Parkinson's Disease Risks Associated with Cigarette Smoking, Alcohol Consumption, and Caffeine Intake

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A reduced risk for Parkinson's disease (PD) among cigarette smokers has been observed consistently during the past 30 years. Recent evidence suggests that caffeine may also be protective. Findings are presented regarding associations of PD with smoking, caffeine intake, and alcohol consumption from a case-control study conducted in western Washington State in 1992–2000. Incident PD cases ($n = 210$) and controls ($n = 347$), frequency matched on gender and age were identified from enrollees of the Group Health Cooperative health maintenance organization. Exposure data were obtained by in-person questionnaires. Ever having smoked cigarettes was associated with a reduced risk of PD (odds ratio (OR) = 0.5, 95% confidence interval (CI): 0.4, 0.8). A stronger relation was found among current smokers (OR = 0.3, 95% CI: 0.1, 0.7) than among ex-smokers (OR = 0.6, 95% CI: 0.4, 0.9), and there was an inverse gradient with pack-years smoked (trend $p < 0.001$). No associations were detected for coffee consumption or total caffeine intake or for alcohol consumption. However, reduced risks were observed for consumption of 2 cups/day or more of tea (OR = 0.4, 95% CI: 0.2, 0.9) and two or more cola drinks/day (OR = 0.6, 95% CI: 0.3, 1.4). The associations for tea and cola drinks were not confounded by smoking or coffee consumption. *Am J Epidemiol* 2002;155:732–8.

caffeine; coffee; neuroprotective agents; Parkinson disease; smoking; tea

Parkinson's disease (PD) is a debilitating neurodegenerative disorder whose cardinal features are bradykinesia, resting tremor, muscular rigidity, gait disturbances, and postural reflex impairment (1). The underlying pathologic lesion is a selective destruction of the dopamine-producing neurons in the pars compacta of the substantia nigra (2). PD is rare before age 50 years, but increases dramatically at older ages, with peak onset occurring during ages 70–85 years (3). In the United States, prevalence of PD for all ages is approximately 150 per 100,000 and is roughly 30 per 100,000 at ages less than 50 years and 800 per 100,000 at ages 70–85 (3, 4). The causes of PD are largely unknown. Mendelian inheritance probably accounts for a small fraction of cases, mainly at younger ages (5). Recent experimental and epidemiologic research has therefore focused on lifestyle and environmental risk factors.

An inverse association between cigarette smoking and PD has been observed consistently during the past 30 years (6). Numerous case-control studies worldwide demonstrate reduced PD risks among smokers (roughly half those of nonsmokers (7–14)) with some studies indicating strong inverse dose-response gradients (11, 13, 14). Cohort studies, in which data on smoking were obtained before the onset of PD, provide corroborative evidence for the seemingly protective effect of smoking (15, 16), which suggests that the association is not an artifact of recall bias. Selective survival of nonsmokers to the natural age of onset of PD also does not appear to be a satisfactory explanation for the effect of smoking (17). Instead, biochemical hypotheses have been advanced. Components of cigarette smoke may afford neuroprotection by reducing enzymatic activity of type B monoamine oxidase (MAO-B) in the brain (18). MAO-B catabolizes dopamine (19) and may activate neurotoxicants similar to the established experimental PD-inducing chemical 1-methyl-4-phenyl-1,2,3,6-tetrahdropyridine (MPTP) (20). Recently, a MAO-B-inhibiting compound in tobacco, 2,3,6-trimethyl-1,4-naphthoquinone, was found to attenuate the dopaminergic system toxicity of MPTP in experiments on mice (21). However, evidence from similar experiments with MPTP and nicotine has been inconsistent (22, 23).

Findings from several case-control studies in Europe and the United States (7, 11, 14, 24) suggest that caffeine intake may lower PD risk. Additionally, two recently reported prospective cohort studies of Japanese-American men in Hawaii (25) and of US health professionals (26) demonstrate inverse PD risk gradients with the amount of caffeine

consumed. Most prior research has focused on coffee and total caffeine intake, although lowered PD risks, specifically among tea drinkers, have also been observed (12, 26). Caffeine has been shown to reduce dopaminergic cell destruction by MPTP in experiments on mice, possibly mediated by blockage of adenosine A_{2A} receptors (27).

There is limited epidemiologic evidence that alcohol is related to PD, despite the established neurotoxicity of ethanol. A decreased risk of PD primarily associated with heavy drinking or a history of alcoholism has been reported in some studies (7, 13, 14, 24).

In this paper, we report findings on smoking, caffeine intake, and alcohol consumption from an ongoing, population-based case-control study of PD in the Seattle, Washington, area.

MATERIALS AND METHODS

Study subjects

Newly diagnosed idiopathic PD cases were identified during 1992–2000 from neurology and general medical practice clinics of Group Health Cooperative (GHC) in western Washington State and the University of Washington Neurology Clinic. Potential cases were identified from diagnosis logs at both institutions and from the GHC pharmacy database, which provides information on prescriptions of antiparkinsonian medications (e.g., L-dopa). Chart reviews for cases not diagnosed by neurologists were reviewed by three of the authors (G. M. F., W. T. L, and P. D. S.) to verify PD diagnoses, indicated by the presence of at least two of the four cardinal signs of PD: bradykinesia, resting tremor, cogwheel rigidity, and postural reflex impairment. Exclusion criteria were the use during the 12 months preceding onset of PD symptoms of certain medications (e.g., phenothiazines, haloperidol, and metoclopramide), whose side effects include parkinsonism signs and symptoms, prior history of multiple cerebrovascular events, or another explanation for parkinsonism symptoms (e.g., brain injury, brain tumor, and encephalitis), as identified in patients' charts. Controls were GHC enrollees without past histories of PD or other progressive neurologic disorders (e.g., Alzheimer's disease or multiple sclerosis), as determined from chart reviews and subject interviews. No other medical history exclusion criteria were imposed on control eligibility. The control group was frequency matched to cases by age in 10-year categories, gender, GHC clinic (which represents geographic location in the Puget Sound area), and original year of GHC enrollment. The target control:case ratio is 1.5. The GHC Center for Health Studies contacted eligible cases and controls by mail with a letter describing the study purposes and procedures and soliciting participation. Human Subjects committees at the University of Washington and the GHC Center for Health Studies reviewed and approved the study.

A total of 309 probable PD cases were identified, of whom 12 were subsequently deemed ineligible because of exclusion criteria. Reasons for exclusions were questionable PD diagnosis on repeat chart review ($n = 6$), recent history of use of parkinsonism-related medications ($n = 5$), and cognitive impairment that prevented interview ($n = 1$). A total of 210 (71 percent) agreed to participate in the study. Among 529 potentially eligible controls, 347 (66 percent) agreed to participate. The demographic characteristics of cases and controls are summarized in table 1. The case group was composed of 131 men and 79 women with a median age of 70 years. The controls included 225 men and 122 women with a median age of 71 years. Non-Hispanic Caucasians accounted for the vast majority of subjects (93 percent of the cases and 92 percent of the controls). Educational attainment was similar in the two groups because 80 percent of cases and 78 percent of controls had at least some college education; a slightly larger proportion of cases than of controls had postgraduate-level education (32 vs. 20 percent).

TABLE 1.   Demographic characteristics of Parkinson's disease cases and controls, western Washington State, 1992–2000

Characteristic	Cases		Controls	
	No.	%	No.	%
Gender				
Men	131	62.4	225	64.8
Women	79	37.6	122	35.2
Age (median (range))	70 (37–88)		71 (44–85)	
Ethnicity				
Non-Hispanic Caucasian	196	93.3	318	91.6
Other	14	6.7	29	8.4
Education				
Less than high school	11	5.2	25	7.2
High school graduate	27	12.9	48	13.8
Some college	82	39.0	162	46.7
College graduate	19	9.0	37	10.7
Postgraduate	68	32.4	70	20.2
Unknown	3	1.5	5	1.4

Data collection

A nurse practitioner administered a structured, in-person questionnaire to study subjects in their homes. The same nurse practitioner interviewed all study subjects. Subjects were first presented with an informed consent form, followed by a brief Mini-Mental State Examination (28) to establish cognitive competence for providing questionnaire responses. The questionnaire elicited data on demographic variables, medical history, lifestyle factors, diet, residential history, occupational history, and environmental exposures. Subjects were asked questions on lifetime tobacco use, including amounts smoked, years smoking started, and number of years smoked. Information on alcohol consumption and consumption of caffeine-containing beverages and foods was determined from questions about typical consumption patterns during most of adult life. The questions on alcohol elicited information on drinks per week without distinguishing the specific types of alcohol consumed. Caffeine consumption was determined from cups or drinks per day of coffee (regular), decaffeinated coffee, tea, decaffeinated tea, cocoa, and cola drinks and servings per day of chocolate.

Data analysis

An ever-smoker was defined as a person who had smoked a total of at least 100 cigarettes. Cumulative cigarette smoking, in pack-years, was estimated as the product of average packs per day and years smoked. A composite caffeine index was constructed as a daily sum of caffeine from these sources, based on published estimates of caffeine in milligrams per serving (29–31) of regular coffee, 70 mg/cup; decaffeinated coffee, 5 mg/cup; tea, 38 mg/cup; decaffeinated tea, 5 mg/cup; cocoa, 4 mg/cup; cola, 34 mg/12-ounce (354.84-ml) serving, and chocolate, 10 mg/1-ounce (29.57-ml) serving.

Odds ratios and 95 percent confidence intervals associated with exposure variables and PD risk were estimated by unconditional logistic regression, with control for age (<60 vs. ≥60 years), ethnicity (non-Hispanic Caucasian vs. other), gender, and education (≤12 vs. >12 years). Grouped linear terms, with categories assigned scores of 0, 1, 2,…, were constructed, and the Wald statistic was used to test for linear trends. The crude and adjusted odds ratios were nearly identical throughout; therefore, only adjusted results are shown.

RESULTS

The associations with cigarette smoking are summarized in table 2. Cigarette smokers had half the PD risk of nonsmokers, with slightly lower risks observed among current smokers (odds ratio (OR) = 0.3) than among ex-smokers

TABLE 2. Associations of Parkinson's disease with cigarette smoking, western Washington State, 1992–2000

Smoking status	All subjects			
	No. of cases	No. of controls	OR*	95% CI†
Never smoked	112	132	1.0	
Ever smoked	98	215	0.5	0.4, 0.8
Current smoker	7	36	0.3	0.1, 0.7
Ex-smoker	91	179	0.6	0.4, 0.9
Packs/day				
0	117	137	1.0	
>0–<1/2	16	44	0.4	0.2, 0.8
1/2–<1	43	94	0.5	0.3, 0.8
1–<2	28	53	0.6	0.3, 1.0
≥2	6	19	0.4	0.1, 1.0
p for trend				0.003
Years smoked				
0	116	139	1.0	
>0–19	39	62	0.7	0.4, 1.2
20–39	38	90	0.5	0.3, 0.8
≥40	17	56	0.4	0.2, 0.7
p for trend				<0.001
Pack-years				
0	119	139	1.0	
>0–19	47	82	0.6	0.4, 1.0
20–39	23	71	0.4	0.2, 0.6
≥40	21	55	0.4	0.2, 0.8
p for trend				<0.001

* Odds ratios (OR) adjusted for age, ethnicity, education, and gender.
† CI, confidence interval.

(OR = 0.6). Compared with risks for never smokers, PD risks were most reduced among ex-smokers who were recent quitters; the adjusted odds ratios according to years since quitting for less than 10, 10–19, and 20 or more years were 0.2 (95 percent confidence interval (CI): 0.1, 0.6), 0.6 (95 percent CI: 0.3, 1.2), and 0.7 (95 percent CI: 0.5, 1.0) (trend $p = 0.001$), respectively. These findings for ex-smokers were not materially altered when adjustments were made for packs smoked/day (adjustments for duration smoked or pack-years were not possible because of collinearity with time since quitting). There were strong inverse gradients detected for amount smoked (packs/day) (trend $p = 0.003$), years smoked (trend $p < 0.001$), and pack-years of smoking (trend $p < 0.001$). Analyses considering packs/day and years smoked simultaneously indicated a slightly stronger effect of duration, although both were significantly related to reduced risk of PD. Subsequent analyses focused on pack-years since most literature supports a clear relation with total amount of cigarettes smoked (11–16).

When mutually adjusted odds ratio trends were computed, the inverse gradient with pack-years smoked persisted, but we found no associations with either coffee or alcohol consumption (table 3). The results for the composite caffeine index were similar to those found for coffee. The adjusted odds ratios for caffeine intake quintiles, based on equal numbers of cases per stratum, of 0–33, 34–120, 121–196, 197–354, and 355 or more mg/day were, respectively: 1.0 (reference), 0.7 (95 percent CI: 0.4, 1.2), 0.9 (95 percent CI: 0.5, 1.5), 0.6 (95 percent CI: 0.3, 1.1), and 0.9 (95 percent CI: 0.5, 1.6), with a trend p value of 0.58. Among the other sources of caffeine, there was a reasonably strong inverse risk gradient for tea (trend $p = 0.03$), a weaker inverse gra-

dient for cola drinks (trend $p = 0.22$), and no association with consumption of decaffeinated coffee (table 4). The adjusted odds ratio for the highest consumption levels of tea (≥2 cups/day) and cola drinks (≥2 drinks/day) were 0.4 (95 percent CI: 0.2, 0.9) and 0.6 (95 percent CI: 0.3, 1.4), respectively. Too few cases reported routine consumption of decaffeinated tea, cocoa, or chocolate to support separate analyses. The findings for the smoking, caffeine, and alcohol variables were similar for subjects aged less than 60 years and 60 years or more (data not shown), suggesting no interactions with age at PD diagnosis.

It was also of interest to examine possible joint effects on PD risks between smoking and caffeine-containing beverages. To avoid very small numbers, we limited the analysis of interaction to binary classifications of exposure variables. The reduced risk among smokers was found consistently among drinkers and nondrinkers of caffeinated beverages, although in no instance was there evidence of an interaction (table 5).

DISCUSSION

The apparently protective effect of cigarette smoking on PD observed in our study was very similar in magnitude to what has been reported previously in the literature. A markedly reduced risk in current smokers (OR = 0.3) agrees with findings from case-control studies in New York (9) and Michigan (13), and the inverse dose-response pattern with pack-years is consistent with trends reported from investigations in Europe and North America (11, 13, 14, 16). Our observations that there was an inverse risk gradient with duration smoked and that, among ex-smokers, PD

TABLE 3.   Mutually adjusted associations of Parkinson's disease with cigarette smoking, coffee consumption, and alcohol consumption, western Washington State, 1992–2000

Variable	No. of cases	No. of controls	OR*	95% CI†
Pack-years				
0	119	139	1.0	
>0–19	47	82	0.6	0.4, 1.0
20–39	23	71	0.4	0.2, 0.6
≥40	21	55	0.4	0.2, 0.8
p for trend				<0.001
Coffee (regular) (cups/day)				
Almost never	63	96	1.0	
>0–1	32	66	0.8	0.4, 1.3
2–3	69	105	1.1	0.7, 1.8
4–6	30	48	1.2	0.7, 2.2
>6	16	32	1.0	0.5, 2.0
p for trend				0.50
Alcohol (drinks/week)				
0	86	132	1.0	
1–2	48	72	1.1	0.7, 1.8
3–9	48	77	1.1	0.6, 1.7
≥10	28	66	0.8	0.4, 1.4
p for trend				0.53

* Odds ratios (OR) adjusted for age, ethnicity, education, and gender.
† CI, confidence interval.

TABLE 4. Associations of Parkinson's disease with consumption of tea, decaffeinated coffee, and cola drinks, western Washington State, 1992–2000

	No. of cases	No. of controls	OR*	95% CI†
Tea (regular) (cups/day)				
Almost never	138	202	1.0	
>0–1	61	110	0.8	0.6, 1.3
≥2	11	35	0.4	0.2, 0.9
p for trend				0.032
Decaffeinated coffee (cups/day)				
Almost never	132	216	1.0	
>0–1	42	75	1.0	0.6, 1.5
≥2	36	56	1.1	0.7, 1.8
p for trend				0.79
Cola (glasses/day)				
Almost never	128	196	1.0	
>0–1	71	125	0.9	0.6, 1.3
≥2	11	26	0.6	0.3, 1.4
p for trend				0.22

* Odds ratios (OR) adjusted for age, ethnicity, education, gender, smoking, and drinking of (regular) coffee.
† CI, confidence interval.

risk was most markedly reduced (OR = 0.2) among recent quitters (<10 years) add further support to a neuroprotective role of prolonged exposure to cigarette smoke. A similar trend with years since quitting smoking was seen in the Michigan study (13). The especially pronounced lower risk among persons who quit smoking relatively recently suggests that neuroprotection might act during a late stage of PD pathogenesis. Alternatively, PD patients may preferentially elect to quit smoking while experiencing prediagnostic symptoms. Reasons for quitting smoking were not elicited in our study, nor has such information been reported in previous literature on PD and smoking; thus, this is a matter of speculation that deserves future examination. The underlying biologic mechanisms or behavioral determinants of the inverse relation with smoking remain unresolved.

We did not confirm an inverse association for either coffee or total caffeine consumption that has been seen in other studies (14, 25, 26). In contrast, we observed reduced risks related to consumption of tea and cola, which were somewhat unanticipated findings. Both tea and cola drinks are sources of caffeine, but our findings are suggestive of protective effects from beverage components other than caffeine, in light of the absence of associations with coffee, decaffeinated coffee, and total caffeine.

A particular strength of our study was the identification of incident, rather than prevalent, PD cases. Selection of prevalent cases, as has been done in most other PD epidemiologic studies, can introduce bias if exposures of interest are related to disease progression or survival. In addition, both cases and controls in our study were selected from a well-

TABLE 5. Joint effects of cigarette smoking and consumption of coffee, tea, and cola drinks, western Washington State, 1992–2000

Beverage consumption	Never smoked				Ever smoked			
	No. of cases	No. of controls	OR*	95% CI†	No. of cases	No. of controls	OR	95% CI
Coffee (cups/day)								
<2	60	76	1.0		35	86	0.5	0.3, 0.9
≥2	52	56	1.2	0.7, 1.9	63	129	0.6	0.4, 1.0
p for interaction				0.98				
Tea (cups/day)								
<1	96	103	1.0		88	177	0.5	0.3, 0.8
≥1	16	29	0.6	0.3, 1.2	10	38	0.3	0.1, 0.6
p for interaction				0.75				
Cola (drinks/day)								
<1	103	114	1.0		83	173	0.5	0.3, 0.8
≥1	9	18	0.5	0.2, 1.2	15	42	0.4	0.2, 0.7
p for interaction				0.53				

* Odds ratios (OR) adjusted for age, ethnicity, gender, education (and coffee in the analysis of tea and cola).
† CI, confidence interval.

defined population base, GHC, which is a health maintenance organization that provides medical care to roughly 400,000 persons in the Puget Sound region of western Washington State. Subject participation rates (71 percent for cases and 66 percent for controls), although less than ideal, were not abnormally low for population-based case-control studies. There is little reason to suspect that there was a serious selection bias due to participation that was related to both exposure and disease status. However, we do not have the necessary exposure data on persons who declined participation to test this assertion.

The principal limitation of this study is reliance on self-report for data on cigarette smoking, caffeine intake, and alcohol consumption. Consequently, the possibility of inaccurate exposure data and resulting misclassification bias should be considered when interpreting our findings. Among the exposures of interest here, data for cigarette smoking were undoubtedly most complete and valid because the questionnaire items elicited information on lifetime smoking habits. We requested only data for typical adult consumption patterns of alcohol and caffeine-containing beverages. Moreover, we did not ask about specific types of alcohol (beer, wine, hard liquor) or tea (black, green, herbal), nor did we request information on changes in dietary habits throughout life.

Tea has not been investigated in relation to PD risk as extensively or explicitly as coffee has, perhaps because consumption of coffee is far more prevalent in North America and Europe, where most research on PD has been undertaken. There is mixed epidemiologic evidence for the relation of tea with PD. Consumption of at least one cup of tea per day has been associated with reduced PD risks of 30–40 percent in China (12) and among male health professionals in the United States (26), although no association was found for female nurses in the latter study. In contrast, a nearly twofold increased risk for PD among tea drinkers was reported from a hospital-based case-control study in France (32). A potentially neuroprotective effect might be inferred from the identification in tea of free-radical scavenging phenolic compounds (33), especially in view of the widely accepted relevance of oxidative stress mechanisms in PD pathogenesis (34). Corroborative epidemiologic and experimental evidence that distinguishes effects among the various tea types and component chemicals will be necessary before firmer conclusions can be reached.

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