Increased Odds of Melanoma: Parkinson's Disease, Essential Tremor, Dystonia versus Controls

Sherif Y. Shalaby[a] and **Elan D. Louis**[a,b,c]

[a]Department of Neurology, Yale School of Medicine, Yale University, New Haven, Conn., USA

[b]Center for Neuroepidemiology and Clinical Neurological Research, Yale School of Medicine, Yale University, New Haven, Conn., USA

[c]Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale University, New Haven, Conn., USA

Abstract

Objective—Patients with Parkinson's disease (PD) have an increased risk of melanoma, although the mechanisms are unclear. We are unaware of studies that have assessed the association between other movement disorders, such as essential tremor (ET) and dystonia, and melanoma. In this study, we assessed the association between ET, PD, dystonia and cancer (esp. melanoma).

Methods—One hundred and eight PD cases, 139 ET cases, and 54 dystonia cases, and 124 controls were enrolled in a research study of the epidemiology of movement disorders (total n = 425). The groups were frequency matched on age and gender. Cancer diagnoses were made based on self-reports. Melanoma diagnoses were further validated.

Results—The prevalence of melanoma was higher in PD cases than controls (13.9 vs. 1.6%, p < 0.001), and was marginally higher in ET cases (5.8%, p = 0.08) and dystonia cases (7.4%, p = 0.06) than controls. In adjusted logistic regression models, the odds of melanoma was 7.09–9.84 times higher in PD cases than controls (p values 0.01–0.003), 3.73–4.10 times higher in ET cases than controls (p values 0.08–0.10), and 4.88–5.27 times higher in dystonia cases than controls (p values 0.06–0.07).

Conclusion—The links between neurological disorders and melanoma, long-known, may not be specific to PD and may extend to other movement disorders.

Keywords

Essential tremor; Parkinson's disease; Dystonia; Movement disorders; Epidemiology; Cancer; Melanoma

Elan D. Louis, MD, MSc, Department of Neurology, LCI 710, 15 York Street, PO Box 208018, New Haven, CT 06520-8018 (USA), elan.louis@yale.edu.

Introduction

Essential tremor (ET) is a common neurological disease with no known cure [1]. It shares a number of clinical features with Parkinson's disease (PD), another tremor disorder; furthermore, prospective epidemiological studies show that patients with ET are at increased risk of developing incident PD [2]. Patients with ET and PD have been reported to share a number of genetic risk factors, suggesting that there may be shared disease mechanisms [3]. For these reasons, association studies carried out in PD patients have often been extended to those with ET [4, 5].

Patients with PD are well known to have an increased risk of developing melanoma; however, the exact mechanism is unknown [6, 7]. Considering the associations between ET and PD, we tested the hypothesis that ET would be associated with an increased odds of cancer, and particularly, an increased odds of melanoma and possibly other integumentary (i.e. skin and appendages) cancers. We also examined whether dystonia, another movement disorder, and one which commonly occurs in patients with PD [8, 9], might be associated with these cancers. To perform these analyses, we capitalized on the enrollment of patients with ET, PD, dystonia as well as controls in research study of the epidemiology of movement disorders [10].

Methods

Participants and Evaluation

ET cases, PD cases, dystonia cases, and controls were enrolled in a case–control study of the epidemiology of movement disorders at Columbia University Medical Center (CUMC; 2009–2014) [10]. Cases had all received a diagnosis of ET, PD, or dystonia from their treating neurologist, one of the movement disorder neurologists at the Neurological Institute, CUMC, and were confined to a geographical area within 2 h driving distance of CUMC [10]. One of the authors (E.D.L.) reviewed the office records of all selected patients, and confirmed the diagnoses of PD and dystonia using published diagnostic criteria for each [11, 12]. ET cases also underwent a videotaped tremor examination and diagnostic confirmation as described further below.

Controls were recruited during the same time period. These controls were identified using random digit telephone dialing within a defined set of telephone area codes that were represented by neurological cases within the New York Metropolitan area, and were selected from the same source population as the cases. There was one group of controls for all neurological disease cases (ET, PD, and dystonia). During recruitment, controls were frequency-matched to ET cases based on age. The CUMC Internal Review Board approved of all study procedures. Written informed consent was obtained upon enrollment. Analysis of data was also approved by the Internal Review Board at Yale Medical School.

It is important to note that the case groups and controls were all derived from the same geographic area in New York, a temperate climate zone. Hence, across the study groups, it is likely that there was a similar environmental exposure to sun.

During the in-person evaluation, the trained research worker administered clinical questionnaires (demographics, smoking history, and medications). This included a 10–15 min, 26-item, structured questionnaire that elicited data on the history of cancer. The questionnaire was an expansion of one used in an earlier study [13], with additional questions abstracted from several validated cancer surveys [14–16]. The first 2 questions asked whether the participants (1) ever had cancer or (2) currently have cancer. The remaining questions were about the specific type of cancer according to the organ, years elapsed since initial diagnosis, recurrence, metastasis, and medical and surgical management. To validate the diagnosis of melanoma, one of the authors (S.Y.S.) contacted the participant's dermatologist and reviewed the medical record and pathology report with them over the telephone.

Medical comorbidity was assessed using the Cumulative Illness Rating Scale (CIRS), in which the severity of medical problems (0 (none)–3 (severe)) was rated in 14 body systems (e.g. cardiac, respiratory) and a CIRS score was assigned (range 0–42 (maximal co-morbidity)) to each participant [17]. Years since the last hospitalization, a measure of comorbidity, was also assessed. Tobacco exposure was assessed, and cigarette smoking was calculated in pack years; participants who never smoked were assigned '0' for pack years. We also recorded whether the participant had a diagnosis of diabetes mellitus, which has been associated with cancer [18]. Likewise, we collected data on the number of births, as a decreased number of live births in females is associated with certain types of cancers, such as endometrial cancers [19]. Also, it has been suggested that levodopa places PD patients at an increased risk of melanoma [20]. Based on a review of medical records, we recorded the most recent daily dosage of levodopa in PD.

All ET cases and controls had an in-person examination conducted by trained research staff during which time they underwent a standardized videotaped tremor examination, which included tests of postural and kinetic tremors and assessments for the presence of other involuntary movements. The aim was to use the videotape to carefully validate ET diagnoses (and lack thereof in controls) using rigorous research-grade diagnostic criteria [21]. Thus, each videotape was reviewed by a senior neurologist specializing in movement disorders (E.D.L.) who confirmed the ET diagnoses using Washington Heights-Inwood Genetic Study of ET diagnostic criteria (moderate or greater amplitude kinetic tremor (tremor rating 2) during 3 or more tests or a head tremor, in the absence of PD, dystonia or another cause) [21].

Final Sample

To frequency-match (i.e. category match) by age and gender across all 4 groups, we excluded 149 (26.0%) of 574 enrollees. This matching was performed by selecting a group of individuals in each of the remaining diagnostic groups (PD, dystonia, controls) whose age and gender conformed to the distribution observed in the ET cases. This matching was performed within each diagnostic category blinded to all data other than age and gender. The final sample comprised 425 enrollees: 139 (100%) of 139 ET cases, 108 (80.6%) of 134 PD cases, 54 (44.6%) of 121 dystonia cases and 124 (68.9%) of 180 controls.

Definitions and Classifications

Cancers were categorized according to embryonic origin (ectodermal, mesodermal, endodermal, or mixed origin) as specified in the embryonic development, regenerative medicine and stem cell database [22]. The endoderm gives rise to the gastrointestinal tract and several other internal organs. The mesoderm gives rise to the dermis, muscles, blood, lymph, and other tissues. The ectoderm gives rise to the central nervous system (CNS). The integumentary system (i.e. skin and appendages such as hair) is composed of the epidermal layer (from the ectoderm) and the dermal and hypodermal layers (from the mesoderm). All integumentary cancers we recorded arise from the epidermal layer (ectoderm) except for squamous cell carcinoma, which originates from the dermis (mesoderm). Other organs are comprised of tissue that derives both from the ectoderm and mesoderm, and thus, we incorporated them in the mixed origin group. This group includes the breast, skin, and head and neck (oral cavity/pharynx) cancers.

The number of participants with cancer was defined as participants with a diagnosis of cancer. The number of cancer diagnoses for each cancer group type (i.e. ectodermal, mesodermal, etc.) was defined as the cumulative sum of all diagnoses (i.e. some participants may have been diagnosed with more than one type of cancer for each group).

Statistical Analyses

Analyses were performed using the statistical software package SPSS (version 21.0; SPSS, Inc., Chicago, Ill., USA). We compared demographic and clinical characteristics across the 4 diagnostic groups (PD, ET, dystonia, controls; table 1). We also compared the mean carbidopa-levodopa dose in PD cases who did have vs. did not have melanoma (Student's t test). When variables were not normally distributed (i.e. Kolmogorov–Smirnov test statistic p value <0.05), non-parametric tests were used. Exact tests were used when appropriate. When a difference was detected across the 4 groups, we further compared each diagnostic group to controls (i.e. PD vs. controls, ET vs. controls, dystonia vs. controls). All tests were two-sided, and significance was accepted at the 5% level.

In the primary analysis (table 2a), we compared the prevalence of all cancer (ever) across diagnostic groups, the prevalence of melanoma (ever) across diagnostic groups, and the prevalence of cancers of integumentary origin (ever) across diagnostic groups. In the secondary analyses (table 2b), we compared the prevalence of all other types of cancer and cancers grouped according to embryonic origin across diagnostic groups. Given the large number of comparisons in the secondary analysis (n = 30; table 2b), a significant p value for the secondary analysis was conservatively set at <0.0017 (i.e. 0.05/30); in this analysis, p values between 0.0017 and 0.05 were viewed as marginally significant.

To assess the relationship of any type of cancer, melanoma, and cancers of integumentary origin to the presence of ET, PD, or dystonia we used logistic regression analyses. We began with an unadjusted model. Then, in adjusted models, we first added variables (i.e. 'enter' function in SPSS) that were associated (p < 0.05) both with the movement disorder (ET, PD or dystonia separately) and with any type of cancer, melanoma, or cancers of integumentary origin (each explored separately). This was the 'conservative model', with more restrictive

criteria for confounding. We then added variables that were associated with either the movement disorder or with any type of cancer, melanoma, or cancers of integumentary origin. This was the 'liberal model', with less restrictive criteria for confounding. These analyses generated ORs with 95% CIs. In some instances, the conservative model resembled the unadjusted model because no variables met stringent criteria for inclusion in the model.

Results

The 4 groups were similar with respect to age, gender, race, and education, as well as CIRS score, years since last hospitalization, diabetes mellitus, number of live births (females) and cigarette pack years (table 1). The total number of prescription medications was significantly higher in PD, ET, and dystonia than controls (table 1).

The prevalence of all cancer and the number of cancer diagnoses were similar across the 4 groups (table 2a). The prevalence of melanoma differed across the 4 diagnostic groups (p = 0.003) and was higher in PD cases than controls (p < 0.001), and was marginally higher in ET cases (p = 0.08) and dystonia cases (p = 0.06) than controls (table 2a). The prevalence of integumentary cancer and/or the number of such diagnoses was higher in PD cases than controls (p values <0.001) and marginally higher in ET cases than controls (p values 0.04–0.10) and marginally higher in dystonia cases than controls (p values 0.04–0.11; table 2a).

In secondary analyses, cancers of ectodermal origin were significantly greater in PD than controls and there was a trend towards an increasing prevalence of basal cell cancers across groups (table 2b). Other cancers were similar across groups (table 2b).

We assessed in our control group whether demographic and clinical variables were associated with all cancer, melanoma, and integumentary cancers; older age and higher CIRS score were associated with all cancer (table 3).

In adjusted logistic regression analysis, the odds of any cancer was higher in PD cases than controls (OR 1.69 (conservative model) and OR 1.97 (liberal model); table 4). In adjusted models, the odds of melanoma was 7.09–9.84 times higher in PD cases than controls (p values 0.01–0.003), 3.73–4.10 times higher in ET cases than controls (p values 0.08–0.10), and 4.88–5.27 times higher in dystonia cases than controls (p values 0.06–0.07; table 4). The odds of integumentary cancer were 2.63–3.63 times higher in PD cases than controls in adjusted models (p values 0.001–0.0002) and 2.21–2.54 times higher in dystonia cases than controls (p values 0.03–0.07; table 4).

Fifty-one PD cases were taking carbidopa-levodopa. PD cases who had melanoma had a higher mean carbidopa-levodopa dose than PD cases who did not have melanoma (892.9 ± 591.2 (n = 7) vs. 523.3 ± 329.7 (n = 44), p = 0.03 (Student's t test)). In an analysis that removed PD cases who were taking levodopa, the odds of melanoma were higher in PD cases than controls (unadjusted OR 9.96, 95% CI 2.04–48.57, p = 0.004; liberal adjusted model OR 8.04, 95% CI 1.55–41.79, p = 0.01).

Discussion

We examined the relationship between cancer and 3 movement disorders, PD, ET and dystonia. PD was associated with an increased risk of cancer and particularly melanoma; the latter is a finding that has been reported previously and which has been the focus of considerable study [6]. We also detected a marginally significant association between ET and melanoma as well as between dystonia with melanoma, findings, which have not been reported previously. These data suggest that the links between certain neurological disorders and melanoma, which have long been known, may not be specific to PD and may extend to other movement disorders. This would suggest that the underlying mechanisms for the association may be broader than previously considered.

Different hypotheses have been proposed to explain the co-occurrence of melanoma and PD; however, the underlying mechanisms remain unclear [7]. Specific variants in the melanocortin 1 receptor gene are associated with PD, suggesting that these variants could modulate the risk of PD in the population [7]. DJ-1, a susceptibility gene for PD [23], is expressed in uveal malignant melanoma cells [24]. Both the epidermal layer of the skin and the CNS are of ectodermal origin; therefore, it is interesting that melanoma is associated with certain disorders of the CNS. Moreover, the neurons that degenerate in PD are pigmented neurons, as are melanocytes.

We are not aware of prior studies that have examined the association between ET and melanoma. The mechanisms for such an association are not clear, although ET and PD may share a number of biological mechanisms as well as genetic risk factors [3, 25]. Interestingly, in 2003, a study of a group of Caucasians of mixed European ancestry was conducted to test the hypothesis that lighter skin color (i.e. lower melanin) was associated with an increased risk of ET, but the study did not detect an association [26]. Confirmatory studies and additional research are needed.

We are similarly unaware of any prior study that examined the association between dystonia and melanoma. Animal studies suggest that alpha melanocyte-stimulating hormone (alpha-MSH) exerts dystonic action; micro-injections of alpha-MSH into the locus coeruleus produce postures that are dystonic in nature [27]. Here, too, additional research is warranted.

The current data should also be interpreted within the broader context of the relationship between cancer and other neurodegenerative and neurological conditions aside from PD. Thus, studies have reported that individuals who are experiencing cognitive decline as well as those with Alzheimer's disease have decreased risk of cancer mortality [28, 29].

Our data should be interpreted within the context of several limitations. First, most cancer diagnoses were by self-report, raising questions about their validity. Validation studies have supported the accuracy of self-reports as a measure of assessing prevalent chronic diseases [15, 30]. Furthermore, for our cancer of primary interest, melanoma, we confirmed the diagnoses with each participant's dermatologist based on the re-review of pathology reports. Our observation that PD is associated with melanoma, a finding that has been reported numerous times previously [6, 7], further suggests that our patients' self-reports were valid. Another limitation is that this was a case–control study rather than a cohort study. Finally,

the case groups and controls were all derived from the same geographic area in New York, a temperate climate zone. Hence, sun exposure is less than other climactic areas (e.g. near the equator) and greater than others (e.g. near the poles). This could limit the generalizability of our findings. Strengths of the study include the novelty of the question we pose (i.e. the association between cancers and other movement disorders aside from PD), the enrollment of more than 400 participants, the fact that cases had all received a diagnosis of ET, PD, or dystonia that was carefully assigned by a movement disorder neurologist, the inclusion of a disease group (PD) with well-known increased odds of melanoma (i.e. enrollment of an internal control), the careful frequency-matching of our 4 study groups by age and gender, the fact that controls were carefully selected from the same source population as the cases, and the ability to assess and adjust for the effects of numerous potential confounding variables.

In summary, we examined the relationship between 3 movement disorders, PD, ET and dystonia, and cancer. As reported often, PD was associated with increased odds of melanoma. A novel finding was the additional association, albeit marginal, between 2 other movement disorders, ET and dystonia, and melanoma. These data suggest that the links between neurological disorders and melanoma, long-known, may not be specific to PD and may extend to other movement disorders. Confirmatory studies are needed as well as cohort (i.e. incidence) studies, which attempt to establish the temporal relationship between these conditions. Studies that explore the mechanisms for these putative associations are also needed.

Acknowledgments

References

1. Louis ED, Ferreira JJ. How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. Mov Disord. 2010; 25:534–541. [PubMed: 20175185]

2. Benito-Leon J, Louis ED, Bermejo-Pareja F. Neurological Disorders in Central Spain Study Group: Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. J Neurol Neurosurg Psychiatry. 2009; 80:423–425. [PubMed: 19289477]

3. Tan EK, Matsuura T, Nagamitsu S, Khajavi M, Jankovic J, Ashizawa T. Polymorphism of NACP-Rep1 in Parkinson's disease: an etiologic link with essential tremor? Neurology. 2000; 54:1195–1198. [PubMed: 10720300]

4. Gerbin M, Viner AS, Louis ED. Sleep in essential tremor: a comparison with normal controls and Parkinson's disease patients. Parkinsonism Relat Disord. 2012; 18:279–284. [PubMed: 22130149]

5. Quagliato LB, Viana MA, Quagliato EM, Simis S. Olfaction and essential tremor. Arq Neuropsiquiatr. 2009; 67:21–24. [PubMed: 19330204]

6. Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. Neurology. 2011; 76:2002–2009. [PubMed: 21646627]

7. Tell-Marti G, Puig-Butille JA, Potrony M, Badenas C, Mila M, Malvehy J, Marti MJ, Ezquerra M, Fernandez-Santiago R, Puig S. The MC1R melanoma risk variant p. R160w is associated with Parkinson disease. Ann Neurol. 2015; 77:889–894. [PubMed: 25631192]

8. Beretta N, Roze E, Breifel-Courbon C, Vidailhet M. Two cases of early dystonia of the trunk in Parkinson's disease. J Neurol. 2015; 262:1579–1580. [PubMed: 25929660]

9. Rossi M, Merello M. Teaching neuroimages: pisa syndrome in Parkinson disease. Neurology. 2014; 83:e177. [PubMed: 25367063]

10. Louis ED, Rao AK. Functional aspects of gait in essential tremor: a comparison with age-matched Parkinson's disease cases, dystonia cases, and controls. Tremor Other Hyperkinet Mov (N Y). 2015 pii:tre-5-308.

11. Fahn S. Concept and classification of dystonia. Adv Neurol. 1988; 50:1–8.

12. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. Neurology. 1992; 42:1142–1146. [PubMed: 1603339]

13. Louis ED, Pellegrino KM, Factor-Litvak P, Rios E, Jiang W, Henchcliffe C, Zheng W. Cancer and blood concentrations of the comutagen harmane in essential tremor. Mov Disord. 2008; 23:1747–1751. [PubMed: 18709680]

14. Schrijvers CT, Stronks K, van de Mheen DH, Coebergh JW, Mackenbach JP. Validation of cancer prevalence data from a postal survey by comparison with cancer registry records. Am J Epidemiol. 1994; 139:408–414. [PubMed: 8109575]

15. Parikh-Patel A, Allen M, Wright WE. California Teachers Study Steering Committee: Validation of self-reported cancers in the California teachers study. Am J Epidemiol. 2003; 157:539–545. [PubMed: 12631544]

16. Ming ME, Levy RM, Hoffstad OJ, Filip J, Gimotty PA, Margolis DJ. Validity of patient self-reported history of skin cancer. Arch Dermatol. 2004; 140:730–735. [PubMed: 15210466]

17. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968; 16:622–626. [PubMed: 5646906]

18. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. Diabetes Care. 2010; 33:1674–1685. [PubMed: 20587728]

19. Yang HP, Cook LS, Weiderpass E, Adami HO, Anderson KE, Cai H, Cerhan JR, Clendenen TV, Felix AS, Friedenreich CM, Garcia-Closas M, Goodman MT, Liang X, Lissowska J, Lu L, Magliocco AM, McCann SE, Moysich KB, Olson SH, Petruzella S, Pike MC, Polidoro S, Ricceri F, Risch HA, Sacerdote C, Setiawan VW, Shu XO, Spurdle AB, Trabert B, Webb PM, Wentzensen N, Xiang YB, Xu Y, Yu H, Zeleniuch-Jacquotte A, Brinton LA. Infertility and incident endometrial cancer risk: a pooled analysis from the epidemiology of endometrial cancer consortium (E2C2). Br J Cancer. 2015; 112:925–933. [PubMed: 25688738]

20. Vermeij JD, Winogrodzka A, Trip J, Weber WE. Parkinson's disease, levodopa-use and the risk of melanoma. Parkinsonism Relat Disord. 2009; 15:551–553. [PubMed: 19501540]

21. Louis ED, Ottman R, Ford B, Pullman S, Martinez M, Fahn S, Hauser WA. The Washington Heights-Inwood Genetic Study of Essential Tremor: methodologic issues in essential-tremor research. Neuroepidemiology. 1997; 16:124–133. [PubMed: 9159767]

22. LifeMap Discovery: Embryonic Development & Stem Cell Compendium: The Embryonic Development, Regenerative Medicine and Stem Cell Database, 2014.

23. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, Dekker MC, Squitieri F, Ibanez P, Joosse M, van Dongen JW, Vanacore N, van Swieten JC, Brice A, Meco G, van Duijn CM, Oostra BA, Heutink P. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science. 2003; 299:256–259. [PubMed: 12446870]

24. Pardo M, Garcia A, Thomas B, Pineiro A, Akoulitchev A, Dwek RA, Zitzmann N. The characterization of the invasion phenotype of uveal melanoma tumour cells shows the presence of MUC18 and HMG-1 metastasis markers and leads to the identification of DJ-1 as a potential serum biomarker. Int J Cancer. 2006; 119:1014–1022. [PubMed: 16570276]

25. Chao YX, Ng EY, Tan L, Prakash KM, Au WL, Zhao Y, Tan EK. Lrrk2 R1628P variant is a risk factor for essential tremor. Sci Rep. 2015; 5:9029. [PubMed: 25761573]

26. Louis ED, Jurewicz EC, Watner D, Factor-Litvak P. Skin color and the risk and severity of essential tremor: a reflectance spectroscopy study. Parkinsonism Relat Disord. 2003; 9:239–241. [PubMed: 12618060]

27. Sandyk R. Alpha-melanocyte-stimulating hormone: possible role in the pathophysiology of acute drug-induced dystonia. Int J Neurosci. 1990; 53:241–242. [PubMed: 2176181]

28. Benito-Leon J, Romero JP, Louis ED, Bermejo-Pareja F. Faster cognitive decline in elders without dementia and decreased risk of cancer mortality: NEDICES study. Neurology. 2014; 82:1441–1448. [PubMed: 24719490]

29. Romero JP, Benito-Leon J, Louis ED, Bermejo-Pareja F. Alzheimer's disease is associated with decreased risk of cancer-specific mortality: a prospective study (NEDICES). J Alzheimers Dis. 2014; 40:465–473. [PubMed: 24448786]

30. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol. 1986; 123:894–900. [PubMed: 3962971]

Table 1

Demographic data and comorbidities of 425 participants

	PD	ET	Dystonia	Control	p value
n	108	139	54	124	
Age, years	71.3±6.4 (71.0)	71.9±12.8 (73.0)	72.1±4.6 (72.0)	71.5±9.1 (72.0)	0.20[a]
Female gender	60 (55.6)	73 (52.5)	36 (66.7)	67 (54.0)	0.34[b]
Caucasian (non-Hispanic) race	98 (90.7)	130 (93.5)	49 (90.7)	108 (87.1)	0.36[b]
Education, years	16.4±2.8 (16.0)	16.1±2.6 (16.0)	15.7±3.2 (16.0)	15.9±2.9 (16.0)	0.31[a]
CIRS score	6.8±3.4 (7.0)	7.3±3.6 (7.0)	6.0±3.2 (7.0)	7.2±3.7 (7.0)	0.54[a]
Number of prescription medications	5.8±2.8 [*] (5.0)	4.9±3.2 [*] (4.0)	4.7±3.1 [*] (5.0)	3.5±2.9 (3.0)	<0.001[a]
Years since last hospitalization	13.4±17.2 (4.0)	11.5±16.4 (4.0)	11.8±13.3 (5.0)	11.7±15.1 (7.0)	0.62[a]
Diabetes mellitus	9 (8.4)	11 (8.1)	1 (1.9)	14 (11.4)	0.17[b]
Number of live births, females	2.0±1.1 (2.0)	2.1±1.1 (2.0)	1.9±1.3 (2.0)	2.1±1.8 (2.0)	0.18[a]
Pack years (cigarettes)	9.3±17.8 (0.0)	11.4±18.9 (1.0)	7.4±14.0 (1.0)	10.6±16.1 (2.0)	0.27[a]
Daily levodopa dosage among participants on levodopa, mg	574.0±389.8 (400.0)	NA	NA	NA	NA

Values are mean ± SD (median) or number (percentage).

NA = Not applicable.

[a]Kruskal–Wallis test comparing all 4 groups.

[b]Chi-square test comparing all 4 groups.

[*]Significantly different from controls (p < 0.05, Mann–Whitney test).

Table 2

Prevalence of cancer in 425 participants

a Primary analyses

	PD	ET	Dystonia	Control	p value
n	108	139	54	124	
Number of participants with any cancer	51 (47.2)	51 (36.7)	21 (38.9)	43 (34.7)	0.23[a]
Number of cancer diagnoses[1]	57 (52.8)	64 (46.0)	23 (42.6)	47 (37.9)	0.15[a]
Number of participants with melanoma	15 (13.9)	8 (5.8)	4 (7.4)	2 (1.6)	0.003[a]
p value	<0.001	0.08	0.06		
Number of participants with integumentary cancers[2]	36 (33.3)	27 (19.4)	14 (25.9)	15 (12.1)	0.001[a]
p value	<0.001	0.10	0.04		
Number of integumentary cancer diagnoses[1,2]	42 (38.9)	34 (24.5)	14 (25.9)	18 (14.5)	<0.001[a]
p value	<0.001	0.04	0.11		

b Secondary analyses

	PD	ET	Dystonia	Control	p value
n	108	139	54	124	
Integumentary cancer					
Basal cell	16 (34.0)	15 (31.9)	9 (19.1)	7 (14.9)	0.07[a]
Squamous	7 (13.5)	8 (13.3)	0 (0.0)	4 (7.7)	0.21[a]
Unknown	4 (3.7)	3 (2.2)	1 (1.9)	5 (4.0)	0.76[a]
Cancers of ectodermal origin					
Number of participants with ectodermal cancers[2,3]	31 (28.7)*	23 (16.5)	13 (24.1)	9 (7.3)	<0.001[a]
Number of ectodermal cancer diagnoses[1–3]	32 (29.6)*	24 (17.3)	13 (24.1)	9 (7.3)	<0.001[a]
Brain	1 (0.9)	1 (0.7)	0 (0.0)	0 (0.0)	0.68[a]
Cancers of mesodermal and mixed origin					
Number of participants with mesodermal and mixed cancers	16 (12.9)	20 (14.4)	5 (9.3)	16 (12.9)	0.77[a]
Number of mesodermal and mixed origin cancer diagnoses[1]	16 (14.8)	21 (15.1)	5 (9.3)	17 (13.7)	0.75[a]
Squamous	7 (13.5)	8 (13.3)	0 (0.0)	4 (7.7)	0.21[a]

b Secondary analyses

	PD	ET	Dystonia	Control	p value
Breast	7 (6.5)	10 (7.2)	4 (7.4)	10 (8.1)	0.98[a]
Lymphoma	2 (1.9)	2 (1.4)	0 (0.0)	0 (0.0)	0.39[a]
Myeloma	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0.56[a]
Leukemia	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.8)	0.30[a]
Oral cavity/pharynx	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.6)	0.18[a]
Cancers of endodermal origin					
Number of participants with endodermal cancers	9 (8.3)	16 (11.5)	4 (7.4)	16 (12.9)	0.58[a]
Number of endodermal cancer diagnoses [1]	10 (9.3)	18 (12.9)	4 (7.4)	16 (12.9)	0.58[a]
Uterine	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.6)	0.46[a]
Ovarian	2 (1.9)	0 (0.0)	1 (1.9)	0 (0.0)	0.18[a]
Prostate	5 (4.6)	9 (6.5)	2 (3.7)	8 (6.5)	0.82[a]
Urinary/bladder	1 (0.9)	3 (2.2)	0 (0.0)	1 (0.8)	0.57[a]
Kidney	0 (0.0)	2 (1.4)	0 (0.0)	2 (1.6)	0.47[a]
Thyroid	1 (0.9)	2 (1.4)	0 (0.0)	1 (0.8)	0.82[a]
Gastric	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Colon	1 (0.9)	1 (0.7)	0 (0.0)	2 (1.6)	0.76[a]
Liver	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Pancreas	0 (0.0)	0 (0.0)	1 (1.9)	0 (0.0)	0.08[a]
Cancers of endodermal, mesodermal, or mixed origin					
Number of participants with endodermal, mesodermal, or mixed cancers	24 (22.2)	34 (24.5)	8 (14.8)	30 (24.2)	0.51[a]
Number of endodermal, mesodermal, or mixed cancer diagnoses [1]	26 (24.1)	39 (28.1)	9 (16.7)	33 (26.6)	0.41[a]
Unspecified cancers					
Number of participants with unspecified cancers	1 (0.9)	3 (2.2)	0 (0.0)	3 (2.4)	0.59[a]
Number of unspecified cancer diagnoses [1]	1 (0.9)	3 (2.2)	0 (0.0)	3 (2.4)	0.59[a]

Values are number (percentage).

[a] Chi-square test comparing all 4 groups.

[1] Some participants had more than one cancer diagnosis.

[2]Including number of cancer diagnoses of melanoma.

The p value in some cells represents the comparison with normal controls (chi-square test or Fisher test).

Values are number (percentage).

[a]Chi-square test comparing all 4 groups.

[1]Some participants had more than one cancer diagnosis.

[2]Including number of cancer diagnoses of melanoma.

[3]Including number of cancer diagnoses of basal cell carcinoma.

*Significantly different from controls (p < 0.0017, chi-square test).

Table 3

Analysis of factors associated with cancer in controls

	All cancer	No cancer	p value	Melanoma	No melanoma	p value	Integumentary cancer	No integumentary cancer	p value
n	43	81		2	122		15	109	
Age, years	74.3±7.7 (74.0)	70.0±9.5 (71.0)	0.02[a]	69.5±0.7 (69.5)	71.5±9.2 (72.0)	0.42[a]	73.1±8.1 (73.0)	71.3±9.3 (72.0)	0.30[a]
Female gender	20 (46.5)	47 (58.0)	0.22[b]	1 (50.0)	66 (54.1)	0.91[b]	7 (46.7)	60 (55.0)	0.54[b]
Caucasian (non-Hispanic)	41 (95.3)	67 (82.7)	0.08[b]	2 (100.0)	106 (86.9)	0.58[b]	15 (100.0)	93 (85.3)	0.11[b]
Education, years	16.1±3.1 (16.0)	16.2±2.4 (16.0)	0.14[a]	15.0±4.2 (15.0)	16.2±2.7 (16.0)	0.70[a]	16.8±3.0 (16.0)	16.1±2.6 (16.0)	0.52[a]
CIRS score	8.1±3.9 (8.0)	6.2±3.7 (6.0)	0.02[a]	9.0±4.2 (9.0)	6.8±3.9 (7.0)	0.43[a]	7.6±4.3 (7.0)	6.7±3.8 (7.0)	0.50[a]
Number of prescription medications	4.0±3.0 (3.0)	3.2±2.9 (3.0)	0.16[a]	1.0±0.0 (1.0)	3.5±2.9 (3.0)	0.19[a]	3.7±2.8 (3.0)	3.5±3.0 (3.0)	0.68[a]
Years since last hospitalization	10.5±13.5 (5.0)	13.5±15.1 (7.5)	0.49[a]	6.0±5.7 (6.0)	12.5±14.7 (7.0)	0.81[a]	17.9±17.6 (13.0)	11.6±14.0 (6.0)	0.04[a]
Diabetes mellitus	3 (7.1)[‡]	11 (13.6)	0.29[b]	0 (0.0)	14 (11.5)	0.61[b]	2 (13.3)	12 (11.1)	0.80[b]
Number of live births, females	1.9±1.8 (2.0)	1.8±1.5 (2.0)	0.98[a]	3.0±0.0 (3.0)	1.8±1.6 (2.0)	0.31[a]	2.0±1.5 (2.0)	1.8±1.6 (2.0)	0.62[a]
Pack years (cigarettes)	11.1±17.9 (0.5)	10.2±15.1 (2.5)	0.57[a]	0±0.0	10.7±16.1 (2.0)	0.13[a]	9.0±13.0 (1.0)	10.8±16.5 (2.0)	0.91[a]

Values are mean ± SD (median) or number (percentage).

[a] Mann–Whitney test.

[b] Chi-square test.

[‡] Data missing for some variables.

Table 4

Logistic regression analysis of factors predicting cancers in movement disorders

Unadjusted model				Liberal adjusted model[1]				Conservative adjusted model[4]			
diagnosis	OR	95% CI	significance	diagnosis	OR	95% CI	significance	diagnosis	OR	95% CI	significance
Any type of cancer				*Any type of cancer*							
PD	1.69	0.99–2.86	0.05	PD	1.97	1.049–3.71	0.04	PD	1.69	0.99–2.86	0.05
ET	1.09	0.66–1.81	0.73	ET	1.08	0.62–1.89	0.79	ET	1.09	0.66–1.81	0.73
Dystonia	1.20	0.62–2.32	0.59	Dystonia	1.16	0.58–2.32	0.67	Dystonia	1.20	0.62–2.32	0.59
Controls	1.00			Controls	1.00			Controls	1.00		
Unadjusted model				Liberal adjusted model[2]				Conservative adjusted model[4]			
Melanoma											
PD	9.84	2.20–44.09	0.003	PD	7.09	1.52–33.0	0.01	PD	9.84	2.20–44.09	0.003
ET	3.73	0.78–17.89	0.10	ET	4.10	0.83–20.2	0.08	ET	3.73	0.78–17.89	0.10
Dystonia	4.88	0.87–27.50	0.07	Dystonia	5.27	0.90–30.93	0.06	Dystonia	4.88	0.87–27.50	0.07
Controls	1.00			Controls	1.00			Controls	1.00		
Unadjusted model				Liberal adjusted model[3]				Conservative adjusted model[4]			
Integumentary cancers											
PD	3.63	1.86–7.11	0.0002	PD	2.63	1.24–5.62	0.01	PD	3.63	1.86–7.11	0.0002
ET	1.75	0.88–3.47	0.10	ET	1.47	0.71–3.06	0.31	ET	1.75	0.88–3.47	0.10
Dystonia	2.54	1.13–5.74	0.03	Dystonia	2.21	0.90–5.45	0.07	Dystonia	2.54	1.13–5.74	0.03
Controls	1.00			Controls	1.00			Controls	1.00		

[1] Adjusted for number of prescription medications, age in years, Caucasian race and Cumulative Illness Rating Scale Score.

[2] Adjusted for number of prescription medications.

[3] Adjusted for number of prescription medications and years since last hospitalization.

[4] The conservative model resembled the unadjusted model because there were no variables that met stringent criteria for inclusion in the model.

Liberal models included variables that were associated either with the cancer in question or the diagnosis in question.

Conservative models included variables that were associated both with the cancer in question and the diagnosis in question.