Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2020 October ; 20(10): 668–676.e5. doi:10.1016/j.clml.2020.05.010.

The influence of rurality, race and ethnicity on non-Hodgkin lymphoma incidence

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Abstract

Introduction—Exposure to lymphomagens vary by geography. The extent to which these contribute to racial and ethnic disparities in non-Hodgkin lymphoma (NHL) incidence is not well understood. We sought to evaluate the association between urban-rural status and racial and ethnic disparities in the three major NHL subtypes - diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL).

Materials and Methods—We used data on NHL incidence from 21 Surveillance, Epidemiology, and End Results (SEER) population-based registries for the period 2000 to 2016. Population characteristics were compared by NHL subtype and urban-rural status, using rural-urban continuum codes from the U.S. Department of Agriculture. Incidence rate ratios were calculated, and Poisson regression was used to assess the association between incidence and rurality.

Results—A total of 136,197 DLBCL, 70,882 FL, and 120,319 CLL incident cases aged ≥ 20 years were reported. The majority of DLBCL patients were non-Hispanic White (73.6%), with 11.8% Hispanic and 7.3% non-Hispanic Black, with a similar distribution observed in FL and CLL. Adjusting for age, sex, and family poverty, we found increased DLBCL incidence among Hispanics in increasingly urban areas compared to rural areas (rural IRR=1.00; nonmetropolitan urban IRR=1.32, 95% CI 1.16, 1.51; metropolitan urban=1.55, 95% CI 1.36, 1.76). Among non-Hispanic Blacks, urban areas, relative to rural areas, were associated with increased CLL incidence (IRR=1.48; 95% CI 1.27, 1.72).

Conclusion—Urban-rural incidence patterns suggest that environmental exposures in urban areas associated with DLBCL and CLL pathogenesis may disproportionately affect Hispanics and non-Hispanic Blacks.

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Conflicts of interest: The authors report no conflicts of interest.

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MicroAbstract

Urban-rural incidence patterns may help clarify underlying racial and ethnic disparities in NHL incidence. In our large study using national SEER data, we found that urban status was associated with increased incidence of diffuse large B-cell lymphoma in Hispanics and chronic lymphocytic leukemia in non-Hispanic Blacks, suggesting a potential differential NHL risk among diverse, urban populations.

Keywords

Diffuse large-B cell lymphoma; Chronic lymphocytic leukemia; Non-Hodgkin lymphoma; Racial disparities; Urban-rural disparities

Introduction

Non-Hodgkin lymphoma is the seventh most common cancer among adults, with an estimated 85,720 incident cases in the United States in 2020 [1]. The three major subtypes, which make up approximately 75 percent of incident cases, are diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukemia (CLL) [2].

Racial and ethnic differences have been found in NHL incidence. Non-Hispanic Whites tend to have higher incidence of DLBCL, FL, and CLL than non-Hispanic Blacks and Hispanics [3]. Non-Hispanic Blacks and Hispanics diagnosed with FL and DLBCL, however, tend to present at an earlier age than non-Hispanic Whites [4–6]. Several potential causes have been proposed to explain these racial disparities in NHL incidence, including differences in environmental exposures, socioeconomic status and lack of access to care [7].

Occupational and environmental exposure to trichloroethylene (TCE) and benzene have been implicated as potential risk factors for hematologic malignancies [8, 9]. Large cohort studies in urban South Asian populations have found an association between occupational exposure levels and increased NHL risk [10]. To date, some of the most robust findings with respect to the role of environmental exposure on subtype-specific disease risk, suggesting a diverse disease etiology, are from the large-scale International Lymphoma Epidemiology Consortium (InterLymph), which consists of 17,471 cases and 23,096 controls [11, 12]. For example, field crop and vegetable farmers, as well as hairdressers have been found to be at increased risk of both DLBCL and CLL [13, 14]. Individuals who worked as spray painters were found to have an increased risk of FL [15]. Within the United States, recent research suggests an association between ambient benzene exposure and risk of follicular lymphoma and other hematologic malignancies among men [16]. Data also suggest disproportionate exposure to benzene among Hispanics, non-Hispanic Blacks, and low income populations in Tampa, Florida [17], with suggestion of similar disparities nationally [18]. Given increased risk of exposure to environmental lymphomagens in urban areas, there may be an increased risk of NHL among these populations, as well.

Recent studies have found lower incidence rates of NHL in rural and nonmetropolitan urban populations, compared to metropolitan populations [19–21]; however, the underlying cause of urban-rural differences in NHL incidence is not yet well understood. To the best of our knowledge, no studies have investigated urban-rural differences in ethnic and racial incidence of NHL. To explore the role of urban status in racial and ethnic disparities, we used national incidence data to investigate the association between rurality and the known racial and ethnic differences in DLBCL, FL, and CLL incidence.

Materials and Methods

Data Source & Population

Incidence data for the years 2000 to 2016 inclusive were obtained from 21 Surveillance, Epidemiology, and End Results (SEER) program population-based registries. The registries included Alaska Native Tumor Registry, Connecticut, Detroit, Georgia Center for Cancer Statistics (Atlanta, Greater Georgia, and Rural Georgia), Greater Bay Area Cancer Registry (San Francisco-Oakland, San Jose-Monterey), Greater California, Hawaii, Idaho, Iowa, Kentucky, Los Angeles, Louisiana, Massachusetts, New Mexico, New Jersey, New York, Seattle-Puget Sound, and Utah (<http://seer.cancer.gov/>). These 21 registries account for approximately 36.7% of the total U.S. population, including 33.6% of the White population, 34.7% of the Black population, and 46.7% of the Hispanic population (source: U.S. Bureau of Census, Census 2010, Summary File 1, Table DP-1). The SEER 18 registry, which accounts for approximately 28% of the U.S. population, was used to supplement data on insurance status.

Individuals diagnosed with incident DLBCL, FL, or CLL were classified according to the World Health Organization (WHO) 2008 classification of hematologic malignancies [22, 23] using International Classification of Diseases for Oncology (ICD-O-3). DLBCL included ICD codes 9680, 9684, 9735, 9688, 9737–9738, 9712, and 9678–9679. FL included ICD-O-3 codes 9690–9691, 9695, and 9698. CLL/SLL included ICD-O-3 codes 9670 and 9823. Only malignant cases were included. Individuals diagnosed under the age of 20 or whose race was unknown were excluded. Race and ethnicity were classified as non-Hispanic White, non-Hispanic Black, and Hispanic. SEER Summary Stage 2018 was used to categorize tumor stage as localized, regional, distant, or unknown [24].

Rurality and Socioeconomic Data

Rurality was determined using rural-urban continuum codes devised by the U.S. Department of Agriculture [25]. Category 1 included all metropolitan counties of any population (rural-urban continuum codes 1–3), while categories 2 and 3 were nonmetropolitan counties further divided by population size. Category 2 included non-metropolitan urbanized areas with populations of at least 20,000 (rural-urban continuum codes 4–5). Category 3 included less urbanized and rural areas with populations of less than 20,000 (rural-urban continuum codes 6–9).

SES was measured by county level data collected through the 2012–2016 American Community Survey (ACS) and 2000 Census [26]. SES levels were assessed by the percent

of the adult population 25 without a high school education and family poverty rates. Insurance categories (insured, Medicaid, uninsured, and unknown) and marital status (married, never married) were included using 18 SEER registries from 2000–2016 (n = 325,684). Analyses using insurance status excluded individuals 65 years and older at time of diagnosis because individuals categorized as uninsured or unknown over the age of 65 years were Medicare eligible.

Statistical Analysis

Baseline population characteristics were compared by NHL subtype (DLBCL, FL, and CLL/SLL) and urban-rural category. Bivariate analyses of continuous variables were performed using ANOVA for normally distributed variables and the Kruskal-Wallis test for variables that were not normally distributed. Categorical variables were compared using the χ^2 test or Fisher's exact test, when appropriate.

SEER-STAT was used for aged-adjusted incidence rate calculations [26]. Incidence rates were calculated per 100,000-person years and age standardized based on the 2000 Census. Incidence rates were calculated for DLBCL, FL, and CLL. Rates were then stratified by race/ethnicity, age at diagnosis (20–64 and 65 years), sex, and measures of SES and compared across urban category by estimating incidence rate ratios (IRRs). Statistical significance was set at an $\alpha = 0.05$, and 95% confidence intervals were estimated using the Tiwari modification [27].

Poisson regression was performed to assess the association between incidence and rurality category. Separate models were created for DLBCL, FL, and CLL. Models were adjusted for sex, age dichotomized at 65 years, race/ethnicity, and county-level family poverty rates (lower 2 poverty quintiles versus higher 3 poverty quintiles). Covariates were assessed for confounding (>15% change in beta in urban-rural status) and all possible first-order interactions with urban-rural category. Final DLBCL, FL and CLL models were stratified by race and ethnicity. Three sensitivity analyses were performed separately by stratifying each model by sex, age dichotomized at 65, and family poverty rates. An additional sensitivity analysis was performed by adjusting models by 5-year age at diagnosis categories (20–24, 25–29, 30–34, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–94, 85 years). Models were also stratified by year of diagnosis (2000–2004, 2005–2008, 2009–2012, 2013–2016) to assess potential period effects.

Results

A total of 482,096 adults aged 20 years and older with incident NHL were reported to SEER between 2000 and 2016. Of these cases, 136,197 were diagnosed with DLBCL, 70,882 were diagnosed with FL, and 120,319 were diagnosed with CLL (Table 1). Across all three major subtypes, approximately 90% of patients lived in metropolitan urban areas, 4% lived in non-metropolitan urban areas (urban population of 20,000 or more), and 6% lived in less urban or rural areas (completely rural or urban population of less than 19,999 or completely rural). The majority of DLBCL patients were non-Hispanic White (73.6%), followed by Hispanics (11.8%) and non-Hispanic Blacks (7.3%). The distribution of race and ethnicity was similar among FL and CLL patients. A majority of DLBCL and CLL patients were male (54% and

59%, respectively), while FL patients were equally distributed between males (49.6%) and females (50.4%). Mean age at diagnosis was highest among CLL patients (69.8 years) compared to DLBCL (65.5 years) and FL patients (63.7 years). Median education, poverty levels, median income, and household crowding were similar between NHL subtypes. Using SEER18 incidence data on insurance status, we observed similar insurance status distributions across urban-rural status for all three subtypes (Supplemental Table 1).

Between 2000 and 2016, DLBCL age-adjusted incidence rates increased 0.4% per year in metropolitan urban areas ($p<0.01$), 0.7% per year in non-metropolitan urban areas ($p<0.01$), and 0.9% per year in less urban and rural areas ($p<0.01$) (Figure 1). Overall the DLBCL incidence rate was higher in urban areas compared to rural areas (9.8 vs. 9.4 per 100,000; IRR = 1.04; 95% CI 1.02, 1.07). We found similar overall trends in DLBCL incidence rates after stratifying by age, sex, and county-level family poverty rates (Supplemental Table 2). This urban versus rural pattern was more pronounced in Hispanics (10.3 vs. 7.0 per 100,000; IRR = 1.47; 95% CI 1.29, 1.70) and non-Hispanic Blacks (7.1 vs. 5.6 per 100,000; IRR = 1.25; 95% CI 1.13, 1.40) than non-Hispanic Whites (9.8 vs. 9.4 per 100,000; IRR = 1.05; 95% CI 1.02, 1.08; Table 2).

Adjusting for age, sex, race, and family poverty, we observed a higher DLBCL incidence rate in metropolitan urban areas compared to rural areas overall (IRR = 1.20, 95% CI 1.11, 1.30), and more specifically among Hispanics in nonmetropolitan urban (IRR = 1.32, 95% CI 1.16, 1.51) and metropolitan urban areas (IRR = 1.55, 95% CI 1.36, 1.76) compared to rural areas (Table 3). After stratifying by year of diagnosis, we found a similar association between overall DLBCL incidence in metropolitan urban areas compared to rural areas among those diagnosed from 2000–2004 (IRR = 1.39; 95% CI 1.37, 1.41), 2005–2008 (IRR = 1.24; 95% CI 1.22, 1.26), and 2013–2016 (IRR = 1.40; 95% CI 1.38, 1.43). Differences in DLBCL incidence in urban areas among Hispanics persisted after stratifying by sex, age, and poverty rates (Supplemental Table 3).

In contrast to DLBCL, we observed a downward trend in overall age-adjusted incidence rates from 2000 to 2016 for CLL (annual percent change -0.4% , $p<0.01$). Further, metropolitan urban areas had a lower overall incidence of CLL than rural areas (8.4 vs. 9.7 per 100,000; IRR = 0.87; 95% CI 0.86, 0.89). We observed similar overall trends in CLL incidence rates after stratifying by age, sex, county-level family poverty rates, and county-level high school graduation rates (Supplemental Table 2). Increased CLL incidence rates were associated with nonmetropolitan urban areas compared to rural areas (IRR = 1.19; 95% CI 1.10, 1.28), particularly among non-Hispanic Blacks (IRR = 1.49, 95% CI 1.27, 1.72). CLL incidence rates were similar between metropolitan urban and rural areas among non-Hispanic Whites and Hispanics. No urban versus rural differences were associated with FL after adjusting for age, sex, and SES (Table 3). We found similar associations between urban-rural status and DLBCL, FL, and CLL incidence when adjusting for 5-year age categories (Supplemental Table 4).

Discussion

In our large study using national SEER data, we found that urban status was associated with an increase in the incidence rate of DLBCL in Hispanics and of CLL in non-Hispanic Blacks, suggesting a potential differential NHL risk among diverse, urban populations. Our findings confirm the known NHL risk for urban populations, while providing a more nuanced understanding of racial and ethnic differences in risk [20, 21].

Known occupational risk factors for NHL include benzene, an IARC group 1 carcinogen, and occupational exposures to TCE, which has been found to be associated with increased risk of DLBCL, FL, and CLL [8, 10, 28–33]. Ambient benzene has been found to be elevated in large urban centers due to the high concentration of mobile sources and urban green spaces [34, 35]. Individuals working with gasoline and degreasing have been found to have highly elevated cumulative exposure to occupation-specific benzenes, with higher lifetime cancer risk among gasoline station workers in urban compared to rural areas [36, 37]. Furthermore, higher concentrations of ambient benzene have been found in urban areas [38], potentially increasing the risk of hematologic malignancies among urban populations.

NHL risk is also associated with HIV, transplantation, and other conditions that may cause immunosuppression [39]. Hepatitis C infection, for example, has been found to be associated with DLBCL and CLL risk in large cohort studies [12]. Obesity is another established risk factor for DLBCL potentially due to a chronic inflammatory state [40, 41], however obesity rates tend to be higher in nonmetropolitan compared to metropolitan areas [42] and would most likely not explain our findings. HIV incidence has been declining among Hispanics, non-Hispanic Blacks, and non-Hispanic Whites [43]. In 2010, the estimated HIV incidence was 16.0 per 100,000, which decreased to 14.3 per 100,000 in 2016 [44]. The highest incidence was among non-Hispanic Blacks (49.6 per 100,000), followed by Hispanics (23.7 per 100,000) and non-Hispanic Whites (5.6 per 100,000). A study of NHL incidence rates in Pennsylvania, however, found increased NHL incidence rates with urbanization even after adjusting for county-level AIDS incidence, suggesting urban status may be independently associated with NHL risk [45]. Furthermore, while DLBCL is considered an AIDS-related lymphoma, FL and CLL have not consistently been attributed to HIV infection [46].

The higher incidence rates in urban areas may be due to lower access to care in rural areas, which would lead to late or missed diagnoses. However, we do not believe this would fully explain our results for a few reasons. First, 63% of rural residents live less than 180 minutes from a parent or satellite National Cancer Institute (NCI) Cancer Center [47], suggesting that the majority of individuals living in rural areas continue to have access to NCI cancer centers. Additionally, if access to care was influencing our results, we likely would have found lower incidence rates of all three NHL subtypes in rural areas. Instead, we observed no difference in FL incidence rates by urban-rural status after adjusting for age, sex, and family poverty rates. Additionally, we observed a similar insurance status distribution by urban-rural status. Urban areas may have a higher incidence of DLBCL due to a greater referral rate to tertiary centers, however, this would not explain differences by race and ethnicity. Finally, our results persisted across counties with high and low poverty rates,

suggesting distinct etiologies affecting DLBCL, FL, and CLL incidence by urban-rural status.

Our study has several strengths and weaknesses. While our research has focused on NHL subtypes of the B-cell origin, recent research suggests potential geographic clustering of cutaneous T-cell lymphoma in urban areas with high concentrations of benzene and TCE [48]. In an exploratory analyses, we found an increased incidence of T-cell lymphoma in nonmetropolitan urban (IRR = 1.12; 95% CI 1.10, 1.34) and metropolitan urban areas (IRR = 1.24; 95% CI 1.22, 1.26) compared to rural areas, further supporting our hypothesis that the increased incidence in urban areas may be attributed to occupational exposures. These exploratory analyses are consistent with prior research [48], and merits further investigation.

To the best of our knowledge, this is the first study to examine the intersection of rurality and race in NHL incidence rates using a large, population-based national registry. In some cases, differences in incidence rates may be statistically significant but not clinically meaningful, however, we believe the differences in DLBCL and FL incidence rates by race/ethnicity and urban-rural status to be of public health significance. At the time of data analysis, HIV status at diagnosis was not available, leading to uncontrolled confounding of the association between DLBCL and CLL incidence rates and urban-rural status. However, we do not believe that differences in HIV prevalence would explain our results, given prior evidence that NHL incidence rates may be associated with degree of urbanization that is not attributed to HIV/AIDS prevalence alone [45, 49]. Additionally, information on environmental and occupational exposures was not available and, while we hypothesize that the urban-rural incidence rate patterns observed in our study may be attributable to differential environmental exposures, additional research is needed to quantify exposures to suspected lymphomagens. Future studies should examine DLBCL, FL, and CLL in diverse, urban and rural populations, as well as the potential role of occupational exposures, infection (e.g. HIV and Hepatitis C), and obesity in NHL risk among racial and ethnic minority populations.

Conclusion

We found that Hispanics and non-Hispanic Blacks have higher incidence rates of DLBCL and CLL, respectively, in urban compared to rural areas, while this was not the case for non-Hispanic Whites. Overall, our findings suggest that factors related to urban status may be associated with DLBCL and CLL pathogenesis. Our results may help provide epidemiological clues to understanding the racial disparities seen among hematological malignancies, particularly regarding the risk of DLBCL in Hispanics and CLL in non-Hispanic Blacks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant Number UL1TR001073.

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Clinical Practice Points

- Hispanics and non-Hispanic Blacks experienced increased incidence of DLBCL and CLL, respectively, in urban areas compared to rural areas, and these differences were not explained by sex, age, or socioeconomic status.
- Urban-rural patterns in NHL incidence rates may help clarify underlying causes of ethnic and racial disparities in NHL incidence rates and can further guide clinical practice and public health measures aimed at reducing racial disparities in NHL.

- Urban-rural incidence patterns may clarify racial/ethnic disparities in NHL incidence
- Increased DLBCL incidence was observed among urban Hispanics versus rural
- Increased CLL incidence was observed among urban non-Hispanic Blacks versus rural
- No differences by urban-rural status were observed among non-Hispanic Whites

Figure 1:
Trends in Diffuse Large B-cell Lymphoma, Follicular Lymphoma, and Chronic Lymphocytic Leukemia Age-Adjusted Incidence Rates by Urban-Rural Category 2000–2016. Red line indicates metropolitan urban areas, green indicates nonmetropolitan urban areas, and blue indicates rural/less urban areas. Dotted line indicates 2000 reference rate.

Table 1:

Baseline Characteristics of Adults with Non-Hodgkin Lymphoma in SEER21 by Subtype (n = 328,118).

	Diffuse Large B Cell (n=136,917)	Follicular (n=70,882)	Chronic Lymphocytic Leukemia (n=120,319)
Age at diagnosis, mean $\pm$ SD	65.5 $\pm$ 16.0	63.7 $\pm$ 13.8	69.8 $\pm$ 12.4
Sex, N (%)			
Male	74,669 (54.5)	35,161 (49.6)	71,294 (59.3)
Female	62,248 (45.5)	35,721 (50.4)	49,025 (40.8)
Race/Ethnicity			
Non-Hispanic White	100,605 (73.5)	57,267 (80.1)	101,772 (84.6)
Non-Hispanic Black	10,037 (7.3)	3,183 (4.5)	8,104 (6.7)
Hispanic	16,239 (11.9)	6,933 (9.8)	5,647 (4.7)
Asian or Pacific Islander	8,899 (6.5)	2,693 (3.8)	2,216 (1.8)
American Indian or Alaskan	535 (0.4)	250 (0.4)	268 (0.2)
Native			
Unknown	602 (0.4)	556 (0.8)	2,312 (1.9)
Stage at Diagnosis, N (%) *			
Localized	28,574 (20.9)	15,364 (21.7)	3,427 (2.9)
Regional	20,697 (15.1)	8,761 (12.4)	2,096 (1.7)
Distant	53,835 (39.3)	28,256 (39.9)	88,389 (73.5)
RUCCL Category, N (%)			
Metropolitan Urban	123,015 (89.9)	62,983 (88.9)	108,886 (88.0)
Non-Metropolitan Urban	5,621 (4.1)	3,214 (4.5)	5,663 (4.7)
Less Urban/Rural	8,195 (6.0)	4,633 (6.5)	8,669 (7.2)
Unknown	388 (0.1)	52 (0.1)	100 (0.1)
Education, median % (IQR) **			
<9 th Grade	5.4 (3.4, 8.7)	5.0 (3.4, 8.6)	4.7 (3.3, 7.8)
<High School	12.5 (9.2, 17.5)	12.0 (9.1, 16.4)	11.7 (9.1, 15.5)
>= College	32.2 (24.6, 38.9)	32.2 (24.0, 39.0)	32.2 (24.0, 39.7)
Poverty, median % (IQR)			
Family Poverty	10.2 (7.0, 13.9)	9.8 (6.9, 13.9)	9.7 (6.9, 13.7)
Individual poverty	14.0 (10.7, 17.8)	13.8 (10.4, 17.8)	13.6 (10.3, 17.8)

	Diffuse Large B Cell (n=136,917)	Follicular (n=70,882)	Chronic Lymphocytic Leukemia (n=120,319)
<150% of poverty line	22.6 (17.6, 29.3)	22.5 (17.1, 29.2)	22.3 (16.9, 29.0)
Unemployed	7.4 (6.3, 8.9)	7.3 (6.3, 8.9)	7.3 (6.3, 8.9)
Household income	59,760 (51,760, 75,510)	59,760 (51,760, 76,930)	59,760 (51,010, 75,510)
Household crowding	3.0 (1.9, 7.2)	2.7 (1.8, 6.7)	2.6 (1.8, 6.4)
Appalachia Region ***	5,920 (4.4)	3,503 (4.9)	5,967 (5.0)

* Unknown stage in 33,811 (24.7%) DLBCL, 18,501 (26.1%) FL, and 26,407 (22.0%) CLL.

** Based on ACS 2012–2016 county data. Missing SES data from 21 DLBCL, 17 FL, and 85 CLL.

*** Unknown in 3 DLBCL, 2 FL, and 16 CLL.

Table 2:

Incidence Rates of NHL Subtypes by Urban-Rural Category & Race/Ethnicity.

	Diffuse Large B Cell Lymphoma			Follicular Lymphoma			Chronic Lymphocytic Leukemia		
	Number	Rate*	IRR (95% CI)	Number	Rate*	IRR (95% CI)	Number	Rate*	IRR (95% CI)
Overall									
Rural/Less Urban	8,163	9.4 (9.2, 9.6)	1.00 (ref.)	4,633	5.3 (5.1, 5.4)	1.00 (ref.)	8,669	9.7 (9.5, 9.9)	1.00 (ref.)
Non-Metropolitan Urban	5,600	9.4 (9.2, 9.7)	1.00 (0.97, 1.04)	3,214	5.4 (5.2, 5.6)	1.02 (0.97, 1.07)	5,664	9.3 (9.0, 9.5)	0.96 (0.93, 0.99)
Metropolitan Urban	122,348	9.8 (9.8, 9.9)	1.04 (1.02, 1.07)	62,983	5.0 (4.9, 5.0)	0.94 (0.91, 0.97)	105,886	8.4 (8.4, 8.5)	0.87 (0.86, 0.89)
Non-Hispanic White									
Rural/Less Urban	7,503	9.8 (9.5, 10.0)	1.00 (ref.)	4,383	5.7 (5.5, 5.9)	1.00 (ref.)	8,070	10.1 (9.9, 10.3)	1.00 (ref.)
Non-Metropolitan Urban	4,883	9.7 (9.4, 10.0)	1.00 (0.96, 1.03)	2,943	5.8 (5.6, 6.1)	1.03 (0.98, 1.08)	5,211	9.9 (9.7, 10.2)	0.99 (0.95, 1.02)
Metropolitan Urban	87,787	10.2 (10.2, 10.3)	1.05 (1.02, 1.08)	49,932	5.8 (5.8, 5.9)	1.02 (0.99, 1.06)	88,438	10.0 (9.9, 10.0)	0.99 (0.97, 1.01)
Non-Hispanic Black									
Rural/Less Urban	348	5.6 (5.1, 6.3)	1.00 (ref.)		1.7 (1.4, 2.1)	1.00 (ref.)	355	6.1 (5.5, 6.8)	1.00 (ref.)
Non-Metropolitan Urban	167	5.6 (4.8, 6.5)	0.99 (0.82, 1.20)	62	2.1 (1.6, 2.8)	1.23 (0.88, 1.70)	185	6.7 (5.8, 7.8)	1.10 (0.91, 1.32)
Metropolitan Urban	9,415	7.1 (6.9, 7.2)	1.25 (1.13, 1.40)	3,013	2.3 (2.2, 2.4)	1.31 (1.08, 1.61)	7,562	6.3 (6.1, 6.4)	1.02 (0.92, 1.14)
Hispanic									
Rural/Less Urban	222	7.0 (6.0, 8.0)	1.00 (ref.)	110	3.5 (2.8, 4.2)	1.00 (ref.)	129	4.4 (3.6, 5.2)	1.00 (ref.)
Non-Metropolitan Urban	252	8.9 (7.8, 10.1)	1.28 (1.05, 1.55)	106	3.4 (2.8, 4.1)	0.98 (0.74, 1.30)	116	4.4 (3.6, 5.3)	1.00 (0.77, 1.31)
Metropolitan Urban	15,617	10.3 (10.1, 10.4)	1.47 (1.29, 1.70)	6,714	4.2 (4.1, 4.3)	1.21 (1.00, 1.48)	5,397	4.0 (3.9, 4.2)	0.95 (0.78, 1.12)

Rate – incidence per 100,000 individuals.

IRR – incidence rate ratio; CI – confidence interval

Table 3:
Multivariate Regression Analysis of Urban-Rural Status and Incidence Rates of Non-Hodgkin Lymphoma Subtypes by Race/Ethnicity.

	Diffuse Large B Cell Lymphoma					
	Overall	Non-Hispanic Whites (n = 100,605)	Non-Hispanic Blacks (n = 10,037)	Hispanics (n = 16,239)		
	IRR (95% CI)	p value	IRR (95% CI)	IRR (95% CI)	p value	p value
Rural/Less Urban (ref.)						
Nonmetropolitan Urban	1.12 (1.03, 1.21)	0.006	0.99 (0.87, 1.11)	1.10 (0.93, 1.30)	0.25	1.32 (1.16, 1.51) < 0.001
Metropolitan Urban	1.20 (1.11, 1.36)	< 0.001	1.01 (0.90, 1.14)	1.11 (0.94, 1.31)	0.21	1.55 (1.36, 1.76) < 0.001
Non-Hispanic White (ref.)						
Non-Hispanic Black	0.52 (0.48, 0.57)	< 0.001				
Hispanic	0.82 (0.76, 0.88)	< 0.001				
Male (ref.)						
Female	0.68 (0.64, 0.72)	< 0.001	0.72 (0.68, 0.79)	0.61 (0.53, 0.70)	< 0.001	0.68 (0.61, 0.76) < 0.001
Age <65 years (ref.)						
Age 65 years	6.49 (5.91, 7.13)	< 0.001	7.66 (6.58, 8.93)	4.36 (3.66, 5.18)	< 0.001	7.21 (6.12, 8.51) < 0.001
Lowest 2 Family Poverty Quintiles (ref.)						
Highest 3–5 th Quintiles	0.85 (0.79, 0.90)	< 0.001	0.91 (0.83, 1.01)	0.80 (0.70, 0.91)	0.001	0.80 (0.72, 0.89) < 0.001
Follicular Lymphoma						
	Overall	Non-Hispanic Whites (n = 57,267)	Non-Hispanic Blacks (n = 3,183)	Hispanics (n = 6,933)		
	IRR (95% CI)	p value	IRR (95% CI)	IRR (95% CI)	p value	p value
Rural/Less Urban (ref.)						
Nonmetropolitan Urban	0.93 (0.83, 1.04)	0.22	1.00 (0.85, 1.19)	0.96 (0.70, 1.30)	0.78	0.83 (0.69, 1.01) 0.06
Metropolitan Urban	0.98 (0.87, 1.09)	0.67	0.99 (0.84, 1.17)	1.26 (0.95, 1.67)	0.11	0.86 (0.71, 1.04) 0.12
Non-Hispanic White (ref.)						
Non-Hispanic Black	0.32 (0.28, 0.37)	< 0.001				
Hispanic	0.81 (0.73, 0.90)	< 0.001				
Male (ref.)						
Female	0.88 (0.80, 0.97)	< 0.001	0.91 (0.79, 1.05)	0.72 (0.57, 0.92)	0.009	0.92 (0.79, 1.07) 0.26
Age <65 years (ref.)						
Age 65 years	5.15 (4.54, 5.85)	< 0.001	5.09 (4.23, 6.13)	4.14 (3.05, 5.61)	< 0.001	5.77 (4.66, 7.15) < 0.001

Lowest 2 Family Poverty Quintiles (ref.) Highest 3–5 th Quintiles	Author Manuscript			Author Manuscript			Author Manuscript		
	IRR (95% CI)	p value	Non-Hispanic Whites (n = 101,772)	IRR (95% CI)	p value	Non-Hispanic Blacks (n = 8,104)	IRR (95% CI)	p value	Hispanics (n = 5,647)
Chronic Lymphocytic Leukemia									
Overall	0.76 (0.69, 0.84)	< 0.001	0.96 (0.83, 1.10)	0.52	1.63 (1.25, 2.13)	< 0.001	0.44 (0.37, 0.51)	< 0.001	
Rural/Less Urban (ref.)									
Nonmetropolitan Urban	1.19 (1.10, 1.28)	< 0.001	0.98 (0.88, 1.10)	0.77	2.20 (1.92, 2.53)	< 0.001	0.76 (0.64, 0.90)	0.002	
Metropolitan Urban	1.04 (0.96, 1.13)	0.30	0.95 (0.85, 1.06)	0.37	1.48 (1.27, 1.72)	< 0.001	0.87 (0.74, 1.02)	0.09	
Non-Hispanic White (ref.)									
Non-Hispanic Black	0.60 (0.56, 0.65)	< 0.001							
Hispanic	0.47 (0.43, 0.51)	< 0.001							
Male (ref.)									
Female	0.57 (0.54, 0.61)	< 0.001	0.53 (0.48, 0.58)	< 0.001	0.62 (0.55, 0.70)	< 0.001	0.61 (0.54, 0.70)	< 0.001	
Age <65 years (ref.)									
Age 65 years	11.71 (10.40, 13.18)	< 0.001	11.31 (9.56, 13.37)	< 0.001	11.59 (9.32, 14.41)	< 0.001	12.84 (9.92, 16.62)	< 0.001	
Lowest 2 Family Poverty Quintiles (ref.)									
Highest 3–5 th Quintiles	0.99 (0.93, 1.06)	0.82	0.87 (0.80, 0.96)	0.004	0.99 (0.88, 1.11)	0.83	1.33 (1.16, 1.54)	< 0.001	

IRR – incidence rate ratio; CI – confidence interval