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Incidence of Non-Hodgkin Lymphoma and Residential Proximity to Superfund Sites in Kentucky

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Abstract **The rates of non-Hodgkin lymphoma (NHL) in Kentucky and the U.S. began to rise in the mid-20th century. Plausible mechanistic explanations exist for linkages between the development of NHL and exposures to specific chemicals. Several of these chemicals are present in sites within the U.S. Environmental Protection Agency's Superfund program. This study investigated a possible association between residential proximity to Superfund sites in Kentucky and incidence of NHL over a period of 18 years. Cumulative incidence rates per 100,000 persons were calculated at the census tract level, within 5 km–10 km and <5 km from Superfund sites. Geographically weighted regression was necessary to create best-fitting models due to spatial autocorrelation and nonstationarity. Residential proximity to Superfund sites in Kentucky was associated with higher incidence of NHL; the average cumulative incidence of NHL per 100,000 decreased as the distance to the hazardous sites increased. This study confirmed previous research findings of an association between residential proximity to environmentally hazardous sites and the cumulative incidence rates of NHL. Future research should take into account the chemical profile of each site, to identify the most hazardous sites. Potential intervention strategies are presented based on the results of this study.**

Introduction

Non-Hodgkin lymphoma (NHL) is currently the eighth most common cancer in the U.S., the sixth most common cancer among males, and the seventh most common cancer among females (U.S. Cancer Statistics Working Group, 2016). Kentucky has the fourth highest NHL death rate (National Cancer Institute, 2014), and parallels the national and international Western trends of increased incidence in the mid-20th century across all sexes and age groups, with the highest overall rates seen in White males (Al-Hamadani et al., 2015; Devesa & Fears, 1992). The rise in NHL incidence, in the U.S. and Kentucky, appears to coincide with the increased use and dispersion of specific chemical substances into the environment, although support for such an association is difficult to establish. Xenobiotics can function as immune system suppressors and immune suppression is a primary known risk factor for NHL (Engels et al., 2005; Freeman & Kohles, 2012; Grulich, Vajdic, & Cozen, 2007; Vajdic et al., 2009). Exposures to lymphomagenic substances can trigger immunosuppressive conditions (Fisher & Fisher, 2004), although persons with a history of allergies, other hyperimmune disorders, or asthma appear to have a reduced risk of developing NHL (Hofmann, Hoppin, Blair, Alavanja, & Freeman, 2014; Pahwa et al., 2012; Zhou & Yang, 2015). Residential neighborhoods located in proximity to Superfund sites, sometimes designated as "high exposure" areas, have higher reports of neurological symptoms than areas with lower exposure (Dayal, Gupta, Trieff, Maierson, & Reich, 1995). Meta-analysis showed that serum immunoglobulin A levels were consistently, but not significantly, elevated for residents near Superfund sites compared with matched controls at least 5 miles away from sites (Williamson et al., 2006). Elevated incidence rates for multiple cancers were also found in areas neighboring a Superfund site in Massachusetts (Ozonoff, Aschengrau, & Coogan, 1994). Another study estimated that multistate Superfund site cleanup activities reduced the rate of infant congenital abnormalities by 20% to 25% for mothers who resided 5 km or less from the sites (Currie, Greenstone, & Moretti, 2011). Tree bark samples within 10 km of a Superfund site in Michigan showed 10- to 100-fold increases in dichlorodiphenyltrichloroethane (DDT), hexabromobenzene, and polybrominated biphenyls compared with sites located beyond 10 km (Peverly, Salamova, & Hites, 2014). Geospatial analysis was used to identify clusters of childhood cancer near Superfund sites in Dade County, Florida (Kearney, 2008), of very low birth weight near multiple Superfund sites in Harris County, Texas (Thompson, Bissett, & Sweeney, 2014), and to investigate and confirm the unequal burden of Superfund sites among specific racial, ethnic, and socioeconomic demographics (Burwell-Naney et al., 2013; Heitgerd & Lee, 2003; Maantay, 2002; Maranville, Ting, & Zhang, 2009; Pais, Crowder, & Downey, 2014). The siting of Superfund sites in neighborhoods with lower value housing disproportionately affects poor and primarily minority populations (Greenstone & Gallagher, 2008; Ringquist, 2005; Smith, 2009; Szasz & Meuser, 1997; Szasz & Meuser, 2000).

TABLE 1

Descriptive Statistics for Patient Data (*N* = 14,373)

Demographics	#	%
Gender		
Female	6,978	48.5
Male	7,395	51.5
Race		
White	13,617	94.7
Black	632	4.4
Other/unknown	124	0.9
Age at diagnosis (year)		
0–9	61	0.4
10–19	127	0.9
20–29	221	1.5
30–39	583	4.1
40–49	1,300	9.0
50–59	2,392	16.6
60–69	3,546	24.7
≥70	6,143	42.7
Tumor type		
Intranodal NHL	10,181	70.8
Extranodal NHL	4,192	29.2
Family history of NHL		
No	7,495	52.2
Yes	533	3.7
Unknown	6,345	44.1
Appalachia region		
No	10,337	71.9
Yes	4,036	28.1
Beale Code classification		
Urban	12,997	90.4
Rural	1,376	9.6
Residential proximity to nearest superfund site (km)		
<5	4,225	29.4
5–10	3,570	24.8
>10	6,578	45.8

NHL = non-Hodgkin lymphoma.

There are only a few published studies on the possible link between residential proximity to hazardous waste sites and NHL cancer cases. One study in Georgia found that residential proximity to areas where benzene had been released and documented in the U.S. Environmental Protection Agency (U.S. EPA) Toxics Release Inventory resulted in a significant increase in NHL incidence (Bulka et al., 2013). Another found that NHL rates were significantly elevated near National Priority Contaminated Sites in Italy (Comba et al., 2014). Studies that examined NHL rates near uranium milling operations in New Mexico (Boice, Mumma, & Blot, 2010) and rates for a specific type of NHL (cutaneous T-cell lymphoma) in Pennsylvania (Moreau, Buchanich, Geskin, Akilov, & Geskin, 2014) did not show higher rates near hazardous sites. Various state and federal health agencies have been tasked to examine possible NHL clusters near Superfund sites, and confirmed higher than expected rates of NHL in all populations near sites in Ohio (Ferron & Frey, 2008), Texas (Texas Department of State Health Services, 2015), California (Greater Bay Area Cancer Registry, 2012), and in females near a site in Connecticut (State of Connecticut Department of Public Health, 1997).

Methods

Following approval of the Institutional Review Board of the University of Kentucky, NHL cancer data for 1995–2012, including 14,373 records, were obtained from the Kentucky Cancer Registry (KCR). All individual identifying data, except for the geographic coordinates for the patients' residence, were removed by KCR staff. While 82.3% of NHL cases could be assigned to census tracts based on high-quality residential geospatial coordinates, the remaining 17.7% used the centroid of residential ZIP code because the patient's recorded address was on rural routes or a post office box.

Census Tract Topologically Integrated Geographic Encoding and Referencing (TIGER) file and basic population data were obtained from the 2010 U.S. Census website; 734 of the 1,115 census tracts in Kentucky had incident cases of NHL at some time between 1995–2012. On average, census tracts in Kentucky had 4,105 people (standard deviation [*SD*] = 1,721) with a median of 3,920 people. The 18-year cumulative number of NHL cases per 100,000 at census tract-level was on average 210 (*SD* = 336) with a median value of 28.5. The 1995–2012 crude cumulative incidence rate for NHL in Kentucky was 331.2 per 100,000 people, while the adjusted rate was 305.2 per 100,000 people.

The environmental exposure was measured by proximity to one or more Superfund sites in Kentucky. There were 133 Superfund sites for which geospatial data was available on the U.S. EPA Superfund website for Region 4 (U.S. EPA, 2017); 970 census tracts in Kentucky did not have a Superfund site within their borders, and the remaining 145 had one to five Superfund sites per tract. The exposure areas were developed in ArcMap by drawing 5 km and 10 km buffers around each Superfund site. When buffers of neighboring Superfund sites intersected, they were dissolved into a single area of exposure, and the perimeter of all of the conjoined buffers became the boundary of the newly created exposure areas. Similarly, the 10 km buffers form a ring around the 5 km exposure areas. Therefore, the exposure areas have different sizes and shapes, including different numbers of census tracts or fragments of census tracts, and different numbers of Superfund sites within their boundaries.

There were 71 areas of exposure within 5 km of one or more Superfund sites, and 45 areas located in the ring around the buffers between 5 km–10 km. For the census tract fragments with missing values, the same cumulative incidence rate of the exposure area was imputed. Finally, the remaining areas of the state, outside the 5 km and 10 km exposure areas, formed the third area of interest, the "unexposed" areas of the state, for which the incidence rates were computed at census tract-level.

The outcome of interest in this study is the age-adjusted cumulative incidence rate of NHL per 100,000 persons in Kentucky. The age-adjusted cumulative rates of NHL were estimated with the direct method for the exposure areas and for all census tracts outside the exposure areas, using the 2000 U.S. Census standard population weights per 100,000 per current recommendations from the Centers for Disease Control and Prevention (Anderson & Rosenberg, 1998; Klein & Schoenborn, 2001). The patient's residential proximity to Superfund sites was measured by the exposure within 5 km, exposure between 5 km and 10 km, as compared with the exposure beyond 10 km, which was the reference group for the analyses.

Traditional statistics were used to describe the patient population, and to test for bivariate associations between the incidence rates and potential explanatory factors available in the dataset. The multivariable association between the exposure and the cumulative incidence rate of NHL per 100,000 persons was measured with spatial regression. Race, smoking status, and NHL family history were tested in the bivariate models but were not retained in the multivariable models due to the very small variation in the data and large proportions of missing values. Diagnostic tools for spatial autocorrelation and clustering confirmed the need for a geographically weighted regression approach.

TABLE **2**

Distribution of Non-Hodgkin Lymphoma (NHL) Cases by Exposure Group

Demographic Variable		Residential Proximity to Nearest Superfund Site # (%)		
		<5 km	5–10 km	>10 km
Gender	Male	2,170 (29.4)	1,793 (24.2)	3,432 (46.4)
	Female	2,055 (29.4)	1,777 (25.5)	3,146 (45.1)
Race	White	3,826 (28.1)	3,400 (25.0)	6,391 (46.9)
	Non-White	351 (55.4)	133 (21.0)	150 (23.7)
Appalachia region	No	3,459 (33.5)	3,070 (29.7)	3,808 (36.8)
	Yes	766 (19.0)	500 (12.4)	2,770 (68.6)
Beale Code classification	Urban	4,157 (32.0)	3,497 (26.9)	5,343 (41.1)
	Rural	68 (4.9)	73 (5.3)	1,235 (89.8)
Family history of NHL	Yes	133 (25.0)	130 (24.4)	270 (50.7)
	No	2,234 (29.8)	1,817 (24.2)	3,444 (46.0)
	Unknown	1,858 (29.3)	1,623 (25.6)	2,864 (45.1)
SEER type	Intranodal	2,969 (29.2)	2,547 (25.0)	4,665 (45.8)
	Extranodal	1,256 (30.0)	1,023 (24.4)	1,913 (45.6)

SEER = Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

TABLE **3**

Age-Adjusted 1995–2012 Cumulative Non-Hodgkin Lymphoma (NHL) Incidence Rates by Exposure

Age-Adjusted NHL Incidence Rates	Exposure Mean (*SD*)			ANOVA	
	<5 km	5–10 km	>10 km	*F*-Statistic	*p*-Value
Overall	457.0 (244.7)	308.6 (100.6)	90.9 (215.7)	17.8	<.001
Male	542.4 (341.2)	338.3 (113.3)	25.8 (249.5)	21.6	<.001
Female	382.9 (240.2)	285.3 (116.7)	62.4 (303.6)	5.1	.006
Intranodal tumor	323.4 (200.2)	218.7 (73.3)	08.5 (180.6)	12.3	<.001
Extranodal tumor	133.7 (82.8)	89.9 (49.6)	82.5 (76.6)	13.4	<.001

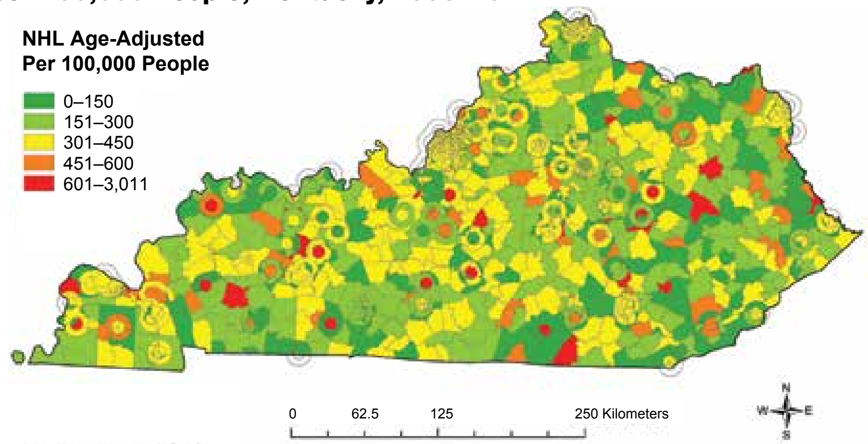
SD = standard deviation

Results

There were 14,373 new NHL cases in Kentucky between 1995–2012 (Table 1), of which 42.7% were diagnosed at age 70 or later and another 24.7% were diagnosed with NHL in their 60s; over 90% of the NHL patient population resided in urban areas. The patient population included 51.5% males and 94.7% of all cases were White. Intranodal NHL accounted for 70.8% of all cases, 71.7% of male cases, and

FIGURE **1**

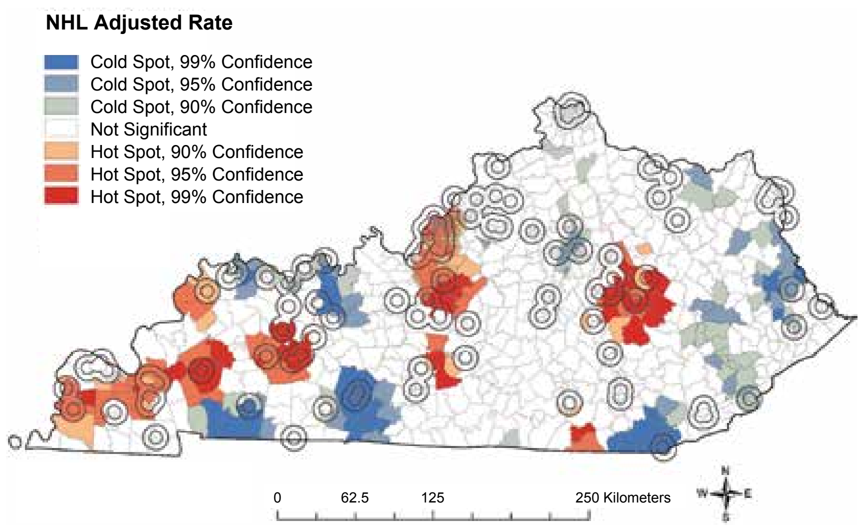
Cumulative Non-Hodgkin Lymphoma (NHL) Incidence Rate per 100,000 People, Kentucky, 1995–2012



Sources: U.S. Census 2000, 2010 Kentucky Cancer Registry, U.S. Environmental Protection Agency

FIGURE **2**

Hot Spot Analysis for Cumulative Non-Hodgkin Lymphoma (NHL) Incidence Rate per 100,000 People



Sources: U.S. Census 2000, 2010 Kentucky Cancer Registry, U.S. Environmental Protection Agency

69.9% of female cases. Of all cases that were of other than White race, only 0.6% were Hispanic or Latino of any race (data not shown) and 4.4% were African American. In accordance with national NHL statistics, 67.4% of all diagnoses occurred in patients age 60 or older. Only 3.7% of the patients had a known prior family history of NHL and 52.2% had no prior family history; data were missing for 44.1% of the caseload. Only 28.1% of patients lived in counties that were part of the designated region of Appalachia and 9.6% of patients lived in rural areas. Finally, 39.1% of patients were current users of tobacco products.

Bivariate analysis of residential proximity to Superfund sites by demographic variables is presented in Table 2. Nearly 30% of all patients lived within 5 km of a Superfund site; non-White NHL patients were more likely to live within 5 km of the Superfund sites, whereas residents of Appalachia or rural areas were less likely to live near them. The percentage of NHL cases with unknown or no family history of NHL were significantly higher for the cases residing within 5 km of Superfund sites. The age-adjusted cumulative NHL incidence rates across exposure groups were significantly greater within 5 km exposure areas than in the other two groups (Table 3); further, the rates within 5 km and 10 km from the Superfund sites were significantly greater than the rates in the unexposed areas. The rates for the unexposed group were significantly lower than those in the exposed groups, at a significance level of $p < .05$.

These data reflect the national trends, in that the male patients have a higher incidence rate than females for both intranodal and extranodal NHL. As expected, an age-related increase in NHL incidence was observed for both males and females, and for both SEER classifications (Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute), with a sharp increase in NHL for females ages 60–69.

The age-adjusted cumulative incidence rates for NHL per 100,000 persons from 1995–2012 in each census tract and buffer zone around Superfund sites (Figure 1) showed that NHL cumulative incidence rates were slightly higher in the western and south-central regions of Kentucky.

Stationarity tests showed that the predictor effects on the outcome were not consistent across the studied area, and the Global Moran's I indicated the presence of spatial autocorrelation among residuals. All *z*-scores were significant and positive, indicating significant autocorrelation and clustering of similar residual values. Hot spot analysis identified the areas of significant high or low spatial clustering of NHL incidence data using the Getis-Ord G_i* statistic at the 99%, 95%, and 90% confidence limits (Figure 2).

Exploratory regression using ordinary least squares (OLS) showed that urbanicity or rurality of an area is a significant predictor for the NHL cumulative incidence rate—but residence in the Appalachian region was not (data not shown). This finding is interesting, as the Appalachian region is generally known to have significantly higher cancer incidence rates than the rest of the state. The OLS models explained a small amount of the variability around the fitted regression line, with a coefficient of determination of about 7%; they had acceptable levels for the variance inflation coefficients, but significant Koenker (BP) statistics indicate nonconsistent relationships between the dependent and independent variables (nonstationarity); thus, geographically weighted regression (GWR) was more appropriate than the OLS models. For GWR models, adaptive kernel density estimation was utilized, along with the corrected Akaike information criterion (AIC) to estimate bandwidth. The AIC's values were compared between the GWR models; the lower AIC value was from the GWR all-case base model (AIC = 24,893.8), indicating that this was the model that best fits the data (Table 4). The GWR models represent a better fit around the regression line than the OLS models, and explain a larger percentage of the variability. The best-fitting model explains approximately 23% of the variability in the overall NHL cumulative incidence rate.

The best-fitting GWR model showed that the confidence interval [*CI*] rate per 100,000 persons was on average 120.7 (t = 62.59, $p < .001$) greater within 5 km from Superfund sites than in the areas beyond 10 km, while all other variables were held constant. Similarly, within the areas located between 5 km–10 km the *CI* rate per 100,000 persons was 45.9 (t = 30.37, $p < .001$) greater than in the unexposed areas. The patterns and magnitudes of residuals (Figure 3) are not surprising, given that the best-fitting GWR model explained only 23.1% of the variability in the dependent variable. There appear to be more areas of "high" standardized residuals than "low" standardized residuals; the highest magnitude areas, where the observed incidence rates exceeded the predicted rates by more than 2.5 standard deviations, were most prominent in the central and western areas of Kentucky. Low areas, where the observed incidence rates were lower than the predicted rates, were randomly scattered throughout the state.

TABLE **4**

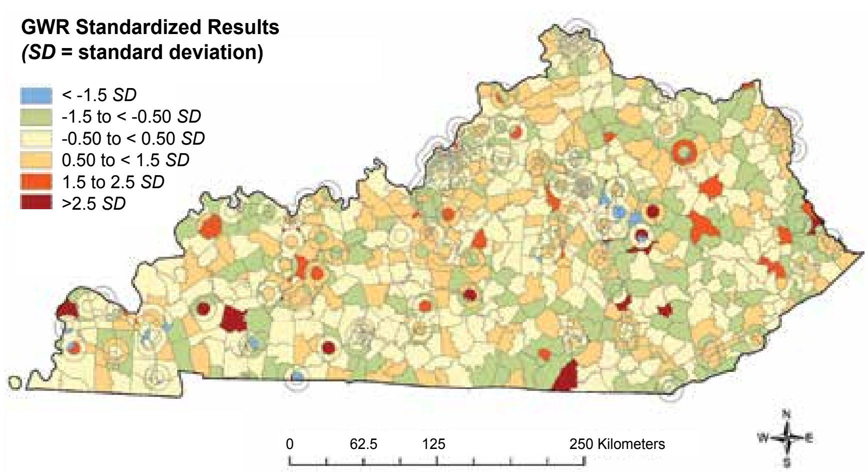
Geographically Weighted Regression Modeling Results

Model	Variables	# of Neighbors	Sigma	Akaike's Information Criterion	R^2
Model 1	Exposure <5 km Exposure 5–10 km	241	155.809	24,893.804	0.231
Model 2	Appalachia region Beale Code Exposure <5 km Exposure 5–10 km	834	163.244	25,047.162	0.134

Dependent variable: cumulative incidence of non-Hodgkin lymphoma per 100,000 people.

FIGURE **3**

Geographically Weighted Regression (GWR) Standardized Residuals, 1995–2012 Age-Adjusted Cumulative Non-Hodgkin Lymphoma Incidence Rates per 100,000 People



Sources: U.S. Census 2000, 2010 Kentucky Cancer Registry, U.S. Environmental Protection Agency

Discussion

This observational study of the distribution of NHL in Kentucky aimed to identify whether the distribution of NHL incident cases follows a different pattern across the state in relationship with the location of Superfund sites. To the investigators' knowledge, this question has not been previously examined in Kentucky, or anywhere else in the U.S. while examining important covariates. Geospatial information and tools in public health research extended our ability to examine spatial patterns within existing data, to understand relationships between outcomes and environmental variables, and to make inferences about exposure patterns (Brewer, 2006). The model data support the hypothesis that residential proximity to Superfund sites in Kentucky explains a significant proportion of variance in the distribution of the cumulative incidence rates of NHL, although a large proportion still remains unexplained.

There are limitations to the present study. The cancer records did not include individual indicators associated with the social determinants of health. Socioeconomic and demographic variables at the census-tract level from the 2010 U.S. Census were imputed, however, and were not found to significantly contribute to the association between residential proximity to Superfund sites and NHL incidence rate. The standardized GWR residuals and the R^2 values suggest that there are other explanatory variables that contribute to NHL incidence that were not captured in the current investigation due to high proportions of missing data regarding the family history of cancer, smoking, or alcohol use.

For the 133 Superfund sites in Kentucky, data on the site-specific chemicals that led to the site's Superfund designation were available for only 20 (15.0%) of the sites. Of these 20 sites with chemical data available, 18 contained contaminants that have been associated with an increased risk of NHL, including benzene and benzyl compounds (Mehlman, 2006), lead (Demir et al., 2011), polychlorinated biphenyls (Müller, Ihorst, Mertelsmann, & Engelhardt, 2005), cadmium (Kelly et al., 2013), trichloroethylene (Bassig, Lan, Rothman, Zhang, & Zheng, 2012), organochlorines other than polychlorinated biphenyls (Brown, Rushton, & British Occupational Cancer Burden Study Group, 2012), and perchloroethylene (Vlaanderen et al., 2013).

It should be noted that the U.S. EPA will place a site on the Superfund list only if there is a plausible threat to human health or the environment. All Superfund sites in the present study were considered as equally likely to contribute environmental exposures that can lead to NHL. This consideration could lead to exposure misclassification, which most likely biases the results toward the null.

Education and awareness campaigns about NHL, risk factors, and symptoms could lead to earlier diagnosis and better outcomes in affected communities. Early detection relies on techniques such as lymph node biopsy, blood cell chemistry and morphology tests, or imaging scans that can detect not just NHL but other hematological malignancies (University of Texas, MD Anderson Cancer Center, 2017). Encouraging people in the communities most affected by NHL to seek screening may improve their health outcomes. Medical research should continue to investigate simple, low-cost, sensitive, and specific methods for detecting NHL, as it will most likely continue to be a cancer of high incidence as the population ages.

Conclusion

NHL incidence in the U.S. and many other Western nations increased throughout the 20th century, in a pattern that suggests greater exposure to chemicals might be a causal factor. Mechanistic research suggests many pathways by which chemicals and xenobiotics can trigger NHL. The present study demonstrated that residential proximity to hazardous waste sites in Kentucky could be a significant risk factor for NHL. Additional research, advocacy, and education should focus on mechanisms of NHL incidence, replicating the present study in other contexts and with monitoring data. Further research needs to be done to address upstream factors that lead to unequal burdens of hazardous material exposures and NHL incidences. Additionally, downstream education and awareness, plus better methods for NHL screening and early detection, are also needed.

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continued on page 28

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