Movement Disorders
Vol. 9, No. 2, 1994, pp. 207–212

Smoking and Parkinson's Disease

*†‡Richard Mayeux, *‡Ming-Xin Tang, *‡Karen Marder, ‡Lucien J. Côté, and *†‡Yaakov Stern

Gertrude H. Sergievsky Center and Departments of †Neurology and ‡Psychiatry, College of Physicians and Surgeons, Columbia University, New York, New York, U.S.A.

Summary: Smoking was examined in relation to Parkinson's disease (PD) in a population-based study in northern Manhattan (New York City) because of its putative "protective effect." Using a case-control design, information on smoking and associated behaviors was obtained in structured interviews after standard diagnostic evaluations in both cases and controls. The overall prevalence of smoking in the population was 43.7%, decreasing to 37% after age 85. Smoking was most frequent in men, Blacks, and in both cases and controls using alcohol once per week or more. Cases had quit smoking more often than controls (87 vs. 64%), and had smoked for significantly fewer years (31 vs. 41 yrs; $p < 0.05$ for both). The age-at-onset for smokers with PD was similar to age-at-onset for nonsmokers with PD. The odds ratio (OR) for a history of smoking associated with PD was 1.1 (95% CI 0.7–1.8). No protective gradient was associated with heavier smoking patterns. However, the odds that patients with PD were still smoking at the time of the interview were significantly less than those for controls (OR = 0.2; 95% CI 0.1–0.5). These results do not support the hypothesis that smoking protects against PD; rather they strongly imply the converse, that PD reduces smoking. **Key Words:** Smoking–Parkinson's disease.

Several case-control studies (1–5) have indicated that patients with Parkinson's disease (PD) are less likely to have smoked than their healthy peers, leading to the inference that smoking may protect against this disorder. However, it has also been proposed that cessation of smoking may be related to a change in personality or a so-called "premorbid attitude" that may exist in patients who develop PD (6). Smoking is thought to reduce the risk of developing PD by protecting the substantia nigra from potentially toxic effects of oxidative radicals produced during the normal metabolism of dopamine (7,8).

There are at least three additional explanations for the negative association between smoking and PD: (a) recall bias, a methodologic problem common to all case-control studies (9); (b) physical or mental limitations imposed by PD result in the cessation of smoking (10); (c) differential mortality in which smokers with PD die earlier than nonsmokers (11,12).

We examined data collected from patients with PD as well as a group of healthy elderly controls identified in a community-based study of age-related degenerative diseases in northern Manhattan (New York City). We postulated that a negative association between smoking and PD would imply that smoking might decrease the risk of developing this disease. We also posited that if the negative association was stronger for current rather than past smoking the presence of a degenerative disease might have led to cessation of smoking.

METHODS

Setting and Subjects

Data were obtained from cases and controls participating in a study of degenerative disease in the elderly residing in the Washington Heights and Inwood communities of New York City during the

Address correspondence and reprint requests to Dr. R. Mayeux at G.H. Sergievsky Center, 630 West 168th Street, Columbia University, New York, NY 10032, U.S.A.

period of April 1, 1988 to December 31, 1990. We had developed a registry of cases of PD from all available sources of medical information: regional hospitals (including inpatient and outpatient services), private practitioners in the community, federal and state health agencies, health maintenance organizations, and senior centers. Each reporting site was also used to identify controls. The primary inclusion criteria for cases and controls was residence in the community for a period of at least 5 years. Exclusion criteria for cases and controls in terms of comorbidity were identical. The refusal rate for both cases and controls was <20% using this method, and did not differ significantly by site.

Parkinson's Disease

Two hundred fifty-eight patients with parkinsonism were identified in the community registry (13). After the diagnosis was confirmed by an experienced neurologist (RM, KM, or LJC), 217 cases satisfied clinical and research criteria for the idiopathic form of PD (14–16). Sixty-seven (30.1%) were also found to be demented at the time of the examination, meeting additional research diagnostic criteria for primary degenerative dementia (17). Patients with dementia were excluded from the main analyses because dementia in PD is a heterogeneous disorder with no firmly established pathologic substrate, and because we wanted accuracy in the subject's smoking history. No other exclusion criteria were imposed. This left 150 nondemented cases. Onset of PD was determined by the examining physician in a semistructured interview, and it was defined as the approximate age at which the patient noted the onset of motor manifestations.

Healthy Controls

During the same period, 416 elderly persons, aged 65 and older, had been identified at the same registry sites as potential controls. Each individual was asked to participate in a community study of aging and health. As with the cases, all controls were examined for dementia and PD using methods developed for this community (18,19). All had a complete medical, neurologic, and psychiatric assessment which included structured interviews of current and past health, current function in daily activities, and a general physical, neurologic, and neuropsychologic examination. The first consecutive 180 subjects without evidence of dementia, another neurologic disease, or a major illness such as cancer or severe heart disease, after clinical examination or neuropsychologic testing, also completed the risk factor interview. As with cases, we included subjects in this group with milder systemic illnesses such as hypertension, diabetes, and arthritis, so long as they were free of major neurologic or medical complications. None of the controls were spouses or caretakers of the patients. Because all cases and controls were from the same community it is conceivable that some were friends or neighbors, but we have no information suggesting this.

Ethnic Group

For ethnic group classification, we used the format suggested by the 1990 United States Census Bureau (20). The 1990 census identified Hispanics as a cultural group, and reported this population as a proportion of the total. No independent counts were available. For this study, we used the categories of Black, White, and Other to be consistent with the census data.

Risk Factor Interview

Patients with PD and the controls were interviewed directly using a structured risk factor questionnaire. The interviews were given in English or Spanish according to the preference of the patient or the control. We assessed reliability by repeating the interview 12 months later with 23 patients and 25 controls.

For smoking there were three sets of questions. A trigger question asked whether or not the individual ever smoked at least one cigarette per day for a period of a year or more. If the answer was no, no further questions were asked; if yes, the individual was asked at what age smoking began, whether or not smoking continued, at what age smoking had stopped if no longer smoking, and how many cigarettes, on average, had been smoked or were still being smoked per day. We computed the total number of pack-years for each person by multiplying the number of years smoked times the number (or fraction) of packages (20 cigarettes per package) smoked per day.

The two other sets of smoking questions asked about cigar and pipe use. Both began with a trigger question asking whether or not the individual had ever smoked a cigar or pipe. If answered no, no further questions were asked; if yes, follow-up questions similar to those for cigarettes were asked but referred to the number of cigars or pipefuls

smoked daily. There were also three similar sets of questions concerning alcohol use and coffee consumption.

Data Analysis

The frequencies for each demographic variable (age, gender, education, and ethnic group), and for smoking and other covariates were compared in cases and controls using χ^2 analyses and Fisher's exact tests (21).

Odds ratios were calculated to assess the relation of PD to smoking and other demographic variables. Both univariate and multivariate OR were estimated from logistic regression models. We examined differences with respect to education and ethnic group identity represented in the community.

First, two continuous independent variables were used in the multivariate analyses for preliminary examination, then they were dichotomized using a reasonable point near the median value because of their bimodal distribution in the cohort: cigarettes per day ($\gtrless$10 per day) and pack-years ($\gtrless$30 years). We examined differences with respect to ethnic group identity. Odds ratios were adjusted for potential confounders and effect modifiers by using logistic regression (22).

Multivariate analysis of variance (23) was used to examine group differences in various characteristics while controlling for the effects of other factors such as age.

RESULTS

Demographics

Table 1 compares cases and controls in terms of the demographic variables. There were significantly more men in the PD group than in the controls, and cases were significantly older than the controls ($p < 0.001$). Cases also had significantly more formal education and were more likely to be White ($p < 0.001$).

TABLE 1. *Demographic characteristics*

Characteristics	Parkinson's disease	Controls
n	150	180
Gender (% women)	75 (50)[a]	145 (81)
Age (SD)	71.3 (10.0)[a]	74.6 (7.0)
Education (SD)	10.4 (4.9)[a]	8.6 (4.1)
Ethnic group (%)		
Black	19 (13)[a]	59 (33)
White	97 (65)	71 (39)
Other	34 (23)	50 (28)

[a] Indicates significant difference from controls, $p < 0.001$.

TABLE 2. *Prevalence of past or current smoking by age, gender, education, ethnic group, and alcohol use among cases and controls*

Characteristic	Total PD (n = 150)	PD smokers (%)	Controls (n = 180)	Controls smokers (%)
Age group (years)				
65–74	44	21 (48%)	91	40 (44%)
75–84	56	25 (45%)	66	28 (42%)
85 and older	10	6 (60%)	17	4 (24%)
Gender				
Women	75	18 (24%)	145	53 (37%)
Men	75	51 (68%)[a]	35	24 (67%)[a]
Education (years)				
0–7	38	19 (50%)	71	28 (39%)
8–11	38	17 (45%)	55	23 (42%)
12 and more	74	33 (45%)	54	27 (50%)
Ethnic group				
Black	19	13 (68%)[a]	59	32 (54%)
White	97	43 (44%)	71	25 (35%)
Other	34	13 (38%)	50	20 (40%)
Alcohol use				
Regular use	39	32 (82%)[a]	33	23 (70%)[a]
Little or none	111	37 (33%)	145	53 (37%)

[a] Significant difference from others in the group, $p < 0.05$.

Smoking

Table 2 indicates that the frequency of smoking (past and current) in all subjects (cases and controls) varied significantly by gender and alcohol use in both cases and controls. A history of smoking was more frequent among black patients, but smoking was similar among controls regardless of ethnic group (Table 2). The test–retest reliability (21) of the risk factor interview was in the good-to-excellent range for the questions regarding smoking (k = 0.72).

The majority of smokers among both cases and controls were cigarette smokers. Only seven patients with PD and five controls restricted their smoking to cigars or a pipe. A few in each group smoked cigars or a pipe as well as cigarettes according to our definition. We did not perform separate analyses for those who use only cigars or pipes because these were relatively infrequent as exposures. However, we did include cigar and pipe smokers in comparing smokers with nonsmokers.

Table 3 indicates that, after adjusting for age differences, patients with PD had smoked for significantly fewer years than controls. There were no significant differences between cases and controls in the average number of cigarettes per day or the total number of pack-years. Significantly more cases, than controls, had stopped smoking.

TABLE 3. *Cigarette smoking characteristics: multivariate analyses controlling for age in the cases and controls*

Characteristics (means)	Parkinson's disease	Controls
Years smoked (SD)	31.3 (17.5)[a]	41.3 (18.1)
Cigarettes/day (SD)	19.5 (16.2)	17.7 (16.9)
Pack-years (SD)[b]	31.4 (26.2)	36.5 (39.2)
Smokers who quit (%)	60 (87%)	49 (64%)[a]

[a] Denotes significant association, $p < 0.01$.
[b] Pack-years was defined as the product of the number of years smoked times the number (or fraction) of packages (20 cigarettes per package) smoked per day.

Parkinson's Disease

The frequency of a past history of smoking was similar among cases and controls (Table 4), whereas current smoking was increased among controls compared with cases. Dose response was not observed with regard to the number of cigarettes smoked per day or the number of pack-years. Results in Table 2 indicate that the only potential confounder to be considered is gender because although ethnic group and alcohol use were related to smoking they were not associated with PD specifically. The OR adjusted for age and gender disclosed a trend toward a negative association between PD and smoking more than 30 pack-years only. When these analyses were repeated excluding current smokers, the point estimates increased toward unity.

We examined the effects of alcohol use and ethnic group identity on the association between smoking and PD. The combination of smoking and alcohol was found to have a significant negative association when adjusted for age and gender (Table 5a). We reanalyzed this relation excluding current smokers among cases and controls and the point estimate was 0.9 (0.4–1.8), suggesting no association. The relation between ethnic group identity and smoking among PD cases and controls indicated a strong correlation with ethnic group, but little change with the addition of smoking (Table 5b). For patients with PD, the age-at-onset of symptoms in smokers and nonsmokers was nearly identical [64.2 (±16.1) smokers vs. 64.5 (±12.4) nonsmokers; $p = 0.88$].

Although we determined our sample size based on the known frequency of smoking in the community and with the objective of observing an OR of 0.5 or less, we had at least 80% power to detect a previously reported OR of 0.7 for PD (24). For the adjusted analyses our power was less. The smallest detectable OR we could have observed in our analyses adjusted for age and gender was estimated to be 0.5 (25). In PD, many of the detailed analyses of smoking included risk factors that were relatively infrequent. A post hoc estimation of the minimal detectable OR that we could have expected for the infrequent exposures such as more than 30 pack-years, present in only 15.4% of the study population, was approximately 0.4 (25).

DISCUSSION

The results of this investigation do not support the hypothesis that smoking prevents PD. Cases with PD were as likely as controls to have smoked and there was no difference in the average number of cigarettes used per day or total number of pack-years smoked. In PD, current smoking was significantly less frequent than in controls, even after adjustment for covariates such as age and gender. A

TABLE 4. *Smoking and Parkinson's disease*

Cigarette smoking			Odds ratios with 95% CI		
Status	Cases	Controls	Unadjusted	Adjusted for age and gender	Excluding current smokers
Never	81	103	1.0 reference	1.0 reference	1.0 reference
Ever	69	77	1.1 (0.7–1.8)	0.8 (0.4–1.5)	—
Past	60	49	1.6 (1.0–2.5)	0.9 (0.5–1.6)	1.0 (0.6–1.7)
Current	9	28	0.4 (0.2–1.0)	0.2 (0.1–0.5)	—
Cigarettes					
<10/day	29	35	1.1 (0.6–1.9)	0.7 (0.4–1.5)	1.0 (0.5–1.9)
>10/day	36	37	1.2 (0.7–2.1)	0.6 (0.3–1.2)	0.9 (0.5–1.8)
Pack-years					
<30	36	36	1.3 (0.7–2.2)	0.8 (0.4–1.5)	1.1 (0.5–2.4)
>30	25	26	1.2 (0.7–2.3)	0.6 (0.3–1.2)	1.0 (0.5–2.0)

Note: In order to calculate pack-years we needed to know when patients began and stopped smoking. This information could not be established in 10 PD smokers and 10 control smokers.

TABLE 5. *Effects of alcohol use and ethnic group on the association between smoking and Parkinson's disease*

a. Smoking and alcohol use			Odds ratios with 95% CI	
Status	Cases	Controls	Unadjusted	Adjusted for age and gender
Neither	62	83	1.0 reference	1.0 reference
Alcohol only	19	19	1.3 (0.7–2.7)	0.8 (0.4–1.5)
Smoking only	27	36	1.0 (0.5–1.9)	0.9 (0.4–2.0)
Both	42	40	1.4 (0.8–2.4)	0.5 (0.3–1.0)
b. Smoking and ethnic group				
White nonsmokers	54	46	1.0 reference	1.0 reference
Other + nonsmokers	27	57	0.4 (0.2–0.8)	0.3 (0.1–0.5)
Other + smokers	26	52	0.4 (0.2–0.8)	0.4 (0.2–0.7)
White smokers	43	25	1.5 (0.8–2.6)	0.8 (0.4–1.7)

Note: Other + in (b) refers to Black and Other nonwhite ethnic groups combined.

negative association between PD and the combination of alcohol use and smoking was suggested after adjustment for age and gender, but this disappeared once current smokers were excluded from the analysis. This suggests that current, not previous, smoking patterns were changed in cases compared with controls. Whites were more likely to have PD regardless of smoking habits. PD has been found to occur less frequently among Blacks than in other ethnic groups in some, but not all studies (26–28).

Although the results of several case-control studies (1–6) have suggested that patients with PD are less likely to have smoked than their healthy peers, the association remains an inconsistent one. The diagnosis of PD has often not been verified, particularly in mortality studies, allowing for nondifferential misclassification (9). No study has found a dose response indicating greater protection with moderate to heavy smoking. Stern et al. (5) found the OR associated with PD to be 0.5, adjusting for a history of head injury and rural residence. However, they did not adjust for gender or age in their analysis, and controls were either "peer nominated" or other people attending the clinic. Thus, their results are difficult to interpret.

Rajput and colleagues (24) reported the onset of PD to be earlier in smokers than nonsmokers, but they found no relation between smoking and PD [OR = 0.7; 95% CI 0.4–1.2]. However, Sasco and Paffenbarger (4) found that patients with PD were less likely to continue smoking, as did we. These studies imply that personality changes or physical limitations caused by PD may have altered smoking habits (29). Moreover, we found that significantly more patients than controls had quit smoking, suggesting that the presence of PD might have affected smoking behavior.

The purported decreased risk of PD associated with smoking might be biased in the case-control design simply because of a more "rapidly fatal course" for patients with PD who continued to smoke (30). Ebmeier et al. (11) reported that a history of smoking was associated with more deaths among patients with PD than among controls over a 3.5-year period. This would result in decreased survival for smokers with PD, leaving them under represented in case-control studies.

As in any case-control study, the potential for recall bias existed in our study. The effect would lead to misclassification of exposure and a trend toward protection, but we have no evidence to support that misclassification occurred. Selective nonparticipation based on the exposure of smoking could have influenced our results, but another study (31) in this community found a similar frequency of smoking. Moreover, nonparticipation would have had to have been different for cases and controls to affect our results. We do not have information on smoking from individuals who have not participated in studies based in the Washington Heights area.

Our study offers little to support a protective effect of smoking on PD. However, the data from this study indicate that smoking most likely decreases as a consequence of PD. Whether smoking cessation was due to changes in personality, addictive behavior, or other disease-related factors remains to be determined.

Acknowledgment: This work was supported by Federal Grants AG07232, AG10963, RR00645, and The Parkin-

son's Disease Foundation. The authors thank Drs. Charles Basch, Maureen Durkin, and Ralph Sacco for their critical review and suggestions for the preparation of the manuscript.

REFERENCES

1. Hofman A, Collette HJ, Bartelds AI. Incidence and risk factors of Parkinson's disease in the Netherlands. *Neuroepidemiology* 1989;8:296–299.
2. Hertzman C, Wiens M, Bowering D, Snow B, Calne D. Parkinson's Disease: a case-control study of occupational and environmental risk factors. *Am J Ind Med* 1990;17:349–355.
3. Wechsler LS, Checkoway H, Franklin GM, Costa LG. A pilot study of occupational and environmental risk factors for Parkinson's disease. *Neurotoxicology* 1991;12:387–392.
4. Sasco AJ, Paffenbarger RS. Smoking and Parkinson's disease. *Epidemiology* 1990;1:460–465.
5. Stern M, Dulaney E, Gruber SB, et al. The epidemiology of Parkinson's disease. A case-control study of young-onset and old-onset patients. *Arch Neurol* 1991;48:903–907.
6. Jimenez-Jimenez FJ, Mateo D, Gimenex-Roland S. Premorbid smoking, alcohol consumption, and coffee drinking habits in Parkinson's disease: a case-control study. *Mov Disord* 1992;7:339–344.
7. Janson AM, Fuxe K, Goldstein M. Differential effects of acute and chronic nicotine treatment on MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) induced degeneration of the nigrostriatal dopamine neurons in the black mouse. *Clin Invest* 1992;70:232–238.
8. Shahi GS, Das NP, Moochhala SM. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity: partial protection against striato-nigral dopamine depletion in C57BL/6J mice by cigarette smoke exposure and by beta-naphthoflavone-pretreatment. *Neurosci Lett* 1991;127:247–250.
9. Rothman KJ. *Modern epidemiology*. Boston: Little Brown and Co., 1986:61.
10. Baron JA. Cigarette smoking and Parkinson's disease. *Neurology* 1986;36:1490–1496.
11. Ebmeier KP, Calder SA, Crawford JR, Steward L, Besson JAO, Mutch WJ. Parkinson's disease in Aberdeen: survival after 3.5 years. *Acta Neurol Scand* 1990;81:294–299.
12. LaCroix AZ, Lang J, Scherr P, et al. Smoking and mortality among older men and women in three communities. *N Engl J Med* 1991;324:1619–1625.
13. Mayeux R, Denaro J, Hemenegildo N, et al. A population-based investigation of Parkinson's disease with and without dementia: relationship to age and gender. *Arch Neurol* 1992; 49:492–497.
14. Ward CD, Gibb WR. Research diagnostic criteria for Parkinson's disease. In: Streifler MB, Korczyn AD, Melamed E, Youdin MBH, eds. *Parkinson's disease: anatomy, pathology and therapy*. New York: Raven Press, 1990:245–248. (Advances in Neurology, vol. 53.)
15. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
16. Hughes AJ, Ben-Shlomo Y, Kilford L, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. *Neurology* 1992; 1142–1146.
17. Diagnostic and statistical manual of mental disorders, third edition-revised, Washington, DC: American Psychiatric Association, 1987:205–224.
18. Pittman J, Andrews H, Tatemichi T, et al. Diagnosis of dementia in a heterogeneous population: a comparison of paradigm-based diagnosis and physician's diagnosis. *Arch Neurol* 1992;49:461–467.
19. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population: development of a neuropsychological paradigm and quantified correction for education. *Arch Neurol* 1992;49:453–460.
20. *Census of Population and Housing, 1990: Summary Tape File 1*. Technical Documentation Prepared by Bureau of the Census. Washington: The Bureau of the Census, 1991.
21. Fleiss JL. *Statistical methods for rates and proportions*. New York: John Wiley and Sons, 1981.
22. Hosmer DW, Lemeshow S. *Applied logistic regression*. New York: John Wiley and Sons, 1989.
23. Kleinbaum DG, Kupper LL, Muller KE. *Applied regression analysis and other multivariate methods*. Boston: PWS-Kent, 1988:341–386.
24. Rajput AH, Offord KP, Beard CM, Kurland LT. A case-control study of smoking habits, dementia and other illnesses in idiopathic Parkinson's disease. *Neurology* 1987;37: 226–232.
25. Schlesselman JJ. *Case-control studies. Design, conduct, analysis*. New York: Oxford University Press, 1982:140–170.
26. Schoenberg BS, Anderson DW, Haerer AF. Prevalence of Parkinson's disease in the biracial population of Copiah County, Mississippi. *Neurology* 1985;26:719–723.
27. Osuntokun BO. The pattern of neurological illness in tropical Africa. Experience at Ibadan, Nigeria. *J Neurol Sci* 1971; 12:417–442.
28. Paddison RM, Griffith RP. Occurrence of Parkinson's disease in black patients at Charity Hospital in New Orleans. *Neurology* 1974;24:688–690.
29. Shahi GG, Moochhala SM. Smoking and Parkinson's disease—a new perspective. *Rev Environ Health* 1991;9:123–136.
30. Riggs JE. Cigarette smoking and Parkinson's disease: the illusion of a neuroprotective effect. *Clin Neuropharmacol* 1992;15:89–99.
31. Shea S, Stein A, Basch CE, et al. Independent associations of educational attainment and ethnicity with behavioral risk factors for cardiovascular disease. *Am J Epidemiol* 1991; 134:567–582.