Cancer Epidemiology, Biomarkers & Prevention

Impact of Treatment and Insurance on Socioeconomic Disparities in Survival after Adolescent and Young Adult Hodgkin Lymphoma: A Population-Based Study

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Abstract

Background: Previous studies documented racial/ethnic and socioeconomic disparities in survival after Hodgkin lymphoma among adolescents and young adults (AYA), but did not consider the influence of combined-modality treatment and health insurance.

Methods: Data for 9,353 AYA patients ages 15 to 39 years when diagnosed with Hodgkin lymphoma during 1988 to 2011 were obtained from the California Cancer Registry. Using multivariate Cox proportional hazards regression, we examined the impact of sociodemographic characteristics [race/ethnicity, neighborhood socioeconomic status (SES), and health insurance], initial combined-modality treatment, and subsequent cancers on survival.

Results: Over the 24-year study period, we observed improvements in Hodgkin lymphoma–specific survival by diagnostic period and differences in survival by race/ethnicity, neighborhood SES, and health insurance for a subset of more recently diagnosed patients (2001–2011). In multivariable analyses, Hodgkin lymphoma–specific survival was worse for Blacks than Whites with early-stage [HR: 1.68; 95% confidence interval (CI): 1.14–2.49] and late-stage disease (HR: 1.68; 95% CI, 1.17–2.41) and for Hispanics than Whites with late-stage disease (HR: 1.58; 95% CI, 1.22–2.04). AYAs diagnosed with early-stage disease experienced worse survival if they also resided in lower SES neighborhoods (HR: 2.06; 95% CI, 1.59–2.68). Furthermore, more recently diagnosed AYAs with public health insurance or who were uninsured experienced worse Hodgkin lymphoma–specific survival (HR: 2.08; 95% CI, 1.52–2.84).

Conclusion: Our findings identify several subgroups of Hodgkin lymphoma patients at higher risk for Hodgkin lymphoma mortality.

Impact: Identifying and reducing barriers to recommended treatment and surveillance in these AYAs at much higher risk of mortality is essential to ameliorating these survival disparities. *Cancer Epidemiol Biomarkers Prev; 25(2); 264–73. ©2016 AACR.*

Introduction

For Hodgkin lymphoma, one of the most common cancers of adolescents and young adults (AYA) 15 to 39 years of age (1), treatment with combined-modality (radiation plus chemotherapy) regimens has led to substantial improvements in survival over time and has been commonly recommended for patients with limited stage disease and those with bulky, advanced stage disease (2, 3). However, these impressive survival gains have not been shared uniformly across the AYA population, as worse outcomes have been documented for 15 to 44 year olds of lower neighborhood socioeconomic status (SES; ref. 4) and non-White race/ethnicity (4, 5).

Among explanations for these disparities, the similarity of disparities for overall and Hodgkin lymphoma–specific survival (4) and the persistent difference in relative survival by neighborhood SES over time (4), implicate variations in initial treatment and management more than variations in the late complications sometimes resulting from Hodgkin lymphoma (6). We previously found that Blacks (52%) and Hispanics (47%) were more likely to receive chemotherapy alone (as compared with combined-modality) than non-Hispanic Whites (38%) or Asian/Pacific Islanders (API; 40%) 15 to 44 years of age (4). Recent (1995–2010) population-based data on AYAs with early-stage Hodgkin lymphoma also showed that Blacks and Hispanics, and patients residing in lower SES neighborhoods, had lower utilization of radiotherapy, and Blacks and Hispanics, and AYAs not receiving radiation had higher mortality (7).

In addition, inadequate health insurance is associated with later stage at diagnosis, undertreatment, and worse survival (8–12). Adult (≥18 years) Hodgkin lymphoma patients with early-stage disease who were uninsured were less likely to receive chemotherapy and radiation (12), and AYAs who were uninsured, had public health insurance, or resided in lower SES neighborhoods were more likely to be diagnosed with advanced-stage Hodgkin lymphoma (11).

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doi: 10.1158/1055-9965.EPI-15-0756

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In efforts to date to understand Hodgkin lymphoma survival disparities, no prior studies have considered the influence of both receipt of initial combined-modality treatment and insurance on the racial/ethnic and socioeconomic disparities in survival among AYAs diagnosed with all stages of Hodgkin lymphoma. Therefore, to identify sociodemographic patient subgroups that have not benefited from well-established and effective treatments, we evaluated the impact of sociodemographic characteristics (race/ethnicity, neighborhood SES, and health insurance), initial combined-modality treatment, and subsequent cancers on survival among AYAs diagnosed with early- and late-stage Hodgkin lymphoma.

Materials and Methods

Patients

Patients eligible for the study were all persons who resided in California when newly diagnosed at ages 15 through 39 years with classical Hodgkin lymphoma [International Classification of Diseases—Oncology, 3rd edition (13) morphology codes 9650–9655, 9663–9667] during the period January 1, 1988 through December 31, 2011 and reported to the California Cancer Registry (CCR). From the CCR, which operates under a state cancer reporting law and comprises three National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) registries, we obtained information routinely recorded in the medical record at diagnosis for each patient on age, sex, race/ethnicity [non-Hispanic White (hereafter called "White"), Hispanic, Black, and API], summary stage [localized (Ann Arbor stage I), regional (stage II), and advanced (stage III/IV)], extent of disease, tumor histologic subtype (nodular sclerosis, mixed cellularity, lymphocyte depletion, lymphocyte rich, or not otherwise specified), marital status (never married, married, previously married, and unknown), hospital providing initial care, and census-block group of residence. With information on extent of disease, we classified patients by the presence of B symptoms (weight loss, night sweats, and fever) and HIV or AIDS. In addition, we obtained registry data on initial treatment modality [radiation (yes, no, unknown) and chemotherapy (yes, no, unknown)], from which we created a combined modality measure; subsequent primary cancer(s) reported during the study period; vital status (routinely determined by the CCR through hospital follow-up and linkages to state and national vital status and other databases) as of December 2012; and, for the deceased, the underlying cause of death as routinely coded by state vital statistics personnel.

We also obtained information on the primary source of payment at initial diagnosis and/or treatment (health insurance), which was reportable to the CCR for patients diagnosed from 2001 forward. Health insurance was grouped into public (Medicaid and other government-assisted programs), private (health maintenance organizations, preferred provider organizations, managed care not otherwise specified, and military care), none, and unknown (11). Consistent with prior observations that the small percentage of AYA cancer patients who were uninsured likely reflect retroactive enrollment in Medicaid at the time of cancer diagnosis (9), we considered publicly insured and uninsured together in the survival analyses. Hospitals were classified according to whether or not they were NCI-designated cancer centers.

We used a multicomponent index of neighborhood SES based on patients' residential census-block group at diagnosis. The index is derived from data from the 2000 U.S. Census (for patients diagnosed through 2005) and the 2006 to 2010 American Community Survey (for patients diagnosed in 2006 forward) on education, occupation, unemployment, household income, poverty, rent, and house values (14). The indices are grouped into quintiles, based on the distribution of SES across all census block groups in California, and, as done previously (4), into one of two categories for models stratified by stage at diagnosis: lower SES (quintiles 1, 2, and 3) and higher SES (quintiles 4 and 5). Each cancer patient was assigned to his/her neighborhood SES category. Based upon the population density of census blocks (15, 16), we defined urbanization level as metropolitan (metropolitan urban and metropolitan suburban blocks), nonmetropolitan (city, town, and rural blocks), or unknown.

The final study population included 9,353 AYA Hodgkin lymphoma patients after exclusion, in a hierarchical manner, of those with: (i) unknown race/ethnicity ($n = 166$); (ii) cancer registry or death certificate evidence of HIV or AIDS (ref. 17; $n = 262$), because of the substantially poorer outcome of HIV-associated Hodgkin lymphoma during the study period (18, 19); and (iii) Hodgkin lymphoma diagnosis at autopsy only, by death certificate only, or with zero/invalid survival time ($n = 40$). All study protocols were overseen by the Institutional review board of the Cancer Prevention Institute of California.

Statistical analyses

Outcomes of interest included overall survival, which considers death from all causes, and Hodgkin lymphoma–specific survival, which considers only death from Hodgkin lymphoma. For deceased patients, survival time was measured in days from the date of diagnosis to the date of death from any cause for overall survival, and to the date of death from Hodgkin lymphoma for Hodgkin lymphoma–specific survival. Patients who died from other causes were censored at the time of death in analyses of Hodgkin lymphoma–specific survival. Patients alive at the study end date (12/31/2012) were censored at this time or at the date of last known contact. Ninety-four percent of censored patients had a follow-up date within 2 years of the study end date, but this number was slightly higher for Whites (95%), Blacks (96%), and APIs (95%) than for Hispanics (89%).

To evaluate associations with survival (overall and Hodgkin lymphoma-specific) controlling for known prognostic factors, we used multivariable Cox proportional hazards regression to estimate hazard ratios (HR) and associated 95% confidence intervals (CI). Models included variables with *a priori* reasons for inclusion (e.g., age, race/ethnicity, gender, year of diagnosis, marital status, B symptoms, histologic subtype, hospital type, neighborhood SES and urbanization, and insurance status) and included stage at diagnosis, combined-modality therapy, and subsequent cancer as stratifying variables to allow for differing baseline hazards associated with these variables. In addition, separate Cox proportional hazards models were conducted by stage at diagnosis. Effect modification was assessed between SES and stage at diagnosis, health insurance, and gender; between race/ethnicity and SES, health insurance, and stage at diagnosis; and between age and marital status, by including interaction terms in the multivariable models. No interaction terms were statistically significant at $P < 0.05$. In all models, the proportional hazards assumption was assessed numerically based on cumulative sums of Martingale residuals (20) and visually based on inspection of the survival curves [log (−log) of the survival distribution function by log (months)]. There was evidence of a violation of this assumption

Table 1. Characteristics of adolescent and young adult Hodgkin lymphoma patients 15 to 39 years of age at diagnosis ($N = 9,353$) by race/ethnicity, California, 1988–2011

	Race/ethnicity										
	All patients		Non-Hispanic White		Black		Hispanic		Asian/Pacific Islander		
Characteristics	***n* = 9,353**	**%**	***n* = 5,919**	**%**	***n* = 643**	**%**	***n* = 2,200**	**%**	***n* = 591**	**%**	***P*-value**
Sex											
Male	4,786	51.2	3,029	51.2	316	49.1	1,140	51.8	301	50.9	
Female	4,567	48.8	2,890	48.8	327	50.9	1,060	48.2	290	49.1	0.70
Age at diagnosis (years)											
15–19	1,478	15.8	820	13.9	91	14.2	459	20.9	108	18.3	
20–24	2,224	23.8	1,374	23.2	139	21.6	541	24.6	170	28.8	
25–29	2,201	23.5	1,421	24.0	154	24.0	500	22.7	126	21.3	
30–34	1,937	20.7	1,279	21.6	140	21.8	413	18.8	105	17.8	
35–39	1,513	16.2	1,025	17.3	119	18.5	287	13.0	82	13.9	<0.001
Year of diagnosis											
1988–1992	2,052	21.9	1,528	25.8	135	21.0	317	14.4	72	12.2	
1993–1997	1,865	19.9	1,297	21.9	125	19.4	369	16.8	74	12.5	
1998–2002	1,800	19.2	1,138	19.2	100	15.6	443	20.1	119	20.1	
2003–2006	1,559	16.7	878	14.8	121	18.8	429	19.5	131	22.2	
2007–2011	2,077	22.2	1,078	18.2	162	25.2	642	29.2	195	33.0	<0.001
Marital status at diagnosis											
Married	3,265	34.9	2,147	36.3	161	25.0	753	34.2	204	34.5	
Not married	5,823	62.3	3,622	61.2	458	71.2	1,372	62.4	371	62.8	
Unknown	265	2.8	150	2.5	24	3.7	75	3.4	16	2.7	<0.001
Stage at diagnosis											
I – localized	1,200	12.8	774	13.1	87	13.5	263	12.0	76	12.9	
II – regional	4,507	48.2	2,960	50.0	264	41.1	986	44.8	297	50.3	
III/IV – advanced	3,128	33.4	1,852	31.3	258	40.1	817	37.1	201	34.0	
Missing	518	5.5	333	5.6	34	5.3	134	6.1	17	2.9	<0.001
B-symptoms											
No	3,530	37.7	2,252	38.0	221	34.4	800	36.4	257	43.5	
Yes	3,343	35.7	1,947	32.9	254	39.5	923	42.0	219	37.1	
Missing/unknown	2,480	26.5	1,720	29.1	168	26.1	477	21.7	115	19.5	<0.001
Histologic subtype											
Nodular sclerosis	7,088	75.8	4,630	78.2	460	71.5	1,548	70.4	450	76.1	
Mixed cellularity	939	10.0	528	8.9	78	12.1	286	13.0	47	8.0	
Lymphocyte depletion	96	1.0	53	0.9	5	0.8	32	1.5	6	1.0	
Lymphocyte rich	212	2.3	114	1.9	26	4.0	59	2.7	13	2.2	
Not otherwise specified	1,018	10.9	594	10.0	74	11.5	275	12.5	75	12.7	<0.001
Combined-modality therapy											
Chemotherapy and radiation	3,421	36.6	2,267	38.3	171	26.6	718	32.6	265	44.8	
Chemotherapy only	4,019	43.0	2,341	39.6	348	54.1	1,082	49.2	248	42.0	
Radiation only	993	10.6	748	12.6	52	8.1	147	6.7	46	7.8	
None/unknown	920	9.8	563	9.5	72	11.2	253	11.5	32	5.4	<0.001
Subsequent cancer											
No	8,802	94.1	5,542	93.6	599	93.2	2,105	95.7	556	94.1	
Yes[a]	551	5.9	92	6.4	14	6.8	11	4.3	4	5.9	
Breast	121	22.0									
Lymphoma	62	11.3									
Thyroid	48	8.7									
Melanoma	39	7.1									
Acute myeloid leukemia	34	6.2									
Head and neck	28	5.1									
Lung	26	4.7									
Uterus	24	4.4									
Colorectal	22	4.0									
Other leukemia	22	4.0									
Soft tissue	17	3.1									
Kidney	13	2.4									
Vulva	11	1.0									
Pancreas	8	1.5									
Acute lymphocytic leukemia	7	1.3									
Anus	6	1.1									
Prostate	6	1.1									
Esophagus	5	0.9									
Testis	5	0.9									
Other	47	8.5									

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Table 1. Characteristics of adolescent and young adult Hodgkin lymphoma patients 15 to 39 years of age at diagnosis ($N = 9,353$) by race/ethnicity, California, 1988–2011 (Cont'd)

	Race/ethnicity										
	All patients		Non-Hispanic White		Black		Hispanic		Asian/Pacific Islander		
Characteristics	***n* = 9,353**	**%**	***n* = 5,919**	**%**	***n* = 643**	**%**	***n* = 2,200**	**%**	***n* = 591**	**%**	***P*-value**
Received care at an NCI-designated cancer center											
No/missing	8,312	88.9	5,245	88.6	605	94.1	1,956	88.9	506	85.6	
Yes	1,041	11.1	674	11.4	38	5.9	244	11.1	85	14.4	<0.001
Neighborhood socioeconomic status (quintiles)											
1 (Lowest)	1,310	14.0	431	7.3	177	27.5	660	30.0	42	7.1	
2	1,805	19.3	961	16.2	157	24.4	605	27.5	82	13.9	
3	2,036	21.8	1,349	22.8	141	21.9	420	19.1	126	21.3	
4	2,161	23.1	1,570	26.5	115	17.9	317	14.4	159	26.9	
5 (Highest)	2,041	21.8	1,608	27.2	53	8.2	198	9.0	182	30.8	<0.001
Urbanization level											
Metropolitan	6,130	65.5	3,662	61.9	497	77.3	1,493	67.9	478	80.9	
Nonmetropolitan	3,072	32.8	2,173	36.7	133	20.7	662	30.1	104	17.6	
Unknown	151	1.6	84	1.4	13	2.0	45	2.0	9	1.5	<0.001
Health insurance status, limited to patients diagnosed from 2001 to 2011 ($n = 4,406$)											
Private/military insurance	3,113	70.7	1,908	78.2	199	61.6	697	55.5	309	79.4	
Public insurance	881	20.0	335	13.7	97	30.0	391	31.2	58	14.9	
No insurance	200	4.5	75	3.1	16	5.0	103	8.2	6	1.5	
Unknown	212	4.8	121	5.0	11	3.4	64	5.1	16	4.1	<0.001
Vital status											
Alive	8,108	86.7	5,148	87.0	518	80.6	1,910	86.8	532	90.0	
Death from Hodgkin lymphoma	678	7.2	388	6.6	72	11.2	183	8.3	35	5.9	
Death from non-Hodgkin lymphoma	113	1.2	64	1.1	14	2.2	29	1.3	6	1.0	
Death from other cancer	108	1.2	80	1.4	11	1.7	12	0.5	5	0.8	
Death from heart/cerebrovascular	102	1.1	75	1.3	5	0.8	17	0.8	5	0.8	
Death from other cause	188	2.0	127	2.1	18	2.8	35	1.6	8	1.4	
Death from unknown cause	56	0.6	37	0.6	5	0.8	14	0.6	0	0	<0.001

[a]Data on type of subsequent cancer are presented for all patients only to protect confidentiality, as many cancer types included <5 adolescent and young adults when presented by race/ethnicity.

with stage at diagnosis, combined-modality therapy, and subsequent cancers; therefore, stratified Cox proportional hazards regression models are presented. Regression analyses were conducted using the SAS version 9.3 software (SAS institute Inc.).

Results

In this cohort of 9,353 AYA Hodgkin lymphoma patients, 32% were followed for 15 years or more, with the mean follow-up time of 11.0 years (SD = 7.1). Sociodemographic and clinical characteristics of AYA Hodgkin lymphoma patients varied by race/ethnicity, with a predominance of Whites (63%) and, to a lesser extent, Hispanics (24%), and an increasing proportion of Asians over time (Table 1). Black (40%) and Hispanic (37%) AYAs were more likely to be diagnosed at an advanced stage than Whites (31%) or APIs (34%), and higher percentages of Black (54%) and Hispanic (49%) AYAs received chemotherapy alone than Whites (40%) or APIs (42%). More than 73% of Blacks and Hispanics resided in the lowest three categories of neighborhood SES compared with fewer than 47% of Whites and APIs. Blacks (35%) and Hispanics (39%) were much more likely to have public or no insurance than Whites (17%) or APIs (16%). Nearly 6% of AYA Hodgkin lymphoma patients were diagnosed with a subsequent primary cancer. As of December 2012, more than 13% of AYA Hodgkin lymphoma patients had died, predominantly from cancer (72%).

In multivariable analyses, worse Hodgkin lymphoma–specific survival was associated with male sex (borderline significance), earlier year of diagnosis, and presence of B symptoms (Table 2). Black AYAs experienced a 62% higher risk of Hodgkin lymphoma death (hereafter referred to as mortality; HR: 1.62; 95% CI, 1.24–2.11) and Hispanics experienced a 35% higher risk of Hodgkin lymphoma mortality (HR: 1.35; 95% CI, 1.12–1.64) than Whites. In addition, AYAs residing in lower SES neighborhoods experienced a 52% to 77% greater risk of Hodgkin lymphoma mortality than those residing in the highest SES neighborhood categories. Worse overall survival (Table 2) was associated with many of the same factors as Hodgkin lymphoma–specific survival, except that earlier age at diagnosis was associated with better all-cause survival.

AYAs with public or no insurance experienced much worse Hodgkin lymphoma–specific survival (HR: 2.08; 95% CI, 1.52–2.84) than those with private or military insurance (Table 2). The addition of health insurance to the multivariable models attenuated the HR for race/ethnicity by less than 9%, but attenuated the HR for neighborhood SES by up to 22%. Nevertheless, the HR for Hodgkin lymphoma-specific survival comparing the highest neighborhood SES to the lowest was still evident, although of borderline significance (HR: 1.67; 95% CI, 0.97–2.86; data not shown in tables).

In separate models for stage at diagnosis (Table 3), Blacks with early- and late-stage disease experienced a 68% greater risk of Hodgkin lymphoma mortality, whereas Hispanics with late-stage, but not early-stage disease experienced a greater risk of Hodgkin lymphoma mortality (HR: 1.58; 95% CI, 1.22–2.04). In addition, the association between lower neighborhood SES and Hodgkin lymphoma–specific survival only was apparent among AYAs diagnosed with early-stage disease (HR: 2.06; 95% CI, 1.59–2.68). AYAs with early or late-stage disease experienced greater than a two-fold increased risk of Hodgkin lymphoma

Table 2. Multivariable adjusted[a] hazard ratio (HR) and 95% confidence interval (CI) estimates for death from all causes (overall survival) and death from Hodgkin lymphoma (Hodgkin lymphoma–specific survival) in adolescent and young adult Hodgkin lymphoma patients, California, 1988–2011

	Overall survival[a]		HL-specific survival[a]	
Characteristic	**Deaths**	**HR (95% CI)**	**Deaths**	**HR (95% CI)**
Sex				
Female	516	Reference	290	Reference
Male	729	1.31 (1.16–1.47)	388	1.16 (0.99–1.35)
Age at diagnosis (years)				
15–19	152	0.59 (0.48–0.74)	108	0.87 (0.65–1.16)
20–24	273	0.72 (0.60–0.86)	155	0.85 (0.66–1.10)
25–29	281	0.72 (0.61–0.86)	153	0.87 (0.68–1.12)
30–34	292	0.93 (0.78–1.10)	152	1.09 (0.85–1.39)
35–39	247	Reference	110	Reference
Year of diagnosis				
1988–1992	520	2.42 (1.88–3.12)	246	2.79 (2.05–3.80)
1993–1997	317	1.83 (1.43–2.34)	160	1.73 (1.28–2.33)
1998–2002	187	1.27 (0.98–1.65)	118	1.29 (0.95–1.77)
2003–2006	129	1.15 (0.88–1.51)	88	1.15 (0.83–1.59)
2007–2011	92	Reference	66	Reference
Marital status at diagnosis				
Married	453	Reference	223	Reference
Not married	764	1.11 (0.98–1.26)	434	1.14 (0.95–1.36)
Unknown	28	0.95 (0.64–1.41)	21	1.30 (0.82–2.07)
Race/ethnicity				
Non-Hispanic White	771	Reference	388	Reference
Black	125	1.40 (1.14–1.71)	72	1.62 (1.24–2.11)
Hispanic	290	1.16 (1.00–1.34)	183	1.35 (1.12–1.64)
Asian/Pacific Islander	59	1.11 (0.85–1.46)	35	1.21 (0.85–1.72)
B symptoms				
No	277	Reference	138	Reference
Yes	499	1.56 (1.34–1.81)	316	1.87 (1.52–2.29)
Missing/unknown	469	1.26 (1.07–1.49)	224	1.42 (1.12–1.80)
Histologic subtype				
Nodular sclerosis	907	Reference	514	Reference
Mixed cellularity	153	0.98 (0.82–1.17)	75	0.86 (0.67–1.10)
Lymphocyte depletion	21	1.34 (0.86–2.07)	14	1.41 (0.82–2.41)
Lymphocyte rich	25	0.88 (0.58–1.33)	6	0.48 (0.21–1.08)
Not otherwise specified	139	1.30 (1.08–1.57)	69	1.06 (0.82–1.37)
Received care at an NCI-designated cancer center				
No/missing	1,114	Reference	606	Reference
Yes	131	0.99 (0.83–1.20)	72	0.98 (0.76–1.25)
Neighborhood socioeconomic status, quintiles				
1 (lowest)	243	1.88 (1.53–2.30)	137	1.77 (1.34–2.33)
2	278	1.53 (1.26–1.85)	154	1.52 (1.17–1.97)
3	278	1.44 (1.20–1.74)	157	1.54 (1.20–1.99)
4	250	1.16 (0.96–1.41)	130	1.17 (0.90–1.51)
5 (highest)	196	Reference	100	Reference
Urbanization level				
Metropolitan	809	Reference	436	Reference
Nonmetropolitan	412	1.04 (0.91–1.17)	225	1.08 (0.91–1.27)
Unknown	24	1.50 (0.99–2.27)	17	1.90 (1.15–3.13)
Health insurance status, limited to patients diagnosed from 2001 to 2011 (n = 4,406)[a]				
Private/military insurance	160	Reference	103	Reference
Public insurance/no insurance	125	2.05 (1.58–2.66)	86	2.08 (1.52–2.84)
Unknown	13	1.25 (0.70–2.24)	9	1.25 (0.62–2.51)

Abbreviation: HL, Hodgkin lymphoma.

[a]Stratified by stage at diagnosis, combined-modality therapy, and subsequent cancer; adjusted for all variables in the table.

mortality if they had public or no insurance. Worse overall survival by stage at diagnosis (Table 3) was associated with many of the same factors as Hodgkin lymphoma–specific survival.

The use of radiation in Hodgkin lymphoma treatment decreased over time (Fig. 1). To compare our results to those in prior studies (7, 12), we also examined the impact of initial combined-modality therapy on survival as an adjustment variable (rather than a stratifying variable due the violation of the proportional hazards assumption). We found that initial treatment with radiation was associated with better Hodgkin lymphoma–specific survival [HR for chemotherapy and radiation (vs. chemotherapy only): 0.85; 95% CI, 0.71–1.02; HR for radiation only (vs. chemotherapy only): 0.34; 95% CI, 0.23–0.51; data not shown in tables]. These associations were similar for early- and late-stage disease (Fig. 2).

Discussion

In this population-based study of more than 9,000 AYAs diagnosed with Hodgkin lymphoma over a 24-year period, we

Table 3. Multivariable adjusted[a] hazard ratio (HR) and 95% confidence interval (CI) estimates for death from all causes (overall survival) and death from Hodgkin lymphoma (HL-specific survival) in adolescent and young adult Hodgkin lymphoma patients, by stage at diagnosis, California, 1988–2011

	Stage I/II				Stage III/IV			
		Overall survival[a]		HL-specific survival[a]		Overall survival[a]		HL-specific survival[a]
Characteristic	Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)	Deaths	HR (95% CI)
Sex								
Female	277	Reference	142	Reference	208	Reference	134	Reference
Male	318	1.33 (1.12–1.57)	150	1.19 (0.94–1.50)	368	1.28 (1.07–1.52)	221	1.13 (0.90–1.40)
Age at diagnosis (years)								
15–19	78	0.67 (0.49–0.91)	55	1.15 (0.74–1.81)	67	0.55 (0.40–0.75)	48	0.68 (0.46–1.01)
20–24	132	0.76 (0.58–0.99)	64	0.91 (0.60–1.39)	128	0.72 (0.55–0.93)	86	0.87 (0.62–1.21)
25–29	132	0.73 (0.57–0.95)	62	0.93 (0.62–1.41)	126	0.72 (0.56–0.92)	85	0.89 (0.64–1.23)
30–34	147	0.94 (0.73–1.21)	74	1.32 (0.89–1.97)	130	0.92 (0.72–1.17)	69	0.91 (0.65–1.28)
35–39	106	Reference	37	Reference	125	Reference	67	Reference
Year of diagnosis								
1988–1992	250	2.49 (1.70–3.67)	98	2.87 (1.79–4.60)	239	2.35 (1.64–3.37)	135	2.64 (1.72–4.05)
1993–1997	160	1.86 (1.28–2.69)	72	1.62 (1.03–2.55)	130	1.68 (1.18–2.39)	75	1.65 (1.08–2.51)
1998–2002	89	1.24 (0.84–1.83)	57	1.28 (0.80–2.03)	92	1.42 (0.99–2.04)	60	1.43 (0.93–2.20)
2003–2006	56	1.09 (0.72–1.64)	36	1.02 (0.62–1.69)	67	1.27 (0.87–1.85)	50	1.33 (0.85–2.07)
2007–2011	40	Reference	29	Reference	48	Reference	35	Reference
Marital status at diagnosis								
Married	221	Reference	92	Reference	210	Reference	122	Reference
Not married	364	1.16 (0.97–1.40)	193	1.31 (0.99–1.72)	358	1.02 (0.85–1.23)	227	1.01 (0.80–1.29)
Unknown	10	1.07 (0.57–2.04)	7	1.57 (0.72–3.42)	8	0.56 (0.27–1.14)	6	0.68 (0.29–1.57)
Race/ethnicity								
Non-Hispanic White	391	Reference	177	Reference	335	Reference	192	Reference
Black	56	1.39 (1.04–1.86)	31	1.68 (1.14–2.49)	62	1.55 (1.17–2.06)	38	1.68 (1.17–2.41)
Hispanic	120	1.04 (0.84–1.29)	68	1.10 (0.82–1.48)	148	1.31 (1.07–1.62)	106	1.58 (1.22–2.04)
Asian/Pacific Islander	28	1.09 (0.74–1.61)	16	1.22 (0.72–2.05)	31	1.19 (0.82–1.74)	19	1.22 (0.76–1.97)
B symptoms								
No	183	Reference	90	Reference	90	Reference	48	Reference
Yes	208	1.66 (1.35–2.03)	121	1.89 (1.44–2.50)	282	1.54 (1.21–1.97)	191	1.95 (1.42–2.69)
Missing/unknown	204	1.08 (0.86–1.35)	81	1.07 (0.76–1.50)	204	1.50 (1.14–1.97)	116	1.83 (1.27–2.65)
Histologic subtype								
Nodular sclerosis	472	Reference	242	Reference	390	Reference	252	Reference
Mixed cellularity	56	0.83 (0.63–1.10)	24	0.76 (0.50–1.17)	89	1.07 (0.84–1.35)	47	0.87 (0.63–1.20)
Lymphocyte depletion	6	1.23 (0.55–2.77)	<5	∼	13	1.40 (0.80–2.45)	10	1.56 (0.82–2.98)
Lymphocyte rich	17	0.92 (0.55–1.51)	<5	∼	8	1.07 (0.53–2.18)	<5	∼
Not otherwise specified	44	1.06 (0.77–1.45)	20	0.87 (0.55–1.38)	76	1.47 (1.14–1.89)	43	1.19 (0.85–1.66)
Received care at an NCI-designated cancer center								
No/missing	536	Reference	265	Reference	511	Reference	312	Reference
Yes	59	1.02 (0.78–1.35)	27	0.94 (0.63–1.41)	65	0.94 (0.72–1.22)	43	1.00 (0.73–1.39)
Neighborhood socioeconomic status								
Low (Quintiles 1–3)	389	1.77 (1.48–2.11)	204	2.06 (1.59–2.68)	366	1.20 (1.00–1.44)	228	1.15 (0.92–1.45)
High (Quintile 4–5)	206	Reference	88	Reference	210	Reference	127	Reference
Urbanization level								
Metropolitan	374	Reference	179	Reference	385	Reference	238	Reference
Nonmetropolitan	212	1.10 (0.93–1.31)	106	1.12 (0.87–1.44)	178	1.04 (0.86–1.24)	108	1.06 (0.84–1.34)
Unknown	9	1.32 (0.68–2.59)	7	1.97 (0.91–4.25)	13	2.01 (1.14–3.55)	9	2.27 (1.14–4.52)
Health insurance status, limited to patients diagnosed from 2001 to 2011 (n = 4,406)[a]								
Private/military insurance	78	Reference	50	Reference	75	Reference	50	Reference
Public insurance/no insurance	53	2.19 (1.49–3.21)	37	2.07 (1.30–3.30)	69	2.09 (1.46–2.99)	49	2.16 (1.41–3.32)
Unknown	5	1.05 (0.42–2.64)	<5	∼	6	1.36 (0.58–3.20)	5	1.63 (0.63–4.21)

Abbreviation: HL, Hodgkin lymphoma.

[a]Stratified by combined-modality therapy and subsequent cancer; adjusted for all variables in the table.

∼Data not shown.

observed improvements in survival over time, but also striking disparities in survival by race/ethnicity, neighborhood SES, and health insurance for a subset of more recently diagnosed patients. In particular, Blacks (regardless of disease stage) and Hispanics with late-stage disease experienced worse survival than Whites. In addition, AYAs diagnosed with early-stage disease experienced worse survival if they also resided in lower SES neighborhoods. Furthermore, more recently diagnosed AYAs with public health insurance or no insurance experienced greater than a 2-fold increased risk of Hodgkin lymphoma mortality. Together, these findings identify vulnerable subgroups of Hodgkin lymphoma patients at higher risk for Hodgkin lymphoma mortality and point to disparities in treatment delivery and follow-up care as likely contributing factors.

Our previous work in outcomes for young adult Hodgkin lymphoma patients suggested that survival disparities by race/ethnicity or neighborhood SES may be due to variations in initial treatment and management (4). Consistent with studies that found initial treatment to vary by race/ethnicity (4, 7), neighborhood SES (7), and health insurance (12), we also observed that Blacks and Hispanics, AYAs residing in lower SES neighborhoods, and AYAs with public or no insurance were more likely to receive

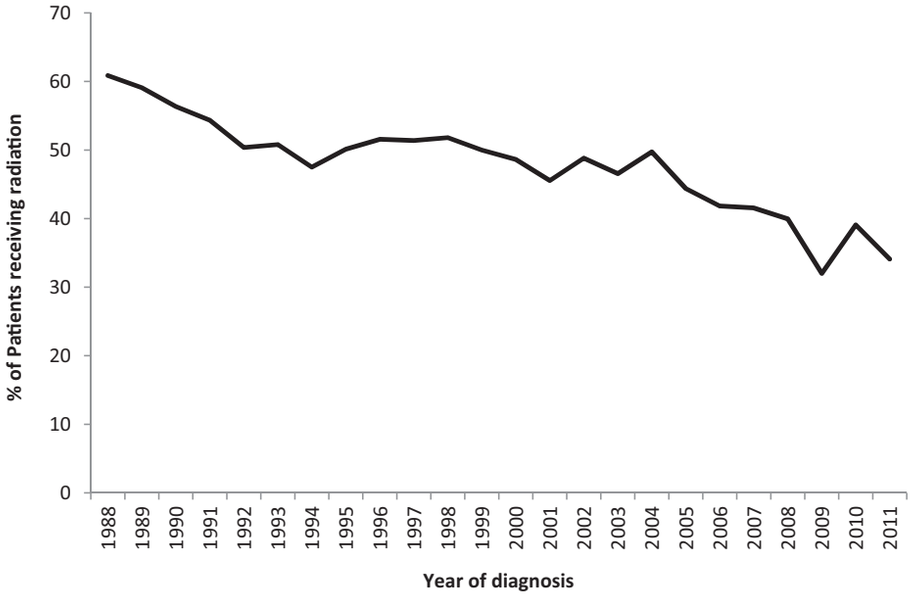

Figure 1.
Percentage (%) of adolescent and young adult Hodgkin lymphoma patients undergoing radiotherapy by year of diagnosis, California, 1988–2011.

chemotherapy alone as initial treatment. Our group and others (7, 12) also found that these disparities in treatment were associated with worse survival. Despite the survival benefits of radiation, this therapy has been associated with subsequent primary malignancies (6, 7, 21), an outcome that we were able to consider in our analyses. Specifically, we found that a somewhat higher proportion of patients who received radiation for their Hodgkin lymphoma had subsequent cancer (4.9% vs. 6.9%), which was associated with worse overall survival (data not shown); modern treatments with lower doses of radiation (7) may result in fewer subsequent cancers (21) and should continue to be monitored. However, even after controlling for initial treatment and subsequent cancers, we still observed differences in survival by race/ethnicity, neighborhood SES, and health insurance, suggesting that other factors are influencing these associations.

Expanding on a prior study that found AYA Hodgkin lymphoma patients who were uninsured or had public health insurance were more likely to be diagnosed with advanced-stage Hodgkin lymphoma (11), we found that AYA Hodgkin lymphoma patients with these types of insurance experienced worse Hodgkin lymphoma–specific survival, whether they had early- or late-stage disease. In studies of AYA cancer survivors, health insurance rates have been found to decrease with time from diagnosis (22, 23), particularly for older AYAs and those with less education (23), and a lack of health insurance is a barrier to receiving any medical care (22, 24). Furthermore, more than two thirds of uninsured survivors have been found to have no personal provider or routine medical care and, even with health insurance, AYA cancer survivors are more likely to forgo medical care due to costs (24). Collectively, these results suggest that health insurance is a critical barrier to receiving cancer-related medical care that can impact prognosis. Although the implementation of the measures from the Patient Protection and Affordable Care Act (ACA) of 2010 and 2014 (25, 26) should improve AYA cancer survivors' access to health insurance, studies should continue to monitor barriers to health insurance enrollment and medical care in AYAs.

Our findings of worse survival among Blacks and Hispanics and AYAs with Hodgkin lymphoma residing in lower SES neighborhoods are consistent with those of prior studies (4, 7). We observed some differences by stage at diagnosis: the impact of neighborhood SES was stronger for early-stage disease and Hispanics with late-stage disease experienced worse Hodgkin lymphoma survival. Although we did not have health insurance information for AYAs throughout our study period, it is likely that factors beyond health insurance are influencing these race/ethnicity and neighborhood SES associations. Inadequate long-term follow-up in patients could result in a delay in diagnosing and treating complications (27), particularly for AYAs, who tend to lack knowledge about their higher risk for developing complications (28–30). Financial concerns, including lost wages, co-payments, high deductibles, childcare, and transportation costs (24, 31–33) can be burdensome and influence follow-up care, particularly for AYAs with financial limitations (e.g., debt from college or starting a career). In addition, if poor health behaviors and comorbid conditions are more prevalent in lower SES and/or non-White Hodgkin lymphoma patients, as found for patients with other cancers (34–38), these factors, too, could increase posttreatment complications and reduce survival.

Our study is subject to some limitations. We considered the first course of treatment, but lacked details (e.g., dosing) on chemotherapy, radiation, and other treatment received after this period, and there is the potential for radiation (39, 40) and chemotherapy (40) to be underascertained; therefore, our findings could be subject to residual confounding from incomplete treatment data (41). Although it is possible that our findings are partially influenced by indication bias (i.e., patients who received radiation alone had more favorable disease characteristics and thus more favorable outcomes), it is also possible that some patients received radiation alone because they had comorbidities that precluded use of chemotherapy. Given that combined-modality therapy was broadly recommended by guidelines across all stages of Hodgkin lymphoma during the study period (2, 3), the most plausible explanation for improved survival among patients who received radiation alone is underascertainment of chemotherapy, particularly for patients with advanced-stage disease. We were

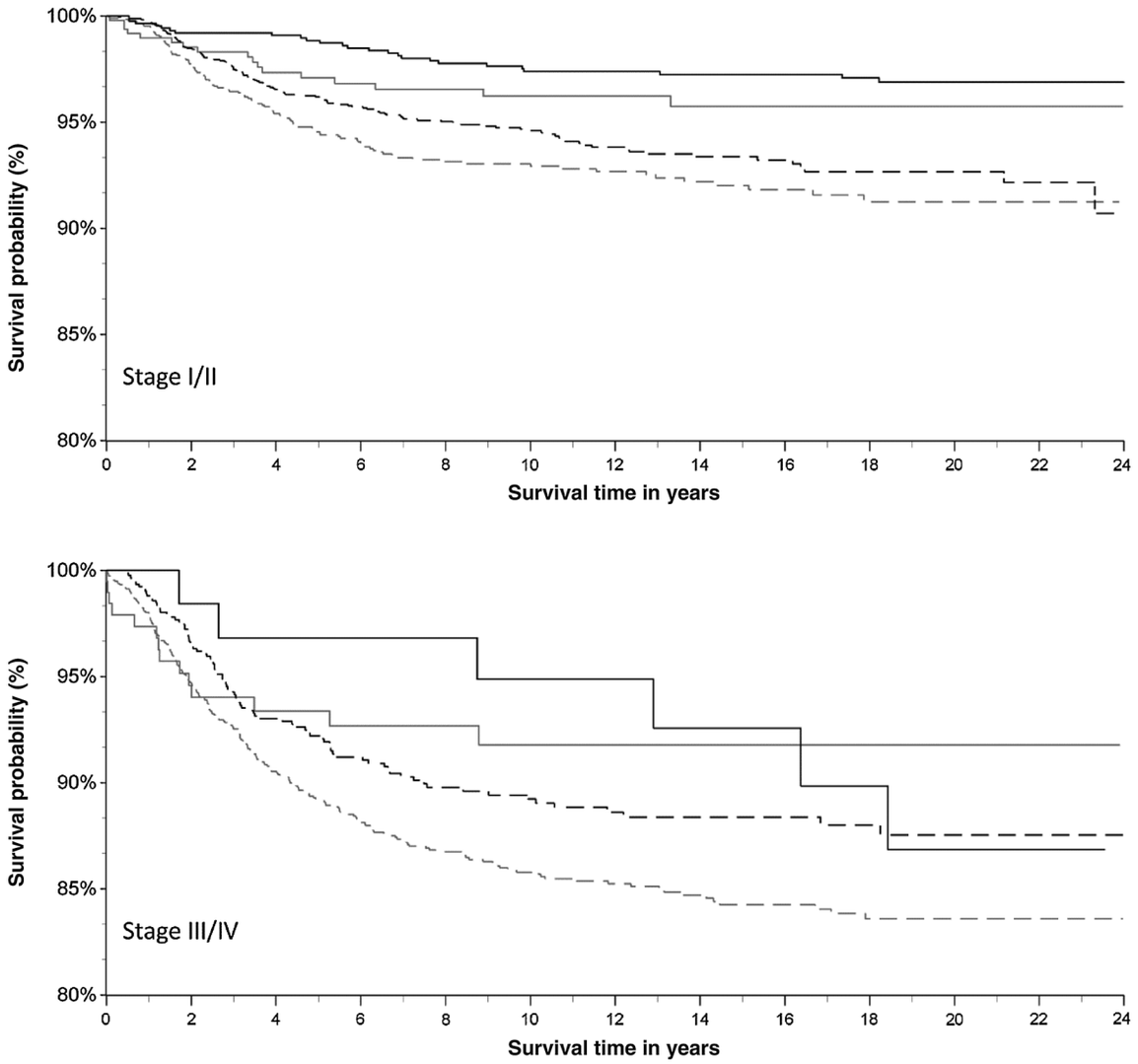

Figure 2.
Kaplan–Meier curve of Hodgkin lymphoma (HL)–specific survival in adolescent and young adult patients, by combined-modality therapy and stage of disease (stage I/II, stage III/IV), California, 1988–2011. The vertical axis represents survival probability; the horizontal axis represents survival time in years. Combined-modality therapy (dotted black line), radiotherapy only (solid black line), chemotherapy only (dotted gray line), no or unknown therapy (solid gray line).

unable to consider health insurance at diagnosis for patients diagnosed before 2001, and lacked information on changes to health insurance after initial treatment, treatment adherence, or quality of care—factors that can influence subsequent care and outcomes. We also were unable to determine whether patients were undocumented and ineligible for public health insurance. Because cancer registry data do not include potentially relevant clinical data such as prognostic serum measures (42), International Prognostic Index, or prognostic tumor characteristics [e.g., presence of Epstein–Barr virus in tumor cells (5)], or information on lifestyle behaviors or comorbid conditions, our analyses could not examine the impact of these factors on survival. Our study also lacked individual-level measures of SES to consider separately or with our neighborhood measure. Although neighborhood and individual SES are associated, neighborhood SES has been found to underestimate associations observed with individual-level SES (43). However, our multifaceted measure of neighborhood SES at the block group-level incorporated several domains of education, income, employment, and cost of living that capture various elements of the socioeconomic environment that may augment individual-level SES. Our study may also be subject to potential misclassification of race/ethnicity, although we previously have detected excellent overall agreement with self-reported race/ethnicity for Whites and Blacks, and good agreement for Hispanics and Asians (44, 45).

Despite these limitations, this study was population-based and included a large diverse population of AYA Hodgkin lymphoma cancer patients who received their care across all types of institutions, increasing the generalizability of these findings. In addition, our study is one of the first to consider the influence of initial combined-modality treatment and health insurance on previously noted racial/ethnic and socioeconomic disparities in survival among AYAs diagnosed with early- and late-stage Hodgkin lymphoma.

This study found that AYA Hodgkin lymphoma patients of Black or Hispanic race/ethnicity, those who resided in lower SES neighborhoods, and those who were uninsured or publicly insured experienced worse Hodgkin lymphoma-specific survival. Although prior studies have noted these racial/ethnic and SES survival disparities, our study extends these previous efforts by considering combined-modality treatment, subsequent primary cancers, and health insurance. With uninsurance rates historically peaking in adolescence and young adulthood (46), AYA Hodgkin lymphoma patients may be particularly vulnerable to failing to receive cancer survivor-focused medical care. The ACA has the potential to influence both access to insurance and use of necessary health care for AYAs and should be evaluated in future studies. In addition, identifying and reducing barriers to recommended treatment and surveillance in these AYAs at higher risk of mortality is essential to ameliorating these survival disparities.

Disclosure of Potential Conflicts of Interest

C.A. Clarke reports receiving a commercial research grant from Genentech. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The funders did not have any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

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Grant Support

This work was supported by the Stanford Cancer Institute (to T.H.M. Keegan), the Cancer Prevention Institute of California (to S.L. Glaser), the NCI's SEER Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California (to M.C. DeRouen, C.A. Clarke, and D. Goldberg), and an NCI Career Development Award (K07CA175063; to H.M. Parsons).

The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the NCI's SEER Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California, Department of Public Health the NCI, and the Centers for Disease Control and Prevention or their contractors and subcontractors is not intended nor should be inferred.

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Received July 17, 2015; revised November 13, 2015; accepted December 4, 2015; published OnlineFirst January 29, 2016.

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