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Geographic Model and Biomarker-Derived Measures of Pesticide Exposure and Parkinson's Disease

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Abstract

For more than two decades, reports have suggested that pesticides and herbicides may be an etiologic factor in idiopathic Parkinson's disease (PD). To date, no clear associations with any specific pesticide have been demonstrated from epidemiological studies perhaps, in part, because methods of reliably estimating exposures are lacking. We tested the validity of a Geographic Information Systems (GIS)-based exposure assessment model that estimates potential environmental exposures at residences from pesticide applications to agricultural crops based on California Pesticide Use Reports (PUR). Using lipid-adjusted dichlorodiphenyldichloroethylene (DDE) serum levels as the "gold standard" for pesticide exposure, we conducted a validation study in a sample taken from an ongoing, population-based case–control study of PD in Central California. Residential, occupational, and other risk factor data were collected for 22 cases and 24 controls from Kern county, California. Environmental GIS–PUR-based organochlorine (OC) estimates were derived for each subject and compared to lipid-adjusted DDE serum levels. Relying on a linear regression model, we predicted log-transformed lipid-adjusted DDE serum levels. GIS–PUR-derived OC measure, body mass index, age, gender, mixing and loading pesticides by hand, and using pesticides in the home, together explained 47% of the DDE serum level variance (adjusted $r^2 = 0.47$). The specificity of using our environmental GIS–PUR-derived OC measures to identify those with high-serum DDE levels was reasonably good (87%). Our environmental GIS–PUR-based approach appears to provide a valid model for assessing residential exposures to agricultural pesticides.

Keywords

pesticides; Geographic Information Systems (GIS); validation; exposure assessment; biomarker

INTRODUCTION

Parkinson's disease (PD) is a complex movement disorder and the second most common neurodegenerative disorder affecting the elderly after Alzheimer's disease. PD continues to grow in public health importance due to the aging of populations in Western nations and the considerable personal and societal burden it represents in the form of loss of quality of life and high health/nursing care costs.[1,2] PD is considered to have a multifactorial etiology with environmental exposures likely playing a major role. For more than two decades now, reports have suggested that pesticides and herbicides may cause idiopathic PD. The pesticide rotenone causes PD-like degeneration in an animal model[3]; the herbicide paraquat is structurally similar to the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that

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induces Parkinsonism in humans,[4] dieidrin has been found in PD brains,[5] and some carbamate fungicides seem to enhance the neurotoxicity of MPTP in animals, raising questions about the biologic interaction of various pesticides.[6,7]

The first epidemiological studies to suggest a link with pesticides were the ecological studies reporting an excess of PD in rural as compared to urban populations.[8–12] Case–control studies investigating pesticide exposures from occupational and non-occupational sources reported two- to six-fold increased risks for PD in exposed subjects.[13–22] However, the conclusion drawn by Checkoway *et al.*[23] in the end 1990s, that "no clear associations with any specific pesticide have been demonstrated from epidemiologic studies," (p. 635) still holds today. Relying on study subjects to recall specific chemical usage for periods in the distant past to evaluate exposures in studies of chronic diseases with long latencies may result in substantial information bias, as has recently been suggested by a German study.[22] As almost all published PD and pesticide case–control studies relied on retrospective self-reports of pesticide use, the validity of their results hinges on whether the exposure assessment suffered from differential recall bias.

An extensive and detailed assessment of occupational exposures to specific pesticides was performed for a large group of licensed pesticide applicators enrolled in the Agricultural Health Study. Results from this study are still forthcoming for PD. Large prospective occupational cohort studies like the Agricultural Health Study[24] are extremely labor-, time-, and cost-intensive, and likely to be rare resources. Pesticides applied from the air or ground may drift from their intended treatment sites, such that there are measurable concentrations of pesticides detected in the air, in plants, and in animals up to several hundred meters from application sites.[25–28] Thus, alternative methods of estimating exposures in rural communities are sorely needed, but accurate exposure assessment may be particularly challenging. Geographic Information System (GIS)-based methods of assessing exposures to pesticides have become popular in recent years and may prove to be an effective solution to this problem. We developed a GIS-based exposure assessment model to estimate pesticide exposures in the residential environment from applications to agricultural crops based on California Pesticide Use Reports (PUR) and land-use maps. We conducted a validation pilot study to examine how well our environmental GIS–PUR model derived exposure estimates predicted biomarkers, specifically dichlorodiphenyldichloroethylene (DDE) serum levels. Although more than 600 unique agricultural pesticides have been reported in the PUR and are available for modeling, only organochlorines (OCs), which provide a biomarker (dichlorodiphenyltrichloroethane [DDT]/DDE serum levels) for longer term exposures, could be used for model validation. OC compounds are stored in adipose tissue, the lipid components of blood, and breast milk. They are resistant to metabolism and have long half-lives; therefore, measurements in humans potentially represent cumulative exposures over many years.[29] In this article, we will describe our environmental GIS–PUR model and the results from the validation study involving biomarkers.

METHODS

Environmental GIS–PUR Model

Employing a geographic model developed by Rull and Ritz,[30] California PUR data and geocoded subject residential histories were linked to obtain estimates of exposures to pesticides in the residential environment based on proximity to agricultural pesticide applications. Briefly, since 1974, agricultural pesticide applications in California are recorded in the PUR system documenting the name of the pesticide's active ingredient, the poundage applied the crop and acreage of the field, the application method, and the date and location (geographic section). We created a cumulative exposure intensity score for a given residence based on the weighted average of OC applications in a public land use (PLS)

section (total lbs. active ingredient ÷ total PLS sections acreage) within a 1000-m buffer from a residence between 1974 and 1989. The following OCs were used in the targeted counties and included in our GIS–PUR model: aldrin, benzene hexachloride (BHC), chlordane, dicofol, dieldrin, dienochlor, endosulfan, heptachlor, lindane, methoxychlor, and toxaphene.

Validation Study Population

To validate our GIS–PUR model derived OC pesticide exposure estimates we employed data from subjects enrolled in a population-based Parkinson's study at UCLA (the PEG Study).[31] We recruited newly diagnosed PD patients for the PEG study from among current residents of Kern, Fresno, and Tuleke counties, California, with the help of healthcare providers, mostly neurologists practicing in this region. We selected 22 patients for whom we had obtained and stored serum samples at random from among all Kern county PEG cases. We also selected 24 controls with serum samples; specifically, controls were recruited from among: (a) a random sample of age- and gender-matched Medicare beneficiaries residing in Kern county in the year 2000 and *(b)* residential parcels randomly sampled from Kern county GIS shape files for the years 1998–2000.

OC Serum Analysis Methods

After obtaining subject's informed consent, a blood sample was drawn and stored in a −20°C freezer at UCLA prior to shipment to Pacific Toxicology Laboratory (Chatsworth, California) for analyses of serum OC levels. Serum was tested for 13 OC pesticides and metabolites; however, as only DDE was found above the detection limit in most subjects, we focused in our analyses on this metabolite. Each serum sample was brought to room temperature and thoroughly mixed by vortexing. Two milliliters of serum was transferred to a 16 mL × 125 mL culture tube. Then, 6 mL of hexane and 20 mL of internal standard was added to the sample. The tube was then tightly capped and rotated at 50 rpm for 2 h. After rotating, 5 mL of the hexane phase was transferred into a graduated centrifuge tube. The volume was then reduced to 1.0 mL under a gentle stream of nitrogen gas after which the centrifuge tube was vortexed briefly before the sample was transferred to an autosampler tube. Analysis was performed on a gas chromatograph with electron capture detection. The column was a 30 m × 0.25 mm inner diameter DB-35 column with a 0.25-mm film thickness. Calibrators, controls, and blank samples were run with every sample batch.

Questionnaire Data

Each subject provided a detailed demographic and residential history, including dates of residence, and landmarks or cross streets when exact street addresses could not be recalled. We also collected information on residential case of pesticides and whether a subject ever worked on a farm, nursery, or orchard, or as a professional pesticide applicator and used pesticides occupationally. Specifically, information on ever having mixed, loaded, or applied pesticides, and work practices were obtained.

Statistical Methods

All lab results and questionnaire data were entered into a Microsoft Access database (Microsoft Corp., Redmond, WA) by the interviewers. First, we generated descriptive statistics and conducted bivariate analyses. Pearson's correlations of the continuous variables and their relation to lipid-adjusted blood levels of DDE were examined. Using a manual step-wise variable selection technique, linear regression models were built in SAS Software (version 9.1, SAS Institute, Inc., Cary, NC). Variables were kept in the model if they were deemed important for the control of confounding or if their inclusion increased the adjusted r^2. Our final "basic" linear regression model included the log-transformation of

lipid-adjusted serum DDE as the outcome, and our environmental GIS–PUR-derived model estimate of OC exposure, age (centered at age 70 years), body mass index (BMI) (centered at 27), the square of BMI, sex, ever mixed and loaded pesticides by hand, and ever used pesticides in the home as predictor variables. The basic regression model was also applied after excluding influential points ($N = 44$) and separately for subjects who had an OC exposure estimate above zero ($N = 26$). Each regression model was tested for overall fit with the F-test (F - the ratio of regression mean square to the residual mean square).

RESULTS

The mean age of the PD cases and matched controls was similar (71.3 and 70.2 years, respectively), but controls were more often male (15 versus 7 male cases) and had a slightly higher BMI, compared to cases (28.8 versus 26.4) (Table 1). The mean level of lipid-adjusted DDE in the serum was 1.2 mcg/g lipid in cases and 0.7 mcg/g lipid in controls; cases also had higher model-derived OC measure (38.6 versus 8.1). Only two cases and three controls reported mixing and loading pesticides by hand, while about half of all cases and controls reported using pesticides in their homes.

In Table 2, we present the proportion of variance explained (adjusted r^2) for our basic regression model, for the basic regression model after two influential observations were removed, and for a regression model from which we removed all subjects with an environmental GIS–PUR-derived pesticide exposure estimate of zero. The basic regression model with the total study population explains 41% of the variance ($P = 0.002$), whereas the basic regression model with the two influential observations removed explains 47% of the variance ($P < 0.001$). Excluding the 20 subjects for whom our environmental GIS–PUR-derived exposure estimated zero OC exposure between 1974 and 1989, the r^2 increased to 0.49 ($P = 0.005$).

The correlation between our environmental GIS–PUR model derived estimate of OCs and log-transformed lipid-adjusted blood DDE level was estimated to be 0.32 ($P = 0.03$, Table 3). The correlation with age was of similar magnitude (Pearson's correlation coefficient 0.35, $P = 0.017$). Age, gender, and mixing and loading pesticides by hand were all important predictors in our linear regression model (all with P value 0.004), as were pesticide use in the home and BMI (P-values 0.007 and 0.045, respectively). Our environmental GIS–PUR exposure estimate alone predicted 6%, mixing and loading of pesticides by hand predicted 13%, and home pesticide use predicted 11% of the variance of log-transformed DDE blood levels when modeled alone (data not shown). Meat, poultry, seafood, fruit, and vegetable consumption all failed to alter the adjusted r^2 when added to the model.

Using the lipid-adjusted DDE blood test as the "gold standard," the sensitivity of our GIS–PUR estimate of OCs is 38%, whereas the specificity is much higher at 87%.

DISCUSSION

Our environmental GIS–PUR pesticide exposure measures were correlated with lipid-adjusted DDE blood levels and predicted a portion of the variance of the log-transformed serum levels in a linear regression model. Thus, residential exposure to OC pesticides seems to be an important contributor to exposure in this population. Occupational exposures, such as mixing and loading pesticides, and home pesticide use are also components of exposure, but are much less prevalent (only 10% of the subjects reported handling pesticides in this manner). Although we did not take the use of personal protective equipment or type of pesticides handled into account, mixing and handling of pesticides alone seems to be a good indicator of blood levels in this elderly population.

Our GIS–PUR measure reflects potential low-level exposures to pesticides in a residential environment. The unexplained portion of the log-transformed lipid-adjusted DDE serum level variance may include dietary exposures that we were unable to assess adequately. In another small pilot study of 30 slightly younger subjects of lower socio-economic status who resided in Kern county and frequented a neurological clinic, we found that apart from having "ever lived in Mexico" reporting to have "loaded and mixed pesticides" also was a major contributor to DDE serum levels (data not shown). DDT was used widely in Mexico long after use had been banned in the United States.

Although the sensitivity of using our GIS–PUR-derived OC measure to identify subjects with high-serum DDE levels is poor (38%), our specificity is quite good (87%). Thus, we are less likely to classify unexposed subjects as having been exposed, important for a population-based case–control study.

Using DDT/DDE as Gold Standard

Even though DDT has been banned in the United States since 1972, it lasts in the soil of temperate areas for 5–30 years. It may evaporate into the air and significant concentrations of DDT have been found in the atmosphere over treated agricultural plots. DDT adheres strongly to soil, and remains on the soil surface layers; thus, people who work or live around or with contaminated soil might be exposed by accidentally ingesting the soil, having skin contact with the soil, inhaling DDT vapor, or breathing in DDT in dust. Because DDT bioconcentrates in aquatic organisms and bioaccumulates in the food chain, the main source of DDT exposure in the general population is from eating meat, fish, poultry, and dairy products. DDT is stored in fatty tissues and has a prolonged physiological half-life of up to 11–14 years, which makes it one of few candidates for a biomarker of long-term pesticide exposure. DDE, the metabolite of DDT, can likely be found in the serum of everyone reading this article.[32–34]

Limitations

The small sample size restricted the statistical power and precision of our validation study and prevented us from conducting more extensive multivariate analyses. We did not have PUR information on pesticide use before 1972 when DDT was commonly used and prior to its use being banned in the United States. Thus, when we chose DDE as our biomarker; we did so under the assumption that a farmer who previously treated a crop with DDT may most likely have substituted this agent with another OC pesticide still available. We relied on self-report of residential and occupational history and pesticide use. However, while there may have been recall error for exact addresses of past residences, we believe that our method of eliciting such information in combination with the extensive maps for residential parcels employed resulted in very accurate data. While subjects may not recall specific pesticides well, they will recall their work practices underscoring our results for mixing/loading of pesticides as a predictor of exposure.

DDE measures in serum may be less accurate than those derived from adipose tissue, but lipid adjustment is expected to increase reliability.[35] Exposure misclassification of DDE levels would be expected to be nondifferential with respect to our environmental GIS–PUR-derived measures of OC exposure, and therefore associations with DDE would likely be attenuated.

Our GIS–PUR model based exposure assessment also had some limitations. We picked a somewhat arbitrary buffer radius for measuring proximity of homes to land on which pesticides have been used (1000 m). Additional factors that could influence residential exposure to agriculturally applied pesticides include wind patterns and pesticide application

equipment type (plane, truck, etc.), whether windows of the home are kept open, and the amount of time the occupant spent at home.

CONCLUSION

Our GIS–PUR approach appears to provide a valid model for assessing exposures to agricultural pesticides in the residential environment. The GIS–PUR model derived OC estimates in conjunction with other predictor variables explained almost half of the variance in our model for our lipid-adjusted DDE biomarker. Although our sensitivity is poor, the specificity of our model is good, reducing exposure misclassification bias in case–control settings commonly applied to study rare diseases.

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TABLE 1

Demographic characteristics of the subjects

	Case (*N* = 22)	Control (*N* = 24)
Age, mean (SD)	71.3 (12.1)	70.2 (10.2)
Male	7 (31.8)	15 (62.5)
BMI, mean (SD)	26.4 (6.7)	28.8 (5.8)
Lipid-adjusted DDE, mean (SD), units are mcg/g lipid	1.2 (0.9)	0.7 (0.8)
OC exposure estimate, mean (SD)	38.3 (72.9)	8.1 (15.6)
Mixed and loaded pesticides by hand	2 (9.1)	3 (12.5)
Used pesticides in the home	12 (54.6)	13 (54.2)

Note: Values are number (percentage) of individuals, unless otherwise specified.

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TABLE 2

Predictors of the natural log of lipid-adjusted serum DDE levels in three linear regression models

Model type	*N*	Adjusted r^2
Basic model †	46	0.412
Basic model without influential observations ‡	44	0.470
Basic model for those with GIS–PUR-based OC estimates greater than zero	26	0.485

† The basic regression model used the log-transformation of lipid-adjusted serum DDE levels as the outcome and the GIS–PUR model based OC estimate, age, BMI, BMI^2, sex, ever mixed or loaded pesticides by hand, and ever applied pesticides in the home as predictor variables.

‡ Influential observations had dffits statistic values greater than 2*sqrt[(k + 1)/(n − k − 1)] where k = number of predictor variables and n = sample size.

TABLE 3

Basic regression model results and correlation coefficients (n = 46 Kern county PEG study subjects)

	Estimate from linear regression	Standard error	*P*	Correlation coefficient†	*P*
GIS–PUR-derived OC estimates	0.005	0.003	0.036	0.321	0.030
BMI	−0.06	0.03	0.045	−0.145	0.337
BMI^2	0.004	0.002	0.096	0.061	0.687
Age	0.04	0.01	0.004	0.349	0.017
Female	1.00	0.32	0.004	—	—
Mixed and loaded pesticides by hand	1.45	0.47	0.004	—	—
Used pesticides in the home	0.90	0.31	0.007	—	—
Regression model adjusted R^2 = 0.412					

†Pearson's correlation coefficients of each continuous variable with the log-transformed DDE serum measure.

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