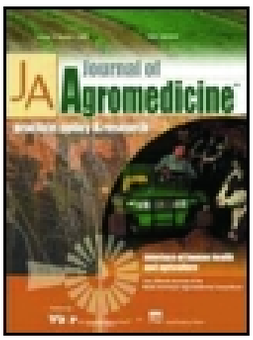

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Amanpreet S. Dhillon MD MS , G. Lester Tarbutton MD MPH , Jeffrey L. Levin MD MSPH , George M. Plotkin MD PhD , Larry K. Lowry PhD , J. Torey Nalbone PhD CIH & Sara Shepherd MAMS

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Pesticide/Environmental Exposures and Parkinson's Disease in East Texas

Amanpreet S. Dhillon, MD, MS
G. Lester Tarbutton, MD, MPH
Jeffrey L. Levin, MD, MSPH
George M. Plotkin, MD, PhD
Larry K. Lowry, PhD
J. Torey Nalbone, PhD, CIH
Sara Shepherd, MAMS

ABSTRACT. Epidemiological evidence suggests that pesticides and other environmental exposures may have a role in the etiology of idiopathic Parkinson's disease (PD). However, there is little human data on risk associated with specific pesticide products, including organic pesticides such as rotenone with PD. Using a case-control design, this study examined self-reports of exposure to pesticide products, organic pesticides such as rotenone, and other occupational and environmental exposures on the risk of PD in an East Texas population. The findings demonstrated significantly increased risk of PD with use of organic pesticides such as rotenone in the past year in gardening (OR = 10.9; 95% CI = 2.5–48.0) and any rotenone use in the past (OR = 10.0; 95% CI = 2.9–34.3). Use of chlorpyrifos products (OR = 2.0; 95% CI = 1.02–3.8), past work in an electronics plant (OR = 5.1; 95% CI = 1.1–23.6), and exposure to fluorides (OR = 3.3; 95% CI = 1.03–10.3) were also associated with significantly increased risk. A trend of increased PD risk was observed with work history in paper/lumber mill (OR

Amanpreet S. Dhillon, MD, MS, is Assistant Professor, Department of Occupational Health Sciences, the University of Texas Health Science Center at Tyler, Tyler, Texas (E-mail: amanpreet.dhillon@uthct.edu).

Jeffrey L. Levin, MD, MSPH, is Professor, Department of Occupational Health Sciences, the University of Texas Health Science Center at Tyler, Tyler, Texas.

Larry K. Lowry, PhD, is Professor, Department of Occupational Health Sciences, the University of Texas Health Science Center at Tyler, Tyler, Texas.

Sara Shepherd, MAMS, is Database Manager, Department of Occupational Health Sciences, University of Texas Health Science Center at Tyler, Tyler, Texas.

G. Lester Tarbutton, MD, MPH, MCS, is Physician at Longview Occupational Medicine Clinic, Longview, Texas.

George M. Plotkin, MD, PhD, is Director, Movement Disorder Center, East Texas Medical Center, Tyler, Texas.

J. Torey Nalbone, PhD, CIH, is Associate Professor, Department of Civil and Environmental Engineering, the University of Texas at Tyler, Tyler, Texas.

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Address correspondence to: Amanpreet S. Dhillon, MD, MS, Assistant Professor, Department of Occupational Health Sciences, the University of Texas Health Science Center at Tyler, 11937 US Hwy 271, Tyler, TX 75708 (E-mail: amanpreet.dhillon@uthct.edu).

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= 6.35; 95% CI = 0.7–51.8), exposure to cadmium (OR = 5.3; 95% CI = 0.6–44.9), exposure to paraquat (OR = 3.5; 95% CI = 0.4–31.6), and insecticide applications to farm animals/animal areas and agricultural processes (OR = 4.4; 95% CI = 0.5–38.1). Cigarette smoking, alcohol use, and fish intake were associated with reduced risk. In summary, this study demonstrates an increased risk of PD associated with organic pesticides such as rotenone and certain other pesticides and environmental exposures in this population.

KEYWORDS. Parkinson's disease, pesticides, organic pesticides, rotenone, agriculture, farming, environmental exposures, chlorpyrifos, smoking, fisheries

INTRODUCTION

Parkinson's disease (PD) is a debilitating progressive neurodegenerative disorder affecting approximately 1% of the US population over 50 years of age.[1] Past research has focused on the interactions between environmental exposures[2] and genetic susceptibilities as potential causes of PD. The results of twin studies suggest that factors other than genetics, including environmental factors, may play a major role,[3,4] and another study demonstrated low rates of concordance (5–8%) in monozygotic and dizygotic twins,[5] again suggesting that factors other than genetics may have a role in the etiology of PD. Epidemiologic evidence from more than two decades of research has demonstrated an increased risk of PD with pesticide exposures.[6–10]

PD predates the modern chemical era, and as such the role of naturally occurring toxins should also be considered. One of these natural toxins, a pesticide called rotenone, is produced by several plant species and has been used in some cultures for hundreds of years. Exposure to rotenone reproduces features of PD in animal models, including selective nigrostriatal dopaminergic degeneration and alpha-synuclein-positive cytoplasmic inclusions.[11,12] In modern society, organic gardeners use rotenone in many forms, including commercial and residential use. Further, rotenone is routinely used in fish farms and fish hatcheries as an agent to kill large fish before restocking the pond. Recent research has suggested that, in addition to rotenone, several other commercially used pesticides directly inhibit mitochondrial complex I and may play a potential role in causing PD.[13]

Although pesticides have been suspected as a causative factor for PD,[14] no firm association has been established in humans despite strong evidence in animal models. Therefore, the objective in this investigation was to examine the association between PD and exposures to specific pesticide products, including organic pesticides such as rotenone as well as other environmental and occupational exposures. In this article, we present findings from a case-control study of PD done in an East Texas population.

METHODS

Study Population

The cases were recruited from a cohort of approximately 800 PD patients followed by the neurology practice of one of the authors and his copartner at a local medical center's neurological institute located in east Texas. Inclusion criteria for the cases in this study were (a) individuals of age 50 years and older (b) living in one of the Texas Department of State Health Services Region 4/5N counties (East Texas region) (c) diagnosed with PD by standard clinical/lab diagnostic criteria by a neurologist specializing in movement disorders. Patients who have been diagnosed with multiple sclerosis, schizophrenia, and Parkinson's plus diseases (including diffuse Lewy body disease, multiple system atrophy, progressive supranuclear palsy, Alzheimer's disease, Pick's disease, Huntington's disease) were excluded from the study because of potential confounding issues related to dopamine. Controls were also selected from the same practice, met the same inclusion and exclusion criteria, and had no history of PD. Eligible cases and controls were contacted by a trained interviewer using a structured telephone script and

mail soliciting the subject's participation. The Institutional Review Board at the University of Texas Health Science Center at Tyler reviewed and approved the study.

A total of 102 PD cases agreed to participate and were enrolled in the study, of which 2 did not complete the study (declined to fully complete the survey questionnaire [n = 1]; cognitive impairment that prevented interview [n = 1]). A total of 84 control subjects were enrolled and completed the study.

Data Collection

A standardized questionnaire was developed and included sections on demographic information (age, sex, race, marital status, education level), lifestyle activities (smoking/tobacco use, alcohol, caffeine, vegetable/fruit/fish intake), personal and family medical history, occupational history (working in a variety of industries, exposures to chemicals such as arsenic, asbestos, benzene, manganese, solvents, etc), and military history (including contact with munitions, spraying herbicides/pesticides such as Agent Orange). Questions on use of rotenone in fish farming and as an "organic" pesticide in home/garden use were also asked. Detailed sections eliciting information on personal use/mixing and average duration of exposure to a variety of herbicides, insecticides, fumigants, fungicides, and "organic" pesticides such as rotenone were also included. Finally, questions about any lifetime use of other pesticide products (such as Paraquat, Maneb, DDT, etc) that were not included in previous sections were also asked. After obtaining informed consent, a trained medical professional administered the questionnaire during a structured interview during a scheduled visit for their routine neurology follow-up.

Data Analyses

As there were more cases (n = 100) than controls (n = 84) who completed the study, analyses of group characteristics were performed. For discrete data such as sex, ethnicity, and marital status, cases and controls were compared using the chi-square test to determine whether there were differences in the proportions in the two groups. Age and years of education were compared using the t-test. The relative risk of PD for various exposures was estimated by odds ratio (OR). Odds ratios were calculated for current, ex-smoker, and ever smokers (persons who had smoked 100 or more cigarettes in their lifetime) using never smokers as a reference. A composite caffeine intake was constructed as a sum of the daily servings of caffeinated coffee, tea, colas, cocoa, and chocolate. A composite total consisting of an affirmative answer to any one of the six questions regarding rotenone use ("any rotenone use") was compared with no rotenone use at all. The chi-square test was used to compare cases and controls for the exposure data. Odds ratios and 95% confidence intervals were calculated. All p-values are two-tailed and considered significant if p-value less than 0.05. Data were analyzed using SPSS version 13.0.

RESULTS

The median age among the cases and controls was comparable, 73 and 71 years, respectively, with almost identical age range (Table 1). The proportion of males to females among the cases (3:2) was comparable to the control group (4:3). Ethnicity, marital status, and educational level of the cases and controls were similar.

Several lifestyle factors were associated with reduced risk for PD. Ex-smokers had lower PD risk than nonsmokers (OR = 0.4; 95% Confidence Interval (CI) = 0.2–0.8) as did ever smokers (OR = 0.5; 95% CI = 0.3–0.8) but current smokers did not show this decreased risk (OR = 1.1; 95% CI = 0.3–5.2). Alcohol intake in the last 12 months was associated with lower PD risk than no alcohol intake (OR = 0.5; 95% CI = 0.3–0.8). Alcohol intake ranging from once a month to once a week was also associated with reduced PD risk (OR = 0.5; 95% CI = 0.2–0.9). Eating fish more than once a month was associated with lower PD risk when compared to eating fish once or less than once a month (OR = 0.5; 95% CI = 0.3–0.9).

A number of occupational and environmental exposures were associated with PD (Table 2). Although increased risk was statistically

TABLE 1. Demographic Characteristics of the Study Population

Variable	Cases		Controls		Odds Ratio (95% CI*)	*p* Value
	No.	%	No.	%		
Median age (range), in years	73 (56–91)		71 (56–90)			
Sex						
Male	60	60.0	47	56.0		
Female	40	40.0	37	44.0		
Ethnicity						
White	99	99.0	83	98.8		
Black	1	1.0	1	1.2		
Marital status						
Married	85	85.0	72	85.7		
Widowed/divorced	15	15.0	12	14.3		
Median education level (range), in years	14.0 (8–22)		15.5 (8–18)			
Smoking status						
Never smoked	60	60.0	34	40.5	—	—
Ever smoked†	40	40.0	50	59.5	0.5 (0.3–0.8)	0.008
Current smoker	4	4.0	3	3.6	1.1 (0.3–5.2)	0.880
Ex-smoker	36	36	47	56.0	0.4 (0.2–0.8)	0.006
Alcohol intake in the last 12 months						
None	60	60.0	34	40.5	—	
Drank alcohol in the last 12 months	40	40.0	50	59.5	0.5 (0.3–0.8)	0.008
Between once a month to once a week	27	27.0	34	40.5	0.5 (0.2–0.9)	0.016
More than once a week	13	13.0	16	19.1	0.5 (0.2–1.1)	0.069
Caffeine intake in the last 12 months						
None	19	19.0	10	11.9	—	
Had at least 1 serving/day or more	81	81.0	74	88.1	0.6 (0.3–1.3)	0.188
Had 1–6 servings/day	75	75.0	67	87.0	0.6 (0.3–1.4)	0.210
Had 7 or more servings/day	6	6.0	7	8.3	0.5 (0.1–1.7)	0.237
Vegetable intake						
0–4 Servings/week	13	13.0	9	10.7	—	
5 Or more servings/week	87	87.0	75	89.3	0.8 (0.3–2.0)	0.634
Fruit intake						
0–4 Servings/week	28	28.0	34	40.5	—	
5 Or more servings/week	72	72.0	50	59.5	1.8 (0.9–3.2)	0.075
Fish intake						
Once or less than once per month	52	52.0	28	33.7	—	
More than once per month	48	48.0	55	66.3	0.5 (0.3–0.9)	0.013

*CI indicates confidence interval.
†Ever smoked: Persons who had smoked 100 or more cigarettes in their lifetime.

significant for having worked in an electronics plant (OR = 5.1; 95% CI = 1.1–23.6) and exposure to fluorides (OR = 3.3; 95% CI = 1.03–10.3), possible associations were also seen with work history in a paper/lumber mill had the highest OR (OR = 6.35; 95% CI = 0.7–51.8) followed by exposure to cadmium (OR = 5.3; 95% CI = 0.6–44.9), arsenic (OR = 4.1; 95% CI = 0.9–19.3), and phenols (OR = 3.5; 95% CI = 0.4–31.5). Among the pesticide applications performed in the past year, a trend of increased risk was observed with insecticide applications to farm animals/animal areas and agricultural processes (OR = 4.4; 95% CI = 0.5–38.1).

Among the exposure to pesticides, elevated risk was associated with personal use of chlorpyrifos products (OR = 2.0; 95% CI = 1.02–3.8; Table 3). A possible association of increased PD risk was also observed with personal use of Paraquat (OR = 3.5; 95% CI = 0.4–31.6)

TABLE 2. Occupational and Environmental Exposures and Risk of PD in the Study Population

Risk Factor	Cases		Controls		Odds Ratio (95% CI*)	*p* Value
	No.	%	No.	%		
Ever Worked in or Around						
Chemical plant	14	14.0	11	13.1	1.1 (0.5–2.5)	0.858
Construction site	25	25.0	22	26.2	0.9 (0.5–1.8)	0.854
Cotton, flax, or hemp mill	11	11.0	5	6.0	2.0 (0.7–5.9)	0.226
Mine	3	3.0	1	1.2	2.6 (0.3–25.1)	0.402
Electronics plant	11	11.0	2	2.4	5.1 (1.1–23.6)	0.023
Farm	52	52.0	41	48.8	1.1 (0.6–t2.0)	0.666
Fiber mill	2	2.0	0	0.0	—	0.192
Foundry	8	8.0	5	6.0	1.4 (0.4–4.4)	0.589
Nursery/greenhouse/garden	27	27.0	27	32.1	0.8 (0.4–1.5)	0.445
Refinery	11	11.0	12	14.3	0.7 (0.3–1.8)	0.502
Shipyard	3	3.0	2	2.4	1.3 (0.2–7.8)	0.797
Paper/lumber mill	7	7.0	1	1.2	6.3 (0.7–51.8)	0.054
Fishery/fish farm/fish hatchery	3	3.0	2	2.4	1.3 (0.2–7.8)	0.797
Military	42	42.0	34	40.5	1.1 (0.6–1.9)	0.834
Ever worked or exposed to						
Arsenic	9	9.0	2	2.4	4.1 (0.9–19.3)	0.059
Asbestos	21	21.0	22	26.2	0.8 (0.4–1.5)	0.407
Benzene	8	8.0	8	9.5	0.8 (0.3–2.3)	0.715
Beryllium	2	2.0	0	0.0	—	0.192
Cadmium	6	6.0	1	1.2	5.3 (0.6–44.9)	0.089
Chromates	4	4.0	3	3.6	1.1 (0.3–5.2)	0.880
Fluorides	14	14.0	4	4.8	3.3 (1.03–10.3)	0.036
Lead	16	16.0	13	15.5	1.0 (0.5–2.3)	0.923
Manganese	6	6.0	2	2.4	2.6 (0.5–13.3)	0.231
Mercury	16	16.0	10	11.9	1.4 (0.6–3.3)	0.427
Carbon tetrachloride	21	21.0	13	15.5	1.5 (0.7–3.1)	0.336
Lasers	6	6.0	8	9.5	0.6 (0.2–1.8)	0.369
Phenols	4	4.0	1	1.2	3.5 (0.4–31.5)	0.243
Phosgene	3	3.0	0	0.0	—	0.109
PVCs	14	14.0	7	8.3	1.8 (0.7–4.6)	0.229
Radioactive materials	9	9.0	9	10.7	0.8 (0.3–2.2)	0.697
Solvents/degreasers	34	34.0	35	41.7	0.7 (0.4–1.3)	0.285
Spray painting	39	39.0	30	35.7	1.2 (0.6–2.1)	0.647
Trichloroethylene	11	11.0	4	4.8	2.5 (0.8–8.1)	0.123
Welding/soldering	26	26.0	20	23.8	1.1 (0.6–2.2)	0.733
Pesticide applications done in the past year						
Insecticide applications to/for farm crops	5	5.0	2	2.4	2.2 (0.4–11.4)	0.355
Farm animals/animal areas	5	5.0	1	1.2	4.4 (0.5–38.1)	0.147
Agricultural processes	5	5.0	1	1.2	4.4 (0.5–38.1)	0.147
Aerial spraying of insecticides	1	1.0	0	0.0	—	0.358
Herbicide use for home/agricultural purposes	34	34.0	34	40.5	0.8 (0.4–1.4)	0.365
Pets	25	25.0	15	17.9	1.5 (0.8–3.2)	0.242
Your home	33	33.0	25	29.8	1.2 (0.6–2.2)	0.638
Other's home	3	3.0	3	3.6	0.9 (0.2–4.3)	0.828
Business/commercial building	2	2.0	0	0.0	—	0.192
Lawn, garden, greenhouse, or areas near your home	32	32.0	31	36.9	0.8 (0.4–1.5)	0.485
Termite control	14	14.0	10	11.9	1.2 (0.5–2.9)	0.674
Rodent control	14	14.0	12	14.3	1.0 (0.4–2.3)	0.956
Ant control	44	44.0	36	42.9	1.1 (0.6–1.9)	0.876

*CI indicates confidence interval.

TABLE 3. Pesticide Exposures and Risk of PD in the Study Population

Risk Factor: "Ever Personally Used/Mixed or Applied:"	Cases		Controls		Odds Ratio (95% CI*)	*p* Value
	No.	%	No.	%		
Herbicides						
Aatrex, Atranex, or other atrazine products	1	1.0	0	0.0	—	0.358
Banvel, Metambane, or other dicamba product	1	1.0	0	0.0	—	0.358
Bladex, Match, or other cyanazine product	2	2.0	0	0.0	—	0.192
Dual, Cycle, or other metochlor product	1	1.0	1	1.2	0.8 (0.05–13.6)	0.901
Eradicane, Eptam, or other EPTC product	0	0.0	2	2.4	—	0.121
Lasso, Chimiclor, or other alachlor product	2	2.0	0	0.0	—	0.192
Pursuit or other imazethapyr product	1	1.0	1	1.2	0.8 (0.05–13.6)	0.901
Roundup, Jury, or other glyphosate product	54	54.0	43	51.2	1.1 (0.6–2.0)	0.704
Treflan, Trilin, Commence, or other trifluralin product	4	4.0	2	2.4	1.7 (0.3–9.6)	0.538
2,4-D	17	17.0	12	14.3	1.2 (0.6–2.8)	0.615
Used any of the above herbicides	54	54.0	43	51.2	1.1 (0.6–2.0)	0.704
Crop and livestock insecticides						
Lorsban, Dursban, or other chlorpyrifos product	35	35.0	18	21.4	2.0 (1.02–3.8)	0.043
Poultry, livestock, and animal confinement						
Area insecticides						
Co-Ral or other coumaphos product	5	5.0	3	3.6	1.4 (0.3–6.1)	0.636
Ectiban, Atroban, or other permethrin product	1	1.0	3	3.6	0.3 (0.03–2.7)	0.233
Vapona, Duravos, or other dichlorvos product	0	0.0	1	1.2	—	0.274
Used any of the above insecticides	6	6.0	7	8.3	0.7 (0.2–2.2)	0.538
Fumigants						
Brom-O-Gas or other methyl bromide product	0	0.0	4	4.8	—	0.027
Fungicides						
Bravo, Evade, or other chlorothalonil product	3	3.0	3	3.6	0.8 (0.2–4.3)	0.828
Orthocide, Clomitane, or other captan product	5	5.0	2	2.4	2.2 (0.4–11.4)	0.355
Used any of the above fungicides	8	8.0	5	6.0	1.4 (0.4–4.4)	0.589
Nursery, lawn, garden insecticides						
Ambush or other permethrin/pyrethroid product	2	2.0	1	1.2	1.7 (0.2–19.0)	0.666
Counter or other terbufos product	1	1.0	0	0.0	—	0.358
Dyfonate or other fonofos product	1	1.0	0	0.0	—	0.358
Dylox or other trichlorfon product	3	3.0	2	2.4	1.3 (0.2–7.8)	0.797
Furadan, Curaterr, or other carbofuran product	2	2.0	2	2.4	0.8 (0.1–6.1)	0.860
Used any of the above insecticides	8	8.0	5	6.0	1.4 (0.4–4.4)	0.589
Complex I acaricides/insecticides						
Boramae, Magister, Pride, or other fenzaquin product	0	0.0	0	0.0	—	—
Acaben, Akari, Ortus, or other fenpyroximate product	0	0.0	2	2.4	—	0.121
Nexter, Oracle, Pyramite, or other pyridaben product	0	0.0	0	0.0	—	—
Miteclean or other pyrimidifen product	0	0.0	0	0.0	—	—
Comanche, Oscar, or other tebufenpyrad product	0	0.0	0	0.0	—	—

*CI indicates confidence interval.

among the herbicides, fungicides, and fumigants (Table 4). Use of "organic pesticides" such as rotenone in gardening in the past year was strongly associated with increased PD risk and had the highest OR for pesticide applications (OR = 10.9; 95% CI = 2.5–48.0; Table 5). In addition, 27 cases had used rotenone in at least one form or manner (any rotenone use) compared with 3 controls (OR = 10.0; 95% CI = 2.9–34.3).

DISCUSSION

Individuals exposed to pesticides have been demonstrated to have a 90% higher incidence of PD than unexposed individuals.[15] In the same study, the hypothesis of a direct effect of pesticides was supported by the finding that the farmers not exposed to pesticides were not at increased risk of PD. Similarly, a meta-analysis of case-control studies also demonstrated that

TABLE 4. Miscellaneous Pesticide/Herbicide Exposures and Risk of PD in the Study Population

Risk Factor: "Ever Personally Used/Mixed or Applied:"	Cases		Controls		Odds Ratio (95% CI*)	*p* Value
	No.	%	No.	%		
Pesticides						
Forlin, Gamaphex, or other lindane products	5	5.0	6	7.1	0.7 (0.2–2.3)	0.541
Malathion	46	46.0	33	39.3	1.3 (0.7–2.4)	0.359
Parathion (ethyl or methyl)	4	4.0	5	6.0	0.7 (0.2–2.5)	0.541
Sevin, Carbamine, or other carbaryl products	58	58.0	48	57.1	1.0 (0.6–1.9)	0.907
Spectracide, Dianon, or other diazinon products	44	44.0	42	50.0	0.8 (0.4–1.4)	0.416
Temik or other aldicarb products	1	1.0	0	0.0	—	0.358
Thimet, Rampart, or other phorate products	2	2.0	0	0.0	—	0.192
Aldrin	1	1.0	0	0.0	—	0.358
Chlordane	37	37.0	34	40.5	0.9 (0.5–1.6)	0.629
Dieldrin	9	9.0	6	7.1	1.3 (0.4–3.8)	0.647
DDT	38	38.0	28	33.3	1.2 (0.7–2.3)	0.511
Heptachlor	5	5.0	2	2.4	2.2 (0.4–11.4)	0.355
Toxaphene	4	4.0	4	4.8	0.8 (0.2–3.4)	0.801
Used any of these above pesticides	70	70.0	59	70.2	1.0 (0.5–1.9)	0.972
Herbicides						
Classic or other chlorimuroethyl product	1	1.0	0	0.0	—	0.358
Lexone, Sencor, or other metribuzin product	1	1.0	0	0.0	—	0.358
Paraquat	4	4.0	1	1.2	3.5 (0.4–31.6)	0.243
Cyperquat	0	0.0	1	1.2	—	0.274
Petroleum oil/petroleum distillate	20	20.0	18	21.4	0.9 (0.5–1.9)	0.812
Prowl or other pendimethalin product	2	2.0	0	0.0	—	0.192
Sutan, Genate, or other butylate product	0	0.0	0	0.0	—	—
Silvex or other 2,4,5-TP product	1	1.0	3	3.6	0.3 (0.03–2.7)	0.233
2,4,5-T	4	4.0	7	8.3	0.5 (0.1–1.6)	0.217
Used any of these above herbicides	23	23.0	22	26.2	0.8 (0.4–1.7)	0.616
Fungicides						
Benlate, Tersan, or other benomyl product	1	1.0	4	4.0	0.2 (0.02–1.8)	0.118
Manex, Manzate, or other maneb/mancozeb product	2	2.0	3	3.6	0.6 (0.09–3.4)	0.514
Rodomil, Subdue, or other metalaxyl product	0	0.0	0	0.0	—	—
Zirex, Corozate, or other ziram product	2	2.0	0	0.0	—	0.192
Used any of these above fungicides	4	4.0	6	7.1	0.5 (0.2–2.0)	0.349
Fumigants						
Phostoxin or other aluminum phosphide product	1	1.0	0	0.0	—	0.358
Carbon tetrachloride or carbon disulfide	24	24.0	17	20.2	1.3 (0.6–2.5)	0.541
EDB, Bromofume, or other ethylene dibromide product	1	1.0	1	1.2	0.8 (0.1–13.6)	0.901
Used any of these above fumigants	25	25.0	17	20.2	1.3 (0.7–2.6)	0.443

*CI indicates confidence interval.

individuals who reported exposures to pesticides had a 90% higher risk of PD than those not exposed.[16] Several epidemiological studies done in the past two decades[17–21] and some of the more recent investigations[22–26] support associations of pesticide exposures with PD; however, no specific agent has been consistently implicated.

To our knowledge, this is the first epidemiologic investigation to explore PD risk associated with exposure to "organic pesticides," specifically rotenone. The present study identified a significantly increased risk (OR = 10.9) with "organic pesticide" use such as rotenone in the past year in gardening. In the interpretation of this finding, it is assumed that the pattern of one's use of pesticides in the previous year is to some extent reflective of the pattern of one's use of pesticides in the past. This assumption was, in part, corroborated by an elevated though nonsignificant risk (OR = 3.6) with use of rotenone in home/garden "ever" in the past.

TABLE 5. "Organic Pesticides"/Rotenone Exposures and Risk of PD in the Study Population

Risk Factor	Cases		Controls		Odds Ratio (95% CI*)	*p* Value
	No.	%	No.	%		
Used "organic pesticides" such as rotenone in the past year in :						
Gardening	21	21.0	2	2.4	10.9 (2.5–48.0)	<0.001
Fisheries	2	2.0	0	0.0	—	0.192
Ever used rotenone while working at a fishery/fish hatcheries or fish farms	1	1.0	0	0.0	—	0.358
Ever used rotenone in home/garden[†]	8	8.0	2	2.4	3.6 (0.7–17.2)	0.094
Ever personally used, mixed or applied Chem-Fish, Cuberol, Derris Root, Fish Tox, Rotacide, or other rotenone product for						
Land use only	5	5.0	5	6.0	0.8 (0.2–3.0)	0.777
Water use only	6	6.0	3	3.6	1.7 (0.4–7.1)	0.447
Any rotenone use[‡]	27	27.0	3	3.6	10.0 (2.9–34.3)	<0.001

*CI indicates confidence interval.

[†]Ever used rotenone in one's home or garden as a liquid, spray, powder, or ground root as an "organic pesticide."

[‡]Any rotenone use: Use of "organic pesticides" such as rotenone in either gardening or fishing in the past year, ever use or mixing of rotenone while working at a fishery/fish hatcheries or fish farms, ever use of rotenone in home as an "organic pesticide," ever use of a rotenone product for land use, or ever use of a rotenone product for water use.

Naturally derived rotenone is listed as a "restricted substance" by the Organic Materials Review Institute (OMRI 2004); however, rotenone is commonly marketed and sold under the category of "organic gardening supplies." Rotenone, a naturally occurring insecticide as a well-characterized, high-affinity inhibitor of complex I, is extremely lipophilic and crosses biologic membranes easily, entering the brain very rapidly.[27] In some studies, rats treated with rotenone have demonstrated many characteristics of PD, including selective nigrostriatal dopaminergic degeneration and loss, possibly through oxidative damage to these neurons, and alpha-synuclein-positive inclusions in the substantia nigra.[11,12,28,29] In another animal experiment, it was shown that dopaminergic synapses in the substantia nigra (SN) and the nigrostriatal pathways were sensitive to the action of rotenone and it was suggested that the (sub)chronic intraperitoneal dosing of rotenone used was comparable with chronic environmental exposure in a real-life situation.[30] The finding that age enhances the sensitivity of dopaminergic SN neurons to rotenone[31] is significant because the etiology of idiopathic PD is age related. Although the use of organic pesticides in gardening may not be due to rotenone use only and this response may reflect other pesticides that individuals consider as organic pesticides, "any rotenone use" was also associated with a significantly elevated odds ratio (OR = 10.0) and the elevated risk may, in fact, be attributable to this specific agent.

Unlike past studies that investigated the risk of PD associated with pesticides as a group, our study sought to identify the risk of PD associated with specific pesticide and chemical products. We found an increased risk (OR = 2.0) for exposure to chlorpyrifos products, a type of organophosphate insecticide. Evidence from animal studies has suggested that striatal dopaminergic neurotransmission is affected by exposure to chlorpyrifos and may contribute to the neurotoxicity caused by these compounds in development of PD.[32] These chemicals are widely used as pesticides in agriculture; in pesticide sprays for institutional use, including the sprays used by professional exterminators; as well as in residential settings for termite treatments and lawn care. Similarly, our results also suggest a nonsignificant but elevated risk (OR = 2.2) for exposure to heptachlor, a type of organochlorine insecticide. Heptachlor has been identified in some animal studies to exert selective effects on striatal dopaminergic neurons,[33] consistent with the pathology seen in PD.

Previous studies have also demonstrated increased risk of PD from exposures

to herbicides[6,9,19,34] and specifically with paraquat.[9,35,36] Paraquat, a widely used bipiridyl herbicide and structurally similar to 1-methyl-4-phenylpyridine (MPP^+), a metabolite of a neurotoxin known to induce PD called 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), can cross the blood-brain barrier and destroy dopaminergic neurons in the substantia nigra.[37–40] Consistent with these results from other studies, we found an elevated risk (OR = 3.5) with exposure to paraquat; however, the numbers of subjects reporting this exposure were small and the results were not statistically significant.

Several lifestyle factors were found to be protective. Our study confirms the previously described inverse association between tobacco smoking and PD,[10,20,41–50] which may be due to a true neuroprotective effect of tobacco smoke constituents.[51] Replication of this previously observed negative association provides evidence for the validity of the other associations we found with workplace and environmental agents and suggests a degree of reproducibility and, therefore, reliability of the current study. Current smoking was not found to be protective in this study and this may be attributable to the very small number of current smokers in our study population. These results also demonstrate that any alcohol intake in the last 12 months was significantly inversely associated with PD risk. Drinking alcoholic beverages with a frequency ranging from once a week to once a month in the past year was also negatively associated with PD risk. The results associated with drinking more than once a week were not significant. Assuming that this pattern of alcohol use in the last year is reflective of one's past usual pattern of drinking, it may be speculated from these results that moderate intake of alcohol may be associated with reduced risk of PD. Epidemiologic evidence has suggested decreased risk of PD with history of alcohol consumption,[48,52] again indirectly supporting the validity of our findings. As seen in some previous studies,[48,49,52–55] caffeine intake was also associated with reduced risk but the results in the present study were not significant, which may be attributable to small sample size. A significantly reduced risk for PD was found with eating fish more than once a month. A study evaluating association of PD with intake of polyunsaturated fatty acids (PUFAs) found in fish reported significantly lower risk of PD associated with intake of these PUFAs.[56]

The current results also suggest an increased risk of PD associated with history of work in electronics plants (OR = 5.1). Work in an electronics plant involves potential exposure to a variety of metals, chemicals, and toxins under various job categories and exposure scenarios. Limited epidemiologic evidence is available on the risk of PD with work in the electronics industry and this association needs to be examined further. Although not significant, a history of work in paper/lumber mills was also associated with elevated risk (OR = 6.3). Work in a paper mill has the potential of exposing workers to a variety of pesticides and toxins. A Swedish study has suggested elevated risk of PD from exposure to a fungicide, diphenyl, in paper mill workers.[57] Past exposure to fluorides, cadmium, arsenic, and phenols was associated with elevated odds ratio in the present study. Limited evidence is available on association of PD with these exposures, such as the case reports of development of Parkinsonism after acute cadmium poisoning.[58]

Insecticide applications for agricultural processes as well as to farm animals/animal areas within the past year were associated with elevated risk (OR = 4.4) in this study, but results were not statistically significant. Associations between agriculture or occupations as "farmers" and PD have been inconsistent in the past. One study had reported an increased risk of PD associated with agricultural work (OR = 1.94, $p = 0.017$)[59] and another has reported that "farming" as an occupation was a risk factor for PD (OR = 2.79).[19] Although a study in South Korea also showed similar results of an association of farming with increased risk of PD,[60] the results from an Italian case-control study did not corroborate this finding.[61] A plausible explanation of these inconsistencies in part may be differences in the nature, frequency, and intensity of use of a variety of pesticides or other confounding exposures in different regions of the world.

Because PD is a relatively uncommon disease, the case-control design offers the

most feasible approach for investigating risk factors, but this design is subject to several potential biases that need to be considered in the interpretation of the results of this study. Diagnostic misclassification is unlikely given that the cases and controls were clinically confirmed by the same neurologist who specializes in movement disorders. Recall bias with possible overreporting of exposures among cases was a concern, as cases may be more likely than controls to reflect on past exposures because of concern about their illness. To minimize this bias, questions seeking information on rotenone and "organic pesticides" use were embedded in different sections of the questionnaire, instead of combining them in one section. Reliance on self-reported data resulting in misclassification bias is another inherent limitation of this type of design. Pesticide use and other infrequent exposures may be more susceptible to inaccurate recall and differential reporting, but in a case-control study of pancreatic cancer, no evidence of recall bias for pesticide exposures was reported.[62] The interviewers were not blinded to subjects' case-control status and this may have introduced some interviewer bias, but given careful training of interviewers as well as no differences in interview duration between cases and controls, interview bias may be considered negligible. Use of a job exposure matrix methodology to define exposures to chemicals was not practical in this study because some of the exposures were not limited to occupations but were related to recreational activities and hobbies. Other limitations to the interpretation of the study findings include limited power and small sample size with some control exposures having fewer than five observations, leading to wide confidence intervals for some of the variables. In addition, statistical analysis did not control for potential confounding.

In conclusion, evidence from this and other epidemiological and toxicological investigations suggests that PD is likely a common end point resulting from interaction of genetic and various environmental exposures. Exposure to pesticides has been associated with an increased risk of PD[14] and our study has further examined the risk of PD associated with specific pesticide products. The significant risk of PD seen with exposure to certain environmental agents and pesticides, including organic pesticides such as rotenone observed in this east Texas population needs to be further explored in other populations with larger sample sizes through multicenter, interdisciplinary collaborations.

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