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Abstract

Background: For decades, non–Hodgkin lymphoma (NHL) incidence has been increasing worldwide. NHL risk is strongly increased among HIV-infected people. Our understanding of trends in NHL incidence has been hampered by difficulties in separating HIV-infected NHL cases from general population rates.

Methods: NHL incidence data during 1992–2009 were derived from 10 U.S. SEER cancer registries with information on HIV status at NHL diagnosis. The CDC estimated the number of people living with HIV in the registry areas. The proportion of NHL cases with HIV and NHL rates in the total and the HIV-uninfected populations were estimated. Time trends were assessed with Joinpoint analyses.

Results: Of 115,643 NHL cases diagnosed during 1992–2009, 5.9% were HIV-infected. The proportions of NHL cases with HIV were highest for diffuse large B-cell (DLBCL; 7.8%), Burkitt (26.9%), and peripheral T-cell lymphomas (3.2%) with low proportions (<1.1%) in the other subtypes. NHL rates in the total population increased 0.3% per year during 1992–2009. However, rates of NHL in HIV-uninfected people increased 1.4% per year during 1992–2003, before becoming stable through 2009. Similar trends were observed for DLBCLs and follicular lymphoma in HIV-uninfected people; rates increased 2.7% per year until 2003 and 1.7% per year until 2005, respectively, before stabilizing.

Conclusions: NHL incidence rates in the United States have plateaued over the last 5–10 years, independent of HIV infection.

Impact: Although the causes of the long-term increase in NHL incidence rates in the United States remain unknown, general population rates of NHL have stabilized since the early 2000s, independent of HIV. Cancer Epidemiol Biomarkers Prev; 22(6); 1069–78. ©2013 AACR.

Introduction

Notable increases in the incidence of non–Hodgkin lymphoma (NHL) have been documented internationally throughout the second half of the twentieth century (1–6). In the United States, rates more than tripled in that interval (7), with similar increases across age groups and among men and women (1). Mortality rates from NHL also have increased, suggesting that changes in NHL classification alone cannot account for increasing rates (7, 8). Although studies have identified etiologic factors that may have contributed to increasing NHL rates, such as viruses, medical conditions and drugs, and occupational or environmental exposures (9), most of the increase in NHL rates remains unexplained.

With the onset of the HIV epidemic in the United States in the 1980s, NHL rates increased more steeply than in previous decades as NHL cases in persons with HIV were added to the long-term increase in NHL incidence (10). Although HIV prevalence in the United States was low, the associated NHL risks were very large (77-fold) compared with the general population (11). The effect of HIV varies by NHL subtype, with risks particularly increased for diffuse large B-cell lymphoma (DLBCL, 30-fold), Burkitt lymphoma (50-fold), and central nervous system (CNS) lymphoma (1,020-fold; ref. 12), 3 types of NHL that are considered acquired immunodeficiency syndrome (AIDS)-defining events by the Centers for Disease Control and Prevention (CDC; ref. 13). In 1996, highly active antiretroviral therapy (HAART) was introduced to treat HIV infection, improving immune function of persons with HIV and resulting in a 58% decline in NHL risk (12, 14). During 1980–2007, 5.5% of DLBCLs, 19.4% of Burkitt lymphomas, and 26.2% of CNS lymphomas in the United States occurred among HIV-infected individuals (15).
In recent years, NHL incidence rates seem to have plateaued, leading some studies to suggest that the NHL epidemic has ended (3, 6, 16, 17). However, previous studies of NHL rates have not separated HIV-infected NHL cases from total NHL rates. To assess whether the long-standing epidemic of NHL in the general population has ended, we combined data from the Surveillance, Epidemiology and End Results (SEER) Program and the CDC from 1992–2009, enabling us to quantify the proportion of NHL cases with HIV infection and estimate NHL incidence rates over time in the absence of HIV-infected NHL cases.

Materials and Methods

Data sources

NHL incidence data were derived from 10 U.S. SEER population-based cancer registries that ascertained cancer diagnoses during 1992–2009 (CT, HI, NM, UT, Atlanta, Detroit, Seattle/Puget Sound, Los Angeles, San Francisco/Oakland, San Jose/Monterey) and collected information on HIV status from medical records at the time of NHL diagnosis (18, 19). A previous study documented high sensitivity of the SEER HIV indicator, despite a large proportion of NHL cases with an unknown HIV status (19). We therefore classified the 71% of cases with unknown HIV status as HIV-uninfected. In a sensitivity analysis, we reclassified NHL cases as HIV-infected if they had HIV listed as the cause of death but did not have a positive HIV indicator (n = 581, 0.5%).

Because NHL is composed of a heterogeneous group of distinct subtypes, we examined NHL overall and by subtype. NHLs were identified using the SEER site recode variable based on morphology codes from the International Classification of Diseases for Oncology, third edition (ICD-O-3; ref. 20). The following subtypes were defined using SEER’s lymphoma subtype recode, based on the International Lymphoma Epidemiology Consortium (InterLymph) classification (21): DLBCL, follicular, marginal zone, peripheral T-cell, and mantle cell lymphomas, mycosis fungoides/Sézary syndrome, other, specified NHL and NHL, not otherwise specified (NOS). We also defined Burkitt lymphoma (ICD-O-3 code 9687), and small lymphocytic lymphoma (9670), excluding Burkitt leukemia and chronic lymphocytic leukemia, respectively, from these entities because lymphoid leukemias were not considered part of NHL until the World Health Organization (WHO) classification was introduced in 2000 (22). HIV status was not collected for cases of mycosis fungoides/Sézary syndrome; thus, all cases were assumed to be HIV-uninfected in the analysis of total NHL. CNS lymphoma (an AIDS-defining cancer) was not analyzed as a separate entity, as we focused on histologically defined NHL subtypes.

To calculate the denominator for NHL incidence rates in HIV-uninfected individuals, data on HIV cases in each cancer registry area were obtained from CDC HIV surveillance data. Since 1982, AIDS diagnoses have been uniformly reported to the CDC by registries in all 50 U.S. states and the District of Columbia. In 1994, CDC integrated national reporting of HIV infection with AIDS case reporting. However, the uptake of HIV reporting was variable by state; thus, data on all people living with HIV (with or without AIDS) only are available during 2006–2009. For this analysis, the CDC estimated the number of people living with AIDS from 1992–2009, and the number of people living with HIV infection from 2006–2009 at the end of each calendar year in strata defined by calendar year, sex, attained age, race/ethnicity, and geographic area, with statistical adjustments made for reporting delays (23, 24).

Statistical analysis

The proportions of NHL cases with HIV infection were estimated by NHL subtype and stratified by sex, age group (0–14, 15–39, 40–59, 60+ year-olds), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic), and calendar period (1992–1995, 1996–1999, 2000–2004, 2005–2009). Incidence rates of HIV-uninfected NHL were estimated by subtracting HIV-infected cases from the numerator and the AIDS population from the denominator. We conducted a sensitivity analysis with data from 2006–2009 that compared HIV-uninfected NHL rates calculated by removing all persons with HIV and only persons with AIDS from the denominator. In an additional analysis, we assessed long-term trends in U.S. NHL incidence rates with data from 8 SEER registries during 1974–2009 (CT, HI, NM, UT, Atlanta, Detroit, Seattle/Puget Sound, San Francisco/Oakland).

All rates were age-standardized to the 2000 U.S. population and stratified by sex and age group. Calendar trends in incidence rates were estimated overall and among HIV-uninfected individuals, and annual percentage age changes in incidence rates were estimated with Joinpoint regression (25, 26).

Results

Characteristics of HIV-infected and HIV-uninfected NHL cases

During 1992–2009, 115,643 persons were diagnosed with NHL in 605 million person-years. Of these, 6,784 persons (5.9%) were HIV-infected at the time of diagnosis. The majority of HIV-infected NHL cases were AIDS-defining cancers: DLBCL (45.5%) and Burkitt lymphoma (8.4%; Table 1). Among HIV-uninfected NHL cases, DLBCLs (33.6%) and follicular lymphoma (17.9%) were the most common subtypes, and Burkitt lymphoma was rare (1.4%). HIV-infected NHL cases predominantly occurred among males and 15–39 and 40–59 year-olds. A greater proportion of NHL cases were HIV-infected in the pre-HAART calendar period (1992–1995) compared with the most recent calendar period (2004–2009).

Proportion of NHL cases with HIV infection

The AIDS-defining NHL subtypes had the highest proportion of cases with HIV, with 26% of Burkitt lymphoma cases and 7.8% of DLBCL cases having HIV.
The proportion of cases occurring in each calendar period was calculated per year because the intervals do not include the same number of years (i.e., 4 years in 1992–1995 and 1996–1999 and 5 years in 2000–2004 and 2005–2009).

The proportion of cases occurring in each calendar period was calculated per year because the intervals do not include the same number of years (i.e., 4 years in 1992–1995 and 1996–1999 and 5 years in 2000–2004 and 2005–2009).
HIV-uninfected populations for individuals younger than 60 years were more pronounced among men than women. For 60+ year-olds, DLBCL rates also increased 2.9% per year during 1992–2004 before stabilizing, with similar estimates in the total and HIV-uninfected populations.

Burkitt lymphoma rates increased during 1992–2009 overall and among 15–39 and 40–59 year-olds in the total population; however, among HIV-uninfected individuals, rates increased dramatically through 2000 overall and 2001 among 40–59 year-olds before stabilizing. (Fig. 2D). Marginal zone lymphoma increased dramatically during 1992–2001, before leveling off in subsequent years (Fig. 2E; Table 3). A similar pattern was observed for mantle cell lymphoma, with rates increasing 21.0% per year during 1992–1996 and 2.9% per year during 1996–2009 (Fig. 2F; Table 3). In contrast, rates of small lymphocytic lymphoma declined across all age groups (Fig. 2G; Table 3).

Among T-cell NHLs, rates of peripheral T-cell lymphoma increased 10.9% per year until 1998 and at a more modest rate of 1.7% per year during 1998–2009 (Fig. 2H; Table 3). In the total population, rates of mycosis fungoides/Sézary syndrome increased through 1996 before stabilizing in subsequent years (data on HIV-uninfected rates were unavailable).

Throughout the study period, rates of other, specified NHLs increased across age groups, particularly among 60+ year-olds (3.5% per year). In contrast, rates of NHL NOS declined sharply during 1994–2002 and have been stable in subsequent years (Fig. 2I and J).

Sensitivity analyses showed that incidence rates calculated during 2006–2009 were similar when all HIV-infected individuals were removed from the denominator compared with our primary analysis, which removed only AIDS cases (Supplementary Table S1). In addition, when we classified HIV status based on both the HIV indicator and cause of death, we observed very similar NHL trends to our main analysis, and the proportion of NHL cases with HIV increased slightly from 5.9% to 6.4% overall (10.4% in males and 1.4% in females).

### Table 2. Proportion of NHL cases that are HIV-infected, by sex, race/ethnicity, and age group, 1992–2009

<table>
<thead>
<tr>
<th>Age group, y</th>
<th>Race/ethnicity</th>
<th>Calendar periods</th>
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<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>0–14</td>
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<tr>
<td>Males</td>
<td></td>
<td></td>
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<tr>
<td>Total NHL</td>
<td>9.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>DLBCL</td>
<td>12.8%</td>
<td>1.7%</td>
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<tr>
<td>Burkitt lymphoma</td>
<td>32.9%</td>
<td>0.4%</td>
</tr>
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<td>Follicular lymphoma</td>
<td>1.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Marginal zone lymphoma</td>
<td>1.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>0.8%</td>
<td>—</td>
</tr>
<tr>
<td>Small lymphocytic lymphoma</td>
<td>1.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>4.5%</td>
<td>0.0%</td>
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<td>Other, specified</td>
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<td>NOS</td>
<td>18.9%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total NHL</td>
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<td>1.8%</td>
</tr>
<tr>
<td>DLBCL</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>9.0%</td>
<td>3.3%</td>
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<tr>
<td>Follicular lymphoma</td>
<td>0.5%</td>
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<tr>
<td>Marginal zone lymphoma</td>
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<td>Mantle cell lymphoma</td>
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</tr>
<tr>
<td>Peripheral T-cell lymphoma</td>
<td>1.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Other, specified</td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>NOS</td>
<td>2.0%</td>
<td>8.5%</td>
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</tbody>
</table>

NOTE: Missing values indicate fewer than 5 total cases in SEER.

Abbreviations: NHB, non-Hispanic Black; NHW, non-Hispanic White.
Although some studies have reported stable NHL incidence rates in the United States in recent years (8, 27), the status of the long-standing epidemic of NHL in the general population has been uncertain because of the superimposition of NHL in persons with HIV over the past three decades. By disentangling the incidence of NHL occurring in HIV-infected and -uninfected individuals, we have shown for the first time that the general population rates of NHL have stabilized since the early 2000s, independent of HIV.

Our results have several implications. First, the pre-HIV increase in NHL incidence rates in the United States in recent years (8, 27), the status of the long-standing epidemic of NHL in the general population has been uncertain because of the superimposition of NHL in persons with HIV over the past three decades. By disentangling the incidence of NHL occurring in HIV-infected and -uninfected individuals, we have shown for the first time that the general population rates of NHL have stabilized since the early 2000s, independent of HIV.

Our analysis also shows that effective therapies for HIV, which have decreased NHL risk in HIV-infected individuals (12, 14), have dramatically altered NHL trends in some population groups. NHL rates in the HIV-infected population declined rapidly in the early to mid-1990s, followed by more gradual declines in more recent years (29). Although the prevalence of HIV is low in the United States (0.4% in 2008; ref. 30), HIV has impacted NHL rates at the national level and a large fraction of certain NHL subtypes in the United States occur among HIV-infected individuals.

Figure 1. Age-standardized incidence rates for NHLs during 1974–2009 for 8 SEER registries: Atlanta, CT, Detroit, HI, NM, San Francisco-Oakland, Seattle-Puget Sound, and UT. The black bars represent overall NHL incidence rates from the time period before the HIV status indicator was available for (A) men and women, (B) men only, and (C) women only. The gray bars represent HIV-uninfected NHL cases and the white bars represent HIV-infected NHL cases during the period when the HIV status indicator was available.
Figure 2. Age-standardized incidence rates stratified by age group during 1992–2009 for (A) NHL overall, (B) DLBCLs, (C) Burkitt lymphoma, (D) follicular lymphoma, (E) marginal zone lymphoma, (F) mantle cell lymphoma.
individuals. In 10 regions of the United States, the proportion of NHL cases with HIV was greatest for NHL subtypes with the strongest associations with HIV [i.e., DLBCL (7.8%) and Burkitt lymphoma (26.9%)] and in subgroups with higher HIV prevalence [i.e., men (9.6%), 15–39 and 40–59 year-olds (24.4% and 10.7%, respectively), and non-Hispanic blacks and Hispanics (14.8% and 10.8%, respectively)]. Notably, the contribution of HIV-infected cases to the total number of NHL cases has declined over time (1 of 8 in 1992–1995 to 1 of 28 NHL cases in 2005–2009). Our results are similar to previously published estimates for the United States during 1980–2007 based on data from the HIV/AIDS Cancer Match Study (DLBCL: 9.4% in men and 0.93% in women; Burkitt lymphoma: 24.4% in men, 5.3% in women; ref. 15). Of note, though not an AIDS-defining cancer, the proportion of peripheral T-cell lymphoma cases with HIV infection was elevated compared to the other subtypes. This is likely driven by the 24-fold elevated risk of peripheral T-cell lymphoma in people with AIDS (31). The proportions of cases of other NHL subtypes with HIV were low, due to weaker associations with HIV infection, and the proportion of cases of NHL NOS with HIV infection was high, suggesting HIV-infected NHL cases are less likely to be assigned a specific NHL subtype (1, 32).

Rates of DLBCL and follicular lymphoma, the 2 most common NHL subtypes, showed similar trends among persons without HIV, despite possible differences in etiology (28). Following years of increasing trends, DLBCL rates have been stable since 2003, and rates of follicular lymphoma have been stable since 2005. For both DLBCL and follicular lymphoma, rates have also been stable since

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**Figure 2.** (Continued) (G) small lymphocytic lymphoma, (H) peripheral T-cell lymphoma, (I) other, specified lymphomas, and (J) lymphoma, NOS. The solid black line represents incidence rates in men overall, the dashed black line [- - -] represents incidence rates in men without HIV infection, the larger dashed line (-----) represents incidence rates in women overall, and the dotted line (-----) represents incidence rates in women without HIV infection.
<table>
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<tr>
<th>Age Group</th>
<th>Years</th>
<th>APC$^a$</th>
<th>Years</th>
<th>APC$^a$</th>
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<th>APC$^a$</th>
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<th>APC$^a$</th>
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<tbody>
<tr>
<td></td>
<td>1992–2009</td>
<td>0.6 (0.1 to 1.0)</td>
<td>1992–2002</td>
<td>0.9 (0.2 to 1.7)</td>
<td>1992–2004</td>
<td>1.7 (1.3 to 2.0)</td>
<td>1992–2003</td>
<td>1.4 (1.1 to 1.8)</td>
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<tr>
<td>Total NHL</td>
<td>1992–2002</td>
<td>−1.0 (−2.0 to 0.1)</td>
<td>2002–2004</td>
<td>−0.7 (−1.9 to 0.6)</td>
<td>2004–2009</td>
<td>2.9 (2.4 to 3.5)</td>
<td>2003–2009</td>
<td>−0.4 (−1.1 to 0.4)</td>
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<td>2.0 (3.4 to 0.3)</td>
<td>2004–2009</td>
<td>−1.7 (−3.4 to 0.1)</td>
<td>2004–2009</td>
<td>−0.7 (−1.9 to 0.6)</td>
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<td>Diffuse large B-cell lymphoma</td>
<td>1992–2009</td>
<td>2.1 (0.9 to 3.3)</td>
<td>1992–2009</td>
<td>−0.7 (−1.9 to 0.6)</td>
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<td>Burkitt lymphoma</td>
<td>1992–2009</td>
<td>14.8 (5.9 to 24.4)</td>
<td>2002–2009</td>
<td>−2.8 (−9.0 to 3.7)</td>
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<td>−0.4 (−1.1 to 0.4)</td>
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<td>Follicular lymphoma</td>
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<td>1992–2009</td>
<td>0.4 (0.2 to 0.9)</td>
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<td>Small lymphocytic lymphoma</td>
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<td>2002–2009</td>
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<td>−0.7 (−2.5 to 1.1)</td>
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Abbreviations: APC, annual percent change; CI, confidence interval.
the mid-2000s among 60+ year-olds, the group with the largest burden of NHL.

We observed strong increases in peripheral T-cell, mantle cell, Burkitt, and marginal zone lymphomas, with rates stabilizing for Burkitt and marginal zone lymphomas in recent years. The striking increases in the rates of marginal zone and mantle cell lymphomas have previously been attributed to the adoption of a specific ICD-O-2 code for marginal zone lymphoma by cancer registries, improved diagnosis of mantle cell lymphoma with immunohistochemical staining, and increased recognition of these subtypes by pathologists (32). Because of the rapid improvements in classification of NHL subtypes during the 1990s, increased incidence of rarer NHL subtypes during this time period should be interpreted cautiously. In contrast, rates of small lymphocytic lymphoma have declined. With the introduction of the WHO classification in 2000 (22), small lymphocytic lymphoma and chronic lymphocytic leukemia were classified as a single entity, but changes in diagnostic practices are unlikely to explain the decline in small lymphocytic lymphoma because rates of chronic lymphocytic leukemia remained stable over the study period (data not shown).

Rates of NHL, NOS decreased over time across age groups, indicating a pronounced period effect likely due to increased diagnostic specificity introduced when the Revised European-American Lymphoma (REAL) classification system was adopted in 1995, followed by the WHO classification system (22, 32–34). As a result, the proportion of total NHLs that were NOS declined from 31% in 1992–1995 to 13% in 2005–2009. It is possible that improved classification of NHLs may have influenced rates of certain NHL subtypes (e.g., mantle cell and marginal zone lymphomas as mentioned above). However, the rates of NHL NOS have been stable since 2002; and thus likely had little impact on observed trends in NHL subtypes in recent years and have had no impact on overall NHL rates. Additional efforts to increase classification of NHLs could have important implications for monitoring and treatment, particularly among HIV-infected individuals where 19% of NHLs were NOS in the most recent time period.

An important strength of our study was the availability of data on the HIV status of lymphoma cases diagnosed in 10 high-quality SEER registries. Although there may be some misclassification due to the large proportion of NHL cases with unknown HIV status, one prior study estimated that the SEER HIV flag has 97% sensitivity and 92% specificity at identifying the HIV status of NHL cases, and another study reported that, compared with other registry indicators of HIV status, the SEER HIV flag was positive in 91% to 95% of HIV-infected NHL cases (19, 35). Furthermore, the inclusion of NHL cases with HIV as a cause of death in the HIV-infected group had little impact on our results. An additional limitation was the lack of data on the number of HIV-infected individuals living in the registry areas during the entire study period. As data on HIV infection were not uniformly collected by the CDC in these regions until recently, in our main analysis, we were only able to subtract out AIDS cases from the populations at risk. In a sensitivity analysis limited to those calendar years where HIV data were available for all registry areas, we showed that removal of all individuals living with HIV resulted in very similar estimates.

Although the causes of the historical increase in general population NHL incidence rates remain unknown, total NHL incidence rates in the United States have plateaued over the last 5 to 10 years, as have the rates of several NHL subtypes, including DLBCLs and follicular lymphoma, independent of HIV. Continued monitoring of trends in NHL incidence among HIV-uninfected people is critical to confirm the end of the long-standing NHL epidemic.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The findings and conclusions in this study are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Authors’ Contributions

Conception and design: M.S. Shiels, E.A. Engels, C.A. Clarke, P. Hartge, L.M. Morton

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.S. Shiels, H.I. Hall

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.S. Shiels, E.A. Engels, M. Linet, J. Li, H.I. Hall, L.M. Morton

Writing, review, and/or revision of the manuscript: M.S. Shiels, E.A. Engels, M. Linet, C.A. Clarke, H.I. Hall, P. Hartge, L.M. Morton

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.M. Morton

Study supervision: L.M. Morton

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