

A Prospective Cohort Study of Cancer Incidence Following the Diagnosis of Parkinson's Disease

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Abstract

Background: Prior studies suggest a decreased risk of cancer among patients with Parkinson's disease (PD).

Methods: Matched cohort analysis among the 22,071 participants in the Physician's Health Study. A total of 487 incident cases of PD without preceding cancer were identified by self-report. Each PD case was matched by age to a reference participant who was alive and cancer free at the time of PD diagnosis. Both cohorts were followed for incident cancer. We used proportional hazards models to calculate adjusted relative risks (RR) for cancer.

Results: A total of 121 cancers were confirmed during a median follow-up of 5.2 years (PD) and 5.9 years (reference). Those with PD developed less cancer (11.0% versus 14.0%), with an adjusted RR of 0.85 [95% confidence interval (95% CI), 0.59-1.22]. Reduced risk was present for smoking-related cancers such as lung (RR, 0.32), colorectal (RR, 0.54), and

bladder (RR, 0.68), as well as for most non-smoking-related cancers such as prostate cancer (RR, 0.74). In contrast, PD patients were at significantly increased risk (RR, 6.15; 95% CI, 1.77-21.37) for melanoma. PD patients who smoked were at reduced risk for smoking-related cancer (RR, 0.33; 95% CI, 0.12-0.92), whereas nonsmokers with PD were at increased risk (RR, 1.80; 95% CI, 0.60-5.39). This interaction was statistically significant ($P_{\text{interaction}} = 0.02$).

Conclusions: Our results suggest a decreased incidence of most cancers in patients with PD. PD patients had a significantly increased risk of malignant melanoma, a finding consistent with prior studies. We confirmed an interaction between smoking and the relationship of PD to smoking-related cancer that may fit the pattern of a gene-environment interaction. (Cancer Epidemiol Biomarkers Prev 2007;16(6): 1260-5)

Introduction

The majority of studies that have examined the relationship between Parkinson's disease (PD) and cancer suggest that patients with PD are at decreased risk of smoking-related and most non-smoking-related malignancies (1-7). A number of hypotheses have been invoked to explain this association. PD is caused by the degeneration and death of cells in the substantia nigra, whereas cancer is the result of inappropriate cell survival and proliferation. Genetic or environmental forces that promote one disease may thus hinder the development of the other. Although smoking is a strong risk factor for some cancers, it is a known protective factor against PD (8). It would be expected, then, to find fewer smoking-related cancers among those with PD.

Of the few cohort studies (2, 3, 5-7) that have examined the incidence of cancer in patients with PD, most have had retrospective data collection (2, 5, 6). The large, population-based databases that have had the power to show a significantly decreased risk of overall cancer in PD have had no ability to adjust for important confounders such as smoking. We thus examined the incidence of cancer following the diagnosis of PD in a prospective cohort with detailed information about smoking status and other potential confounders.

Materials and Methods

Study Population. The Physician's Health Study (PHS) is a completed randomized, placebo-controlled trial of aspirin and β -carotene for the primary prevention of cardiovascular disease and cancer among 22,071 U.S. male physicians. A detailed description of the trial cohort, methods, and findings of the study has previously been described (9, 10). At baseline, the participants ranged in age from 40 to 84 years, were apparently healthy, had no history of cancer (with the exception of non-melanoma skin cancer), cardiovascular disease, or other serious illnesses, and had no indication or contraindication for aspirin or other pain medication use. About 92.2% of the participants identified their race as white. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular and cancer risk factors as well as lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other medical information during the study period. Post-trial follow-up is ongoing (11). We excluded those who reported a history of PD before the receipt of the baseline questionnaire ($n = 21$) and those who had missing information on the history of smoking ($n = 67$), leaving 21,979 individuals for the analysis.

Ascertainment of PD Cases and Reference Subjects. Incident cases of PD were self-reported by the participating physicians on follow-up questionnaires that asked about new medical diagnoses. To evaluate the accuracy of the physicians' self-report of PD, we did a validation study using the available medical records of 73 participants who indicated a new diagnosis of PD. Records were obtained during the PHS when participants reported a study end point (cardiac event, TIA, stroke, cancer, pulmonary embolism, or death). The records of

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participants who reported PD before a study end point were first screened by a physician (J.D.) for evidence for PD. The records were then reviewed independently by two trained neurologists (T.K. and G.L.).

The clinical diagnosis of PD was considered valid if record review revealed one or more of the following: (a) established diagnosis of PD in the medical record or PD as cause of death on the death certificate; (b) current use of PD medication such as 3,4-dihydroxy-L-phenylalanine (DOPA) or a DOPA agonist; (c) neurologic examination with physical findings consistent with parkinsonism (rest tremor, rigidity, bradykinesia, or postural instability) with no evidence of a secondary cause of parkinsonism such as stroke, history of encephalitis, brain tumor or neuroleptic treatment in the year before disease onset; patients who developed dementia or dysautonomia within the first year of PD diagnosis were also not considered valid cases of idiopathic PD; (d) patient followed by a neurologist for idiopathic PD.

Of the 73 patients with available medical records, the self-reported PD diagnosis was found to be valid in 90% (66 patients). Of these, 26 patients had an established diagnosis and confirmatory neurologic exam and were on PD medication. Thirty-six patients had an established diagnosis and were taking PD medication, and eight had an established diagnosis or were taking PD medication. In 7% (5 patients), criteria for a clinical diagnosis of parkinsonism was present, but a secondary cause could not be ruled out. The diagnosis was found to be incorrect in only 3% (2 patients): one patient had intention tremor, and the other did not have adequate evidence for a diagnosis of PD.

We randomly selected for each PD patient a reference participant who was of the same baseline age (± 1 year) and who was alive and cancer free on the date of diagnosis of PD in the case and remained free of PD for an additional 5 years (to avoid the possibility of subclinical PD).

Ascertainment of Cancer. The development of cancer following the diagnosis of PD (exposed cohort) or the index date (reference cohort) was the study outcome. Nonfatal cases of cancer were reported by the participants on follow-up questionnaires and were confirmed by a review of medical records and pathology reports by an EndPoints Committee of study physicians. Only confirmed cases of cancer were used in this analysis. We categorized cancers into smoking related (lung, colorectal, bladder, kidney, pancreas, and head and neck) and non-smoking-related groups (12).

Statistical Analysis. We first described the baseline characteristics of the two cohorts by means of descriptive statistics using proportions for categorical variables and medians for continuous variables. Each reference subject was given the date of PD diagnosis of the matched case as an index date. Individuals who did not develop cancer were censored at death or the date of last follow-up. Survival curves for those with and without PD were calculated from the date of PD diagnosis or index date using the Kaplan-Meier method. The log-rank test was used to compare the differences between curves.

Cox proportional hazards models were used to estimate the relative risk of cancer in those with and without a history of PD. We adjusted the analysis for the following known or suspected confounders: smoking status (never versus ever), body mass index (BMI, <25 kg/m², ≥ 25 kg/m²), alcohol use (rarely, weekly, daily), and physical activity vigorous enough to work up a sweat (less than once a week, greater than or equal to once a week). The incidence of both PD and cancer is strongly determined by age. In addition to matching on age, we used age (in years) as the time scale for the proportional hazards model to further account for this variable. All of our models met proportional hazards assumptions. We did analyses for overall cancer, smoking- and non-smoking-related cancers,

and various cancer subtypes. When there were zero cancers of a certain type in one of the cohorts, to estimate relative risk we generated an odds ratio (OR) and 95% confidence interval (95% CI) using the Peto formula with a correction for the zero cell by adding 0.5 to each cell (13).

We ran separate models to determine if the relationship between PD and overall cancer was modified by smoking status (ever smoker versus never smoker), age at study randomization (<55 versus ≥ 55), or age at PD diagnosis or index date (<60 versus ≥ 60). We included an interaction term in the model to test for statistically significant effect modification. We then did subgroup analyses to determine if smoking modifies the relationship between PD and smoking-related or non-smoking-related cancers. All statistical calculations were done using SAS statistical software (SAS Institute, Inc., version 9.1). All *P* values are two tailed, and we considered a *P* < 0.05 as statistically significant.

Results

A total of 572 participants reported incident PD in the PHS over the 23-year follow-up period. Of these, 85 were excluded due to a history of preceding cancer, leaving a cohort of 487 PD patients. These were matched by age to 487 reference subjects.

The median age at PHS randomization of the PD cohort was 59.7 years, and the reference cohort was 59.8 years. The median age at PD diagnosis was 72.2 years (range, 45.7-93.9). There were fewer heavy smokers (≥ 20 cigarettes/day) among PD patients (3.9%) than reference subjects (5.1%). In contrast, PD patients were more likely to be daily drinkers (28.9%) than reference subjects (24.7%). The cohorts were very similar in terms of BMI and physical activity. The baseline characteristics of participants are summarized in Table 1.

A total of 121 cancers were confirmed over a median follow-up of 5.2 years in the PD cohort and 5.9 years in the reference cohort. About 25% of the study population was followed for at least 10 years. The association between PD and cancer is presented in Tables 2 and 3. Overall cancer was less frequent in those with PD (11.0%) than in reference subjects (14.0%), with a crude relative risk (RR) of 0.84 (95% CI, 0.59-1.21) and multivariable adjusted RR of 0.85 (95% CI, 0.59-1.22). The decreased risk was more evident in smoking-related cancers such as lung (RR, 0.32), colorectal (RR, 0.54), and bladder (RR,

Table 1. Baseline characteristics of PD patients and reference subjects

Characteristic	PD patients (N = 487)	Reference subjects (N = 487)
Median age at PHS randomization	59.7 (40.1-85.0)	59.8 (39.8-84.6)
Median age at PD diagnosis	72.2 (45.7-93.9)	
History of smoking	<i>n</i> (%)	
Never	250 (51.3)	246 (50.5)
Past	206 (42.3)	204 (41.9)
Current (<20/d)	12 (2.5)	12 (2.5)
Current (≥ 20 /d)	19 (3.9)	25 (5.1)
Alcohol use		
0 to thrice per month	115 (23.9)	136 (28.3)
1-6 times per week	227 (47.2)	226 (47.0)
\geq Daily	139 (28.9)	119 (24.7)
Physical activity		
Exercise to sweat \geq once per week	333 (69.5)	331 (69.0)
Exercise to sweat \leq once per week	146 (30.5)	149 (31.0)
WHO BMI category*		
<25 kg/m ²	281 (57.7)	281 (57.8)
25 to <30 kg/m ²	188 (38.6)	193 (39.7)
≥ 30 kg/m ²	18 (3.7)	12 (2.5)

*Effective sample size of groups may vary due to missing variables.

Table 2. Crude and adjusted association between PD and subsequent cancer

	PD patients (N = 487)	Reference subjects (N = 487)	Crude RR	Multivariable adjusted RR*
	n (%)	n (%)		
Overall cancer (n = 121)	53 (43.8)	68 (56.2)	0.84 (0.59-1.21)	0.85 (0.59-1.22)
Non-smoking-related cancers (n = 86)	39 (45.4)	47 (54.6)	0.90 (0.59-1.37)	0.91 (0.60-1.40)
Smoking-related cancers (n = 35)	14 (40.0)	21 (60.0)	0.73 (0.37-1.44)	0.70 (0.35-1.38)

*Multivariable analysis adjusted for smoking status, alcohol use, BMI category, and exercise category.

0.68), but was also seen in most non-smoking-related cancers such as prostate (RR, 0.74) and hematologic malignancies (RR, 0.81). However, none of these associations reached statistical significance. An exception was malignant melanoma, for which PD patients had a statistically significant increased risk (RR, 6.15; 95% CI, 1.77-21.37).

When the relationship between PD and overall cancer was stratified by smoking status, PD patients who had ever smoked had a decreased risk (RR, 0.72; 95% CI, 0.44-1.20), whereas those who had never smoked did not (RR, 1.01; 95% CI, 0.60-1.71). This interaction, however, did not reach statistical significance.

However, when the analysis was restricted to smoking-related cancers, we found that smoking significantly modified the relationship between PD and cancer ($P_{\text{interaction}} = 0.02$). PD patients who smoked were significantly protected from cancer (RR, 0.33; 95% CI, 0.12-0.92), whereas those who had never smoked were at increased risk (RR, 1.80; 95% CI, 0.60-5.39). The results of stratification by smoking status are presented in Table 4.

Among reference subjects who had ever smoked, there were 16 cases of smoking-related cancer (6 colorectal cancers, 5 lung cancers, 4 bladder cancers, and 1 head and neck cancer). PD patients who smoked developed only five smoking-related cancers (two colorectal, two pancreas, and one head and neck). In contrast, there were nine cases of smoking-related cancers among the PD patients who had never smoked (three bladder, two pancreas, two lung, one colorectal, and one head and neck), whereas reference never smokers had only five cases (two lung, two head and neck, and one bladder).

We found no evidence of effect modification by age at PHS randomization or age at diagnosis of PD on the relationship between PD and cancer.

Discussion

In this large prospective cohort of men, we found the suggestion of a decreased incidence of overall, smoking- and non-smoking-related cancer among patients with PD. In contrast, those with PD had a significantly increased risk of malignant melanoma. We confirmed the presence of an interaction between smoking and the relationship of PD to smoking-related cancer.

Our paper contributes to the epidemiologic evidence that patients with PD have an increased risk of malignant

melanoma, an association that can now be considered well established (4, 7, 14). In studies using the Danish Cancer Registry, Olsen et al. (7, 14) found an increased risk of melanoma both before (OR, 1.44; 95% CI, 1.03-2.01) and after (OR, 1.95; 95% CI, 1.4-2.6) the diagnosis of PD. This finding suggests the possibility that PD and melanoma share genetic or environmental risk factors.

A number of case reports have implicated levodopa use as a risk factor for melanoma, but more recent reviews of the evidence do not support a causal association (15, 16). Zanetti et al. (16) have proposed that the association between PD and melanoma might be due to a shared genetic pattern or to an external factor such as social class. Higher social class is a strong predictor of melanoma, most likely due to increased opportunities for sun exposure (17). PD is also more common in those of higher social class, perhaps due to lower rates of tobacco use or physical activity (18). Our results argue against confounding by social class because our cohort is very homogeneous with respect to socioeconomic factors, and we still find PD to be a significant risk factor for melanoma. Our findings support the theory that PD and melanoma share genetic risk factors.

Despite the absence of a clear biological explanation, our data support previous findings of a significantly increased risk of malignant melanoma in patients with PD and, if confirmed, suggest that these patients may benefit from increased melanoma screening.

Our findings of a decrease in overall cancer in patients with PD are consistent with four (2, 3, 5, 7) of the five (6) prior cohort studies, the results of which are summarized in Table 5. In the largest study to date, Olsen et al. (7) reported a standardized incidence ratio (SIR) of 0.88 for all cancers (95% CI, 0.8-1.0) among 14,088 patients with PD identified from the Danish National Hospital Register. There was a decreased risk of both smoking-related [risk ratio (RR), 0.58; 95% CI, 0.4-0.6] and non-smoking-related cancer (RR, 0.81; 95% CI, 0.7-0.9).

An obvious explanation for a decreased incidence of cancer in patients with PD is the well-known negative association between PD and smoking. Current smokers have a 60% decreased risk of PD, and past smokers have a 20% decreased risk (8). Although this may account for much of the difference in smoking-related cancer seen in our study, it fails to explain the decrease in non-smoking-related cancer.

Some have suggested that decreased cancer incidence in PD patients represents a survival bias because they are exposed to

Table 3. Association between PD and subsequent cancer by subtype

	PD patients (N = 487)	Reference subjects (N = 487)	Crude RR
	n (%)	n (%)	
Prostate (n = 58)	24 (41.4)	34 (58.6)	0.74 (0.44-1.25)
Hematologic malignancies (n = 10)	4 (40.0)	6 (60.0)	0.81 (0.22-2.90)
Colorectal (n = 9)	3 (33.3)	6 (66.7)	0.54 (0.14-2.16)
Melanoma (n = 9)	9 (100.0)	0 (00.0)	6.15 (1.77-21.37)
Lung (n = 9)	2 (22.2)	7 (77.8)	0.32 (0.07-1.53)
Bladder (n = 8)	3 (37.5)	5 (62.5)	0.68 (0.16-2.84)
Head and neck (n = 5)	2 (40.0)	3 (60.0)	0.83 (0.14-4.96)
Other (n = 13)	6 (46.2)	7 (53.8)	0.93 (0.31-2.77)

NOTE: "Other" cancers: cases: pancreas (4), thymus (1), thyroid (1); controls: unknown type (1), bone (1), meninges (1), hepatobiliary (2) brain (1), thyroid (1).

Table 4. Association between PD and cancer according to smoking status

	PD patients (N = 487)	Reference subjects (N = 487)	Adjusted RR*	P value for interaction
All cancers				
Smoking status				0.35
Never smoker (n = 496)	28 (50.0)	28 (50.0)	1.01 (0.60-1.71)	
Ever smoker (n = 478)	25 (38.5)	40 (61.5)	0.72 (0.44-1.20)	
Smoking-related cancers				0.02
Smoking status				
Never smoker (n = 496)	9 (64.3)	5 (35.7)	1.80 (0.60-5.39)	
Ever smoker (n = 478)	5 (23.8)	16 (76.2)	0.33 (0.12-0.92)	
Non-smoking-related cancers				0.68
Smoking status				
Never smoker (n = 496)	19 (45.2)	23 (54.8)	0.83 (0.45-1.53)	
Ever smoker (n = 478)	20 (45.5)	24 (54.6)	1.00 (0.55-1.82)	

*Adjusted for alcohol use, BMI category, and exercise category.

a higher mortality rate than the general population, and survivors may be less susceptible to cancer (19). Such bias is unlikely to explain the findings of our study, which uses only incident cases of PD and cancer and accounts for censoring and survival time.

A number of studies have found a decreased incidence of cancer before the diagnosis of PD (2, 14, 20, 21). This suggests the possibility that PD and cancer share common biological pathways, a theory bolstered by genetic evidence.

Genes linked to familial PD and other neurodegenerative diseases, such as *PARK1*, *PARK2*, and the α -synuclein gene, have been identified in a number of human cancers (22). Conversely, mutations in well-known cancer genes such as the tumor-suppressor gene *PTEN* have been found in patients with PD (23). Mutations that predispose the cell toward apoptosis would lead to the expression of PD and a decrease in cancer risk, whereas those that favor cell growth would lead to increased cancer and less frequent

Table 5. Prior cohort studies on the incidence of cancer following the diagnosis of PD

Study	Study population	Definition of PD	Definition of cancer	Adjustment for smoking or other covariates	Incidence of cancer (excluding non-melanoma skin cancer)	Comments
Jansson, 1985 (USA; ref. 2)	406 PD patients in hospital-based practice, 242 men; 164 women; no reference group—compares to cancer rate in general population. Average f/u 8.6 y.	Case series, neurologist diagnosed	Medical records	Smoking status, gender	Observed versus expected: men: RR, 0.40 (P = 0.003); women: RR, 0.58 (P = 0.10)	RR, 0.77 (P = 0.36) in smokers (n = 101); RR, 0.37 (P < 0.001) in nonsmokers (n = 305); increased frequency of melanoma in PD cases
Moller, 1995 (Denmark; ref. 3)	7,046 patients with PD (3,470 men, 3,576 women) identified from the National Danish Hospital Register; followed from first admission for PD; no reference group—compares to cancer rate in general population; average f/u: 4.6 y	International Classification of Diseases code, not verified	National Cancer Registry	None	Observed versus expected; RR, 0.88 (0.8-1.0)	Smoking related: RR, 0.49 (0.4-0.6); non-smoking related: RR, 1.01 (0.9-1.1); melanoma: 1.96 (1.1-3.2)
Minami, 1999 (Japan; ref. 5)	228 PD patients identified by population-based survey; no reference group—compares to cancer rate in general population; retrospective analysis	Hospital register, not verified	Cancer registry	Age, gender	Observed versus expected; both sexes: SIR, 0.83 (0.46-1.37); men: SIR, 0.79 (0.34-1.55); women: SIR, 0.88 (0.35-1.81)	Increased risk of breast cancer in women with PD: SIR, 5.49 (1.10-16.03)
Olsen, 2005 (Denmark; ref. 7)	Update of Danish Hospital Registry Study; 14,088 PD patients; follow-up from first outpatient visit or hospitalization for PD; no reference group—compares to cancer rate in general population; average f/u 5 y	International Classification of Diseases code, not verified	Cancer Registry	Age, gender	Observed versus expected; SIR, 0.88 (0.8-0.9); men: SIR, 0.79 (0.7-0.9); women: 0.98 (0.9-1.1)	Smoking related: RR, 0.58 (0.4-0.6); non-smoking related: RR, 0.81 (0.7-0.9); melanoma: 1.95 (1.4-2.6)
Elbaz, 2005 (USA; ref. 6)	196 patients with PD identified from population database and 185 reference subjects matched by age; median f/u 8 y for patients and 9.7 y for reference subjects	Medical records	Medical records	Age, smoking status, gender	RR, 1.28 (0.81-2.04); excluding non-melanoma skin cancers	Smoking-related cancer: RR, 0.77 (0.29-2.03); increased frequency of melanoma in PD patients; significantly increased risk of non-melanoma skin cancer in PD patients

PD. Decreased cancer incidence has also been noted in patients with Alzheimer's disease, another neurodegenerative disease of aging (24).

Elbaz et al. (21) first observed that smoking modifies the relationship between PD and smoking-related cancer, such that smokers with PD are relatively protected from smoking-related cancer, whereas never smokers with PD are at increased risk. They suggested that this was not simply due to confounding by smoking but had the nature of an interaction. In our nested case-control study of cancer preceding the diagnosis of PD in the PHS cohort (25), we found this interaction to be statistically significant. The present study confirms this finding. Overall, this pattern of association suggests a gene-environment interaction.

Smokers who develop PD despite the "protective effect" of tobacco may represent a subgroup with a particularly strong genetic predisposition for PD. PD is known to be associated with polymorphisms of the detoxifying enzyme P450 D6 (CYP2D6) that lead to poor toxin metabolism (26), and this may be the basis for the increased risk of PD in those exposed to certain pesticides (27). Poor metabolism by CYP2D6 is also associated with a decreased risk of lung cancer because there is decreased activation of procarcinogens in cigarette smoke (28). One could hypothesize that poor metabolism of toxins by CYP2D6 might account for an increased risk of toxin-related cancer in the absence of smoking. In our study, there were five cases of lung cancer among reference subjects who smoked, but the two patients with PD who developed lung cancer were nonsmokers.

The strengths of our study include the prospective nature of our analysis that used only incident cases of PD and cancer. Survival analysis techniques allowed us to account for competing causes of death and censoring, thus decreasing the possibility of bias due to differential survival between the cohorts. The study outcomes were confirmed after medical record review and included both fatal and nonfatal malignancies. We controlled for confounding by important risk factors such as age and smoking. Unlike prior studies, we were able to provide a more accurate assessment of relative risk for cancer by limiting our analysis to those who were free of cancer at study baseline. The homogeneity of our study cohort allowed us to control for socioeconomic factors that are associated with both PD and cancer risk.

Our study also had a number of important limitations. Our diagnosis of PD was based on self-report. However, prior work has shown the self-reported diagnosis of PD to be highly valid in a population of health professionals (29). Our validation study using available medical records revealed an accuracy of 90%, which is similar to that found in other validation studies of self-report in the PHS (30).

Our cohort was composed of men of the same educational level and profession who were predominantly white. Thus, our results may not be generalizable to the population at large. The distribution of cancer types in our study also differs from what one would expect in a general population of men, reflecting the fact that our subjects are physicians. Rates of prostate cancer and melanoma were higher than expected, suggesting the effect of increased surveillance. The incidence of melanoma in our population may thus be partly amplified by screening. There was a lower incidence of lung cancer than expected, likely due to the decreased frequency of smoking in our cohort as compared with the general population. Finally, despite our attempts to adjust for confounding, our results may be limited by the presence of residual confounding and the inability to account for unmeasured confounders.

In summary, our data suggest a decreased incidence of both smoking-related and non-smoking-related cancer in those with PD. These findings may support the theory that the inverse relationship between PD and cancer has a genetic

basis. This association was not significant, however, due to a lack of statistical power. Our analyses should be repeated in a prospective cohort with larger numbers of incident PD cases.

We confirmed the positive relationship between PD and melanoma, a finding with potential clinical significance for the 1.5 million Americans with PD. Finally, we confirmed a significant interaction between smoking and PD with regard to smoking-related cancer. This may represent a gene-environment interaction and suggests that future studies of PD and cancer should be stratified by smoking status and cancer type (smoking related and non-smoking related). Further studies are needed to further clarify these findings. Discovery of the causes of these associations may advance our understanding of the pathophysiology of both diseases.

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