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Cancer in Parkinson's disease

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Abstract

INTRODUCTION—We examined the prevalence of cancer in patients with Parkinson's disease (PD) and controls evaluated at the Mayo Clinic Florida between 2003 and 2014.

METHODS—We retrospectively collected information regarding cancer diagnoses and diagnosis of PD in a total of 971 unrelated PD patients and 478 controls, and all were white. For PD patients,

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Author Contributions

All authors have contributed substantially to this research study. Study concept and design (ZKW). Drafting of the manuscript (PT). Acquisition of data (SC, SF, PT, RJU, JAVG, ZKW). Analysis and interpretation of data (MGH, NND). Revising of the manuscript (PT, NND, MGH, AS, SF, SC, RJU, JAVG, ZKW).

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we examined cancers diagnosed before and after PD diagnosis separately in addition to considering all cancer diagnoses.

RESULTS—Twenty different cancers were identified. In PD patients, the most common types of cancer were skin cancer (17.3% overall; 10.6% before PD), followed by nonmelanoma skin cancer (16.0% overall; 9.7% before PD), prostate cancer in men (12.8% overall; 9.2% before PD), breast cancer in women (10.6% overall; 6.3% before PD), and melanoma (2.4% overall; 1.1% before PD). Compared to controls, a significantly lower frequency of nonmelanoma skin cancer (odds ratio [OR]: 0.62, $P=0.0024$) and any skin cancer (OR: 0.57, $P=0.0002$) was observed in PD patients. These differences were greater when considering only cases with cancers that occurred before PD diagnosis (OR: 0.49, $P<0.0001$; OR: 0.45, $P<0.0001$, respectively), and there was a lower frequency of melanoma and any cancer preceding PD diagnosis compared to controls (OR: 0.31, $P=0.003$; OR: 0.36, $P<0.0001$). There was no evidence of a frequency difference for any other cancer.

CONCLUSIONS—PD patients had a lower frequency of skin cancers or any cancer prior to PD diagnosis compared to controls, suggesting that cancer may have a protective effect on PD risk.

Keywords

Parkinson's disease; Parkinsonism; Cancer; Basal ganglia; Primary brain tumor; Melanoma

INTRODUCTION

There is growing epidemiological evidence suggesting that patients with Parkinson's disease (PD) have a lower risk of developing most types of cancer compared with the general population [1]. However, high rates of melanoma have often been associated with PD [1–14]. Other reports suggest a similar association between PD and nonmelanoma skin cancer, thyroid cancer, and breast cancer, but the evidence is less compelling [12, 15].

The aim of this study was to examine the prevalence of various types of cancer in PD patients compared with healthy controls from the Mayo Clinic Florida.

MATERIAL AND METHODS

Study subjects

A total of 971 patients with PD and 478 healthy controls seen at the Mayo Clinic Florida between September 2003 and December 2014 were included in this retrospective study. All PD patients were seen by Mayo Clinic movement disorder specialists and met the UK Parkinson's Disease Society Brain Bank (UKPDSBB) clinical diagnostic criteria [16]. However, no distinction was made between sporadic and familial cases. The diagnosis of cancer was either made or confirmed by Mayo Clinic specialists. Control subjects had neither a history of neurologic disorders nor any neurological abnormalities during clinical examination. All individuals were white and none of the subjects were related. A detailed medical history, including history of cancers, was obtained from each individual.

For every individual, data on 22 different cancers (listed in Table 1) was collected from medical charts until the date of the last clinic visit. For patients who had PD and cancer, we also recorded whether the cancer occurred before or after PD diagnosis.

Statistical analysis

For cancers that occurred in fewer than five subjects in the overall series of PD patients and controls, these were descriptively summarized, but no statistical comparison between PD patients and controls was performed. Odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression models were used to compare frequencies of the remaining more common types of cancer, and also the presence of any cancer, between patients with PD and controls. For types of cancer that occurred in ten or more individuals, these logistic regression models were adjusted for age and sex, with the exception of sex-specific cancers (breast, prostate, ovarian, uterine, testicular) which were not adjusted for sex. For types of cancer that occurred in fewer than ten individuals, no model adjustment was made.

Two approaches were utilized to compare each type of cancer between PD patients and controls. In the first approach, all cancers that occurred for PD patients were considered, regardless of whether the cancer occurred before or after PD diagnosis in order to perform a more general comparison with controls. For the second approach, only cancers that occurred prior to PD diagnosis were included in order to evaluate whether various cancers may act as risk factors (or protective factors) for PD. When age was adjusted for in logistic regression analysis, age at the last clinic visit was used for the first approach in PD patients, while age at PD diagnosis was used for the second approach. We used a Bonferroni correction to adjust for multiple testing, after which P-values ≤ 0.0033 were considered statistically significant. Statistical analysis was performed with the use of SAS (version 9.2; SAS Institute, Inc., Cary, North Carolina).

RESULTS

The median age of patients at PD diagnosis was 67 years (range: 29–95 years). The median length of time between PD diagnosis and the last clinic visit was 4.6 years (range: 0 days–40 years), and 79 PD patients (8.1%) had no clinic visits following PD diagnosis. For PD patients, the median age at the last clinic visit was 73 years (range: 29.4–100.2 years), which was relatively similar to that of controls (median: 69 years, range: 18–96 years). There were more men in the PD group compared to controls (64.2% vs. 45.2%).

Of the 22 cancers that were examined, 20 were identified, and 18 of these were observed in PD patients. A comparison of the frequency of each type of cancer between patients with PD and controls is shown in Table 1, where age and sex were adjusted for when possible in order to address the possibility that the aforementioned small to moderate differences in those two variables may affect our results. In PD patients, the most common types of cancer were skin cancer (17.3%, 10.6% before PD diagnosis), nonmelanoma skin cancer (16.0% overall, 9.7% before PD diagnosis), prostate cancer (12.8% in men overall, 9.2% before PD diagnosis), breast cancer (10.6% in women overall, 6.3% before PD diagnosis), and melanoma (2.4% overall, 1.1% before PD diagnosis). Compared to controls and after adjustment for age and sex, there was a lower frequency of nonmelanoma skin cancer (OR:

0.62, $P=0.0024$), any skin cancer (OR: 0.57, $P=0.0002$), and cancer of any type (OR: 0.68, $P=0.0034$) for PD patients, but the latter finding was not quite significant after adjustment for multiple testing ($p=0.0033$ considered significant). A similar but nonsignificant protective finding was observed for melanoma (OR: 0.52, $P=0.052$). When considering only cancers that occurred before PD diagnosis in PD patients, these differences strengthened for each of nonmelanoma skin-cancer (OR: 0.49, $P<0.0001$), any skin cancer (OR: 0.45, $P<0.0001$), cancer of any type (OR: 0.36, $P<0.0001$), and melanoma (OR: 0.31, $P=0.0030$).

Of note, simply comparing the frequencies of melanoma, nonmelanoma skin cancer, any skin cancer, and cancer of any type (occurring before or after PD diagnosis) indicated that there were few differences between the outcomes of these four cancer between PD patients and controls, but as previously mentioned, the age and sex-adjusted ORs were relatively strong and statistically significant (Table 1). This is due to the fact that both age and especially sex differed notably between PD patients and controls and were also very highly associated with these cancer outcomes. This creates a very strong confounding situation that is only properly addressed in age and sex-adjusted analyses. To better illustrate the differences in these types of cancer between PD patients and controls, Table 2 displays their frequencies when stratifying by median age at the last clinic visit in the overall cohort (72.0 vs. > 72.0 years) and sex.

There were no statistically significant differences in the frequency of any other cancer between PD patients and controls (Table 1). The frequency of esophageal cancer before PD diagnosis was lower in PD patients than in controls (0.0% vs. 0.6% , $P=0.036$) only when cancers that occurred prior to PD diagnosis were examined; however this finding did not remain significant after adjustment for multiple testing.

A total of 892 PD patients of the 971 PD patients included in the study had at least one return clinic visit following PD diagnosis. In this group a median follow-up length after PD diagnosis was 5.0 years (range: 1 day–39.8 years). Among the types of cancer that occurred after PD diagnosis, the most frequent types were skin cancer (6.8%), nonmelanoma skin cancer (6.2%), breast cancer in women (4.5%), prostate cancer in men (3.5%), and melanoma (1.2%) (Table 3).

DISCUSSION

Our results show that the risk of developing melanoma in this study was lower in PD patients compared to controls. This difference was statistically significant when considering only melanoma cases that occurred before PD diagnosis in PD patients (Table 1). A caveat of our study that must be acknowledged is the lack of information regarding other potential confounding factors. However, since it seems unlikely that such factors would differ noticeably between PD patients and controls given that melanoma and PD do not share common risk factors, it is probable that they would have minimal impact on our results. Therefore, acknowledging this issue, our findings suggest that melanoma may have a protective effect on PD risk.

Although most reports have shown a positive association between PD and melanoma, the temporal relationship between PD and melanoma risk varies among PD patients in different studies [17]. Only a few studies showed an association between PD and melanoma prior to PD diagnosis. Based on the Danish Cancer Registry an increased risk for melanoma was seen (OR 1.44; 95% CI, 1.03–2.01) [11]. However, another publication that used the same database found an increase in melanoma incidence following PD diagnosis (OR 1.95; 95% CI, 1.4–2.6) [12]. The results from a publication by Fois et al. [7] were similar to the findings of our study. Fois et al. examined an incidence of cancer in a cohort of 4355 PD patients and a control group. The frequency of malignant melanoma in PD patients was significantly lower before PD diagnosis compared to controls [7].

However in the majority of publications, an association between PD and melanoma was found in cases in which the diagnosis of melanoma followed the diagnosis of PD. In a meta-analysis of 12 studies [3, 7, 9, 11, 12, 14, 18–21], a higher occurrence of melanoma was also found with an overall pooled OR of 2.11 (95% CI, 1.26–3.54) [22]. A detailed analysis of the temporal relationship between PD and melanoma showed that the occurrence of melanoma was significantly higher only after PD diagnosis (OR 3.61; 95% CI, 1.49–8.77 vs. OR 1.07; 95% CI, 0.62–1.84 prior to PD diagnosis) [22]. Of note, although a consistent pattern of increased melanoma occurrence was associated with PD and vice versa was seen across all 12 publications except the one by Fois et al. [7], the aforementioned association between PD and melanoma was not statistically significant in most of the 12 studies included in this meta-analysis [22]. However, a higher relative risk for melanoma following PD diagnosis was also identified in four additional publications [4, 7, 9].

The results of a higher risk of melanoma after PD are in line with a hypothesis on the causative role of levodopa [23]. The findings from our study neither support nor oppose this hypothesis because this statistically significant decrease in melanoma occurrence was seen only prior to PD diagnosis. In order to adequately address whether PD (or levodopa) may somehow increase risk of melanoma, controls would need to be matched to PD patients based on age at diagnosis and evaluated for occurrence of cancer prospectively over time, and this was not the case for our study.

In another meta-analysis of 29 publications that investigated the association between cancer and PD in a cohort of 107598 PD patients, PD was found to be associated with an overall increased risk of melanoma [1].

In many publications the race of the study participants was not given [7]. In contrast, only white patients were included in our study, whereas in a publication by Driver et al. [6] 92.2% of study participants, and 80.3% of PD patients recruited for the study of Lo et al. [9] were white. Race is an important aspect because the incidence of melanoma is higher in white than in black populations [24].

Melanoma is a malignant tumor of melanocytes that most commonly affect the skin with an estimated incidence rate of 3% per year [24], but it is also an uncommon finding in PD. In our study, the incidence of melanoma reached the rate of 2.4%, but in previous publications melanoma occurred even less frequently, 1.11 % [5, 14]. General risk factors for developing

melanoma include ultraviolet light exposure, blistering burns, red hair, blue eyes, an increased number of pigmented skin changes, such as nevi [24]. It remains open as to whether these risk factors might have contributed to the differences in association between PD and melanoma in this analysis and most of the previous studies. It should also be acknowledged that some PD patients and controls from our cohort might have obtained a diagnosis of cancer at other institutions following their final visit at the Mayo Clinic. Alternatively, under- or overdiagnosis of cancer in both controls and PD patients might have been due to the quality and availability of medical care in their regions as well as individual awareness on the importance to undergo medical examinations and their frequency. Importantly, it seems unlikely that underdiagnosis or overdiagnosis of cancer would differ systematically between the PD patients and controls in our study, and therefore this issue should have little if any effect on our findings.

As an etiologic factor for melanoma in PD, levodopa treatment was suggested. Levodopa is converted to melanin by the enzyme tyrosine hydroxylase, and melanin is overexpressed in melanoma tumor cells [23]. This observation led to the labeling of levodopa and dopamine agonists with precautionary statements about a possible causal association between these drugs and the risk of developing melanoma by the United States Food and Drug Administration. Thus, one could argue that the differences between our database and the observation from most of the studies on an increased risk of melanoma in PD might be explained by higher and longer levodopa exposure of patients enrolled in those studies. However, the association between levodopa treatment and the risk of developing melanoma has not been confirmed by epidemiologic studies, and some authors argue that the occurrence of melanoma in PD patients is unrelated to dopaminergic therapy [14, 25], pointing to the importance of environmental and genetic factors such as mutations in the genes related to pigmentation [20, 21, 26].

In our study, melanoma was the fifth most common cancer independently from the point in time of cancer diagnosis and in those cases in which cancer was diagnosed after PD diagnosis (Table 1 and Table 3). The remaining 17 types of cancer identified in PD patients included cancers of the breast, colon, prostate, bladder, pancreas, ovaries, lungs, bile duct, uterus, esophagus, thyroid, kidney, and testicles as well as leukemia, lymphoma, nonmelanoma skin cancer, and any skin cancer (Table 1). Fois et al. [7] identified additional cancer types, including cancers of the oropharynx, stomach, rectum, and cervix, brain and bone tumors, and multiple myeloma. In accordance with the results from other publications [1], PD patients in our study were found to have a significantly decreased risk of nonmelanoma skin cancer. The frequency of nonmelanoma skin cancer was significantly lower in all PD patients compared to controls. However, the difference increased when considering only those cases with nonmelanoma skin cancer that occurred before a diagnosis of PD (Table 2). The same findings were seen with regard to any skin cancer (Table 2). In the analysis by Fois et al., the incidence of nonmelanoma skin cancer was significantly lower after PD diagnosis as was the incidence of cancers of the oropharynx, stomach, and prostate and non-Hodgkin's lymphoma [7].

The aforementioned differences between PD patients and controls with regard to the frequency of melanoma, nonmelanoma skin cancer, and any skin cancer, as a simple

examination of observed frequencies without adjusting for age at the last clinic visit and sex provided evidence of little difference for these three cancer types. However, the results differed after adjustment for age and sex (Table 2). In most publications the risk of cancers was adjusted for covariates between PD cases and controls. In the study by Foiss et al. [7], the rate of cancer was adjusted for sex, age in 5 year bands, time period in single calendar years and district of residence. The risk of melanoma was also adjusted for age and sex in the study by Bertoni et al. [4]. In the publication based on the Danish Cancer Registry each PD case was matched to four controls on sex, year of birth and survivorship [11, 12]. The relative risks of cancer in PD were computed by comparison PD patients with cohorts matched for sex, age, and birth place in the study by Kareus et al. [8].

A high morbidity in PD patients has also been reported for some other cancers, including breast and prostate cancers, although the results are ambiguous [1, 17]. In our study, the incidence of breast cancer, prostate cancer or brain tumors did not differ between PD patients and the control groups (pancreatic cancer= PD 0.2% vs. controls 0/478 0.0%; lung cancer= PD 0.6% vs. controls 0.6%; brain tumor= PD 0.0% vs. controls 0.0%).

PD is thought to carry a reduced risk of cancer overall compared to the general population [1, 7]. In the meta-analysis of 29 studies described above, PD was associated with a 27% decreased risk of developing cancer [1]. The risk reduction was even greater (38%) when melanoma and other skin tumors were excluded. In our study, there was also an overall risk reduction of developing any type cancer in PD patients compared to controls and after adjusting for age and sex. However, this finding became stronger and statistically significant, only when considering the cancers that occurred before PD diagnosis. These results suggest a protective effect of cancer on PD risk and argue against the common observation that PD is a protective factor for developing cancer [1]. In addition, the frequent argument that the incidence of cancer in PD is lower due to the shorter life expectancy of PD patients [1] cannot be applied to our study because the age at last follow-up for PD patients was older than that of controls (median: 73 vs. 69 years).

This decreased risk of developing cancer in PD in the aforementioned meta-analysis was particularly seen for smoking-related cancers (40% risk reduction) [1], and this tendency was independent of study design, setting, or length of follow-up. As an explanation neuroprotective effects of smoking were proposed [1, 7]. We could not confirm this observation in our study. Smoking-related cancers, including lung, bladder, pancreatic, stomach, esophageal, liver, and kidney cancers [11], showed no difference in frequency between PD patients and controls with and without the consideration of cancers that occurred before PD diagnosis (all $P = 0.12$). The only exception was esophageal cancer; its frequency before PD diagnosis was lower than its frequency in controls (0.0% vs. 0.6%, $P = 0.036$), but this did not remain significant after multiple testing adjustment. In general and except for skin cancers, all of the types of cancer we studied had a similar frequency in PD patients and controls (Table 1). Not all studies provided a clear definition of PD [1]. In contrast, PD patients included in our study were unrelated and met the UKPDSBB clinical diagnostic criteria [16]. However, no distinction was made between sporadic and potentially hereditary forms of PD. Recently, there have been some studies on cancer in hereditary PD, such as those caused by mutations in PARK1 (*SNCA*), PARK2 (*PARK*), PARK6 (*PINK1*),

PARK7 (*DJ-1*), and PARK8 (*LRRK2*) [17]. Breast, lung, and prostate cancers as well as melanoma have been most frequently reported associated with patients who have mutations in these genes [17]. In a large family with the LRRK2 p.R1441C mutation identified in 23 affected members, eight different types of cancer were diagnosed, including lung, testicular, colon, bladder, pancreatic, and gall cancer [27, 28]. Colon cancer was found in four members, suggesting a potential link between the LRRK2 p.R1441C mutation and colon cancer. Of note, only one of these patients developed PD, whereas the rest remained asymptomatic mutation carriers.

Our study has some weaknesses and limitations. Both PD and cancer have variable latency periods that sometimes make the early diagnosis difficult and highlights a challenge of analyzing the temporal association between the two diseases. This issue is important to consider when interpreting our results that attempt to separate cancers into whether they occurred before or after PD diagnosis. The UKPDSBB clinical diagnostic criteria [16] are focused on motor symptoms and neglect preceding non-motor symptoms, such as autonomic dysfunction, anosmia, mood and sleep disorders. In addition, none of the enrolled PD patients was examined with DaTscan due to the non-availability of this diagnostic method during most of the study time. We did not search for neuropathology data of PD patients that may have been autopsied to confirm the clinical diagnosis. However, all enrolled PD patients met the stringent UKPDSBB criteria at every clinic visit and no change of diagnose from PD to atypical parkinsonism was recorded throughout the study period. Environmental factors including diet, occupation, and exposure to toxins or metals that may contribute to both cancer and PD were not included in our analysis, either. As mentioned above excessive sunlight exposure promotes skin cancers. This effect, however, is difficult to measure. The Mayo Clinic is a tertiary referral center for patients from the whole USA and abroad. In addition, residents of states with high sun exposure, such as Florida, were often temporary, and among permanent residents, sun exposure may depend on individual habits and differences in insolation of their places of residence.

In conclusion, skin cancers occur significantly less often in PD patients than controls, especially in cases who have skin cancer that occurs before PD diagnosis. The risk of developing cancer of any type preceding PD is also significantly lower compared to controls, which suggests that skin cancers and cancer in general may have a protective effect on PD risk. All other types of cancer from the Mayo Clinic Florida database occurred at a similar frequency in PD patients and controls.

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Abbreviations

CI	confidence interval
OR	odds ratio
PD	Parkinson's disease

<i>SNCA</i>	alpha-synuclein gene
<i>PARK</i>	parkin gene
<i>PINK1</i>	PTEN induced putative kinase 1 gene
<i>DJ-1</i>	DJ-1 gene
<i>LRRK2</i>	leucine-rich repeat kinase 2 gene

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Highlights

- Skin cancers occur less often in Parkinson's disease (PD) patients than controls.
- The risk of developing any cancer preceding PD is significantly lower than in controls.
- Skin cancers and cancer in general may have a protective effect on PD risk.
- All other types of cancer occur at a similar frequency in PD patients and controls.

Table 1

Comparison of different types of cancer between PD patients and controls

Cancer type	Fraction (%) of subjects with the given type of cancer				PD patients vs. Controls			PD patients (only considering cancer before PD diagnosis) vs. controls		
	PD patients	PD patients (only considering cancer before PD diagnosis)	Controls		OR (95% CI)	P-value		OR (95% CI)	P-value	
Breast cancer (women only)	37/348 (10.6%)	22/347 (6.3%)	18/262 (6.9%)		1.32 (0.73, 2.40) ^a	0.36		0.95 (0.50, 1.83) ^a	0.88	
Colon cancer	17/971 (1.8%)	12/970 (1.2%)	5/478 (1.0%)		1.19 (0.43, 3.30) ^{a,g}	0.74		1.12 (0.38, 3.26) ^{a,g}	0.84	
Leukemia	6/971 (0.6%)	2/971 (0.2%)	2/478 (0.4%)		1.48 (0.30, 7.36)	0.63		0.49 (0.07, 3.50)	0.48	
Lymphoma	15/971 (1.5%)	10/971 (1.0%)	10/478 (2.1%)		0.77 (0.34, 1.76) ^{a,g}	0.54		0.61 (0.25, 1.50) ^{a,g}	0.28	
Prostate cancer (men only)	80/623 (12.8%)	57/620 (9.2%)	24/230 (11.1%)		1.01 (0.61, 1.66) ^a	0.97		1.00 (0.59, 1.67) ^a	0.99	
Bladder cancer	15/971 (1.5%)	7/971 (0.7%)	6/478 (1.3%)		0.88 (0.33, 2.35) ^{a,g}	0.80		0.55 (0.18, 1.69) ^{a,g}	0.30	
Pancreatic cancer	2/971 (0.2%)	1/971 (0.1%)	0/478 (0.0%)		N/A	N/A		N/A	N/A	
Melanoma	23/971 (2.4%)	11/970 (1.1%)	16/478 (3.3%)		0.52 (0.26, 1.01) ^{a,g}	0.052		0.31 (0.14, 0.67) ^{a,g}	0.0030	
Nonmelanoma skin cancer	155/971 (16.0%)	94/966 (9.7%)	85/478 (17.8%)		0.62 (0.45, 0.84) ^{a,g}	0.0024		0.49 (0.35, 0.69) ^{a,g}	<0.0001	
Any skin cancer	168/971 (17.3%)	102/966 (10.6%)	97/478 (20.3%)		0.57 (0.42, 0.77) ^{a,g}	0.0002		0.45 (0.33, 0.62) ^{a,g}	<0.0001	
Ovarian cancer (women only)	1/348 (0.3%)	0/348 (0.0%)	1/262 (0.4%)		N/A	N/A		N/A	N/A	
Lung cancer	6/971 (0.6%)	1/971 (0.1%)	3/478 (0.6%)		0.98 (0.25, 3.95)	0.98		0.16 (0.02, 1.57)	0.12	
Brain cancer	0/971 (0.0%)	0/971 (0.0%)	0/478 (0.0%)		N/A	N/A		N/A	N/A	
Stomach cancer	0/971 (0.0%)	0/971 (0.0%)	0/478 (0.0%)		N/A	N/A		N/A	N/A	
Bile duct cancer	1/971 (0.1%)	0/971 (0.0%)	0/478 (0.0%)		N/A	N/A		N/A	N/A	
Uterine cancer (women only)	6/348 (1.7%)	4/348 (1.1%)	5/262 (1.9%)		0.79 (0.24, 2.66) ^a	0.71		0.60 (0.16, 2.25)	0.45	
Esophageal cancer	2/971 (0.2%)	0/971 (0.0%)	3/478 (0.6%)		0.33 (0.05, 1.97)	0.22		N/A	0.036	
Liver cancer	0/971 (0.0%)	0/971 (0.0%)	1/478 (0.2%)		N/A	N/A		N/A	N/A	
Thyroid cancer	6/971 (0.6%)	5/971 (0.5%)	5/478 (1.0%)		0.49 (0.15, 1.66) ^{a,g}	0.25		0.46 (0.13, 1.62) ^{a,g}	0.22	
Bone cancer	0/971 (0.0%)	0/971 (0.0%)	1/478 (0.2%)		N/A	N/A		N/A	N/A	
Kidney cancer	10/971 (1.0%)	8/971 (0.8%)	2/478 (0.4%)		1.54 (0.33, 7.14) ^{a,g}	0.58		1.72 (0.36, 8.24) ^{a,g}	0.50	
Testicular cancer (men only)	2/623 (0.3%)	2/623 (0.3%)	1/230 (0.5%)		N/A	N/A		N/A	N/A	
Any cancer	315/971 (32.4%)	202/971 (20.8%)	159/478 (33.3%)		0.68 (0.53, 0.88) ^{a,g}	0.0034		0.36 (0.27, 0.47) ^{a,g}	<0.0001	

For cancer types that occurred in fewer than five subjects in the combined series of PD patients and controls, statistical tests were not performed. ORs, 95% CIs, and p-values result from logistic regression models.

$\hat{g}$ Indicates a model that was adjusted for age alone.

$\hat{g}_{age}$ Indicates a model that was adjusted for age and gender.

For cancer types that occurred in ten or fewer subjects, no superscript is given, and logistic regression models were not adjusted for any variables. For PD patients, the age that was adjusted for in logistic regression analysis was age at the last clinic visit when considering all cancer and age at PD diagnosis was considering only cancer that occurred before PD diagnosis. The temporal relationship between the occurrence of cancer and PD diagnosis was unknown for breast cancer (n=1), colon cancer (n=1), prostate cancer (n=3), melanoma (n=1), nonmelanoma skin cancer (n=5), and any skin cancer (n=5). P-values 0.0033 were considered as statistically significant after applying a Bonferroni correction for multiple testing. OR=odds ratio; CI=confidence interval.

Table 2

Comparison of the frequency of nonmelanoma skin cancer, melanoma, and any skin cancer between PD patients and controls when stratifying by age at last clinic visit and sex

Fraction (%) of subjects with the given type of cancer			
Cancer type/patient subgroup		PD patients	Controls
Nonmelanoma skin cancer			
Age	72.0 years & Female	8/161 (5.0%)	16/164 (9.8%)
Age	72.0 years & Male	24/287 (8.4%)	15/111 (13.5%)
Age >	72.0 years & Female	32/187 (17.1%)	23/98 (23.5%)
Age >	72.0 years & Male	91/336 (27.1%)	31/105 (29.5%)
Melanoma			
Age	72.0 years & Female	1/161 (0.6%)	2/164 (1.2%)
Age	72.0 years & Male	3/287 (1.1%)	1/111 (0.9%)
Age >	72.0 years & Female	6/187 (3.2%)	2/98 (2.0%)
Age >	72.0 years & Male	13/336 (3.9%)	11/105 (10.5%)
Any skin cancer			
Age	72.0 years & Female	8/161 (5.0%)	17/164 (10.4%)
Age	72.0 years & Male	26/287 (9.1%)	16/111 (14.4%)
Age >	72.0 years & Female	38/187 (20.3%)	25/98 (25.5%)
Age >	72.0 years & Male	96/336 (28.6%)	39/105 (37.1%)
Any cancer			
Age	72.0 years & Female	25/161 (15.5%)	33/164 (20.1%)
Age	72.0 years & Male	55/287 (19.2%)	24/111 (21.6%)
Age >	72.0 years & Female	71/187 (38.0%)	41/98 (41.8%)
Age >	72.0 years & Male	164/336 (48.8%)	61/105 (58.1%)

Age at last clinic visit was categorized based on the median for the overall cohort of PD patients and controls, which was 72.0 years.

Table 3

Occurrence of various types of cancer after PD diagnosis for the 892 PD patients who had at least one clinic visit following PD diagnosis

Cancer type	Fraction (%) of patients
Breast cancer (women only)	14/314 (4.5%)
Colon cancer	4/891 (0.5%)
Leukemia	4/892 (0.5%)
Lymphoma	5/892 (0.6%)
Prostate cancer (men only)	20/574 (3.5%)
Bladder cancer	8/892 (0.9%)
Pancreatic cancer	1/892 (0.1%)
Melanoma	11/891 (1.2%)
Nonmelanoma skin cancer	55/887 (6.2%)
Any skin cancer	60/887 (6.8%)
Ovarian cancer (women only)	1/315 (0.3%)
Lung cancer	5/892 (0.6%)
Bile duct cancer	1/892 (0.1%)
Uterine cancer (women only)	2/315 (0.6%)
Esophageal cancer	2/892 (0.2%)
Thyroid cancer	1/892 (0.1%)
Kidney cancer	2/892 (0.2%)
Testicular cancer (men only)	0/577 (0.0%)