Research Article

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Disparities in Mortality from Noncancer Causes among Adolescents and Young Adults with Cancer

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Abstract

Background: Few studies have examined noncancer outcomes among patients diagnosed with cancer as adolescents and young adults (AYA). We examined risk of mortality from noncancer causes after an AYA cancer diagnosis and investigated disparities according to race/ethnicity and other characteristics.

Methods: Patients with a first primary cancer at ages 15 to 39 years diagnosed during 1987 to 2015 were identified in the Surveillance, Epidemiology, and End Results database ($N = 242{,}940$ women, 158,347 men). Survival months were accrued from diagnosis until death or December 2015. Multivariable-adjusted HRs were used to examine disparities in mortality from all noncancer causes, cardiovascular diseases (CVD), and infectious diseases (ID) according to race/ethnicity, geographic region, and county-level characteristics.

Results: For all cancer types combined, the 10-year cumulative incidence of noncancer-related death after AYA cancer was 2% and 5% among women and men, respectively. With adjustment for cancer type, all noncancer mortality was increased among non-Hispanic Black AYAs [HR vs. non-Hispanic White: $HR_{Women} = 2.31$; 95% confidence interval (CI): 2.16–2.47; $HR_{Men} = 2.17$; 95% CI: 2.05–2.30] and those in the South (HR vs. Northeast: $HR_{Women} = 1.18$; 95% CI: 1.07–1.29; $HR_{Men} = 1.42$; 95% CI: 1.31–1.55) or in rural counties (HR vs. metro: $HR_{Women} = 1.74$; 95% CI: 1.47–2.07; $HR_{Men} = 1.57$; 95% CI: 1.33–1.86). Mortality from CVD and ID was also elevated among non-Hispanic Black AYAs.

Conclusions: Results of this study suggest that noncancer mortality after AYA cancer is highest among survivors who are non-Hispanic Black or live in the South or in rural counties.

Impact: Our analyses highlight disparities among AYAs with cancer and identify subgroups that may be targeted for increased medical surveillance or behavioral interventions.

Introduction

As a consequence of exposure to intensive treatment regimens, many patients with cancer have increased risks of noncancer health conditions, which may persist long after initial cancer treatment is complete (1). For patients diagnosed at younger ages, who have many potential years of life remaining after cancer, the implications of excess morbidity and mortality from noncancer conditions are especially profound. Several reports from the Childhood Cancer Survivor Study and other cohorts have described patterns of mortality from noncancer causes among long-term survivors of childhood cancers (2–7). However, for patients diagnosed as adolescents and young adults (AYA, age 15–39 years; ref. 8), who represent approximately 70,000 incident cancer diagnoses each year in the United States, or roughly seven times the number of new cases in children under age 15 (1), little research has examined long-term patterns of mortality from causes other than cancer. Identifying subgroups of AYA patients at highest risk of adverse outcomes may facilitate planning for long-term survivorship care in this population.

In addition to cancer type and cancer treatment–related exposures (9, 10), sociodemographic characteristics may also be important predictors of noncancer health outcomes among AYAs with cancer in the United States Reports from California have demonstrated disparities in all-cause and cancer-specific mortality among AYA cancer survivors according to race/ethnicity and area-level socioeconomic status (SES; refs. 11–15). However, the long-term risk of mortality from noncancer causes, such as cardiovascular diseases (CVD) and infectious diseases (ID), according to race/ethnicity, SES, and other factors has not been described in the AYA cancer survivor population.

Using population-based data, we investigated factors associated with noncancer mortality among AYAs with cancer, with a focus on disparities related to race/ethnicity, county-level SES indicators, geographic region, and the rural–urban continuum. Outcomes of interest included mortality from all noncancer causes combined and from the cause-specific categories of cardiovascular diseases and infectious diseases.

Materials and Methods

Study population

We identified AYA patients using data from the SEER registries (16). The SEER program is a system of population-based cancer registries that collects and reports data on cancer incidence and survival. SEER registries are located strategically across the

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United States, currently cover approximately 35% of the total U.S. population, and are demographically representative (https://seer.cancer.gov/about/overview.html). Demographic information, primary tumor site and morphology, disease stage, and first course of treatment are collected by SEER, as are the number of months survived since cancer diagnosis and the cause of death ascertained from state death certificates. For our analyses, we included all patients with a first malignant primary cancer diagnosed at ages 15–39 years between 1985 and 2015. We used 1985 as the earliest diagnosis year for inclusion to accommodate analyses according to county-level characteristics, as described below. Death certificate and autopsy only cases were excluded, as were those for whom the death certificate was unavailable, or was available but lacked information on the specific cause of death. We also excluded patients with Kaposi sarcoma, due to its strong association with HIV infection (17), and those with unknown race. We classified cancer type using an AYA recode of the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3) primary site and histology codes (https://seer.cancer.gov/ayarecode/aya-who2008.html). Testicular cancer, which is not classified separately within the AYA recode, was defined using the SEER ICD-O-3/WHO 2008 recode (https://seer.cancer.gov/siterecode/).

Patient characteristics

Race/ethnicity was categorized for our analyses as non-Hispanic White, non-Hispanic Black, Hispanic (all races), and other non-Hispanic. SEER registry was used to determine geographic region, with categories of West (San-Francisco-Oakland, San-Jose Monterey, Los Angeles, Greater California, New Mexico, Seattle/Puget Sound, Utah), South (Atlanta, Rural Georgia, Greater Georgia, Kentucky, Louisiana), Northeast (Connecticut, New Jersey), and Midwest (Detroit, Iowa). Patients in the Alaska native and Hawaii registries were excluded from analyses according to geographic region, as sample sizes from these registries were too small to define them as separate regions.

To assess disparities according to socioeconomic characteristics, we used county-level information on the percent of persons below poverty and percent of persons with less than a high school education. These variables are based on data from the U.S. Census Bureau that are linked to patient data in SEER (https://seer.cancer.gov/seerstat/variables/countyattribs/#ruralurban). Lists of all U.S. counties and their corresponding percent of persons below poverty and percent of persons with less than a high school education were generated for the 1990 U.S. Census, the 2000 U.S. Census, and the 2008–2012 American Community Survey. Quartiles were created separately for percent of persons below poverty and percent of persons with less than a high school education using the distribution of these variables for all U.S. counties from each respective census. We used quartiles from the 1990 U.S. Census for patients diagnosed in 1985–1994, from the 2000 U.S. Census for patients diagnosed in 1995–2004, and from the 2008–2012 American Community Survey for patients diagnosed in 2005–2015.

We also categorized AYA patients based on their county's rural–urban continuum code, a classification scheme that was developed by the U.S. Department of Agriculture and is also linked to patient data within the SEER database (https://seer.cancer.gov/seerstat/variables/countyattribs/ruralurban.html). Counties are assigned to one of nine categories, with metropolitan counties classified on the basis of population size, and nonmetropolitan counties classified on the basis of degree of urbanization and adjacency to metropolitan area(s). We used the rural–urban designation from the year 2003 for patients diagnosed in 1998–2007, and from the year 2013 for patients diagnosed in 2008–2015, allowing a maximum of 5 years between cancer diagnosis and the year for which the rural–urban continuum was defined. Patients diagnosed before 1998 were therefore excluded from analyses according to rural–urban code. For our analyses, we used rural–urban continuum code values to define the categories of metro (1–3), urban (4–6), and rural (7–9), as used previously (18).

Noncancer-related deaths

SEER recodes cause of death information from state death certificates and reports deaths from noncancer causes in 26 major categories (https://seer.cancer.gov/codrecode/1969+_d04162012/index.html). These categories have been defined consistently over time and include many of the leading causes of death in the U.S. population, such as "Pneumonia and Influenza," and "Diseases of the Heart." Although SEER includes deaths from "*In situ*, benign or unknown behavior neoplasm" among its 26 categories of noncancer causes of death, we did not consider deaths from this cause as noncancer-related deaths. Outcomes in our analyses included deaths from all noncancer causes combined and deaths from CVD (diseases of the heart; hypertension without heart disease; cerebrovascular disease; atherosclerosis; aortic aneurysm and dissection; other diseases of arteries, arterioles, capillaries) or ID (tuberculosis; syphilis; septicemia; pneumonia and influenza; other infectious and parasitic diseases including HIV), the two cause-specific categories with the largest number of total deaths.

Statistical analysis

We estimated the cumulative incidence of death from all noncancer causes, CVD, and ID at 5, 10, and 20 years postdiagnosis using nonparametric methods to account for deaths from other causes, including cancer, as a competing risk (19). Person-time of follow-up was accrued from cancer diagnosis until death or end of December, 2015, whichever occurred first. Patients recorded in SEER as having 0 completed months of survival were assigned a survival time of 0.5 months for analysis (20). To evaluate disparities according to race/ethnicity, county-level economic characteristics, rural–urban continuum, and geographic region, we estimated cause-specific HRs using Cox proportional hazards regression models. Patients were censored at death from other causes (including cancer) or end of December 2015. On the basis of *a priori* consideration of factors likely to be strongly associated with noncancer mortality after cancer, multivariable regression models included age at diagnosis, cancer type, calendar year of diagnosis, and race/ethnicity. All analyses were performed separately for males and females. The proportional hazards assumption was assessed through visual inspection of plots of the survival function versus time and the log(-log(survival)) versus log(time). Because cancer type and age at diagnosis appeared to violate this assumption, these variables were included as stratification variables in multivariable models. To assess potential modification by age at diagnosis, we conducted subgroup analyses according to age (15–29 vs. 30–39). In sensitivity analyses, we excluded AYAs with non-Hodgkin lymphoma (NHL) to minimize the potential influence of the HIV/AIDs epidemic on estimated associations with race/ethnicity, geographic region,

county-level economic characteristics, and rural–urban continuum. As an additional sensitivity analysis, we estimated subdistribution HRs for noncancer mortality accounting for cancer-related deaths (or deaths from all other causes) as competing risks using the method of Fine and Gray (21). As a secondary analysis, we evaluated disparities in noncancer mortality among 5-year survivors, with person-time of follow-up time for non-cancer-related deaths beginning at 5 years after diagnosis. Analyses were performed using SAS version 9.4 (SAS Institute).

Results

A total of 242,940 AYA women and 158,347 AYA men with cancer were included in these analyses. The most common cancer types among women were breast cancer (24%), thyroid cancer (17%), and melanoma (11%); those among men were testicular cancer (21%), melanoma (10%), and NHL (10%; Table 1). The median follow-up was 7.1 years (IQR = 2.5–13.5) among women and 6.1 years (IQR = 1.7–13.1) among men.

Among AYA women with cancer, 5,418 deaths from noncancer causes occurred during the follow-up period, with 1,216 deaths from CVD and 1,017 from ID (Supplementary Table S1). Overall, the cumulative incidence of all noncancer-related deaths among women was 1.24%, 1.94%, and 3.77% at 5, 10, and 20 years postdiagnosis, respectively (Table 2). When women with NHL were excluded, these values were 1.07%, 1.76%, and 3.55% (data not shown). At 10 years, the cumulative incidence of all noncancer-related deaths was highest among women diagnosed with NHL (6.59%), leukemia (5.20%), and central nervous system tumors (2.54%). NHL and leukemia also had the highest 10-year incidence of deaths from CVD and ID (Supplementary Table S2). Across the study period, the cumulative incidence of all noncancer-related deaths, CVD deaths, and ID deaths was consistently lowest among women with melanoma and thyroid cancer.

Among AYA men with cancer, there were a total of 8,452 deaths from noncancer causes, of which 1,268 and 3,789 were from CVD and ID, respectively (Supplementary Table S1). Overall, the cumulative incidence of all noncancer-related deaths was 3.83%, 4.99%, and 7.78% at 5, 10, and 20 years postdiagnosis, respectively (Table 3). When men with NHL were excluded, these values were 2.11%, 3.21%, and 5.96% (data not shown). At 10 years, the incidence of all noncancer-related deaths was highest among AYA men with NHL (20.31%) and leukemia (5.33%), followed by Hodgkin lymphoma (4.71%), head and neck cancers (4.29%), and colorectal cancers (4.23%). For CVD deaths, the 10-year incidence was highest among those with leukemia (0.85%) and NHL (0.74%), while that for ID deaths was highest among those with NHL (16.99%) and Hodgkin lymphoma (2.70%; Supplementary Table S3).

The cumulative incidence of all noncancer mortality, cardiovascular mortality, and infectious disease mortality according to race/ethnicity is shown in Fig. 1. In models accounting for age at diagnosis, calendar year, and cancer type, non-Hispanic Black women had more than double the risk of all noncancer mortality (HR = 2.31; 95% confidence interval (CI): 2.16–2.47), CVD mortality (HR = 2.77; 95% CI: 2.41–3.18), and ID mortality (HR = 5.24; 95% CI: 4.55–6.03) than non-Hispanic White women (Table 4). ID mortality was also elevated among Hispanic women (HR = 1.48; 95% CI: 1.22–1.80) relative to non-Hispanic White women. Further adjustment for county-level poverty or

Table 1. Characteristics of AYAs diagnosed with cancer, 1985–2015

	Women *N* (%)	Men *N* (%)
Total	242,940 (100%)	158,347 (100%)
Cancer type		
Leukemia	7,691 (3%)	10,977 (7%)
Non-Hodgkin lymphoma	9,387 (4%)	16,418 (10%)
Hodgkin lymphoma	11,658 (5%)	12,310 (8%)
Central nervous system tumors	7,674 (3%)	10,019 (6%)
Soft-tissue sarcomas	6,853 (3%)	6,886 (4%)
Melanoma	25,645 (11%)	16,454 (10%)
Thyroid carcinoma	41,414 (17%)	8,598 (5%)
Head and neck carcinomas[a]	4,063 (2%)	5,499 (3%)
Colorectal carcinomas	9,583 (4%)	10,474 (7%)
Breast carcinoma[b]	59,472 (24%)	—
Testicular cancer	—	32,739 (21%)
Cervical/uterine carcinomas	27,623 (11%)	—
Other[c]	31,877 (13%)	27,973 (18%)
Age at diagnosis		
15–19	12,168 (5%)	14,029 (9%)
20–24	21,491 (9%)	20,642 (13%)
25–29	38,522 (16%)	29,265 (18%)
30–34	65,525 (27%)	39,473 (25%)
35–39	105,234 (43%)	54,938 (35%)
Calendar year		
1985–1994	38,449 (16%)	26,987 (17%)
1995–2004	79,249 (33%)	52,322 (33%)
2005–2015	125,242 (52%)	79,038 (50%)
Race/ethnicity		
Non-Hispanic White	151,716 (62%)	104,370 (66%)
Non-Hispanic Black	26,628 (11%)	13,925 (9%)
Hispanic	41,443 (17%)	28,165 (18%)
Other Non-Hispanic	23,153 (10%)	11,887 (8%)
Geographic region[d]		
West	126,560 (53%)	86,611 (56%)
South	45,811 (19%)	27,423 (18%)
Northeast	35,105 (15%)	21,895 (14%)
Midwest	29,686 (13%)	18,785 (12%)
% of persons below poverty (quartiles, Q)[e]		
Q1	91,689 (38%)	59,806 (38%)
Q2	58,791 (24%)	39,617 (25%)
Q3	57,346 (24%)	36,496 (23%)
Q4	35,031 (14%)	22,383 (14%)
Missing	83	45
% persons with <high school education (quartiles, Q)[f]		
Q1	87,705 (36%)	58,162 (37%)
Q2	58,624 (24%)	38,051 (24%)
Q3	45,208 (19%)	28,702 (18%)
Q4	51,320 (21%)	33,387 (21%)
Missing	83	45
Rural–urban continuum code[g]		
Metro	171,295 (91%)	109,340 (91%)
Urban	11,794 (6%)	7,501 (6%)
Rural	5,464 (3%)	3,489 (3%)
Missing	715	430

[a]Includes nasopharyngeal carcinoma; carcinoma of other sites in the lip, oral cavity, and pharynx; nasal cavity, mid ear, sinuses, larynx, and other ill-defined head/neck carcinomas.
[b]Male breast carcinomas ($N = 146$) are included in the "Other" category.
[c]"Other" includes osseous and chondromatous neoplasms, germ cell and trophoblastic neoplasms (excluding testicular), skin carcinomas, genitourinary tract carcinomas (excluding cervical/uterine), gastrointestinal tract carcinomas (excluding colorectal), carcinomas of other/ill-defined sites, miscellaneous specified neoplasms, and unspecified malignant neoplasms.
[d]Alaska native and Hawaii registries are omitted.
[e]Quartile cutpoints were 11.15%, 15.15%, and 20.4% for AYAs diagnosed in 1985–1994; 9.54%, 12.95%, and 17.52% for AYAs diagnosed in 1995–2004; and 11.68%, 15.58%, and 19.81% for AYAs diagnosed in 2005–2015.
[f]Quartile cutpoints were 22.77%, 28.58%, and 38.07% for AYAs diagnosed in 1985–1994; 15.99%, 20.78%, and 28.71% for AYAs diagnosed in 1995–2004; and 10.56%, 14.41%, and 20.35% for AYAs diagnosed in 2005–2015.
[g]Includes AYAs diagnosed in 1998–2015 only.

Table 2. Cumulative incidence of all noncancer-related deaths among AYA women with cancer, 1985–2015

	Cumulative incidence (%)		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	1.24 (1.19–1.28)	1.94 (1.88–2.01)	3.77 (3.64–3.89)
Cancer type			
Leukemia	4.26 (3.80–4.76)	5.20 (4.66–5.78)	7.48 (6.59–8.43)
Non-Hodgkin lymphoma	5.37 (4.91–5.86)	6.59 (6.05–7.15)	9.28 (8.43–10.17)
Hodgkin lymphoma	1.08 (0.90–1.30)	1.93 (1.66–2.23)	4.32 (3.76–4.95)
Central nervous system tumors	1.57 (1.30–1.89)	2.54 (2.16–2.98)	4.84 (4.09–5.69)
Soft-tissue sarcomas	1.20 (0.95–1.49)	1.94 (1.59–2.34)	3.89 (3.21–4.67)
Melanoma	0.36 (0.29–0.45)	0.66 (0.55–0.78)	1.64 (1.40–1.91)
Thyroid carcinoma	0.32 (0.27–0.39)	0.71 (0.61–0.83)	1.81 (1.56–2.09)
Head and neck carcinomas	1.16 (0.85–1.56)	2.25 (1.76–2.84)	4.88 (3.87–6.06)
Breast carcinoma	0.76 (0.69–0.84)	1.38 (1.28–1.50)	2.96 (2.75–3.19)
Cervical/uterine carcinomas	1.14 (1.01–1.28)	2.02 (1.83–2.22)	4.69 (4.30–5.12)
Colorectal carcinomas	1.31 (1.08–1.57)	2.15 (1.83–2.53)	4.10 (3.42–4.87)
Age at diagnosis			
15–19	1.35 (1.14–1.58)	1.81 (1.56–2.09)	2.57 (2.18–3.02)
20–24	1.19 (1.05–1.36)	1.76 (1.57–1.98)	3.27 (2.89–3.68)
25–29	1.28 (1.17–1.41)	1.79 (1.65–1.95)	3.27 (2.99–3.56)
30–34	1.16 (1.08–1.26)	1.78 (1.67–1.90)	3.53 (3.30–3.77)
35–39	1.26 (1.19–1.33)	2.14 (2.04–2.24)	4.31 (4.11–4.51)
Calendar year			
1985–1994	1.40 (1.29–1.52)	2.06 (1.92–2.21)	3.69 (3.50–3.88)
1995–2004	1.24 (1.17–1.32)	1.96 (1.86–2.06)	3.83 (3.61–4.06)
2005–2015	1.17 (1.11–1.24)	1.91 (1.79–2.04)	—
Race/ethnicity			
Non-Hispanic White	0.99 (0.94–1.03)	1.64 (1.57–1.71)	3.37 (3.23–3.51)
Non-Hispanic Black	2.96 (2.75–3.18)	4.14 (3.88–4.42)	7.25 (6.75–7.77)
Hispanic	1.23 (1.11–1.35)	1.84 (1.68–2.00)	3.34 (3.01–3.71)
Other Non-Hispanic	0.89 (0.77–1.03)	1.57 (1.38–1.77)	3.09 (2.72–3.49)

geographic region did not substantially change HRs according to race/ethnicity (data not shown). Compared with women in the Northeast region, those in the South had higher mortality from all noncancer causes (HR = 1.18; 95% CI: 1.07–1.29) and from CVD (HR = 1.40; 95% CI: 1.15–1.71). In contrast, ID mortality was higher among women in the Northeast than in any other geographic region. Both all noncancer mortality and CVD mortality were higher among women in urban and rural areas than in metro areas, and appeared to increase with increasing county-level poverty. Compared with women in the lowest quartile of county-level poverty, the HR for CVD mortality for women in the highest quartile was 1.41 (95% CI: 1.17–1.70). County-level poverty, education, and rural–urban continuum were not clearly associated with ID mortality among women. Patterns were generally similar in sensitivity analyses excluding women with NHL, although the HR for ID mortality among non-Hispanic Black women was somewhat attenuated (HR = 4.20; 95% CI: 3.52–5.01; Supplementary Table S4). Patterns were also similar in analyses restricted to 5-year survivors (Supplementary Table S5), in age-stratified analyses (data not shown), and in analyses estimating subdistribution HRs (data not shown).

Relative to non-Hispanic White men, non-Hispanic Black men had higher mortality from all noncancer causes (HR = 2.17; 95% CI: 2.05–2.30), CVD (HR = 2.44; 95% CI: 2.09–2.84), and ID (HR = 2.39; 95% CI: 2.20–2.58; Table 5). Hispanic men also had higher mortality from all noncancer causes (HR = 1.43; 95% CI: 1.34–1.52) and ID (HR = 1.74; 95% CI: 1.59–1.90) than non-Hispanic White men. In contrast, all noncancer mortality (HR = 0.75; 95% CI: 0.67–0.83) and ID mortality (HR = 0.59; 95% CI: 0.49–0.71) were significantly lower among men of other non-Hispanic race/ethnicities than among non-Hispanic White men. Additional adjustment for quartile of county-level poverty or geographic region did not appreciably alter HRs according to race/ethnicity (data not shown). Compared with AYA men with cancer in the Northeast region, those in the South had higher mortality from all noncancer causes, CVD, and ID, while those in the West had higher mortality from all noncancer causes and from ID. No clear trends were observed for associations with county-level poverty or education. Men in rural areas had higher all noncancer mortality (HR = 1.57; 95% CI: 1.33–1.86) and CVD mortality (HR = 2.13; 95% CI: 1.47–3.09) than men in metro areas; CVD mortality was also elevated among men in urban areas (HR = 1.55; 95% CI: 1.15–2.07). Patterns tended to be similar in analyses of 5-year survivors (Supplementary Table S6), in age-stratified analyses (data not shown), and in analyses estimating subdistribution HRs (data not shown).

When men with NHL were excluded, the HR for ID mortality for non-Hispanic Black compared with non-Hispanic White was of greater magnitude (HR = 3.97), while that for Hispanic men was slightly attenuated (HR = 1.57; Supplementary Table S7). An increase in ID mortality among men in rural counties (vs. metro) was also apparent (HR = 1.61), while the HR for ID mortality among those in the West region (vs. Northeast) was attenuated in analyses were restricted to patients with non-NHL.

Discussion

AYAs with cancer continue to represent an understudied patient population in the United States. In this population-based study, we investigated patterns of mortality from noncancer causes after an AYA cancer diagnosis, and examined disparities according to race/ethnicity and other patient characteristics. Among AYAs of all cancer types, we found a cumulative incidence of deaths from noncancer causes of approximately 2% and 5% among women

Table 3. Cumulative incidence of all noncancer-related deaths among AYA men with cancer, 1985–2015

	Cumulative incidence (%)		
	5-year (95% CI)	10-year (95% CI)	20-year (95% CI)
Total	3.83 (3.73–3.93)	4.99 (4.87–5.11)	7.78 (7.58–7.98)
Cancer type			
Leukemia	4.08 (3.70–4.49)	5.33 (4.86–5.82)	8.20 (7.35–9.10)
Non-Hodgkin lymphoma	18.60 (17.99–19.21)	20.31 (19.67–20.97)	23.43 (22.62–24.24)
Hodgkin lymphoma	2.87 (2.57–3.19)	4.71 (4.30–5.15)	9.50 (8.71–10.32)
Central nervous system tumors	2.39 (2.08–2.72)	3.35 (2.96–3.76)	5.73 (5.06–6.44)
Soft-tissue sarcomas	1.97 (1.64–2.34)	2.74 (2.33–3.19)	4.28 (3.64–4.99)
Melanoma	0.76 (0.63–0.92)	1.53 (1.33–1.76)	3.47 (3.05–3.94)
Thyroid carcinoma	0.98 (0.77–1.23)	1.82 (1.49–2.19)	4.57 (3.78–5.45)
Head and neck carcinomas	2.71 (2.28–3.19)	4.29 (3.70–4.93)	8.41 (7.32–9.59)
Colorectal carcinomas	2.85 (2.52–3.21)	4.23 (3.80–4.70)	6.81 (6.05–7.61)
Testicular cancer	1.13 (1.01–1.26)	2.05 (1.88–2.24)	4.63 (4.26–5.03)
Age at diagnosis			
15–19	1.57 (1.36–1.80)	2.24 (1.97–2.54)	4.03 (3.51–4.60)
20–24	2.09 (1.89–2.31)	3.00 (2.74–3.28)	4.91 (4.45–5.39)
25–29	3.06 (2.85–3.27)	3.99 (3.75–4.25)	6.40 (5.99–6.83)
30–34	4.67 (4.46–4.89)	5.79 (5.55–6.05)	8.47 (8.08–8.87)
35–39	4.85 (4.67–5.04)	6.36 (6.14–6.59)	9.92 (9.55–10.29)
Calendar year			
1985–1994	7.62 (7.31–7.94)	8.91 (8.57–9.26)	11.48 (11.10–11.87)
1995–2004	3.88 (3.71–4.04)	4.99 (4.80–5.18)	7.48 (7.17–7.80)
2005–2015	2.35 (2.23–2.47)	3.29 (3.11–3.48)	—
Race/ethnicity			
Non-Hispanic White	3.22 (3.11–3.33)	4.30 (4.17–4.44)	7.03 (6.80–7.25)
Non-Hispanic Black	9.00 (8.51–9.50)	11.04 (10.48–11.62)	15.34 (14.47–16.23)
Hispanic	4.22 (3.97–4.48)	5.52 (5.21–5.85)	8.27 (7.66–8.90)
Other Non-Hispanic	2.29 (2.01–2.59)	2.99 (2.65–3.36)	5.31 (4.66–6.02)

and men, respectively, at 10 years postdiagnosis. Accounting for cancer type, patient characteristics associated with higher risk of mortality from all noncancer causes combined included non-Hispanic Black race/ethnicity and living in the South or in rural counties. Non-Hispanic Black race/ethnicity was also a consistent predictor of mortality from both CVD and ID. Our analyses highlight disparities in noncancer mortality among AYAs with cancer, and identify subgroups of survivors that may be targeted for increased medical surveillance.

A number of reports have demonstrated that cancer survivors, including those diagnosed as AYAs, have elevated mortality from noncancer causes relative to the general population (2–5, 22–25), likely reflecting the direct effects of cancer therapies on the risk and severity of noncancer health conditions, the indirect effects of cancer and its treatment on overall health and well-being, and shared risk factors for cancer and noncancer conditions. Our results, like those reported among childhood cancer survivor cohorts (2–7), suggest that cancer type is an important predictor of noncancer mortality among survivors, with some of the highest risks among patients with hematologic malignancies and central nervous system tumors, cancer types typically associated with more intensive treatment regimens. Among AYAs, we identified head and neck cancers and colorectal cancers as additional cancer types with relatively high mortality from noncancer causes throughout the survivorship period, findings which may be at least partially attributable to factors such as smoking, obesity, or other lifestyle and behavioral characteristics. Our descriptive analyses also indicated that overall, and within most cancer types, AYA men had a higher cumulative incidence of all noncancer mortality across the study period than AYA women. This is consistent with higher mortality at younger ages for men than women in the general population (https://www.prb.org/thegendergapinusmortality/), due, in part, to higher rates of risky behaviors such as smoking among men (26), and with previous reports suggesting a higher absolute risk of death for males than females among childhood cancer survivors (9).

While previous studies have documented disparities in both all-cause and cancer-specific mortality according to race/ethnicity among AYAs with cancer in the United States (11–15), considerably less research has examined race-related disparities in noncancer health outcomes in this population. Racial differences in CVD mortality may be particularly critical to examine, as a cancer diagnosis and treatment could exacerbate disparities in cardiovascular outcomes between non-Hispanic Blacks and non-Hispanic Whites that have been reported in the general population (27). In a study of 79,176 AYA patients with cancer diagnosed in California during 1996–2012, the 10-year risk of incident CVD among African-Americans was 1.55 (95% CI: 1.33–1.81) times that among non-Hispanic Whites with adjustment for cancer type (28). Likewise, a prior SEER-based analysis of AYAs diagnosed at ages 15–34 from 1973 to 2011 found a nonsignificant increase in death from CVD among Black survivors compared with White (HR = 1.33; 95% CI: 0.60–2.95), although estimates were imprecise and models did not appear to account for cancer type (29). Results of this study also indicate a higher burden of CVD mortality among non-Hispanic Black AYAs with cancer, but suggest that the magnitude of this disparity may be considerably greater than previously reported. Differences between non-Hispanic Black AYAs and other race/ethnicities persisted over time since cancer diagnosis, underscoring the importance of long-term follow-up care for cardiovascular health, particularly for non-Hispanic Black AYA cancer survivors.

Although our analyses indicate that deaths from ID are relatively rare among AYAs with cancer types other than NHL,

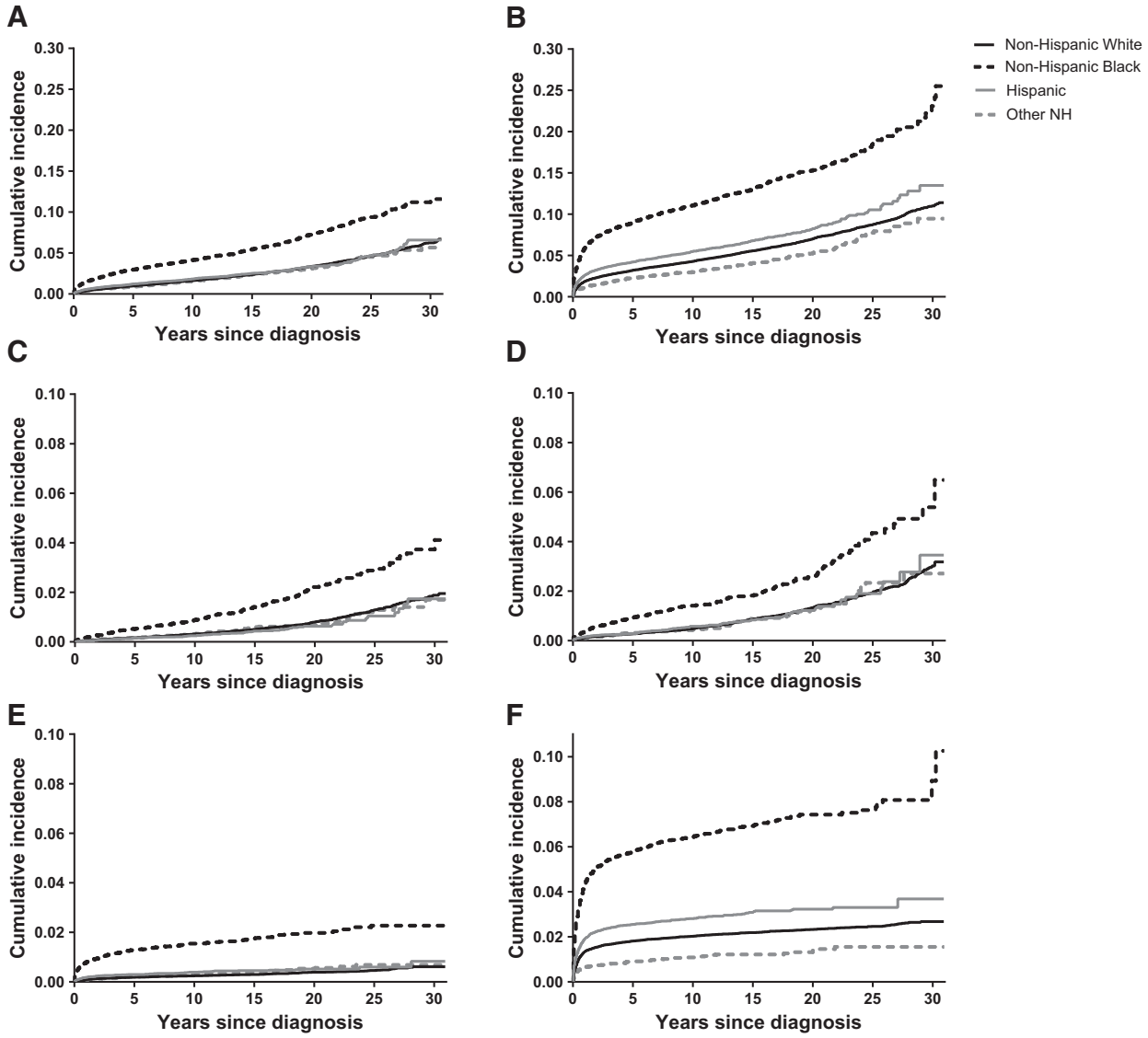

Figure 1.

Cumulative incidence of mortality from all noncancer causes among AYA women with cancer (**A**), all noncancer causes among AYA men with cancer (**B**), cardiovascular diseases among AYA women with cancer (**C**), cardiovascular diseases among AYA men with cancer (**D**), infectious diseases among AYA women with cancer (**E**), and infectious diseases among AYA men with cancer (**F**).

characteristics that we identified as predictors of higher ID mortality may also be those associated with a higher incidence of life-threatening infections in this population. We found that non-Hispanic Black AYAs had a higher risk of ID mortality after cancer than non-Hispanic White AYAs, a relationship that remained apparent when patients with NHL were excluded to minimize the influence of potential differences in HIV-related deaths according to race/ethnicity. Most ID deaths occurred within the first few years after cancer diagnosis, suggesting that many of these may be the result of acute complications of treatment for the primary cancer or relapse. Little large-scale research has examined infections among patients with cancer and survivors, particularly those with solid tumors, and further investigation may be needed to identify cancer treatment–related and other contributors to disparities in ID incidence and mortality after AYA cancer.

To our knowledge, our study is the first to investigate variability in noncancer mortality among AYA cancer survivors according to U.S. geographic region and county-level characteristics such as poverty, education, and rural–urban continuum. One prior study, using data from the California Cancer Registry, reported that living in a lower SES neighborhood, defined on the basis of a composite index of census tract-level poverty, education, and other characteristics, was associated with a higher risk of developing CVD after AYA cancer (28). In our analyses, we observed few clear trends in noncancer mortality outcomes according to county-level poverty and education, aside from relatively weak increases in all noncancer mortality and CVD mortality with increasing county-level poverty among women. On the other hand, living in the South or in a rural county was associated with higher mortality from all noncancer causes and CVD among both

Table 4. HRs for all noncancer-related deaths, cardiovascular disease deaths, and infectious disease deaths according to patient characteristics among AYA women with cancer, 1985–2015

		All noncancer-related deaths			Cardiovascular disease deaths			Infectious disease deaths		
	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Race/ethnicity										
Non-Hispanic White	1,492,030	3,135	1	1	720	1	1	408	1	1
Non-Hispanic Black	206,468	1,203	2.75 (2.57–2.94)	2.31 (2.16–2.47)	299	3.16 (2.76–3.62)	2.77 (2.41–3.18)	400	6.48 (5.64–7.44)	5.24 (4.55–6.03)
Hispanic	285,446	690	1.14 (1.05–1.24)	1.04 (0.95–1.13)	109	0.88 (0.71–1.07)	0.85 (0.69–1.04)	140	1.56 (1.29–1.89)	1.48 (1.22–1.80)
Other non-Hispanic	188,076	390	0.98 (0.89–1.09)	0.91 (0.82–1.01)	88	1.02 (0.82–1.27)	0.96 (0.77–1.20)	69	1.25 (0.97–1.61)	1.20 (0.93–1.55)
Geographic region										
West	1,121,237	2,372	0.83 (0.76–0.89)	0.88 (0.81–0.95)	496	0.85 (0.71–1.02)	0.93 (0.77–1.11)	387	0.53 (0.45–0.63)	0.59 (0.49–0.70)
South	341,555	1,171	1.34 (1.22–1.47)	1.18 (1.07–1.29)	273	1.64 (1.34–1.99)	1.40 (1.15–1.71)	240	1.00 (0.83–1.20)	0.79 (0.65–0.96)
Northeast	303,211	777	1	1	156	1	1	201	1	1
Midwest	342,289	950	1.06 (0.97–1.17)	1.03 (0.94–1.13)	256	1.28 (1.05–1.56)	1.20 (0.98–1.47)	162	0.80 (0.65–0.99)	0.72 (0.58–0.88)
% of persons below poverty (quartiles, Q)										
Q1	991,051	2,164	1	1	502	1	1	407	1	1
Q2	482,194	1,155	1.12 (1.04–1.20)	1.10 (1.03–1.19)	251	1.16 (1.00–1.35)	1.18 (1.01–1.38)	186	0.84 (0.71–1.00)	0.82 (0.68–0.97)
Q3	414,122	1,263	1.40 (1.31–1.50)	1.21 (1.12–1.30)	289	1.57 (1.36–1.82)	1.37 (1.18–1.60)	256	1.27 (1.08–1.48)	0.98 (0.83–1.15)
Q4	283,828	836	1.44 (1.32–1.56)	1.27 (1.17–1.38)	174	1.51 (1.27–1.80)	1.41 (1.17–1.70)	168	1.30 (1.08–1.55)	1.00 (0.82–1.21)
% persons with <HS education (quartiles, Q)										
Q1	1,030,204	2,351	1	1	552	1	1	409	1	1
Q2	454,285	1,083	1.10 (1.02–1.18)	1.07 (0.99–1.15)	217	1.13 (0.96–1.32)	1.15 (0.97–1.36)	226	1.06 (0.90–1.25)	1.06 (0.89–1.26)
Q3	345,265	1,129	1.45 (1.35–1.56)	1.23 (1.14–1.32)	280	1.77 (1.53–2.04)	1.53 (1.32–1.79)	247	1.51 (1.29–1.77)	1.15 (0.97–1.36)
Q4	341,442	855	1.15 (1.06–1.24)	1.09 (1.00–1.19)	167	1.22 (1.02–1.46)	1.29 (1.06–1.57)	135	0.78 (0.64–0.95)	0.78 (0.63–0.96)
Rural–urban continuum code[b]										
Metro	1,136,296	2,655	1	1	473	1	1	527	1	1
Urban	80,490	231	1.24 (1.08–1.41)	1.27 (1.11–1.45)	50	1.50 (1.12–2.00)	1.52 (1.14–2.04)	33	0.90 (0.63–1.27)	1.05 (0.74–1.49)
Rural	35,891	137	1.63 (1.38–1.94)	1.74 (1.47–2.07)	33	2.22 (1.56–3.15)	2.37 (1.66–3.39)	17	1.02 (0.63–1.65)	1.41 (0.87–2.29)

[a]Adjusted for race/ethnicity, calendar year; cancer type and age are stratification variables.

[b]Includes AYAs diagnosed in 1998–2015 only.

Table 5. HRs for all noncancer-related deaths, cardiovascular disease deaths, and infectious disease deaths according to patient characteristics among AYA men with cancer, 1985–2015

		All noncancer-related deaths			Cardiovascular disease deaths			Infectious disease deaths		
	Total person-years	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Deaths	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
Race/ethnicity										
Non-Hispanic White	978,730	5,163	1	1	828	1	1	2,093	1	1
Non-Hispanic Black	86,152	1,552	3.02 (2.85–3.20)	2.17 (2.05–2.30)	221	3.19 (2.74–3.70)	2.44 (2.09–2.84)	865	3.63 (3.35–3.90)	2.39 (2.20–2.58)
Hispanic	165,373	1,358	1.35 (1.27–1.43)	1.43 (1.34–1.52)	146	1.15 (0.96–1.37)	1.18 (0.99–1.42)	709	1.47 (1.35–1.60)	1.74 (1.59–1.90)
Other non-Hispanic	81,894	379	0.80 (0.72–0.89)	0.75 (0.67–0.83)	73	1.10 (0.87–1.40)	0.98 (0.77–1.25)	122	0.57 (0.48–0.69)	0.59 (0.49–0.71)
Geographic region										
West	704,855	4,605	1.30 (1.21–1.40)	1.31 (1.22–1.40)	549	0.86 (0.73–1.03)	0.91 (0.76–1.09)	2,322	1.80 (1.61–2.02)	1.72 (1.53–1.93)
South	186,783	1,518	1.52 (1.40–1.65)	1.42 (1.31–1.55)	247	1.56 (1.28–1.90)	1.42 (1.16–1.73)	671	1.71 (1.50–1.95)	1.59 (1.39–1.82)
Northeast	182,410	912	1	1	164	1	1	332	1	1
Midwest	202,449	1,208	1.28 (1.17–1.40)	1.09 (1.00–1.19)	265	1.32 (1.09–1.61)	1.24 (1.01–1.51)	383	1.26 (1.09–1.46)	0.92 (0.80–1.07)
% of persons below poverty (quartiles, Q)										
Q1	605,693	3,132	1	1	550	1	1	1,225	1	1
Q2	300,442	2,289	1.36 (1.29–1.44)	1.42 (1.34–1.50)	265	1.07 (0.93–1.25)	1.11 (0.96–1.29)	1,250	1.67 (1.54–1.81)	1.76 (1.63–1.91)
Q3	240,034	1,781	1.26 (1.18–1.33)	1.29 (1.21–1.37)	285	1.46 (1.27–1.69)	1.35 (1.16–1.57)	769	1.16 (1.06–1.27)	1.33 (1.21–1.47)
Q4	165,527	1,248	1.37 (1.28–1.46)	1.37 (1.28–1.47)	168	1.35 (1.13–1.61)	1.31 (1.09–1.58)	545	1.30 (1.18–1.44)	1.37 (1.23–1.52)
% persons with <HS education (quartiles, Q)										
Q1	632,247	3,855	1	1	609	1	1	1,798	1	1
Q2	278,332	1,590	0.84 (0.79–0.89)	1.02 (0.96–1.09)	225	1.03 (0.88–1.20)	1.08 (0.92–1.27)	647	0.60 (0.55–0.66)	0.90 (0.81–0.99)
Q3	198,167	1,625	1.17 (1.10–1.24)	1.17 (1.10–1.25)	248	1.48 (1.27–1.72)	1.32 (1.13–1.54)	747	0.95 (0.87–1.03)	1.08 (0.99–1.18)
Q4	202,951	13,380	0.93 (0.87–0.99)	1.13 (1.06–1.22)	186	1.21 (1.02–1.43)	1.28 (1.06–1.54)	597	0.67 (0.61–0.73)	1.00 (0.90–1.11)
Rural–urban continuum code[b]										
Metro	680,340	3,445	1	1	483	1	1	1,306	1	1
Urban	47,994	243	1.01 (0.89–1.15)	1.10 (0.97–1.26)	50	1.47 (1.10–1.97)	1.55 (1.15–2.07)	58	0.64 (0.49–0.83)	0.79 (0.60–1.02)
Rural	21,468	145	1.33 (1.13–1.57)	1.57 (1.33–1.86)	30	1.97 (1.36–2.84)	2.13 (1.47–3.09)	30	0.72 (0.50–1.04)	1.07 (0.74–1.54)

Abbreviation: HS, high school.

[a]Adjusted for race/ethnicity and calendar year; cancer type and age are stratification variables.

[b]Includes AYAs diagnosed in 1998–2015 only.

men and women, potentially reflecting higher rates of smoking (https://www.cdc.gov/statesystem/cigaretteuseadult.html), obesity (https://www.cdc.gov/obesity/data/prevalence-maps.html), or other risk factors in these areas. AYA patients with cancer in the South and/or in rural areas may therefore be priority groups for intervention efforts to improve health outcomes throughout survivorship.

Strengths of this study include the large population-based sample of AYA patients with cancer and the long follow-up, which allowed us to estimate the cumulative incidence of noncancer-related death up to 20+ years postdiagnosis and to investigate disparities according to race/ethnicity and other characteristics. Our study also has limitations. Cause of death, as recoded from state death certificates, is subject to misclassification, potentially leading to some misattribution of cancer-related deaths to noncancer causes. However, the cause-specific death classification scheme utilized by SEER was developed to improve identification of cancer-specific deaths and may mitigate this concern (https://seer.cancer.gov/causespecific/). Furthermore, we do not expect that misclassification would be strongly differential with respect to factors such as race and other patient characteristics that we examined. Also, SEER registries do not collect individual-level SES characteristics, and our analyses thus relied on county-level characteristics to investigate disparities related to SES. Estimates therefore reflect the impact of living in a county with, for example, high poverty, rather than the impact of living in a household below the poverty level. It is possible that adjustment for individual-level poverty, if this measure were available, would attenuate associations between characteristics such as non-Hispanic Black race/ethnicity, living in the South, or living in rural areas and noncancer mortality risk. Because information on body mass index, lifestyle/behavioral characteristics, and preexisting medical conditions is not available in cancer registry data, we also could not assess whether adjustment for these factors would attenuate observed associations. In addition, we were unable to consider the impact of health insurance status on noncancer mortality risk, as this information has only been available in SEER since 2007 (https://seer.cancer.gov/seerstat/variables/seer/insurance-recode/). Future investigations of noncancer outcomes in AYA cancer survivors may wish to consider joint associations between insurance status and race/ethnicity or other patient characteristics. Finally, the number of deaths among AYAs in our study was too small to conduct meaningful analyses of noncancer mortality from cause-specific categories other than CVD and ID, or to examine individual causes within the categories of CVD and ID.

Conclusions

In conclusion, results of this study suggest that the risk of noncancer mortality after AYA cancer is highest among survivors who are non-Hispanic Black or live in the South or in rural counties. Further research is needed to better understand the specific factors underlying the risk of poor outcomes in these groups. Identifying subgroups of AYA cancer survivors at increased risk of adverse noncancer health outcomes may inform the development of surveillance recommendations and policies or interventions designed to ensure access to coordinated care in survivorship.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Anderson, M.A. Weaver, W.A. Wood, A.F. Olshan
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Anderson, J.L. Lund, H.B. Nichols
Writing, review, and/or revision of the manuscript: C. Anderson, J.L. Lund, M.A. Weaver, W.A. Wood, A.F. Olshan, H.B. Nichols

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