Cancer Epidemiology, Biomarkers & Prevention

Contributions of HIV to Non-Hodgkin Lymphoma Mortality Trends in the United States

Nadia Howlader[1,2], Meredith S. Shiels[3], Angela B. Mariotto[1], and Eric A. Engels[3]

Abstract

Background: The human immunodeficiency virus (HIV) epidemic has strongly influenced non-Hodgkin lymphoma (NHL) incidence in the U.S. general population, but its effects on NHL mortality trends are unknown.

Methods: Using SEER cancer registry data, we assessed NHL mortality rates in the United States (2005–2012) and mapped NHL deaths to prior incident cases. Data included HIV status at NHL diagnosis. We describe the proportion of NHL deaths linked to an HIV-infected case, for 3 AIDS-defining subtypes [diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and central nervous system (CNS) lymphoma] and within demographic categories. We also present incidence-based mortality (IBM) rates showing the impact of HIV on mortality trends and describe survival after NHL diagnosis by calendar year.

Results: Of 11,071 NHL deaths, 517 (4.6%) were in HIV-infected persons. This proportion was higher in deaths mapped to DLBCL (7.3% with HIV), Burkitt lymphoma (33.3%), and CNS lymphoma (17.6%), and among deaths from these subtypes, for people aged 20–49 years (46.6%), males (15.2%), and blacks (39.3%). IBM rates declined steeply during 2005–2012 for HIV-infected NHL cases (−7.6% per year, $P = 0.001$). This trend reflects a steep decline in incident NHL among HIV-infected people after 1996, when highly active antiretroviral therapy was introduced. Five-year cancer-specific survival improved more markedly among HIV-infected cases (9%–54%) than HIV-uninfected cases (62%–76%) during 1990–2008.

Conclusions: The HIV epidemic has strongly contributed to NHL deaths, especially for AIDS-defining NHL subtypes and groups with high HIV prevalence.

Impact: Declining NHL mortality rates for HIV-infected cases reflect both declining incidence and improving survival. *Cancer Epidemiol Biomarkers Prev; 25(9); 1289–96. ©2016 AACR.*

Introduction

People infected with the human immunodeficiency virus (HIV) have an elevated risk of developing several cancers compared with the general population (1), in large part due to the effects of immunosuppression. Among these cancers, three subtypes of non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and central-nervous system (CNS) lymphoma, manifest particularly elevated risks (2–4). These NHLs are to a great extent caused by loss of immune control of Epstein–Barr virus (EBV) infection and are included (along with Kaposi sarcoma and cervical cancer) as acquired immunodeficiency syndrome (AIDS)-defining cancers (i.e., they mark the onset of advanced immunodeficiency in HIV-infected people). Overall, the incidence of NHL in HIV-infected people fell in 1996 with introduction of highly active antiretroviral therapy (HAART) for treating HIV infection (3). Among HIV-infected people, survival following a diagnosis of NHL is poor (4), although it may be improving with better treatments for HIV and NHL (5).

In the U.S. general population, both NHL incidence and mortality increased until reaching a peak in the mid-1990s (6). For example, the NHL mortality rate went from 5.8 per 100,000 person-years in 1975 to 9.2 per 100,000 person-years in 1997, corresponding to a 58% increase (6). The NHL mortality rate after mid-1990s has been falling. Several studies have quantified the contribution of HIV/AIDS to NHL incidence trends (7–10), but the impact of HIV/AIDS on NHL mortality in the U.S. general population has not been previously studied.

Understanding the contributions of HIV to NHL mortality rates is important. Because HIV is a strong risk factor for some NHLs (especially for the AIDS-defining NHL subtypes), trends related to the HIV epidemic may have affected NHL mortality rates. Mortality rates reflect contributions of both cancer incidence and survival after cancer diagnosis, so they capture the overall impact of exposures and medical conditions on disease burden. Nonetheless, quantifying the effects of HIV on the general population NHL mortality burden is challenging because death certificates lack detailed information pertaining to risk factors that led to a cancer diagnosis (e.g., HIV infection) and cancer subtypes.

In this study, we assessed the contribution of HIV to the general population mortality burden of NHL. To do that, we used information from Surveillance, Epidemiology, and End Results (SEER) cancer registries regarding the HIV status of NHL cases, along with linked mortality records. This allowed us to calculate the proportion of NHL deaths that occurred in HIV-infected people, both overall and in subgroups defined by NHL subtype and demographic characteristics, and to assess the change over time in NHL

[1]Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland. [2]Department of Epidemiology and Biostatistics, The George Washington University Milken Institute School of Public Health, Washington, D.C. [3]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda Maryland.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Author: Nadia Howlader, Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892. Phone: 240-276-6891; Fax: 240-277-6591; E-mail: howladern@mail.nih.gov

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mortality associated with HIV infection (11). The great majority of deaths from NHL occur within 15 years of diagnosis (12). In the current study, we assessed HIV-infected NHL cases from 1990 onward, which allowed us to evaluate NHL deaths from 2005 onward (i.e., well into the HAART era). We also assessed changes in NHL incidence rates and survival after NHL diagnosis, as these contributed to calendar trends in NHL mortality.

Materials and Methods

Data sources

We identified NHL cases diagnosed in adults (age 20+ years) during 1990–2012 using data from eight population-based SEER-9 registries (the four states of Connecticut, New Mexico, Utah, and Hawaii, and the four metropolitan areas of Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound); Iowa was excluded from the SEER9 registries in our study because they are prohibited by state law to share HIV infection status on their cancer cases. These eight registries cover approximately 8% of the U.S. population. We began the analysis in 1990 when information on HIV status was first captured uniformly.

We selected NHL cases based on the SEER variable "Lymphoma Subtype Recode ICD-O-3/WHO 2008" (13, 14). We used histology codes to identify cases of two AIDS-defining NHL subtypes, DLBCL and Burkitt lymphoma, based on the 2001 WHO classification (13, 14). The remaining histologies were collapsed into an "other/unspecified" subtype category. The third AIDS-defining subtype, CNS lymphoma, was identified using topographical codes (C71 or C72), so it overlapped with the other three NHL histology categories (see Fig. 2 legend for specific codes for the three AIDS-defining NHL subtypes). We further restricted analysis to NHL cases that were a person's first or only cancer, to allow accurate mapping to cancer-specific deaths in mortality records (based on underlying cause of death, see below) and also to allow comparison of mortality trends with trends in cancer-specific survival after diagnosis, which are typically derived using first or only cancers. There were 21,599 second or later NHLs which were excluded from the analysis (17% of all NHL cases). Likewise, there were 582 second or later NHLs in people with HIV that were excluded (13% of all HIV-infected NHL cases), as identified using the HIV flag described below. Cases diagnosed using only death certificate or autopsy results were excluded.

SEER HIV flag

The eight cancer registries recorded HIV status at the time of NHL diagnosis as part of the extent of disease field, based on any mention of HIV or AIDS in clinical records at the time of data abstraction; there is no reporting requirement for follow-up or to record a later HIV diagnosis. Cancer registrars code this "HIV flag" as positive or negative based on physician or laboratory documentation of HIV. Because cases are coded as having unknown status if there is no mention of HIV infection in the medical record, we considered these cases as negative for analyses (9, 15–18). HIV status was not ascertained for some cancer diagnoses [e.g., chronic lymphocytic leukemia (CLL)] that are now considered NHLs according to the 2001 WHO definition. Among our cases, 3.7% had known HIV^+ status, 15.9% had known HIV^- status, 52.6% had unknown HIV status (considered HIV^-), and 27.8% had no information on HIV status because this information was not ascertained for the cancer diagnosis. As the majority (76%) of these cancer diagnoses for which HIV status was not ascertained were CLL, and as this subtype is not elevated in HIV-infected people (18), we assumed in our primary analysis that these cases were HIV-uninfected (we present results of a sensitivity analysis in the Discussion). In addition, we reset the NHL flag as "HIV^+" if an individual had HIV listed as underlying cause of death (COD) but did not have a positive indicator on the HIV flag; this reclassification updated the flag for only $n = 325$ cases (0.31% of total cases).

Underlying cause of death

Underlying CODs were ascertained by cancer registries from death certificate codes obtained from the National Center for Health Statistics (19). In our study, we sought to identify deaths due to NHL and linked to an incident SEER NHL case. To correct for known errors with COD attribution, the SEER program recently developed a special COD variable that maps underlying CODs to the primary cancer diagnosis (20). We used this variable to assign a broad set of CODs to capture deaths due to NHL among people with an incident NHL diagnosis. Specifically, for NHL cases in SEER we considered a death as due to NHL if it was coded to a death from any hematologic malignancy, another cancer (if the person had NHL as the only incident cancer), a related neoplastic condition, or HIV/AIDS (20). We validated this COD variable in a separate analysis of HIV-infected people based on a comparison with relative survival, which is considered a gold standard for population-based survival rates (ref. 21; see Supplementary Materials for details).

Statistical analysis

The partitioning of deaths according to NHL subtype and HIV status at diagnosis utilizes incidence-based mortality (IBM) methods (11, 22). IBM rates are valid for a shorter range of calendar years than death certificate mortality. As IBM rates are calculated on the basis of the registry incident cases, and some deaths may occur many years after cancer diagnosis, IBM rates are underestimated in the initial years of cancer registration. Because median survival after NHL diagnosis is more than a decade, some cancer-specific deaths occur late after NHL diagnosis. For this reason, we required 15 years of data on incident cases (sometimes known as the "burn-in" period for IBM rates), before each year of mortality data (12).

Thus, we assessed NHL deaths from 2005 onward and used 15 years of incident cases (beginning in 1990) before each year of NHL deaths to classify the NHL subtype and HIV status (12). For deaths occurring in SEER areas during 2005–2012 that were from one of the specified CODs and were linked to a SEER NHL case, we ascertained whether the person was HIV-infected on the basis of the information provided by the SEER HIV flag as described above. We then describe the proportion of these NHL deaths and incident NHL cases that were in HIV-infected people. For AIDS-defining NHLs, we additionally describe the proportion of cases that were HIV^+ stratified by subtype, age, gender, race, and registry.

We also describe IBM rates for NHL (11, 22). For example, the IBM rate associated with HIV-infected cases in 2005 equals the number of NHL deaths during 2005 among NHL cases reported to SEER during 1990 to 2005 and diagnosed with HIV infection, divided by the corresponding population in the SEER catchment area during calendar year 2005. It is important to note that the incidence and IBM rates corresponding to HIV-infected NHL cases use the general population, rather than the HIV population, as the

Table 1. Characteristics of NHL death and diagnosis by HIV status

	NHL death 2005–2012			NHL diagnosis 1990–2012		
	Total	**HIV$^+$ NHL**	**HIV$^+$ NHL**	**Total**	**HIV$^+$ NHL**	**HIV$^+$ NHL**
a. All NHLs						
Total	13,487	572	4.2%	103,475	3,788	3.7%
Subtype						
DLBCL	4,396	320	7.3%	29,089	2,103	7.2%
Burkitt lymphoma	279	93	33.3%	1,377	449	32.6%
Other/unspecified	8,812	159	1.8%	73,009	1,236	1.7%
CNS lymphoma[a]	522	92	17.6%	2,604	945	36.3%
b. AIDS-defining NHLs						
Total	4,819	468	9.7%	31,632	3,215	10.2%
Age at death/diagnosis						
20–49	614	292	47.6%	8,357	2,545	30.5%
50–64	1,044	145	13.9%	8,063	582	7.2%
65+	3,161	31	1.0%	15,212	88	0.6%
Gender						
Male	2,653	402	15.2%	17,926	2,899	16.2%
Female	2,166	66	3.0%	13,706	316	2.3%
Race[b]						
White	3,738	267	7.1%	25,587	2,253	8.8%
Black	476	187	39.3%	2,818	844	30.0%
Other	593	13	2.2%	3,074	110	3.6%
Registry						
San Francisco[c]	938	134	14.3%	6,710	1,231	18.3%
Atlanta	455	131	28.8%	3,099	630	6.5%
Seattle	879	57	6.5%	5,623	454	6.1%
Connecticut	705	55	7.8%	5,167	335	4.7%
Detroit	833	52	6.2%	5,158	315	4.8%
New Mexico	344	18	5.2%	1,971	95	8.1%
Utah	359	8	2.2%	2,356	83	3.5%
Hawaii	306	13	4.2%	1,548	72	20.3%

NOTE: SEER-9 excluding Iowa. 1990–2012.

[a]CNS NHL overlaps with other NHL subtype categories. There were 1,320 cases and 359 deaths with DLBCL, 20 cases and 2 deaths with Burkitt lymphoma, and 429 cases and 82 deaths with other/unspecified subtypes that overlapped with the total 2,604 CNS NHL cases and 522 CNS deaths.

[b]Race categories do not add up to total. There were total 12 NHL deaths and 1 NHL death with HIV infection with missing race information. Similarly, 153 NHL diagnosed cases and 8 NHL diagnosed cases with HIV infection had missing race information.

[c]San Francisco registry captures cases from the Alameda, Contra Costa, Marin, San Francisco, and San Mateo counties.

denominator; therefore, one cannot interpret these estimates as "rates of lymphoma in HIV-infected people." Instead, the estimates capture the contribution of HIV-infected cases to the general population rates. To examine time trends, we present rates (IBM and incidence) age-standardized to the 2000 U.S. population. Incidence rates were adjusted for reporting delays. We used Joinpoint to fit log-linear trends to the age-standardized IBM rates from 2005 to 2012, and to incidence rates for the HAART era (1996–2012; ref. 23). The resulting trend across the calendar intervals is described by the slope (i.e., annual percentage change). We used *t* tests to assess whether trends were statistically different from zero. All statistical tests were two-sided. The rates and trends were calculated using SEER*Stat and Joinpoint software programs (24, 25).

We present estimates of five-year cancer-specific survival according to NHL subtype and diagnosis year, among HIV-infected and HIV-uninfected individuals. Cases alive with no survival time were excluded from the survival analysis. Cancer-specific survival was calculated using the actuarial method with the SEER special COD variable (20). Survival times were censored at loss to follow-up, death from causes other than NHL, or December 31, 2012, whichever occurred first. We also calculated the annual percentage change of the death rates with respect to diagnosis year among NHL cases. The annual percentage change (allowing up to 2 joinpoints) and corresponding *P* value were calculated using JPSurv (26, 27). Although we allowed up to 2 joinpoints, no joinpoints were identified. We therefore report the annual percentage change of the death rates with respect to diagnosis year across the entire interval.

Results

During 2005–2012 in the SEER areas, a total of 13,487 NHL deaths were observed following an NHL diagnosis (Table 1). Of these, 572 (4.2%) deaths were in people who had HIV infection documented at the time of NHL diagnosis. The proportion of NHL deaths that were linked to HIV infection varied by NHL subtype. We observed a substantial burden of HIV infection among deaths for Burkitt lymphoma ($n = 93$; 33.3% of cases had HIV infection), CNS lymphoma ($n = 92$; 17.6%), and DLBCL ($n = 320$; 7.3%); HIV infection was much less common among NHL deaths from all "other/unspecified" NHL subtypes combined ($n = 159$; 1.8%).

We focused the remaining analyses on the AIDS-defining NHL subtypes (Table 1). Among people who died from AIDS-defining NHL subtypes, HIV prevalence was the greatest among those who were <50 years old (47.6%), male (15.2%), or black (39.3%). Finally, we found a notable variation in HIV prevalence by geographic location. For example, the highest HIV prevalence in this subgroup was seen in Atlanta (28.8%) followed by San Francisco (14.3%), while the lowest fractions were in Utah (2.2%) and Hawaii (4.2%).

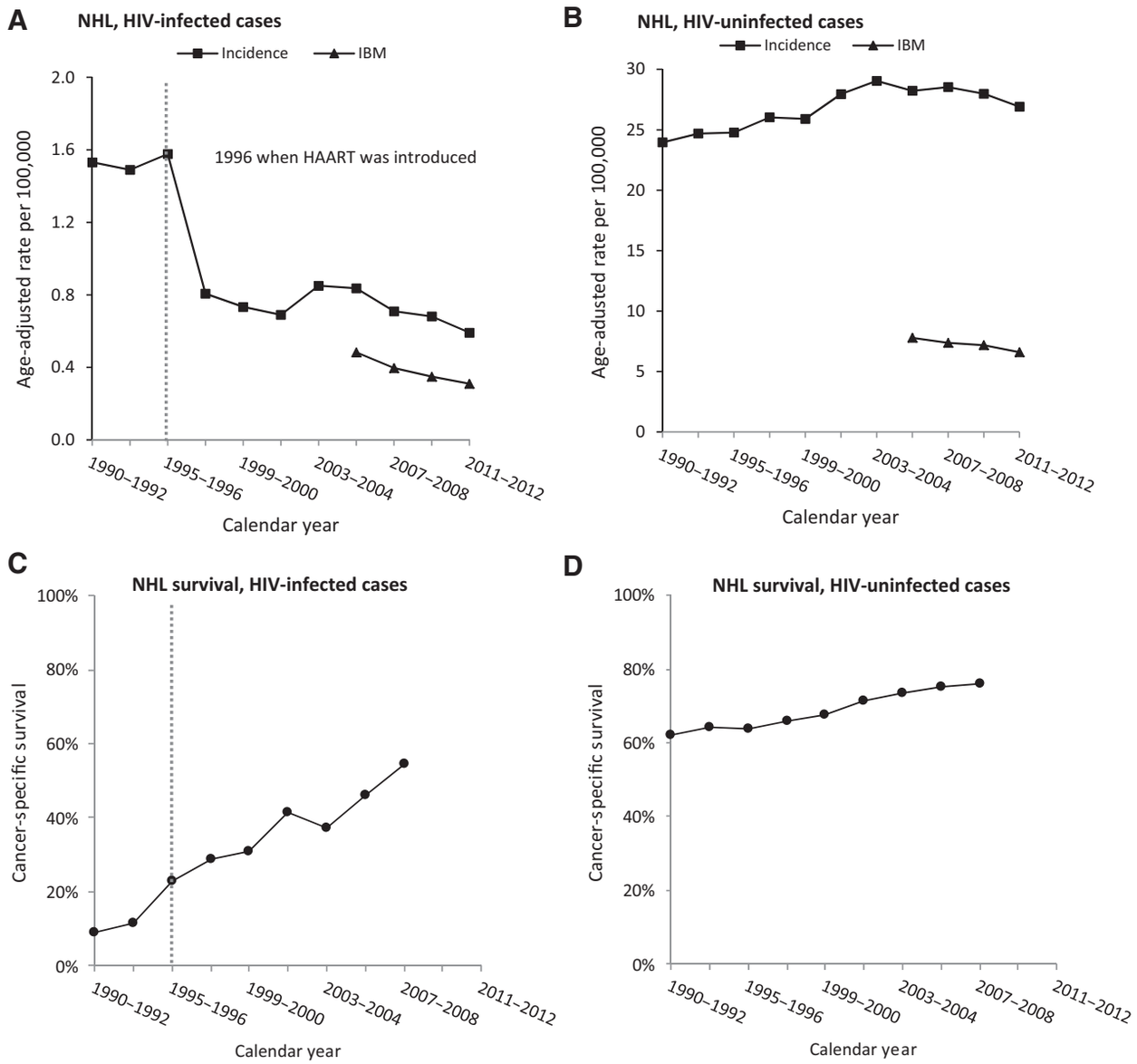

Figure 1.

NHL incidence, IBM, and survival stratified by HIV status. Results are shown for overall NHL among HIV-infected individuals (**A**) and overall NHL among HIV-uninfected individuals (**B**). For each panel, we show age-adjusted incidence rates as squares and age-adjusted IBM rates as triangles. We also show 5-year cancer-specific survival according to year of NHL diagnosis among HIV-infected individuals (**C**) and among HIV-uninfected individuals (**D**). Note that the vertical axis differs in panels **A** and **B**. Results are shown for eight SEER registries (San Francisco, Connecticut, Detroit, Hawaii, New Mexico, Seattle, Utah, and Atlanta).

Table 1 also presents the corresponding prevalence of HIV infection among incident NHL cases during 1990–2012 for comparison as these cases contributed to deaths examined during 2005–2012. Of 103,475 NHL cases, there were 3,788 (3.7%) cases with documented HIV infection. For the most part, the proportions of NHL cases that were in HIV-infected people were similar to the proportions of deaths, but there were a few notable exceptions, for example, for CNS NHL (36.3% of incident cases vs. 17.6% of deaths were in HIV-infected people), and among AIDS-defining NHL subtypes, for the 20–49 year-old age group (30.5% vs. 47.6%), blacks (30.0% vs. 39.3%), and in Atlanta (20.3% vs. 28.8%). HIV prevalence among cases with AIDS-defining NHL subtypes fell dramatically beginning in 1997 (17.6% of incident cases in 1990–1992, 19.3% in 1995–1996, 9.3% in 1997–1998, 6.8% 2001–2002, and 6.0% in 2011–2012).

Figure 1 shows trends in NHL incidence and mortality, in which the cases that contribute to these rates have been separated by HIV status. As shown in Fig. 1A, the incidence of NHL related to HIV-infected cases was flat beginning in 1990 until there was a sharp decrease between 1995 and 1996 when HAART was introduced; subsequently, incidence rates for HIV-infected cases continued to decline at −2.8% per year ($P = 0.007$). In contrast, incidence rates

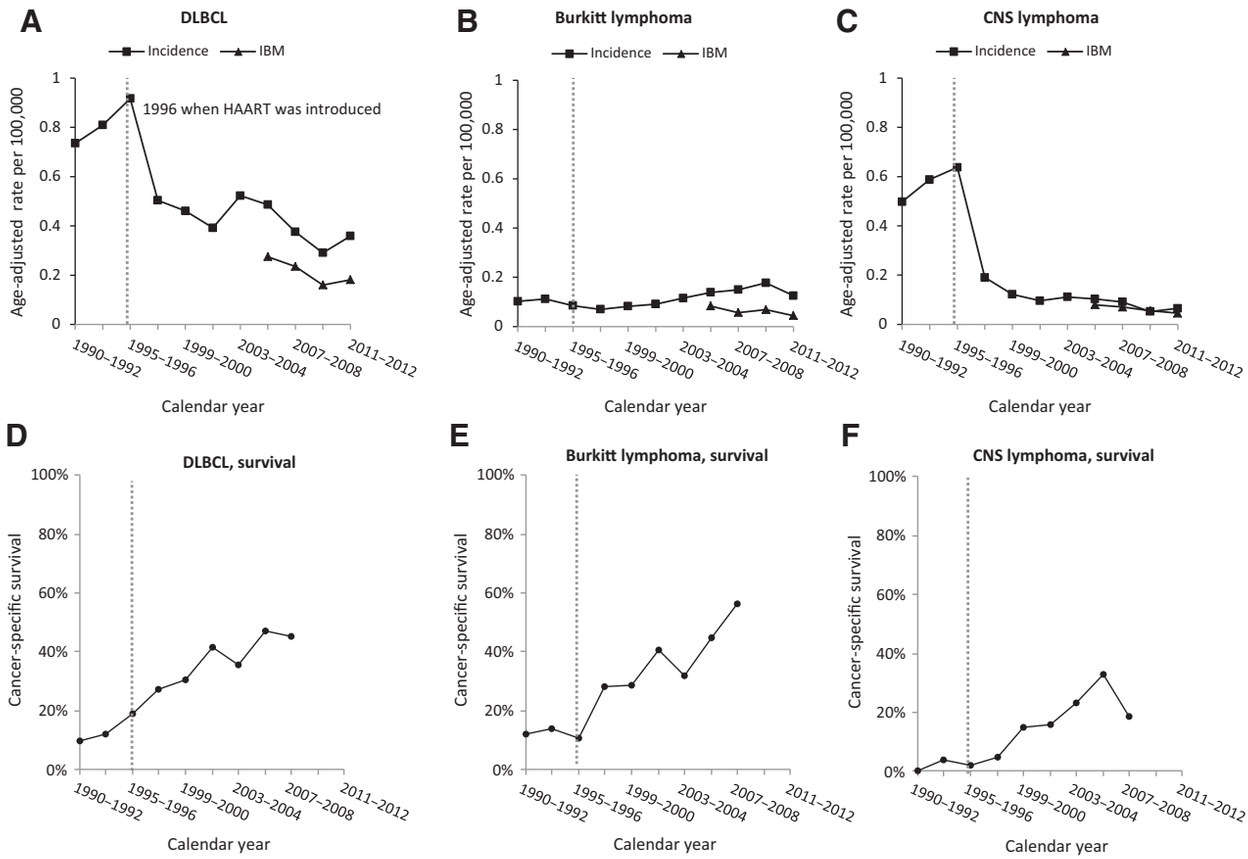

Figure 2.

Incidence, IBM, and survival among HIV-infected cases, for AIDS-defining NHL subtypes. Results are shown for DLBCL (**A**), Burkitt lymphoma (**B**), and CNS lymphoma (**C**). For each panel, we show age-adjusted incidence rates as squares and age-adjusted IBM rates as triangles. Incidence rates were adjusted for reporting delays. The corresponding 5-year cancer-specific survival according to year of NHL diagnosis is shown for DLBCL (**D**), Burkitt lymphoma (**E**), and CNS lymphoma (**F**). The following ICD-O-3 codes were used to define each of the three AIDS-defining NHL subtypes: DLBCL (histology codes 9678, 9679, 9680, 9684, 9688, 9712, or 9737-9738), Burkitt lymphoma (histology code 9687), and CNS lymphoma [topography code (C71 or C72) with histology codes (9590-9595 or 9670-9719)]. Results are shown for eight SEER registries (San Francisco, Connecticut, Detroit, Hawaii, New Mexico, Seattle, Utah, and Atlanta).

for cases that were not linked to HIV increased until about 2004 then started to decline at −0.85% per year ($P = 0.006$, Fig. 1B).

The corresponding IBM rates for 2005–2012 partition NHL mortality according to the HIV status of cases. IBM rates declined for both HIV-infected and uninfected cases, but the decline was steeper for the HIV-infected cases (−7.6% per year, $P = 0.007$, vs. −2.5% per year, $P = 0.009$; Fig. 1A and B). Cancer-specific survival increased over time for both HIV-infected and uninfected cases, but the improvement was much more marked for HIV-infected cases (from 9% cancer-specific survival at five years after diagnosis for cases diagnosed in 1990–1992, to 54% in 2007–2008) than for uninfected cases (62% to 76%; Fig. 1C and D). This corresponded with a −13.7% decrease per year ($P < 0.001$) in death rates among HIV-infected NHL cases and a −6.7% decrease per year ($P < 0.001$) among HIV-uninfected NHL cases.

Figure 2 presents similar results for HIV-infected cases for the three AIDS-defining NHL subtypes separately. In Fig. 2A, the incidence rates of HIV-infected DLBCL lymphoma dropped sharply after 1996 and then continued to decline at −4.0% per year ($P = 0.002$). In parallel, IBM rates decreased from 2005 to 2012 (−8.0% per year, $P = 0.02$), and five-year cancer-specific survival for HIV-infected cases improved dramatically, from 10% for cases diagnosed in 1990–1992 to 45% for cases diagnosed in 2007–2008 (Fig. 2D), corresponding with a −13.1% decrease per year ($P < 0.001$) in death rates among HIV-infected DLBCL cases.

For Burkitt lymphoma (Fig. 2B), incidence rates associated with HIV-infected cases fell slightly in the pre-HAART era (1990–1996), but then went back up and continued to increase at 5.2% per year ($P = 0.001$) during 1996–2012. The corresponding IBM rate did not change significantly during 2005–2012 ($P = 0.23$), even though five-year cancer-specific survival among HIV-infected cases improved from 12% to 56% (Fig. 2E). The survival improvement corresponded with a −13.1% decrease per year ($P < 0.001$) in death rates among HIV-infected Burkitt lymphoma cases.

The incidence rates of HIV-infected CNS lymphoma increased steeply in the pre-HAARRT era (Fig. 2C), but then decreased drastically beginning in 1996 (−11.7% per year, $P = 0.0001$). IBM rates were similar to the incidence rates but the decline across 2005–2012 was not significant ($P = 0.08$). Five-year cancer-specific survival was very poor but improved over time from 0% to 19% (Fig. 2F) during 1990–2008, corresponding to a

decrease of 13.5% per year ($P < 0.001$) in death rates among CNS lymphoma cases.

Discussion

In this study, we estimate that 4.2% of all NHL deaths in the U.S. general population during 2005–2012 were in people with HIV infection. The contributions of HIV to mortality from NHL varied substantially depending on clinical and demographic characteristics. Notably, we found a large fraction of NHL deaths linked to HIV infection for NHLs that are considered AIDS-defining subtypes, especially Burkitt and CNS lymphomas. For the AIDS-defining NHL subtypes, the HIV epidemic has greatly impacted deaths in population subgroups with a high prevalence of HIV. For example, the proportion of NHL deaths with HIV infection was very high among 20–49 year-olds (47.6%), males (15.2%), black individuals (39.3%), and cases residing in the urban areas of San Francisco (14.3%) and Atlanta (28.8%).

Several aspects of HIV epidemiology are important to consider in assessing the contribution of HIV to NHL mortality in the United States. The prevalence of HIV infection in the U.S. general population is quite low (approximately 0.3% in 2008; ref. 28). Importantly, however, HIV-related immunosuppression leads to a very high risk of NHL, especially for DLBCL, Burkitt lymphoma, and CNS lymphoma (3, 4). There are, therefore, a large proportion of incident NHL cases attributable to HIV (29, 30). According to Robbins and colleagues (30), an estimated 1,650 NHLs occurred among HIV-infected people in the United States in 2010, of which 88% cases were in excess above the number expected on the basis of background rates. Although NHL incidence remains elevated in HIV-infected people compared with the general population, there has been a decline in incidence over time (1, 2, 31).

In our analyses, we decomposed the overall general population trends in incidence and mortality by dividing the cases according to HIV status. For DLBCL and CNS lymphoma, the component of incidence linked to HIV infection dropped sharply after 1996 and then continued to decline at −4.0% and −11.7% per year, respectively. This decline is likely related to improvements in HAART regimens and increased utilization of HAART in the population beginning in 1996 (3, 29, 30). In contrast, for Burkitt lymphoma incidence rates corresponding to HIV-infected cases fell slightly in the pre-HAART era, but then went back up and continued to increase at 5.2% per year during 1996–2012. The lack of decline for Burkitt lymphoma may partly reflect a more complex relationship with immunosuppression (32).

Overall, we found that IBM rates of HIV-infected NHL are decreasing in the recent calendar period (Fig. 1A). This mortality trend reflects two major contributions: (i) declining NHL incidence after 1996, and (ii) improving cancer-specific survival among HIV-infected individuals with NHL. These two trends both contribute to the decline in DLBCL and CNS lymphoma mortality associated with HIV infection. For Burkitt lymphoma, the absence of a clear decline in IBM rates associated with HIV is explained by the rising incidence rates for this subtype, counterbalancing the improvement in survival. As we reported previously for NHL overall (12) and as suggested in Fig. 1B for HIV-uninfected cases, mortality decreased before there was a decline in incidence, indicating that the reduction in NHL mortality can best be explained by improved survival after NHL diagnosis.

Outcomes following an NHL diagnosis have improved markedly over time among HIV-infected people with NHL. For example, in our analyses, we show that five-year cancer-specific survival for DLBCL increased from 10% to 45%, and for Burkitt lymphoma from 12% to 56%. The introduction of HAART approximately 20 years ago has had a dramatic effect on NHL outcomes among HIV-infected people. HAART not only reduces mortality from AIDS-related opportunistic infections but also may help control EBV infection and thus prevent relapse of NHL (33). Concurrently, cancer therapy has also been evolving. Prior to the availability of HAART, standard chemotherapy was considered to depress the immune system and increase risk of opportunistic infection too much in HIV-infected patients, leading physicians to use less aggressive therapy to reduce complications (34). However, the availability of effective and tolerable HAART regimens has facilitated use of full-intensity chemotherapy regimens. Recent studies support a role of rituximab plus infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH) chemotherapy for treating NHL in HIV-infected patients (33). CNS lymphoma largely remains incurable in most patients, although there has been some improvement in five-year cancer-specific survival (increasing from 0% and 19% over the period we assessed; ref. 35). Total brain irradiation remains standard of care in HIV-infected people with CNS lymphoma (33), although the role of systemic therapy and rituximab is being explored.

For the most part, the proportions of NHL cases that were linked to HIV-infected people were similar to the proportions of NHL deaths, but there were a few notable exceptions. These differences result from the dramatic changes over time in NHL incidence and survival, as many years of incident cases were used to contribute to each mortality estimate. For example, we found that 33.0% of incident CNS lymphoma cases were in HIV-infected people, similar to what has been reported previously (29, 36), but 17.6% of CNS lymphoma deaths were in HIV-infected people (Table 1). Roughly, two-thirds of CNS lymphoma cases diagnosed in the pre-HAART era (1990–1996) were in HIV-infected people, but survival in this group was extremely poor (0% to 2% five-year cancer-specific survival rate). Therefore, few of these cases contributed to the NHL deaths during 2005–2012. Instead, the CNS NHL deaths during 2005–2012 largely arose from cases diagnosed more recently, when HIV prevalence was lower.

There are several strengths of our study. Our results are population-based and incorporate high quality cancer registry data from the SEER program, which reliably captures and classifies newly diagnosed cancer cases in the registry catchment areas. In addition, the SEER registries must have complete follow-up information for greater than 95% of their cancer cases, so that reporting of survival is reliable. While these SEER areas have varying HIV prevalence, they are not a random sample of the country, so our results may not be generalizable to the entire United States.

We modified the standard IBM methods slightly to include a range of CODs, based on a validated algorithm, as long as they linked to an incident NHL case in SEER (20). The rationale behind choosing this broader set of CODs is that some deaths among NHL cases that are due to the NHL are misattributed or classified as deaths from other cancers, or as HIV/AIDS-related deaths among NHL patients infected with HIV (20). If we instead included only deaths for which NHL was listed as the COD on the death certificate, we would have identified fewer NHL deaths, and a smaller fraction of those deaths would have been linked to HIV-infected cases. In particular, it was important to consider

deaths coded as due to HIV/AIDS as NHL deaths. This may seem counter-intuitive, but we validated this method in a separate analysis of HIV-infected people based on a comparison with relative survival, which is considered a gold standard for population-based survival rates (see Supplemental Materials; ref. 21). Because NHL is an AIDS-defining cancer, it is possible that clinicians code NHL deaths in HIV-infected patients as due to AIDS. In addition, according to death certificate coding rules, the underlying COD is defined as "the disease or injury which initiated the train of morbid events leading directly to death" (37). Therefore, based on this coding rule, death certificates that mention CODs from both HIV and NHL would have been coded to give "HIV" priority as the underlying COD, even if HIV was under effective treatment at this time of death.

Study limitations should also be noted. The SEER HIV flag was frequently missing, which we interpreted as indicating an absence of HIV infection. This approach has been used previously (9, 17), but because some infections may not be recorded, it is not 100% sensitive, and the sensitivity likely varies across cancer registries and over time. For example, among 2,211 NHL cases in SEER whose COD was specified as HIV, 85% had a positive HIV flag (indicating a sensitivity of 85%), while 1% had a negative flag and 14% were missing a result. We classified the small fraction of cases with "negative" or "unknown" HIV flag, but having HIV as the COD, as "positive" for our analyses. In addition, four SEER registries are included in the HIV/AIDS Cancer Match (HACM) Study, which includes linked HIV registry data. For the NHL cases in the HACM Study that linked to an HIV registry, indicating that the person had HIV infection, the sensitivity of the SEER HIV flag was low before 2004 (e.g., 58% at one registry), but sensitivity improved (77%–88%) after 2004 when the flag was collected as a Collaborative Stage site specific factor. In contrast, studies from the California SEER registry have indicated that the HIV flag was over 95% sensitive among NHL cases (15, 16).

HIV status was not ascertained for some cancer diagnoses in the other/unknown NHL category. In our primary analysis, we assigned these cases an HIV^- status, which would lead to an underestimate of the overall proportion of NHL deaths with HIV infection. We performed a sensitivity analysis by setting the HIV prevalence in this group to that observed among cases with small lymphocytic lymphoma, as CLL (a synonymous diagnosis) comprised the majority of the other/unknown group. With this approach, we estimated that 4.9% of total NHL deaths were in HIV-infected cases, compared with the estimate of 4.2% in our primary analysis. In addition, we excluded NHLs that were a person's second or later cancer because we are unaware of a validated COD algorithm for assessing cancer-specific mortality in these cases. Therefore, incidence and mortality rates presented in our article slightly underestimate the true NHL burden. However, it is unclear how this issue might affect the time trends or the estimated contribution of HIV infection.

A final limitation is that the IBM approach did not allow us to assess NHL mortality burden before the HAART era. Although we were able to present incidence and survival trends before and after the HAART era as these analyses were indexed by calendar year of NHL diagnosis. IBM rates are derived using deaths that are linked to incident cases from previous years. Therefore, extended follow-up of cancer cases diagnosed in the past is required. The number of years required is a function of the pattern of recurrences, that is, more years of follow-up are required for cancers with late recurrences (12). Because patients with NHL can experience late recurrences, we required 15 years of follow-up after an NHL diagnosis, which restricted the range of years (i.e., 2005–2012) for which we could derive IBM rates.

In conclusion, these are the first estimates quantifying how the HIV epidemic has impacted the U.S. general population mortality burden from NHL. We show that HIV has measurably affected deaths from NHL, especially for AIDS-defining NHL subtypes and for demographic groups among whom HIV infection is common. The declines over time in NHL mortality for cases linked to HIV reflect both declining NHL incidence and improving survival after NHL diagnosis as a result of HAART. HIV-infected people still face barriers to care related to HIV infection and cancer (38), which need to be addressed for continued progress with regards to these outcomes. HIV testing of NHL patients is justified to identify unsuspected infections and allow for appropriate treatment (39).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N. Howlader, E.A. Engels
Development of methodology: N. Howlader, E.A. Engels
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Howlader, M.S. Shiels, A.B. Mariotto, E.A. Engels
Writing, review, and/or revision of the manuscript: N. Howlader, M.S. Shiels, A.B. Mariotto, E.A. Engels
Study supervision: E.A. Engels

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Nadia Howlader, Meredith S. Shiels, Angela B. Mariotto, et al.

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