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ORIGINAL RESEARCH

Parkinson's Disease as a Risk Factor for Melanoma: A Review

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ABSTRACT

Objective: To review the literature and place into a quantified context the relationship of Parkinson's disease diagnosis to a subsequent diagnosis of malignant melanoma, and to briefly explore potential molecular associations between the two diseases.

Methods: The Medline database was queried with terms related to Parkinson's disease (PD) and malignant melanoma, with use of Boolean operator AND to identify studies involving both diseases. Studies were divided into primary and meta-analyses, with exclusive evaluation of those quantifying risk of malignant melanoma after an established diagnosis of Parkinson's disease. Critical studies were identified using Medline searches to identify established quantified risk metrics between classic melanoma risk factors and subsequent development of malignant melanoma.

Results: Twelve primary studies and three meta-analyses were evaluated and their risk metrices tabulated. Three studies offered estimated risk of development of malignant melanoma in patients with classic melanoma risk factors. These metrices were also tabulated and compared with the metrices established by the twelve primary studies. This demonstrated a similarity in overall risk of developing malignant melanoma in a patient with a diagnosis of Parkinson's disease as compared to a patient with classical melanoma risk factors.

Conclusion: It is wise to consider the presence of Parkinson's disease in a patient as one factor when clinicians decide on the appropriateness of regular full body screening examinations.

INTRODUCTION

Characterizing the association between malignancy and Parkinson's disease (PD) has been an enormous challenge. While most malignancies are generally observed to be less common in patients with PD, melanoma appears to be a notable exception. Many studies have evaluated the cellular and epidemiological connections, and most conclude that patients with PD are at a higher risk for developing melanoma.[1–14] Genetic studies of melanoma and PD have complicated the picture, highlighting exceedingly complex pathogenic models for each disease. Although the understanding of each particular disease has progressed, details of their relationship are elusive.

The relationship between melanoma and PD seems natural, as both diseases involve the biological pigment melanin. In PD, neuromelanin depletion from the brain's

substantia nigra (SN) is a disease hallmark.[15–17] In melanoma, eumelanin-producing melanocytes are the malignant cells responsible for disease.[18] These two pigment types share structural similarities, and there is evidence of shared synthetic pathways involving tyrosinase.[19,20] While the association of both diseases with melanin is intriguing, it remains unclear whether this association is fundamentally related to their pathogenic relationship.

Though the precise molecular relationship continues to elude, further understanding the epidemiology of melanoma and PD may improve screening practices and prevent recent trends in melanoma overdiagnosis.[21] The epidemiology of the two disorders considered together is critical for establishing accurate, evidence-based screening and diagnostic procedures.

METHODS

In this review, we first searched the Medline database for studies evaluating the epidemiological link between PD and any form of melanoma, regardless of the time of publication or the particular demographic studied. Results were divided into primary studies and meta-analyses and reviewed separately. Only those primary studies that specifically addressed the increased risk of melanoma after an established PD diagnosis were evaluated further. These primary studies were analyzed for the components of their analyses that addressed this specific association. Corresponding risk metrics were tabulated for each of these studies.

We also searched the MEDLINE database for recent primary studies and meta-analyses evaluating the strength of individual clinical risk factors for developing melanoma. The approximate degree of risk increase for each risk factor was tabulated based on recent meta-analyses to compare the degree of the increased risk of melanoma reported in patients with diagnosed PD.

RESULTS

The epidemiology of PD and melanoma is directly relevant to the daily practice of a clinical dermatologist. A quantitative appreciation for melanoma incidence helps answer the following questions:

1. How much elevated risk are patients with PD at for developing melanoma?
2. How does this elevated risk compare to traditional melanoma risk factors?
3. Do skin screening practices need to change based on a PD diagnosis?
4. Do patients with melanoma deserve closer monitoring for early symptoms of PD?

The quantitative epidemiologic association must be considered with regard to the natural history of both diseases. For early detection and screening for melanoma, we focused on the risk of any melanoma after an established PD diagnosis.

Several primary epidemiologic studies and meta-analyses have attempted to quantify the relationship between PD and a subsequent diagnosis of melanoma (Table 1), with the association measures referencing the risk of melanoma diagnosis in a patient with a pre-established PD diagnosis.[1,3–10,12,14,22]

Systematic meta-analyses have supported the conclusions of primary studies, strengthening the epidemiologic association by ensuring adequate controls across studied populations for potential confounders, such as age and gender. Huang et al. 2015 showed a pooled odds ratio of developing melanoma of 2.43 (95% CI: 1.77-3.32) for PD patients compared to those without, as determined across multiple studies.[13] Similarly, Liu et al. 2011 found a pooled odds ratio of 3.61 (95% CI: 1.49–8.77).[11] An extensive metanalysis by Bajaj et al. in 2010 suggested a pooled relative risk of 1.41 (95% CI: 0.90-2.19).[2]

Understanding the above data in the context of other, more classic melanoma risk factors becomes critical to making evidence-based decisions. Despite the disagreement among specialties, task forces, and societies in the U.S. and abroad regarding the frequency and timing of full body skin exams, many dermatologists recommend full-body skin exams for patients who are at notably increased risk for melanoma.[23,24]

Some of the widely accepted melanoma risk factors include light skin and eye color, patients with multiple atypical nevi, a history of severe sunburns, and a history of prior treated melanomas.[25–27] The most recent prospective cohort study in Australia found the highest hazard ratios of invasive melanoma to be 2.34 for age >65, 2.13 for the male gender, 4.79 for inability to tan, 4.42 for many moles at age 21, and 2.51 for >21 moles removed in the past. This study stratified risk for both invasive melanomas and any melanoma.[28]

Similar findings are reflected in a recent analysis of the American Academy of Dermatology's (AAD) Skin Cancer Screening Program. This analysis found the odds ratios for the development of melanoma to be 1.2 for those over age 50, 1.4 for males, 1.4 for the presence of changing moles, 2.0 for the absence of regular visits to a dermatologist, and 3.5 for a history of melanoma. When combined, exposures to several of these risk factors resulted in an odds ratio of 1.0, 1.7, 2.5, and 4.4 for zero to one, two, three, and four to five risk factors, respectively. The "age over 50 years" risk factor may seem to capture the older population associated with a higher risk for PD diagnosis. However, compared to risk metrics for developing melanoma after PD diagnosis, this criterion appears to carry at least half the risk and, by itself, is unlikely to prompt a primary care referral to dermatology for a full-body skin exam.[29]

The most recent and most extensive analysis of the AAD SPOTme skin cancer screening program found the adjusted odds ratio for cutaneous melanoma to be 1.54 for males, 1.38 for patient's with an uninsured status, 1.28 for patients with no regular access to a dermatologist, 2.54 for personal history of melanoma, 1.65 for a recent change in moles, 1.68 for >26 moles, 1.44 for >30 hours per week in the sun, and 1.39 for 4-6 years of indoor tanning. Beaulieu et al. concluded that targeting these groups will lead to more effective screening campaigns.[30] Table 2 summarizes the above risk metrics and their ranges to compare the metrics reported in Table 1.

The magnitude of increased for melanoma risk in patients with a PD diagnosis over multiple studies approximates the increased risk for melanoma in patients with multiple classic risk factors, including such critical elements of a patient's history as a previous melanoma diagnosis. These standard risk factors would typically prompt more thorough and regular skin exams by a dermatologist. Citing this evidence, we advocate for periodic skin exams for people

with PD, even in the absence of the above more classically appreciated risk factors, patients who would otherwise go unchecked. The requisite shared decision

Table 1. The relationship between PD and a subsequent diagnosis of melanoma.

Authors	Publication Date	Study Design	Risk Metric (95% CI)
Moller et al.	March 1995	Retrospective Cohort	RR: 1.96 (1.1-3.2)
Olsen et al.	December 2004	Retrospective Cohort	SIR: 1.95 (1.4-2.6)
Constantinescu et al.	April 2007	Retrospective Cohort	SER: 3.3 (1.1-7.8)
Driver et al.	June 2007	Prospective Cohort	RR: 6.15 (1.77-21.37)
Bertoni et al.	March 2010	Prospective Cohort	RR: 2.24 (1.21-4.17)
Becker et al.	March 2010	Case-Control	OR: 2.72 (0.66-11.12)
Lo et al.	September 2010	Retrospective Cohort	RR: 1.6 (0.71-3.6)
Schwid et al.	September 2010	Prospective Cohort	SIR: 20.9 (9.6-39.7)
Sun et al.	October 2011	Prospective Cohort	HR: 2.11 (0.21-21.3)
Rugbjerg et al.	October 2013	Prospective Cohort	SIR: 1.41 (1.09-1.34)
Constantinescu et al.	December 2013	Prospective Cohort	SER: 3.6 (2.2-5.6)
Ryu et al.	April 2020	Retrospective Cohort	HR: 2.83 (1.39-5.72)

Odds ratio (OR), Standardized event ratio (SER), Relative risk (RR), Standardized incidence ratio (SIR), Hazard ratio (HR).

Table 2. Summary of risk metric ranges for commonly considered risk factors for the development of melanoma reported by several recent studies.

Study	Risk Metric Range for All Risk Factors Evaluated
Olsen et al. 2018	HR: 2.13-4.79
Goldberg et al. 2007	OR: 1.2-3.5
Beaulieu et al. 2018	OR: 1.28-2.54

Odds ratio (OR), Relative risk (RR), Hazard ratio (HR).

must recognize that the risks of full body skin exams and unnecessary procedures include anxiety from overly frequent monitoring and possible increased costs to personal and public insurance systems. These risks are especially important to consider since not all melanomas follow a predictable path, and early detection may not always improve outcomes.

DISCUSSION

The epidemiologic association between PD and melanoma belies a molecular relationship that has so far remained incompletely characterized. A short list of the commonly associated genes with both melanoma and PD is offered in Table 3.[31,32] The absence of common entries is telling; suggested molecular connections between PD and melanoma are numerous but convincing evidence remains scarce. Table 4 outlines some of the prominent suggested molecular connections.[34-50] Recent literature is accelerating our understanding of this molecular relationship, and multiple potential connections between the two diseases exist. Several of the molecular candidates outlined in Table 4 are critical players in various protein quality control (PQC) pathways, suggesting that a more developed understanding of this process has the potential to improve understanding of both diseases. The molecular links between the two diseases, however, remains mostly academic. It remains to be seen if understanding the pathways will lead to the identification of new therapies, or otherwise meaningfully improve our ability to combat the human costs of either disease. While studies continue, there are essential things

that we can do in the clinic now, armed with our knowledge of the association of PD and melanoma.

Table 3. Proteins and their respective genes are linked to increased susceptibility to melanoma and Parkinson's disease

Proteins (Genes) Linked to Melanoma
Adrenocortical dysplasia homologue (*ACD*)
BRCA-associated protein 1 (*BAP1*)
Cyclin-dependent kinase inhibitor 2A (*CDKN2A*)
Cyclin-dependent kinase 4 (*CDK4*)
Micropthalmia-associated transcription factor (*MITF*)
Melanocortin 1 receptor (*MC1R*)
Protection of telomeres 1 (*POT1*)
Telomerase reverse transcriptase (*TERT*)
TERF2-interacting protein (*TERF2IP*)
Proteins (Genes) Linked to PD
Alpha-synuclein (*SNCA*)
Dardarin (*LRRK2*)
F-box only protein 7 (*FBXO7*)
Microtubule-associated protein tau (*MAPT*)
Paired immunoglobulin type 2 receptor beta (*PILRB*)
Parkin (*PARK2*)
Protein deglycase DJ-1 (*PARK7*)
PTEN-induced kinase 1 (*PINK1*)
Siglec 3 (*CD33*)

Based on our review, a diagnosis of PD is a significant risk factor for melanoma. We suggest that the timing and frequency of full-body skin exams are thoughtfully considered for patients diagnosed with PD. While the clinical utility of full-body skin exams in the general population with few to no risk factors for melanoma remains ambiguous, consistent epidemiologic evidence included herein suggests a likely benefit in patients with PD. The diagnosis of PD increases the subsequent risk of developing melanoma at rates similar to established melanoma risk factors, and it should be added to the list of risk factors considered during screening. Given the relative ease, speed, and low risks of a full-body skin exam, dermatologists can directly benefit patients with a diagnosis of PD, lead the specialty in improving our understanding of melanoma, and challenge the field to consider novel factors in melanoma pathogenesis. Other authors have made similar recommendations.[33] With such targeting toward higher-risk patients, melanoma screenings will be optimized, increasing detection in higher-risk populations and decreasing overdiagnosis. A more accurate set of risk factors can also help establish a consensus risk threshold to guide screening practices, which has been done in Australia.[28]

CONCLUSION

Finally, our review highlights the need for future studies to characterize the molecular link between melanoma and PD and the outcomes of melanoma diagnosed in patients with PD, such as the stage of melanoma at diagnosis and the relative survival of these patients. These future studies will help us better understand both

Table 4. Proteins and their respective genes are proposed as potential links between PD and melanoma in the literature

Gene	Protein	Proposed Link
SNCA	Alpha-synuclein	Mutations in *SNCA* are rare.[34,35] Alpha-synuclein's association with PD is primarily histopathological; abnormal inclusions of alpha-synuclein into so-called Lewy Bodies are a disease hallmark. While mutations can be associated with increased risk, the alpha-synuclein in Lewy Bodies is often genetically wild-type.[36] Increased levels of alpha-synuclein have also recently been found in melanoma cells.[34,37]
PARK2	PARKIN	An E3 ligase, PARKIN has been linked to PD in, with sequence mutations being important to the association.[38,39] In fact, mutations in *PARK2* are the most frequent cause of autosomal recessive juvenile-onset PD.[34,40] The studies of PARKIN in the context of melanoma have been mixed; some results suggest that it may function as a tumor suppressor in melanoma cell lines,[41] while others have suggested that PARKIN may promote melanoma proliferation.[42]
LRRK2	Dardarin	Architectural similarities exist between the kinase domain of dardarin and the protein Braf.[43] Braf is encoded by *BRAF*, which is the most common site of somatic mutations in melanoma.[44] The kinase domain of dardarin has been implicated in PD pathogenesis,[45] with sequence mutations in this gene being the most common cause of autosomal dominant PD.[34,46]
PARK7	DJ-1	The protein deglycase DJ-1 has been associated with PD, with data suggesting that it interacts with alpha-synuclein to prevent its adoption into pathologic conformations.[47] Results from DJ-1 knockout mice suggest that loss of DJ-1 function enhances melanoma metastasis.[48]
PINK1	Pink1	Implicated in the degradation of abnormal mitochondria, mutations in pink1 have an association with PD.[49] It is also associated with malignancy development in general, with evidence that mutations in *PINK1* promote tumorigenesis and metastasis.[50]

diseases' underlying pathology and promote more accurate prognostic models.

Abbreviations:

PD: Parkinson's disease
PQC: Protein quality control
SN: Substantia nigra

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