23 (22.5%) | 62 (33.7%) | |
| Stages IA and IB | 24 (29.3%) | 34 (33.3%) | 58 (31.5%) | |
| Stages IIA, IIB, and IIC | 16 (19.5%) | 16 (15.7%) | 32 (17.4%) | |
| Stages IIIA, IIIB, IIIC, IIID, and IV | 3 (3.7%) | 29 (28.4%) | 32 (17.4%) | |
| Histologic subtype | | | | |
| Melanoma in situ | 39 (47.6%) | 23 (22.5%) | 62 (33.7%) | |
| Lentigo maligna | 4 (4.9%) | 2 (2.0%) | 6 (3.3%) | |
| Superficial spreading | 12 (14.6%) | 36 (35.3%) | 48 (26.1%) | |
| Nodular | 5 (6.1%) | 7 (6.9%) | 12 (6.5%) | |
| Invasive desmoplastic | 2 (2.4%) | 2 (2.0%) | 4 (2.2%) | |
| Invasive spindle cell | 4 (4.9%) | 0 (0.0%) | 4 (2.2%) | |
| Mucosal | 2 (2.4%) | 2 (2.0%) | 4 (2.2%) | |
| Malignant blue nevus | 0 (0.0%) | 1 (1.0%) | 1 (0.5%) | |
| Unspecified | 14 (17.1%) | 29 (28.4%) | 43 (23.4%) | |
| Histologic subtype (in situ versus all invasive subtypes) | | | | <0.001[1] |
| Melanoma in situ | 39 (47.6%) | 23 (22.5%) | 62 (33.7%) | |
| Invasive melanoma | 43 (52.4%) | 79 (77.5%) | 122 (66.3%) | |
| Clark level | | | | 0.005[1] |
| Missing | 12 | 15 | 27 | |
| 1 | 39 (55.7%) | 23 (26.4%) | 62 (39.5%) | |
| 2 | 6 (8.6%) | 11 (12.6%) | 17 (10.8%) | |
| 3 | 7 (10.0%) | 11 (12.6%) | 18 (11.5%) | |
| 4 | 16 (22.9%) | 35 (40.2%) | 51 (32.5%) | |
| 5 | 2 (2.9%) | 7 (8.0%) | 9 (5.7%) | |
| Overall Breslow depth (mm) | | | | 0.003[2] |
| Missing | 2 | 1 | 3 | |
| Mean (SD) | 1.3 (2.7) | 1.7 (2.2) | 1.5 (2.4) | |
| Median (Q1–Q3) | 0.2 (0.0–2.0) | 0.9 (0.2–2.3) | 0.5 (0.0–2.1) | |
| Range | 0.0–15.0 | 0.0–13.0 | 0.0–15.0 | |
| Breslow depth (mm) for invasive tumors | | | | 0.93[2] |
| Not applicable | 39 | 23 | 62 | |
| Missing | 2 | 1 | 3 | |
| Mean (SD) | 2.6 (3.3) | 2.1 (2.3) | 2.3 (2.7) | |
| Median (Q1–Q3) | 2.0 (0.5–2.8) | 1.5 (0.5–2.9) | 1.5 (0.5–2.9) | |
| Range | 0.2–15.0 | 0.2–13.0 | 0.2–15.0 | |
| Breslow depth (mm) grouped by depth of invasion | | | | 0.001[1] |
| Missing | 2 | 1 | 3 | |
| 0 mm | 39 (48.8%) | 23 (22.8%) | 62 (34.3%) | |
| 0.1–1 mm | 19 (23.8%) | 32 (31.7%) | 51 (28.2%) | |
| 1.1–2 mm | 3 (3.8%) | 18 (17.8%) | 21 (11.6%) | |
| 2.1–4 mm | 12 (15.0%) | 16 (15.8%) | 28 (15.5%) | |
| >4 mm | 7 (8.8%) | 12 (11.9%) | 19 (10.5%) | |
| Distant metastasis | 6 (7.3%) | 14 (13.7%) | 20 (10.9%) | 0.17[1] |

(*continued*)

**Table 2. Continued**

| Variable | Case (n = 82) | Control (n = 102) | Total (n = 184) | Unadjusted P-Value |
|---|---|---|---|---|
| Systemic therapy for melanoma | 6 (7.3%) | 12 (11.8%) | 18 (9.8%) | 0.31[1] |
| Wide local excision | 56 (68.3%) | 80 (78.4%) | 136 (73.9%) | 0.12[1] |
| Mohs micrographic surgery | 19 (23.2%) | 16 (15.7%) | 35 (19.0%) | 0.16[1] |
| | **Clinicopathologic Characteristics of Invasive Malignant Melanoma (Melanoma In Situ Excluded)** | | | |
| **Variable** | **Case[4] (n = 43)** | **Control[4] (n = 79)** | **Total[4] (n = 122)** | **Unadjusted *P*-Value** |
| Ulceration | | | | 0.32[1] |
| Missing | 4 | 3 | 7 | |
| Yes | 7 (17.9%) | 20 (26.3%) | 27 (23.5%) | |
| Mitotic rate (per $mm^2$) | | | | 0.38[2] |
| Missing | 9 | 14 | 23 | |
| Mean (SD) | 2.5 (3.4) | 3.7 (5.5) | 3.3 (4.9) | |
| Median (Q1–Q3) | 1 (0–4) | 2 (0–5) | 1 (0–5) | |
| Range | 0–15 | 0–31 | 0–31 | |
| Lymphovascular invasion | | | | 0.66[3] |
| Missing | 9 | 11 | 20 | |
| Yes | 1 (2.9%) | 4 (5.9%) | 5 (4.9%) | |
| Perineural invasion | | | | 0.33[3] |
| Missing | 9 | 11 | 20 | |
| Yes | 3 (8.8%) | 2 (2.9%) | 5 (4.9%) | |
| Tumor-infiltrating lymphocytes | | | | <0.001[1] |
| Missing | 10 | 19 | 29 | |
| Yes | 9 (27.3%) | 39 (65.0%) | 48 (51.6%) | |
| Regression | | | | 0.88[1] |
| Missing | 8 | 14 | 22 | |
| Yes | 5 (14.3%) | 10 (15.4%) | 15 (15.0%) | |

Abbreviations: Q1, first quartile; Q3, third quartile; SLNB, sentinel lymph node biopsy.
[1]Chi-square
[2]Wilcoxon
[3]Fisher exact
[4]For ulceration, mitotic rate, lymphovascular invasion, perineural invasion, tumor-infiltrating lymphocytes, and regression, patients with malignant melanoma in situ as the histologic subtype were excluded from the analysis. The total sample size for these variables is n = 43 for the case group and n = 79 for the control group.

subtype (n = 39, 47.6%). Of the invasive melanomas, 17.9% (n = 7) had ulceration, the median mitotic rate was 1 per $mm^2$ (quartile 1–quartile 3 = 0–4), 2.9% (n = 1) had lymphovascular invasion, 8.8% (n = 3) had perineural invasion, 27.3% (n = 9) had tumor-infiltrating lymphocytes, 14.3% (n = 5) had regression, 7.3% (n = 6) had metastasis, and 7.3% (n = 6) of the 82 tumors were treated with systemic therapy. For the control group, stage I melanomas were most common (n = 34, 33.3%), followed by malignant melanoma in situ (n = 23, 22.5%). Of the control-group invasive melanomas, 26.3% (n = 20) had ulceration, the median mitotic rate was 2 per $mm^2$ (first quartile–third quartile = 0–5), 5.9% (n = 4) had lymphovascular invasion, 2.9% (n = 2) had perineural invasion, 65.0% (n = 39) had tumor-infiltrating lymphocytes, 15.4% (n = 10) had regression, 13.7% (n = 14) had metastasis, and 11.8% (n = 12) were treated with systemic therapy.

### Tumor site analysis

There were 43 invasive melanomas (52.4%) and 39 noninvasive melanomas (47.6%) in the case group. Two patients with invasive melanomas were missing Breslow depth data. Of the invasive melanomas, the majority were located on the head and neck region (n = 17, 39.5%); likewise, noninvasive tumors also favored the head and neck region (n = 19, 48.7%). Invasive tumors most commonly had a Breslow depth of 0.1–1.0 mm (n = 19 of 43, 44.2%), with most of these occurring on the trunk (n = 7, 36.8%) or head/neck (n = 6, 31.6%). For tumors with Breslow depths of 1.1–2.0 mm (n = 3, 7.0%), the most common site was the upper extremity (n = 2, 66.7%). Tumors with Breslow depths of 2.1–4.0 mm (n = 12 of 43, 27.9%) most commonly originated on the head/neck (n = 7, 58.3%). Tumors with Breslow depths exceeding 4.0 mm (n = 7 of 43, 16.3%) were distributed across the head/neck (n = 2, 28.6%), lower extremities (n = 2, 28.6%), the choroid (n = 2, 28.6%), and the upper extremities (n = 1, 14.3%). These data are reported in Table 3. Six melanomas were associated with metastasis (7.3%), with associated primary tumor sites of the head and neck region (n = 3, 50.0%), the upper extremities (n = 2, 33.3%), and the lower extremities (n = 1, 16.7%).

For the control group, there were 79 invasive melanomas (77.5%) and 23 noninvasive melanomas (22.5%). One patient with an invasive melanoma was missing Breslow depth data. Of the invasive melanomas, the majority were located on the trunk (n = 26, 32.9%). Noninvasive tumors favored the head/neck region (n = 9, 39.1%), much like the case

**Table 3. Tumor Site by Breslow Depth**

**Control Group**

| Tumor Site | 0 mm (n = 23) | 0.1–1 mm (n = 32) | 1.1–2 mm (n = 18) | 2.1–4 mm (n = 16) | >4 mm (n = 12) | Total (n = 101) |
|---|---|---|---|---|---|---|
| Head/neck | 9 (39.1%) | 5 (15.6%) | 4 (22.2%) | 5 (31.3%) | 5 (41.7%) | 28 (27.7%) |
| Upper extremity | 4 (17.4%) | 9 (28.1%) | 3 (16.7%) | 6 (37.5%) | 0 (0.0%) | 22 (21.8%) |
| Lower extremity | 4 (17.4%) | 1 (3.1%) | 6 (33.3%) | 2 (12.5%) | 4 (33.3%) | 17 (16.8%) |
| Trunk | 6 (26.1%) | 17 (53.1%) | 4 (22.2%) | 2 (12.5%) | 3 (25.0%) | 32 (31.7%) |
| Choroidal | 0 (0.0%) | 0 (0.0%) | 1 (5.6%) | 1 (6.3%) | 0 (0.0%) | 2 (2.0%) |

**Case Group**

| Tumor Site | 0 mm (n = 39) | 0.1–1 mm (n = 19) | 1.1–2 mm (n = 3) | 2.1–4 mm (n = 12) | >4 mm (n = 7) | Total (n = 80) |
|---|---|---|---|---|---|---|
| Head/neck | 19 (48.7%) | 6 (31.6%) | 1 (33.3%) | 7 (58.3%) | 2 (28.6%) | 35 (43.8%) |
| Upper extremity | 6 (15.4%) | 3 (15.8%) | 2 (66.7%) | 3 (25.0%) | 1 (14.3%) | 15 (18.8%) |
| Lower extremity | 5 (12.8%) | 3 (15.8%) | 0 (0.0%) | 2 (16.7%) | 2 (28.6%) | 12 (15.0%) |
| Trunk | 9 (23.1%) | 7 (36.8%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 16 (20.0%) |
| Choroidal | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (28.6%) | 2 (2.5%) |

group. Invasive tumors in the control group predominantly had Breslow depths of 0.1–1.0 mm (n = 32 of 79, 40.5%), with most of these tumors occurring on the trunk (n = 17, 53.1%) or upper extremities (n = 9, 28.1%). For tumors with Breslow depths of 1.1–2.0 mm (n = 18 of 79, 22.8%), the most common site was the lower extremities (n = 6, 33.3%). Tumors with Breslow depths of 2.1–4.0 mm (n = 16 of 79, 20.3%) most commonly originated on the head/neck (n = 5, 31.3%). Tumors with Breslow depths exceeding 4.0 mm (n = 12 of 79, 15.2%) involved the head/neck (n = 5, 41.7%), lower extremities (n = 4, 33.3%), and the trunk (n = 3, 25.0%). These data are reported in Table 3. Fourteen melanomas were associated with metastasis (13.7%), with associated primary tumor sites of the head/neck (n = 6, 42.9%), upper extremities (n = 4, 28.6%), lower extremities (n = 3, 21.4%), and trunk (n = 1, 7.1%). Logistic regression analysis showed that the odds of having a head/neck melanoma for patients who had PD was 2.09 times higher than that for the patients who did not have PD (OR = 2.09, 95% confidence interval = 1.13–3.86; $P = 0.020$).

### History of previous skin cancers and dysplastic nevi

In the case group, 26.5% of patients previously had SCC (n = 18), 36.2% had BCC (n = 25), and 15.7% had both (n = 11). Two case-group patients were missing data regarding a history of nonmelanoma skin cancer. For those who had SCC, the majority had one SCC (n = 11 of 68, 16.2%), and for those who had BCC, the majority had one BCC (n = 18 of 68, 26.5%). Eleven patients (15.7%) had a history of dysplastic nevi. For the control group, 9.8% of patients had a history of SCC (n = 10), 19.6% of patients had a history of BCC (n = 20), and 6.8% of patients had a history of both (n = 7). The most common number of SCCs for control-group patients was one (n = 6 of 102, 5.9%) and that of BCCs was one (n = 13 of 102, 12.7%). Twelve control-group patients (12.4%) had a history of dysplastic nevi. This information is summarized in Table 4.

### Characteristics of PD

Nine patients (12.9%) had a family history of PD. The major PD subtype was unspecified (n = 53, 77.9%). The most frequently used medication among the study patients was carbidopa-levodopa (n = 60, 85.7%). A full report of medications used to treat PD is shown in Table 5.

## DISCUSSION

In our single-center retrospective case-control study, most case-group patients had a diagnosis of melanoma that

**Table 4. History of Nonmelanoma Skin Cancer and Dysplastic Nevi**

| Variable | Case (n = 70) | Control (n = 102) | Total (n = 172) |
|---|---|---|---|
| Number of previous squamous cell carcinomas | | | |
| Missing | 2 | 8 | 10 |
| 0 | 50 (73.5%) | 84 (89.4%) | 134 (82.7%) |
| 1 | 11 (16.2%) | 6 (6.4%) | 17 (10.5%) |
| 2 | 3 (4.4%) | 2 (2.1%) | 5 (3.1%) |
| 3 | 1 (1.5%) | 1 (1.1%) | 2 (1.2%) |
| 4 | 1 (1.5%) | 0 (0.0%) | 1 (0.6%) |
| 5 | 0 (0.0%) | 1 (1.1%) | 1 (0.6%) |
| 7 | 1 (1.5%) | 0 (0.0%) | 1 (0.6%) |
| 10 | 1 (1.5%) | 0 (0.0%) | 1 (0.6%) |
| Number of previous basal cell carcinomas | | | |
| Missing | 1 | 9 | 10 |
| 0 | 44 (63.8%) | 73 (78.5%) | 117 (72.2%) |
| 1 | 18 (26.1%) | 13 (14.0%) | 31 (19.1%) |
| 2 | 2 (2.9%) | 2 (2.2%) | 4 (2.5%) |
| 3 | 0 (0.0%) | 1 (1.1%) | 1 (0.6%) |
| 4 | 2 (2.9%) | 1 (1.1%) | 3 (1.9%) |
| 5 | 1 (1.4%) | 1 (1.1%) | 2 (1.2%) |
| 6 | 0 (0.0%) | 1 (1.1%) | 1 (0.6%) |
| 8 | 1 (1.4%) | 0 (0.0%) | 1 (0.6%) |
| 9 | 1 (1.4%) | 0 (0.0%) | 1 (0.6%) |
| 10 | 0 (0.0%) | 1 (1.1%) | 1 (0.6%) |
| History of dysplastic nevi | | | |
| Missing | 0 | 5 | 5 |
| Yes | 11 (15.7%) | 12 (12.4%) | 23 (13.8%) |

**Table 5. Parkinson Disease Characteristics and Medications**

| Characteristics | Total (n = 70) |
|---|---|
| Family history of Parkinson disease | 9 (12.9%) |
| Major Parkinson disease subtype | |
| Missing | 2 |
| Unspecified | 53 (77.9%) |
| Tremor dominant | 8 (11.8%) |
| Akinetic rigid | 3 (4.4%) |
| Postural instability and gait difficulty | 4 (5.9%) |
| Medications | |
| Carbidopa/levodopa | 60 (85.7%) |
| Ropinirole | 8 (11.4%) |
| Pramipexole | 9 (12.9%) |
| Donepezil | 7 (10.0%) |
| Rivastigmine | 2 (2.9%) |
| Memantine | 2 (2.9%) |
| Trihexyphenidyl | 1 (1.4%) |
| Entacapone | 5 (7.1%) |
| Selegiline | 2 (2.9%) |
| Rasagiline | 7 (10.0%) |
| Pregabalin | 2 (2.9%) |

preceded a PD diagnosis, the predominant site of primary melanoma was the head/neck region, and the most common melanoma subtype was melanoma in situ. Using logistic regression analysis, we found that patients with PD had 2.09 times higher odds of having a head/neck melanoma than the control group. Of the 43 invasive tumors in our case group, most originated on the head/neck (n = 17, 39.5%). Although metastasis was uncommon, 50% of metastatic melanomas in patients with PD originated on the head/neck compared with the 42.9% of metastatic melanomas with a primary head/neck site in the control group.

Although our study is limited by a small case-group sample size, we recommend increased surveillance for melanoma in patients with newly diagnosed PD because early detection may result in a more favorable prognosis, including detection of melanoma in situ or early invasive disease and reducing the need for sentinel lymph node biopsy, systemic treatment, and imaging surveillance. Heightened suspicion of and increased screening for concerning pigmented lesions in patients with PD in the primary care setting with a focus on surveilling the head and neck regions may provide an appropriate first intervention and access point to skin screening for this population, with referral to dermatology being warranted if lesions suspicious for malignancy are identified. Dermatology consultation may be considered for full-body skin examinations for patients newly diagnosed with PD to also include surveillance for nonmelanoma skin cancer. Given the effects of PD on motor function, including tremors, rigidity, bradykinesia, freezing gait, and disordered balance, patients with PD are at high risk for falling, with approximately 60% of patients with PD experiencing at least one fall each year; therefore, care must be taken to support these patients as they don gowns or ambulate to the examination table (Kim et al., 2018). Strategies for mitigating fall risk include employing assistance from healthcare staff or patient family members during the removal of clothing; performing skin examinations of one body segment at a time; and examining the head and neck, upper extremities, and trunk while patients are seated upright on the ground level. Examination of the lower extremities, groin, and buttocks can be performed while patients with PD support themselves using assistive devices (i.e., walkers) or use countertops or the examination table to support their upper body. Dermatologists should perform a full-body skin examination when possible for patients with PD, but our results support emphasized screening of the head and neck for melanoma surveillance.

Existing literature emphasizes the pathophysiological link between melanoma and PD as well as discussions on the PD medications hypothesized to increase the risk for melanoma. However, the literature lacks studies reporting the clinicopathologic characteristics of primary melanomas in patients with PD. Matsuo and Kamitani (2010) found an association with the expression of alpha-synuclein in melanocytic lesions, including benign nevi, primary melanoma, and metastatic melanoma, indicating that the link between PD and melanoma warrants further clinicopathologic and genetic studies. The authors were unable to find other clinicopathologic studies to contextualize the results of this study, which further highlights the need for future larger studies of melanoma characteristics in patients with PD to better inform skin cancer screening recommendations.

This study reported the pharmacotherapy for patients with PD with melanoma, including carbidopa-levodopa, dopamine receptor agonists (i.e., ropinirole and pramipexole), catechol-o-methyltransferase inhibitors (i.e., entacapone), and monoamine oxidase inhibitors (i.e., selegiline and rasagiline). It is worth noting that some patients had initially been treated with dopamine receptor agonists before transitioning to carbidopa-levodopa therapy, although only 11.4% of patients (n = 8) were still taking these medications. Interestingly, there was a recent case of palmar eruptive melanocytic nevi in a male aged 86 years diagnosed with PD and treated with carbidopa-levodopa, in which his new-onset eruptive melanocytic nevi increased in both number and pigmentation after doubling his dose of carbidopa-levodopa (Haraszti et al., 2018). Dopaminergic drugs are the mainstay of PD treatment, and levodopa has been well-characterized as an important intermediate in melanogenesis; furthermore, increased melanogenesis in melanoma, particularly invasive subtypes, is a poor prognostic factor (D'Mello et al., 2016; Haraszti et al., 2018).

Our study found that a diagnosis of melanoma predominantly preceded the diagnosis or treatment of PD, suggesting the possibility of an alternative pathophysiological link between the disease processes beyond the previously reported association with levodopa. Supporting our results, a 2017 retrospective cohort study examining the association between melanoma and PD concluded that patients with PD had a 3.8-fold increased probability of having pre-existing melanoma and that patients with melanoma had a 4.2-fold increased risk of developing PD compared with the controls (Dalvin et al., 2017). These results may weaken the hypothesis that melanoma may be induced by medications used in the treatment of PD; in contrast, a 2015 meta-analysis

examining the temporal relationship of melanoma in 292,275 patients with PD found that there was a significant risk for melanoma after PD diagnosis but no significant risk before the PD diagnosis (Huang et al., 2015). An analysis of data from the DATATOP clinical trial examined the incidence of malignant melanoma in a PD cohort before and after levodopa therapy, reporting an increased risk of melanoma in patients with PD compared with that in the general population; however, it failed to support an association between levodopa and development of melanoma because the study was limited by a small number of definite malignant melanomas (n = 5) (Constantinescu et al., 2007). Finally, it is important to recognize that PD and melanoma may develop independently with advancing age, that older non-Hispanic white males are a demographic group at high risk for head and neck and thick melanomas independent of PD diagnosis, and that the results of our study are insufficient to confirm a definite link.

This study and previous work show the need for deeper exploration of the mechanisms linking PD and melanoma because there is a lack of high-powered cohort studies along with conflicting reports on the temporality of the association (Huang et al., 2015). Our study was limited by a small sample of patients with PD with pathology-confirmed melanoma (n = 70), and validation of the reported trends in tumor site could contribute to the development of more robust guidance for detecting melanoma early in patients with PD. We propose increased screening for melanoma in patients with PD with a particular focus on the head and neck because most noninvasive, invasive, and metastatic melanomas originated from these anatomic locations. Our case cohort lacked diversity in terms of race, ethnicity, and sex, although it is possible that this is reflective of the demographics of patients living with PD and melanoma. We recognize the importance of ensuring that our data can be applied to a wide range of patients across multiple clinical settings. Future studies with larger sample sizes could provide more power to validate the findings of this study.

## MATERIALS AND METHODS

### Overview and inclusion criteria

After approval by the Duke Health Institutional Review Board, case-group patients were identified by a review of a prospectively maintained institutional database, DEDUCE (Duke Enterprise Data Unified Content Explorer), for all patients with melanoma with a concurrent diagnosis of PD at Duke University Medical Center (Durham, NC) from January 1, 2007 to January 1, 2020. Patients were excluded from the review if a full pathology report for primary melanoma was not in the electronic records at Duke University. We conducted a retrospective review of 70 total patients aged ≥ 18 years. For our control group, we first identified all patients with melanoma and without PD in the DEDUCE database in our study's date range, limiting this group on the basis of patients who also had pathology reports available in the DEDUCE Text Reports system (n = 6,405). We then performed a 2:1 match between the control group and the case group. Each patient was matched for age (maximum age difference: 2 years), sex, and race. Age was defined as the age at first diagnosis of melanoma corresponding to International Classification of Diseases codes documented in the DEDUCE database. We then performed chart reviews to collect clinicopathologic data regarding the primary melanomas of these control-group patients. The pathology reports of some patients in our study date range were related to nodal metastasis or distant metastatic disease and did not include a full report regarding the primary melanoma, thus these patients were excluded during chart review. Subsequent rounds of matching were performed until each patient in the case group had at least one matching control randomly selected from control patients meeting the criteria. Our final control cohort comprised 102 patients. The matching variables were comparable between the case group and the control group as shown in Table 1.

Pertinent information regarding the lesion characteristics of the primary melanoma including the anatomic location; histologic subtype; American Joint Commission on Cancer, Eight Edition stage; Clark level; Breslow depth; ulceration; mitotic rate; presence or absence of lymphovascular and perineural invasion; tumor-infiltrating lymphocytes; regression; nodal involvement; and metastasis was collected. In addition, we examined patient characteristics, including the dates of diagnosis for both PD and melanoma, personal or family history of melanoma, personal history of non-melanoma skin cancers, personal history of dysplastic nevi, and the medications used for treating PD.

### Statistical analysis

Descriptive statistics were used to summarize patient demographics and characteristics of melanoma and PD. Continuous variables were summarized using the mean, median, SD, 25th and 75th percentiles (first quartile–third quartile), and range. Categorical variables were summarized with frequency counts and percentages of nonmissing values. Melanoma characteristics were compared between the case group and the control group using the chi-square test, Fisher's exact test, or Wilcoxon rank-sum test as appropriate. To compare the percentages of head and neck primary melanomas between the case group and the control group, a logistic regression model was fit, with head/neck location (yes/no) as the outcome and the patient group as the independent variable. Compound symmetry covariance structure was used to account for the correlation between matched patients and correlations between multiple melanomas from the same patient. The OR of having head/neck location of melanoma between the two groups, together with its 95% confidence interval, was reported. The significance of the test was assessed at alpha = 0.05, and unadjusted *P*-values are reported. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

### Data availability statement

Datasets related to this article can be found at https://doi.org/10.7924/r4f47t77k, hosted at the Duke Data Repository.

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### CONFLICT OF INTEREST

The authors state no conflict of interest.

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## AUTHOR CONTRIBUTIONS

Conceptualization: MP; Data Curation: MSF, CR, SP; Formal Analysis: BL, CG; Funding Acquisition: MP, BL; Investigation: MP, MSF, CR, SP; Methodology: MP, SP, MSF, CR; Project Administration: MP; Supervision: MP, CG; Validation: MSF, CR, SP; Visualization: MSF, CR, SP, BL; Writing - Original Draft Preparation: MSF, CR, SP; Writing - Review and Editing: MSF, CR, SP, MP, BL, CG

## Disclaimer

The content of this study is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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