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Second primary malignancy risk after Hodgkin lymphoma treatment among HIV-uninfected and HIV-infected survivors

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Abstract

We compared secondary primary malignancy risk (SPM) in HIV-uninfected and HIV-infected Hodgkin lymphoma (HL) survivors. We used data from the California Cancer Registry on patients diagnosed with HL from 1990 to 2015 (all ages included), and standardized incidence ratios (SIRs) and multivariable competing risk models for analyses. Of 19,667 survivors, 735 were HIV-infected. Compared with the general population, the risk of SPM was increased by 2.66-fold in HIV-infected and 1.92-fold in HIV-uninfected survivors. Among HIV-infected survivors, median time to development of SPM was shorter (5.4 years) than in HIV-uninfected patients (8.1 years). Additionally, the highest risk of SPM was observed <2 years after diagnosis in HIV-infected survivors (SIR = 4.47), whereas risk was highest ≥20 years after diagnosis (SIR = 2.39) in HIV-uninfected survivors. The risk of SPMs persisted for decades and was higher among HIV-infected survivors, suggesting that these patients should benefit from long-term surveillance and cancer prevention practices.

Keywords

Hodgkin lymphoma; second primary malignancy; HIV; population-based

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Conception and design: RA, THMK, AB; Acquisition of data: THMK, AB, TW; Data analysis: AB, QL; Drafting of the manuscript: RA; Final review and approval of the manuscript: All authors.

Supplemental data for this article can be accessed here.

Disclosure statement

The authors declare no conflict of interests.

Introduction

Approximately 9000 patients are diagnosed with Hodgkin lymphoma (HL) annually in the United States (U.S.) and about 1000 die of the disease [1]. In patients living with human immunodeficiency virus (HIV), HL is one of the most common non-AIDS-defining malignancies and their risk of developing HL is up to 15 times higher than that in the general population [2,3].

Over the past three decades, refinements of risk-directed, combined-modality therapy (chemotherapy and radiation) have resulted in excellent outcomes for patients with HL, both in the up-front and relapsed treatment settings [4,5]. Between 2010 and 2016, 5-year survival for patients <65 years with HL exceeded 90% [6]. However, for patients living with HIV, 5-year HL survival remains lower than that observed in HIV-uninfected patients, currently approaching 70% in high-income countries [7].

Survivors of HL are at increased risk for second primary malignancies (SPM), which is often related to radiation therapy, but may also be the result of patient, disease and treatment-related immune defects that predispose to carcinogenesis [8–11]. The most common SPMs in HIV-uninfected patients treated for HL are solid tumors. Over the last three decades, efforts to address the risk of SPM have focused on reducing exposure to radiation for patients with good initial response to chemotherapy [12], along with efforts to mitigate chemotherapy toxicity [13].

To date, little is known about the risk of SPM among HL survivors living with HIV and, to our knowledge, no study has compared SPM risk between HIV-infected and HIV-uninfected survivors of HL. A better understanding of the differences in risk and time to SPM development in these populations may guide screening strategies aimed at cancer prevention or early detection. In addition, it remains unclear whether modifications in radiation approaches over the last decades have translated into decreased risk of SPMs in HL survivors. Some studies showed little or no risk reduction [8,14], while other studies suggested decreased risk for selected cancers, such as breast cancer [15–18]. The purpose of this study was to quantify the burden of SPMs in both HIV-uninfected and HIV-infected HL survivors, and to evaluate the potential effect of changes in therapeutic management on SPM risk across treatment eras.

Patients and methods

Patient selection

Data were obtained from the California Cancer Registry (CCR). Eligible patients were those diagnosed with a first primary invasive HL between 1 January 1990 and 31 December 2015 (all ages included). Patients with a SPM diagnosed within 2 months of HL diagnosis were excluded to avoid inclusion of patients with simultaneous primary cancers. Those with unknown dates of diagnosis and/or last follow-up or with zero survival time were also excluded (total = 859, 4.2%), leaving a cohort of 19,667 survivors. Our analyses were restricted to invasive SPMs and followed the rules of the Surveillance, Epidemiology, and End Results (SEER) Program for multiple primaries determination [19].

Based on the Third Edition of the International Classification of Diseases for Oncology (ICD-O-3) [20], HL was classified into classical HL and nodular lymphocyte-predominant HL, using the morphology codes 9650–9667. Histologic subtypes included nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte-depleted, and HL not otherwise specified. HIV status at time of HL diagnosis was assessed using the extent of disease variable, standard information abstracted for lymphomas in the CCR from 1990 onwards. Data on first course of treatment were grouped into chemotherapy only, chemotherapy plus radiation, radiation only, and no/unknown. Stage at diagnosis was based on SEER Summary Stage 2000 (local, regional, distant, or unknown) and age at diagnosis was categorized as children (0–14 years), adolescents and young adults (AYAs, 15–39 years), and older adults (≥40 years). Race/ethnicity included non-Hispanic White (White), non-Hispanic Black (Black), Hispanic, and non-Hispanic Asian/Pacific Islander (Asian/PI).

Statistical analysis

The time at risk of a SPM began at the date of HL diagnosis and continued until the date of the SPM, date of death, last known date of contact, or end of the study (31 December 2017), whichever occurred first. Chi-squared tests were used to examine whether patient's characteristics differed by HIV status. We calculated standardized incidence ratio (SIRs) with corresponding 95% confidence intervals (CIs) and absolute excess risk (AER) in order to compare SPM incidence in our HL cohort to the expected number of first primary cancers that would be expected based on the incidence rates for the general California population. SIRs were calculated using the Multiple Primary-SIRs method available in SEER*Stat software [21]. Expected numbers were based on the sex- race/ethnicity-, 5-year attained age-, calendar period- (3-year intervals), and cancer site-specific incidence rates in the general population multiplied by person-years at risk. The AER was calculated as the observed number of SPM minus that expected in the general population, divided by the number of person-years at risk, multiplied by 10,000.

We further investigated the risk of selected SPMs by follow-up time, treatment era (1990–1996, 1997–2006. and 2007–2015), age at diagnosis and sex. These analyses were limited to HIV-uninfected patients due to the relatively small numbers of survivors with HIV. In order to investigate whether changes in radiation exposure led to a decreased risk of solid SPMs across treatment eras and to allow sufficient time for solid SPM development, we restricted the analysis by era to patients who survived at least 5 years after HL diagnosis. As done in previous studies [14,17], treatment era was used as a surrogate for changes in radiation over time because detailed data on treatment are not available in the CCR. We also conducted sensitivity analyses: 1) including all HIV-uninfected survivors in the analysis by treatment era and 2) by the most prevalent histological subtypes (nodular sclerosis, mixed cellularity, and HL not otherwise specified) and HIV status. *P* values for SIR trends by treatment era were estimated using Poisson regression with log of expected count included as an offset term.

Additionally, in HIV-uninfected patients who survived ≥5 years after HL diagnosis, we used Fine & Gray subdistribution proportional hazard models [22] to examine the association between incidence of select solid SPMs with treatment era, adjusting for age at diagnosis,

sex, and race/ethnicity. Subdistribution hazard ratios (HR) and 95% CIs were estimated accounting for death as a competing risk. All reported *p* values were two-sided and considered statistically significant if ≤ .05. Ethics approval was obtained by the California Health and Human Services Agency Committee for the Protection of Human Subjects and the University of California, Davis Institutional Review Boards.

Results

During 1990–2015, we identified 19,667 patients with HL. Of those, 735 (3.7%) had HIV infection. The median follow-up (from HL diagnosis to SPM development, death or study-censoring date, whichever occurred first) was 5.9 years for HIV-infected and 9.3 years for HIV-uninfected survivors. During the study period, 1772 (9.0%) patients developed a SPM (1705 in HIV-uninfected and 67 in HIV-infected survivors). The median time to the development of a SPM was shorter among HIV-infected (5.4 years, range 0.2–26.3) than in HIV-uninfected patients (8.1 years, range 0.1–27.3).

Compared to HIV-uninfected survivors, a higher proportion of HIV-infected survivors were older, male, of Black or Hispanic race/ethnicity, and had more advanced stage disease (Table 1). The proportion HIV-infected patients who died were higher than HIV-uninfected patients (43.1 *vs.* 27.3%). The proportion of patients who received radiation decreased from 45.6% in 1990–1996 to 41.4% in 1997–2006 and to 29.5% in 2007–2015.

Among HIV-uninfected HL survivors, risk of SPM was higher among females, children, and those of Hispanic and Asian/PI race/ethnicity (Table 2). In contrast, in HIV-infected patients, risk was higher among males, AYAs, and Whites and Hispanics.

Risk of SPM by HIV status

Compared with the general population, the risk of developing SPMs was increased for both HIV-infected and HIV-uninfected HL survivors (SIR = 2.66, CI 2.06–3.38 and SIR = 1.92, 95% CI 1.83–2.01, respectively) (Table 3). This translates into a 39% higher incidence of SPM among HIV-infected patients. Likewise, the excess risk of SPM among HIV-infected survivors was nearly twice that of patients without HIV (AERs = 75.3 *vs.* 41.4 per 10,000 person-years).

The types of SPMs also differed by HIV status. Among HIV-infected patients, the AER of SPM were highest for Kaposi sarcoma and anorectal cancer (21.3 and 21.4 cases/10,000 person-years, respectively, each representing about 28.3% of any SPM), head and neck cancers (HNC, 19.8 cases/10,000 person-years, representing 26.3% of any SPM), and non-Hodgkin lymphoma (NHL, 13.9 cases/10,000 person-years, representing 18.5% of any SPM). In these patients, risk was also elevated for lung and non-melanoma skin cancers.

Among HIV-uninfected patients, malignancies that contributed the most to AER were NHL (12.8 cases/10,000 person-years, representing 30.9% of any SPM), female breast (7.9 cases/10,000 person-years, representing 19.1% of any SPM) and lung cancers (5.7 cases/10,000 person-years, representing 13.8% of any SPM). In these patients, risk was also elevated for leukemia, gastrointestinal cancers, soft tissue sarcoma, skin melanoma, thyroid, HNC, and

renal tumors. The general pattern of risk of SPMs between survivors with and without HIV infection were comparable to that of the overall analysis in the most prevalent histological subtypes, with the exception that among HIV-uninfected patients, the risk of melanoma, kidney, and female breast cancers were significantly higher after nodular sclerosis, but not following mixed cellularity or classical HL, not otherwise specific (Supplemental Table S4).

Risk of SPM by age at diagnosis and sex among HIV-uninfected survivors

Among HIV-uninfected male survivors, younger patients aged 0–39 years had an increased risk of most SPMs than those aged ≥40 years, except for HNC, NHL, and melanoma where risk was similar (Supplementary Table S1). Among females, SPM risk was higher among younger than older survivors for leukemia, soft tissue sarcoma, and lung and breast cancers. Of note, younger and older female, but not male, HL survivors were at increased risk of melanoma.

Risk of SPM by follow-up interval

In HIV-infected patients, the highest risk of any SPM was observed < 2 years after HL diagnosis, whereas among HIV-uninfected patients, the greatest risk of any SPM occurred ≥ 20 years after diagnosis (Figure 1). For both groups of patients, risk remained elevated ≥ 20 years after diagnosis compared with the general population, but there were differences in temporal patterns and types of SPMs. For example, in HIV-uninfected patients, risk of SPM for HNC and lung cancer was increased from 2 to 5 years, whereas for breast cancer, risk was elevated later, from 5 to 10 years after HL diagnosis (Supplementary Table S2).

Risk of SPM by treatment era

Among HIV-uninfected 5-year survivors (N = 13,200), we observed a trend toward decreased risk of SPM for all solid cancers combined (SIR = 1.88, CI 1.71–2.06 in 1990–1996 and SIR = 1.30, CI 0.96–1.70 in 2007–2015, p value for trend = .0049). The analysis by tumor site showed a reduced risk for lung (SIR = 3.09, CI 2.46–3.84 in 1990–1996 and SIR = 1.75, CI 0.71–3.61 in 2007–2015, p value for trend = .0451), and female breast (SIR = 2.47, CI 2.02–2.99 in 1990–1996 and SIR = 1.58, CI 0.76–2.91 in 2007–2015, p value for trend = .0014) cancers (Table 4). In the sensitivity analysis including all HIV-uninfected HL survivors, we observed similar trends of reduced risk of solid SPM for female, breast cancers. In addition, there is also a suggestion of a decrease risk of gastrointestinal cancers (Supplementary Table S3).

In a multivariable analysis restricted to HIV-uninfected 5-year survivors, after adjusting for age at diagnosis, sex, HL subtype, and race/ethnicity, the risk of SPM was lower for lung and breast cancers in the more modern eras of treatment (Table 5). Specifically, compared to HL patients diagnosed during 1990–2006, those diagnosed during 2007–2015 had 55% lower hazard of lung (HR = 0.45, CI 0.20–1.00, p value for trend = .0026). For breast cancer, risk was 34% lower for patients diagnosed with HL during 1997–2006 compared to those diagnosed during 1990–2006 (HR = 0.66, CI 0.47–0.93, p value for trend = .0584), but the risk did not seem to change significantly in the later period (HR = 0.78, CI 0.40–1.51).

Similar associations were observed when all HIV-uninfected survivors were included in the model (data not shown in Tables).

Discussion

In our analyses of nearly 20,000 survivors of HL in California, the overall risk of SPM for both HIV-uninfected and HIV-infected survivors was ≥2-fold higher than the risk in the general population, with the greatest risk in those with HIV infection. The temporal patterns and types of SPMs varied across the two groups of patients, with the greatest overall risk occurring <2 years after diagnosis for HIV-infected survivors, and ≥20 years after diagnosis for HIV-uninfected patients. These findings suggest that earlier or more intensive surveillance strategies should be implemented to help address the high incidence of early SPM in HL survivors who live with HIV.

Among HIV-uninfected patients, we observed a trend toward decreased risk of specific solid SPMs, which may be related to reduction in radiation exposure across treatment eras. The greatest excess risk of SPM among HIV-uninfected survivors was observed for breast, lung, and NHL cancers. In contrast, HIV-infected survivors experienced the highest excess risk for anorectal cancer, Kaposi sarcoma, HNC, and also NHL. In the U.S., cancer screening strategies are defined by the National Comprehensive Cancer Network (NCCN) and American Cancer Society guidelines. In addition, the International Guideline Harmonization Group provide updated recommendations to survivors of childhood and AYA cancer. For example, the 2019 guideline recommends annual screening for female survivors who received ≥10 Gy chest radiation at least up to 60 years of age, initiating at age 25 years or ≥8 years from radiation, whichever occur last [23].

Compared with the general population, people living with HIV have a higher incidence of both first and second primary cancers.[3] Careful assessment of the efficacy, potential harms and benefits of various screening strategies are needed, especially for high-risk HIV-infected cancer survivors in whom there are no specific post-treatment recommendations. Since the introduction of antiretroviral therapy (ART) in 1996, the incidence of and mortality from AIDS-defining cancers (NHL, Kaposi sarcoma, and cervical cancer) have decreased significantly due to an improved immune function [24,25]. Yet, ART does not completely restore the immunodeficiency and systemic inflammation caused by HIV, and a shift toward increased risk of non-AIDS-defining malignancies has been observed in the last decades [25,26]. Importantly, even in the era of ART, the survivors in our cohort were likely to develop SPMs relatively soon after HL therapy. It is plausible that the chemotherapy administered during HL treatment further suppresses the immune system and contributes to development of these tumors. In addition, lifestyle behaviors such as increased exposures to smoking, alcohol, sun exposure, and viral co-infections can contribute to the increased risk of SPMs in HIV-infected survivors, underscoring the need for health interventions aimed at decreasing these modifiable risk factors [27,28].

Because lung cancer is the leading cause of cancer mortality in HIV-infected patients [29], recent studies in the U.S. [30] and Europe [31] have used simulation approaches to investigate the value of low-dose computed tomography (CT) for lung cancer screening

in HIV-infected patients. These simulations suggested a reduction in lung cancer mortality [30] and higher lung cancer detection [31], particularly when CT screening was done at earlier ages and/or a lower smoking threshold criterion was applied. Despite potential benefits, careful consideration of the individualized risk, life expectancy, ART adherence, and possible harms of CT screening should guide clinicians in the decision-making process on whether to recommend lung screening for HL survivors with HIV [32].

Anal cancer is the most frequent non-AIDS-defining malignancy in patients living with HIV. As we demonstrated in this study, it is also the malignancy that contributed the most to the excess SPM risk in HIV-infected survivors, along with Kaposi sarcoma. To date, there is no consensus screening guideline for anal cancer. In the U.S., some clinicians currently support anal cancer screening for high-risk populations, such as patients with HIV infection [33]. Our data support this recommendation for HL survivors with HIV infection. Additionally, as human papillomavirus (HPV) is detected in over 90% of anal cancers, the administration of HPV vaccine in eligible HIV-infected patients should be encouraged as it can potentially prevent both the development and progression of most anal cancers [34]. Furthermore, NCCN guidelines recommend that HIV-infected patients should be co-managed by an oncologist and HIV specialist during cancer treatment [35], and our findings suggest that this should be also considered for long-term cancer survivorship care.

In HIV-uninfected patients who survived at least 5 years after HL diagnosis, there was a trend toward decreased incidence of solid SPMs in more recent treatment eras, especially lung and breast cancers, which is likely a reflection of strategies to reduce the use of radiation therapy in patients with HL [5,12,36]. In multivariable analysis among 5-year HL survivors, the risks of breast and lung cancers were lower in the more recent treatment eras. Trends were similar when we included all HIV-uninfected survivors. Our results contrast with studies from Europe that used data from earlier periods [8,14], but are consistent with recent US studies [16,17]. In particular, Schaapveld et al. [18] examined 5-year survivors aged 15–50 years diagnosed with HL in the Netherlands during 1965–2000, and found that the overall risk of solid SPMs was not lower in patients treated during 1990s compared to those treated in earlier periods. There was a decreased risk of lung cancer in men but not in women, whereas breast and gastrointestinal tumors were unchanged. It was noted however, that more recent changes in radiation therapy (e.g. involved-node radiation therapy, radiation doses lower than 36 Gy, and three-dimensional conformal radiation treatment) were not applied to their study population.

In contrast, Kumar et al. [17] investigated SPM risk in patients ≥20 years treated for HL during 1973–2014 in the SEER 9 database, which includes approximately 10% of the US population. The authors found a decreased risk of gastrointestinal and breast cancers risk in more recent times. Lung cancer risk decreased during 2001–2014 compared with earlier treatment eras, but only among patients aged 20–59 years. Overall, their results are consistent with our findings of lower risk for specific SPMs in more recent treatment eras. Similarly, in another U.S. study using SEER 9 data from 1973 to 2011, Giri et al. [16] demonstrated a decreased incidence of secondary breast cancer in female survivors of HL associated with a decline in radiation use.

The main limitations of our analyses include a lack of detailed information on therapy, including new frontline therapies, and a shorter follow-up time in the more recent treatment eras, which likely underestimated the eventual occurrence of malignancies that develop later, such as gastrointestinal cancers. We also lacked data on factors that might have contributed to the increased risk of SPM after HL, such as family history of cancer [14], behavioral factors [37], individual-level socioeconomic factors [38], adherence to ART therapy, and CD4 count in HIV-infected patients [39]. Finally, it is possible that we did not capture all patients with HIV, which would lead to an underestimation of SPM risk. However, our prevalence of HIV-infected patients was similar to a previous population-based study of HL patients in the U.S. [40]. Despite these limitations, we had high-quality data on virtually all patients diagnosed with a primary HL during the study period. To our knowledge, this is the first comprehensive population-based study to compare SPM risk between HIV-uninfected and HIV-infected survivors of HL.

In summary, compared with the general population, the risk of developing a SPM following HL treatment was significantly higher among both HIV-uninfected and HIV-infected patients, with the AER greatest for those with HIV infection. Time to development a SPM was shorter for HIV-infected survivors, with the highest risk occurring < 2 years after HL diagnosis, compared with ≥ 20 years after diagnosis in HIV-uninfected patients. These findings underscore the need for decades-long follow-up across all patients treated for HL and suggest that earlier cancer surveillance may be beneficial for HIV-infected patients.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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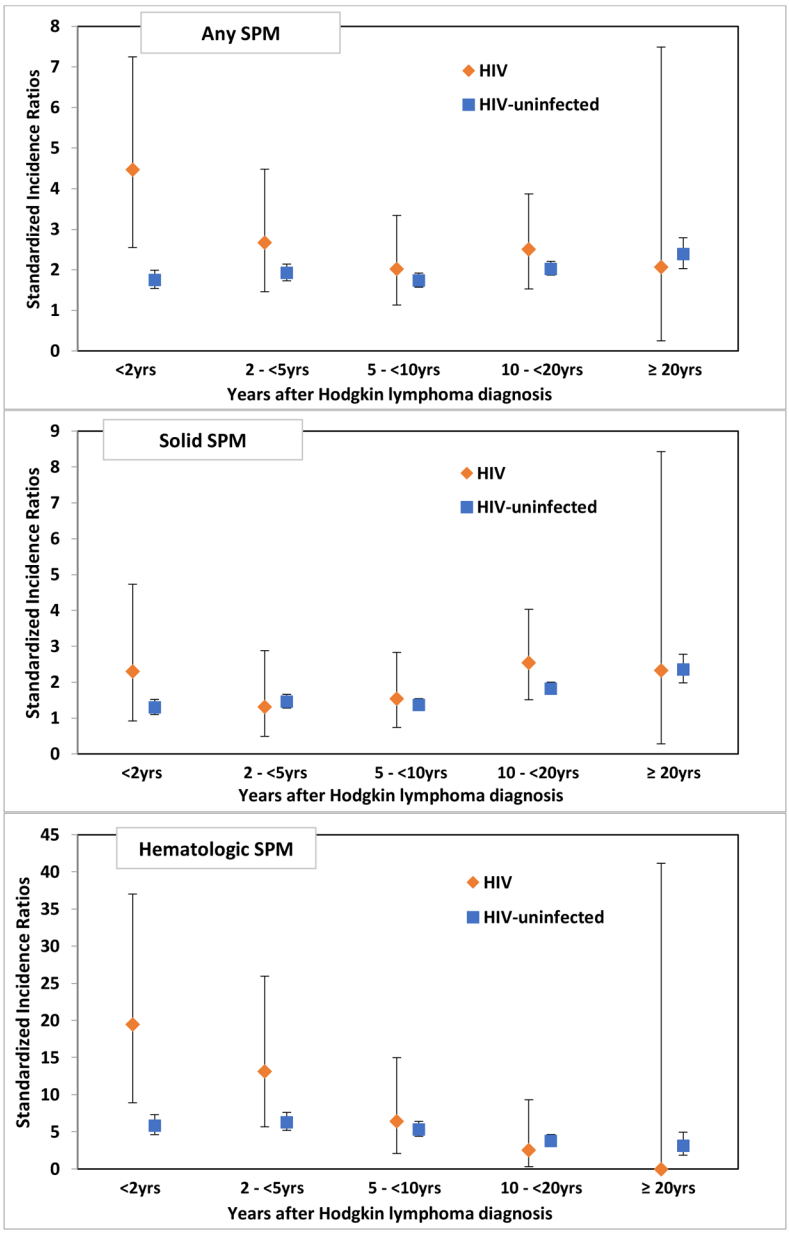

Figure 1.

Standardized incidence ratios and 95% confidence intervals of second primary malignancies (SPM) after Hodgkin lymphoma in California, 1990–2015, by follow-up time.

Table 1.

Characteristics of Hodgkin lymphoma survivors (*N* = 19,667), by HIV status, 1990–2015, California.

Characteristics[b]	HIV-uninfected *N* (%)	HIV-infected *N* (%)	*p* value[b]
All patients	18,932 (100.0)	735 (100.0)	
Year of Diagnosis			
1990–1996	4793 (25.3)	140 (19.0)	.0001
1997–2006	7234 (38.2)	330 (44.9)	.0003
2007–2015	6905 (36.5)	265 (36.1)	.8172
Sex			
Male	10,248 (54.1)	659 (89.7)	<.0001
Female	8684 (45.9)	76 (10.3)	<.0001
Race/ethnicity			
Non-Hispanic White	11,521 (60.9)	347 (47.2)	<.0001
Non-Hispanic Black	1270 (6.7)	120 (16.3)	<.0001
Hispanic	4642 (24.5)	253 (34.4)	<.0001
Asian/Pacific Islander	1242 (6.6)	9 (1.2)	<.0001
Other/unknown[a]	257 (1.4)	6 (0.8)	.2101
Age at diagnosis, years			
<15	1078 (5.7)	5 (0.7)	<.0001
15–39	10,304 (54.4)	306 (41.6)	<.0001
≥40	7550 (39.9)	424 (57.7)	<.0001
Hodgkin lymphoma (HL) subtype			
Classic HL	18,189 (96.1)	729 (99.2)	<.0001
Classical HL, NOS	3033 (16.0)	245 (33.3)	<.0001
Lymphocyte rich	545 (2.9)	12 (1.6)	.0457
Mixed cellularity	2530 (13.4)	215 (29.3)	<.0001
Lymphocyte-depleted	249 (1.3)	16 (2.2)	.0468
Nodular sclerosis	11,832 (62.5)	241 (32.8)	<.0001
Nodular lymphocyte predominant HL	743 (3.9)	6 (0.8)	<.0001
Stage at diagnosis			
Localized	2922 (15.4)	103 (14.0)	.2949

Characteristics[b]	HIV-uninfected *N* (%)	HIV-infected *N* (%)	*p* value[b]
Regional	7876 (41.6)	129 (17.6)	<.0001
Distant	7050 (37.2)	470 (63.9)	<.0001
Unknown	1084 (5.7)	33 (4.5)	.1555
First course of treatment			
Chemotherapy plus radiation (RT)	5732 (30.3)	94 (12.8)	<.0001
Radiation only (no/unknown chemotherapy)	1647 (8.7)	19 (2.6)	<.0001
Chemotherapy only (no/unknown RT)	9392 (49.6)	507 (69.0)	<.0001
None/unknown	2161 (11.4)	115 (15.6)	.0004
Deceased	5164 (27.3)	317 (43.1)	<.0001

HIV: human immunodeficiency virus; *N*: number; NOS: not otherwise specified.

[a] Other race/ethnicity includes American Indian/Alaska Native.

[b] Chi-squared test *p* values.

Table 2.

Standardized incidence ratio (SIR) and absolute excess risk (AER) by HIV status and sociodemographic and clinical characteristics, 1990–2015, California.

	HIV-uninfected			HIV-infected		
Characteristics	**O[a]**	**SIR (95% CI)**	**AER[b]**	**O[a]**	**SIR (95% CI)**	**AER[b]**
Age at diagnosis, years						
0–14	42	9.01 (6.50, 12.18)	27.14	<5	*d*	*d*
15–39	607	2.73 (2.52, 2.96)	30.40	29	5.52 (3.69, 7.92)	85.21
≥ 40	1056	1.60 (1.50, 1.70)	69.41	38	1.91 (1.35, 2.62)	67.13
Sex						
Males	879	1.73 (1.62, 1.85)	35.33	62	2.83 (2.17, 3.62)	83.91
Females	826	2.17 (2.02, 2.32)	48.42	5	1.55 (0.50, 3.62)	22.77
Race/ethnicity[c]						
Non-Hispanic White	1191	1.86 (1.75, 1.96)	43.38	45	3.04 (2.22, 4.07)	103.01
Non-Hispanic Black	122	2.15 (1.78, 2.57)	49.35	6	1.47 (0.54, 3.20)	22.20
Hispanic	298	2.48 (2.21, 2.78)	41.18	14	2.65 (1.45, 4.45)	53.06
Asian/Pacific Islander	89	2.81 (2.26, 3.46)	50.08	<5	7.20 (0.18, 40.13)	126.09
Initial treatment[c]						
Chemotherapy + radiation	464	2.02 (1.84, 2.22)	34.20	<5	0.77 (0.16, 2.25)	−10.01
Chemotherapy only	751	1.85 (1.72,1.99)	40.53	43	2.57 (1.86, 3.46)	72.37
Radiation only	275	2.08 (1.84, 2.34)	60.48	6	14.95 (5.49, 32.53)	464.88
Calendar period						
1990–1996	727	2.06 (1.91, 2.21)	48.71	21	3.93 (2.43, 6.00)	116.47
1997–2006	696	1.83 (1.69, 1.97)	37.28	34	2.40 (1.66, 3.35)	66.84
2007–2015	282	1.83 (1.63, 2.06)	35.64	12	2.13 (1.10, 3.72)	51.10
Stage at diagnosis[c]						
Localized	340	1.69 (1.51, 1.88)	41.26	10	3.00 (1.44, 5.51)	74.02
Regional	675	2.12 (1.97, 2.29)	40.03	11	2.23 (1.11, 3.99)	52.14
Distant	579	1.91 (1.76, 2.07)	43.10	41	2.68 (1.92, 3.71)	79.45
Hodgkin lymphoma subtype						

Characteristics	HIV-uninfected			HIV-infected		
	O[a]	SIR (95% CI)	AER[b]	O[a]	SIR (95% CI)	AER[b]
Classic HL						
Classical HL, NOS	238	1.85 (1.62, 2.1)	50.3	17	2.11 (1.23, 3.38)	62.48
Lymphocyte Rich	58	1.50 (1.14, 1.94)	32.86	<5	*d*	
Mixed cellularity	288	1.63 (1.44, 1.83)	43.57	25	3.42 (2.21, 5.04)	107.30
Lymphocyte-depleted	25	1.70 (1.10, 2.52)	51.62	<5	3.98 (0.48, 14.39)	162.02
Nodular sclerosis	1017	2.08 (1.95, 2.21)	39.01	22	2.53 (1.58, 3.83)	60.43
Nodular lymphocyte predominant HL	79	2.01 (1.59, 2.5)	57.16	<5	6.48 (0.16, 36.12)	112.80

HIV: human immunodeficiency virus; SIR: standardized incidence ratio; CI: confidence interval; NOS: not otherwise specified.

[a] Observed second primary malignancy (O) in the California cohort.

[b] Absolute excess risk (AER) per 10,000 person-years.

[c] Unknown categories not shown.

[d] Not reported due to too few cases.

Table 3.

Standardized incidence ratio (SIR) and absolute excess risk of selected second primary malignancies, by HIV Status, 1990–2015, California.

	HIV-uninfected			HIV-infected		
Cancer site	**O[a]**	**SIR (95% CI)**	**AER[b]**	**O[a]**	**SIR (95% CI)**	**AER[b]**
Any malignancy[c]	1705	1.92 (1.83, 2.01)	41.43	67	2.66 (2.06, 3.38)	75.31
Hematologic malignancies	419	5.01 (4.54, 5.51)	17.00	24	8.84 (5.67, 13.16)	38.32
Non-Hodgkin lymphoma	292	7.46 (6.63, 8.37)	12.82	9	7.12 (3.26, 13.52)	13.93
Leukemia	101	4.27 (3.48, 5.19)	3.92	<5	2.86 (0.35, 10.35)	2.34
Kaposi sarcoma	4	1.29 (0.35, 3.31)	0.05	12	70.98 (36.68, 123.99)	21.30
Myeloma	14	1.25 (0.68, 2.10)	0.14	<5	2.52 (0.06, 14.03)	1.09
Solid malignancies	1255	1.59 (1.51, 1.69)	23.73	43	1.95 (1.41, 2.63)	37.81
Female breast	200	1.57 (1.36, 1.80)	7.88	<5	0.90 (0.02, 5.02)	−1.40
Lower respiratory system	208	2.27 (1.97, 2.60)	5.91	6	2.72 (1.00, 5.93)	6.83
Lung and bronchus	201	2.25 (1.95, 2.59)	5.66	6	2.80 (1.03, 6.09)	6.94
Other respiratory	7	3.12 (1.26, 6.44)	0.24	<5	*e*	
Skin cancer	97	1.52 (1.23, 1.85)	1.68	<5	1.69 (0.35, 4.95)	2.21
Melanoma	91	1.53 (1.23, 1.88)	1.60	<5	0.60 (0.02, 3.36)	−1.18
Non-melanoma	6	1.35 (0.50, 2.94)	0.08	<5	17.49 (2.12, 63.18)	3.39
Thyroid	114	4.23 (3.49,5.08)	4.41	<5	1.80 (0.05, 10.03)	0.80
Urinary system	101	1.51 (1.23, 1.84)	1.74	<5	0.88 (0.11, 3.19)	−0.48
Kidney	48	1.65 (1.22, 2.19)	0.96	<5	0.83 (0.02, 4.64)	−0.36
Other urinary	53	1.41 (1.05, 1.84)	0.78	<5	0.94 (0.02, 5.24)	−0.11
Gastrointestinal system	219	1.41 (1.23, 1.61)	3.25	15	2.92 (1.63, 4.81)	17.74
Stomach	25	1.79 (1.16, 2.64)	0.56	<5	*e*	*e*
Esophagus	17	2.11 (1.23, 3.38)	0.45	<5	*e*	*e*
Pancreas	29	1.39 (0.93, 2.00)	0.41	<5	*e*	*e*
Colorectal	115	1.45 (1.20, 1.74)	1.81	<5	0.82 (0.10, 2.98)	−0.77
Anorectal	7	1.70 (0.68, 3.51)	0.15	12	86.82 (44.86, 151.66)	21.35
Other gastrointestinal	24	0.96 (0.62, 1.43)	−0.05	<5	0.95 (0.02, 5.29)	−0.10
Head and neck cancer[d]	65	2.61 (2.01, 3.33)	2.03	12	11.66 (6.02, 20.37)	19.75

	HIV-uninfected			HIV-infected		
Cancer site	**O[a]**	**SIR (95% CI)**	**AER[b]**	**O[a]**	**SIR (95% CI)**	**AER[b]**
Male genital organs	135	0.91 (0.76, 1.08)	−1.26	<5	0.31 (0.04, 1.14)	−9.13
Prostate	125	0.91 (0.76, 1.09)	−1.16	<5	0.33 (0.04, 1.21)	−8.34
Other male genital	10	0.91 (0.43, 1.67)	−0.10	<5	*e*	*e*
Female genital organs	53	1.09 (0.81, 1.42)	0.46	<5	2.34 (0.06, 13.02)	7.33
Corpus uteri	22	0.97 (0.61, 1.42)	0.54	<5	5.14 (0.13, 28.65)	10.32
Other female genital	31	1.19 (0.81, 1.69)	0.54	<5	*e*	*e*
Soft tissue sarcoma	29	4.06 (2.72, 5.83)	1.11	<5	*e*	*e*
Central nervous system	9	0.67 (0.31, 1.28)	−0.22	<5	*e*	*e*

HIV: human immunodeficiency virus; SIR: standardized incidence ratio; CI: confidence interval.

[a]Observed (O) second primary malignancy in the California Cancer Registry.

[b]Absolute excess risk (AER) per 10,000 person-years.

[c]Any malignancies among HIV-uninfected patients also include Hodgkin Lymphoma ($n = 8$), cranial nerves other nervous system ($n < 5$), and miscellaneous ($n = 39$).

[d]Head and neck cancer include oral cavity, oropharynx, hypopharynx, and larynx.

[e]Not reported due to small number of cases (<5).

Table 4.

Standardized incidence ratio and absolute excess risk of select solid second primary malignancies in HIV-uninfected patients who survived ≥ 5 years after Hodgkin lymphoma diagnosis, by treatment era, 1990–2015 (N = 13,200).

	1990–1996		1997–2006		2007–2015		
	SIR (95% CI)	ER[a]	SIR (95% CI)	ER[a]	SIR (95% CI)	ER[a]	*p* value[b]
Solid malignancies	1.88 (1.71, 2.06)	37.99	1.58 (1.42, 1.75)	24.43	1.30 (0.96, 1.70)	11.43	.0049
Lung and bronchus	3.09 (2.46, 3.84)	9.75	2.07 (1.53, 2.74)	4.71	1.75 (0.71, 3.61)	2.96	.0451
Thyroid	4.39 (3.09, 6.05)	5.02	4.39 (3.12, 6.00)	5.59	2.40 (0.65, 6.14)	2.29	.4314
Kidney and renal pelvis	1.56 (0.86, 2.63)	0.89	0.99 (0.45, 1.88)	−0.02	1.18 (0.14, 4.28)	0.31	.5514
Gastrointestinal system	1.62 (1.28, 2.03)	5.12	1.59 (1.24, 2.00)	4.88	0.89 (0.36, 1.82)	−0.89	.2383
Head and neck cancer	1.99 (1.14, 3.23)	1.40	3.13 (1.98, 4.70)	2.90	0.78 (0.02, 4.36)	−0.27	.1371
Soft tissue sarcoma	5.14 (2.57, 9.20)	1.56	3.29 (1.32, 6.79)	0.90	12.15 (3.94, 28.35)	4.51	.1085
Female breast	2.47 (2.02, 2.99)	23.69	1.37 (1.03, 1.80)	5.60	1.58 (0.76, 2.91)	7.59	.0014

HIV: human immunodeficiency virus; SIR: standardized incidence ratio; CI: confidence interval.

[a]Absolute excess risk (AER) per 10,000 person-years.

[b]*p* value for trend for SIR.

Table 5.

Multivariable competing risk analysis of a solid second primary malignancy (SPM) among HIV-uninfected 5-year survivors of Hodgkin lymphoma in California, 1990–2015.

Variables	Any SPM HR (95% CI)	Any solid SPM HR (95% CI)	Lung HR (95% CI)	Female breast HR (95% CI)	Gastrointestinal HR (95% CI)
Sex					
Male	Reference	Reference	Reference	N/A	Reference
Female	1.27 (1.13, 1.43)	1.34 (1.18, 1.53)	1.10 (0.79, 1.53)	N/A	0.80 (0.56, 1.12)
Race/ethnicity[a]					
Non-Hispanic White	Reference	Reference	Reference	Reference	Reference
Non-Hispanic Black	1.05 (0.84, 1.33)	1.01 (0.77, 1.31)	0.86 (0.43, 1.72)	1.38 (0.82, 2.31)	1.28 (066, 2.48)
Hispanic	1.00 (0.86, 1.17)	0.88 (0.74, 1.06)	0.46 (0.25, 0.83)	0.53 (0.32, 0.88)	1.76 (1.17, 2.64)
Asian/Pacific Islander	0.89 (0.66, 1.20)	0.73 (0.51, 1.04)	1.02 (0.47, 2.20)	0.87 (0.40, 1.86)	1.43 (0.69, 2.94)
Year of diagnosis					
1990–1996	Reference	Reference	Reference	Reference	Reference
1997–2006	0.83 (0.73, 0.94)	0.88 (0.76, 1.01)	0.56 (0.39, 0.80)	0.66 (0.47, 0.93)	0.94 (0.66, 1.34)
2007–2015	0.73 (0.57, 0.95)	0.67 (0.50, 0.91)	0.45 (0.20, 1.00)	0.78 (0.40, 1.51)	0.52 (0.22, 1.21)
p value for trend	0.0047	0.0201	0.0026	0.0584	0.3115
Age at diagnosis, y					
<25	Reference	Reference	Reference	Reference	Reference
25–29	1.02 (0.81, 1.30)	1.00 (0.76, 1.30)	3.04 (0.99, 9.33)	0.97 (0.58, 1.60)	1.60 (0.69, 3.74)
30–34	1.51 (1.21, 1.88)	1.54 (1.21, 1.95)	4.18 (1.42, 12.32)	1.36 (0.85, 2.16)	3.55 (1.73, 7.28)
35–39	1.64 (1.30, 2.08)	1.61 (1.24, 2.08)	8.35 (3.03, 23.02)	0.96 (0.52, 1.75)	5.55 (2.80, 11.03)
40–49	2.71 (2.23, 3.29)	2.54 (2.05, 3.16)	15.52 (6.08, 39.60)	1.39 (0.85, 2.30)	4.00 (1.99, 8.03)
≥ 50	4.34 (3.63, 5.18)	3.81 (3.12, 4.66)	26.44 (10.66, 65.62)	1.69 (1.06, 2.69)	8.92 (4.73, 16.84)
Hodgkin lymphoma subtype					
Classic HL					
Nodular Sclerosis	Reference	Reference	Reference	Reference	Reference
Classical HL, NOS	1.01 (0.83, 1.23)	0.94 (0.75, 1.18)	0.88 (0.50, 1.56)	1.22 (0.73, 2.05)	0.26 (0.09, 0.70)
Lymphocyte-depleted	1.01 (0.61, 1.66)	0.75 (0.39, 1.46)	1.40 (0.45, 4.42)	*b*	0.44 (0.06, 3.32)
Lymphocyte rich	0.86 (0.62, 1.21)	0.71 (0.47, 1.08)	0.83 (0.33, 2.05)	0.67 (0.21, 2.14)	0.71 (0.26, 1.95)
Mixed cellularity	0.88 (0.74, 1.05)	0.85 (0.70, 1.03)	0.95 (0.60, 1.50)	0.66 (0.37, 1.18)	1.61 (1.06, 2.43)

Variables	Any SPM HR (95% CI)	Any solid SPM HR (95% CI)	Lung HR (95% CI)	Female breast HR (95% CI)	Gastrointestinal HR (95% CI)
Nodular lymphocyte predominant HL	1.20 (0.89, 1.62	0.87 (0.59, 1.27)	0.99 (0.41, 2.34)	1.14 (0.44, 2.95)	0.71 (0.26, 1.97)

HL: Hodgkin lymphoma; HR: subdistribution hazard ratio; CI: confidence interval; NH: non-Hispanic; y: years; PI: Pacific Islander; N/A: not applicable; y: years; NOS: not otherwise specified.

[a]Result for unknown race/ethnicity not shown.

[b]Not reported due to small number of cases (<5).