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Research Article

Prevalence of HIV Infection among U.S. Hodgkin Lymphoma Cases

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Abstract

Background: Hodgkin lymphoma is uncommon in the U.S. general population; however, Hodgkin lymphoma risk is elevated in people with human immunodeficiency virus (HIV) infection. Thus, despite the low HIV prevalence in the United States, the HIV epidemic may have contributed substantially to the general population burden of Hodgkin lymphoma.

Methods: We used data from 14 U.S. cancer registries in the Surveillance, Epidemiology, and End Results Program that recorded HIV status of Hodgkin lymphoma cases at diagnosis during 2000 to 2010. We computed the HIV prevalence in Hodgkin lymphoma cases by demographic and tumor characteristics, the proportion of deaths among Hodgkin lymphoma cases because of HIV, and 5-year mortality by HIV status.

Results: Of 22,355 Hodgkin lymphoma cases, 848 (3.79%) were HIV infected at diagnosis. HIV prevalence in Hodgkin lymphoma cases was greater among males than females (6.0% vs. 1.2%). Among males, HIV prevalence was greatest among 40- to 59-year-olds (14.2%), non-Hispanic blacks (16.9%), Hispanics (9.9%), and among cases of lymphocyte-depleted (15.1%), and mixed cellularity Hodgkin lymphoma (10.5%). Eight percent of male and 1.5% of female Hodgkin lymphoma cases died from HIV. Five-year mortality was two-fold higher in HIV-infected Hodgkin lymphoma cases (36.9% vs. 17.5%).

Conclusion: In the United States, a substantial proportion of lymphocyte-depleted and mixed cellularity Hodgkin lymphoma cases and Hodgkin lymphoma cases among non-Hispanic black, Hispanic, and middle-aged men are HIV infected. In addition, HIV is an important cause of death among Hodgkin lymphoma cases.

Impact: Clinicians should be aware of the high prevalence of HIV in certain subgroups of patients with Hodgkin lymphoma and routine HIV testing should be recommended for all patients presenting with Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev; 23(2); 274–81. ©2013 AACR.*

Introduction

Human immunodeficiency virus (HIV) is associated with the elevated risk of a number of cancers, including Hodgkin lymphoma (1). HIV increases Hodgkin lymphoma risk by causing progressive immune suppression [i.e., acquired immunodeficiency syndrome (AIDS)] and likely loss of immunologic control of Epstein–Barr virus (EBV; refs. 2, 3). Ninety percent of Hodgkin lymphoma tumors in HIV-infected people are EBV positive, compared with 32% in HIV-uninfected people (4). The association with immune suppression is weaker than that observed for non-Hodgkin lymphoma (NHL). NHL rates declined dramatically with the introduction of highly active antiretroviral therapy (HAART) to treat HIV. In contrast, it is unclear whether rates of Hodgkin lymphoma among people with HIV have changed in the HAART era (2, 5–7).

The magnitude of the elevated risk of Hodgkin lymphoma in people with AIDS varies across histologic subtypes of Hodgkin lymphoma, with 18-fold increased risk for mixed cellularity Hodgkin lymphoma, 35-fold for lymphocyte-depleted Hodgkin lymphoma, 5-fold for nodular sclerosis Hodgkin lymphoma, and 32-fold for unspecified Hodgkin lymphoma (8). Mixed cellularity is the most common Hodgkin lymphoma subtype among HIV-infected individuals in contrast with the predominance of nodular sclerosis in the general population (5).

Hodgkin lymphoma is uncommon in the U.S. general population, with only 9,060 cases estimated to have occurred in 2012 (9), but it is the fifth most common type of cancer in people with HIV (10). Despite the documented elevations in risk of Hodgkin lymphoma among HIV-infected individuals, the impact of HIV-infected Hodgkin

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lymphoma cases on the general population burden of Hodgkin lymphoma has not been assessed. Using data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program for 14 U.S. regions, we estimated the proportion of Hodgkin lymphoma cases during 2000 to 2010 who had HIV infection. We also assessed the proportion of deaths among Hodgkin lymphoma cases because of HIV, and mortality among Hodgkin lymphoma cases according to HIV status.

Materials and Methods

Data sources

Data on incident Hodgkin lymphoma cases were derived from 14 U.S. SEER population-based cancer registries for 2000 to 2010. These registries (Connecticut, Hawaii, New Mexico, Utah, Atlanta, Detroit, Seattle-Puget Sound, Los Angeles, San Francisco-Oakland, San Jose-Monterey, greater California, New Jersey, Louisiana, Kentucky) represent 24.7% of the U.S. population.

Hodgkin lymphoma cases and histologic subtypes were defined using the SEER lymphoma subtype recode based on classifications proposed by the International Lymphoma Epidemiology Consortium (InterLymph) Pathology Working Group: nodular lymphocyte predominant, lymphocyte-rich, mixed cellularity, lymphocyte-depleted, nodular sclerosis, and classical Hodgkin lymphoma, not otherwise specified (NOS; ref. 11). Disease staging was based on the Ann Arbor classification system, according to the extent of tumor and the presence or absence of "B" symptoms (i.e., systemic symptoms of night sweats, fever, and weight loss; ref. 12).

SEER registries recorded HIV serostatus at the time of cancer diagnosis (i.e., "HIV flag") as part of the extent of disease field for individuals diagnosed with Hodgkin lymphoma (13, 14). However, 61% of Hodgkin lymphoma cases had unknown values for the HIV flag. We classified these cases as HIV uninfected, as the majority of cases with known values were HIV uninfected. For Hodgkin lymphoma cases who died, SEER records the underlying cause of death from death certificates. In a sensitivity analysis, we reclassified Hodgkin lymphoma cases without a positive HIV flag, but with HIV listed as the cause of death, as HIV infected. The number of reclassified cases was small ($n = 43$, or 0.20% of cases without a positive HIV flag), supporting our assignment of Hodgkin lymphoma cases with an unknown HIV flag to uninfected status. For comparison, 24.5% of deaths among Hodgkin lymphoma cases classified as HIV-infected by the HIV flag had HIV as the cause of death.

Statistical analysis

We computed the prevalence of HIV in Hodgkin lymphoma cases by sex, age group, race/ethnicity, HIV prevalence of the registry catchment area, histology, stage, and the presence of "B" symptoms. Registry catchment areas were classified as having high (San Francisco-Oakland, New Jersey, Louisiana, Atlanta, Los Angeles, Detroit, Connecticut) or low HIV prevalence (Seattle-Puget Sound, greater California, Hawaii, San Jose-Monterey, Kentucky, New Mexico, Utah) compared with the national average (0.28% HIV prevalence) based on Centers for Disease Control and Prevention data from 2011 (15).

For Hodgkin lymphoma cases who died, the underlying cause of death was ascertained by SEER using death certificates and was classified as because of HIV (ICD-10: B20-B24), Hodgkin lymphoma (ICD-10: C81), or other causes (16). We computed the fraction of deaths among Hodgkin lymphoma cases who had HIV as the underlying cause of death. The cumulative 5-year overall mortality was estimated for HIV-infected and HIV-uninfected cases of Hodgkin lymphoma with the Kaplan–Meier method. The cumulative 5-year mortality because of Hodgkin lymphoma and HIV (only for HIV-infected cases) was also estimated, treating other causes of death as competing events, using the survival session module in SEER*-Stat (17).

Results

During 2000 to 2010, a total of 22,355 Hodgkin lymphoma cases were diagnosed in 14 U.S. SEER regions. Of these cases, 848 (3.8%) were HIV-infected at the time of diagnosis. Table 1 presents the characteristics of Hodgkin lymphoma cases by HIV status. Compared with Hodgkin lymphomas in people without HIV infection, a larger proportion of Hodgkin lymphomas in people with HIV infection were mixed cellularity (25.0% vs. 12.2%), and a smaller proportion were nodular sclerosis (30.7% vs. 59.6%). HIV-infected cases were predominantly male (86.2%), whereas HIV-uninfected cases were more evenly divided between genders (53.7% male). The early peak in Hodgkin lymphoma diagnoses in HIV-uninfected cases among 20- to 29-year-olds was not observed in HIV-infected cases; instead, 82.9% of HIV-infected cases occurred in 30- to 59-year-olds (Fig. 1). The median age at Hodgkin lymphoma diagnosis was between 40 and 44 years for HIV-infected cases and between 35 and 39 years for HIV-uninfected cases. HIV-infected cases were more likely to be diagnosed at advanced stages (stage IV: 41.5% of HIV-infected individuals vs. 17.0% of HIV-uninfected individuals) and with "B" symptoms (57.4% of HIV-infected cases versus 34.2% of HIV-uninfected cases).

Table 2 displays the prevalence of HIV infection among subgroups of Hodgkin lymphoma cases. HIV prevalence was greater among male (5.96%) than among female (1.16%) Hodgkin lymphoma cases. Among male Hodgkin lymphoma cases, HIV prevalence was highest (14.2%) in 40- to 49-year-olds. Non-Hispanic black and Hispanic males had the highest proportion of Hodgkin lymphoma cases with HIV (16.9% and 9.89%, respectively). The fraction of male Hodgkin lymphoma cases with HIV infection was higher in regions with HIV prevalence above the national average than in regions with HIV prevalence below the national average (7.65% vs. 3.99%). Among males, a higher proportion of lymphocyte-depleted Hodgkin lymphoma (15.1%), mixed

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Table 1. Characteristics of HIV-uninfected and HIV-infected Hodgkin lymphoma cases in 14 U.S. SEER registries, 2000 to 2010

	HIV-uninfected	HIV-infected
	N (%)	*N* (%)
Total	21,507 (100)	848 (100)
Sex		
Male	11,539 (53.7)	731 (86.2)
Female	9,968 (46.4)	117 (13.8)
Age group		
0–9	314 (1.5)	1 (0.1)
10–19	2,369 (11.5)	10 (1.2)
20–29	4,814 (22.4)	73 (8.6)
30–39	3,848 (17.9)	220 (25.9)
40–49	2,994 (13.9)	305 (36.0)
50–59	2,262 (10.5)	178 (21.0)
60–69	1,983 (9.2)	38 (4.5)
70+	2,823 (13.1)	23 (2.7)
Race/ethnicity		
Non-Hispanic white	14,778 (68.7)	343 (40.5)
Non-Hispanic black	2,105 (9.8)	225 (30.1)
Hispanic	3,347 (15.6)	229 (27.0)
Other	1,277 (5.9)	21 (2.5)
Registry HIV prevalence		
Below national average	9,917 (46.1)	264 (31.1)
Above national average	11,590 (53.9)	584 (68.9)
Histologic subtype		
Lymphocyte-rich	679 (3.2)	16 (1.9)
Mixed cellularity	2,632 (12.2)	212 (25.0)
Lymphocyte-depleted	268 (1.3)	31 (3.7)
Nodular sclerosis	12,819 (59.6)	260 (30.7)
Classical NOS	4,160 (19.3)	321 (37.9)
Nodular lymphocyte predominant	949 (4.4)	8 (0.9)
Ann Arbor stage		
Stage I	3,956 (18.4)	121 (14.3)
Stage II	8,489 (39.5)	149 (17.6)
Stage III	4,115 (19.1)	190 (22.4)
Stage IV	3,660 (17.0)	352 (41.5)
Unknown	1,287 (6.0)	36 (4.3)
"B" symptoms		
Absent	9,445 (43.9)	245 (28.9)
Present	7,356 (34.2)	487 (57.4)
Unknown	4,706 (21.9)	116 (13.7)

cellularity Hodgkin lymphoma (10.5%), and classical Hodgkin lymphoma NOS (10.8%) were HIV-infected compared with lymphocyte-rich (3.42%), nodular sclerosis (3.22%), and nodular lymphocyte predominant Hodgkin lymphoma (0.60%). Also, among males, HIV prevalence was higher in stage IV Hodgkin lymphoma cases and Hodgkin lymphoma cases with "B" symptoms (13.0% and 9.13%, respectively) compared with less advanced cases. Patterns were similar among females, albeit with much lower prevalence (Table 2).

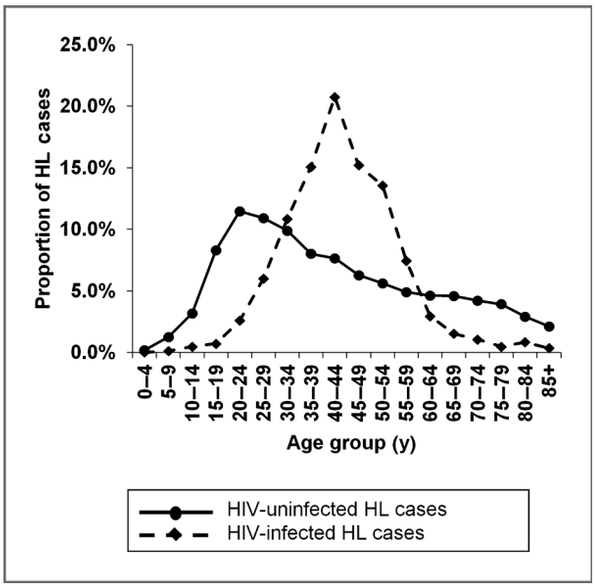

Figure 1. Proportion of Hodgkin lymphoma cases in each 5-year age group in 14 SEER registries during 2000 to 2010, by HIV status. The solid line indicates HIV-uninfected Hodgkin lymphoma cases and the dashed line indicates HIV-infected cases.

In a sensitivity analysis, we reclassified 43 Hodgkin lymphoma cases without a positive HIV flag, but with HIV as the cause of death, as HIV-infected. The overall proportions of Hodgkin lymphoma cases with HIV infection were similar (6.22% in men, 1.26% in women), and the patterns were consistent with our main analysis (not shown).

Overall, 8.33% of deaths in male Hodgkin lymphoma cases and 1.50% of deaths in female Hodgkin lymphoma cases were because of HIV (Table 3). The patterns for the fraction of deaths because of HIV infection were similar to those described for HIV prevalence in Hodgkin lymphoma cases. Among males, the proportion of deaths among Hodgkin lymphoma cases that were because of HIV infection was particularly high among 30- to 39-year-olds and 40- to 49-year-olds (21.0% and 24.6%, respectively), and non-Hispanic blacks and Hispanics (24.7% and 12.9%, respectively). In addition, a large fraction of deaths among male cases of mixed cellularity (9.64%) and lymphocyte-depleted (15.4%) Hodgkin lymphomas, stage IV Hodgkin lymphomas (14.7%), and Hodgkin lymphomas with "B" symptoms (11.3%) were because of HIV.

The 5-year risk of death among HIV-infected Hodgkin lymphoma cases was 36.9% compared with 17.5% among HIV-uninfected Hodgkin lymphoma cases (Fig. 2A and B). The majority of deaths among HIV-infected Hodgkin lymphoma cases were because of HIV (65.6% of deaths; absolute risk of death because of HIV: 23.3% in 5 years). In contrast, the risk of death because of Hodgkin lymphoma was similar among HIV-uninfected and HIV-infected Hodgkin lymphoma cases (9.0% vs. 6.2% in 5 years, respectively).

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Table 2. Prevalence of HIV among cases of Hodgkin lymphoma in 14 SEER registries, 2000 to 2010

	Males			Females		
	N	Proportion with HIV, %	95% CI	*N*	Proportion with HIV, %	95% CI
Total	12,270	5.96	(5.54–6.37)	10,085	1.16	(0.95–1.37)
Age group						
0–9	227	0.44	0–1.30	88	0	(0–0)
10–19	1,267	0.55	0.14–0.96	1,212	0.25	(0–0.53)
20–29	2,448	2.04	1.48–2.60	2,439	0.94	(0.56–1.33)
30–39	2,199	8.87	7.68–10.1	1,869	1.33	(0.82–1.88)
40–49	1,982	14.2	12.6–15.7	1,317	1.82	(1.10–2.54)
50–59	1,518	10.1	8.63–11.7	922	2.60	(1.58–3.63)
60–69	1,182	2.54	1.64–3.43	839	0.95	(0.30–1.61)
70+	1,447	0.90	0.41–1.39	1,399	0.71	(0.27–1.16)
Race/ethnicity						
Non-Hispanic white	8,243	3.64	(3.24–4.04)	6,878	0.63	(0.44–0.81)
Non-Hispanic black	1,273	16.9	(14.8–18.9)	1,087	3.68	(2.56–4.80)
Hispanic	2,032	9.89	(8.59–11.2)	1,544	1.81	(1.15–2.48)
Other	707	2.08	(1.04–3.12)	576	1.04	(0.21–1.87)
Registry HIV prevalence						
Below national average	5,669	3.99	(3.48–4.50)	4,096	0.78	(0.51–1.05)
Above national average	6,601	7.65	(7.01–8.29)	5,074	1.32	(1.01–1.63)
Histologic subtype						
Lymphocyte-rich	423	3.42	(1.72–5.13)	257	0.39	(0–1.15)
Mixed cellularity	1,796	10.5	(9.05–11.9)	1,048	2.29	(1.38–3.20)
Lymphocyte-depleted	185	15.1	(9.97–20.3)	114	2.63	(0–5.57)
Nodular sclerosis	6,561	3.22	(2.79–3.64)	6,518	0.75	(0.54–0.96)
Classical NOS	2,628	10.8	(9.66–12.0)	1,853	1.94	(1.31–2.57)
Nodular lymphocyte predominant	662	0.60	(0.01–1.19)	295	1.36	(0.04–2.68)
Ann Arbor stage						
Stage I	2,354	4.33	(3.51–5.16)	1,600	1.19	(0.66–1.72)
Stage II	4,148	2.87	(2.36–3.38)	4,071	0.64	(0.39–0.88)
Stage III	2,567	6.19	(5.26–7.13)	1,523	1.61	(0.99–2.24)
Stage IV	2,493	13.0	(11.6–14.3)	1,360	1.59	(0.93–2.25)
Unknown	680	3.95	(2.52–5.39)	562	1.23	(0.32–2.14)
"B" symptoms						
Absent	4,966	3.99	(3.44–4.53)	4,724	0.99	(0.71–1.28)
Present	4,731	9.13	(8.31–9.95)	3,112	1.77	(1.30–2.23)
Unknown	2,472	3.93	(3.18–4.68)	2,249	0.67	(0.33–1.00)

Discussion

In recent decades, HIV has had an important impact on the overall general population burden of Hodgkin lymphoma in the United States, and is an important cause of mortality in Hodgkin lymphoma cases. For 14 U.S. areas during 2000 to 2010, we estimated that 6% of Hodgkin lymphoma cases in men and 1% of Hodgkin lymphoma cases in women were HIV infected. In addition, 8% of deaths in male Hodgkin lymphoma cases and 1.5% of deaths in female Hodgkin lymphoma cases were because of HIV infection. At 5 years after Hodgkin lymphoma diagnosis, the overall risk of death was twice as high in HIV-infected Hodgkin lymphoma cases compared with HIV-uninfected Hodgkin lymphoma cases.

We have shown that a substantial fraction of Hodgkin lymphoma cases are HIV infected and an even larger fraction of deaths in Hodgkin lymphoma cases are because of HIV. It has long been recognized that the risk of Hodgkin lymphoma is elevated in HIV-infected individuals (18). However, for clinicians, a diagnosis of Hodgkin lymphoma may not raise the same level of suspicion of HIV infection as other HIV-related cancers (e.g., Kaposi sarcoma or anal cancer in younger men), and may be less likely to result in an HIV test. Therefore, clinicians need to be aware that for mixed cellularity and lymphocyte-depleted Hodgkin lymphoma, and for Hodgkin lymphomas occurring among 30- to 59-year-old men and minorities, a notable fraction may be HIV infected. For patients with HIV-infected Hodgkin lymphoma, especially those

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Table 3. Proportion of deaths in Hodgkin lymphoma cases with HIV as the cause of death in 14 SEER registries, 2000 to 2010

	Men			Women		
	N	HIV deaths, %	95% CI	*N*	HIV deaths, %	95% CI
Total	2,689	8.33	(7.29–9.37)	1,799	1.50	(0.94–2.06)
Age group						
0–9	9	0	(0–0)	2	0	(0–0)
10–19	49	0	(0–0)	68	0	(0–0)
20–29	187	3.21	(0.81–6.74)	131	0	(0–0)
30–39	252	21.0	(16.5–27.3)	107	5.61	(1.25–9.97)
40–49	358	24.6	(21.3–30.9)	139	10.1	(5.07–15.1)
50–59	422	14.2	(10.1–17.2)	177	2.82	(0.38–5.27)
60–69	463	3.02	(1.29–4.53)	279	0.36	(0–1.06)
70+	949	0.32	(0–0.79)	896	0.11	(0–0.33)
Race/ethnicity						
Non-Hispanic white	1,560	4.56	(3.59–5.53)	1,268	0.47	(0.10–0.85)
Non-Hispanic black	280	24.7	(20.0–29.3)	189	7.94	(4.08–11.8)
Hispanic	391	12.9	(9.84–16.0)	264	2.27	(0.47–4.07)
Other	104	2.36	(0–5.00)	78	0	(0–0)
Registry HIV prevalence						
Below national average	1,212	3.88	(2.79–4.96)	807	0.87	(0.23–1.51)
Above national average	1,477	12.0	(10.3–13.6)	992	2.02	(1.14–2.89)
Histologic subtype						
Lymphocyte-rich	71	2.82	(0–6.67)	52	0	(0–0)
Mixed cellularity	477	9.64	(6.99–12.3)	332	2.71	(0.96–4.46)
Lymphocyte-depleted	91	15.4	(7.97–22.8)	45	1.92	(0–5.66)
Nodular sclerosis	1,065	4.60	(3.34–5.86)	700	0.63	(0.08–1.18)
Classical NOS	928	12.2	(10.1–14.3)	753	2.24	(0.99–3.49)
Nodular lymphocyte predominant	57	0	(0–0)	32	0	(0–0)
Ann Arbor stage						
Stage I	402	6.47	(4.06–8.87)	294	1.36	(0.04–2.68)
Stage II	571	3.50	(1.99–5.01)	444	1.58	(0.42–2.74)
Stage III	634	5.84	(4.01–7.66)	413	0.24	(0–0.72)
Stage IV	875	14.7	(12.4–17.1)	476	2.73	(1.27–4.20)
Unknown	207	5.80	(2.61–8.98)	172	1.16	(0–2.76)
"B" symptoms						
Absent	741	5.67	(4.00–7.33)	599	0.83	(0.11–1.56)
Present	1,234	11.3	(9.50–13.0)	692	2.31	(1.19–3.43)
Unknown	714	6.02	(4.28–7.77)	508	1.18	(0.24–2.12)

with substantial immunosuppression, clinicians may recommend initiation of HAART before or concurrently with chemotherapy (19). Patients with undiagnosed and untreated HIV-infected Hodgkin lymphoma who undergo chemotherapy may have an increased risk of AIDS- or chemotherapy-related complications. Currently, treatment guidelines issued by the National Comprehensive Cancer Network encourage HIV testing for patients with Hodgkin lymphoma with "risk factors for HIV or unusual disease presentations," but do not classify HIV testing as essential (20). Given the high prevalence of HIV infection in patients with Hodgkin lymphoma, and the United States Preventive Services Task Force's current recommendation for universal HIV testing in the United States (21), we would argue that HIV testing for all patients with Hodgkin lymphoma should be incorporated into cancer management guidelines.

Among males, the fraction of Hodgkin lymphoma cases with HIV is quite high in specific demographic subgroups. For example, 1 in 7 Hodgkin lymphoma cases in 40- to 49-year-old males, 1 in 6 Hodgkin lymphoma cases in non-Hispanic black males, and 1 in 10 Hodgkin lymphoma cases in Hispanic males were HIV infected. In addition, a quarter of all deaths occurring among Hodgkin lymphoma cases in 40- to 49-year-old and non-Hispanic black men were because of HIV. These demographic patterns are likely driven by the high prevalence of HIV in these subgroups of the general population (15). In

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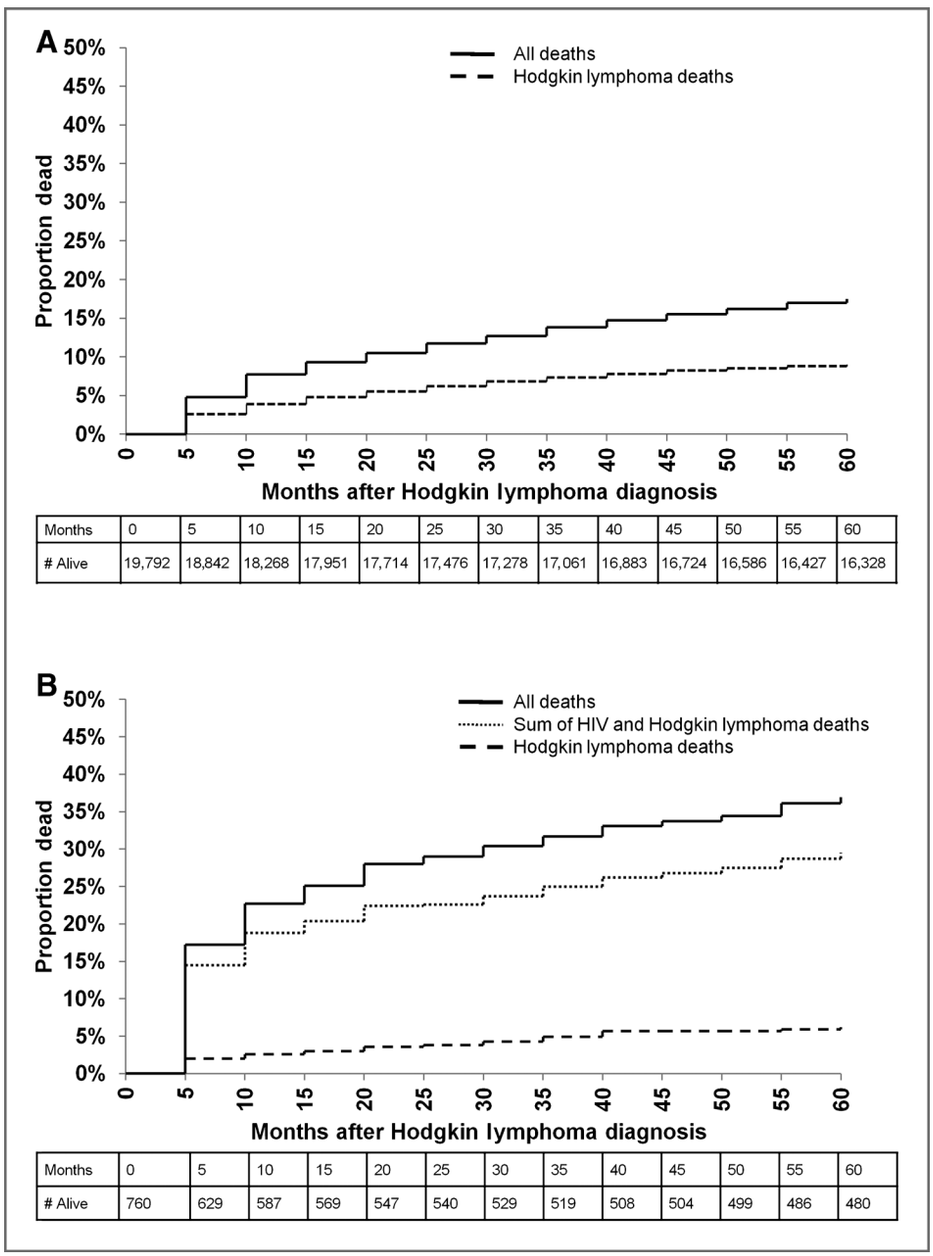

Figure 2. Five-year overall and cause-specific survival of Hodgkin lymphoma cases by HIV status in 14 SEER registries during 2000 to 2010. A, HIV-uninfected Hodgkin lymphoma cases; B, HIV-infected Hodgkin lymphoma cases. In both A and B, the solid line indicates overall mortality and the dashed line indicates Hodgkin lymphoma–specific mortality. In B, the dotted line indicates the sum of HIV and Hodgkin lymphoma–specific mortality.

addition, the incidence rate of Hodgkin lymphoma in the general population in middle age groups is lower than in younger and older age groups; thus, the contribution of HIV-infected cases has a greater impact among middle-aged men.

The fraction of Hodgkin lymphoma cases with HIV also varied by tumor histology, stage, and the presence of "B" symptoms. Among males, 1 in 10 cases of mixed cellularity Hodgkin lymphoma and 1 in 7 cases of lymphocyte-depleted Hodgkin lymphoma were HIV infected. Furthermore, 1 in 8 stage IV Hodgkin lymphoma cases and 1 in 11 Hodgkin lymphoma cases with "B" symptoms were HIV infected. Similar proportions of death because of HIV were observed in these subgroups. These results are consistent with many prior studies that have shown mixed cellularity and lymphocyte-depleted Hodgkin lymphoma to be more common among HIV-infected individuals, and have shown the risk of these subtypes is particularly high (5, 8, 22, 23). These subtypes are also known to have the strongest association with EBV (24). EBV is present in the majority of tumors in HIV-infected cases, with one prior study reporting 90% of HIV-infected cases as EBV positive (4). HIV-related immune suppression likely increases the risk of Hodgkin lymphoma by impairing control of EBV infection (4). The role of immune suppression in increasing the risk of Hodgkin lymphoma

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is further supported by the 4-fold increased risk of Hodgkin lymphoma observed among solid organ transplant recipients (25).

The 5-year mortality was 2-fold higher in HIV-infected Hodgkin lymphoma cases compared with HIV-uninfected Hodgkin lymphoma cases. These results contrast with findings in recent trials, which have shown that overall 5-year survival following standard treatment for Hodgkin lymphoma is the same for HIV-infected and HIV-uninfected individuals (26, 27). In our study, poorer survival in HIV-infected Hodgkin lymphoma cases was largely driven by deaths because of HIV, which may reflect less adequate treatment of HIV outside a clinical trial setting. In contrast to overall survival, the 5-year risk of dying from Hodgkin lymphoma was similar among HIV-infected individuals. This result may seem counterintuitive, given the large fraction of HIV-infected Hodgkin lymphoma cases that are late stage and have systemic symptoms at diagnosis. However, the high risk of death from HIV (as a competing event) may preclude death because of Hodgkin lymphoma. In addition, it is possible that the underlying cause of death in an HIV-infected individual is preferentially coded as HIV, even if the death was ultimately because of another cause, leading to a smaller number of deaths coded as Hodgkin lymphoma.

The primary limitation in this study was incomplete ascertainment of the HIV status of HIV-infected cases with the SEER HIV flag. Prior studies have shown the SEER flag to be >90% sensitivity in the identification of HIV-infected NHL (13, 14); however, similar analyses have not been carried out for Hodgkin lymphoma. In a sensitivity analysis, the reclassification of a small number of Hodgkin lymphoma cases without a positive HIV flag, but with HIV as a cause of death, had little impact on our estimates. Because we classified all individuals with an unknown HIV flag as HIV-uninfected, our estimates are conservative. We also note that the 14 SEER registries included in our analysis may not be representative of the entire U.S. population. In particular, they included registries with wide variation in HIV prevalence in the general population (e.g., San Francisco-Oakland: 0.55% and Utah: 0.11%; ref. 15). However, because the proportion of Hodgkin lymphoma cases with HIV varies based on regional HIV prevalence, the proportion of Hodgkin lymphoma cases with HIV in the entire United States probably lies somewhere between our estimates for low and high prevalence regions and therefore close to our overall estimate.

In conclusion, we have presented the first estimates of the contribution of HIV-infected cases to the overall Hodgkin lymphoma burden in 14 regions of the United States across subgroups defined by demographics and tumor characteristics. A substantial fraction of Hodgkin lymphoma cases occurring in middle-aged, non-Hispanic black, and Hispanic men are HIV-infected, as well as a large fraction of mixed cellularity and lymphocyte-depleted Hodgkin lymphoma cases. As the HIV-infected population in the U.S. continues to grow, the absolute number of HIV-infected Hodgkin lymphoma cases will likely increase, resulting in an increasing proportion of Hodgkin lymphoma cases in the general population with HIV infection (10). Clinicians should be aware of the high prevalence of HIV in certain subgroups of patients with Hodgkin lymphoma, particularly middle-aged males and African-American males, and routine HIV testing should be recommended for all patients presenting with Hodgkin lymphoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.S. Shiels, L.M. Morton, E.A. Engels
Development of methodology: E.A. Engels, M.S. Shiels
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.M. Morton
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.S. Shiels, E. Koritzinsky, L.M. Morton, E.A. Engels
Writing, review, and/or revision of the manuscript: M.S. Shiels, E. Koritzinsky, G. Suneja, L.M. Morton, E.A. Engels
Study supervision: E.A. Engels

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