BIOMEDICAL AND ENVIRONMENTAL SCIENCES 16, 173-179 (2003)

Parkinson's Disease and Smoking: An Integral Part of PD's Etiological Study

JIAN-QUN DONG*,[1], ZHEN-XIN ZHANG† AND KONG-LAI ZHANG*

*School of Basic Medicine, Peking Union Medical College/Chinese Academy of Medical Sciences, Beijing 100005; †Department of Neurology, Peking Union Medical College Hospital, Beijing 100073, China

Objective To explore the association of Parkinson's disease (PD) with cigarette smoking. **Methods** One hundred of fourteen PD patients were compared with 205 control subjects who were matched by gender, race and residency. A previously validated questionnaire including smoking, alcohol/tea consumption as well as some other environmental exposure data was administered. **Results** With never-smokers as the reference category, we observed reduced risk for PD among ever smokers (*OR*=0.49, 95% CI: 0.30 to 0.79) current smokers (*OR*=0.44, 95% CI: 0.23 to 0.86) and ex-smokers (*OR*=0.54, 95% CI: 0.30 to 0.96). When ever smokers were stratified by years of smoking, there was an inverse correlation between those whose smoking history was longer than 20 years (*OR*=0.40 95% CI: 0.21 to 0.81) and an even mild protective correlation between those who smoked less than 20 years (*OR*=0.57, 95% CI: 0.33 to 0.99). Those who had quitted smoking for more than 20 years were less likely to have the disease than never smokers, and those who had quitted for less than 20 years were least likely to have PD, while those who were current smokers were still least likely to have the disease. We found significant inverse gradient with pack-day smoking (trend $P<0.05$), and the inverse correlation between cigarette smoking and PD was not confounded by alcohol/tea consumption and other confounding bias. **Conclusions** The inverse correlation between Parkinson's disease risk and smoking as well as the trend of gradient dose response is again observed in our study. More future researches are needed to confirm these correlations and to explore further biochemical evidence.

Key words: Parkinson's disease; Cigarette smoking; Risk factors

INTRODUCTION

Parkinson's disease (PD), a debilitating neurodegenerative disorder, is featured with bradykinesia, resting, muscular rigidity, gait disturbances, and postural reflex impairment[1]. PD is rare before age of 50 years, but it increases dramatically with older ages, with peak onset occurring during the age of 70-85 years. In the United States, prevalence of PD in all age groups is approximately 150 per 100 000 and is roughly 30 per 100 000 at age of less than 50 years and 800 per 100 000 at age of 70-85[3-4]. Age-specific prevalence of PD in China is 92 per 100 000 at age of 50-59, and 615 per 100 000 at ages above 70 years[5]. Numerous experimental and epidemiological studies have been conducted to explore the risk factors of Parkinson's disease (PD), especially lifestyle and environmental factors.

[1]To whom correspondence should be addressed. Tel: 86-10-65296973/ 86-10-65284031, E-mail: jqdong1717@163.com

Biographical note of the first author: Jian-Qun DONG, male, born in 1965, Graduated from Heidelberg University, Germany, Ph. D. candidate, majoring in epidemiology and bio-statistics.

0895-3988/2003
CN 11-2816

Although an inverse correlation between cigarette smoking and PD has been consistently observed in worldwide epidemiological researches over the past decades[4,7-12], few studies have demonstrated strong inverse dose-response gradients of PD and smoking, and even fewer in China.

A PD prevalence survey was commenced on July 1, 1997 in Beijing to investigate whether China remained to belong to a low-risk area for PD and to probe risks for PD. In this paper, we report the observed inversion correlation cigarette smoking and PD risk.

STUDY SUBJECTS AND METHODS

Study Subjects

One hundred and fourteen idiopathic PD cases were recruited from an ongoing PD prevalence survey in urban and rural communities of Beijing commenced since 1997. A total of 8 694 residents aged 55 years or older in 12 urban communities and 15 village communities in 3 districts (Haidian, Tongzhou, and Dongcheng) and in 2 counties (Pinggu and Shuiyi) were selected by a multi-stratified cluster sampling method. Two rounds of follow-up visits were carried out in 1999 and 2001, respectively. Of all the study cases (n=114), 52 patients were currently confirmed for their diagnosis when they re-visited the neurological clinic of Parkinson's Disease Research Center, Beijing Union Medical College Hospital from August 2002 to January 2003.

Parkinsonism was characterized by the presence of the following two or more cardinal signs: resting tremor, bradykinesia, rigdity and impaired postural reflexes. PD was defined in the context of parkinsonism. Our diagnostic criteria for PD were modified "clinically definite" criteria recommended by Calne and his coworkers[2]. Specifically, after ruling out secondary parkinsonism and parkinson-plus syndromes, three or more cardinal signs were required, or alternatively two cardinal signs were accepted as sufficient provided additional conditions were all met, which meant that at least one sign (not impaired postural reflexes) was asymmetric, the other one was either resting tremor or bradykinesia, and finally there was no levodopa unresponsiveness (if applicable).

Controls were individuals without past histories of PD or other progressive neurological disorders (such as Alzheimer's disease or multiple sclerosis), who are residing in Beijing and had been enrolled in the PD prevalence survey. No other medical history exclusion criteria were imposed on their control eligibility. The control group was matched to the study group by gender, race and residence categories. In particular, this population was racially homogeneous and representative of the whole population at large. The Research Center made personal contails with all the eligible cases and controls making them understand the study purposes and procedures and soliciting their participation. Briefly, a total of 114 eligible cases and 205 controls were enrolled in the study with informed consent.

Data Collection

All subjects were first presented with an informed consent form, followed by a brief Min-Mental State Examination (MMSE) to establish cognitive competence for providing questionnaire responses. A well structured, in-person questionnaire elicited data on demographic variables, medical history, lifestyle factors, diet, residential and occupational histories, and environmental exposures. The interviewers were thus generally unaware of patient status regarding PD. They were first asked whether they ever smoked, and if applicable, additional questions focusing on the age of start and quiting, years of smoking, and numbers of cigarettes

smoked per day were asked.

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 of smoking (the total number of pack-years was calculated as the number of years of smoking and the number of packs per day).

Initial analyses were conducted separately for the study, dichotomizing smoking into "ever", "current" and " ex" versus "never". The relative risk was estimated by calculating the odds ratio and 95 percent confidence intervals association by chi-square test variables of age, amount and durations of smoking and years of quitting smoking. Statistical testing was done at the two-tailed alpha level of 0.05. Data were analyzed using the SAS 6.12 software package.

RESULTS

The demographic characteristics of the study cases and controls are summarized in Table 1.

Study cases and controls had similar sex, and race distribution as expected. The average age the study and control groups were 70.09 ± 10.96 and 74.03 ± 8.11 respectively. The average age for PD onset for the study group was 64.01 ± 9.59.

TABLE 1

Demographic Characteristics of Parkinson's Disease Cases and Controls Recruited in Beijing

Characteristics	Cases (n=114)		Controls (n=205)	
	No.	%	No.	%
Gender				
Men	60	52.6	96	46.8
Women	54	47.4	109	53.2
Marital Status				
Married	84	73.7	137	66.8
Divorced/Separated	1	0.9	1	0.5
Widowed	29	25.4	67	32.7
Education Years				
<12 years	69	60.5	172	83.9
≥12 years	45	39.5	33	16.1

The associations with cigarette smoking are summarized in Table 2. With those subjects who never smoked serving as the reference category, cigarette smokers had half the PD risk of non-smokers, with almost the same low risks observed between current smokers and ever-smokers (OR=0.44, OR=0.49). Also, the dose-response gradients were seen with regard to OR=0.61 (95% CI: 0.35 to 1.07) for subjects whose smoking history was less than 20 years while OR was equavalent to 0.35 (95% CI: 0.18 to 0.70) for those longer than 20 years. These findings were not substantially altered when further stratified by pack-smoked per day. The findings demonstrated a strong inverse gradient detected for both amount of smoking (packs/day) (trend p=0.002) and years of smoking (trend p=0.002).

Moreover, when individuals with a smoking history were further categorized by having quitted for more than 20 years, and less than 20 years, and by being current smokers, still, there was a dose-response relationship in the likelihood of having PD. Those who quitted smoking more than 20 years ago were less likely to have the disease than never smokers, and those who quitted less than 20 years ago were least likely to have PD, while those who were current smokers were still least likely to have the disease. This dose-response relationship still had a gradient trend with *OR* falling from 0.61 (95% CI: 0.31 to 1.12) among those who quited more than 20 years ago, to 0.47 (95% CI: 0.17 to 1.13) among those who quitted less than 20 years ago, and to 0.44 (95% CI: 0.23 to 0.86) among current smokers.

The correlation between cigarette smoking and PD risks was also examined with alcohol and tea consumption as the adjusted factors. As demonstrated in Tables 3 and 4, results of *Brewlow-Day tests* showed that the data were of homogeneity. Being stratified by alcohol and tea consumption as confounding factors, the protective effect of cigarette smoking on PD was still observed in this study.

TABLE 2

Association of Parkinson's Disease With Cigarette Smoking

Smoking status	All Study Subjects			
	No. of Cases	No. of Controls	*OR*	95% CI
Never Smoked	77	104	1.00	
Ever Smoked	37	101	0.49	0.30, 0.79
Current Smoker	15	46	0.44	0.23, 0.86
Ex-smoker	22	55	0.54	0.30, 0.96
Years Smoked				
0	77	104	1.00	
<20	25	55	0.61	0.35, 1.07
⩾20	12	46	0.35	0.18, 0.70
p for Trend				0.002
Packs/day (n)				
$n=0$	77	104	1.0	
$n \leqslant 0.5$	32	80	0.54	0.32, 0.95
$n > 0.5$	5	21	0.32	0.12, 0.86
p for Trend				0.002

In unconditional multivariate logistic regression analysis, we observed the possible environmental risk factors related to PD occurrence (Table 5). Still, there was a negative correlation between PD risk and cigarette smoking (*OR*=0.518) and tea consumption (*OR*=0.201). In contrast, it was found that head injury was a strong predictor of PD (*OR*=6.454), followed by gender and age, which showed that gender and age were probably risk predictors for PD occurrence. In this analysis, well water drinking, use of pesticide/herbicide or chemical fertilizer or farming experience failed to exhibit significant positive associations with PD risk.

TABLE 3

Joint Effects of Cigarette Smoking and Alcohol Drinking[a, b]

	Alcohol Consumption				None-alcohol Consumption			
	No. of Cases	No. of Controls	*OR*	95% CI	No. of Cases	No. of Controls	*OR*	95% CI
Never smoked	18	58	1.00	0.10, 0.77	19	43	1.0	0.34 1.18
Ever smoked	11	10	0.28		66	94	0.63	

Note: [a]Mantel-Haenszel test OR=0.51 (95% CI: 0.30, 0.86).
[b]Brewlow-Day test for homogeneity of the odds ratios: Chi-square=1.78, *P*=0.18.

TABLE 4

Joint Effects of Cigarette Smoking and Tea Consumption[a, b]

	Tea Consumption				None-tea Consumption			
	No. of Cases	No. of Controls	*OR*	95% CI	No. of Cases	No. of Controls	*OR*	95% CI
Never smoked	24	62	1.0	0.22, 0.96	53	42	1.0	0.41 1.68
Ever smoked	14	79	0.46		23	22	0.83	

Note: [a]Mantel-Haenszel test *OR*=0.62 (95% CI: 0.37, 1.00).
[b]Brewlow-Day test for homogeneity of the odds ratios: Chi-square=1.29, *P*=0.26.

TABLE 5

Estimated Associations of PD Risks and Different Variables by Multivariate Logistic Regression

Variables	β	Ste	x^2	*P*	*OR*
Intepercpt	-4.4487	2.6646	2.7875	0.0950	-
Gender	0.9017	0.3088	8.5241	0.0035	2.464
Age	0.0286	0.0149	3.6778	0.0551	1.039
Smoking	-0.6577	0.3288	4.0018	0.0455	0.518
Tea Consumption	-1.6023	0.2926	29.9889	0.0001	0.201
Alcohol Consumption	-0.0426	0.3534	0.0146	0.9039	1.043
Well-water Drinking	-0.0385	0.3530	0.0119	0.9132	0.962
Pesticide/herbicide Use	0.1708	0.4025	0.1801	0.6713	1.186
Farming Experience	-0.2918	0.2909	1.0064	0.3158	0.747
Head Injuries	1.8648	0.5741	10.5507	0.0012	6.454
Chemical Fertilizer Use	0.2181	0.2726	0.6403	0.4236	1.244
Organic-solvent use	0.5836	1.0024	0.3389	0.5604	1.792

DISCUSSION

The underlying pathologic lesion is a selective destruction of the dopamine-producing neurons in the pars compacta of the substanita nigra[6]. The apparent protective effect of cigarette smoking on PD observed in our study was very similar in magnitude to what have been reported in previous researches. A reduced risk of PD among cigarette smoking is consistent with findings from case-control studies conducted in western Washington State[7], Detroit[8] and New York of USA[9] and in Europe[10]. In China, few studies addressed systematically the relationship between cigarette smoking and PD. But, the most striking results of our

study is the remarkable inverse dose-response pattern with cigarette smoking amount (pack/days), years of smoking and with duration of smoking cessation. These findings further supported what have been reported previously in the literature. Although some previous studies ended with spurious results, cohort studies, in which data on smoking were obtained before the onset of PD, provided corroborative evidence for the apparent protective effect of smoking[11,12]. The findings of study suggest that such relationship is not a satisfactory explanation for the effect of smoking. A biochemical research has provided critical evidences for supporting the hypotheses of the inverse correlation between PD incidence and cigarette smoking[13,14]. Components of cigarette smoke may afford neuro-protection by reducing enzymatic activity of type B monoamine oxidase (MAO-B) in the brain. MAO-B catabolizes dopamine and may activate neurotoxicants similar to the established experimental PD-inducing chemical 1-methyl-4-phenyl-1,2,3,6-tetrahdropyridine (MPTP). Recently, a MAO-B compound in tobacco, 2,3,6-trimethly-1,4-naphthoquinone, was found to attenuate the dopaminergic system toxicity of MPTP in experiments on mice[15].

A strong point of our study lies in the fact that all the studied patients were diagnosed by a team of neurologists headed by a noted expert, according to established criteria. In addition, the subjects in our study were selected from a well defined population base, lending credibility regarding the selection of representative patients and suitable control subjects. Therefore, there is little reason to suspect that our findings in this study can be explained by bias or confounding.

Our results were not confounded by alcohol or tea consumption, although heavy drinking or tea consumption and some other factors might have effect on the protection afforded by smoking via some currently unclear mechanism. In this study, we did not assess coffee or cola consumption, and cannot comment on these possible effects on our study population. This was partially due to rare consumption of coffee or cola by most Chinese elderly people or partially due to limitted data availability. Concerning this aspect, earlier case-control studies did not demonstrate a consistent effect of either alcohol or coffee/tea intake on PD disease status. However, a recent study has shown that a dose-response relationship between smoking and PD is maintained when adjustment is made for coffee and tea habits[16].

The etiology of Parkinson's disease is still unknown, but accumulating evidence supports the hypothesis that some environmental factors might have a major impact on pathogenesis. We finally employed unconditional multivariate logistic regression model to probe the correlation between cigarette smoking and PD risk and the results showed that cigarette smoking still had a protective effect on PD while head injury was a strong predictor for the PD risk (OR=6.454).

The principal limitation of this study is heavy reliance on self-reported data on cigarette smoking and alcohol consumption. Consequently, the possibility of inaccurate exposure data and possible resulting recalling and misclassification biases should be considered when interpreting our findings. Nevertheless, data concerning exposures to cigarette smoking presented in this study were undoubtedly most complete and valid because of lifetime habits elicited by the questionnare items.

Briefly, the inverse correlation between Parkinson's disease risk and smoking as well as the trend of gradient dose-response is again observed in our study. More future researches are needed to confirm such correlation and to explore further biochemical evidence.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the excellent professional and technical work of the dedicated nurses, interviewers and all the staff members involved in the survey. We also thank the secretarial personnel for their

sincere help offered to this study.

REFERENCES

1. Lang, A.E. and Lozano, A.M.(1998). Parkinson's disease. *N. Engl. J. Med.* **339**, 1044-53.
2. Calne, D.B., Snow, B.J., and Lee, C. (1992). Criteria for diagnosing Parkinson's disease. *Ann. Neurol.* **32(Suppl.)**, S125-S127.
3. Tanner, C.M. and Ben-Shlomo, Y. (1999). Epidemiology of Parkinson's disease. In: Stern GM, ed. Parkinson's disease: advances in neurology. Philadelphia, PA: Lippincott Williams & Wilkins, **80**, 153-9.
4. Mayeux, R., Marder, K., Cote, L.J., Denaro, J., Hemenegildo, N., Mejia, H., Tang, M.X., Rafael, Lantigua, Wilder, D., Gurland, B., and Hauser, A. (1995). The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. *Am. J. Epidemiol.* **142**, 820-7.
5. Gustavo, C., Roman, Zhen-xin, Zhang, and Jonas, H., Ellenberg (1995). The neuroepidemiology of Parkinson's disease. pp.203-245. See:Jonas H. Ellenberg ed., Etiology of Parkinson's Disease..Marcel Derker, New York.
6. Agid, Y. (1991). Parkinson's disease: patho-physiology. *Lancet* **337**, 1321-7.
7. Harvey, Checkoway, Karen, Powers, Terri, Smith-Weller, Gary, M., and Franklin, W.T. (2002). Longstreth Jr and Phillip D. Swanson. Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake. *American J. of Epidemiology* **155**(8), 732-738.
8. Jay, M., Gorell, Benjamin, A., Rybicki, Christine, C., Johnson, and Edward, L., Peterson (1999). Smoking and Parkinson's disease:a dose response relationship. *Neurology* **52**, 115-119.
9. Mayeux, R., Ting, M-X, Marder, K., Cote, L.T., and Stern, Y. (1994). Smoking and Parkinson's disease. *Mov. Disord.* **9**, 207-212.
10. C., Tzourio, W.A., Rocca, M.M., Breteler, M., Baldereschi, J.F., Dartigues, S., Lopez-Pousa, J.M. Manubens-Bertran and A. Alperovitch. (1997). Smoking and Parkinson's disease, an age-dependent risk effect? *Neurology* **49**, 1267-1272.
11. Sasco, A.J. and Paffenbarger, R.S. (1990). Smoking and Parkinson' disease. *Epidemiology* **1**, 460-5.
12. Grandinetti, A., Morens, D.M., Reed, D., and MacEachern, D. (1994). Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. *Am. J. Epidemiol.* **139**, 1129-38.
13. J.S., Fowler, N.D., Volkow, G-J, Wang, N., Pappas, J., Logan, R., MacGregor, D., Alexoff, C., Shea, D., Schlyer, A.P., Wolf, D., Warner, I., Zezulkova, and R., Cilento (1996). Inhibition of monoamine oxidase B in the brains of smokers. *Nature* **379**, 733-6.
14. Riederer, P., Konradi, C., Hebestreit, G., and Youdim, M-B. (1989). Neurochemical perspectives to the function of monoamine oxidase. *Acta Neurol. Scand.* **126(Suppl.)**, 41-5.
15. Castagnoli, K.P., Steyn, S.J., Petzer, J.P., Vanderschyf, C.J., and Castagnoli, NJr. (2001). Neuroprotection in the MPTP parkinsonian C57BL/6 mouse model by a compound isolated from tobacco. *Chem. Res. Toxicol.* **14**, 523-7.
16. Tanner, C.M. and Goldman, S.M. (1996). Epidemiology of Parkinson's disease. *Neurol. Clin.* **14**, 317-335.

(*Received January* 5, 2002 *Accepted March* 28, 2003)