Residential Herbicide Use and Risk of Non-Hodgkin Lymphoma

Patricia Hartge,[1] Joanne S. Colt,[1] Richard K. Severson,[2] James R. Cerhan,[3] Wendy Cozen,[4] David Camann,[5] Shelia Hoar Zahm,[1] and Scott Davis[6]

[1]Department of Health and Human Services, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland; [2]Department of Family Medicine and Karmanos Cancer Institute, Wayne State University, Detroit, Michigan; [3]Mayo Clinic, College of Medicine, Rochester, Minnesota; [4]University of Southern California, Los Angeles, California; [5]Southwest Research Institute, San Antonio, Texas; and [6]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, Washington

Abstract

Context: **Environmental exposure to herbicides has been hypothesized to contribute to the long-term increase in non-Hodgkin lymphoma (NHL).**
Objective: **To estimate the effects of residential herbicide exposure on NHL risk.**
Design: **Population-based case-control study.**
Setting: **Iowa and metropolitan Detroit, Los Angeles, and Seattle, 1998 to 2000.**
Participants: **NHL patients ages 20 to 74 years and unaffected residents identified by random digit dialing and Medicare eligibility files.**
Main Outcome Measures: **Computer-assisted personal interviews (1,321 cases, 1,057 controls) elicited data on herbicide use at each home occupied since 1970. Levels of 2,4-dichlorophenoxy-acetic acid and dicamba were measured in dust taken from used vacuum cleaner bags in the current home (679 cases, 510 controls who had owned at least half of their carpets for ≥5 years).**
Results: **Herbicide use on the lawn or garden was similar among cases and controls (adjusted relative risk, 1.02; 95% confidence interval, 0.84-1.23). Estimated risk did not increase with greater duration, frequency, or total number of applications of herbicides to the lawn, the garden, or to both combined. Risk was not elevated for respondents who applied the herbicides themselves and not for those exposed during the 1970s, 1980s, or 1990s. We detected 2,4-dichlorophenoxy-acetic acid equally often in homes of cases and controls (78%). We found dicamba in homes of 15% of cases and 20% of controls. We also found no elevation in risk among the respondents who had the highest dust levels and highest self-reported exposures. We found no consistent patterns for specific histologies.**
Conclusions: **We found no detectable excess associated with residential exposures. Residential herbicide exposures are unlikely to explain the long-term increase in NHL.** (Cancer Epidemiol Biomarkers Prev 2005;14(4):934–7)

Introduction

Non-Hodgkin lymphoma (NHL) comprises dozens of histologic entities (1-4), many with distinct etiologies. NHL incidence and mortality rates rose strikingly during the second half of the 20th century in the United States and around the world (5). Apart from the role of HIV, most of the long-term increase remains unexplained (6). Exposure to pesticides in the general environment increased during the same period, and several studies have linked NHL with occupational use of pesticides, especially herbicides. We therefore conducted a population-based, case-control study, with detailed histories of pesticide use from interviews and measured pesticide residues from carpet dust samples.

Materials and Methods

Four Surveillance Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, metropolitan Detroit, and metropolitan Seattle) identified residents ages 20 to 74 years with a first primary diagnosis of NHL (*International Classification of Diseases for Oncology, 3rd edition* codes 967-972) between July 1998 and June 2000. To increase the number of African American cases, we chose all African Americans but only a random sample of White cases in two of the centers (Los Angeles and Detroit). We sampled population controls ages 20 to 64 years by random digit dialing and those ages ≥65 years from Medicare files, stratifying on age, sex, race, and center. We excluded HIV-infected cases and controls. The study was approved by human subjects review boards at all institutions.

Of 2,248 presumed eligible cases, we did not attempt to schedule interviews with 520 (death, unlocatability, physician refusal, or relocation outside of the study area), did attempt with 1,728, and interviewed 1,321 (participation rate, 76%; response rate, 59%). Of 2,409 presumed eligible controls, we did not attempt to schedule interviews with 363, did attempt with 2,046, and interviewed 1,057 (participation rate, 52%; response rate, 44%).

During the home visit, we obtained written informed consent, gave a computer-assisted personal interview and collected biological and environmental samples. For each home occupied for ≥2 years since 1970, the interviewer asked whether the residence was on a farm and about treatments for specific categories of pests (e.g., flying insects) using a graphic aid to increase respondent attention and accuracy. For each pest category, the interviewer asked whether a pesticide was used, who applied it, and the application frequency and product form (e.g., fogger). We report here on treatment of weeds either on the lawn or on ''outdoor plants and trees'', here referred to as ''garden''. Unless otherwise noted, use of herbicides includes application to the respondent's lawn or garden, whether by the respondent, a professional, or someone else.

Details of carpet dust sampling and analysis are given elsewhere (7). Subjects were eligible for carpet dust collection if they had used their vacuum cleaner in the past year and owned at least half of their carpets for ≥5 years. The laboratory

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Requests for reprints: Patricia Hartge, National Cancer Institute, Epidemiology and Biostatistics Program, 6120 Executive Boulevard, Room 8090, Rockville, MD 20852. Phone: 301-496-7887; Fax: 301-402-2623. E-mail: hartgep@mail.nih.gov

used a neutral extraction for the herbicide dacthal and 22 other pesticides, 10 polycyclic aromatic hydrocarbons, and 6 polychlorinated biphenyl congeners, and an acid extraction for four herbicides [2,4-dichlorophenoxy-acetic acid (2,4-D), dicamba, MCPA, and 2,4,5-T] and pentachlorophenol. Extracts were analyzed using gas chromatography/mass spectrometry in selected ion monitoring mode. The data set contained missing values when a concentration was below the minimum level detectible by the gas chromatography/mass spectrometry, or when compounds coeluted with the target analyte. We used an imputation procedure to assign a value for each missing measurement (8) if the herbicide was detected in at least 10% of the samples (2,4-D and dicamba, detection limits 84.3 and 85.3 ng/g, respectively). The final data set included measured and imputed values for 2,4-D and dicamba for 679 cases and 510 controls.

We estimated the relative risk (RR) of developing NHL with adjusted odds ratios and 95% confidence intervals (95% CI) from multiple unconditional logistic regression models that included education as a potential confounder and the design variables of geographic location, age (in decades), sex, and race. For analyses of selected histologic types, we used polytomous regression. We evaluated family history of lymphoma, whether currently or previously working as a farmer, insecticide use, and other variables as potential confounders. We did computations in SAS version 8.2 and used two-sided tests for statistical significance.

Results

The interviewed cases were approximately evenly drawn from the four areas and were disproportionately male, white, and ages ≥55 years (Table 1). Both cases and controls had lived in three residences since 1970, on average, and most lived in single family homes at the time of diagnosis or selection. The median length of residence in homes with carpet dust samples was 20 years for both cases and controls.

Lawns were treated more often than gardens. The products and techniques used for lawns and gardens can differ somewhat; thus, we evaluated the exposures separately (data not shown) and together (Table 2). For respondents who reported use of weed killers on the lawn or garden, estimated RR was 1.02 (95% CI, 0.84-1.23). Estimates were slightly below the null for ≥20 years of treatment, >12 treatments per year, ≥100 applications overall, and ≥50 applied by themselves. Risk estimates were similar across decades and among respondents with or without carpet dust samples (data not shown).

Treatment of the lawn was unrelated to risk (RR, 0.99; 95% CI, 0.81-1.19), as were duration, frequency, and cumulative exposure. Treatment of the garden was weakly related to risk (RR, 1.12; 95% CI, 0.80-1.55), but the estimates were lower with longer duration or more frequent application. Application by the respondent was associated with a higher RR than application by a lawn care professional, but the number of applications was inversely related to risk. Garden treatments in the 1990s were slightly related to risk (RR, 1.16; 95% CI, 0.81-1.67), but treatments in the earlier decades were not.

Among the respondents with carpet dust samples (Table 3), neither 2,4-D nor dicamba was consistently related to NHL risk, even among respondents with the highest levels. As expected, we detected higher levels of 2,4-D and dicamba in samples from the current carpets of respondents who reported more applications of weed killers over the period since 1970. For example, in dust from the homes of controls reporting no herbicide applications, 56 had no detected 2,4-D and 39 had high levels, whereas in the homes of controls reporting at least 50 uses, 8 had no detected 2,4-D but 52 had high levels.

Table 1. Characteristics of cases and controls

	Cases (%), n = 1,321	Controls (%), n = 1,057
Center		
Detroit	24	20
Iowa	27	26
Los Angeles	24	26
Seattle	24	28
Sex		
Male	54	52
Female	46	48
Race		
African American	8	14
White	85	80
Other	7	6
Age at diagnosis or selection		
20-34	6	5
35-44	13	10
45-54	22	19
55-64	27	24
65-74	33	42
Education (y)		
<12	10	11
12-15	62	58
>16	29	31
Residence at diagnosis or selection*		
Single family	76	73
Duplex, townhouse, or row house	5	7
Apartment	9	13
Mobile home	2	3
Other/unknown	8	4
Residences* since 1970		
Mean	3.1	3.1
Median (range)	3.0 (1.0-11.0)	3.0 (1.0-9.0)

*Includes homes occupied for two or more years.

We defined a low-exposure group (60 cases and 56 controls) who had no 2,4-D detected in the dust sample and reported no use of herbicides in the interview. Compared with them, the participants reporting ≥50 applications of herbicide with at least 1,000 ng/g of 2,4-D showed a RR of 0.89 (95% CI, 0.49-1.59). We defined another low exposure group (187 cases and 146 controls) with no dicamba detected in the dust and no reported herbicide exposure. For respondents reporting ≥50 applications with levels of dicamba at or above 500 ng/g, the estimate was 0.85 (95% CI, 0.20-3.62).

The estimates for any herbicide use were generally similar among men and women, among older and younger respondents, and among farmers and nonfarmers (data not shown). Among African Americans, we observed an elevated risk for any herbicide use (RR, 1.63; 95% CI, 0.88-3.01). With the very small number of African American respondents, the risk estimates were unstable, and the difference between African Americans and Caucasians was not statistically significant (P = 0.11). Similarly, we observed an association with detectible 2,4-D among African Americans (RR, 3.34; 95% CI, 1.16-9.63). We found no dose-response gradients with number of applications or levels of 2,4-D.

We found no consistent differences among the main histologic types. For instance, follicular B-cell lymphoma was positively associated with reported use but negatively with 2,4-D levels, and T-cell lymphoma was positively associated with 2,4-D but negatively with reported use.

Discussion

Exposure of the general population to herbicides used on the lawn or garden did not result in detectible increase in the risk of developing NHL in this study. We found limited evidence of an association restricted to African Americans, but the

number of participants was very small and the estimates correspondingly unstable. We found no consistent pattern of risk for specific histologies.

There are very few data on NHL risk and residential pesticide exposures, with one study in Kansas reporting no association (9). There is a larger body of evidence on occupationally exposed populations. Case-control studies of farmers exposed to herbicides as a group have reported overall RRs ranging from 1.3 to 1.6 (9-11). Higher risks were reported with longer duration, greater frequency, direct application, lack of protective equipment, or greater acreage treated (9, 12, 13). Another study found elevated risk with spraying herbicides in forests (14).

Of particular interest are occupational studies of phenoxyacetic acid herbicides, a group which includes 2,4-D and dicamba. NHL or malignant lymphoma risk was linked to phenoxyacetic acid herbicides, in several studies (9, 10, 15) but not in others (11, 16-18). Cohorts of workers who manufacture 2,4-D and other phenoxy herbicides have not shown statistically significant excesses of NHL (19-21), but most were small cohorts that lacked sufficient power to detect moderate increases in risk (22).

A major strength of the study was the use of two exposure assessments, personal interviews and carpet dust samples. The residence-based, pest-specific interview, with graphical aids to improve recall, decreased the need for the respondent to integrate or summarize overall exposures to pesticides. From the carpet dust samples, we measured five selected herbicides, which correlated very well with self-reported usage patterns (7). The agreement adds credibility to both indices. Additional strengths were the population basis of the selection of cases and controls, the considerable size of the study population, and the detailed data on potential confounders or modifiers.

An important limitation was the loss of information from death, nonlocation, or refusal of eligible cases and controls. Bias could have occurred if survival from lymphoma (among the cases) or willingness to participate in the study (in the cases but especially in the controls) were strongly related both to herbicide exposure and to disease status, but there is some evidence that such biases may have been minimal. In the geographic areas and the demographic subgroups with the higher response rates, there was no evidence of an association with any measure of herbicide exposure. African Americans (the only subgroup in which there was some evidence of an association with herbicide use) had particularly low response rates. Analyses specific for education revealed no pattern of risk differing by social class, a likely correlate of the response rate. Additional limitations include inaccuracy in reporting of herbicide use and measurement errors in the environmental pesticide samples. Some degree of misclassification is inevitable, probably nondifferential, and thus producing bias towards the null. However, we found no effect even among those with the greatest total number applications or highest pesticide levels.

If, as the present study suggests, residential exposures to herbicides do not increase NHL risk, it may be because the frequency and intensity of exposure are low compared with those exposed occupationally. It is notable that one study found that farmers exposed to herbicides for fewer than 11 days per year had NHL risk similar to that of farmers who never used herbicides (9). Another found a nonsignificant, 20% elevation in farmers handling 2,4-D for fewer than 6 days per year (10). Another found no risk on farms of <100 acres (13). In our study, only five cases and eight controls reported that their lawns or gardens were treated for weeds >12 times in any given year, and home lawns and gardens are considerably smaller than agricultural fields. In the alternative, we may have failed to detect a real but small increase in risk because of random misclassification. Nonetheless, the lack of increased risk among the more heavily exposed groups in this study indicates that the explanation for the steady increase in NHL risk in the last half of the 20th century lies elsewhere.

Table 2. RR of non-Hodgkin lymphoma according to treatment of weeds

	Lawn or garden weeds		
	Cases	Controls	RR* (95% CI)
Never lawn or garden	421	346	1 (reference)
Ever treated for weeds	708	565	1.02 (0.84-1.23)
Years of treatment			
<10	411	314	1.04 (0.84-1.29)
10-19	190	148	1.04 (0.80-1.36)
>20	107	102	0.92 (0.67-1.27)
Trend test (*P*)			0.69
Average no. treatments/y (highest reported)			
<2	259	189	1.13 (0.88-1.44)
2-12	443	364	0.99 (0.80-1.21)
>12	5	8	0.43 (0.14-1.36)
Trend test (*P*)			0.59
Estimated total applications			
<10	190	153	1.01 (0.77-1.31)
10-19	101	64	1.28 (0.90-1.83)
20-49	173	115	1.21 (0.91-1.61)
50-99	95	83	0.92 (0.66-1.28)
>100	148	146	0.84 (0.64-1.11)
Trend test (*P*)			0.38
Total applications by the respondent			
<10	121	97	0.98 (0.72-1.35)
10-19	53	33	1.27 (0.80-2.03)
20-49	73	46	1.25 (0.83-1.88)
>50	113	121	0.81 (0.60-1.10)
Trend test (*P*)			0.48
Total applications by lawn care professional			
<10	58	41	1.20 (0.78, 1.85)
10-19	35	30	0.97 (0.58, 1.62)
20-49	83	57	1.14 (0.78, 1.66)
>50	110	95	0.94 (0.68-1,29)
Trend test (*P*)			0.71
Ever treated in 1970s	504	407	1.02 (0.83-1.26)
Ever treated in 1980s	585	469	1.01 (0.83-1.23)
Ever treated in 1990s	643	512	1.02 (0.84-1.24)

NOTE: Some respondents reporting treatment of lawn or garden for weeds had missing information for years of treatment or no. treatments/y.
*Relative risk estimated from logistic regression model with terms for geographic location, age, sex, race, and education.

Table 3. RR of non-Hodgkin lymphoma according to herbicides in carpet dust

	Cases, n = 679	Controls, n = 510	RR* (95% CI)
2,4-D (ng/g)			
Below detection limit	147	110	1.00 (reference)
<500	257	161	1.10 (0.78-1.55)
500-999	86	59	0.91 (0.58-1.45)
1,000-9,999	165	162	0.66 (0.45-0.98)
>10,000	24	18	0.82 (0.41-1.66)
Dicamba (ng/g)			
Below detection limit	578	410	1.00 (reference)
<500	84	87	0.63 (0.45-0.89)
500-999	11	7	1.16 (0.44-3.09)
<1,000	6	6	0.70 (0.22-2.23)

*RR estimated from logistic regression model with terms for geographic location, age, sex, race, and education.

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