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Age-Adjusted Incidence Rates and Time Trends of Non-Hodgkin Lymphoma by Subtype, 2000-2015

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Abstract

Background: Non-Hodgkin lymphomas (NHL) are a group of diverse and complex cancers of the lymphocytes. More than 60 subtypes have been identified based on certain characteristics of the cancer cell. The objectives of this study were to: 1) determine NHL age-adjusted incidence rates from 2000 to 2015 in the U.S. by age, sex, and race/ethnicity; 2) to examine age-adjusted subtype-specific NHL incidence rates by age, sex, and race/ethnicity; 3) to determine if there was significant time trend in age-adjusted NHL incidence rate from 2000-2015 in the U.S by age, sex, and race/ethnicity.; 4) and to examine time trend in age-adjusted subtype-specific NHL incidence rate from 2000-2015 in the U.S. by age, sex, and race/ethnicity.

Methods: We used Surveillance Epidemiology and End Results (SEER) Program registries of 18 geographical locations 2000-2015. There were a total of 259,228 incident cases of NHL. Subtypes were coded using the World Health Organization (WHO) 2008 classification scheme and International Classification of Disease – Oncology, 3rd Edition (ICD-O-3) site codes. Subgroups analyzes were based on sex, race (white, black, American Indian/Alaska Native, or Asian/Pacific Islander), ethnicity (non-Spanish/Hispanic/Latino or Spanish/Hispanic/Latino) and age group (20-29, 30-39, 40-49, 50-59, 60-69, or 70+). Age-adjusted incidence rates and rate ratios were calculated using SEER*Stat software. Statistical significance was determined by comparing 95% confidence intervals. Annual percentage change (APC) was calculated using Joinpoint regression software.

Results: All subtypes had decreasing incidence except mantle-cell lymphoma, which had increasing incidence (APC 0.77%, $p<0.05$) and cutaneous T-cell lymphomas, which had a stabilized incidence ($p=0.9$). All subtypes had a higher male incidence rates except marginal-zone lymphoma, which had similar incidence rates in males and females ($p=0.36$). Whites had highest incidence rates in all subtypes except cutaneous T-cell lymphomas and peripheral T-cell lymphomas, in which blacks had the highest incidence

rates and significantly higher incidence rates than whites (RR=1.54, $p<0.05$; RR=1.90, $p<0.05$). Non-Hispanics had higher incidence in all subtypes except Diffuse Large B-Cell Lymphoma and Burkitt Lymphoma, in which non-Hispanics had higher incidence rates (RR=1.05, $p<0.05$; RR=1.17, $p<0.05$). Finally, incidence increases as age increases for all subtypes, although the increase is smaller in Burkitt lymphoma, which is more common in younger populations.

Conclusion: Analysis by subtype and subgroups revealed incidence rates and time trends that were not obvious when analyzing data for all subtypes of subpopulations combined. Some subgroups were at higher risk than others, but only for certain subtypes, meaning that etiology and risk may vary by subtype. This was apparent in the higher risk for blacks compared to whites in T-cell lymphomas and Hispanics compared to non-Hispanics in diffuse large B-cell lymphoma and Burkitt lymphoma. Understanding these differences can help us identify population-specific prevention methods and treatments for each subtype.

Background

Non-Hodgkin lymphoma (NHL) is a lymphoid neoplasm that starts in white blood cells called lymphocytes. It is the seventh most common cancer and the ninth leading cause of cancer death in the U.S. (American Cancer Society (ACS), 2017). It accounts for about 4% of all cancers in the U.S. (ACS, 2018). The World Health Organization (WHO) has identified more than 60 subtypes of NHL based on certain characteristics of the cancer cell (Leukemia and Lymphoma Society, 2015). Some characteristics that determine WHO subtype include the type of lymphocyte affected (B-cell, T-cell, or NK cell), the rate of cancer growth (indolent or aggressive), and the location of the cancer (e.g., spleen, lymph nodes, bone marrow) (ACS, 2018). Some of the most common subtypes of non-Hodgkin lymphoma are Diffuse Large B-Cell lymphoma (33% of cases), follicular lymphoma (20% of cases), mantle-cell lymphoma (5-7% of cases), and small-cell lymphoma (5% of cases) (ACS, 2017).

Because of the abundance of subtypes of non-Hodgkin lymphoma and the complexity of the disease, classification of NHL has evolved many times over the years. In the 1960s, the Rappaport classification was used, which focused on the appearance of cancer cells. Small cells were “lymphocytic” and large cells were “histiocytic” (Jaffe et al., 1992). The Rye classification, which focused on prognosis (most favorable, favorable, guarded, least favorable), was also used (National Cancer Institute (NCI), 2018). The Kiel classification focused on the type of lymphocyte affected (B-cell or T-cell) and tumor grade (high or low) (NCI, 2018). In 1982, the Working Formulation (WF) was developed and combined many previous classification schemes and grouped according to prognosis and tumor grade (NCI, 2018). In 1994, the International Lymphoma Study group published the Revised European-American Lymphoma (REAL) system that was used as a basis for the WHO classification in 2001 (Campo et al., 2011). The introduction of the WHO classification system in 2001 resolved many issues regarding lymphoma classification and recognized more subtypes based on morphology, immunophenotype, genetic, molecular, and clinical features (Campo et al., 2011). The system was revised in 2008 and its terminology

has been incorporated into the International Classification of Diseases – Oncology, 3rd Edition (ICD-O-3) codes used by the Surveillance, Epidemiology, and End Results (SEER) Program (NCI, n.d.).

Between 1970 and 1980, NHL age-adjusted incidence rate in the U.S. increased annually by 3-4%. During the 1990s, this dropped to <1% increase per year (Howe et al., 2001). However, trends over time may be misleading without subgroup analysis as observed with other types of cancer. For example, overall breast cancer mortality rate has decreased from 2002 to 2011 (Average annual percentage change (AAPC) -0.2%) (Kohler et al., 2015). Further analysis by race/ethnicity found that this decrease trend was driven by the decrease in the mortality rate among Non-Hispanic Whites. Among African American and Asian/Pacific Islander (API) women the mortality rate actually increased (AAPC 0.7%, $p<0.05$; AAPC 0.8%, $P>0.05$) Kohler et al., 2015). Another example is colorectal cancer trends. While the overall colorectal cancer incidence and mortality rates decreased from 2000 to 2013, the incidence rate in younger individuals (<50 years old) increased substantially (5.9 to 7.2 per 100,000) and the mortality rate remained the same (Siegel et al., 2017).

An examination of incidence and mortality rates by race/ethnicity and age group can provide important clues to further understanding the etiology of the disease and potential differences in response to treatment (Rudan et al., 2013; Koivunen et al., 2015). Furthermore, each subtype of NHL may have different risk factors, some of which may be exacerbated in different demographic subgroups. Therefore, understanding the heterogeneity of NHL can help us identify populations with higher risk and burden of cancer. The objectives of this study were to: 1) determine NHL age-adjusted incidence rates from 2000 to 2015 in the U.S. by age, sex, and race/ethnicity; 2) to examine age-adjusted subtype-specific NHL incidence rates by age, sex, and race/ethnicity; 3) to determine if there was significant time trend in age-adjusted NHL incidence rate from 2000-2015 in the U.S by age, sex, and race/ethnicity.; 4)

and to examine time trend in age-adjusted subtype-specific NHL incidence rate from 2000-2015 in the U.S. by age, sex, and race/ethnicity.

Methods

Data were obtained from the SEER Program's database, which contains data from 18 geographical registries (standard metropolitan statistical area of San Francisco (SF)/Oakland, Connecticut, Metropolitan Detroit, Seattle/Puget Sound, Metropolitan Atlanta, San-Jose/Monterey (SJM), Los Angeles (LA), Alaska Natives, Rural Georgia, Greater Georgia, California (excluding SF/SJM/LA), Hawaii, Iowa, New Mexico, Utah, Kentucky, Louisiana, and New Jersey). This accounts for approximately 27.8% of the US population.

NHL subtypes were classified using the WHO 2008 lymphoma classification scheme based on the ICD-O-3 site codes. The ICD-O-3 system codes for tumor site, histology, and malignant behavior (International Agency for Research of Cancer (IARC), 2018). The WHO 2008 scheme classifies by morphology and grade of tumor (NCI, 2018). Subtypes and codes are listed in Table 1. Some rare subtypes were excluded due to the low number of cases, which precluded analysis.

For this study, eligible patients were at least 20 years of age and diagnosed with NHL between 2000 and 2015. Individuals under the age of 20 were excluded because most NHL subtypes are rare in younger populations (Georgakis et al., 2016). Age at diagnosis was coded as 20-29, 30-39, 40-49, 50-59, 60-69, ≥70. Race was limited to white, black, API, or AI/AK. Ethnicity was defined as Spanish/Hispanic/Latino (Hispanic) or non-Spanish/Hispanic/Latino (non-Hispanic). The "unknown" race group and age group were excluded. Only the first matching record for each person was used. This resulted in 259,228 incident cases. Incidence per 100,000 was age-standardized to the 2000 U.S. standard population using SEER*Stat software. We used the WHO classification scheme revised in 2008 for this study because it is recognized as the least controversial classification scheme (Campo et al.,

2011). Subtypes, along with the WHO classification and corresponding ICD-O-3 codes, are shown in Table 1.

Table 1. WHO Subtypes and Corresponding ICD-O-3 codes.

Subtype	**WHO Subtype**	**ICD-O-3 codes**
Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL)	2(a)2.1.1. Chronic/Small lymphocytic leuk/lymph	9670, 9823
Mantle-cell lymphoma (MCL)	2(a)2.1.3. Mantle-cell lymphoma	9673
Lymphoplasmacytic lymphomas (LPL)	2(a)2.2.1. Lymphoplasmacytic lymphoma 2(a)2.2.2. Waldenstrom macroglobulinemia	9671, 9761
Diffuse large B-cell lymphoma (DLBCL)	2(a)2.3.1. DLBCL, NOS 2(a)2.3.2. Intravascular large B-cell lymphoma 2(a)2.3.3. Primary effusion lymphoma 2(a)2.3.4. Mediastinal large B-cell lymphoma	9680, 9688, 9737-9738, 9684, 9712, 9678-9679
Burkitt lymphoma (BL)	2(a)2.4. Burkitt lymphoma /leukemia	9687, 9826
Marginal-zone lymphoma (MZL)	2(a)2.5.1. Splenic MZL 2(a)2.5.2. Extranodal MZL, MALT type 2(a)2.5.3. Nodal MZL	9689, 9699, 9760, 9764
Follicular Lymphoma (FL)	2(a)2.6. Follicular Lymphoma	9690-9691, 9695, 9698
Cutaneous T-cell lymphomas (CTCL)	2(b)2.1.1. Mycosis fungoides 2(b)2.1.2 Sezary syndrome	9700, 9701
Peripheral T-cell lymphoma (PTCL)	2(b)2.2.1. Peripheral T-cell lymphoma, NOS 2(b)2.2.2. Angioimmunoblastic T-cell lymphoma 2(b)2.2.3. Subcutaneous panniculitis-like T-cell lymphoma 2(b)2.2.4. Anaplastic large cell lymphoma, T- or Null-cell 2(b)2.2.5. Hepatosplenic T-cell lymphoma 2(b)2.2.6. Enteropathy-type T-cell lymphoma 2(b)2.2.7. Cutaneous T-cell lymphoma, NOS 2(b)2.2.8. Primary cutaneous anaplastic large cell lymphoma	9702, 9675, 9705, 9708, 9714, 9716, 9717, 9718, 9709, 9726

Age-adjusted incidence rates were calculated using SEER*Stat 8.3.5 statistical software. Incidence rates between groups are considered to be significantly different when 95% confidence intervals (CI) between groups do not overlap. The relative risk or incidence rate ratio (RR) was calculated to compare female incidence to male incidence; black, AI/AN, and API incidence to white incidence; and

Hispanic incidence to non-Hispanic incidence. RRs are considered statistically significant when 95% CIs do not include 1.

Joinpoint Regression Program 4.6.0.0 was used to visualize incidence trends and calculate annual percentage change (APC). Joinpoint uses regression analysis and identifies significant changes in annual incidence rates. Any point in time that represents a significant trend change is called a "joinpoint." Incidence trends from 2000 to 2015 were calculated using weighted least squares for non-constant variance and log transformation of the dependent variable. APC was statistically different from zero when $p<0.05$. When there were zero cases for a group, Joinpoint could not process the records to calculate APC. Therefore, some groups did not have calculated APC.

Results

Age-Adjusted Incidence Rates and Time Trends for All Subtypes Combined

Between 2000 and 2015, there were a total of 259,288 incident cases of NHL. The age-adjusted incidence rate of NHL (all subtypes combined) in 2000 and 2015 was 27.8 per 100,000 population (95% CI: 27.35, 28.25) and 23.82 per 100,000 population (95% CI: 23.46, 24.19), respectively (Figure 1). The Joinpoint analysis indicates that the age-adjusted rate actually increased from 2000 to 2004 (APC 0.76%, $p<.05$) but then the decreased between 2004 and 2015 (2004-2008: APC -1.13%, $p<0.05$; 2008-2015 -2.10%, $p<0.05$) (Table 2).

The age-adjusted incidence rate for males has been consistently higher than that of females during the study period (Figure 2, Table 3). For instance, in 2015 the age-adjusted rate was 29.05 per 100,000 for males and 19.5 per 100,000 for females. For males, the age-adjusted incidence rate increased from 2000 to 2005 and then decreased from 2005 to 2015 (APC -1.94%, $p<0.05$). For females, there was an increase in the age-adjusted incidence rate from 2000 to 2004 (APC 1.51%, $p<0.05$) and a decrease from 2004 to 2015 (APC -1.80%, $p<0.05$) (Figure 2, Table 2).

Age-adjusted incidence rate has been consistently higher in older age groups compared to younger age groups throughout the study period (Figure 3). In 2015, the age-adjusted incidence rate per 100,000 population was 85.29 for the 70+ group, 50.83 for the 60-69 group, 25.19 for the 50-59 group, 10.61 for the 40-49 group, 4.52 for the 30-39 group, and 2.27 for the 20-29 group. For the 70+ group, age-adjusted incidence rate increased from 2000 to 2005 (APC 1.34%, $p<0.05$) and decreased from 2005 to 2015 (APC-2.21%, $p<0.06$). For the 60-69 group, an increase in the age-adjusted rate occurred from 2000 to 2003 and a decrease from 2003 to 2015 (APC-1.68%, $p<0.05$). For the 50-59 group, age-adjusted rates have been decreasing from 2000 to 2015 (APC-1.18%, $p<0.05$). For the 40-49 group, rates decreased from 2000 to 2008 and decreased more drastically from 2008 to 2015 (APC-2.29, $p<0.05$). For the 30-39 group, a decrease occurred from 2000 to 2015 (APC -0.98%, $p<0.05$). For the 20-29 group, an insignificant increase has been occurring since 2000 (APC 0.11%), though it should be noted that rates were still lower than all other age groups throughout the study period (Table 2).

The overall age-adjusted incidence rate for whites has been consistently higher than all other races during the study period. In 2015, age-adjusted incidence rate per 100,000 was 25.88 for whites, 17.40 blacks, 11.58 for AI/AN, and 15.41 for API (Figure 4). For whites, an increase occurred from 2000 to 2006 and a decrease occurred from 2006 to 2015 (APC-1.93%, $p<0.05$). For blacks, a decrease has occurred throughout the study period (APC -0.94%, $p<0.05$). This is also true for AI/AN (APC -1.18%) and API (APC -1.02%, $p<0.05$) (Table 2).

Overall age-adjusted rate for non-Hispanics has also been consistently higher than Hispanics throughout the study period (Figure 5). In 2015, age-adjusted incidence rate was 24.6 per 100,000 for non-Hispanics and 19.31 per 100,000 for Hispanics. From 2000 to 2003, rates increased in non-Hispanics. Rates decreased from 2003 to 2008 and more drastically from 2008 to 2015 (APC -2.06%, $p<0.05$). For

Hispanics, rates have been decreasing since 2000, but decrease was only significant from 2010 to 2015 (APC -2.9%, $p<0.05$) (Table 2).

Age-Adjusted Incident Rates by Subtype

For the period 2000-2015, the overall age-adjusted incidence rate for all subtypes combined was 26.9 per 100,000 population (Table 3). The incidence rate per 100,000 population was the highest for diffuse large B-cell lymphoma (8.70) followed by chronic lymphocytic leukemia/small lymphocytic lymphoma (7.24) and follicular lymphoma (4.45). Age-adjusted incidence rates increased as age increased for all subtypes. As far as the sex difference, for all subtypes males had higher incidence rates than females except for marginal-zone lymphoma, in which there was no statistical difference between males and females (Table 3). Age-adjusted incidence rates were highest in whites for all subtypes except cutaneous T-cell lymphoma and peripheral T-cell lymphoma, in which blacks had the highest incidence rates (RR=1.65, $p<0.05$; RR=1.90, $p<0.05$) (Table 3). AI/AN had the lowest incidence rates for all subtypes except chronic lymphocytic leukemia/small lymphocytic lymphoma and Mantle-cell lymphoma , in which API and blacks had the lowest incidence rates, respectively. Finally, non-Hispanics had higher age-adjusted incidence rates than Hispanics for all subtypes except Diffuse Large B-Cell Lymphoma and Burkitt lymphoma, in which Hispanics had significantly higher incidence (RR=1.05, $p<0.05$; RR=1.17, $p<0.05$) (Table 3).

Time Trend in Age-Adjusted Incidence Rate for All Subtypes

Figures 6-14 show the Joinpoint analysis results for different subtypes. The age-adjusted incidence rates have been decreasing since 2004 in chronic lymphocytic leukemia/small lymphocytic lymphoma (APC -2.63%, $p<0.05$) (Figure 6). The Mantle-cell lymphoma incidence rate has been increasing since 2000 (APC 0.77%, $p<0.05$) (Figure 7). Lymphoplasmacytic lymphomas incidence rate has been decreasing since 2000 (APC -2.01%, $p<0.05$) (Figure 8). Incidence rate has been decreasing since

2003 in diffuse large B-cell lymphoma (APC -1.11%, $p<0.05$) (Figure 9), since 2009 in Burkitt lymphoma (APC -7.06%, $p<0.05$) (Figure 10), since 2007 in marginal-zone lymphoma (APC -1.14%) (Figure 11), and since 2006 in follicular lymphoma (APC -3.48%, $p<0.05$) (Figure 12). Incidence rate has been steady in cutaneous T-cell lymphoma (mycosis fungoides and Sezary) syndrome (APC -0.03%) (Figure 13). Incidence rate has been decreasing since 2000 in peripheral T-cell lymphoma (APC -2.08%, $p<0.05$) (Figure 14).

Analysis of subtype time trends by demographic subgroups revealed more hidden trends. For marginal-zone lymphoma, incidence time trends have been decreasing in the overall population (APC -1.14%) (Figure 11) and in males (APC -2.01%, $p<0.05$) but has been increasing in females (APC 0.47%) (Table 2). For all subtypes, incidence rates increased as age increased. However, for some subtypes, incidence trends measured by APC were different for different age groups (Table 2). For mantle-cell lymphoma, the overall APC for all age groups was 0.77% ($p<0.05$) (Figure 7). However, the APC for the 30-39 age group 6.25% ($p<0.05$), more than 8 times the overall APC. For Burkitt lymphoma, overall incidence increased from 2000-2009 (APC 1.73%) and has been decreasing since 2009 (APC -7.06%, $p<0.05$). However, in the 20-29 age group, it has been increasing (APC 1.00%) since 2000 (Table 2). For racial time trends, there were many differences. For marginal zone lymphoma, overall incidence has been decreasing since 2007 (APC-1.14%, $p<0.05$) (Figure 11), but in blacks it has been increasing (APC 0.98%). For lymphoplasmacytic lymphomas, overall incidence has been decreasing since 2000 (APC-2.01%, $p<0.05$). While this is consistent across most demographic groups, it is lower in the black population (APC -0.19%) (Table 2). For trends in marginal-zone lymphoma, Hispanic population incidence trends have been constant (APC-0.03%) while the overall population has been decreasing since 2007 (APC-1.14%, $p<0.05$) (Table 2). For follicular lymphoma, overall trends have been decreasing since 2006 (APC-3.48%, $p<0.05$) and this pattern is reflected in all groups except the Hispanic group, in which has remained relatively constant (APC 0.08%) (Table 2).

Discussion

We examined the incidence rate trends of NHL by subtype and demographic factors using SEER 18 program data 2000-2015. Findings from this study are mostly consistent with findings from studies using earlier data – the increase in the age-adjusted incidence rates slowed down since the 1990s (Howe et al., 2001). Chiu and Hou (2015) reported that this trend continued into the early 2000s and leveled off.

Time Trends by Subtype

The subtype with the most notable time trend was observed for Mantle-cell lymphoma. The age-adjusted incidence rate increased between 2000 and 2015 for Mantle-cell lymphoma while the rate decreased for many other subtypes during the same period. It is unlikely that the increase is due to improved detection since increase in incidence was mostly limited to stage IV (Zhou et al., 2008). Clinical symptoms do not manifest until late stages, making it difficult to detect and treat and giving Mantle-cell lymphoma the poorest prognosis of all subtypes of NHL (Zhou et al., 2008). Early diagnosis of Mantle-cell lymphoma continues to be a challenge as the incidence rate continues to increase.

Cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome) incidence has stabilized, which is consistent with findings in other studies. A study of the 1973-2009 SEER registry found that APC increased from 1973 to 1998 (APC 5.7%) and has been stable from 1998 to 2009 (APC 0.1%) (Korgavkar, Xiong, & Weinstock, 2013). This study showed that trends have not changed since 2009. This stabilization of incidence is thought to be due to improved detection in the 70's (which would have caused the increase) reaching a natural maximum presently as physicians can now detect all cases. Though this would appear to be a stabilization of incidence, the reason for stabilization is largely unknown (Korgavkar, Xiong, & Weinstock, 2013).

The decline in age-adjusted incidence rates of all other subtypes may be due to a number of reasons. Hardell & Eriksson (2003) hypothesized that the decline was due to a decrease in chemical

exposure to phenoxyacetic acids and chlorophenols. These chemicals were used as herbicides in the 1970s but they have since been prohibited, thus becoming less prominent in the environment. The reduction in exposure eventually led to a reduction in the disease. Hardell & Eriksson (2003) along with many others (Clarke & Glaser, 2002; Grulich et al., 2000), have also shown that the increase in the 70's and 80's coincided with the Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) epidemic. Studies have shown that prolonged immune deficiency greatly increases risk for NHL (Grulich et al., 2000). The slowing incidence, and now decrease, is thought to be due to the introduction of successful antiviral therapy (Shiels et al., 2013). However, the increase in Mantle-cell lymphoma incidence rates does not follow this.

Age-Adjusted Incidence Rates by Subtype

This study found that incidence rates differed by sex, race, and ethnicity in some subtypes. Most notable was the higher incidence in blacks compared to whites in cutaneous T-cell lymphomas (mycosis fungoides and Sezary syndrome) and peripheral T-cell lymphomas. This has been confirmed in many studies using older data and the disparity continues, but the reason is not known (Imam et al., 2013; Korgavkar, Xiong, & Weinstock, 2013). Imam et al (2013) recommended controlling for factors not in the SEER database such as access to care, referral rate to dermatologists, and insurance coverage to understand if the disparity is due socioeconomic factors or biological factors.

Marginal-zone lymphoma presented difference in age-adjusted incidence rates between men and women compared to other subtypes. While all other subtypes showed higher male incidence rates, marginal-zone lymphoma showed that male and female incidence rates were not statistically different (RR=0.99, 95% CI: 0.96, 1.01). Female incidence rates were higher than male incidence rates in white, AI/AN, and blacks, but was only significant in blacks (RR=1.1, $p<0.05$). Female incidence rates were also higher in all age groups, except the 70+ age group. This may be explained by the association between

marginal-zone lymphoma and autoimmune diseases and Helicobacter pylori infection. Marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT), the most common type of marginal-zone lymphoma, is associated with autoimmune disease inflammation and gastritis due to H. pylori. Because autoimmune diseases are more prevalent in women and H. pylori infection has similar prevalence in men and women, this is thought to balance out the incidence rates between men and women (Morton et al., 2006; Kiesewetter et al., 2016).

Although most subtypes of NHL are rare in children, Burkitt lymphoma is one of the most common subtypes of NHL found in children and is rare in adults (Georgakis et al., 2016). When comparing the age-adjusted incidence rates of Burkitt lymphoma in the 20-29 age group to the 70+ age group, the difference is not as great compared to other subtypes (RR=3.42, $p<0.05$) (Table 3). Time trends have also been increasing in the 20-29 age group (APC 1.00%) while they has been decreasing since 2007 in all other subtypes (APC –7.06%, $p<0.05$). As far as we are aware, the higher incidence rates in Hispanics compared to non-Hispanics (RR=1.16, $P<0.05$) in Burkitt lymphoma are not reported in any other studies, although this is a more recent trend and may not have been adequately explored yet. Endemic Burkitt lymphoma, a type found in Africa, is very well understood and is linked to Epstein - Barr virus (EBV) and *Plasmodium falciparum* malaria infection. Sporadic Burkitt lymphoma, a type found in the United States, is not strongly linked to EBV. Additionally, since malaria is not a prevalent issue in the United States, sporadic Burkitt lymphoma's epidemiology and etiology are not well-understood. As of 2005, it is known to be one of the most common childhood non-Hodgkin lymphomas and is more common in males than females (Mbulaiteye et al., 2009).

Diffuse large B-cell lymphoma is another subtype in which Hispanic incidence rates are higher than non-Hispanic incidence rates (RR=1.05, $p<0.05$). Li et al (2015) found this to be true only in females; males still had higher non-Hispanic incidence rates compared to Hispanics. Further analysis by sex in this

study found that Hispanic incidence rates were higher than non-Hispanic incidence rates for females only, also. However, in males, the non-Hispanic and Hispanic incidence rates were identical - something not reported in other studies.

Summary

Many of the findings in this study were corroborated by past studies in terms of age-adjusted incidence rates by subtypes and subgroups. Similarly, many trends seemed to continue logically from past studies with data before the year 2000. However, there were some new findings that have not been reported in any published studies, to our best knowledge. Many of these were related to APC in different age groups not following the same trends as the overall APC in subtypes. The APC in the 30-39 age group for Mantle-cell lymphoma (APC 6.25, $p<0.05$) was significantly higher than the overall APC (0.77%, $p<0.05$). Marginal-zone lymphoma incidence has been increasing in the 20-29 age group (APC 1.47%), 30-39 age group (APC 2.97%, $p<0.05$) when the overall incidence has been decreasing (APC –1.14%). Overall cutaneous T-cell lymphoma incidence has been stable but has been increasing in the 20-29 (APC 2.39%) and 30-39 (APC 2.36%) age groups. Peripheral T-cell lymphoma incidence has but decreasing (APC -2.08%, $p<0.05$), but is increasing in the 20-29 age group (APC 1.55%).Further analysis comparing age groups between sexes or among races may reveal trends that are more meaningful. These trends may also predict that incidence will rise or fall in certain age groups due to new risk factors that are not yet apparent.

One of the limitations of this study is the existence of multiple classification systems and constant changing of classification. Many subtypes have been re-coded many times, making it difficult to correctly classify subtypes over a long period of time. The last WHO recode occurred in 2008, meaning that some subtypes may have been coded differently previously. As classification schemes evolve, the number of not otherwise specified (NOS) cases decrease. The incidence of some subtypes may appear to

increase after a subtype is no longer classified as NOS and given a new classification. Additionally, some subtypes such as diffuse large B-cell lymphoma and peripheral T-cell lymphoma included many types within themselves (Table 1). Some of these types may need to be classified as their own subtype because their epidemiological or etiological differences may influence discrepancies in trends and rates. Another limitation lies in the reporting of cases in the AI/AN population. Only cases that are within a Contract Health Service Delivery Area (CHSDA) are included in SEER data (NIH, 2018). Therefore, data is sporadic may not be representative of actual NHL incidence in the AI/AN population. Finally, the registry only includes data for 27.8% of the US population until 2015, so it is not representative of the entire current U.S. population. Strengths of this study include the sheer size of the sample (259,228 incident cases) and the use of the most current and accurate WHO classification scheme and ICD-O-3 codes. The SEER data was very diverse in terms of geographical area, age, race, and ethnicity.

Moving forward, differences in incidence rates and trends found in this study can be used as hypotheses for future studies to better understand the epidemiology and determine etiology of these cancers. Further sub-analysis can also be performed, such as comparing racial trends among different age groups or between sexes, to reveal more hidden rates and trends that might help us understand more about subtypes. Additionally, some subgroups that were not analyzed in this study such as geographical location and stage of cancer may also provide more epidemiological information. The SEER database is very useful for analyzing data, but it does not include some variables that may be crucial in understanding differences in trends and rates such as access to care, patient compliance, education level, or insurance coverage. If such data could be merged with the data available in SEER's database, we might be able to better explain variations in incidence among subtypes and subgroups.

NHL is a very complex and diverse group of cancers. The etiology of most subtypes remains largely unknown. Continued data collection and analysis as well as further development classification

schemes are needed to understand and interpret the differences in trends and rates in subtypes. This understanding can help identify etiology and help reduce risks and prevent new cases. Despite certain limitations, the findings of this study can be a stepping stone in predicting and preventing new NHL cases.

References

American Cancer Society (2017). Cancer Facts and Figures 2017. Atlanta: American Cancer Society.

American Cancer Society. (2018, August 1). Key Statistics for Non-Hodgkin Lymphoma. Retrieved September 30, 2018, from https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/key-statistics.html.

Campo, E., Swerdlow, S. H., Harris, N. L., Pileri, S., Stein, H., & Jaffe, E. S. (2011). The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*, *117*(19), 5019-32.

Chiu, B. C. H., & Hou, N. (2015). Epidemiology and etiology of non-hodgkin lymphoma. In *Non-Hodgkin Lymphoma* (pp. 1-25). Springer, Cham.

Clarke, C. A., & Glaser, S. L. (2002). Changing incidence of non-Hodgkin lymphomas in the United States. Cancer, 94(7), 2015-2023.

Georgakis, M. K., Karalexi, M. A., Agius, D., Antunes, L., Bastos, J., Coza, D., ...&Ryzhov, A. (2016). Incidence and time trends of childhood lymphomas: findings from 14 Southern and Eastern European cancer registries and the Surveillance, Epidemiology and End Results, USA. *Cancer Causes & Control*, *27*(11), 1381-1394.

Grulich, A. E., Wan, X., Law, M. G., Milliken, S. T., Lewis, C. R., Garsia, R. J., ... &Kaldor, J. M. (2000). B-cell stimulation and prolonged immune deficiency are risk factors for Non-Hodgkin's Lymphoma in people with AIDS. *Aids*, *14*(2), 133-140.

Howe, H. L., Wingo, P. A., Thun, M. J., Ries, L. A., Rosenberg, H. M., Feigal, E. G., & Edwards, B. K. (2001). Annual report to the nation on the status of cancer (1973 through 1998), featuring cancers with recent increasing trends. *Journal of the National Cancer Institute*, *93*(11), 824-842.

Imam, M. H., Shenoy, P. J., Flowers, C. R., Phillips, A., &Lechowicz, M. J. (2013). Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. Leukemia & lymphoma, 54(4), 752-759

International Agency for Research on Cancer (2018). *International Classification of Diseases for Oncology.* Retrieved 06, October 2018, from http://codes.iarc.fr/.

Jaffe, E. S., Raffeld, M., Medeiros, L. J., &Stetler-Stevenson, M. (1992). An overview of the classification of non-Hodgkin's lymphomas: an integration of morphological and phenotypical concepts. *Cancer research*, *52*(19 Supplement), 5447s-5452s.

Kiesewetter, B., Lukas, J., Dolak, W., Simonitsch-Klupp, I., Mayerhoefer, M. E., &Raderer, M. (2016). Gender Aspects in Extranodal Marginal Zone B-Cell Lymphoma of the Mucosa-Associated Lymphoid Tissue: Does Sex Matter?.*Oncology*, *91*(5), 243-250.

Kohler, B. A., Sherman, R. L., Howlader, N., Jemal, A., Ryerson, A. B., Henry, K. A., ... & Henley, S. J. (2015). Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *JNCI: Journal of the National Cancer Institute*, *107*(6).

Koivunen, R. J., Satopää, J., Meretoja, A., Strbian, D., Haapaniemi, E., Niemelä, M., ... & Putaala, J. (2015). Incidence, risk factors, etiology, severity and short‐term outcome of non‐traumatic intracerebral hemorrhage in young adults. *European journal of neurology*, *22*(1), 123-132.

Korgavkar, K., Xiong, M., & Weinstock, M. (2013). Changing incidence trends of cutaneous T-cell lymphoma. JAMA dermatology, 149(11), 1295-1299.

Leukemia and Lymphoma Society, (2015, February 26). Non-Hodgkin Lymphoma. Retrieved May 8, 2018 from https://www.lls.org/lymphoma/non-hodgkin-lymphoma/diagnosis/nhl-subtypes

Li, Y., Wang, Y., Wang, Z., Yi, D., & Ma, S. (2015). Racial differences in three major NHL subtypes: descriptive epidemiology. *Cancer epidemiology*, *39*(1), 8-13.

Mbulaiteye, S. M., Biggar, R. J., Bhatia, K., Linet, M. S., &Devesa, S. S. (2009). Sporadic childhood Burkitt lymphoma incidence in the United States during 1992–2005. *Pediatric blood & cancer*, *53*(3), 366-370.

Morton, L. M., Wang, S. S., Devesa, S. S., Hartge, P., Weisenburger, D. D., &Linet, M. S. (2006). Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. *Blood*, *107*(1), 265-276.

National Cancer Institute. (n.d.). Lymphomas & Leukemias. Retrieved from https://training.seer.cancer.gov/icdo3/new/lymphomas-leukemias.html.

National Cancer Institute. (2018). Morphology & Grade. Retrieved October 06, 2018, from https://training.seer.cancer.gov/lymphoma/abstract-code-stage/morphology.

National Cancer Institute. (2018). Race Recode Changes. Retrieved October 12, 2018, from https://seer.cancer.gov/seerstat/variables/seer/race_ethnicity/.

Rudan, I., O'Brien, K. L., Nair, H., Liu, L., Theodoratou, E., Qazi, S., Lukšić, I., Fischer Walker, C. L., Black, R. E., Campbell, H., Child Health Epidemiology Reference Group (CHERG) (2013). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *Journal of global health*, *3*(1), 010401.

Shiels, M. S., Engels, E. A., Linet, M., Clarke, C. A., Li, J., Hall, H. I., ...& Morton, L. M. (2013). The epidemic of non-Hodgkin lymphoma in the United States: disentangling the effect of HIV, 1992-2009. *Cancer Epidemiology and Prevention Biomarkers*, cebp-0040.

Siegel, R. L., Miller, K. D., Fedewa, S. A., Ahnen, D. J., Meester, R. G., Barzi, A., &Jemal, A. (2017). Colorectal cancer statistics, 2017. *CA: a cancer journal for clinicians*, *67*(3), 177-193.

Zhou, Y., Wang, H., Fang, W., Romaguer, J. E., Zhang, Y., Delasalle, K. B., ... & Wang, M. (2008). Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer: Interdisciplinary International Journal of the American Cancer Society, 113(4), 791-798.

Tables and Figures

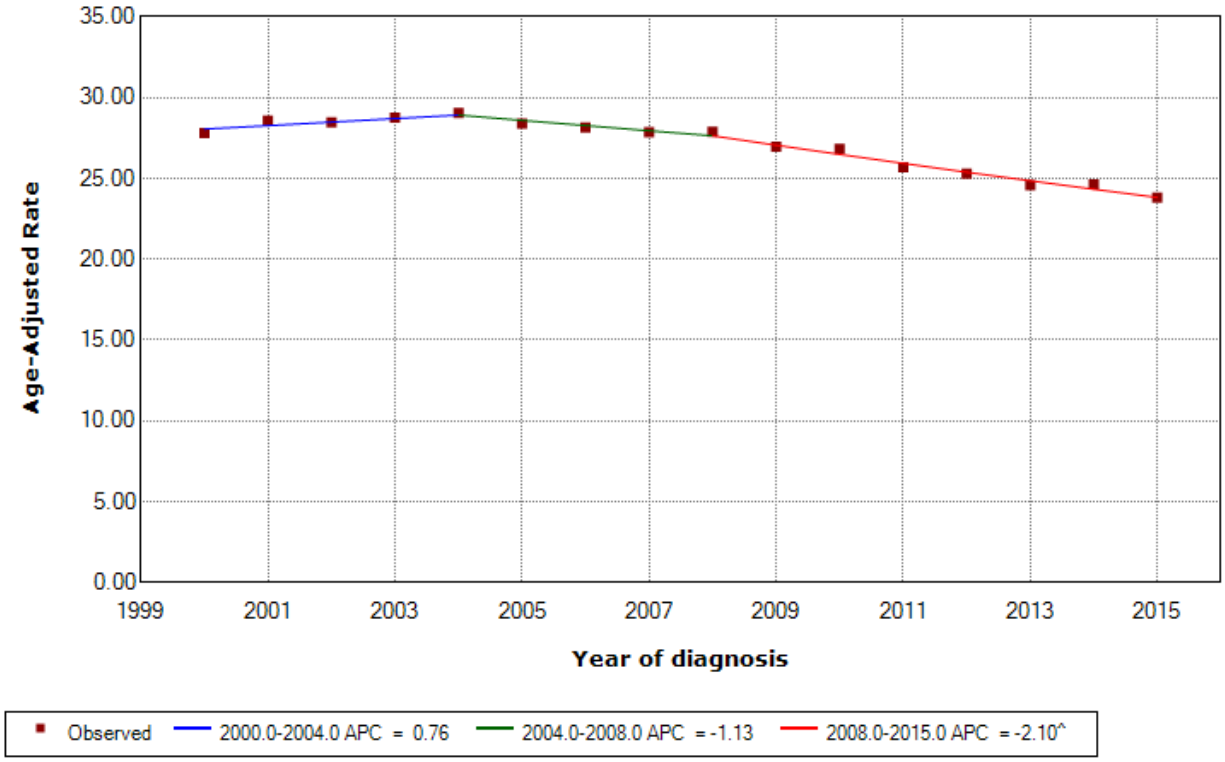

Figure 1. Age-adjusted NHL incidence rate 2000-2015: SEER 18 Program

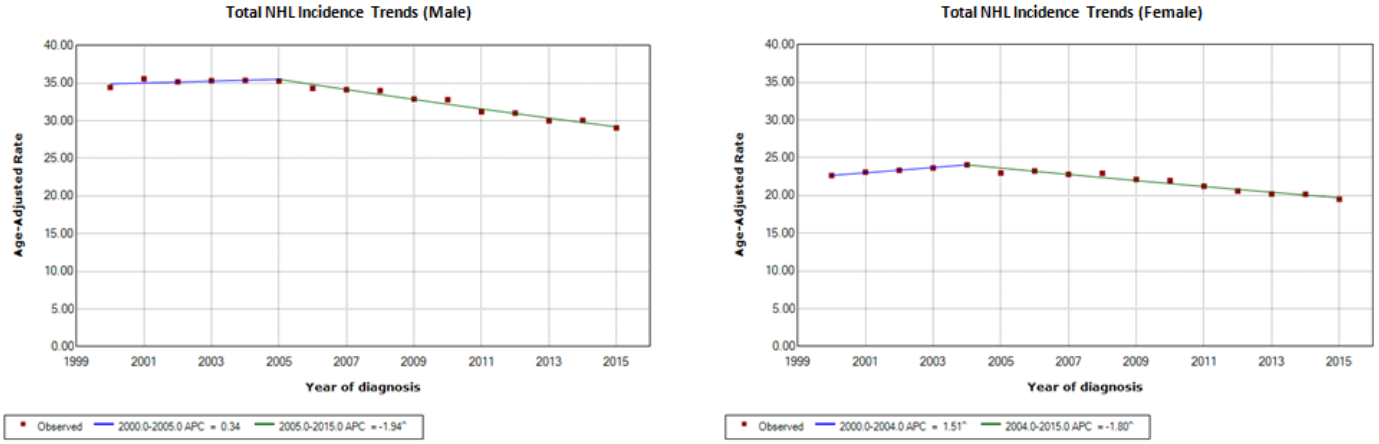

Figure 2. Comparing overall NHL incidence trends between males and females.

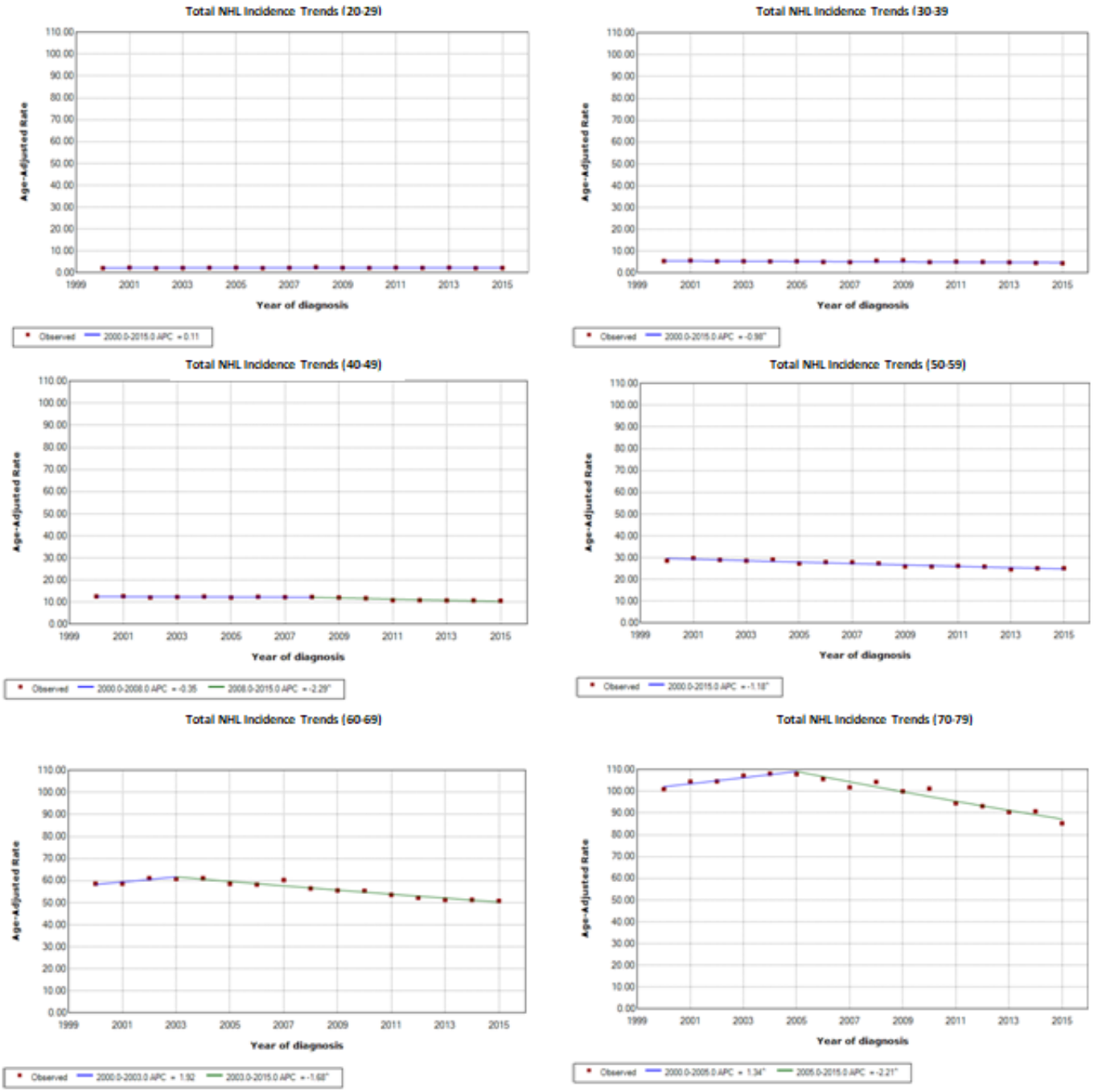

Figure 3. Comparing overall NHL incidence trends among age groups.

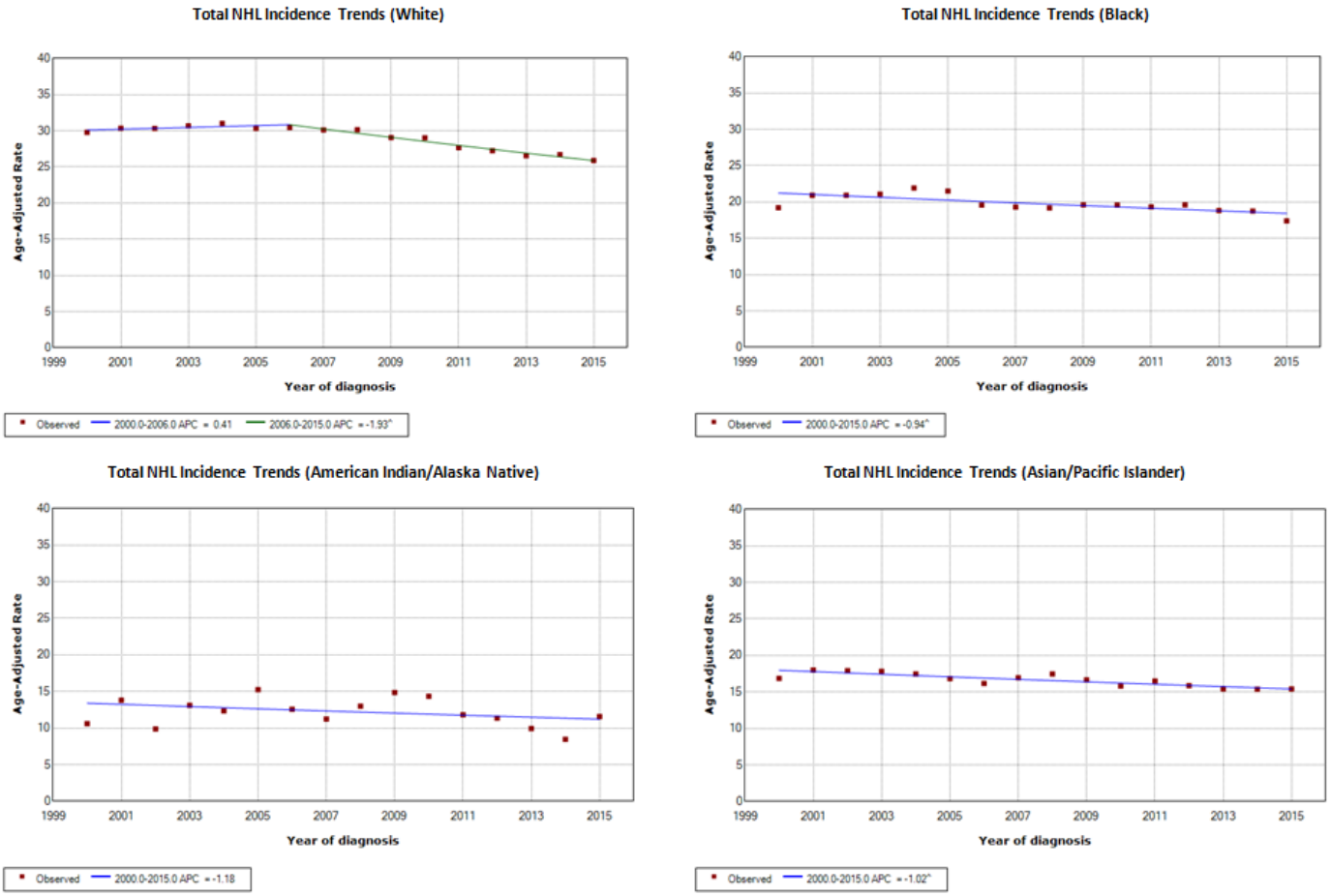

Figure 4. Comparing overall NHL incidence trends among races.

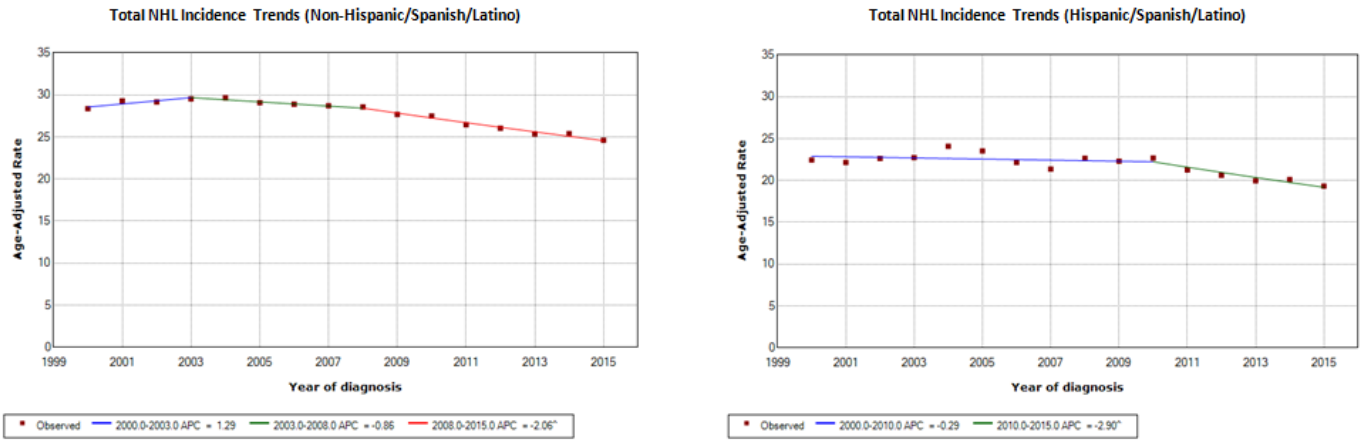

Figure 5. Comparing overall NHL incidence trends between Hispanic/non-Hispanic groups.

Age-Adjusted Incidence Rate of Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, 2000-2015

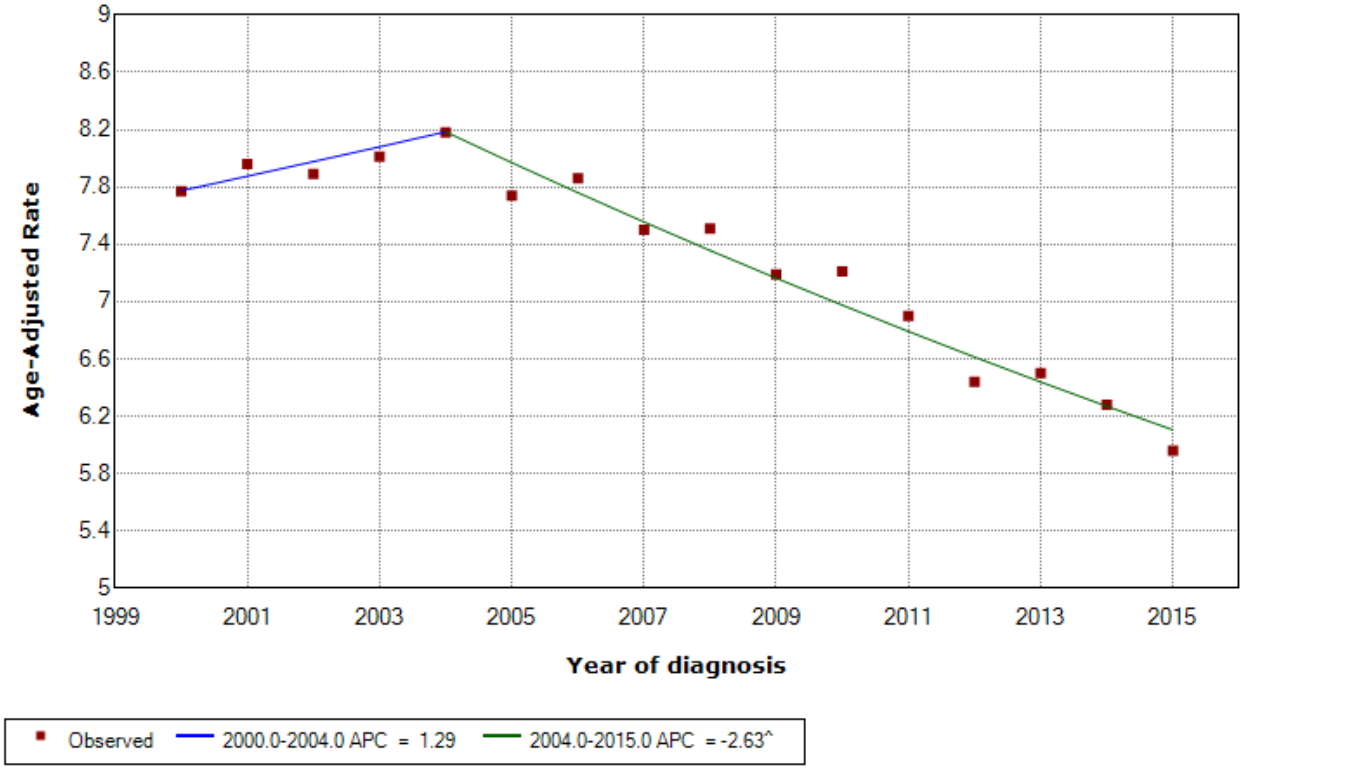

Figure 6. Age-Adjusted Incidence Rate Time Trend for CLL/SLL

Age-Adjusted Incidence Rate of Mantle-Cell Lymphoma, 2000-2015

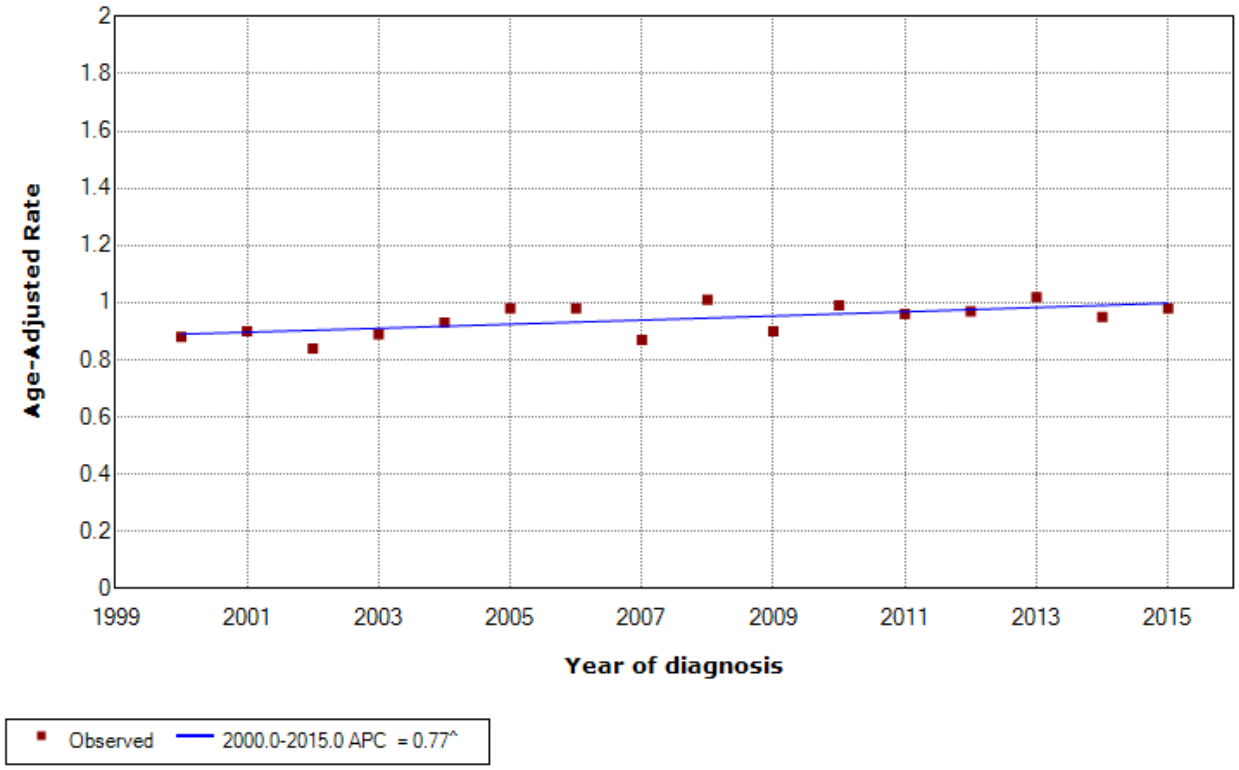

Figure 7. Age-Adjusted Incidence Rate Time Trend for MCL

Age-Adjusted Incidence Rate of Lymphoplasmacytic lymphomas, 2000-2015

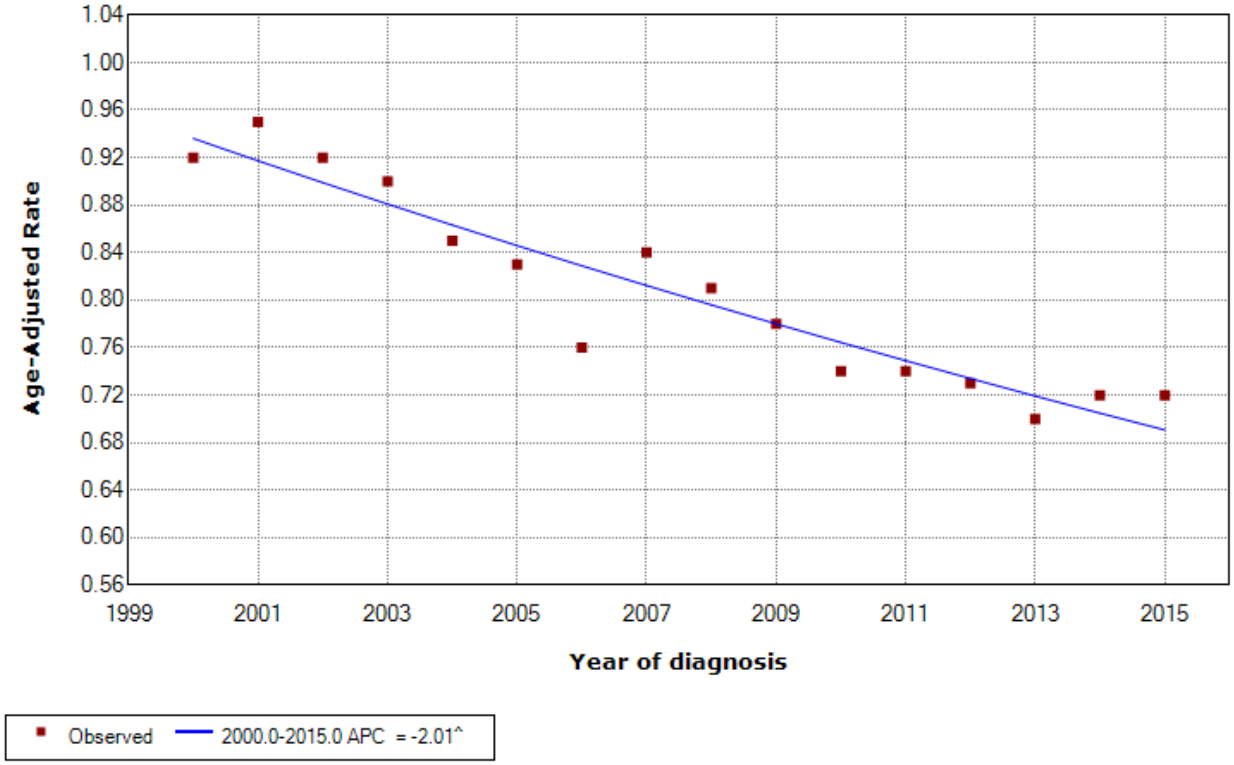

Figure 8. Age-Adjusted Incidence Rate Time Trend for LPL

Age-Adjusted Incidence Rate of Diffuse Large B-Cell Lymphoma, 2000-2015

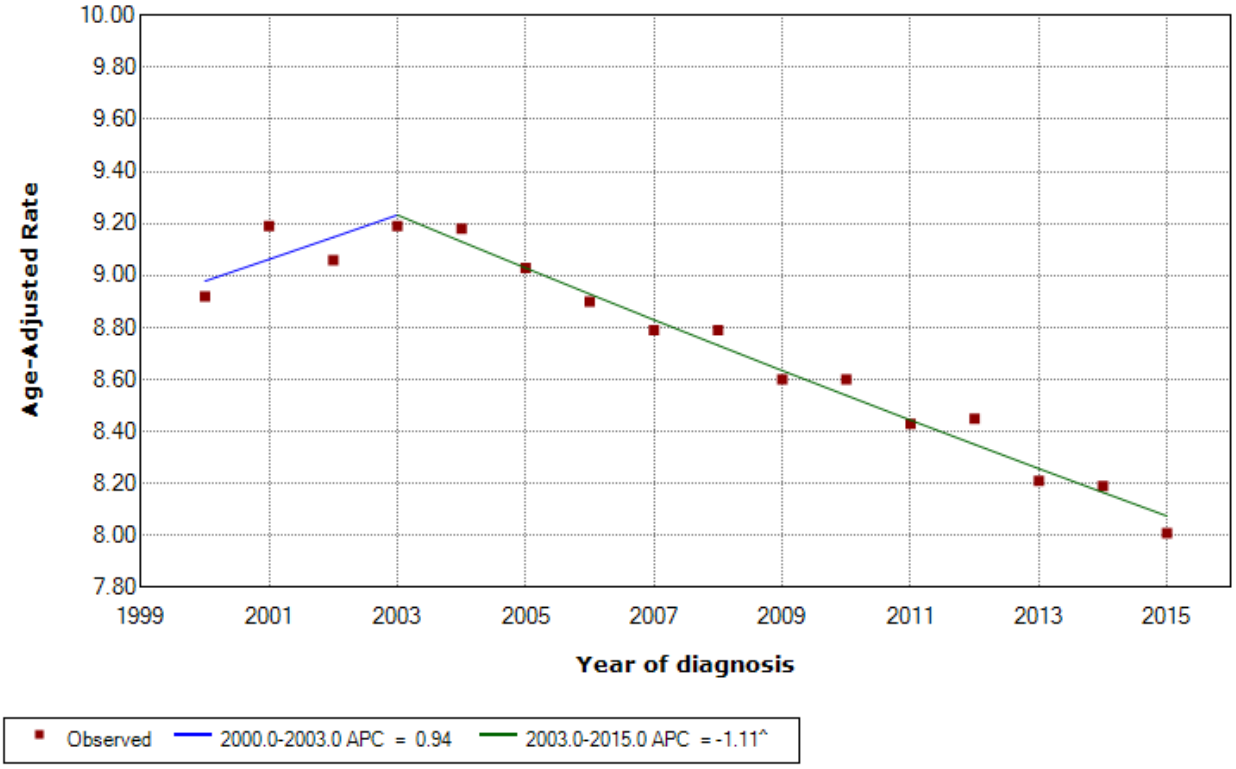

Figure 9. Age-Adjusted Incidence Rate Time Trend for DLBCL

Age-Adjusted Incidence Rate of Burkitt Lymphoma, 2000-2015

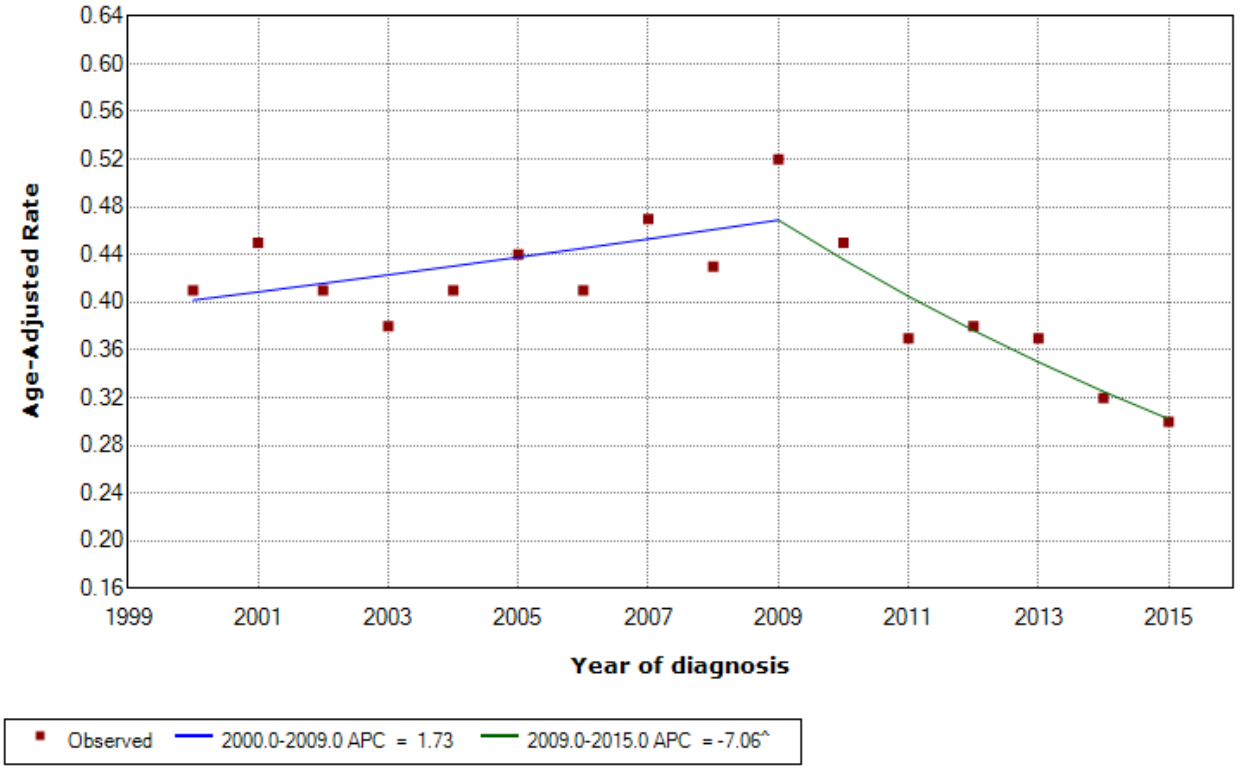

Figure 10. Age-Adjusted Incidence Rate Time Trend for BL

Age-Adjusted Incidence Rate of Marginal-Zone Lymphoma, 2000-2015

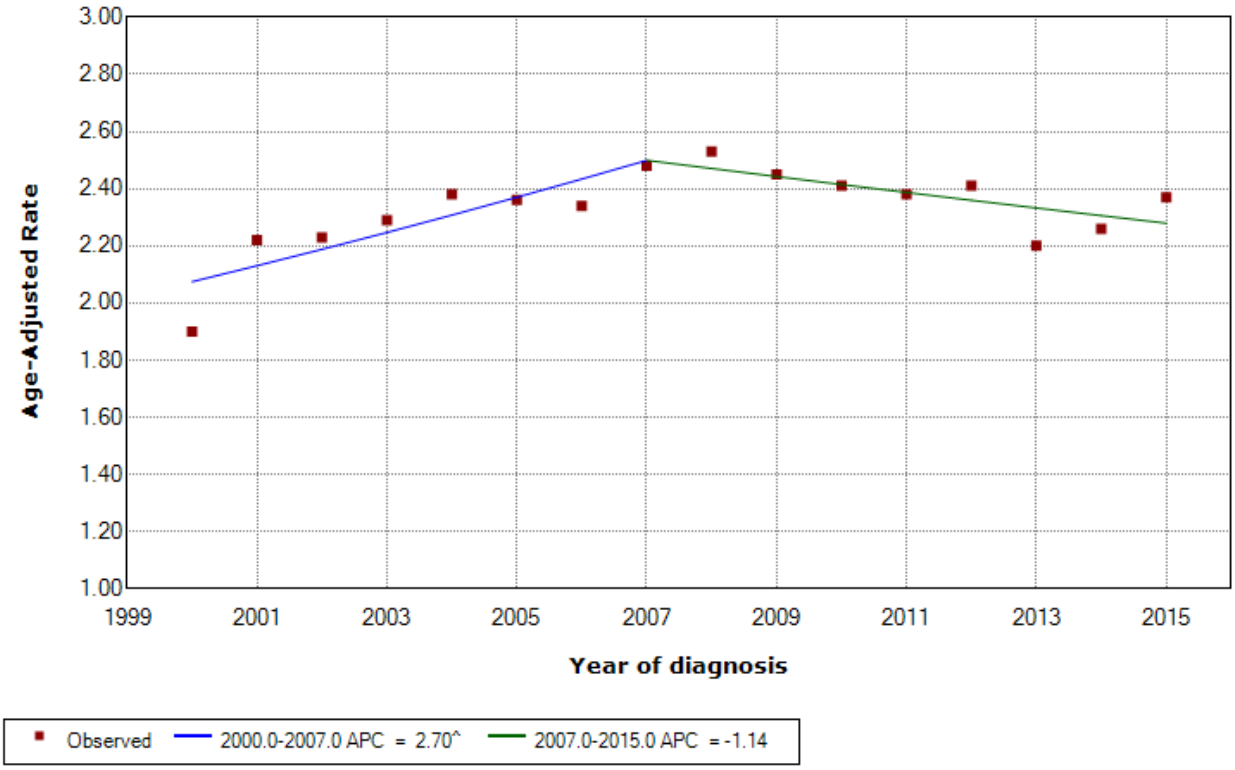

Figure 11. Age-Adjusted Incidence Rate Time Trend for MZL

Age-Adjusted Incidence Rate of Follicular Lymphoma, 2000-2015

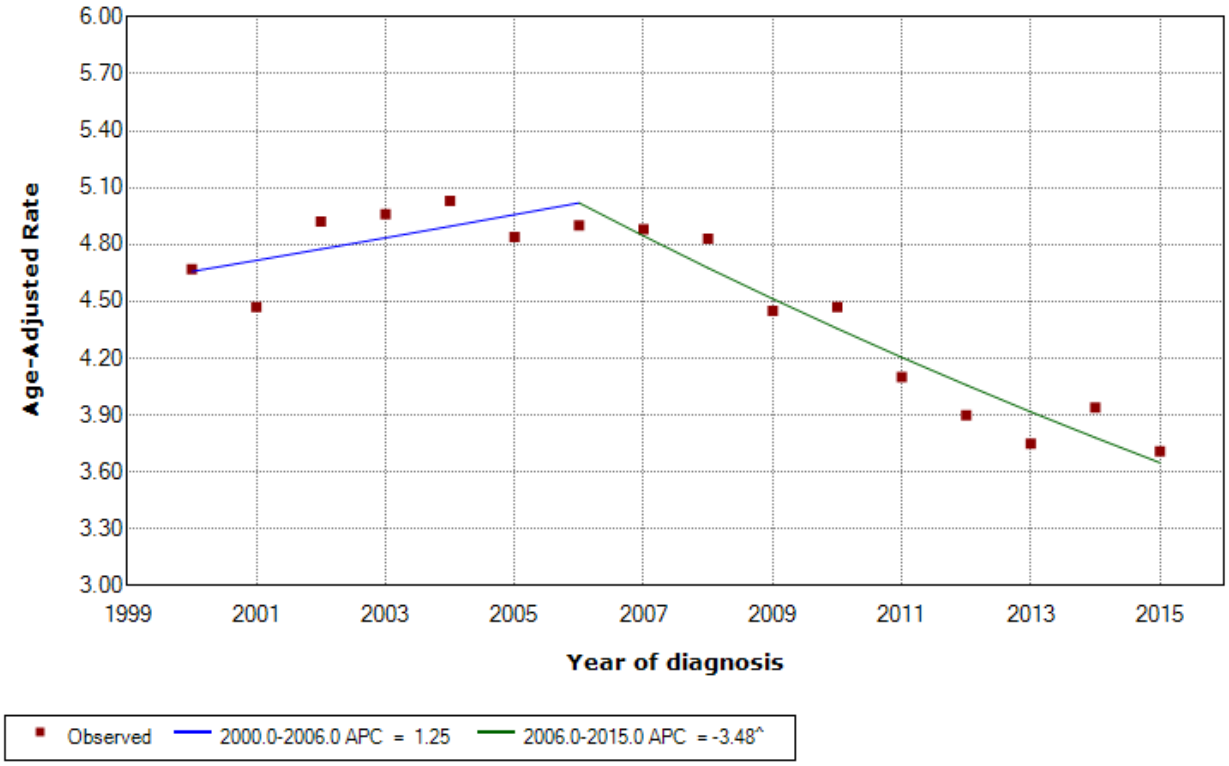

Figure 12. Age-Adjusted Incidence Rate Time Trend for FL

Age-Adjusted Incidence Rate of Cutaneous T-Cell Lymphomas, 2000-2015

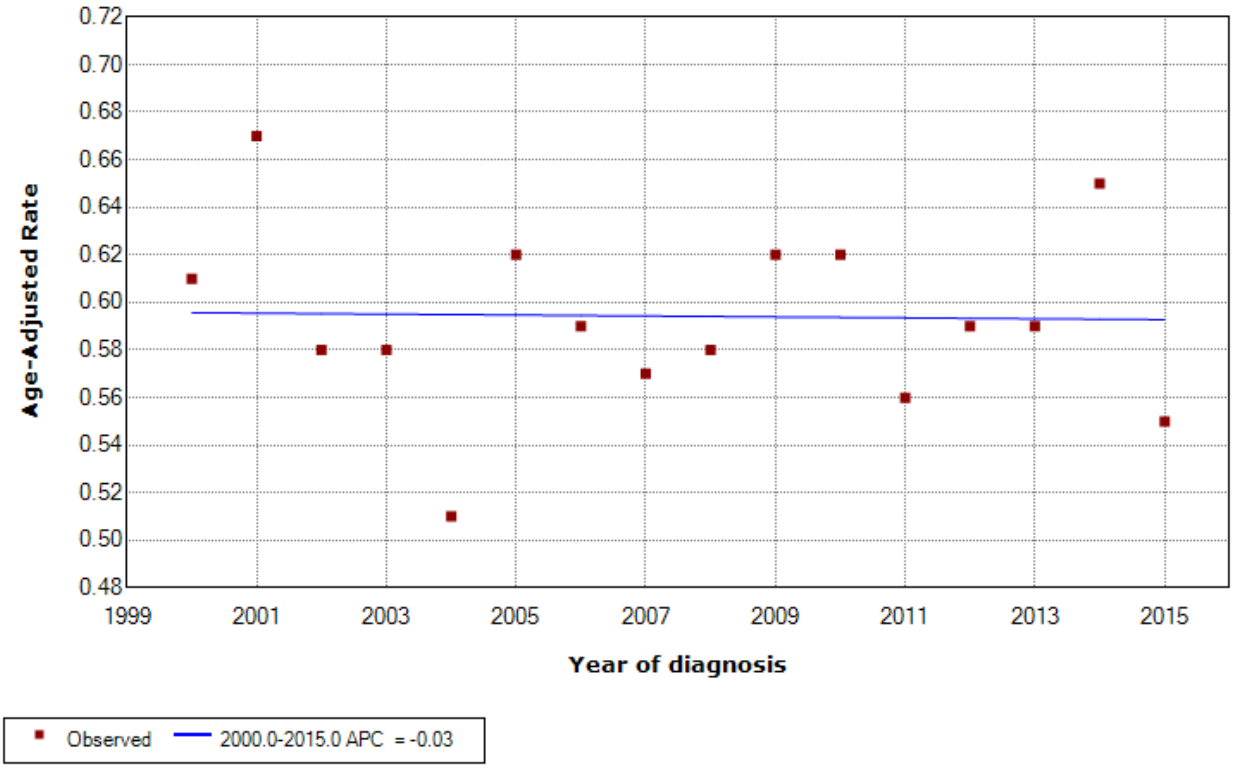

Figure 13. Age-Adjusted Incidence Rate Time Trend for CTCL

Age-Adjusted Incidence Rate of Peripheral T-Cell Lymphoma, 2000-2015

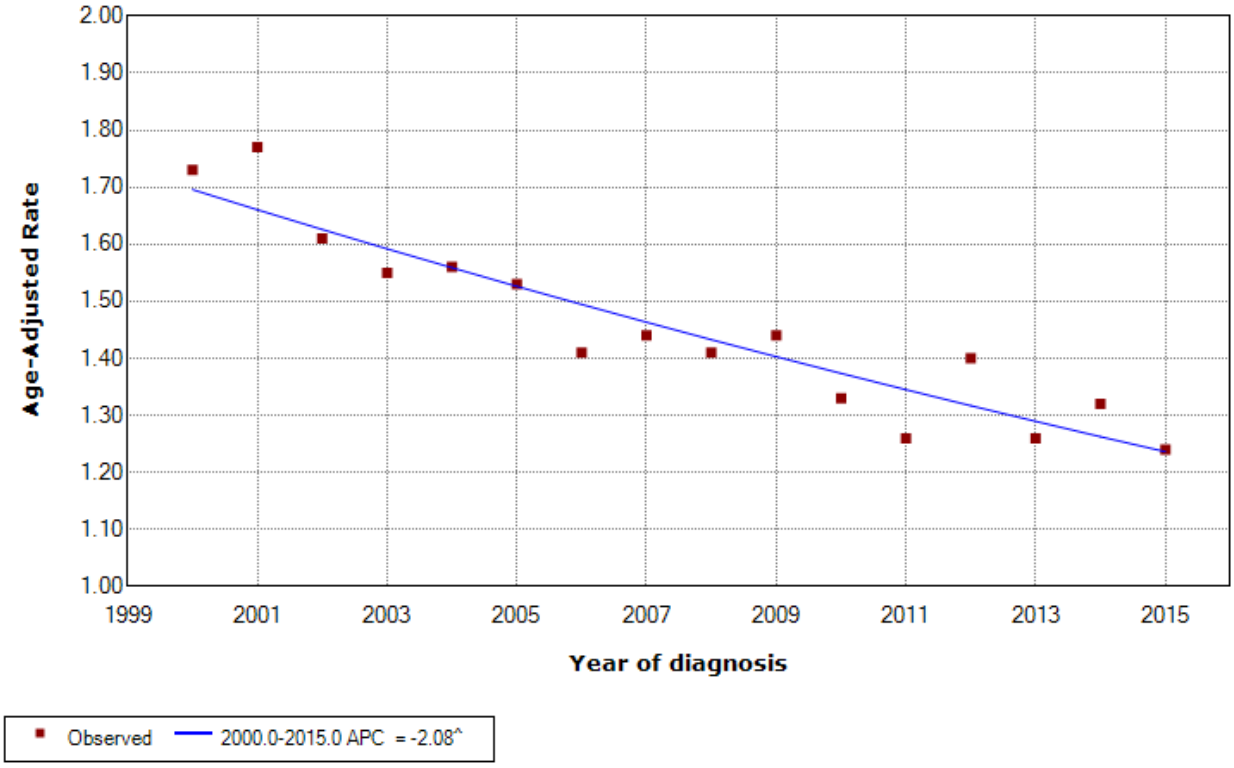

Figure 14. Age-Adjusted Incidence Rate Time Trend for PTCL

Table 2. Annual Percentage Change (APC) by Age, Sex, Race, and Ethnicity for each Subtype, 2000-2015

	APC for CLL/SLL	APC for Mantle Cell Lymphoma	APC for Lympho-plasmacytic Lymphomas	APC for DLBCL	APC for Burkitt lymphoma	APC for Marginal Zone Lymphoma	APC for Follicular Lymphoma	APC for Cutaneous T-Cell Lymphoma	APC for Peripheral T-Cell Lymphoma	APC for Total NHL
Sex										
Male	2000-2004: 0.24 2004-2010: -2.15* 2010-2015: -3.75*	2000-2015: 0.62*	2000-2015: -2.55*	2000-2015: -0.85*	2000-2009: 1.99* 2009-2015: -6.44*	2000-2005: 5.39* 2005-2015: -1.09*	2000-2005: 2.02 2005-2015: -3.14*	2000-2015: -0.44	2000-2015: -2.28*	2000-2005: 0.34 2005-2015: -1.94*
Female	2000-2004: 1.82 2004-2015: -2.59*	2000-2015: 0.78	2000-2015: -1.48*	2000-2003: 1.77 2003-2015: -1.29*	2000-2010: 0.65 2010-2015: -10.58	2000-2015: 0.47	2000-2007: 0.88 2008-2015: -4.05*	2000-2015: 0.08	2000-2002: -7.06 2002-2015: -1.66*	2000-2004: 1.51* 2004-2015: -1.80*
Race										
White	2000-2006: 0.39 2006-2015: -2.74*	2000-2015: 1.12*	2000-2015: -1.88*	2000-2004: 0.04 2004-2015: -1.07*	2000-2009: 1.92 2009-2015: -7.13*	2000-2007: 3.42* 2007-2015: -1.33*	2000-2006: 1.47 2006-2015: -3.31*	2000-2015: -0.20	2000-2015: -2.37*	2000-2006: 0.41 2006-2015: -1.93*
Black	2000-2015: -1.99*	2000-2015: -0.53	2000-2015: -0.19	2000-2015: -1.11*	2000-2015: -0.77	2000-2015: 0.98	2000-2008: 0.89 2008-2015: -5.51*	2000-2015: 0.78	2000-2015: -0.71	2000-2015: -0.94*
AI/AN	2000-2015: -1.5	UNKNOWN	UNKNOWN	2000-3015: -0.89	UNKNOWN	2000-2015: -0.15	2000-2015: -2.86	UNKNOWN	UNKNOWN	2000-2015: -1.18
API	2000-2015: -2.12*	2000-2015: -0.38	2000-2015: -2.90	2000-2015: -0.37	2000-2015: -2.62*	2000-2015: -1.19*	2000-2015: -1.39*	2000-2015: -1.21	2000-2015: -1.43*	2000-2015: -1.02*
Ethnicity										
NSHL	2000-2004: 1.45 2004-2015: -2.37*	2000-2015: 0.80*	2000-2015: -1.8*	2000-2003: 1.00 2003-2015: -1.12*	2000-2003: -4.5 2003-2009: 3.37 2009-2015: -7.81*	2000-2002: 9.1 2002-2008: 1.54 2008-2015: -1.28*	2000-2006: 1.21 2006-2015: -3.68*	2000-2015: 0.10	2000-2015: -2.01*	2000-2003: 1.29 2003-2008: -0.86 2008-2015: -2.06*
SHL	2000-2015: -3.02*	2000-2015: 1.79*	2000-2015: -3.38*	2000-2015: -0.97*	2000-2015: -1.42	2000-2015: -0.03	2000-2015: -0.08	2000-2015: -0.86	2000-2015: -1.94*	2000-2010: -0.29 2010-2015: -2.90*
Age Group										
20-29	2000-2015: -1.62	UNKNOWN	UNKNOWN	2000-2015: -0.25	2000-2015: 1.00	2000-2015: 1.47	2000-2015: -4.58*	2000-2015: 2.39	2000-2015: 1.55	2000-2015: 0.11
30-39	2000-2015: -0.74	2000-2015: 6.25*	UNKNOWN	2000-2015: -1.49*	2000-2009: 5.4* 2009-2015: -9.91*	2000-2015: 2.97*	2000-2015: -2.44*	2000-2015: 2.36	2000-2015: -1.19	2000-2015: -0.98*
40-49	2000-2015: -1.42*	2000-2015: -0.03	2000-2015: -2.39	2000-2015: -1.32*	2000-2009: 3.41 2009-2015: -9.82*	2000-2015: -0.22	2000-2007: 0.82 2007-2015: -3.30*	2000-2015: 0.02	2000-2015: -1.41*	2000-2005: -0.35 2005-2015: -2.29*
50-59	2000-2015: -1.41*	2000-2015: 0.08	2000-2015: -3.7*	2000-2015: -0.61*	2000-2015: -0.95	2000-2002: 14.73 2002-2015: -0.46	2000-2004: 1.81 2004-2015: -2.80*	2000-2015: -1.02*	2000-2015: -2.36*	2000-2015: -1.18*
60-69	2000-2002: 5.13 2002-2015: -2.45	2000-2015: 0.48	2000-2015: -0.97*	2000-2015: -0.87*	2000-2015: -2.72	2000-2015: 0.5	2000-2004: 3.02 2004-2015: -3.01*	2000-2015: -0.16	2000-2015: -2.19*	2000-2005: 1.92 2005-2015: -1.68*
70+	2000-2005: 1.33 2005-2015: -3.25*	2000-2015: 1.25*	2000-2015: -1.91*	2000-2004: 1.26 2004-2015: -1.29*	2000-2013: -2.14* 2013:2015: -19.27*	2000-2008: 3.08* 2008-2015: -2.43*	2000-2005: 3.67 2005-2015: -3.54*	2000-2015: -0.88	2000-2015: -2.69*	2000-2005: 1.34* 2005-2015: -2.21*
Total	2000-2004: 1.29 2004-2015: -2.63*	2000-2015: 0.77*	2000-2015: -2.01*	2000-2003: 0.94 2003-2015: -1.11*	2000-2009: 1.73 2009-2015: -7.06*	2000-2007: 2.70* 2007-2015: -1.14	2000-2006: 1.25 2006-2015: -3.48*	2000-2015: -0.03	2000-2015: -2.08*	2000-2004: 0.76 2004-2008: -1.13 2008-2015: -2.10*

*APC is significantly different from 0

UNKNOWN means Joinpoint was unable to calculate APC due to incidence rate being 0 for at least one year

Green represents significant increases, red represents significant decreases

Table 3. Age-Adjusted Incidence Rates by Age, Sex, Race, and Ethnicity for each Subtype, 2000-2015

	Incidence Rate for NHL total	Incidence Rate for CLL/SLL	Incidence Rate for Mantle Cell Lymphoma	Incidence Rate for Lympho-plasmacytic Lymphomas	Incidence Rate for DLBCL	Incidence Rate for Burkitt lymphoma	Incidence Rate for Marginal Zone Lymphoma	Incidence Rate for Follicular Lymphoma	Incidence Rate for Cutaneous T-Cell Lymphoma	Incidence Rate for Peripheral T-Cell Lymphoma
Total										
	26.9	7.24	0.94	0.8	8.7	0.41	2.33	4.45	0.59	1.44
Age										
20-29	2.35	0.04	0	0.01	1.26	0.23	0.15	0.19	0.14	0.33
30-39	5.34, RR=2.27*	0.31, RR=8.50*	0.05, RR=14.47*	0.03, RR=3.55*	2.41, RR=1.91*	0.33, RR=1.41*	0.40, RR=2.33*	0.96, RR=5.03*	0.29, RR=2.12*	0.55, RR=1.70*
40-49	12.28, RR=5.23*	1.84, RR=50.00*	0.29, RR=79.18*	0.17, RR=19.52*	4.38, RR=3.47*	0.43, RR=1.83*	1.04, RR=6.86*	2.77, RR=14.41*	0.46, RR=3.40*	0.90, RR=2.77*
50-59	28.75, RR=12.24*	6.91, RR=188.32*	1.06, RR=288.42*	0.69, RR=77.65*	8.49, RR=6.74*	0.44, RR=1.90*	2.62, RR=17.30*	6.12, RR=31.87*	0.79, RR=5.82*	1.62, RR=4.98*
60-69	62.27, RR=26.51*	18.21, RR=495.91*	2.63, RR=716.44*	1.91, RR=214.09*	17.80, RR=14.12*	0.54, RR=2.32*	5.69, RR=37.53*	11.13, RR=58.02*	1.31, RR=9.64*	3.05, RR=9.36*
70+	114.78, RR=48.88*	36.15, RR=984.84*	4.44, RR=1,208.82*	4.29, RR=481.43*	37.08, RR=29.42*	0.80, RR=3.42*	9.99, RR=65.91*	15.32, RR=79.81*	1.62, RR=11.89*	5.09, RR=15.65*
Sex										
Male	32.96	9.7	1.48	1.07	10.45	0.6	2.36	4.77	0.73	1.8
Female	22.05, RR=0.67*	5.32, RR=0.55*	0.51, RR=0.35*	0.60, RR=0.56*	7.25, RR=0.69*	0.22, RR=0.37*	2.33, RR=0.99	4.19, RR=0.88*	0.48, RR=0.66*	1.14, RR=0.63*
Race										
White	28.96	8.02	1.06	0.88	9.11	0.43	2.44	5.03	0.57	1.42
Black	19.70, RR=0.68*	5.77, RR=0.72*	0.41, RR=0.39*	0.43, RR=0.49*	6.11, RR=0.67*	0.36, RR=0.84*	1.81, RR=0.74*	2.04, RR=0.40*	0.88, RR=1.54*	1.90, RR=1.34*
AI/AN	12.01, RR=0.41*	2.20, RR=0.25*	0.50, RR=0.47*	0.26, RR=0.30*	4.80, RR=0.53*	0.19, RR=0.44*	1.21, RR=0.50*	1.89, RR=0.37*	0.27, RR=0.47*	0.70, RR=0.49*
API	16.48, RR=0.57*	1.87, RR=0.23*	0.43, RR=0.40*	0.46, RR=0.52*	7.71, RR=0.85*	0.33, RR=0.78*	1.90, R=0.78*	2.21, RR=0.44*	0.43, RR=0.75*	1.14, RR=0.80*
Ethnicity										
NSHL	27.64	7.71	0.96	0.84	8.68	0.4	2.36	4.57	0.63	1.48
SHL	21.65, RR=0.78*	3.41, RR=0.44*	0.81, RR=0.88*	0.43, RR=0.51*	9.10, RR=1.05*	0.47, RR=1.17*	2.09, RR=0.89*	3.70, RR=0.81*	0.39, RR=0.63*	1.24, RR=0.84*

*RR is significantly different from reference group for age, sex, race, and ethnicity