Control Selection and Pesticide Exposure Assessment Via GIS in Prostate Cancer Studies

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Background: Pesticide exposures have recently been linked to prostate cancer, but accurate exposure assessment to date has been challenging. Additionally, historical exposures have rarely been examined. The utility of a geographic information system (GIS)–based model for assessing residential exposure to pesticides is examined in a population-based case–control setting among groups easily recruited as control subjects.

Methods: Historical pesticide and land-use data were used to generate exposure measures for two distinct pesticides previously linked to prostate cancer risk for control series and prostate cancer cases in three rural California counties. Simple estimates of residential exposures for different exposure periods are compared between case and control groups and the value of complete residential histories is examined.

Results: Residential exposure to methyl bromide based on current address resulted in an overestimation of exposure for distant exposure periods, whereas exposures to organochlorines were similar regardless of availability of historical residence information. A response bias was detected in Medicare controls such that unexposed elderly control subjects were characterized by a higher response rate.

Conclusions: The frequency and amount of application of pesticides seem to affect the bias introduced into GIS-based exposure assessments. Inclusion of subjects' complete residential histories into the computation of exposure estimates seems to reduce bias from this source, but it may also introduce an additional bias through control self-selection. The use of randomly sampled controls from Medicare and residential parcels listings independent of subject response seems to result in the opportunity for relatively unbiased estimates of pesticide exposures.

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Introduction

Prostate cancer has been reported to be more common among farmers, with a recent meta-analysis of 13 studies estimating the relative risk for farmers as 1.29 (95% CI=1.10–1.51).[1] Exposure to specific pesticides was assessed in detail in the Agricultural Health Study, which found chlorinated pesticides and methyl bromide to be associated with increased prostate cancer risk.[2] Still, further assessment remains necessary, especially concerning low-level pesticide exposures in the general population. Large prospective cohort studies, however, are time and cost intensive and do not consider historical exposures, which may be those most significant to the etiology of chronic disease. Thus, alternative methods of estimating relevant exposures in large populations are sorely needed.

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. Exposure in rural communities occurs as a result of pesticides applied from the air or ground drifting from their intended treatment sites, with measurable concentrations detected in the air, in plants, and in animals up to several hundred meters from application sites.[3–6] When examining these exposures in study populations, however, three major methodological concerns require exploration. First, for cancers, the most relevant exposures may have occurred in the distant past, so migration between areas of differing exposure levels needs to be addressed. Second, it may not be possible to obtain valid population controls, i.e., to enumerate the population at risk. In the U.S., no readily accessible registries exist for residents and the method of choice for control selection in many population-based studies to date is random digit dialing.[7] The validity of this method, however, is compromised by the increased use of cellular telephones, answering

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machines, and caller identification.[8] Finally, response rates for research have dropped over the past decade especially for controls,[8] and there are increasingly extensive restrictions imposed by institutional review boards about the manner of contact and how many times subjects may be contacted and invited to participate in research.

Data from a pilot study are used to illustrate the influence of exposure assessment and control selection on exposure measures for pesticides derived from a GIS-based model comprising pesticide and land-use data. Different exposure estimates are created for prostate cancer cases and several control groups available for a population-based study of prostate cancer in California. The potential for bias when relying on current address versus complete residential history is examined specifically.

Methods

Selection of Cases and Controls

All prostate cancer cases diagnosed in 2000 in Fresno, Kern, and Tulare counties were obtained from the California Cancer Registry (CCR) (N =789). Two different control series were assembled: (1) Medicare beneficiaries residing in Fresno, Kern, and Tulare counties sampled from a Medicare enrollee list for the year 2000; and (2) residential parcels in the same tri-county area sampled from shape files from 1998 to 2000. The sample of Medicare enrollees was marginally matched to the age and gender distributions of Parkinson disease patients in a concurrent study, which mostly resulted in the over-sampling of older males. Letters inviting Medicare enrollees were sent to a total of 700 individuals. For analysis purposes Medicare subjects were separated into two groups: (1) those who participated in the Parkinson's study and for whom residential histories were obtained by telephone interview (n =104); and (2) those with no more than Medicare reported addresses for the year 2000, who were never interviewed (n =596). Because this random sample of Medicare enrollees comprised primarily older males, for a subgroup of whom complete residential histories are available, it made for an appropriate and convenient control group for this pilot study of prostate cancer. The decision to include a smaller group of female beneficiaries was based on the assumption that a male spouse of similar age would likely also be living at the Medicare reported address, and it allowed for an increased sample size of eligible residences to be evaluated. For parcel controls, 700 identifiers were randomly sampled directly from a combined shape file of residential parcels from the three study area counties.

Geocoding Procedures

Prostate cancer cases. Five hundred eighteen cases aged 65 and older were identified from among the prostate cancer cases.

Medicare controls. Geocoding of subjects' street addresses was carried out using ArcView 3.3 GIS software including Streetmap 2000 (ESRI, Redlands CA, 2000-02) in conjunction with the web sites MSNMaps.com and WhitePages.com in a multi-step process similar to that described by McElroy et al.[9] Addresses were accepted as matches according to the following algorithm: (1) updated street addresses were recorded and used instead of post office boxes only when first and last names matched exactly; and (2) nearest intersections were used to approximate street addresses not found in the 2000 street map as long as the intersection was within 150 meters of the actual address.

Residential parcel controls. Each residential parcel was geocoded according to its centroid using ArcView.

Pesticide Exposure Assessment Procedures

Digital land-use maps were downloaded from the California Department of Water Resources (CDWR) website[10] and paper maps of historical land-use were used to correct these maps for earlier periods. Employing the geographic model developed by Rull and Ritz,[11] Pesticide Use Reports (PUR), and land-use survey data were linked to obtain estimates of residential exposures to pesticides based on residential proximity to agricultural crop application sites.

One pesticide, methyl bromide (MB), and a group of pesticides, organochlorines (OCs), were selected for assessment because both have been linked to prostate cancer previously.[2,12,13] Furthermore, they represent distinct patterns of environmental persistence: OCs are known to persist in soil, leading to longer-term exposures near fields even after applications are suspended. Methyl bromide, on the other hand, vaporizes upon release and dissipates quickly,[14] representing a less permanent and more acute type of residential exposure from drift during application.[15]

Long-term exposure estimates. Historical exposure estimates were calculated using 500- and 1000-meter radii buffers around each geocoded location. These distances were suggested by the literature on pesticide drift and previous studies.[3–6] Pounds of pesticide applied annually per acre were summed for each residential buffer and weighted by the proportion of treated acreage in the buffer. These rates were then averaged over 5- and 10-year periods. Cumulative residential pesticide exposures were estimated for 1999, 1995 to 1999, 1990 to 1999, and 1980 to 1989. Use of this last estimate allows for a 10-year latency period for prostate cancers diagnosed in 2000.

Current versus historical exposure estimates. For all subjects, 1998 to 2000 addresses were used as proxies for residential histories. For Medicare subjects with residential histories and at least one mapped tri-county address for the period 1980 to 1999, another set of exposure estimates was calculated based on actual residences during the periods of interest.

When a mapped address fell into an area not surveyed for land use, zero exposure was assumed for all PUR years corresponding to the land-use year in question because, according to the DWR, agriculture was unlikely to occur in unsurveyed areas. Similarly, all unmappable addresses and addresses outside of the study area were also assigned zero exposure values. Zero exposures were imputed for 6% of addresses self-reported by interviewed Medicare controls, 16% of addresses reported by Medicare for non-responsive controls, 5% of all randomly selected parcel locations, and 3% of prostate cancer addresses.

Statistical Methods

Mean application rates for MB and OCs and mean percent of subjects potentially exposed to any amount of these pesticides were calculated by group.

For interviewed Medicare controls, logistic regression was employed to determine whether those who had moved within a 20-year period could be distinguished from non-movers according to gender, race, age and education as a proxy measurement for socioeconomic status. Recent movers were additionally compared to past and non-movers by gender, age, and urban/rural status of last address without formal statistical testing.

Year 2000 U.S. Census block group demographics including birth origin, residence type, age, employment status, and education were compared between case and all control groups to determine whether they noticeably differed with respect to these characteristics.

Results

Geocoding

A total of 104 Medicare subjects reported lifetime residential histories in interviews. Among the remaining 596 individuals, some were found to be ineligible for the Parkinson's study ($n=86$), whereas others withdrew from the study before being interviewed ($n=19$), or did not respond to mailings ($n=491$). A total of 834 lifetime historical addresses were self-reported by the 104 interviewees, 391 (47%) of which were located in the tri-county area. Subjects resided at only 151 (39%) of these addresses during the period of interest, 1980 to 1999, and 140 (93%) were successfully geocoded. These 140 addresses comprised the residential histories of 103 individuals, excluding one subject with no mappable address. Sixty-four (11%) of the 596 addresses reported by Medicare for those not interviewed were found to be unmappable and six mapped addresses fell outside of the tri-county area, leaving 526 mapped addresses. Previous studies in rural areas have reported similar geocoding success rates.[16]

All prostate cases in the sample were previously geocoded by the CCR and all residential parcels were assigned centroid markers automatically in ArcView, leaving no unmapped addresses in either of these groups.

Pesticide Applications in the Three Counties Over Time

Agricultural applications of MB and OCs changed in Public Land-Survey System (PLSS) sections in which controls resided over the 20-year period of interest (Table 1). The total acreage treated with MB and the poundage of MB applied increased considerably in the 1980s, peaking in 1985 to 1990 at about four times the acreage treated/poundage applied in 1980, and declined again somewhat over the 1990s, but was still about three times higher at the end compared to the beginning of the study period. OC use similarly increased from 1980 to 1990 in acreage and pounds, but decreased considerably thereafter, falling to almost half the amounts applied in 1999 compared to 1980.

Table 1. Methyl bromide and organochlorine use from 1980–99 in Public Land Survey System (PLSS) sections where Medicare and parcel controls resided (N=572)

Pesticide	Pesticide use report year	Total treated acres	Total pounds applied
Methyl bromide	1980	229	48453
	1985	848	86619
	1990	700	51824
	1995	508	128935
	1999	626	130008
Organochlorines	1980	6146	7928
	1985	5970	7222
	1990	10585	13627
	1995	5071	6307
	1999	3386	4041

Demographic Information Derived From Census and Interviews

Comparing demographic characteristics by census block group shows the greatest differences for interviewed Medicare controls as compared to all other groups (Table 2). With respect to country of origin, the interviewed controls seem to be somewhat less likely to have been born outside of the U.S. and, although nearly twice as likely to live in areas designated as rural, are less likely to reside on farms. Additionally, a slightly higher percentage of older males live in block groups of interviewed Medicare controls. Finally, according to census designations, interviewed Medicare controls reside in urban blocks with fewer men without a high school diploma and more holding a graduate diploma. Slightly more prostate cancer cases live in block groups designated by the census as farm residences, otherwise cancer case block groups are comparable to all control groups especially those selected randomly from parcels and Medicare controls not interviewed.

No differences in gender or age regarding moving behavior for the period of 1980 to 1999 were observed, but a slightly higher percent of movers living in designated rural areas was detected (Table 3). When more recent periods were considered, however, movers became increasingly more urban as well as slightly younger and more often male. Logistic regression analysis showed that the least and most educated seemed to have a somewhat more stable residential history than those with a high school diploma; persons without a high school diploma and those with a bachelor's degree showed odds ratios (OR) <1 (OR=0.19, 95% CI=0.04–0.80, and OR=0.28, 95% CI=0.09–0.89, respectively).

Table 2. 2000 U.S. Census block group demographics by case and control group

Demographic variable	Medicare controls with residential histories, mean % (n=104)	Medicare controls without residential histories, mean % (n=526)	Residential parcel controls, mean % (n=700)	Prostate cancer cases, mean % (n=518)
Census block birth origin				
Native born	88.6	84.1	84.2	84.2
Foreign born	11.4	15.9	15.8	15.8
Census residence type				
Urban	71.3	84.6	84.5	82.9
Rural	28.7	15.4	15.5	17.1
Farm	6.7	9.5	8.1	11.0
Non-farm	93.3	90.6	91.9	89.0
Census block age, male				
<40 years	56.5	59.8	62.4	59.5
40+ years	43.5	40.2	37.6	40.5
Census block employment status (16+), male				
In labor force	68.1	66.8	68.9	66.8
Not in labor force	31.9	33.2	31.1	33.2
Educational attainment (25+), male				
Urban residence				
No high school diploma	19.3	30.9	28.8	29.5
High school diploma	21.1	21.9	21.0	21.6
Some college	25.8	22.4	23.3	22.7
College diploma	23.8	18.3	19.7	18.9
Graduate diploma	10.0	6.5	7.2	7.3
Rural residence				
No high school diploma	25.0	29.1	27.1	29.5
High school diploma	28.1	24.7	23.1	22.2
Some college	25.0	23.3	25.2	23.9
College diploma	16.1	17.4	18.3	17.9
Graduate diploma	5.7	5.5	6.3	6.5

Average Pesticide Exposures at Residential Addresses by Group

For prostate cancer cases, OC mean exposure estimates are similar to both parcel and Medicare controls during all periods, but the mean percent of case subjects exposed to OCs is slightly higher than for parcel controls and for all Medicare controls (Table 4). For MB, both exposure means and percents of subjects exposed are higher for cases compared to parcel controls except when longer-term lagged exposures for 1980 to 1989 are estimated from current addresses. Prostate cases again have slightly higher mean and percent exposures to MB compared to all Medicare controls with exception of the 10-year lagged exposure period. Estimates for 1000m buffers showed similar patterns and are not presented.

For Medicare controls with and without residential histories, current and historical mean exposures to OCs are similar when only the most recent address is used for exposure assessment (Table 5). However, among

Table 3. Moving status by gender, age, and residence type for Medicare controls with residential histories (N=104)

Demographic variable	All Medicare controls with residential histories, n (%) (n=104)	Non-movers in past 20 years, n (%) (n=47)	Movers in past 20 years, n (%) (n=57)	Movers in past 10 years, n (%) (n=31)	Movers in past 5 years, n (%) (n=12)
Gender					
Male	69 (66.3)	32 (68.1)	37 (64.9)	23 (74.2)	9 (75.0)
Female	35 (33.7)	15 (31.9)	20 (35.1)	8 (25.8)	3 (25.0)
Age					
65–75	59 (56.7)	28 (59.6)	31 (54.4)	19 (61.3)	8 (66.7)
76–86	45 (43.3)	19 (40.4)	26 (45.6)	12 (38.7)	4 (33.3)
Census residence type[a]					
Urban	75 (72.1)	36 (76.6)	39 (68.4)	24 (77.4)	12 (100)
Rural	29 (27.9)	11 (23.4)	18 (31.6)	7 (22.6)	0

[a]Designation for most recent, mappable address based on 2000 U.S. census cartographic boundary files for urbanized areas.

Table 4. 500m exposure estimates[a] for methyl bromide and organochlorines in prostate cases and controls

	Pesticide exposure period							
	1999 current exposure		**1995–1999 5-year exposure**		**1990–1999 10-year exposure**		**1980–1989 10-year lagged exposure**	
Pesticide and group	**Mean exposure rate, pounds/acre, (SD, *n*)**	**Mean % exposed**	**Mean exposure rate, pounds/acre, (SD, *n*)**	**Mean % exposed**	**Mean exposure rate, pounds/acre, (SD, *n*)**	**Mean % exposed**	**Mean exposure rate, pounds/acre, (SD, *n*)**	**Mean % exposed**
Methyl Bromide								
Prostate cancer cases over 65 (n=518)	9.6 (20.8, 73)	14.1	7.4 (23.2, 139)	14.1	5.7 (20.7, 175)	12.6	1.3 (10.0, 169)	8.4
All Medicare controls, last address only (n=628)	7.1 (15.0, 83)	13.2	6.2 (16.4, 168)	12.4	5.0 (16.3, 216)	11.7	1.0 (7.7, 217)	8.7
Residential parcel controls (n=700)	6.6 (21.6, 76)	10.9	6.3 (28.1, 156)	10.4	5.6 (39.2, 191)	9.8	1.9 (14.6, 248)	8.4
Organochlorines								
Prostate cancer cases over 65 (n=518)	0.2 (0.4, 66)	12.7	0.3 (0.6, 146)	15.3	0.4 (1.0, 205)	19	0.2 (0.7, 237)	15.9
All Medicare controls, last address only (n=628)	0.2 (0.4, 72)	11.5	0.2 (0.6, 146)	13.1	0.3 (0.9, 219)	16.4	0.2 (0.6, 279)	15.5
Residential parcel controls (n=700)	0.3 (0.8, 64)	9.1	0.3 (0.8, 141)	10.9	0.3 (0.8, 218)	14.5	0.2 (0.7, 286)	12.8

[a]All estimates include data on only those individuals found to be exposed to either organochlorines or methyl bromide at least 1 year of the exposure period under consideration.
SD, standard deviation.

Medicare controls without residential histories compared to those with residential histories a higher percent of subjects are counted as ever exposed to OCs based on last address. This disparity is greatest during recent exposure periods: Nearly three times as many Medicare controls without than with residential histories are classified as exposed to OCs. Differences become less dramatic for longer term lagged exposures.

Mean exposures to MB are also similar for both groups when considering longer term and lagged exposures but, contrary to OCs, differ slightly during the most recent periods. The mean percent of subjects with any exposure to MB differed between the two Medicare control groups regardless of the exposure period considered, such that almost double the percent of controls not interviewed were classified as ever exposed during more recent periods. When using a full residential history rather than last address, estimates of MB exposure were comparable except during the most distant period.

For residential parcel controls, both current and historical OC mean exposure estimates are comparable to those of all Medicare controls combined, whereas mean percent of subjects exposed to OCs tends to be lower (Table 4). MB mean exposures are similar to those for all Medicare controls combined, regardless of exposure period. Mean percent of parcel controls exposed to any MB, however, is consistently lower than for all Medicare controls combined, although this difference is only slight for lagged exposures.

Discussion

Given the expense of collecting self-reported pesticide exposure data in population studies and its often-poor quality when collected retrospectively, researchers must frequently resort to models to assess individual level exposures. For agricultural pesticides, proxy measures such as proximity to likely application sites are typically employed, because residential addresses of subjects and some pesticide application data on crops may be easily accessible. In many cases, however, available data have further limitations e.g., residential information is limited to a single address. When lacking residential history information, one may be tempted to assume zero residential mobility for an individual. Data for interviewed Medicare controls allowed examination of the influence of such an assumption on exposure estimates in an elderly population living in mostly rural counties in California. This group reported between one and four tri-county addresses per individual between the years 1980 and 1999, i.e., 55% moved at least once over a 20-year period. When a single current address was used for all subjects in this group to derive pesticide exposure estimates, means for exposures in the distant past were somewhat overestimated for methyl bromide, because the use of this chemical had increased in the most recent years, but the observed exposure trend over time was the same for single and multiple address estimates. Use of organochlorines, however, remained fairly stable over time and thus, current address seemed sufficient to estimate even longer-term exposures to these pesticides at the group level.

Because residential histories were available only for a small subgroup of Medicare controls, to compare cases and controls to each other, one might assume that the individual addresses reported by Medicare are in fact a random sample of the population at risk. This seems to be the case, because no obvious differences in spatial distribution or demographic characteristics between the two selected control groups were detected (note that the parcel controls can be used as the gold standard because they, by design, were a random sample from all residential parcels, although there is uncertainty as to whether an eligible individual resides at a given location). Furthermore, the data suggested no relevant differences between movers and non-movers with respect to general demographic factors among interviewed Medicare controls.

If, in addition, we make the assumption of no effect of disease status on moving behavior, prostate cancer cases as a group would have a mobility pattern similar to that of controls. It is possible that disease status might have an effect on moving behavior of cases, such that rural residents would move to more urban areas for care, yet census block group demographics failed to show a greater representation of urban residences among cases. Absent any evidence for differential moving behavior, the relative ranking of exposures in each group should be preserved over time. Thus, it may be justified to use a simplified approach based on current address in future GIS-based research of prostate cancer and pesticide exposure. The single-address approach may even offer the advantage of greater validity and precision in effect estimation by both circumventing the issue of response bias and increasing sample size for controls. Because estimated mean exposures to MB and OCs in controls with residential histories seemed similar whether or not exposures were assigned according to full residential history or last address, this seems to suggest a response bias among Medicare controls, i.e., a higher response rate among unexposed elderly control subjects. Thus, use of responding individuals only as a control population may not represent a truly random sample of the population at risk with respect to exposures, making it preferable to include exposure estimates for non-responding individuals as well. Hence, along with potentially improving the validity of control comparisons with respect to exposure status, this approach additionally offers the advantages of a larger sample size.

Another limitation of research conducted outside of California involves the lack of a comprehensive pesti-

Table 5. 500m exposure estimates[a] for methyl bromide and organochlorines in Medicare controls with and without residential histories

Pesticide and group		1999 current exposure: Mean exposure rate, pounds/acre, (SD, *n*)	1999 current exposure: Mean % exposed	1995–1999 5-year exposure: Mean exposure rate, pounds/acre, (SD, *n*)	1995–1999 5-year exposure: Mean % exposed	1990–1999 10-year exposure: Mean exposure rate, pounds/acre, (SD, *n*)	1990–1999 10-year exposure: Mean % exposed	1980–1989 10-year lagged exposure: Mean exposure rate, pounds/acre, (SD, *n*)	1980–1989 10-year lagged exposure: Mean % exposed
Methyl Bromide									
Medicare controls with residential histories (*n*=104)	Last address, (*n*=102)[b]	5.9 (12.3, 9)	8.8	8.6 (20.5, 17)	8.4	5.5 (16.2, 25)	8.3	1.0 (7.5, 25)	6.8
	20-yr residential history (*n*=103)[c]	5.9 (12.3, 9)	8.7	7.5 (19.2, 16)	7.8	4.8 (15.1, 25)	7.4	0.4 (3.5, 21)	4.3
Medicare controls without residential histories (*n*=526)		7.2 (15.3, 74)	14.1	6.0 (15.9, 151)	13.2	4.9 (16.3, 191)	12.3	1.0 (7.7, 192)	9.0
Organochlorines									
Medicare controls with residential histories (*n*=104)	Last address (*n*=102)	0.1 (0.2, 5)	4.9	0.1 (0.4, 11)	4.9	0.2 (0.8, 26)	8.9	0.1 (0.4, 44)	12.4
	20-yr residential history (*n*=103)	0.1 (0.2, 4)	3.9	0.1 (0.4, 12)	5	0.2 (0.8, 26)	8.0	0.1 (0.4, 32)	8.3
Medicare controls without residential histories (*n*=526)		0.2 (0.4, 67)	12.7	0.2 (0.6, 141)	14.7	0.3 (0.9, 193)	17.8	0.2 (0.6, 235)	16.1

[a]All estimates include data on only those individuals found to be exposed to either organochlorines or methyl bromide at least one year of the exposure period under consideration.
[b]Two addresses were unable to be mapped, but were located in the Sequioa National Park and so were unlikely to be exposed.
[c]One individual had no mappable addresses in the tri-county study area between 1980 and 2004.
SD, standard deviation.

cide use reporting system. In many states pesticide application data may be limited to knowledge about general application patterns on types of crops and pesticide sales data such that exposure measures would be any versus no use of a particular pesticide in proximity of homes. Without information on pounds of a specific pesticide applied, an even simpler model ignoring the quantity of application might be employed. Such a model counts a home as exposed when any application of a pesticide occurred within a residential buffer, allowing for calculation of the percent of subjects with any exposure. Although this method provides no information concerning cumulative exposures, it seems to preserve the exposure rankings of all groups.

Conclusion

The results from this exposure assessment exercise using a model based primarily on proximity show that the frequency and amount of application of pesticides over time affect the bias introduced into exposure assessments. Although the inclusion of subjects' complete residential histories into the computation of exposure estimates seems to reduce bias from this source, it may introduce an additional bias through control self-selection. The use of randomly sampled controls from Medicare and residential parcel listings independent of subject response, however, seems to result in the opportunity for relatively unbiased estimates of pesticide exposures in controls. Therefore, when detailed control characteristics are not needed, relying on controls such as those from Medicare or residential parcels to estimate exposure may be adequate, offering a valuable resource for control series in future population-based studies of pesticide exposure and chronic disease. Residential histories, however, should become an integral source of data for exposure assessment in studies of environmental factors and cancer. A recent report by the California Policy Research Center addressing Environmental Public Health Tracking recommends the collection of historical residential data by cancer registries to improve disease tracking and allow for linkage to environmental databases.[17] Such data would enable exposure models that incorporate residential histories such as the one used here in future cancer studies and would also allow addressing timing and latency components of exposure, thus advancing exposure and disease modeling techniques.

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