

# Contributions of Subtypes of Non-Hodgkin Lymphoma to Mortality Trends

Nadia Howlader<sup>1,2</sup>, Lindsay M. Morton<sup>3</sup>, Eric J. Feuer<sup>1</sup>, Caroline Besson<sup>3,4</sup>, and Eric A. Engels<sup>3</sup>

## Abstract

**Background:** Non-Hodgkin lymphoma (NHL) comprises distinct tumor subtypes. Although mortality from NHL overall has changed dramatically in the United States over time, little is known about trends for subtypes, because death certificates do not record this information.

**Methods:** Using data from U.S. Surveillance, Epidemiology, and End Results (SEER) areas, we assessed NHL mortality rates and mapped NHL deaths to incident NHL cases in SEER cancer registries. This allowed us to evaluate population-level mortality trends attributed to specific NHL subtypes (incidence-based mortality; IBM). We also describe NHL incidence and survival after NHL diagnosis by calendar year. We used Joinpoint to identify years when IBM and incidence rate trends changed slope.

**Results:** Overall NHL mortality rates increased during 1975–1997, peaking at 10.9 per 100,000 person-years, then decreased subsequently in 1997–2011. Overall IBM rates mirror this trend

during 1990–2011. For B-cell NHL subtypes, IBM rates decreased beginning in the mid-1990s, with yearly declines of –3.0% for diffuse large B-cell lymphoma (DLBCL), –2.7% for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and –5.3% for follicular lymphoma. Incidence rates for these subtypes did not decrease until after 2003. Corresponding 5-year cancer-specific survival increased dramatically over time for DLBCL (from 37%–66%), CLL/SLL (69%–84%), and follicular lymphoma (69%–82%). IBM for peripheral T-cell lymphoma was flat during 2006–2011, although incidence increased.

**Conclusions:** Mortality due to three common B-cell NHL subtypes has fallen over time in the United States.

**Impact:** This decline reflects better survival after NHL diagnosis, likely from improved therapies, because the decline in NHL incidence occurred later. *Cancer Epidemiol Biomarkers Prev*; 25(1); 174–9. ©2015 AACR.

## Introduction

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of malignancies arising from lymphoid tissue, with varied clinical and biologic features (1). The three most common NHL subtypes, accounting for about two-thirds of NHLs, are derived from B cells: diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and follicular lymphoma (FL; refs. 2–5). Peripheral T-cell lymphoma (PTCL) is the most common subtype derived from T cells and accounts for about approximately 50% of T-cell NHLs (2–5).

Although incidence trends for distinct NHL subtypes are well described (6–11), little is known about trends in mortality, which reflect the combined effects of NHL incidence and survival after NHL diagnosis. Notably, treatment advances may have improved

survival for some but not all NHL subtypes (12–18). U.S. national data on causes of death (COD) reported on death certificates make it possible to assess trends in mortality for NHL overall. Overall NHL mortality rates showed a steady and significant increase from 1975–1991 at a rate of 2.5% annually, followed by a slower but steady increase in mortality rates during 1991–1997 at a rate of 1.6% annually (5). After reaching a peak in 1997, NHL mortality started to decline with a 3.1% yearly decrease through 2006 and a continuous decrease through 2011 (5). Decomposing this mortality, however, into trends for NHL subtypes is not directly possible because death certificates do not record the subtype.

To provide a resource to address this limitation in mortality data, the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer registry program has linked mortality records to incident cancer cases. As a result, it is possible to calculate "incidence-based mortality" (IBM) rates, which capture population-level mortality attributable to particular tumors reported to SEER registries (19, 20). The numerator for the IBM rate consists of the number of cancer-specific deaths among persons with a particular cancer diagnosis reported to the cancer registry. The denominator for the rate is the person-time in the general population who are at risk at the time of death in the SEER areas. This approach allows for the partition of the general population mortality rate according to characteristics associated with the cancer diagnosis (e.g., tumor subtypes) that are recorded in the SEER registries. The IBM method has been used to assess the impact of screening and treatment on the mortality trends for several different cancer types (19, 21–27).

In this study, we applied IBM methods to SEER data to evaluate population-level mortality trends attributed to DLBCL, CLL/SLL,

<sup>1</sup>Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland.

<sup>2</sup>Department of Epidemiology and Biostatistics, The George Washington University Milken Institute School of Public Health, Washington DC. <sup>3</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland. <sup>4</sup>Université Paris Sud, Faculté de Médecine Paris Sud, Le Kremlin-Bicêtre, France.

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

**Corresponding Author:** Nadia Howlader, National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892. Phone: 240-276-6891; Fax: 240-277-6591; E-mail: [howladern@mail.nih.gov](mailto:howladern@mail.nih.gov)

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FL, and PTCL in the United States during 1975–2011. We also assessed contributions of NHL incidence and survival after NHL diagnosis to these trends.

## Materials and Methods

All analyses used data from nine US SEER cancer registries (1975–2011; ref. 28) and were restricted to adults (age at least 20 years). We identified cases of DLBCL, CLL/SLL, FL, and PTCL using histology codes (29). PTCL was only assessed beginning in 1992 because of lack of specific coding in earlier years. Cases diagnosed by death certificates or autopsy were excluded. We further restricted analysis to NHLs that were the first or only cancer, to facilitate mapping to cancer-specific deaths in mortality records 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. NHL incidence rates were calculated after accounting for reporting delays (30).

CODs were ascertained from death certificates obtained by the National Center for Health Statistics (31). We report mortality rates based on deaths from NHL (see Supplementary Fig. S1 legend for specific codes for NHL). For IBM rates, we used linked SEER data on NHL cases to classify these NHL deaths according to NHL histologic subtype. In addition, because some deaths in NHL patients may have been inaccurately recorded as deaths from other hematologic malignancies (32), we also included in the IBM rates deaths recorded as due to Hodgkin lymphoma, plasma cell neoplasms, or leukemia if they linked to a SEER NHL case (Fig. 1, legend). Of the 57,301 total hematologic cancer deaths observed among incident NHL cases in SEER, 42,582 (74.3%) deaths were coded as NHL COD in the death certificate, 14,179 (24.7%) as leukemia COD, 316 (0.6%) as Hodgkin lymphoma COD, and 224 (0.4%) as plasma cell neoplasms COD. With the 2001 WHO classification, CLL is now considered to be synonymous with SLL and is considered part of NHL; therefore, we felt it was especially important to include leukemia CODs to capture deaths related to this subtype of NHL. Indeed, of the 14,179 deaths among NHL cases that were classified as due to leukemia, 9,679 (68.2%) were in CLL/SLL cases, less than 1% were found in DLBCL, FL, or PTCL cases, and the remaining 3,579 (25.2%) were in cases with other NHL subtypes that we did not assess. Also, among the 54,369 deaths during 1975–2011 that had NHL as the COD, 7,704

(14.2%) did not link to a SEER NHL diagnosis. These deaths may have been misclassified, or the person may have had NHL diagnosed outside a SEER area or before SEER ascertainment of cancer diagnoses in 1975.

IBM rates are valid for a shorter range of calendar years than death certificate mortality. Because IBM rates are calculated based on 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 (see Supplementary Fig. S1 for more details). 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 before each year of mortality data (sometimes known as the "burn-in" period for IBM rates), to ensure capture of almost all deaths from NHL. Thus, we present IBM rates only for 1990–2011 (2006–2011 for PTCL).

We present rates for mortality, IBM, and incidence according to calendar year. We used Joinpoint to characterize piecewise log-linear time calendar trends in the age-standardized rates (33, 34). Incidence trends during 1975–2011 were fitted with up to a maximum of 5 joinpoints, whereas the PTCL incidence trend during 1992–2011 was fitted with up to 3 joinpoints. Because IBM rates were available for a shorter range of calendar years, these trends were fitted with up to 3 joinpoints (1 joinpoint for PTCL). The resulting trend across each calendar interval is described by the slope of the line segment (i.e., annual percentage change, APC; ref. 34). We used *t* tests to assess whether APCs were statistically different from zero. All statistical tests were two sided.

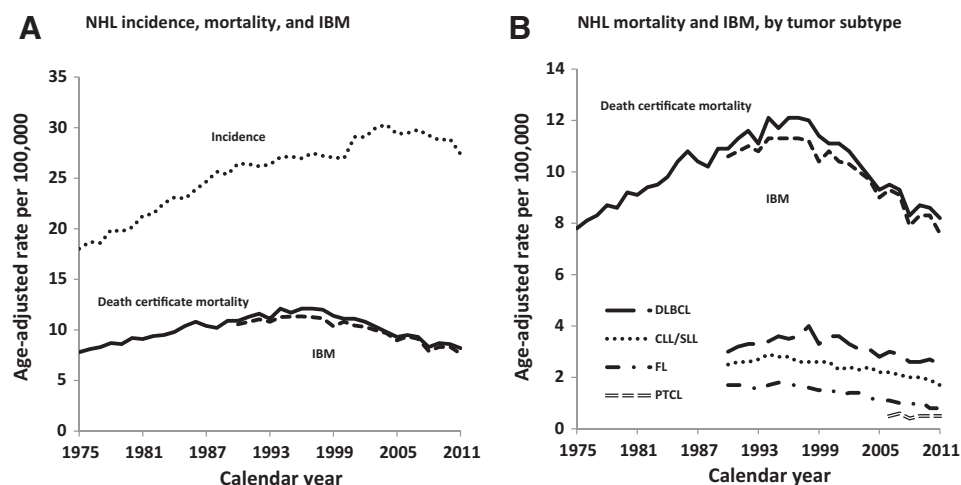
Finally, we present estimates of 5-year cancer-specific survival (i.e., the probability that a person with NHL did not die from NHL) according to NHL subtype and diagnosis year. All estimates except those for survival were age-standardized to the 2000 U.S. general population. We age-adjusted NHL cancer-specific survival using the International Cancer Survival Standard 1 (35).

## Results

Among people living in U.S. SEER areas during 1975–2011, overall NHL mortality rates increased during 1975–1997, peaking at 10.9 per 100,000 person-years, then decreased subsequently in 1997–2011 (Fig. 1A). IBM rates closely mirrored overall NHL

**Figure 1.**

NHL incidence, death certificate mortality, and IBM rates. SEER-9, 1975–2011. A, results are shown for NHL death certificate mortality (solid line), IBM (dashed line, starting in 1990), and incidence (black dotted line). B, the results for NHL death certificate mortality and IBM are presented again along with the IBM for four NHL subtypes: DLBCL (big dashed line), CLL/SLL (dotted line), FL (dashed followed by dotted line), and PTCL (double dashed line). Note that the vertical axis differs in A and B. Results are shown for SEER-9 registries. See Supplementary Fig. S1 legend for a description of these registries and codes for NHL mortality and IBM CODs.



mortality rates for the period for which they could be evaluated (1990–2011). When IBM rates were examined for individual NHL subtypes, the IBM rates for each subtype excluding PTCL increased or were flat during the early 1990s and then decreased after approximately 1995, depending on the subtype (Fig. 1B). Of note, incidence rates for NHL overall increased during 1975–2002 and then started decreasing, so that the decline in incidence started later than the decline in mortality (Fig. 1A).

On the basis of the IBM rates, DLBCL contributed the most to NHL mortality, followed by CLL/SLL, FL, and PTCL. For example, in 2011, 33% of all NHL deaths were due to DLBCL, 22% to CLL/SLL, 11% to FL, and 7% to PTCL. The remaining 27% of NHL deaths were due to other subtypes combined. The proportion of total NHL incident cases that contributed to NHL deaths over the recent 15-year period (1997–2011) are as follows: 27% DLBCL, 23% CLL/SLL, 14% FL, 5% PTCL, and 31% from other subtypes combined (however, we note that the proportion for PTCL is underestimated because the IBM for this subtype could be assessed only for 2006–2011).

Figure 2 presents results for each NHL subtype separately. For DLBCL (Fig. 2A), incidence increased steeply during 1977–1990 and more slowly through 2004, then decreased beginning in 2004. In contrast, IBM increased only until 1998 and subsequently fell by  $-3.0\%$  per year. Five-year age-standardized cancer-specific survival increased dramatically over time, from 37% for cases diagnosed in 1975 to 66% in 2005.

For CLL/SLL (Fig. 2B), incidence fluctuated during 1975–2011. In contrast, IBM increased during 1990–1995 and then declined by  $-2.7\%$  per year. Five-year age-standardized cancer-specific survival increased from 69% to 84% during 1975–2005.

Beginning in 1975, FL incidence increased steeply for 3 years and gradually until 2007, then declined (Fig. 2C). The corresponding IBM trend was flat during 1990–1997 and then declined steeply ( $-5.1\%$  per year). Five-year age-standardized cancer-specific survival for FL was better than for DLBCL and CLL/SLL, although there was a less clear improvement over calendar time until after 1999 (improving from 75% in 1999 to 82% in 2005).

For PTCL (Fig. 2D), incidence increased sharply during 1992–1998 then moderated in slope. In contrast with the three other subtypes, there was no clear trend in IBM, although the range of calendar years was limited and the subtype was much rarer. Five-year age-standardized cancer-specific survival seemed to be decreasing over 1993–2005 (64%–56%); however, there is substantial uncertainty in these estimates (data not shown).

## Discussion

This is the first study to describe trends in mortality for individual NHL tumor subtypes in the context of changing patterns of incidence and survival. We found that overall mortality rates for NHL increased in the U.S. general population from 1975–1997 and then decreased. Similar patterns in mortality, based on IBM methods, were observed specifically for DLBCL, CLL/SLL, and FL subtypes during the 1990–2011 period, with peaks in IBM noted in 1995–1998. Mortality rates for PTCL remained unchanged over a shorter time period (2006–2011).

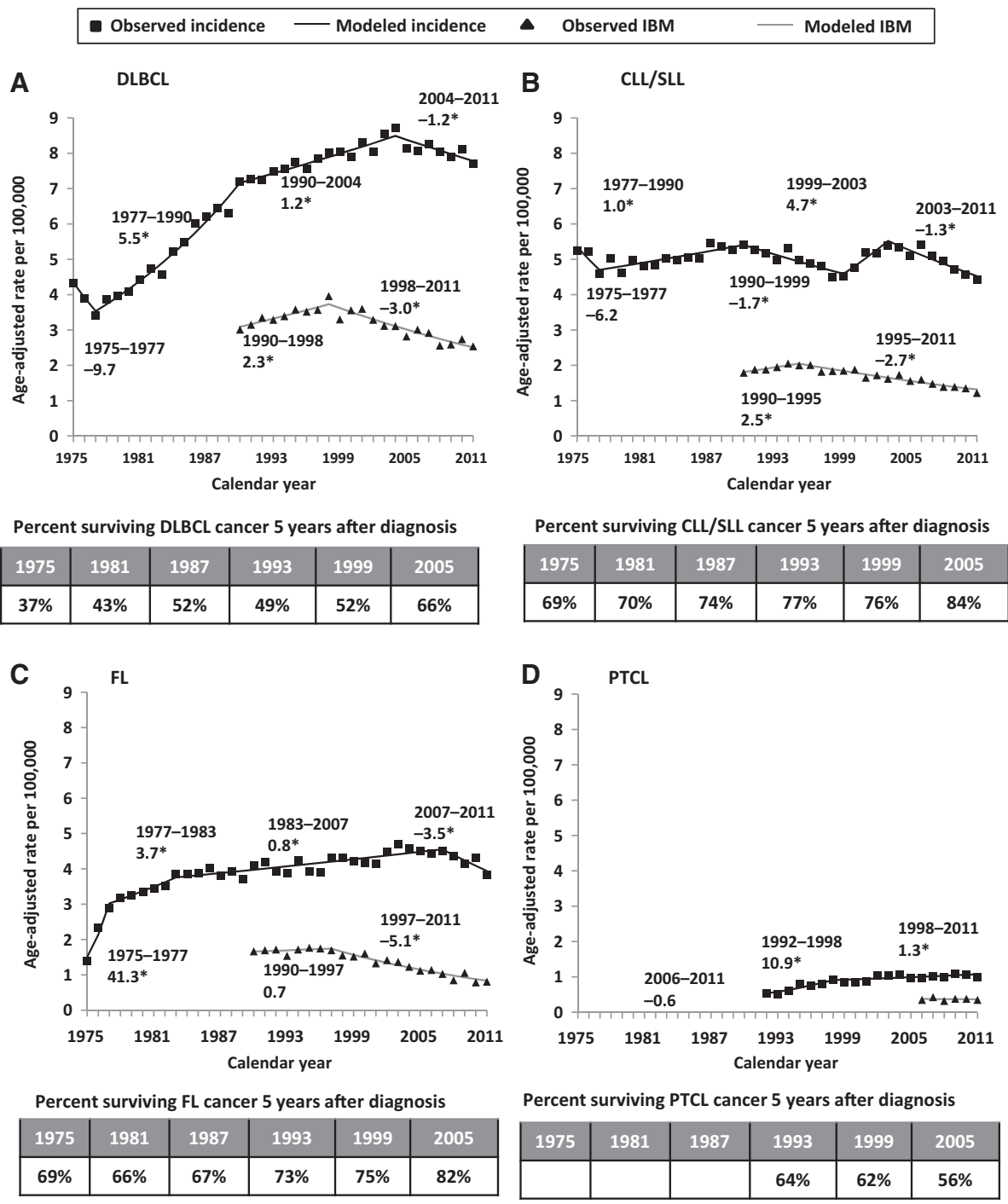
Notably, the mortality trends for the three most common NHL subtypes (DLBCL, CLL/SLL, and FL) decreased before there was a decline in incidence, indicating that the reduction in NHL mortality can best be explained by improved survival after NHL diagnosis. We hypothesize that these changes in survival reflect

improvements in NHL therapy. One notable improvement was the addition of rituximab to standard chemotherapy (CHOP, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone) beginning in 1998 (14). With the advent of rituximab, most DLBCL and FL cases have been treated with this initial regimen (14, 17, 18, 36), which has led to improved survival. For example, DLBCL survival increased from 52% to 66% and FL survival increased from 75% to 82% during 1999–2005. In the 1990s, fludarabine and rituximab were also introduced as new agents to treat CLL/SLL (37).

The incidence of DLBCL, CLL/SLL, and FL increased until the mid-2000s before declining. Many factors could have contributed to these incidence trends. Our analyses classify incident NHL using morphology codes abstracted from pathology reports by SEER registries. An overall reliability of 77% for translation of individual codes from International Classification of Diseases for Oncology, 2nd edition to 3rd edition, (ICD-O-2) to (ICD-O-3) has been reported by Clarke and colleagues (38). Moreover, Clarke and colleagues (2) and Morton and colleagues (38, 39) reported that when the individual codes were grouped into subtypes, reliability was even greater ( $>80\%$ ) for the major subtypes that we include in our analysis. In a recent study, Proctor and colleagues (40) reported a similar level of discordance (20%–26%) between expert versus nonexpert pathology review of DLBCL, FL, and CLL/SLL subtypes. Agreement among pathologists has increased over time (40), but it is unclear how this might have impacted the trends we present. Because we recognized that the classification has evolved for T-cell lymphomas, we conservatively started analyses for the PTCL subtype later (1992+). Also, some known risk factors may have also affected the trends. For example, the human immunodeficiency virus epidemic contributed to the increase in NHL incidence in the 1980s and through the mid-1990s, especially for DLBCL (6, 41, 42). It is unclear whether changes in the prevalence of other NHL risk factors (e.g., cigarette smoking, autoimmune conditions, hepatitis C virus infection, organ transplantation) might explain the incidence trends (43–47).

Our results are population based and incorporate high-quality cancer registry data from the SEER program, which reliably capture and classify newly diagnosed cancer incident cases in the registry catchment areas. Nonetheless, some challenges of IBM methods should be considered. First, because IBM rates are derived based on deaths that are linked to incident cases from previous years, the follow-up of cancer cases diagnosed in the past is required. The number of years that are required is a function of the pattern of recurrences for the cancer under study, i.e., for cancers with late recurrences, more years of follow-up are required to capture the majority of deaths (19). Because patients with NHL can experience late recurrences, we chose to require 15 years of follow-up after an NHL diagnosis, which restricted the range of years for which we could derive IBM rates. Second, cancer patients moving in or out of their registry catchment area can cause mismatches between IBM and death certificate mortality rates (19). Third, IBM methods underestimate mortality if the cancer registries under-ascertain the incident cancer cases. Although SEER registries have high standards for completeness in capturing incident cancers, this is a concern for CLL/SLL, which is increasingly diagnosed and treated in physicians' offices rather than hospital settings (48).

We modified the standard IBM methods slightly to include a range of CODs related to hematologic malignancies, and counted



**Figure 2.** NHL incidence, IBM, and survival trends. Results are shown for DLBCL (A), CLL/SLL (B), FL (C), and PTCL (D). For each panel, we show age-adjusted incidence rates (observed rates as squares, modeled rates as lines) and age-adjusted IBM rates (observed rates as triangles, and modeled rates as lines). Incidence rates were adjusted for reporting delays. The line segments of each curve were selected using the Joinpoint program, and the numbers on the graph indicate the slopes of each line segment denoted as annual percent change (APC). Asterisks (\*) are used to denote APCs that are significantly different from zero ( $P < 0.05$ ). We also show 5-year age-standardized cancer-specific survival according to year of NHL diagnosis in a table at the bottom of each panel. Results are shown for SEER-9 registries. The following ICD-O-3 histology codes were used to define each of the four main subtypes: DLBCL (9678, 9679, 9680, 9684, 9688, 9712, 9737-9738), CLL/SLL (9670, 9823), FL (9690, 9691, 9695, 9698), and PTCL (9675, 9702, 9705, 9708, 9714, 9716, 9717, 9718, 9709, 9726). See Supplementary Fig. S1 legend for a description of these registries and codes for NHL mortality and IBM CODs.



such deaths as long as they linked to an incident NHL case in SEER. This approach, which recognizes that some cancer deaths are miscoded to the wrong type of cancer (32), was especially important given the evolving classification of hematologic malignancies over the last two decades. By using broad hematologic death coding, we attributed treatment-related myeloid leukemia deaths to the index NHL diagnosis. Such attribution would be appropriate in these cases, because the NHLs can be considered the indirect cause of the leukemia death, and in any event, these outcomes were likely very rare (49, 50). Our approach allowed us to assign 69% of all NHL deaths to three common NHL subtypes for the period 1990–2011, and 73% to four subtypes for 2006–2011. Reassuringly, our overall IBM rates closely mirrored the death certificate mortality rates for 1990–2011 (Fig. 1A and B), although given some of the challenges listed above in mapping cancers to the corresponding deaths, this similarity may be somewhat fortuitous.

We note that data on PTCL were limited. This subtype is uncommon and was reliably identified only beginning in 1992 due to evolving diagnostic methods and classification. Indeed, the steep increase in incidence before 1998 likely reflects the increasing recognition and improved reporting of this subtype. CHOP is the standard therapy for PTCL (51) although new drugs (pralatrexate and romidepsin) received approval in 2009 (52, 53). Survival is generally described as poor, although our cancer-specific survival estimate of approximately 65% for PTCL was higher than previously suggested (54, 55). We find that 5-year cancer-specific survival for the PTCL cases not otherwise specified was 40%, similar to what is reported in the literature (54, 55). Our PTCL classification does include Alk+ T-cell lymphoma, and this also has a low survival rate (5-year survival 52%). The survival for the overall PTCL group is pulled up by cutaneous T-cell lymphoma not otherwise specified, which makes up a major fraction of the cases (28%) and has a relatively good survival (5-year survival 82%). Thus, inclusion of various subtypes of PTCL, especially cutaneous T-cell lymphoma, that have fairly good survival leads to the higher cancer-specific survival estimates for PTCL in our data.

In conclusion, we demonstrate a significant reduction in NHL mortality in the U.S. general population, which was initially due to improved survival after NHL diagnosis for the three most common subtypes (DLBCL, CLL/SLL, and FL), and more recently due to a decline in incidence. Survival benefit from R-CHOP and other novel therapies for treating NHL has been demonstrated in clinical trials, but our study highlights the impact of these therapies at the population level. IBM methods should also be valuable for evaluating mortality trends for other cancer subtypes.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

**Conception and design:** N. Howlader, L.M. Morton, E.J. Feuer, E.A. Engels  
**Development of methodology:** N. Howlader, E.J. Feuer, E.A. Engels  
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** N. Howlader  
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** N. Howlader, L.M. Morton, E.J. Feuer, C. Besson, E.A. Engels  
**Writing, review, and/or revision of the manuscript:** N. Howlader, L.M. Morton, E.J. Feuer, C. Besson, E.A. Engels  
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** N. Howlader

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# BLOOD CANCER DISCOVERY

## Contributions of Subtypes of Non-Hodgkin Lymphoma to Mortality Trends

Nadia Howlader, Lindsay M. Morton, Eric J. Feuer, et al.

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