Pesticides and Risk of Parkinson Disease

A Population-Based Case-Control Study

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Background: Pesticide exposures are suspected risk factors for Parkinson disease (PD), but epidemiological observations have been inconsistent.

Objective: To investigate associations between pesticide exposures and idiopathic PD.

Design: Population-based case-control study.


Participants: Two hundred fifty incident PD case patients and 388 healthy control subjects (age- and sex-matched). We assessed self-reported pesticide exposures using a structured interview. Odds ratios (ORs) and 95% confidence intervals (CIs) were determined using logistic regression models, controlling for age, sex, and smoking.

Results: Odds ratios for occupational exposures were not significant but suggested a gradient that paralleled occupational exposures (pesticide worker: OR, 2.07; 95% CI, 0.67-6.38; crop farmer: OR, 1.65; 95% CI, 0.84-3.27; animal and crop farmer: OR, 1.10; 95% CI, 0.60-2.00; and dairy farmer: OR, 0.88; 95% CI, 0.46-1.70). Odds ratios for organophosphates paralleled the World Health Organization hazard classifications, with parathion much higher than diazinon or malathion. We also found elevated ORs from herbicides (OR, 1.41; 95% CI, 0.51-3.88) and paraquat (OR, 1.67; 95% CI, 0.22-12.76). We found no evidence of risk from home-based pesticide exposures. We found significantly increased ORs from lifelong well water consumption (OR, 1.81; 95% CI, 1.02-3.21).

Conclusions: The findings for occupational pesticide exposures are consistent with a growing body of information linking pesticide exposures with PD. However, the lack of significant associations, absence of associations with home-based exposures, and weak associations with rural exposures suggest that pesticides did not play a substantial etiologic role in this population.

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INTERACTIONS BETWEEN GENETIC susceptibilities and environmental exposures are the focus of current research regarding the cause of idiopathic Parkinson disease (PD).1-4 Pesticide exposure may be an important environmental risk factor for PD.5,6 Toxicological studies in vitro7-9 and in vivo10,11 have demonstrated specific neurodegenerative effects from exposure to certain pesticides, and human case reports have suggested causal relations between pesticide exposures and PD.12,13

Epidemiological evidence linking PD with pesticides has been inconsistent. Some studies14-18 detected increased risk from surrogates for pesticide exposures, such as well water consumption or living in rural agricultural regions, whereas others19-21 have not. More consistent results have been seen with occupational exposures, including farming activities and application of herbicides or insecticides.16-18,21-23 The potential association between home-based pesticide exposures and PD is concerning, as environmental sampling shows that such exposures can be substantial.23

We report findings from an ongoing population-based case-control study of PD in western Washington State. We reviewed subjects’ histories of occupational and home-based pesticide exposures and estimated the risks for PD from these exposures.

METHODS

SUBJECTS

The methods have been previously described.26 Briefly, all newly diagnosed, idio-
Pesticides were grouped according to active ingredients' chemical class (eg, organophosphates) and primary use category (eg, insecticides).27 All products, including those containing mixtures of ingredients from more than 1 chemical class, were grouped into the “any pesticide” category. Exposures were only counted when a period of exposure (first and last year) was reported; duration was determined as the inclusive time span. All negative or incomplete responses were considered as “not exposed.”

To avoid counting exposures after disease onset, when subclinical symptoms of PD could have affected the chance of exposure by interfering with cases’ mobility, exposures during the 5 years before the interview date were discounted. Controls’ exposure histories were discounted similarly. Analyses with and without this 5-year discount period were nearly identical; therefore, only the discounted results were shown. Cumulative exposures were categorized as ordinal variables (low/high or low/medium/high), based on the product of duration and frequency of use. Analyses were limited to agents reported by at least 5 subjects, although paraquat was also included because of a priori interest.18,28

Relative risks were estimated with adjusted odds ratios (ORs) using unconditional logistic regression models (Stata 7.0; StataCorp LP, College Station, Tex). Models included known PD risk factors of age, sex, and smoking status (never vs ever smoked >100 cigarettes) to control for potential confounding. The crude and adjusted ORs were nearly identical throughout; therefore, only adjusted results were shown. Analyses of occupational exposures were limited to men only, as few women reported occupations outside the home. For home-based exposures, values shown were for the entire population, as subanalyses by sex showed similar results for men and women, and results of formal tests based on a multiplicative model for interaction between exposure and sex were not significant. Significance was set a priori at α = .05 using 2-tailed tests.

Several sensitivity analyses were done to test our methodological assumptions. None of the results from four separate sensitivity analyses (omitting the 32 cases identified from the University of Washington, focusing on subjects aged <50 years at diagnosis, discounting prediagnosis exposures for 10 years, and examining men and women separately) differed from the reported results in the magnitude of observed associations or their statistical significance.

## RESULTS

The demographic characteristics of the study population are summarized in Table 1. These characteristics are representative of GHC enrollees, who in turn reflect the demographics of western Washington State. The time spent on each interview (mean, 60 minutes) did not differ significantly between groups. Of those who met study criteria, participation rates were 73% for cases and 66% for controls, resulting in a final study population of 250 cases and 388 controls. The possibility of selection bias could not be assessed, as privacy issues prevented access to detailed information about nonparticipants. The only significant difference between groups was their smoking status, as previously reported.26

## STUDY POPULATION

### EXPOSURES

During a structured interview, subjects provided information on demographics, medical and occupational history (job duration, ≥6 months), occupational and home-based pesticide use, drinking water source, residential history, and smoking history. The same nurse practitioner conducted all interviews at subjects’ homes. Occupational pesticide exposures were identified from a checklist of common chemical agents and home-based pesticide exposures from a checklist of commercial brand name products. Affirmative answers to occupational exposures were based on having personally worked on machines that sprayed chemicals, applied pesticide sprays or powders by hand, or worked in an area that had recently been sprayed with pesticide chemicals. For home-based exposures, subjects had to report personal use of the products in or around their homes. Subjects reported first and last year of use and frequency of exposure (number of exposed days per year).

### DATA ANALYSES

### Table 1. Demographic Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 250)</th>
<th>Controls (n = 388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>70.1 (37-88)</td>
<td>70.8 (37-85)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>156 (62.4)</td>
<td>241 (62.1)</td>
</tr>
<tr>
<td>Female</td>
<td>94 (37.6)</td>
<td>147 (37.9)</td>
</tr>
<tr>
<td>Ethnicity‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>231 (92.8)</td>
<td>353 (91.0)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (1.2)</td>
<td>10 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (6.0)</td>
<td>25 (6.4)</td>
</tr>
<tr>
<td>Education†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ High school</td>
<td>41 (17.0)</td>
<td>83 (21.6)</td>
</tr>
<tr>
<td>≥ College</td>
<td>206 (83.4)</td>
<td>301 (78.4)</td>
</tr>
<tr>
<td>Smokers‡</td>
<td>112 (44.8)</td>
<td>235 (60.6)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) unless otherwise indicated.
†Some subjects did not answer question.
‡The proportion of smokers (ever smoked ≥100 cigarettes) differs significantly between groups (P < .05, unconditional logistic regression model).
Associations with various occupational exposures are summarized in Table 2. Although none of the ORs was significant, we observed a range of risk estimates that paralleled the predicted level of exposure: pesticide worker (OR, 2.07; 95% confidence interval [CI], 0.67-6.38) greater than crop farmer (OR, 1.65; 95% CI, 0.84-3.27) greater than combined animal and crop farmer (OR, 1.10; 95% CI, 0.60-2.00) greater than dairy farmer (OR, 0.88; 95% CI, 0.46-1.70). Among the organophosphates, parathion had the highest OR (OR, 8.08; 95% CI, 0.92-70.85), whereas ORs for diazinon (OR, 1.04; 95% CI, 0.35-3.06) and malathion (OR, 1.01; 95% CI, 0.37-2.72) were not increased. Other agents with modestly increased ORs were herbicides (OR, 1.41; 95% CI, 0.51-3.88) and paraquat (OR, 1.67; 95% CI, 0.22-12.76). No significant trend was seen with duration of employment or with duration or cumulative exposure to pesticides (data not shown).

HOME-BASED PESTICIDE EXPOSURES

The ORs associated with various home-based exposures are shown in Table 3. We found no significant associations with home-based pesticide exposures, although ORs were slightly increased for living at least 5 years on a farm during childhood (OR, 1.21; 95% CI, 0.82-1.79) or within 1 mile of an agricultural area sprayed with pesticides (OR, 1.31; 95% CI, 0.84-2.03). Well water use throughout lifetime was associated with significantly increased risk (OR, 1.81; 95% CI, 1.02-3.21). No significant trend was seen with duration or cumulative exposure to home-based pesticides, and ORs for living at other locations with the potential for pesticide exposure were not elevated (data not shown).

COMMENT

In this large population-based case-control study of incident PD from western Washington State, our findings do not provide strong support for the hypothesis that pesticide exposure is a risk factor for PD. Although some previous reports have demonstrated increased risk from agricultural exposures to pesticides, our study differs in that it examines a predominantly urban population, not particularly enriched for agricultural exposures.

Our results suggest the possibility that occupational exposures increase risk for PD in persons whose work involves pesticide use (Table 2), with an apparent gradient of risk for occupational titles that parallels the predicted level of pesticide exposure (pesticide worker > crop farmer > combined animal and crop farmer > dairy farmer). Among individual agents, the highest OR was seen with parathion, an organophosphate carrying the World Health Organization’s highest hazard classification. This seems particularly relevant, as organophosphates rely on direct neurotoxic effects for their efficacy, and parkinsonian effects have been reported with organophosphate intoxication.

We were particularly interested in herbicide exposures, as previous reports have demonstrated increased risks from exposures to herbicides and specifically from paraquat. Although the numbers of subjects reporting occupational exposure to herbicides (n = 17) and paraquat (n = 4) were small and the ORs were not significant, the results suggest moderately increased risk from occupational exposure to these agents. The recent description of rotenone intoxication as a model of PD is also notable, although we did not collect data specifically on rotenone exposure. We attempted to refine our risk estimates by examining duration of exposure and cumulative exposure; however, no significant trends were seen.

Our results related to home-based pesticide exposures (Table 3) were somewhat surprising because, al-
though the ORs were not significant, ORs below 1.0 suggested home use of pesticides was protective. The contrast between decreased ORs from home-based exposures and increased ORs from occupational exposures may reflect essential differences between patterns and intensity of these exposures. It is also possible that an increased awareness among the PD community of the pesticide hypothesis has biased the data because of differential recall. Typically, recall bias produces artificially increased risk estimates. However, because home-based use of pesticides may be viewed as a self-imposed hazard, differential underreporting by cases may have artificially lowered risk estimates. Also, when each stratum contains few subjects, as with occupational exposures, misclassification can easily be nondifferential, increasing the chance of biased exposure estimates.

To minimize recall bias, subjects were blinded to the study hypotheses. To minimize interview bias, the interviewer was not told the subjects’ case-control status, although complete complete blinding is not possible for a disease like PD that has obvious outward manifestations. The fact that the interview duration did not differ significantly between cases and controls provides reassurance that interview bias did not occur.

Well water use and farm residence have been associated with increased risk for young-onset PD, although reports from studies of PD in more typical older populations like ours indicate that these may not be independent risk factors. In our population, only the subgroup who had used well water throughout life had significantly increased ORs, suggesting a cumulative dose effect. Our data on residential locales indicate no significant increase in risk for PD ascribed to ever having lived on a farm, although a higher OR was seen for subjects who lived on a farm before age 25 than for those who lived on a farm at age 25 or older, consistent with the concept of a critical window of exposure during a period of rapid neural development. Of course, well water use and farm residence are only surrogates for pesticide exposure. Therefore, it is relevant that we observed a similarly elevated OR for subjects who reported living within 1 mile of an agricultural area sprayed with pesticides, consistent with recent exposure assessments that have demonstrated a gradient of pesticide exposures within agricultural communities surrounding pesticide application areas.

The fact that our results replicated the commonly observed inverse association between smoking and PD provides reassuring internal validity to our study. However, the nondifferential misclassification that can result from inaccurate self-report may have decreased our chance of identifying significant risks from other exposures. Another potential source of misclassification for home-based exposures is that we did not capture information about residential treatments by commercial applicators, instead only including information about subjects’ personal use. To account for the possibility of reverse causation, in which cases may have been less likely to use pesticides because of preclinical motor dysfunction, we discounted exposure histories for the 5 years before diagnosis. Unfortunately, we have no environmental monitoring data to confirm individual exposure patterns, which can vary considerably even between workers within a single occupational category. Despite its limitations, the case-control study design is the standard approach used to study uncommon diseases such as PD.

The growing consensus is that PD is not a single disorder but instead reflects a common pathologic end point resulting from the interaction of various environmental and genetic risk factors. Therefore, the attributable risk from any single factor is likely to be small and is likely to differ depending on specific population characteristics. Confounding the evaluation of pesticides is the complexity and ubiquity of exposures, producing misclassification that can mask true associations. Contemporary work on aggregate assessments of pesticide exposures may provide a useful model to improve future risk estimates. It is increasingly clear that using an epidemiological approach to identify etiologic factors with small attributable risk for PD will require large study populations. Such studies can best be accomplished with interdisciplinary, multicenter collaborations.

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