ORIGINAL CONTRIBUTION

Plantation Work and Risk of Parkinson Disease in a Population-Based Longitudinal Study

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Context: Parkinson disease (PD) has an unknown cause; however, convincing evidence is emerging that indicates pesticides can selectively injure the dopaminergic system in laboratory animals. Retrospective studies in humans demonstrate a link between exposure to agricultural lifestyle factors and PD.

Objective: To determine whether working on a plantation in Hawaii and exposure to pesticides are associated with an increased risk of PD decades later.

Design and Setting: Prospective cohort study based on the island of Oahu, Hawaii, with 30 years of follow-up. Years of work on a plantation were assessed by questionnaire at study enrollment in 1965. Self-reported information on pesticide exposure was collected at a separate examination 6 years later.

Participants: Participants were 7986 Japanese American men born between 1900 and 1919 who were enrolled in the longitudinal Honolulu Heart Program.

Main Outcome Measures: Incident PD was determined by medical record review or by an examination conducted by a study neurologist at a later date.

Results: During follow-up, 116 men developed PD. Age-adjusted incidence increased significantly among men who worked more than 10 years on a plantation. The relative risk of PD was 1.0 (95% confidence interval, 0.6-1.6), 1.7 (95% confidence interval, 0.8-3.7), and 1.9 (95% confidence interval, 1.0-3.5) for men who worked on a plantation 1 to 10 years, 11 to 20 years, and more than 20 years compared with men who never did plantation work ($P=.006$, test for trend). Age-adjusted incidence of PD was higher in men exposed to pesticides than in men not exposed to pesticides although this was not statistically significant ($P=.10$, test for trend).

Conclusion: These longitudinal observations regarding plantation work in Hawaii support case-control studies suggesting that exposure to pesticides increases the risk of PD.

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THE CAUSE of Parkinson disease (PD) is unknown. There is no treatment that prevents the disease or slows progression, and there are no confirmed modifiable risk factors. However, the description in 1983 of parkinsonism secondary to exposure to the protoxin MPTP (*N*-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine) intensified the search for environmental risk factors.[1] The chemical structure of MPP+ (1-methyl-4-pyridinium), the toxic metabolite of MPTP, is similar to the herbicide paraquat.[2] Additionally, the toxic mechanism of action of MPP+, inhibition of mitochondrial respiration at complex I, is similar to that of the insecticide rotenone.[3] Supporting a possible role for these compounds in the cause of PD are recent reports of decreased motor activity commensurate with dopamaminergic system damage in rats given rotenone and mice given paraquat and the dithiocarbamate fungicide maneb in combination.[2,3] In humans, there are reports of increased levels of the organochlorine compound dieldrin in brains of patients with PD compared with healthy controls and controls with Alzheimer disease.[4,5] These discoveries have focused suspicion on exposure to agricultural chemicals as a risk factor for PD.

Numerous case-control studies in humans have found well water drinking, farming, rural living, and exposure to pesticides and herbicides to be associated with an increased risk of PD.[6-15] Although these findings have been consistent, retrospective assessment of exposure can be subject to recall bias. In this article, prospectively collected data about sugarcane and pineapple plantation work among participants in the Honolulu Heart Program are used to examine the

relationship of midlife years of plantation work with incident PD in late life.

METHODS

POPULATION AND STUDY DESIGN

The Honolulu Heart Program began in 1965 with examination of 8006 men of Japanese ancestry, 45 to 68 years old, living on the island of Oahu, Hawaii. The initial examination consisted of face-to-face interviews and physical evaluation. Demographic, dietary, and health status data were obtained.[16,17] There are 36 years of follow-up with continued hospitalization and death record surveillance. Follow-up examinations were performed from 1968-1970, 1971-1974, 1991-1993, and 1994-1996. Research on neurodegenerative diseases of aging began in 1991 with establishment of the Honolulu-Asia Aging Study. An institutional review committee approved the procedures; informed consent was obtained from all participants. Details regarding study design were previously published.[18-20]

PD CASE FINDING AND DIAGNOSIS

For this article, 30 years of follow-up data were available. Incident cases of PD were identified through 4 sources.[21] Sources prior to 1991 were (1) review of all cohort member's hospitalization records for all diagnoses of PD after 1965, (2) ongoing review of all Hawaiian death certificates, and (3) review of medical records of all patients with PD from the offices of local neurologists cross checked with the cohort member list.[18,21]

After 1991, diagnosis of PD was based on complete reexamination of the entire cohort from 1991-1993 and 1994-1996. During the 1991-1993 examination,[21] all subjects were questioned about a history of PD and PD medications. Subjects with a history of PD or parkinsonian symptoms or signs were referred to a study neurologist (G.W.R. or J.S.P.) who administered standardized questions about symptoms and onset of parkinsonism, previous diagnoses, and medication usage, followed by a comprehensive and standardized neurological examination including the Unified Parkinson's Disease Rating Scale.[22] Diagnosis of PD was based on consensus from at least 2 neurologists (G.W.R., C.M.T., and/or J.S.P.) according to published criteria.[23] These required that the subject have (1) parkinsonism, (2) a progressive disorder, and (3) any 2 of the following: a marked response to levodopa treatment, asymmetry of signs, asymmetry at onset, or initial onset tremor. Cases of parkinsonism related to other neurodegenerative disorders, cerebrovascular disease, medications, trauma, or postencephalitic parkinsonism were not included among the cases of PD. Additional cases of PD were identified during the 1994-1996 examination through structured interviews inquiring about a history of PD or PD medications. A study neurologist (G.W.R.) confirmed these cases by medical record review and application of the above criteria.

Age at diagnosis was used instead of age at onset to avoid inaccuracies associated with recall of symptom onset for a chronic disease with gradual onset. Two prevalent cases of PD identified at the 1965-1968 examination were excluded from analysis.

YEARS WORKED ON A PLANTATION AND OTHER VARIABLES

When follow-up began (1965-1968), study participants were asked if they ever had a regular job on a plantation and for how many years. Among the 8004 men without PD, responses were collected from 7986. No differentiation was available between sugarcane and pineapple plantations. Intensity of exposure was relatively accurate since subjects were asked only about holding a regular job on a plantation and the number of years. At a follow-up examination 6 years after the baseline examination (1971-1974), fieldwork was further broken down by work on sugar and pineapple plantations. However, self-reported years of work on either type of plantation combined regular employment with sporadic and part-time work, making it difficult to quantify the regularity and intensity of exposure. For this reason primary analyses presented in this article use the combined measure of either sugarcane or pineapple plantation work collected at the baseline examination. Secondary analyses also use the less accurate exposure data broken down by type of plantation available at the follow-up examination.

At the same 1971-1974 examination, participants were asked about exposure to pesticides for at least 1 year at home or at work. Duration of exposure was collected by asking about mean days per year of exposure, age at which exposure started and stopped, and number of nonoverlapping intervals of exposure. Years of pesticide exposure were then calculated by summing total days of exposure across all nonoverlapping years of exposure duration. Data on pesticide exposure were available for 6854 men, about 90% of the surviving members of the original Honolulu Heart Program cohort.

Information on other potentially confounding variables collected at the beginning of follow-up included age, pack-years of cigarette smoking, and intake of coffee. Cigarette smoking and intake of coffee and caffeine have previously been shown to be associated with a decreased risk of PD in this cohort of men,[18,24] and analyses of plantation work were adjusted for these covariates.

STATISTICAL ANALYSIS

Crude and age-adjusted incidence rates of PD in person-years were estimated according to years worked on a plantation based on 30 years of follow-up available in the sample of 7986 men.[25] Similar person-year rates of PD were also estimated across years of pesticide exposure based on the remaining 24 years of follow-up in the 6854 men in whom such data on exposure to pesticides were collected 6 years later (1971-1974). Age-adjusted risk factor comparisons across ranges of years worked on a plantation are also provided based on analysis of covariance procedures.[25] Proportional hazards regression models were used to test for effect of years worked on a plantation and years of pesticide exposure on risk of PD.[26] Effects were also estimated after adjusting for age, pack-years of cigarette smoking, and daily intake of coffee. Years worked on a plantation and years of pesticide exposure were modeled as continuous variables composing a test for trend or a dose-response relationship between plantation work and pesticide exposure and the risk of PD. Relative risks of PD (and associated confidence intervals [CIs]) were also estimated comparing the risk of PD in men who worked various amounts of time on a plantation to risk in those who never worked on a plantation. All reported *P* values were based on 2-sided tests of significance.

RESULTS

The median age of the 7986 men at study enrollment (1965-1968) was 53 years (age range, 45-68 years). Median length of follow-up was 27 years. Range of follow-up was 1 month to 30 years. We identified 116 men who developed PD. Median age of diagnosis was 73.7 years (age range, 54-89 years). Median interval between baseline examination and PD onset was 17.5 years (range, 2-30 years).

Table 1. Distribution of Years Worked on a Plantation According to Age at the Time of Study Enrollment

Age, y	Sample Size	Mean (SD) No. of Years Worked*	Range of Years Worked	Men Who Worked on a Plantation >10 y, %*
45-49	1829	2.5 (6.1)	0-34	6.3
50-54	2785	3.2 (7.4)	0-41	8.9
55-59	1590	3.6 (8.7)	0-47	10.9
60-68	1782	5.3 (11.2)	0-52	13.6
Overall	**7986**	3.6 (8.5)	0-52	9.8

*Values increased a significantly with age ($P<.001$).

Table 2. Average Age and Age-Adjusted Measures of Cigarette Smoking, Coffee Intake, and Exposure to Pesticides According to Number of Years Worked on a Plantation*

Variable	Reported No. of Years Worked on a Plantation (1965-1968)			
	0 (n = 5363)	1-10 (n = 1843)	11-20 (n = 315)	>20 (n = 465)
Age, y†	54.1 (5.4)	54.8 (6.0)	55.0 (5.3)	56.5 (6.0)
Pack-years of smoking	31.2 (29.9)	33.0 (29.8)	32.9 (28.7)	30.4 (28.4)
Current smoking status, %				
Past	24.5	27.2	23.3	27.8
Current	46.0	48.0	51.2	46.6
Coffee intake, oz/d	13.3 (12.9)	13.6 (12.2)	14.4 (12.0)	13.4 (11.5)
Pesticide exposure, y†‡	0.8 (2.8)	0.9 (2.9)	1.2 (3.1)	2.0 (5.1)

*Data are given as mean (SD) unless otherwise indicated.
†Values increased significantly with increasing number of years worked on a plantation ($P<.001$).
‡Self-reported values collected at examinations received from the 1971-1974 period.

Table 3. Incidence of PD (Rate per 10 000 Person-years) According to Number of Years Worked on a Plantation and Years of Exposure to Pesticides

Duration, y	Sample Size	No. of PD Cases	Unadjusted	Age-Adjusted
Self-reported Plantation Work, 1965-1968				
0	5363	73	5.7	5.8
1-10	1843	24	5.5	5.4
11-20	315	7	9.6	9.2
>20	465	12	11.3*	10.3
Test for trend†	. . .	. . .	$P = .002$	$P = .01$
Overall	**7986**	**116**	6.1	. . .
Self-reported Exposure to Pesticides, 1971-1974				
0	3154	46	7.9	7.8
1	2663	33	6.5	6.5
2-3	587	9	8.1	8.2
>3	450	11	12.9	12.7
Test for trend†	. . .	. . .	$P = .08$	$P = .10$
Overall	**6854**	**99**	7.7	. . .

*Value indicates a significant excess risk of Parkinson disease (PD) compared with men who never worked on a plantation ($P = .02$).
†Test for trend is based on modeling the number of years worked on a plantation and the number of years of pesticide exposure as continuous variables.

Table 4. Estimated Relative Risk of Parkinson Disease in Men Who Worked on a Plantation Compared With Those Who Never Worked on a Plantation

Reported No. of Years Worked on a Plantation (1965-1968)	Estimated Relative Risk (95% Confidence Interval)	
	Age-Adjusted	Risk Factor Adjusted*
0	Reference	Reference
1-10	0.9 (0.6-1.5)	1.0 (0.6-1.6)
11-20	1.6 (0.7-3.5)	1.7 (0.8-3.7)
>20	1.8 (1.0-3.3)	1.9† (1.0-3.5)
Test for trend‡	$P = .011$	$P = .006$

*Values were adjusted for age, pack-years of smoking, and coffee intake. Reference indicates all comparisons are made to the group with 0 years worked on a plantation.
†Value indicates significant excess of Parkinson disease compared with men who never worked on a plantation ($P = .046$).
‡Test for trend is based on modeling the number of years worked on a plantation as a continuous variable.

Table 1 lists the percentage of men who worked on a plantation for more than 10 years and mean duration of plantation work according to age at the time of study enrollment. In each instance, the duration and percentage of men who worked on a plantation for more than 10 years increased significantly with increasing age ($P<.001$). **Table 2** summarizes how other factors varied according to years worked on a plantation. There were no associations of smoking or coffee intake with plantation work. Pesticide exposure measured 6 years after study enrollment, however, increased consistently with years worked on a plantation ($P<.001$).

Table 3 gives observed incidence of PD according to the years worked on a plantation at the time of study enrollment and by the years of pesticide exposure reported 6 years later. After adjustment for age, the incidence of PD increased significantly with increasing years of plantation work ($P=.01$). The risk of developing PD nearly doubled in those who worked on a plantation for more than 20 years (10.30 per 10 000 person-years) compared with those who never worked on a plantation (5.80 per 10 000 person-years). Age-adjusted incidence of PD tended to increase with increasing years of exposure to pesticides ($P=.10$) although findings were not statistically significant. In this instance, reductions in sample size together with misclassification of pesticide exposure by recall may have limited statistical power.

Table 4 summarizes the excess risk of PD observed in plantation workers vs nonworkers after adjusting for potentially confounding effects of age, pack-years of smoking, and coffee intake. Compared with men who never worked on a plantation, the risk of PD was similar in those who worked from 1 to 10 years. The risk of PD in men who worked more than 20 years was nearly doubled compared with men who never worked on a plantation (relative risk [RR], 1.9; 95% CI, 1.0-3.5; $P=.046$). Although a threshold effect seemed to exist at more than 10 years of plantation work, a modest increase in risk con-

tinued to occur with further years of exposure ($P=.006$, test for trend).

As noted in the "Methods" section, data on exposure to either sugarcane or pineapple plantation work specifically were collected only at the later examination (1971-1974) and the intensity of exposure is less certain because part-time work was not differentiated from full-time work. Also, pineapple plantations employed fewer men (N=1243) than sugarcane plantations (N=2666). Based on 24-year follow-up, it appears that risk of PD increased with years of work on either type of plantation. For sugar plantation work, PD incidence increased from 6.6 per 10 000 person-years in men who never worked on a plantation to 14.3 per 10 000 person-years in men who worked more than 10 years (RR, 2.1; 95% CI, 0.9-5.1). For pineapple plantation work the risk of PD increased from 7.5 per 10 000 person-years in men who never worked on a pineapple plantation to 11.0 in men who worked more than 10 years (RR, 1.4; 95% CI, 0.5-4.6).

COMMENT

Between 1885 and 1908, approximately 180 000 Japanese workers migrated to the Hawaiian Islands to provide labor for sugar and pineapple plantations.[27] First- and second-generation Japanese American men enrolled in the Honolulu Heart Program were all born in the period 1900-1919 and those who worked on plantations would have done so between 1920 and 1985. Most (68%) of the men involved in plantation work were employed on sugarcane plantations. Case-control studies from China, Hong Kong, Taiwan, Canada, Sweden, and the United States suggest that agricultural work is associated with an increased risk of PD.[28-33] To our knowledge, this is the first prospective study demonstrating an association between agricultural work during midlife and the incidence of PD. Only relatively long-term work on a plantation (>10 years) was associated with this increase in risk.

While growing evidence implicates the neurotoxic effects caused by pesticide exposure as a possible factor in the pathogenesis of PD, it is important to emphasize that plantation workers experienced many other exposures unrelated to pesticides. Our data cannot discern which of these exposures may have influenced the development of the disease. The plantation environment was dusty and workers were highly exposed to all substances contained in dust including agrichemicals, metals, and soil pathogens. Interestingly, a common soil microorganism, *Nocardia asteroides*, has been found to cause selective nigral injury, with cytoplasmic inclusions resembling Lewy bodies and a movement disorder responsive to levodopa treatment in laboratory animals.[34-37] However, a case-control study in humans found no association between *N asteroides* in serologic test results and PD.[35] Exposures to metals such as copper, manganese, and combined exposures to lead-copper, lead-iron, and iron-copper and manganese have been associated with increased risk of PD.[38] Notably, soil manganese content is known to be very high in Hawaii.[39]

Plantation living quarters were typically close making it possible that epidemics of pathogens selectively damaging dopaminergic neurons occurred similar to the worldwide epidemic of von Economo disease that caused postencephalitic parkinsonism.[40] A recent study found that persons with PD were more likely to work in either teaching or health care services than control subjects. Since these occupations are associated with high respiratory pathogen exposures, these findings were interpreted as consistent with an infectious cause of PD.[41] Recent work has examined the hypothesis that influenza A and other viruses may lead to formation of Lewy bodies and nigral cell death.[42]

The exposure most consistent with current theories of environmental causes of PD is agricultural chemicals. There are 2 commonly proposed pesticide exposure routes for farmworkers. One is direct dermal and inhalation exposure and the other is consumption of contaminated well water. Four studies demonstrated a link between exposure to pesticides and PD.[29-32] In 3 of the 4, the entire relationship between agricultural work and PD was thought to be due to pesticide exposure after statistical adjustment for confounding data.

While not examining agricultural work directly, other studies of PD in rural settings have noted increased rates of PD associated with pesticide exposure[6,29,30,43-47] and consumption of well water.[8,11,48,49] Two studies have had negative results.[50,51] Interestingly, in the study by Tanner et al[51] conducted in China, no relationship between agricultural work and PD risk was found. Pesticides were not commonly used in Chinese farming at the time the study was conducted.

Although well water drinking was not directly assessed in our study, 92% of water used on the island of Oahu (and virtually all water used by plantations) during the time the cohort would have been working was well water according to the City and County of Honolulu Board of Water Supply. Since 1929, the Board of Water Supply Chemistry and Microbiology Laboratories have monitored the quality of Oahu's public water supply. Chemical agents including such metals as lead, mercury, and arsenic that could confound the observed association have not been detected.[52] However, it is possible that pesticides as field runoff could have contaminated wells on Hawaii's plantations.

Complete documentation of the historical use of pesticides in Hawaiian agriculture is unavailable. There are 2 reports that evaluate pesticide use in Hawaii during the period 1945-1970.[53,54] Pineapple growers used large amounts of insecticides and fumigants to control insect pests. Soil fumigants, primarily used to control nematodes in the pineapple industry, accounted for 60.7% (7 364 500 pounds) of all pesticides used in Hawaii, with 1,3-dichloropropene-1 and 1,2-dichloropane, 1,2-dibromoethane, and bromobenzylcyanide (Nemagon) the most common fumigants used. Synthetic insecticides came into common use between 1944 and 1964.[54] The insecticides most frequently used in the pineapple industry were the organochlorines dichlorodiphenyltrichloroethane (DDT), heptachlor, lindane, and chlordane and the organophosphates malathion and diazinon.[53]

Historically, biological controls have primarily been used to eradicate insect pests on sugarcane, and chemical insecticides have seldom been required. Herbicides

constituted more than 90% of the total amount of pesticides used on sugarcane and 32% of all pesticides used in Hawaii. Before 1945 only a few inorganic arsenic compounds were available to control weeds. Between 1945 and 1965 use of synthetic herbicides dramatically increased.[54] Commonly used herbicides during this period were pentachlorophenol, diuron, dalapon, sodium trichloroacetate, and the triazines—trazine and ametryn.[53]

The greatest application of insecticides in Hawaii was for termite control. Chlordane and DDT were the most commonly used organochlorine insecticides. Organochlorines were introduced into agricultural use immediately after World War II and pineapple plantations used these compounds extensively. During the latter years that cohort members would have worked on plantations (the 1960s and 1970s) organochlorines were replaced by organophosphate insecticides malathion, diazinon, dibrom, parathion, dimethoate, and DDVP (2,2-dichlorovinyl dimethyl phosphate).

While the incidence of PD increased for those who were exposed to pesticides compared with unexposed individuals, this difference was not statistically significant. Sample size issues may play a role in these statistical findings because (1) data on pesticide use were unavailable in the full cohort of men, (2) follow-up for PD was shortened from 30 to 24 years, and (3) population incidence of PD is low. In addition, self-report of pesticide exposure is far less certain than data on plantation employment, since it depends on personal knowledge and recall of cumulative exposure episodes. Regular exposure to pesticides on plantations in Hawaii may have been more common than perceived by the worker, and many of those who reported not being exposed to pesticides could have had high levels of exposure. An effort is underway to identify specific work processes used when applying herbicides and insecticides on plantations in Hawaii during various periods.

Data presented herein together with recent reports of pesticide-induced animal models of parkinsonism[2,3] implicate occupational pesticide exposure as a likely factor responsible for increased incidence of PD in study subjects who had worked on plantations for more than a decade. Nevertheless, infectious agents or metals in soil and dust could also have contributed to the destruction of dopaminergic neurons.

Most pesticides that our subjects would have been exposed to are no longer used in the United States; however, they may still be used in other nations, especially in nations without rigorous regulatory agencies. Even if these substances are not in wide use, strong evidence implicating 1 or more could provide significant clues to the underlying cause of PD and might facilitate recognition of potential neurotoxins to which persons may be exposed in industrial, military, or other agricultural circumstances. Continued investigation of specific herbicides and insecticides and application methods used during the years the cohort worked on plantations is ongoing, as is surveillance for additional PD cases. Analysis of these more specific and statistically powerful data may help strengthen the link between use of certain pesticides and risk of PD.

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