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Ruth Moytca Parks
University of Iowa

A REVIEW OF CASE-CONTROL AND COHORT STUDIES EXAMINING PESTICIDES AND THE RISK OF PARKINSON'S DISEASE

Ruth Moytca Parks, MT (ASCP), MPH candidate
The University of Iowa
Iowa City, Iowa

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer disease, having an annual incidence of approximately 20 per 100,000 people (Schapira 2004, Fischer 1999). An estimated one million persons in the United States have PD, and this prevalence is likely to rise as the population ages (Schapira 2004). This disorder is characterized pathologically by a loss of dopamine neurons in the substantia nigra pars compacta that produces the neurotransmitter dopamine. The clinical features of PD are motor function abnormalities including tremor, rigidity, slowness of movement, and difficulty with balance. In the early stages of PD, treatments may help to control symptoms, but over time the disease progresses with the development of symptoms such as freezing, falling, autonomic dysfunction, and dementia (Schapira 2004). While the cause of PD is unknown, genetic susceptibility and environmental factors seem to be associated with the disease based on epidemiologic and laboratory studies. Among the environmental risk factors, exposures to pesticides have been researched as a possible cause of PD. This focus on pesticides was sparked by the discovery that a chemical metabolite, similar in structure to the pesticide Paraquot, caused PD-like symptoms in heroin users who were exposed to a synthetic impurity of the drug (Li 2005).

Interest in pesticides as a possible cause of PD was also increased by epidemiologic studies conducted in the early 1980s; these studies reported that a history of farming or living on a farm was associated with increased risk of PD, possibly due to pesticide exposure (Li 2005). This review will discuss more recent epidemiologic studies linking various possible pesticide exposures to Parkinson's disease.

A large case-control study conducted in Washington State assessed both occupational and household pesticide exposures, including specific pesticides. This study included 250 PD patients and 388 healthy control subjects (Firestone 2005). The PD cases were identified by a combination of provider referrals and databases of diagnostic coding and pharmacy information. A neurologist conducted chart reviews of all cases; the diagnosis of PD was confirmed in all cases included in the study. The control subjects were selected from the same care center population as the PD cases, and were frequency-matched to cases by age and sex. Despite careful selection of cases and controls, the possibility of selection bias could not be analyzed, because of privacy issues which prevented the interviewing of non-participants (73% of cases and 66% of controls participated). The cases and controls were from a predominantly urban population whereas most studies concentrate on rural-based populations. The exposures to pesticides, both occupational and home-based, were assessed through a home-based structured interview. The same interviewer, blinded to the subject's case-control status, conducted all interviews. Even

though the interviewer could probably identify some cases by outward symptoms, the same amount of time was spent in conducting the interviews for cases and controls. The authors of the study indicated this was reassurance that interview bias did not occur. In order to minimize recall bias, the subjects were blinded to the study hypothesis. However, many PD patients are aware that pesticides are suspected in the etiology of PD, so recall bias may have occurred. The authors speculate that PD patients who were exposed to pesticides occupationally may be more likely to recall their exposures, increasing exposure risk estimates. The authors of the study also theorize that since home-based use of pesticides would be "viewed as a self-imposed hazard", underreporting of these exposures may have lowered exposure estimates. From the exposure assessments, relative risks were estimated with odds ratios, and adjusted for known PD risk factors including age, sex, and smoking status. For occupational exposures, none of the OR estimates were statistically significant because the odds ratios (OR) had 95% confidence intervals (CI) that contained unity. However, the risk estimates did parallel the predicted level of exposure, with pesticide workers having a greater risk (OR= 2.07, 95% CI, 0.67-6.38) than a crop farmer (OR=1.65, 95% CI, 0.84-3.27). The analysis of specific pesticides used in occupational settings did not achieve statistical significance, but the highest OR was found for the use of parathion (OR=8.08, 95% CI, 0.92-70.85). This higher risk is of interest due to the known neurotoxic effect of this chemical. The estimated risk for PD showed no significant associations with home-based pesticide exposures, although living in an agricultural region increased the estimated risk (OR= 1.31, 95% CI, 0.84-2.03). The only exposure that achieved statistical significance was the use of well water throughout life (OR=1.81, 95% CI, 1.02-3.21). As stated, "well water use and farm residence are only surrogates for pesticide exposure". The authors of the study conclude these findings do not provide strong support for the hypothesis that pesticide exposure is a risk factor for PD; the results suggest the possibility that occupational exposures can increase the risk, depending on the amount of exposure. These conclusions are supported by the results of this study; it was conducted with careful attention towards reducing bias, within the limits of the case-control study design and dependence on selfreported exposure estimates.

A case-control study consisting of 215 PD patients in Hong Kong, China did not find a relationship between rural residence, farming, or drinking well water (Chan 1998). This study found only a marginally increased risk of PD for pesticide exposure during farming (OR= 1.05; 95% CI 1.01-1.09; p= 0.018). However, when this group was analyzed according to sex, the odds ratio increased to 6.84 for women (CI 1.90-24.7; p= 0.003). It should be noted the numbers of patients and controls exposed to pesticides were few in both groups (patients: 19, controls: 16). The study noted this "low exposure reflects the farming habits in Hong Kong over the past decades".

This low population exposure makes this study a less valuable assessment of pesticide exposure in relation to PD. Otherwise, the study was conducted well, controlling for confounders and addressing biases. The confounders measured in this study included age, smoking habits, and family history. Selection bias was minimized by the selection of patients and controls from two hospitals, the only facilities that serve patients living in their areas. In addition, the controls were selected to have similar characteristics in

age, sex, and locality compared with the PD subjects. Observation bias was minimized by blinding participants to the specific hypothesis being investigated and by instructing interviewers not to prompt the interviewees for answers. All PD cases were examined and confirmed by a specialist geriatrician or neurologist.

It is interesting to compare this Hong Kong, China study (Chan 1998) with another case-control study in Taiwan, China (Liou 1997). As stated in the Hong Kong study, the farming practices of that area did not include frequent use of pesticides. In contrast, the study in Taiwan, a small island, noted extensive pesticide use. Since Taiwan has very limited cultivable land, it uses pesticides to increase the efficiency of farming on that land. In addition to determining a history of rural residence, farming, and well water consumption, this study attempted to determine paraquat exposure separately from other pesticides. A total of 120 PD patients and 240 matched controls (age, sex) were studied. Both the patients and controls were native residents of Taiwan, equalizing some environmental factors. The study reduced the tendency of case-control studies to be weakened by interviewer bias by assuring that neither interviewers nor PD patients were aware of the study hypothesis. It was also assumed that since there were no previous studies on risk factors of PD in Taiwan, these biases would be minimized. A repeat of the interview, which included a history of multiple environmental factors, was conducted 4 to 10 months after the initial interview to check for reliability, a precaution unique to this study. In order to avoid misclassification bias, neurologists examined PD patients and control subjects. The data collected was adjusted for multiple risk factors, including smoking, through conditional logistic regression. There was an increased estimated risk of PD for those who used pesticides (other than paraquat) compared to those who had no exposure (OR=2.17, 95% CI, 0.85 to 5.57).

This risk estimate did not achieve statistical significance since the 95% CI contains unity. However, a statistically significant association was calculated for the exposure to paraquot compared to those who were not exposed to pesticides (OR=4.74, 95% CI, 1.95 to 11.52). In comparing the risk of PD from paraquot exposure to other pesticides the OR was 2.0 ($p< 0.01$). Although the unadjusted data for rural residence and farming suggested an increase risk for PD, these risks were no longer significant after adjustment for the herbicide/pesticide and paraquot use. As suggested in the study, rural living and farming might serve as a factor for identifying potentially high-risk groups that may have direct contact with herbicides/pesticides and paraquat. This study found no association between drinking well water and PD. The authors conclude these results suggest that people with the following risk factors are at an increased PD risk: "living in a rural environment for more than 20 years, farming...for more than 20 years, or using herbicides/pesticides or paraquat." The authors also conclude, the results "suggest a dose-response relation between the duration of cumulative lifetime exposure to these environmental factors and the PD risk." The use of the word, "suggest", rather than "confirm" in these conclusions is justified, considering the limitations of the case-control design, and the data which falls short of statistical significance. Despite these limitations, this study was conducted well, with numerous controls for bias and confounders.

While these case-control studies have suggested that exposure to pesticides or other agricultural exposures are sometimes associated with an increased risk of PD, the study

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recall bias.

In order to provide evidence of the relationship between PD and pesticides that is not subject to this recall bias weakness, a prospective cohort study is valuable. Such a study was conducted in Hawaii on sugarcane and pineapple plantation workers over a 30-year period (Petrovitch 2002). In this study, 7986 Japanese American men who were enrolled in a longitudinal Honolulu Heart Program were questioned at the start of the study as to the number of years of plantation work they had performed. Information on lifestyle factors such as smoking and coffee intake was also collected at the start of the study, allowing for adjustment for these covariates. Six years after the initial questionnaire, self-reported information on pesticide exposure was collected. Follow-up investigations identified 116 incident cases of PD. Before 1991, incident cases were identified through multiple records. After 1991, the diagnosis of PD was based on complete reexamination of the entire cohort by questionnaire. A comprehensive and standardized neurological exam by a neurologist confirmed all cases of PD. The analysis of these cases suggested the incidence of PD increased with increasing years of plantation work. After adjusting for the potentially confounding effects of age, smoking, and coffee intake, the risk of PD in men who worked more than 20 years was nearly twice that of men who never worked on a plantation (relative risk [RR]= 1.9; 95% CI, 1.0-3.5; P= .045). The self-reported use of pesticides showed an increase with increasing years of exposure, but these results were not statistically significant (P=.10). Although this study reduced recall bias by its prospective nature, the self-reporting of pesticide exposure was probably less accurate than the reporting of years of plantation work. As noted, regular exposure to pesticides on plantations in Hawaii may have been more common than perceived by the worker. The comment section of the study identified additional exposures to the plantation workers. Since the environment was dusty, workers would have been exposed to agrichemicals, metals such as manganese, and soil pathogens. As stated, "Our data cannot discern which of these exposures may have influenced the development of the disease". The limited quantification of pesticide exposure the plantation workers received is an unfortunate weakness in this study. Positive aspects of this study include the cohort design, careful classification of cases, and control for confounders. There is an ongoing investigation of specific pesticides and the application methods used by this cohort. Surveillance for additional PD cases is also continuing. The additional data may increase the value of this study.

The assessment of pesticide exposure is a challenge for all of these studies. A study in France of neurodegenerative diseases and pesticide exposure used a unique method to attempt quantification of exposure (Baldi 2003). In this cohort study of 1507 people aged 65 years or older, detailed occupation histories were collected. All jobs were coded using a standard classification system. A panel of six experts independently determined the likelihood of exposure to pesticides for each job classification, and the median of the experts' assessment was used. There were 19 job titles assigned pesticide exposures of various levels. For example, workers on small farms were given an exposure level of 3 since they had probably mixed and sprayed pesticides themselves using older and less efficient equipment. The lowest exposure level of 0.5 was assigned to occupations with limited exposure such as an animal breeder or a veterinarian. For 228 of the exposed

efficient equipment. The lowest exposure level of 0.5 was assigned to occupations with limited exposure such as an animal breeder or a veterinarian. For 228 of the exposed subjects in the study, the cumulative occupational exposure to pesticides was calculated, with exposure equal to the product of the period duration and the exposure level for each occupation. Data on rural residency and residency in a district with vineyards was also collected on each cohort. A total of 24 incident cases of PD occurring within 5 years after the occupational survey were analyzed. In men, the relative risk, adjusted for smoking and educational level, was significant at 5.6 (95% CI: 1.5, 21.6). The adjusted relative risk in men increased relative to the degree of exposure, except the highest quartile exposure had no cases of PD. In addition, only occupational exposure was association with an increase risk of PD. In women, there was no significant association between PD and any pesticide exposure; the authors attribute this to the fact that women do not usually perform pesticide treatment tasks. Although this study makes an attempt to quantify pesticide exposure, this information is based on recall from many years in the past.

The study is also limited by its use of an elderly cohort; cases of PD that occur in a younger population would be excluded from this study, limiting the generalizability of the results. Another significant weakness is the lack of validation of incident cases of PD following the occupational survey. Assessment of these cases relied solely on answers to the question, "Do you have Parkinson's disease". These weaknesses make this study a less valuable assessment of the risk of PD associated with pesticide exposure. The focus of this study on multiple neurodegenerative diseases may have limited the resources devoted to the accurate assessment of PD.

In contrast to this lack of diagnosis validation in the study in France (Baldi 2003), a case control study in Sweden took several measures to insure that PD cases were correctly diagnosed (Fall 1998). This study stressed, "a correct diagnosis is of fundamental importance", and used more restrictive criteria for inclusion of cases than most studies. The cases were found by recording all prescriptions for antiparkinsonian drugs in the area and by requesting doctors to report on PD patients. Cases were confirmed by a specialist in neurology, based on the presence of 5 characteristics. The control subjects were randomly drawn from a population register of people living in the same district as the cases. The cases and controls were all sent the same lengthy questionnaire, which included occupational information and related environmental factors. The authors attempted to reduce bias by not indicating any interest in PD in the questionnaire. The response rate was similar in both cases and controls, and resulted in 124 cases and 263 controls. The analysis, stratified by age, for those who worked in agriculture shows a small increase in risk of PD (OR=1.4, 95% CI 0.68 - 2.9). A greater estimated risk of PD is associated with those who claimed to have handled pesticides within any occupation (OR=2.8, 95% CI 0.89 - 8.7. After multivariate adjustment (including smoking), this risk increases (OR=3.3, 95% CI 1.0 - 10). These 95% confidence intervals are broad and contain unity, meaning the results and not statistically significant. The author attributes this to a small sample size and multivariate logistic regression analysis with many variables. Despite the limitations of the results, this study was conducted with careful

selection and classification of cases as well as attention to possible biases in reporting. An increase in the number of PD cases studied may have increased the value of this study.

Another European case-control study, conducted in Italy, compared 136 cases of PD with 272 controls (Zorzon 2002). This study initiated case selection by considering consecutive patients with neurologist-confirmed PD referred to a neurological clinic. These cases were then included in the study if they exhibited two or more clinical features of PD and had a history of chronic progression of symptoms. Some cases were excluded for various symptoms, other causes of PD, and low scores on a cognitive impairment screening. The controls were selected from the rosters of outpatients at the same clinic and were sex and age matched to the PD patients. Patients with neurodegenerative diseases were excluded as controls, as were patients that scored low on the cognitive impairment screening. All PD cases and controls were subjected to a face-to-face interview, comprised of 21 questions on a structured questionnaire. All exposures were self-reported, with exposures to environmental risk factors considered only prior to disease onset. After adjusting for smoking, exposure to pesticides as compared to those not exposed to pesticides was significant (AOR=1.6, 95% CI 1.0-2.4, p=0.035). When comparing the mean length of exposure to pesticides for cases to the mean length of exposure for controls, the difference was significant (cases: 4.1 years, SD 10.9 and controls: 2 years, SD 6.4). Rural living also increased the estimated risk for PD as compared to urban living in the adjusted analysis (AOR 1.5, 95% CI 1.0-2.4, p=0.044). Also after adjusting for smoking, well water drinking (p=0.051) was of borderline significance, with the mean length of exposure to well water use significantly longer in cases when compare to controls (Cases: 5.7 years, SD 13.2, Controls: 2 years, SD 6; P<0.01). In a multivariate analysis, farming as an occupation was independently associated with PD (OR=7.7, 95% CI 1.4-44.1; p=0.0212). Also in this analysis, well water use was independently associated with PD (OR=2.0, 95% CI 1.1-3.6; p= 0.03008).

A multivariate analysis of pesticide exposure and rural living did not reach statistical significance. The authors summarize these results stating, "Our study shows a significant positive association of some factors related to rural environment with PD.". The authors correctly conclude that statistical analyses did produce twoome statistically significant associations with rural factors and PD. However, the data these results were based on may have been subject to biases. The description of the interview process did not include any controls for bias. It was not stated whether the interviewers or the interviewees were aware of the study hypothesis. It was also not stated whether the interviewer was aware of the case/control status of the subjects interviewed. The answers to the questions relied on self-reported exposures that may have been biased, with cases overstating or recalling more exposures. Although some care was taken in selecting and confirming cases of PD, the potential for bias in the collection of exposure data makes this study less valuable for the assessment of the risk of PD from pesticide exposure.

The results of these studies suggest an association may exist between pesticides and PD. The most compelling result from the studies discussed here is the data from the Taiwan study showing a marked increase in the rsk of PD from paraquot (Liou 1997). Other studies showed an increase risk, but one that was not statistically signifi-

cant (Firestone 2005, Baldi 2003). Two other case-control studies reported statistically significant risks, but remarkable study weaknesses cast doubt on the results (Baldi 2003, Zorzon 2002). Despite some data suggesting associations between pesticide exposure and PD, proving this relationship is seriously limited by pesticide exposure assessment and case identification. The assessment of pesticide exposure in all of these studies was limited to self-reporting. In addition, all of the case-control studies are subject to recall bias to varying degrees, depending on the use of controls attempting to reduce this bias. While the cohort study in Hawaii eliminated recall bias by its prospective design, the assessment of pesticide exposure was subject to limited awareness of worker pesticide exposure (Petrovitch 2002). Most studies assessed pesticide exposures as a group, reducing the likelihood of linking specific pesticides as causative agents of PD. An ideal pesticide exposure assessment would include biomonitoring of specific pesticide exposures. While this degree of monitoring may not be feasible, records of the pesticides used and some quantification of exposure would aid the accurate assessment of exposures to pesticides.

The methods used to identify cases of PD in these studies varied considerably. While most studies identified cases of PD through medical records and had them verified by neurologists, one study relied on survey responses alone (Baldi 2003). Even among the cases verified by neurologists, they used a variety of criteria to identify cases, either by exam or chart review. In addition, autopsy studies have demonstrated that PD is often misdiagnosed by various accepted criteria (Litvan 2003). Since there are no biological markers for the diagnosis of PD before death, a task force is attempting to establish a set of widely accepted diagnostic criteria for PD that may be reproduced in a "blinded fashion". It is also possible that in the future, imaging studies such as MRI scans or electrophysiological tests may be used to diagnose PD (Litvan 2003).

The seven epidemiologic studies examined in this review are a small portion of the studies that have been conducted to identify the relationship between pesticides exposures and PD. A review of 38 case-control studies published since 1983 found only two studies reporting an OR <1, and 12 studies reporting a significant association between pesticide exposure and the risk of PD, the ORs ranging from 1.6 to 7.0 (Brown 2006). This review also noted a meta-analysis of 19 case-control studies that found a combined OR for PD risk of 1.94 (95% CI, 1.49-2.53). Since articles that do not find statistically significant results are not published as frequently, publication bias may lead to a false degree of certainty of the magnitude of the risk. Despite this possible publication bias, this reviewer concluded, "the epidemiologic studies suggest a relatively consistent association between exposure to pesticides and an increased risk of developing PD".

In contrast to this review, an analysis of 27 case-control studies found a lack of consistency among the studies (Li 2005). This reviewer rated the studies according to their quality, finding no studies of high quality. Studies of low to medium quality included four studies discussed in this review: Zorzon 2002, Liou 1997, Fall 1999, and Chan 1998 received scores of 5,7,7, and 8 points out of a possible 13 points respectively. As this reviewer notes, the limited quality of the studies "precludes the ability to draw a firm conclusion regarding the association between pesticides and PD. Further studies

with stronger designs and improved exposure assessments are needed to elucidate any potential associations between classes of pesticides and PD."

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