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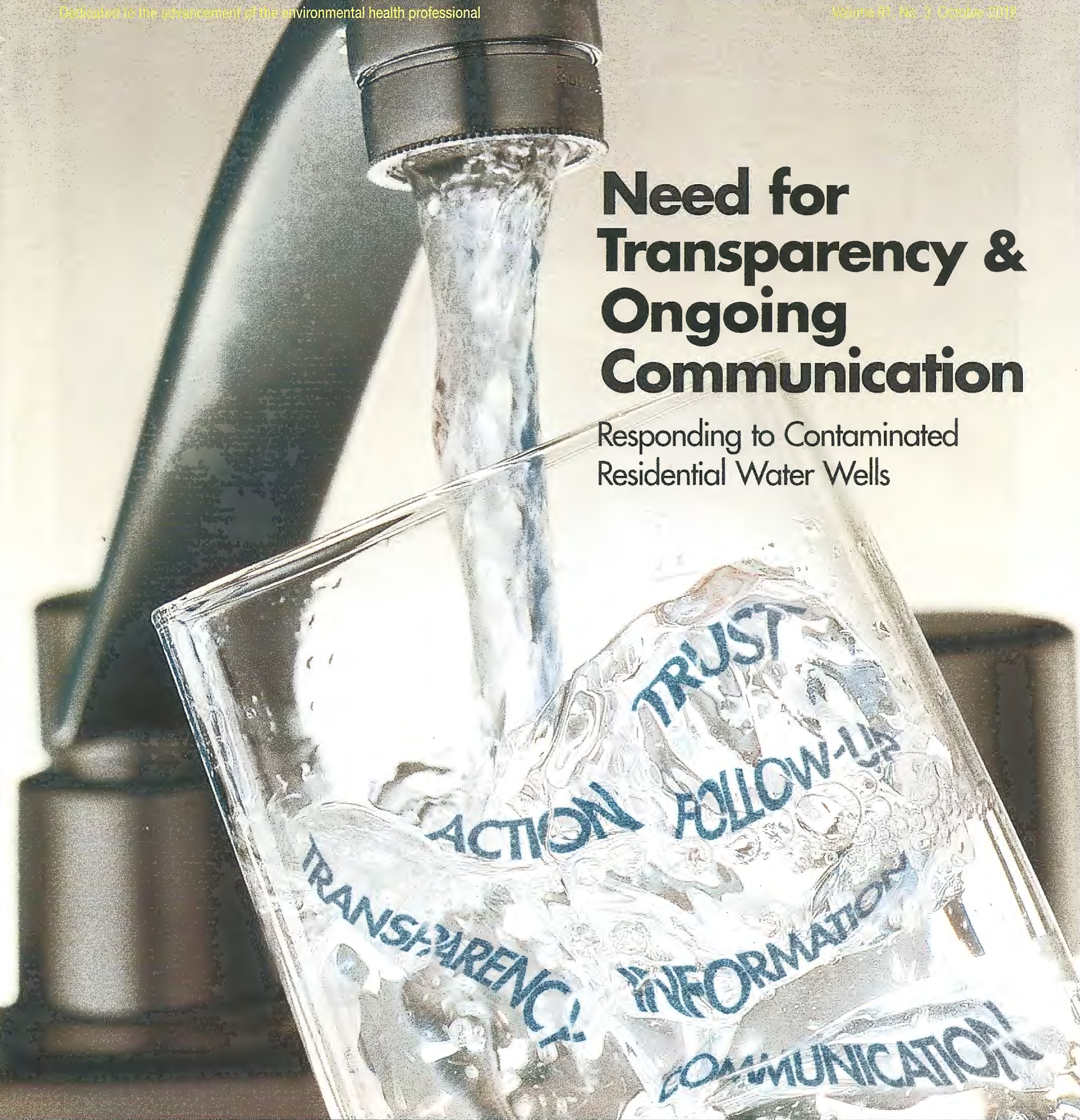

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Male–Female Differences in the Prevalence of Non-Hodgkin Lymphoma and Residential Proximity to Superfund Sites in Kentucky

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Abstract Non-Hodgkin lymphoma (NHL) is a category of cancers that arise from lymphocytes. Previous work by the authors demonstrated a significant association between residential proximity to Superfund sites in Kentucky and cumulative incidence rates of NHL. In both the U.S. and Kentucky, age-adjusted NHL rates in males consistently exceed rates in females, despite NHL often arising later in the lifespan when females outnumber males. The current investigation sought to determine whether the NHL rate difference by sex is associated with proximity to environmental toxicants. Cancer data for a period of 18 years were obtained from the Kentucky Cancer Registry. Superfund geospatial coordinate data were obtained from the U.S. Environmental Protection Agency. Cumulative incidence rates per 100,000 males and females were calculated at the 2010 U.S. Census Bureau tract level, within <5 km and 5–10 km buffer zones around Superfund sites. Ordinary least squares and geographically weighted regression analyses were conducted. Significant associations existed between residential proximity to Superfund sites and cumulative NHL incidence rates in male and female populations. At all exposures levels, incidence rates were significantly higher for males than females. Possible reasons for this male–female imbalance in outcomes are presented, along with implications for public health.

Background

Throughout much of the 20th century, the rates of non-Hodgkin lymphoma (NHL) have increased in the U.S. and other developed countries for reasons that are still not fully understood. A recent article indicated that residential exposure to U.S. Environmental Protection Agency (U.S. EPA)-designated Superfund sites was a significant risk factor for an individual's risk to develop NHL (Webber & Stone, 2017). In this article, we are reporting on the disparities in the age-adjusted prevalence rates of NHL for males and females as associated with individual residential proximity to Kentucky's Superfund sites. In Kentucky, like national and global trends, age-adjusted NHL rates in males consistently exceed rates in females (Al-Hamadani et al., 2015; Devesa & Fears, 1992; Roman & Smith, 2011), even though NHL is typically a cancer that impacts the older population where females outnumber males.

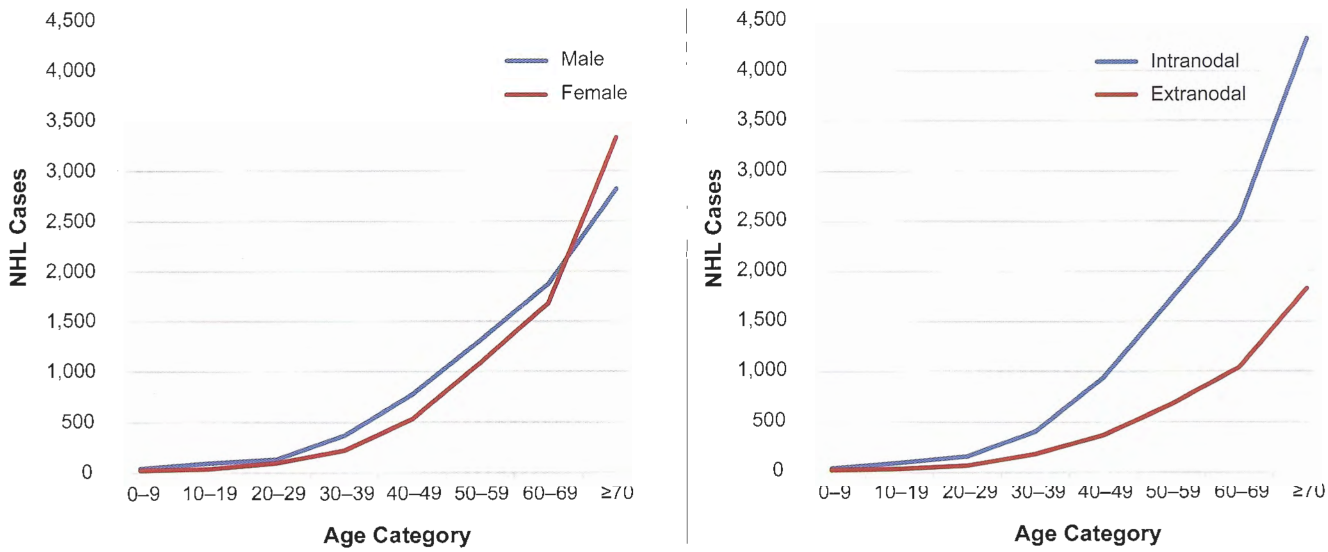
Although there are known links between autoimmune diseases and NHL (Ekström Smedby et al., 2008), and autoimmune diseases are more frequent in females (Ansell et al., 2011), males continue to experience higher rates of all types of NHL. Differences among males and females are less pronounced in regions of the world with the highest human development indices; however, those areas experience higher cases of Burkitt's lymphoma (Roman & Smith, 2011). Higher NHL rates in males are seen across all subtypes, from more common intranodal subtypes such as diffuse large B-cell lymphoma (Hedström et al., 2015), follicular lymphoma (Nabhan et al., 2016), and mantle cell lymphoma (Aschebrook-Kilfoy, Caces, Ollberding, Smith, & Chiu, 2013), to the rarest forms of extranodal NHL such as primary central nervous system lymphoma (Villano, Koshy, Shaikh, Dolecek, & McCarthy, 2011) and primary gastric lymphoma (Padhi et al., 2012).

Male–female differences were observed not only in NHL rates but also in NHL comorbid diseases. A European observational study, including 40 countries, reported that males were more likely to be diagnosed with cutaneous melanoma and NHL, whereas in females the association between NHL and melanoma was negative (Allam et al., 2015). In addition, significant associations were found between NHL and renal cell carcinoma in males, but not in females (Lossos, Ferrell, Duncan, & Lossos, 2011). Another study found that a high body mass index at age 18 is associated with a significantly higher NHL risk for females, but there was no such association observed in males (Kelly et al., 2012).

Males with certain subtypes of NHL do not appear to respond as well to the immunochemotherapeutic compound rituximab as females do (Pfreundschuh et al., 2010; Riihijärvi, Taskinen, Jerkeman, & Leppä, 2011).

FIGURE 1

Non-Hodgkin Lymphoma (NHL) Age-Adjusted Prevalence Rates by Age at Diagnosis (by Sex and SEER Type)



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

Yet, other studies showed that only female patients responded well to the chemotherapeutic compound lenalidomide (Eve et al., 2012) and that, based on a murine T-cell lymphoma model, aspirin demonstrated greater antitumor properties in females than in males (Kumar, Vishvakarma, Bharti, & Singh, 2012).

Endocrine regulation might partially explain the differences noted in the prevalence of NHL, survival rates, and differences in response to NHL treatments in males and females (Yakimchuk et al., 2011). In vivo murine models revealed that the estrogen receptor beta-agonists inhibited the proliferation, vascularization, and dissemination of lymphoid tumors (Yakimchuk et al., 2014). Reduction in serum interleukin-6 triggered by 17-beta-estradiol is another mechanism by which estrogen might lower NHL risk (Horesh & Horowitz, 2014; Rachón, Myśliwska, Suchecka-Rachoń, Wieckiewicz, & Myśliwski, 2002). Pregnancy has also been shown to be a protective factor for NHL prevalence (Horesh & Horowitz, 2014; Prescott et al., 2009), as has the use of oral contraceptives (Lee, Bracci, & Holly, 2008).

Differences among males and females in NHL prevalence and treatment response appear to indicate that efficacy of chemotherapeutics is possibly connected to unidentified and sex-specific polymorphisms in genes that code for glutathione S-transferases (Cho et al., 2010; Riihijärvi et al., 2011).

Methods

This correlational study used 1998–2012 cancer registry records, obtained in 2014 from the Kentucky Cancer Registry, for the first diagnosis of intranodal or extranodal NHL; cancer records from adjacent states were not available for analyses. The following variables were included in the analyses at the individual level: sex, race, and ethnicity; age at diagnosis; family history of NHL; county of residence; Appalachia residence; and Beale Code for the level of urbanization. Using the geographic coordinates for the patient's residential address, the census tract was identified for 82.3% of the NHL cases, while for 17.7% the residential ZIP centroid was used instead. We obtained the census tract Topologically Integrated Geographic Encoding and Referencing (TIGER) file from the 2010 U.S. Census website. With the TIGER file, we could identify the residential census tract only for 82.3% of cases; the rest (17.7%) could not be placed in a census tract, most likely because their listed address was a post office box or rural route. For those we could not place in a census tract, we had to estimate where they lived by placing their residence in the exact middle (centroid) of their ZIP code.

According to the 2010 U.S. Census, Kentucky included 1,115 census tracts. Of the 1,115, 734 tracts reported cases of NHL between 1995 and 2012. Only 145 census tracts (13%) in Kentucky had Superfund sites located within their borders and there was a maximum of 5 sites per tract. At the time of this study in 2014, the U.S. EPA website listed 133 Superfund sites located in Kentucky. The exposure risk is defined as the patient's residential proximity to Superfund sites and it was operationalized as an ordinal variable with three categories: 0 = exposure risk beyond 10 km; 1 = exposure risk within 10 km, but beyond 5 km; and 2 = exposure risk within a radius of 5 km. Thus, exposure risk is based on the distance to the nearest Superfund site.

The dependent variables in this study are the age-adjusted prevalence rates for males and females for each type of NHL cancer, extranodal or intranodal. Data were age-adjusted using the 2000 U.S. Census standard population to account for aging effects on health. We estimated the age-adjusted prevalence rates of NHL at the census tract level with the tract 2010 population in the denominator and the 1995–2012 NHL cases as the numerator, along with the 2000 U.S. standard population weighting factors. We performed spatial regression analyses for each dependent variable and the presence of spatial autocorrelation and clustering were tested with diagnostic tools. Finally, we confirmed the appropriateness of ordinary least squares (OLS) and geographically weighted regression (GWR).

Results

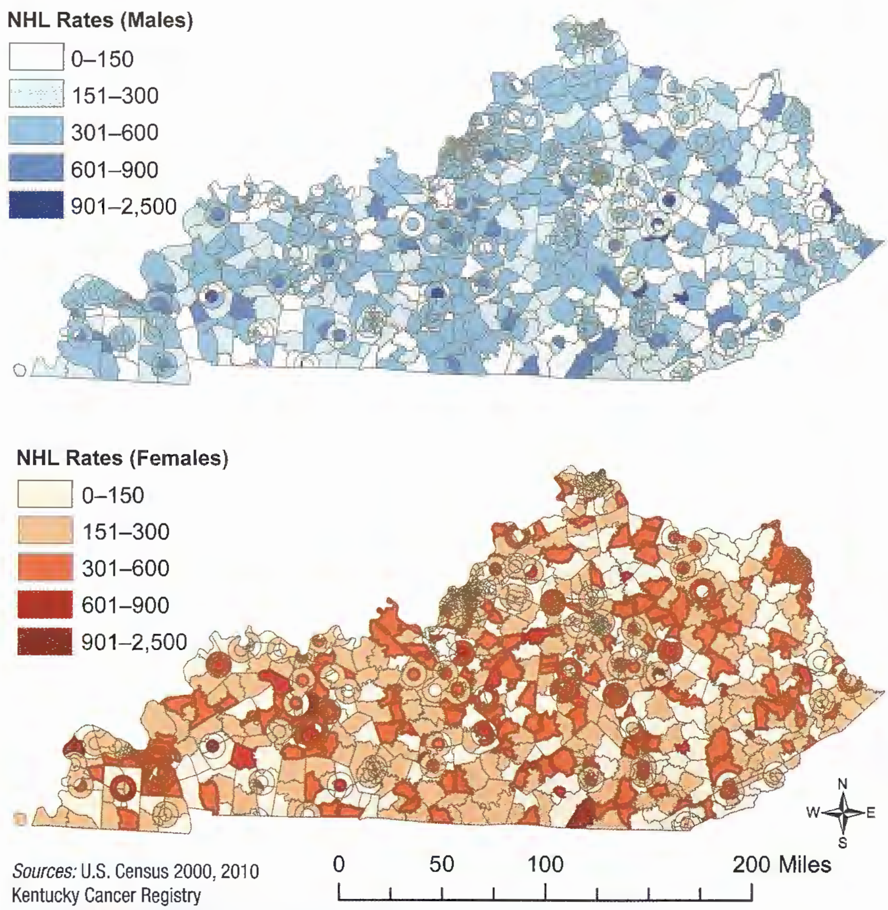
There was a total of 14,373 NHL cases in Kentucky from 1995–2012 and 70.8% were classified as intranodal NHL. The distribution of NHL cases was slightly lower in females (48.5%) than in males (51.5%), almost all patients with NHL were white (94.7%), and a majority (67.4%) of patients were ≥60 years with no known prior family history (52.2%). About one third of the patients in the records we looked at lived in the Appalachian region (28.1%); very few were residents of rural areas (9.6%). Figure 1 shows the distribution of cases by age categories separated by sex and tumor classification of intranodal and extranodal types.

As expected, an age-related increase in NHL prevalence was observed in both males and females for both nodal types. There was only a small difference across sex between ages 20 and 60, but there was a sharp increase of NHL prevalence in females who were 60–69 years. Intranodal NHL cases were consistently more than double the extranodal cases across all age groups; both cases exhibited sharp increases within the 60–69 age group.

In Figure 2, we illustrate the 1995–2012 age-adjusted prevalence rates for NHL per 100,000 males and 100,000 females by U.S. Census tracts, with 5-km and 10-km buffer zones around the 133 Superfund sites in Kentucky. Some areas—mostly around the western and central regions of Kentucky—had noticeably higher NHL prevalence rates for males while other areas had higher NHL prevalence rates for females.

FIGURE **2**

Non-Hodgkin Lymphoma (NHL) Age-Adjusted Prevalence Rates for Males and Females



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

Bivariate descriptive analyses were conducted for sex, race, residence in Appalachian regions, Beale code, family history of NHL, and primary surveillance, epidemiology, and end results (SEER) tumor type by the three categories of residential proximity to the nearest Superfund site. Results show (Table 1) that the few non-White NHL patients were more likely to live within 5 km of the Superfund sites, whereas residents of Appalachian- and Beale Code-designated rural areas were less likely to live near the sites.

Specifically, Table 1 displays the number and proportion of NHL patients by various demographic characteristics by exposure risk zone. Although data on race were missing for a large proportion of patients, among those for whom the information was available, the majority (55.4%) resided within 5 km from the Superfund sites ($p < .001$); the majority (68.6%) of the Appalachian residents resided more than 10 km away from the Superfund sites ($p < .001$); the majority of the urban residents (58%) were split between the two areas closer to the Superfund sites; and the majority (89.8%) of the rural residents resided at a distance greater than 10 km from the Superfund sites. It is noteworthy that among those with a known family history of NHL, 50.7% resided 10 km or more from the Superfund sites. The percentage of NHL cases with no family history of NHL (or without a known

TABLE **1**

Case Data by Exposure

Demographic Variable		Indicator		Residential Proximity to Superfund Site						F-Statistic	p-Value
				<5 km		5–10 km		>10 km			
		#	%	#	%	#	%	#	%		
Sex	Male	6,978	48.5	2,170	29.4	1,793	24.2	3,432	46.4	3.54	.170
	Female	7,395	51.5	2,055	29.4	1,777	25.5	3,146	45.1		
Race	White	13,617	94.7	3,826	28.1	3,400	25.0	6,391	46.9	234.04	<.001
	Non-White	756	5.3	351	55.4	133	21.0	150	23.7		
Appalachian region	No	10,337	71.9	3,459	33.5	3,070	29.7	3,808	36.8	1,198.44	<.001
	Yes	4,036	28.1	766	19.0	500	12.4	2,770	68.6		
Beale Code classification	Urban	12,997	90.4	4,157	32.0	3,497	26.9	5,343	41.1	1,186.59	<.001
	Rural	1,376	9.6	68	4.9	73	5.3	1,235	89.8		
Family history of NHL	Yes	7,495	52.2	133	25.0	130	24.4	270	50.7	9.94	<.001
	No	533	3.7	2,234	29.8	1,817	24.2	3,444	46.0		
	Unknown	6,345	44.1	1,858	29.3	1,623	25.6	2,864	45.1		
SEER type	Intranodal	10,181	70.8	2,969	29.2	2,547	25.0	4,665	45.8	1.12	.572
	Extranodal	4,192	29.2	1,256	30.0	1,023	24.4	1,913	45.6		

NHL = non-Hodgkin lymphoma; SEER = Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.

family history) was significantly higher for the cases residing within 5 km of Superfund sites. It is noteworthy that there were no significant differences in the distribution of males and females ($p = .170$) or in the distribution of NHL SEER type ($p = .572$) across the three exposure risk zones.

The results of a one-way analysis of variance (ANOVA) indicate that the average age-adjusted overall NHL prevalence rates were significantly different across the three exposure risk zones (Table 2), with rates significantly greater within 5 km than in the other two zones. In addition, ANOVA results show that the prevalence rates for individuals residing in the second zone (5 km–10 km from Superfund sites) were significantly greater than the rates in the areas beyond 10 km. For all types of prevalence rates, except for the intranodal NHL in females ($p = .064$), the differences between the "unexposed" areas—beyond 10 km—were statistically significant ($p < .05$). Specifically, the NHL prevalence rates were significantly smaller in the unexposed group (beyond 10 km) than those in the two exposure risk groups (<5 km, respectively 5–10 km). These data reflect the observed national trends, in that males have a higher prevalence rate of intranodal and extranodal NHL than females have.

Hot spot analysis was conducted to identify areas of significant high or low spatial clustering of NHL age-adjusted prevalence data using the Getis-Ord G_i^* statistic. Hot and cold spots were mapped at the 99%, 95%, and 90% confidence limit (Figure 3). The hot spots were more prominent for male cases, particularly in the western (Paducah area) and central regions of the state (metro Louisville and Hardin County). The Anselin's Local Indicators of Spatial Association (LISA) confirmed the presence of autocorrelation, clustering, and spatial outliers.

Figure 4 shows that for the sex-stratified NHL rates, there are multiple geographic areas where significant high and low clustering of NHL rate data were reported, along with areas where significant spatial outliers occurred. In other words, low-NHL local areas were more likely to be adjacent to high-NHL areas, and vice versa. The pattern was slightly different from the hot spot analysis data from Figure 3. The high clusters for male subjects remained in the western and central regions, whereas low clusters and high-low outliers were predominately located in the eastern and southern regions of Appalachia in Kentucky.

Table 3 depicts the sex-specific OLS base models (exposure risk categories) and full models (exposure risk categories, Appalachian status, and Beale Code). The OLS models explained only a small amount of the variability, as shown by the coefficients of determination ranging from 2.7–8.9%. The variance inflation coefficients were within acceptable levels, but the significant Koenker (BP) statistics for males indicated nonconsistent relationships between the dependent and independent variables (nonstationarity).

When compared with the reference areas of beyond 10 km, the NHL prevalence rate for males increased by an average of 147.4/100,000 within a 5 km buffer zone and by 59.2/100,000 in the areas between 5 km and 10 km. For females, the NHL prevalence rate was 85/100,000 greater within the 5 km buffer zone and 44.6/100,000 greater in the areas between 5 km and 10 km buffer zones when compared with the reference areas. Next, the regression model showed that as the Beale Code value increases by one unit, TABLE **2**

Age-Adjusted Non-Hodgkin Lymphoma Prevalence Rates by Proximity to Superfund Sites in Kentucky

Variable	Residential Proximity to Superfund Site Mean (*SD*)			*F*-Statistic	*p*-Value
	<5 km	5–10 km	>10 km		
Overall	457.0 (244.7)	308.6 (100.6)	290.9 (215.7)	17.8	<.001
Male	542.4 (341.2)	338.3 (113.3)	325.8 (249.5)	21.6	<.001
Female	382.9 (240.2)	285.3 (116.7)	262.4 (303.6)	5.1	.006
Intranodal	323.4 (200.2)	218.7 (73.3)	208.5 (180.6)	12.3	<.001
Extranodal	133.7 (82.8)	89.9 (49.6)	82.5 (76.6)	13.4	<.001
Intranodal (male)	384.1 (294.8)	239.7 (89.6)	235.8 (196.6)	15.8	<.001
Intranodal (female)	267.7 (215.1)	202.4 (84.6)	185.9 (281.1)	2.8	.064
Extranodal (male)	158.3 (154.3)	98.6 (60.2)	90.0 (102.1)	12.3	<.001
Extranodal (female)	115.2 (83.5)	82.8 (60.3)	76.5 (97.4)	5.0	.007

and areas become more rural, and the intranodal NHL rate increased 8.3/100,000 males and 3.6/100,000 females. Appalachian status was not significant in males or females.

To verify whether results of the standard OLS regression modeling alone would suffice or if GWR would be necessary, exploratory regression and diagnostic tests were conducted (Table 4). The Global Moran's *I* tool in ArcGIS quantifies the presence of spatial autocorrelation among residuals; it showed that there was significant spatial autocorrelation that might affect the results of the OLS models.

Using the ArcMap software, spatial regression models were developed with the exposure risk areas beyond 10 km used as the reference group for the analyses. Results from full and base models are depicted in Table 4. When the Akaike's information criterion (AIC) values were compared between each GWR model and their analogous OLS models from Table 3, the lower AIC values for the GWR models indicate a better fit for the data. Comparing the adjusted R^2 values from the OLS models, the GWR models explain a larger percentage of the variability. Adjusted R^2 values should not be used to make inferences about the proportion of variance explained by GWR models, as these values are sensitive to bandwidths used to calculate degrees of freedom (ESRI Resources, 2009). The best-fitting model is the GWR base model for male subjects, which explains approximately 24.6% of the variability in NHL prevalence rate.

Discussion

This ecological study supports the hypothesis that residential proximity to Superfund sites in Kentucky is significantly correlated with the prevalence of NHL. More specifically, the prevalence rates in males and females were significantly associated with the residential proximity to Superfund sites, even though the distribution was not statistically significant across the three exposure risk zones. The nature and pathways of exposure to potentially hazardous substances from Superfund sites in Kentucky are unknown; however, hypotheses for future research could be drawn from existing, although limited, data.

Among the 20 sites in Kentucky reported on the National Priorities List that had the highest scores in the U.S. EPA's Hazard Ranking System, the majority had one or more on-site contaminants known or suspected to increase NHL prevalence. The most commonly found contaminants in these 20 Superfund sites were benzene, lead, polychlorinated biphenyls (PCBs), cadmium, trichloroethylene, organochlorines other than PCBs, and perchloroethylene. It is important to note, however, that the type of contaminant plausibly attributable to higher rates of contracting NHL was not the focus of this article, as data on contaminants were not available for all 133 Superfund sites included in this study.

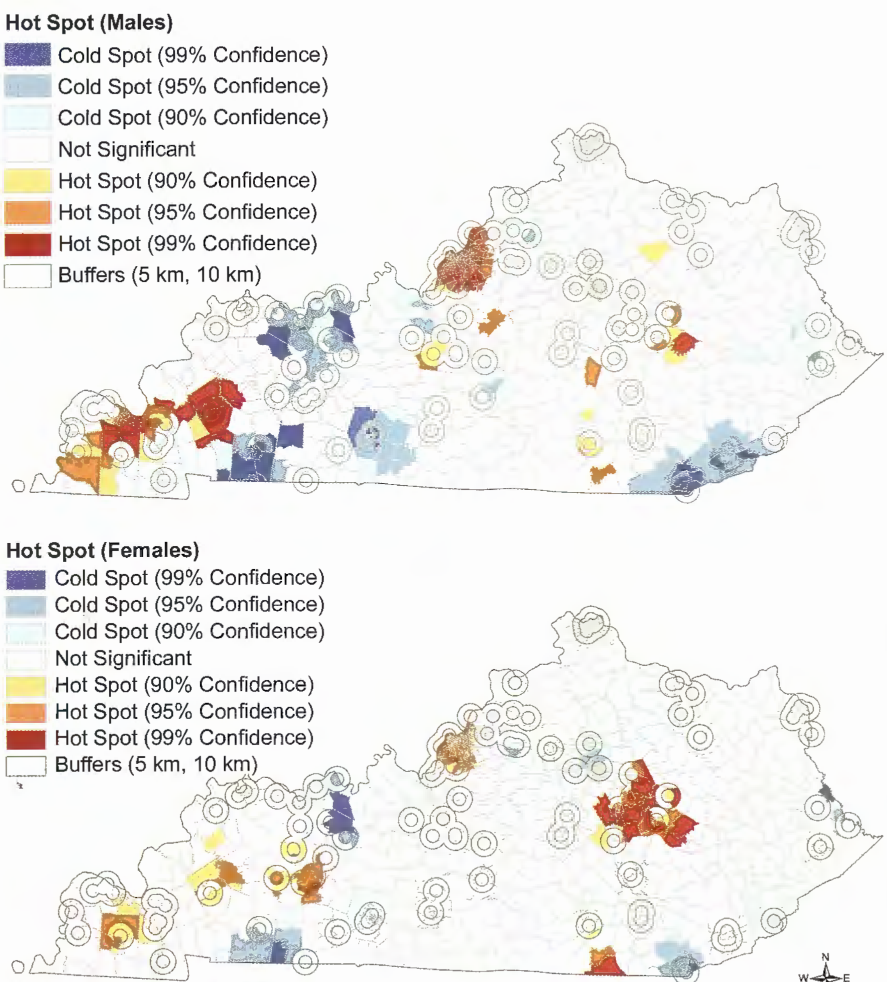
Limitations to the present work are specific to observational ecological studies. While we recognize the relationship between health and individual sociodemographic characteristics, key social determinants of health factors were not present in the cancer records made available for this research. Data on occupational history were not available; we attempted to account in our analysis for the patient's employment position at the time of diagnosis.

As the data were not collected for research purposes, it was extremely difficult to code qualitative information into meaningful categories. Indeed, it is well documented that housing in the proximity of industrial or commercial sites are lower in value than those located in more pristine areas; implicitly, lower housing values attract individuals and families with lower incomes—such as minorities and migrant populations—populations that have higher rates of chronic diseases.

The socioeconomic and demographic variables at the census tract level obtained from the 2010 U.S. Census were not significant, likely due to the confounding effect that property values are lower in the proximity of industrial sites, making them more affordable for economically disadvantaged populations. The small proportion of minorities with NHL in Kentucky was more likely to reside in closer

FIGURE 3

Hot Spot Analyses of Non-Hodgkin Lymphoma Age-Adjusted Prevalence Rates for Males and Females



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

proximity to the Superfund sites when compared with white individuals. The coefficients of determination (R^2) and standardized GWR regression residuals suggest unmeasured or missing explanatory variables contributed to NHL prevalence.

Finally, we would like to emphasize that the main purpose of our paper is to establish whether the prevalence of NHL for males and females is significantly different in residential areas that are located closer to Superfund sites than in areas located farther away. This study shows that although there was no significant difference in the sex distribution across the three exposure risk zones, there were significant differences in the prevalence of NHL for males (intranodal and extranodal) and for females (extranodal).

Conclusion

NHL age-adjusted prevalence rates in the U.S. and many other developed countries around the world increased throughout the 20th century, possibly due to greater exposures to chemicals stemming from the onset of the industrial revolution. This study reports on the significant association between residential proximity to Superfund sites and the age-adjusted prevalence rates of NHL in male and female populations residing in Kentucky, despite no differences in sex distribution across the three exposure risk zones. More specifically, this study found that the prevalence rates of intranodal and extranodal NHL are consistently higher in males than in females in all three exposure risk zones (<5 km, 5–10 km, >10 km).

In addition, the age-adjusted prevalence of intranodal and extranodal NHL in males and the age-adjusted prevalence of intranodal NHL in females were significantly greater in the proximity of the Superfund sites. Specifically, the areas within 5 km had greater prevalence rates than the areas located beyond 5 km but less than 10 km away, which had higher rates than the areas located beyond 10 km. There was no significant difference (95% confidence level) in the prevalence rate of intranodal NHL in females ($p = .064$).

These findings raise new questions regarding sex differences in susceptibility to NHL associated with exposures to environmental toxicants. Despite higher prevalence of NHL in males, the association between NHL and residential proximity to Superfund sites is significant for both males and females. Thus, public health interventions such as cancer screenings should target the entire population living near an environmentally hazardous site. There is continuing need to improve the public knowledge and awareness of NHL, screening and early detection for NHL, and to continue to elaborate on existing research and advocacy, as rates of NHL are likely to increase with the aging population.

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FIGURE **4**

Anselin's Local Indicators of Spatial Association (LISA) of on-Hodgkin Lymphoma Age-Adjusted Prevalence Rates for Males and Females

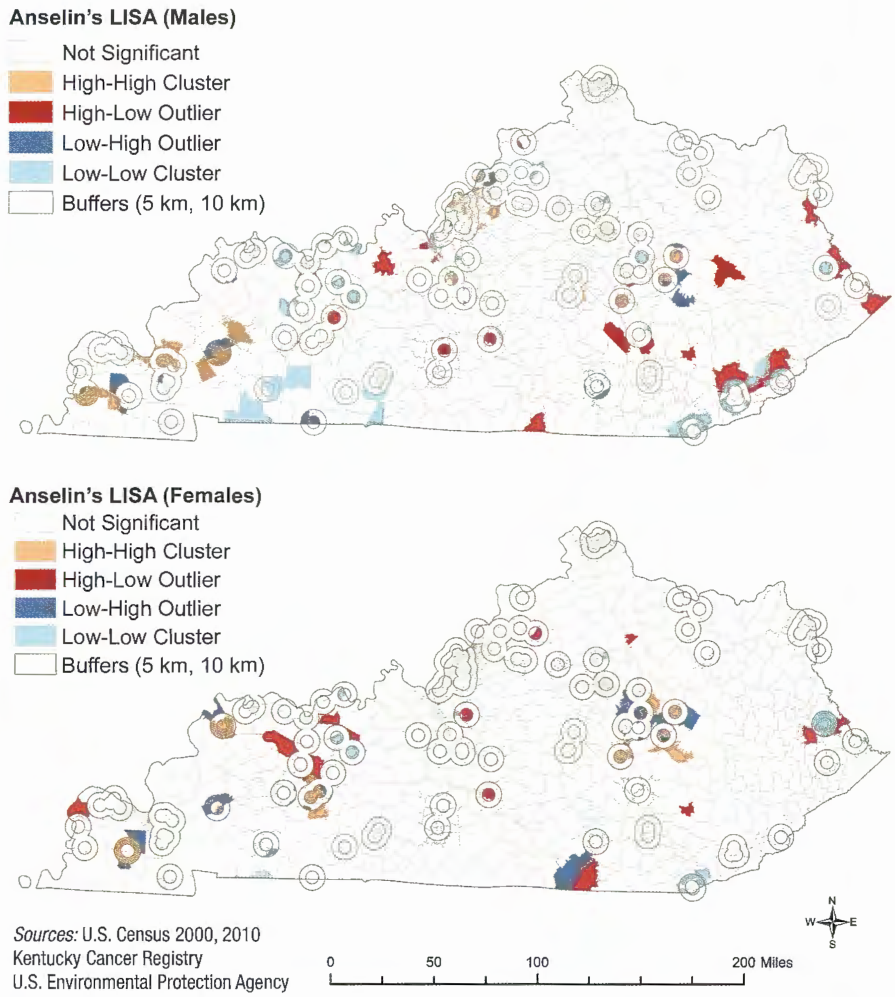

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TABLE 3

Predicting Age-Adjusted Prevalence Rates For Males and Females: Ordinary Least Squares Regression Coefficients

Model	Variable	Coefficient	*SE*	Probability	Wald (Pr > χ^2)	Koenker (BP) Statistic (Pr > χ^2)	Akaike's Information Criterion	Adjusted R^2
Male cases	Intercept Exposure <5 km Exposure 5–10 km	292.56 147.43 59.19	9.70 13.01 10.36	<.001 <.001 <.001	137.81*	29.59*	25,825.84	8.2%
	Intercept Appalachian region Beale Code classification Exposure <5 km Exposure 5–10 km	269.53 -23.89 8.28 157.92 65.03	11.61 14.36 2.38 14.17 10.52	<.001 .10 <.001 <.001 <.001	141.04*	47.17*	25,814.09	8.9%
Female cases	Intercept Exposure <5 km Exposure 5–10 km	235.61 85.05 44.61	11.30 13.10 11.80	<.001 <.001 <.001	50.01*	4.20	25,938.92	2.7%
	Intercept Appalachian region Beale Code classification Exposure <5 km Exposure 5–10 km	215.19 16.51 3.56 94.96 51.42	13.13 18.60 2.49 13.91 11.80	<.001 .38 .15 <.001 <.001	66.92*	7.25	25,933.66	3.0%

*$p < .001$.
Pr = Poisson regression.

TABLE 4

Geographically Weighted Regression Modeling Results

Model	Variable	# of Neighbors	Sigma	Akaike's Information Criterion	Moran's *I*	R^2
Male cases	Exposure <5 km Exposure 5–10 km	241	185.75	25,569.11		24.6%
	Appalachian region Beale Code classification Exposure <5 km Exposure 5–10 km	834	194.50	25,720.15	.039*	15.2%
Female cases	Exposure <5 km Exposure 5–10 km	241	196.84	25,791.99		15.4%
	Appalachian region Beale Code classification Exposure <5 km Exposure 5–10 km	836	204.10	25,905.25	.022*	6.6%

*$p < .001$.

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