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Residence proximity to benzene release sites is associated with increased incidence of non-Hodgkin lymphoma

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Abstract

Background—Increased risk of Non Hodgkin Lymphoma (NHL) has been observed in persons occupationally exposed to benzene, but the risk among persons living near benzene release sites has not been well described.

Methods—To investigate the spatial patterns of NHL incidence and the association between NHL incidence and distance to benzene release sites, we linked and geocoded data on benzene release sites in Georgia 1988–1998 from the Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI), census tract level population statistics, and NHL incidence from the Georgia Comprehensive Cancer Registry (GCCR) 1999–2008. We mapped standardized incidence ratios by census tract and performed Poisson regression on NHL and NHL subtype incidence data, using the mean distance between the tract centroids and release sites as a marker of exposure. Cluster analyses were conducted at the global, local, and focal levels.

Results—Poisson regression indicated that for every mile the average distance to benzene release sites increased, there was an expected 0.31% decrease in the risk of NHL. Similar results were observed for all NHL subtypes analyzed. Clusters of NHL were spatially associated with benzene release sites located in metropolitan areas, but not with release sites in other areas of the state.

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Conclusions—NHL incidence is significantly higher in census tracts which are closer, on average, to benzene release sites. Additional studies are needed to examine spatial patterns of NHL incidence in other geographic regions and interactions between benzene and other exposures.

Keywords

Lymphoma; Non-Hodgkin; Geographic Information Systems; Benzene; Surveillance

INTRODUCTION

Since the 1970s, the incidence of non-Hodgkin lymphoma (NHL) has increased by 3–4% annually [1] driven by: modifications of the lymphoma classification system, improved techniques for diagnosis and reporting hematological malignancies, and the human immunodeficiency virus (HIV) epidemic. However, these factors account for approximately 50% of the additional cases of NHL [2, 3]. The rise of NHL cases also appears to trail expanded industrial production in the U.S., suggesting occupational chemical exposures are risk factors for NHL [4].

Among carcinogenic occupational chemicals, benzene has been consistently linked to hematological cancers [5]. Numerous studies in human populations support a link between occupational benzene exposure and NHL, although some controversy remains [6–8]. Biologically, benzene exposure produces chromosomal aberrations and genetic changes, and toxic effects of benzene exposure can occur at air levels of 1 ppm or less, suggesting that even low levels of benzene exposure can be harmful [9]. Additional research is necessary to investigate associations between benzene exposure and NHL in residential settings since urban and rural populations are exposed to benzene through release into ambient air and surface waters. The purpose of this study was to examine the relationships between the incidence of NHL at the census tract level and benzene release sites to determine whether NHL incidence varies with distance from these sites.

MATERIALS AND METHODS

We linked and geocoded data on benzene release sites in Georgia 1988–1998 from the Environmental Protection Agency's (EPA) Toxics Release Inventory (TRI), NHL incidence from the Georgia Comprehensive Cancer Registry (GCCR) 1999–2008, and population and demographic data from the 2000 U.S. Census. This study was approved by the Emory University Institutional Review Board, the Winship Cancer Institute Clinical Research Committee, and the Georgia Department of Public Health Institutional Review Board. Because individual patients were not contacted and unmasked data were handled according to Health Insurance Portability and Accountability Act of 1996 privacy standards, individual informed consent was not required for this study.

Benzene Release Site Data

The EPA requires that facilities meeting thresholds defined by Section 313 of Emergency Planning and Community Right-to-Know Act annually report their disposal or releases for listed toxic chemicals. Launched in 1987, the TRI captures release information about certain

chemicals, including the quantities, media type, and geographic coordinates of the releases from sources such as manufacturing facilities, service business, and federal facilities [10]. Between 1988 and 1998, 19 facilities in Georgia reported benzene releases. Total releases, calculated as the sum of fugitive air releases, stack air releases, and surface water discharges between 1988 and 1998 for each site ranged from 52 to 3,830,097 pounds of benzene. Some release sites reported releases for only one year while others reported benzene releases for multiple years during this period.

Census Tract Population and Demographic Data

Census tracts are subdivisions of counties with an average population of 4,000 persons. At the time of the 2000 census, there were 1,618 census tracts within the state of Georgia. Population and demographic data were available for 1,616 of these tracts, and data on sex, age, and race were obtained from Summary File 1 [11]. Because accurate yearly population values were not available for each census tract, we used 2000 census data and census tract boundaries to geocoded GCCR data and calculate standardized incidence ratios (SIRs) for each census tract. We used census data on median year moved into residence (MYMI) derived from a sample of individuals residing within a census tract, to provide information on the length of time residents were in their current home and on their residential exposure to benzene release sites.

Non-Hodgkin Lymphoma Data

GCCR provided data for all 12,716 incident NHL cases among adults 20 years residing in Georgia at the time of diagnosis, for the period 1999–2008. We have previously examined similar population-level incidence data for NHL and Hodgkin lymphoma subtypes in the United States [12–16]. In order to standardize the NHL incidence rates from Georgia to national NHL incidence rates, SEER*Stat Version 7.05 (National Cancer Institute, Bethesda, MD) was used to access the SEER 13 Registries Database [17]. Age-sex-race-specific crude incidence rates were obtained for the period from 1999–2008 for NHL and NHL subtypes in order to standardize Georgia incidence data by age, sex, and race. Incident cases were separated into B-cell NHL (NHL-B), T-cell NHL (NHL-T), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL) using ICD-O-3 codes based on the proposed WHO-based nested classification of malignant lymphoid neoplasms for epidemiologic research from InterLymph [18]. Cases without age, sex, or race information were excluded from all analyses. We used four major race categories (White, Black, American Indian/Alaskan Native, and Asian or Pacific Islander); cases whose race was categorized as “other” or “unknown” were excluded. Cases that were geocoded successfully were aggregated to the census tract level [19]. SIRs were calculated for each census tract by dividing the number of observed cases by expected cases.

Geographic Data and Spatial Analyses

We utilized GIS data through ArcGIS 10 (ESRI, Redlands, CA) to examine the spatial distribution of benzene release sites and SIRs by census tract. Census tract shapefiles were obtained from the U.S. Census Bureau's 2000 TIGER/Line files [20]. GIS was used to calculate the distances between the 1,616 census tract centroids to each of the 19 benzene release sites. Descriptive spatial analysis was performed using ArcGIS. Choropleth maps

were created to depict the NHL and NHL subtype SIRs by census tract. Locations of benzene release sites were overlaid upon the SIR maps. Since sparse data can pose statistical problems in small area analyses, spatial smoothing was performed to allow census tracts to borrow strength from spatial neighbors and produce more stable estimates of SIRs while maintaining geographic precision. Spatial Empirical Bayes (SEB) smoothing was performed on the SIR values using GeoDa 1.01 (Luc Anselin, Tempe, AZ) [21]. We defined neighbors as census tracts with common borders or vertices and constructed choropleth maps of smoothed SIRs for NHL and NHL subtypes.

To assess spatial correlation of SIRs, we conducted global, local, and focal spatial analyses. A global measure of spatial autocorrelation, the global Moran's I, was calculated for SIR patterns of NHL and NHL subtypes using GeoDa. It is important to note that smoothing will induce additional spatial correlation, thus we expected to see higher and more statistically significant Moran's I values for the SEB-smoothed SIRs. To measure spatial autocorrelation at the local scale, a local Moran's I, also termed Local Indicators of Spatial Autocorrelation (LISA) [21], was calculated for SIR patterns of NHL and NHL subtypes using GeoDa. LISA cluster maps were created to identify the locations of any significant clusters of SIRs. Both the global and local spatial statistics based significance on 999 Monte Carlo simulations, with neighbors defined by shared boundaries and vertices [21].

We used indirectly standardized incidence rates to test for focal clustering, calculated by multiplying the crude incidence rate by the non-smoothed SIR, to test the hypothesis that there was no spatial clustering near the benzene release sites (the focus). The Lawson-Waller Score test was used to individually assess each of the 19 benzene release sites for focal clustering of NHL [21]. Each census tract was scored for the difference between the observed and expected counts of NHL, weighted by inverse distance from each census tract centroid to the focus [21]. The standard normal distribution was used to estimate upper-tail p-values in ClusterSeer 2.3 (BioMedware, Ann Arbor, MI). Because the Lawson-Waller test was conducted 19 times (once for each release site), we adjusted our significance level using the Bonferroni correction method [22].

Poisson regression models were constructed under the assumption that the number of observed incident cases for each census tract had a Poisson distribution that was dependent on the number of expected cases for that census tract, based on its age, sex, and race demographics, and the explanatory variable of mean distance from benzene release site. Median year moved into residence was also assessed as a potential confounder and/or effect modifier. The models were estimated using the maximum likelihood method. Models were fitted for each subtype of NHL, in addition to the total NHL cases model using SAS Version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Of the 12,716 incident cases of NHL in our original dataset, 11,355 cases were successfully geocoded to the census tract level. Among these, 11,323 had age, sex, and race information available and could be classified into the U.S. census race categories of "white," "black," "American Indian/Alaskan Native," or "Asian or Pacific Islander." We mapped SIRs and

SEB-smoothed SIRs for NHL, NHL-B, NHL-T, DLBCL, and FL with location data for each benzene release site (Figure 1). Two census tracts were not included due to a lack of demographic data from the U.S. Census Bureau. Fourteen of the nineteen benzene release sites were in the greater metropolitan Atlanta area.

Spatial Analyses

The global Moran's I values were greater than 0 and significant at the $\alpha=0.05$ level for the NHL, NHL-B, NHL-T, and DLBCL raw SIRs demonstrating positive spatial autocorrelation (Table 2). This indicates that census tracts with similar incidence rates (high or low) were clustered. When spatial smoothing was performed to allow census tracts to borrow strength from spatial neighbors, there was significant positive spatial autocorrelation for the SEB-smoothed SIRs for NHL and all subtypes, which was expected due to the smoothing process inducing additional spatial correlation. LISA cluster maps of SEB-smoothed SIRs (Figure 2) show the locations of “hot-spots” (high-high clusters) and “cold-spots” (low-low clusters). High-high areas indicate significant clustering of census tracts with high SIR values surrounded by tracts that also have high SIR values while low-low areas indicate significant clustering of census tracts with low SIR values surrounded by tracts that also have low SIR values. Low-high areas indicate census tracts with low SIR values surrounded by tracts with high SIR values, and high-low areas indicate census tracts with high SIR values surrounded by tracts with low SIR values. Clustering of high SIRs appears to be located in the metro-Atlanta area for NHL and NHL subtypes, while clustering of low SIRs appears to be mostly in the southern region of the state.

For 15 of the 19 benzene release sites, the Lawson-Waller test was statistically significant at the $\alpha=0.0026$ level (using Bonferroni's correction for 19 comparisons, Table 4). All benzene release sites located within the metro-Atlanta area had significant focal clustering, with greater incidence rates observed near these sites than expected. Incidence rates were lower than expected surrounding sites 6, 8, 9, and 10. Only one benzene release site associated with increased NHL incidence was located outside of the metropolitan Atlanta area; this site was located near Savannah, GA. No statistically significant Poisson coefficients emerged for the interaction term between mean distance to benzene release site and median year moved into residence (MYMI), so this variable was dropped. Additionally, comparing models with and without MYMI suggested that it was not a confounder. A 0.31% decrease in NHL risk is expected for every mile the average distance to benzene release sites increases. Results of the Poisson regression analyses are displayed in Table 3.

DISCUSSION

We examined residential proximity to benzene release sites and risk of NHL in Georgia using census tract level data. Our Poisson regression results suggest an approximate 0.3% decrease in NHL risk is expected for a given population in a census tract when increasing the average distance to a benzene release site by 1 mile. Among NHL subtypes, mean distance had the least effect on FL incidence, but cases were still significantly more likely to occur in census tracts that were closer, on average, to benzene release sites. It is unclear as to why the effect was weakest on FL incidence, but recent research on FL suggests that

genetics and lifestyle are more predictive of FL than environmental factors, and that these genetic and lifestyle risk factors are more associated with FL than other NHL subtypes [23, 24]. While the overall incidence of NHL in Georgia is low (17.4 per 100,000 individuals per year), NHL was significantly higher in tracts that were closer to benzene release sites. Cluster analyses identified several hot spots and cold spots for NHL and NHL subtypes throughout the state. The metropolitan Atlanta area was almost always identified as a hot spot, while other urban areas, namely Augusta and Savannah, were sometimes implicated. Cold spots were most often located in the southern half of the state. A test of focal clustering identified significantly increased NHL incidence surrounding 15 of the 19 benzene release sites. These results suggest that focal clustering is present around benzene release sites located in the metropolitan Atlanta, but this phenomenon was not observed in other areas of the state. An alternative hypothesis that could explain the results observed from our cluster analyses is that populations living in urban areas are exposed to some unmeasured factor or an unaccounted for confounder. Other sources of benzene exposure associated with urban areas include mainstream smoke from cigarettes and auto exhaust [25]. However, neither of these have been consistently associated with an increased risk of NHL [26]. Additionally, pesticides, which have also been associated with increased risk of NHL, would more commonly be found in rural areas [27].

Strengths of this study include the use of publicly available data from EPA and the U.S. Census Bureau. Spatial smoothing of NHL incidence data addressed differences in census tract population size that could result in variance instability and spurious outliers. By standardizing the data indirectly, we eliminated the effects of age, sex, and race on NHL incidence. Our study is the first to examine the relationship between passive benzene exposure and the incidence of NHL at the state population level. One limitation of this study is the use of aggregated data, as our findings may not hold true at the individual level. Furthermore, the presence of chemical releases into the environment is not sufficient to determine personal exposure, or to calculate potential risks to human health.

A potential weakness of this study was the lack of quantitative exposures and temporal analyses. A nationwide study revealed that amounts of benzene emissions may be as much as five times higher than reported by the TRI [28]. Thus, while data on the amounts of benzene released from facilities in Georgia between 1988 and 1998 were available, these were not incorporated into the models due to concerns about reliability. However, we attempted to control for time and latency by only including benzene release sites from 1988 to 1998 and using incidence and population data from 1999 to 2008, as well as assessing MYMI as a potential confounder and effect modifier. The average value for MYMI for all census tracts used in this investigation was 1989, which is during the period for potential benzene exposure (1988–1998) and allows for a theoretical period of ten years to develop NHL as our incidence data was for the years 1999–2008. Changes in the population of Georgia between 1999 and 2008 and the use of 2000 U.S. Census data as denominators for incidence rates also may have introduced bias to this study. In addition, any unmeasured confounding variables could have been spatially correlated which could have biased our Poisson regression coefficients.

Associations between exposure to benzene and hematological effects were observed as early as the 1940s[8]. In a 35-year cohort study of rubber workers from this time period, significant decreases in white and red blood cell counts were observed among workers exposed to benzene. More recent occupational studies have shown similar associations [5,7]. In China, workers exposed to benzene for 10 or more years were 4.2 (95% CI = 1.1–15.9) times more likely to develop NHL [6]. Development of NHL has been most strongly linked to benzene exposures that occurred > 10 years before diagnosis, suggesting that benzene-related NHL may be associated with longer induction periods. Often, it is difficult to discern the specific role benzene plays in the elevation of NHL risk, because workers exposed to benzene in an occupational setting tend to be exposed to other potential carcinogens. In a systematic review of 43 case-control studies by Smith et al. that analyzed occupational benzene exposure and risk of NHL, 40 studies (93%) indicated an increase in NHL risk, and 23 studies (53%) demonstrated statistically significant associations between NHL risk and benzene exposure [29]. Additional meta-analyses have been supportive of this finding [30], while other meta-analyses have reached different conclusions [31]. For example, a recent meta-analysis by Kane and Newton found no effect of occupational benzene exposure on NHL risk, regardless of the amount or duration of benzene exposure [32]. One explanation for differences in these findings is that NHL represents a heterogeneous group of diseases and benzene exposure may be more strongly associated with some variants than others [30]. The Kane and Newton meta-analysis showed no association between occupational benzene exposure and NHL, DLBCL, and FL, whereas our study showed associations between passive benzene exposure and NHL and NHL subtypes. The latency period before NHL development also may explain why some studies failed to observe an association with NHL. Future studies can examine temporal relationships between passive benzene exposure and incidence of NHL.

Our study contributes to a growing body of literature that has identified the association between NHL and organic solvents such as benzene. Previous studies of non-occupational exposure and NHL have been limited by their reliance on subject recall [33], whereas more recent studies have used geographic approximations such as zip code or municipality centroids to conduct their analyses [34–36]. Johnson et al found an increased risk of NHL in individuals living in proximity to copper smelters and sulfite pulp mills, while Ramis et al. found an association between NHL and proximity to paper industries. Another study found an increased risk of NHL in subjects living in wards surrounding a municipal solid waste incinerator that was known to exude dioxins [37].

A recent study by Wheeler et al. used case residential histories to examine spatio-temporal clustering of NHL in Iowa, Los Angeles, Detroit, and Seattle. Despite adjusting for PCB exposure and genetic polymorphisms (known risk factors for developing NHL), spatio-temporal clusters of high NHL incidence remained unexplained [38]. Other studies have found associations between NHL and proximity to petroleum refineries and toxic industrial waste sites [39, 40]. De Roos et al. conducted a case control study of industrial facilities and NHL in 2010 that utilized geographic positioning systems to identify the exact coordinates of residence for 99% of their 1548 participants [4]. Their study was unique in its ability to determine risk estimates for individual NHL subtypes and to assess trend with increasing proximity to various industrial facilities. Although they did not study benzene exposure

specifically, their study found that subjects living within 2 miles of petroleum refineries (which are known to contain benzene) for more than 10 years had a 90% increased risk of NHL (OR 1.9, 95% CI: 1.0–3.6, p-trend = 0.04). Continued improvements in the GIS analysis techniques employed to study the associations between benzene and NHL will contribute to an improved understanding of NHL etiology.

This study identified a significant association between distance to benzene release sites and NHL incidence at the census tract level. Future studies should examine this association using individual-level geographic data, temporal trends, and dose-response relationships between benzene exposure and NHL. Additional future directions for this research will evaluate other potential sources of benzene exposure, other environmental exposures, and genetic and clinical factors that may explain the higher incidence of NHL observed in certain areas. These studies investigating the etiology of NHL are critical to identify and enact public health policies that may decrease or prevent NHL.

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Figure 1.

In these standardized incidence ratio (SIR) maps of non-Hodgkin lymphoma (NHL) among adults in Georgia from 1999 to 2008, blue represents an SIR of 0.00 to 0.50, green represents an SIR of 0.51 to 1.00, yellow represents an SIR from 1.01 to 1.25, orange represents an SIR from 1.26 to 2.00, and red represents an SIR >2.00. Maps show (a) SIRs for NHL, (b) spatial empirical Bayes-smoothed SIRs for NHL, (c) SIRs for B-cell NHL (NHL-B), (d) SIRs for T-cell NHL (NHL-T), (e) SIRs for diffuse large B-cell lymphoma (DLBCL), and (f) SIRs for follicular lymphoma (FL).

Figure 2.

Local Indicators of Spatial Autocorrelation cluster maps of spatial empirical Bayes-smoothed standardized incidence ratios show (a) non-Hodgkin lymphoma (NHL), (b) B-cell NHL (NHL-B), (c) T-cell NHL (NHL-T), (d) diffuse large B-cell lymphoma (DLBCL), and (e) follicular lymphoma (FL).

Table 1

Study population demographics

Variable	<u>Cases, N = 11,323^a</u>		<u>Georgia Population, N = 5,582,707^b</u>	
	No.	%	No.	%
Age group, y				
20–59	4585	40.5	4,521,891	81.0
60	6738	59.5	1,060,816	19.0
Sex				
Women	5274	46.6	2,907,559	52.1
Men	6049	53.4	2,675,148	47.9
Race				
White	8991	79.4	3,922,068	70.3
Black	2208	19.5	1,521,316	27.3
American Indian/Alaskan	4	0.0	15,326	0.3
Native				
Asian or Pacific Islander	120	1.1	123,997	2.2
NHL subtype				
B-cell NHL	8925	78.8		
Diffuse large B-cell lymphoma	3851	34.0		
Follicular lymphoma	2171	19.2		
T-cell NHL	1489	13.2		
Median year moved into residence			1989	
Mean distance from benzene release sites: Mean±SD, miles			99.5±55.2	

Abbreviations: NHL, non-Hodgkin lymphoma; SD: standard deviation.

^aTotal number of NHL cases in Georgia from 1999 to 2008.

^bThis population was based on 1616 census tracts in Georgia from the 2000 US Census.

Table 2

Global measures of spatial autocorrelation

Measure	NHL	NHL-B	NHL-T	DLBCL	FL
Nonsmoothed SIR					
Moran I	0.2009	0.0628	0.0430	0.0179	−0.0011
<i>P</i>	.0010	.0010	.0020	.1090	.5150
SEB-smoothed SIR					
Moran I	0.8317	0.6377	0.5879	0.6403	0.5938
<i>P</i>	.0010	.0010	.0010	.0010	.0010

Abbreviations: DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; NHL-B, B-cell non-Hodgkin lymphoma; NHL-T, T-cell non-Hodgkin lymphoma; SEB, Spatial Empirical Bayes; SIR, standardized incidence ratio.

Table 3

Lawson-Waller Score Test for Focal Clustering

Benzene Site		Score	<i>P</i>
1.	Metropolitan Atlanta	13.1831	<.0001 ^a
2.	Metropolitan Atlanta	18.0533	<.0001 ^a
3.	Metropolitan Atlanta	36.3879	<.0001 ^a
4.	Metropolitan Atlanta	14.9471	<.0001 ^a
5.	Metropolitan Atlanta	15.6043	<.0001 ^a
6.	Homerville	-23.6137	1.0000
7.	Metropolitan Atlanta	15.8019	<.0001 ^a
8.	Macon	-3.8011	.9999
9.	Columbus	-3.4838	.9999
10.	Augusta	-6.7270	1.0000
11.	Metropolitan Atlanta	26.9324	<.0001 ^a
12.	Metropolitan Atlanta	20.8564	<.0001 ^a
13.	Metropolitan Atlanta	14.9068	<.0001 ^a
14.	Metropolitan Atlanta	15.6043	<.0001 ^a
15.	Metropolitan Atlanta	15.0695	<.0001 ^a
16.	Savannah	9.2829	<.0001 ^a
17.	Metropolitan Atlanta	29.9130	<.0001 ^a
18.	Metropolitan Atlanta	37.9698	<.0001 ^a
19.	Metropolitan Atlanta	18.4694	<.0001 ^a

^aThese *p* values are significant at $\alpha = .0026$ (Bonferroni correction for multiple comparisons).

Table 4

Poisson regression results

Variable	Model 1: NHL	Model 2: NHL-B	Model 3: NHL-T	Model 4: DLBCL	Model 5: FL
Intercept	0.1407	0.3453	0.0762	2.4831	0.1460
Explanatory variables					
Mean distance from benzene release site					
β	-0.0031	-0.0035	-0.0032	-0.0032	-0.0020
Standard error	0.0002	0.0002	0.0006	0.0004	0.0003
Wald chi-square statistic	227.27	223.85	31.25	80.09	55.72
<i>P</i>	< .0001	< .0001	< .0001	< .0001	< .0001
Model fit					
Deviance, df = 1614	2599.96	2913.62	1843.55	2118.79	8964.21
Deviance/df	1.61	1.81	1.14	1.31	5.55

Abbreviations: df, degrees of freedom; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; NHL-B, B-cell non-Hodgkin lymphoma; NHL-T, T-cell non-Hodgkin lymphoma.