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Article

Risk of early death in adolescents and young adults with cancer: a population-based study

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Abstract

Background: Advancements in treatment and supportive care have led to improved survival for adolescents and young adults (AYAs) with cancer; however, a subset of those diagnosed remain at risk for early death (within 2 months of diagnosis). Factors that place AYAs at increased risk of early death have not been well studied.

Methods: The Surveillance, Epidemiology, and End Results registry was used to assess risk of early death in AYAs with hematologic malignancies, central nervous system tumors, and solid tumors. Associations between age at diagnosis, sex, race, ethnicity, socioeconomic status, insurance status, rurality, and early death were assessed.

Results: A total of 268 501 AYAs diagnosed between 2000 and 2016 were included. Early death percentage was highest in patients diagnosed with hematologic malignancies (3.1%, 95% confidence interval [CI] = 2.9% to 3.2%), followed by central nervous system tumors (2.5%, 95% CI = 2.3% to 2.8%), and solid tumors (1.0%, 95% CI = 0.9% to 1.0%). Age at diagnosis, race, ethnicity, lower socioeconomic status, and insurance status were associated with increased risk of early death in each of the cancer types. For AYAs with hematologic malignancies and solid tumors, risk of early death decreased statistically significantly over time.

Conclusions: A subset of AYAs with cancer remains at risk for early death. In addition to cancer type, sociodemographic factors also affect risk of early death. A better understanding of the interplay of factors related to cancer type, treatment, and health systems that place certain AYA subsets at higher risk for early death is needed to address these disparities and improve outcomes.

Over recent decades, improvements in treatment and supportive care for adolescents and young adults (AYAs; age 15-39 years at diagnosis) with cancer have led to statistically significantly increased survival, with current 5-year survival rates of more than 80% (1-3). Despite overall improvements, there remains a subset of AYAs that do not survive long enough to begin treatment or die soon after initiation of treatment. Factors that place AYAs at higher risk for early death (death <2 months from diagnosis) (4) have not been well studied. Identifying these factors is an important step toward improving outcomes.

In the childhood cancer population, sociodemographic factors including Black race or Hispanic ethnicity, and cancer-related factors, including diagnoses of acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), non-Hodgkin lymphoma, hepatoblastoma, or malignant brain tumors, place patients at higher risk of death within 1 month of diagnosis (5-9). Recent data suggest similar factors may be associated with increased risk of early death in AYAs with cancer; however, data are limited to patients diagnosed with leukemia. Among children and AYAs with AML, increasing age at diagnosis, treatment at a non-National Cancer Institute (NCI)-designated cancer center, Black race, and lack of health insurance are associated with increased risk of death within 1 month of diagnosis compared with younger age at diagnosis, treatment at an NCI-designated cancer center, White race, and having private or public insurance, respectively (10). Among AYA ALL patients, treatment at a non-Children's

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Oncology Group or NCI-designated center has also been associated with increased risk of death within 2 months of diagnosis (11).

This study used the Surveillance, Epidemiology, and End Results (SEER) database, a population-based registry, to characterize early mortality patterns in AYA cancer patients with leukemias, central nervous system (CNS) tumors, and solid tumors to examine the association between sociodemographic and cancer-related factors and risk of early death, defined as death within 2 months of diagnosis.

Methods

Study design and patient population

This is a retrospective cohort study using the SEER Cancer Registry. Individuals diagnosed with cancer between 15 and 39.99 years old between January 2000 and December 2016 whose data were available in SEER 17 were included. Cancer diagnoses included are listed using the AYA site recode World Health Organization 2008 categorization in Supplementary Table 1 (available online) (12). All cancer diagnoses and stages were included; however, second and subsequent malignancies were excluded. Diagnoses were grouped into 3 categories: CNS tumors, hematologic malignancies, and solid tumors. Cancer stage was only included as a variable for patients with solid tumors (Supplementary Methods, available online).

Study variables

Early death was defined as death within 2 months from the date of diagnosis, reported as 0- or 1-month survival in the SEER "survival months" variable. The definition of early death has been variable across previous studies. In the childhood cancer population, early death is often defined as within 1 month of diagnosis, whereas among older adults, analyses of early death have often assessed death within 3 months of diagnosis (5,13). The only prior population-based studies (single-state analyses of childhood and AYA leukemia patients) that have assessed early death in AYAs defined early death as within 1 or 2 months from diagnosis (10,14). We similarly defined early deaths as those that occur within 2 months of diagnosis.

Race and origin were defined per the variable "race and origin recode Non-Hispanic White (hereafter, White), Non-Hispanic Black (hereafter, Black), Non-Hispanic American Indian/Alaska Native, Non-Hispanic Asian or Pacific Islander (hereafter, Asian or Pacific Islander), Hispanic," per coding as "White," "Hispanic (all races)," "Black," "Asian or Pacific Islander." Rural or urban status was per "rural-urban commuting area-based categorization C (2 categories)." Insurance status was assessed per the variable "insurance recode (2007+)," classified as "uninsured" vs "insured" if coded as "insured," "any Medicaid," "insured/no specifics," or as "unknown" if coded as "insurance status unknown" or "blank(s)." The SEER census tract–level socioeconomic status (SES) index, defined as Yost quintiles, is constructed from the following census tract variables: percent less than 150% of poverty line, median rent, median household income, median house value, percent unemployed, percent working class, and education index (15-17). Using census data and American Community Survey data, SES indices are calculated for each year and categorized into quintiles. Quintile 1 and quintile 5 are those with the lowest and highest SES, respectively.

Statistical analysis

Overall specific cancer types (per AYA Site Recode 2008), disease types (solid tumors, hematologic malignancies, CNS tumors), and annual incidence of early death by disease types were summarized by frequency with percentage as well as by early death percentage with 95% Agresti-Coull confidence intervals. Demographic variables were summarized by early death status as frequency with percentage or mean and median with SD. Data for solid tumors, hematologic malignancies, and CNS tumors were independently analyzed. For each disease type, a logistic regression model was used to assess the association between incidence of early death with relation to year of diagnosis, age at diagnosis, race and origin, sex, rurality, Yost quintile, insurance status, and stage (only for solid tumors); year of diagnosis and age at diagnosis were modeled as continuous covariates, whereas other covariates were discrete. Model selection via minimizing the Akaike Information Criterion was used to identify up to 3-way interactions among these variables, which yielded improved models, and generalized additive models (binomial distribution with logit link) with penalized splines used to further identify models with nonlinear associations between incidence of early death and year of diagnosis or age at diagnosis, considering interactions with other variables (Supplementary Methods, available online).

Table 1. Characteristics of 268 501 AYAs diagnosed with cancer between the years 2000 and 2016 identified in the SEER database

Characteristic	Hematologic malignancies (n = 49 706) No. (%)	CNS tumors (n = 12 766) No. (%)	Solid tumors (n = 206 029) No. (%)
Sex			
Female	21 541 (43.3)	5578 (43.7)	139 172 (67.5)
Male	28 165 (56.7)	7188 (56.3)	66 857 (32.5)
Age at diagnosis, y			
Mean (SD)	28.5 (7.2)	28.6 (7.1)	32.1 (5.8)
Median (IQR[a])	29 (22-35)	29 (23-35)	29 (29-37)
Race and ethnicity			
Asian or Pacific Islander	3918 (7.9)	914 (7.2)	17 392 (8.4)
Black	6723 (13.5)	1032 (8.1)	19 081 (9.3)
Hispanic	11 266 (22.7)	2472 (19.4)	40 895 (19.8)
White	27 799 (55.9)	8348 (65.4)	128 661 (62.4)
Rurality			
Nonrural	46 123 (92.8)	11 792 (92.4)	190 663 (92.5)
Rural	3583 (7.2)	974 (7.6)	15 366 (7.5)
Yost quintile[b]			
1	9843 (19.8)	2150 (16.8)	34 640 (16.8)
2	9980 (19.9)	2429 (19.0)	38 815 (18.8)
3	10 029 (20.2)	2558 (20.0)	41 770 (20.3)
4	9974 (20.1)	2787 (21.8)	44 868 (21.8)
5	9970 (20.1)	2842 (22.3)	45 936 (22.3)
Insurance			
Uninsured	2235 (4.5)	548 (4.3)	6978 (3.4)
Insured	26 768 (53.9)	6887 (53.9)	115 383 (56.0)
Unknown	20 703 (41.7)	5331 (41.8)	83 668 (40.6)
Stage			
Locoregional	N/A	N/A	184 036 (89.3)
Distant	N/A	N/A	21 993 (10.7)

[a] AYA = adolescents and young adults; CNS = central nervous system; IQR = interquartile range; SEER = Surveillance, Epidemiology, and End Results; SES = socioeconomic status.

[b] The SEER census tract level SES index, defined as Yost quintiles is constructed from the following census tract variables: percent less than 150% of poverty line, median rent, median household income, median house value, percent unemployed, percent working class, and education index. Using census data and American Community Survey data, SES indices are calculated for each year and categorized into quintiles. Quintile 1 are those with the lowest SES and quintile 5 are those with the highest SES.

Table 2. Percentage of early death among 268 501 AYAs diagnosed with cancer between 2000 and 2016 identified in SEER database by sex, race and ethnicity, rurality, SES, insurance status, and cancer stage at diagnosis

	Hematologic malignancies (49 706 patients)		CNS tumors (12 766 patients)		Solid tumors (206 029 patients)	
Characteristic	No. (%)	P	No. (%)	P	No. (%)	P
Sex		<.001		.02		<.001
Female	502 (2.3)		121 (2.2)		862 (0.6)	
Male	1027 (3.6)		202 (2.8)		1140 (1.7)	
Race and ethnicity		<.001		<.001		<.001
Asian or Pacific Islander	121 (3.1)		22 (2.4)		251 (1.4)	
Black	326 (4.8)		33 (3.2)		408 (2.1)	
Hispanic	500 (4.4)		96 (3.9)		486 (1.2)	
White	582 (2.1)		172 (2.1)		857 (0.7)	
Rurality		.39		>.99		.37
Nonrural	1428 (3.1)		299 (2.5)		1842 (1.0)	
Rural	101 (2.8)		24 (2.5)		160 (1.0)	
Yost quintile		<.001		.002		<.001
1	467 (4.7)		73 (3.4)		599 (1.7)	
2	345 (3.5)		70 (2.9)		433 (1.1)	
3	313 (3.1)		66 (2.6)		414 (1.0)	
4	210 (2.1)		68 (2.4)		338 (0.8)	
5	194 (1.9)		46 (1.60)		218 (0.5)	
Insurance		<.001		<.001		<.001
Uninsured	123 (5.5)		23 (4.2)		177 (2.5)	
Insured	635 (2.3)		123 (1.8)		921 (0.8)	
Unknown	781 (3.8)		177 (3.3)		904 (1.1)	
Stage						
Locoregional	N/A		N/A		362 (0.2)	<.001
Distant	N/A		N/A		1640 (7.5)	
Total	1529 (3.1) [95% CI = 2.9 to 3.2]		323 (2.5) [95% CI = 2.3 to 2.8]		2002 (0.97) [95% CI = 0.93 to 1.01]	

[a] AYA = adolescents and young adults; CI = confidence interval; CNS = central nervous system; SEER = Surveillance, Epidemiology, and End Results; SES = socioeconomic status.

Results

Patient characteristics

The study cohort included 268 501 AYAs diagnosed with cancer between the years 2000 and 2016. Patient demographics are summarized in Table 1 and Supplementary Table 1 (available online).

Percentages of early death

Overall, 3854 early deaths were reported, representing 1.4% of the total cohort (Table 2). The percentage of patients with early death was highest in those with hematologic malignancies (3.1%, 95% confidence interval [CI] = 2.9% to 3.2%), followed by CNS tumors (2.5%, 95% CI = 2.3% to 2.8%) and solid tumors (1.0%, 95% CI = 0.9% to 1.0%). Patients diagnosed with liver, biliary, and pancreatic carcinoma, AML, gastric carcinoma, osteosarcoma, and tracheal, bronchus, and lung carcinoma had the highest risk of early death, whereas patients diagnosed with thyroid carcinoma, melanoma, and breast cancer had the lowest risk of early death (Figure 1; Supplementary Table 1, available online).

Predictors of early death in AYAs with hematologic malignancies

Among AYAs with hematologic malignancies, those with AML (9.4%, 95% CI = 8.6% to 10.2%) and ALL (4.3%, 95% CI = 3.7% to 4.9%) had the highest risk of early death, and AYAs with Hodgkin lymphoma (0.4%, 95% CI = 0.4% to 0.6%) had the lowest (Supplementary Table 1, available online). In multivariable analyses, males in their 20s and 30s had approximately 1.5% absolute increased probability of early death compared with females in their 20s and 30s. (Figure 2, A). Increasing age at diagnosis was associated with a higher probability of early death among male AYAs. Compared with White AYAs, Asian or Pacific Islander (odds ratio [OR] = 1.57, 95% CI = 1.29 to 1.92), Black (OR = 1.95, 95% CI = 1.69 to 2.23), and Hispanic (OR = 1.89, 95% CI = 1.66 to 2.16) AYAs each had an increased risk of early death (Table 3; Figure 2, B). Patients with high SES had lower risk of early death compared with patients with low SES (Yost quintile 5 vs quintile 1; OR = 0.55, 95% CI = 0.45 to 0.66; Figure 2, C), and AYAs with insurance had lower risk of early death compared with AYAs without insurance (OR = 0.55, 95% CI = 0.45 to 0.67; Figure 2, D). The risk of early death decreased over time (OR = 0.95, 95% CI = 0.93 to 0.97; Table 3; Supplementary Figure 1, A, available online).

Predictors of early death in AYAs with CNS tumors

AYAs with glioblastoma and anaplastic astrocytoma (4.9%, 95% CI = 4.2% to 5.7%) had the highest risk of early death, and AYAs with ependymoma (0.9%, 95% CI = 0.4% to 1.8%) had the lowest (Supplementary Table 1, available online). In multivariable analyses, males had increased probability of early death compared with females (OR = 1.28, 95% CI = 1.02 to 1.61; Table 3; Figure 3, A). Increasing age at diagnosis was associated with a higher probability of early death (Figure 3, B). Black (OR = 1.51, 95% CI = 1.02 to 2.23) and Hispanic (OR = 1.75, 95% CI = 1.33 to 2.30) AYAs had increased risk of early death compared with White AYAs (Figure 3, C). Patients with the highest SES had lower risk of early death compared with patients with the lowest SES (Yost quintile 5 vs quintile 1; OR = 0.57, 95% CI = 0.39 to 0.85; Figure 3, D). AYAs with insurance also had statistically significantly lower risk of early death compared with AYAs without insurance (OR = 0.52, 95% CI = 0.33 to 0.82; Figure 3, E). Risk of early death did not statistically significantly differ by rurality or year of diagnosis (Table 3; Supplementary Figure 1, B, available online).

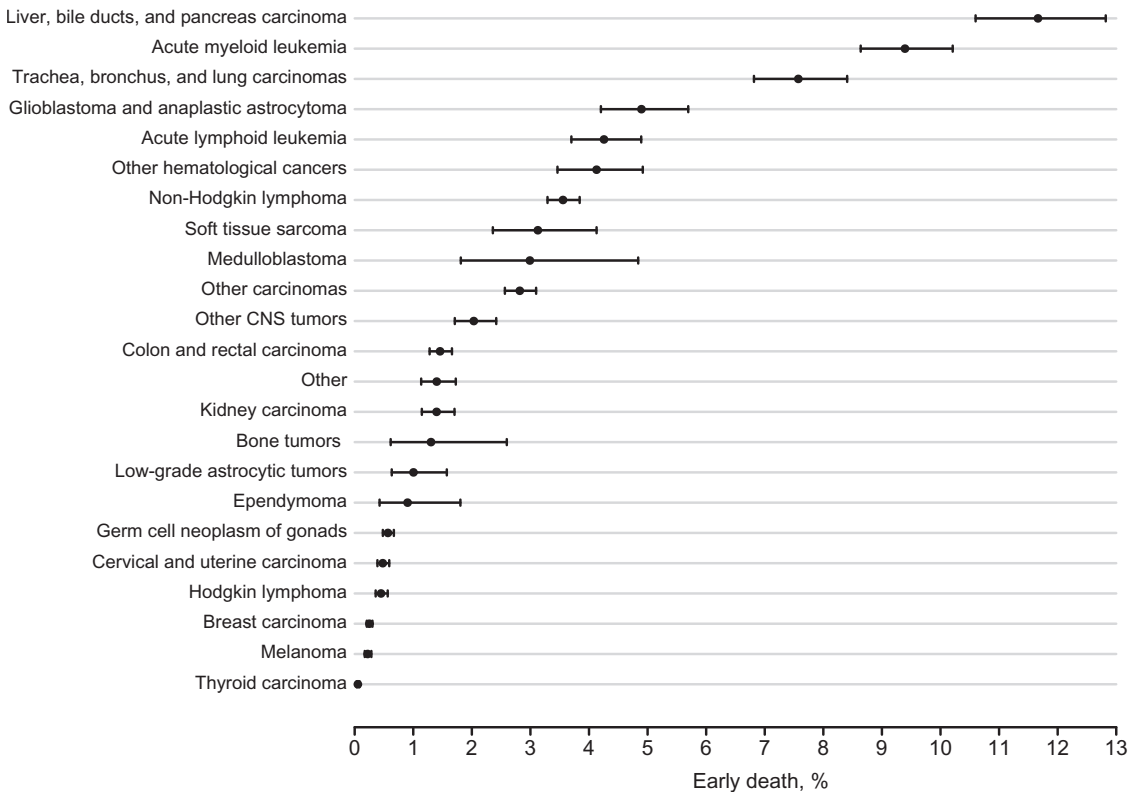

Figure 1. Early death percentage (%) in adolescents and young adults (AYAs) by cancer type. **Bars** represent 95% confidence intervals.

Predictors of early death in AYAs with solid tumors

AYAs diagnosed with breast cancer, thyroid cancer, and melanoma represented 40.9% of the total study population but only 4.9% of total early deaths (Supplementary Table 1, available online). AYAs with liver/biliary duct/pancreatic cancer or those with lung/tracheal/bronchial cancers had the highest rates of early death and also had high percentages of distant disease at presentation. Among AYAs with liver/biliary/pancreatic cancer, 41% had distant disease at presentation. The percentage of early death was 17.5% (95% CI = 15.5% to 19.6%) and 7.6% (95% CI = 6.5% to 8.9%) among those with distant disease and locoregional disease at presentation, respectively. Among AYAs with tracheal/bronchial/lung cancers, 58% presented with distant disease. The percentages of early death in those with distant disease and locoregional disease at presentation were 12.2% (95% CI = 10.9% to 13.5%) and 1.2% (95% CI = 0.8% to 1.9%), respectively. In the overall solid tumor cohort, patients with distant disease had a statistically significantly higher percentage of early death compared with patients with locoregional disease (7.5% vs 0.2%; $P < .001$; Table 2; Supplementary Figures 2, A-D, available online).

Male AYAs had higher percentage of early death than females (Supplementary Tables 2 and 3, available online). When stratifying by disease stage at diagnosis, there were differences in percentages of early death by race and ethnicity, with Black AYA patients having higher percentages (locoregional: 0.6% and distant: 9.8%) than other racial and ethnic groups. Although there was no difference in percentage of early death in AYAs with locoregional disease, there was an increased percentage of early death in older AYAs with distant disease (Supplementary Tables 2 and 3, available online).

In multivariable analyses, AYAs with higher SES had statistically significantly lower risk of early death compared with patients with lower SES (Yost quintile 5 vs quintile 1; OR = 0.48, 95% CI = 0.40 to 0.57; Table 3; Supplementary Figure 3, A, available online). AYAs with insurance also had statistically significantly lower risk of early death compared with AYAs without insurance (OR = 0.54, 95% CI = 0.46 to 0.65; Supplementary Figure 3, B, available online). The risk of early death statistically significantly decreased over time (OR = 0.97, 95% CI = 0.96 to 0.99; Supplementary Figure 1, C, available online).

Discussion

We found that percentage of early death was highest among AYAs with hematologic malignancies and lowest in those with solid tumors. We also found sociodemographic disparities in risk of early death. Males, AYAs of Asian or Pacific Islander and Black race or Hispanic ethnicity AYAs in census tracts with low SES indices, and AYAs without insurance had increased risk of early death compared with females, AYAs of White race, AYAs in high SES census tracts, and AYAs with insurance, respectively.

Prior studies in the childhood cancer population that assessed risk of death within 1 month of diagnosis have similarly found highest risk of early death in those with hematologic malignancies (5-7). Treatment-related complications, particularly infectious causes, are the most common etiology of death during induction therapy for leukemia patients (18-22). Treatment-induced neutropenia as well as immune cell dysfunction place patients at increased risk of infection, and AYAs with leukemia have excess infection-related mortality compared with younger leukemia patients (23-25). The decreased risk of early death seen over the study period may be attributable to improvements in supportive care, including increased use of antimicrobial prophylaxis during induction therapy (26-28).

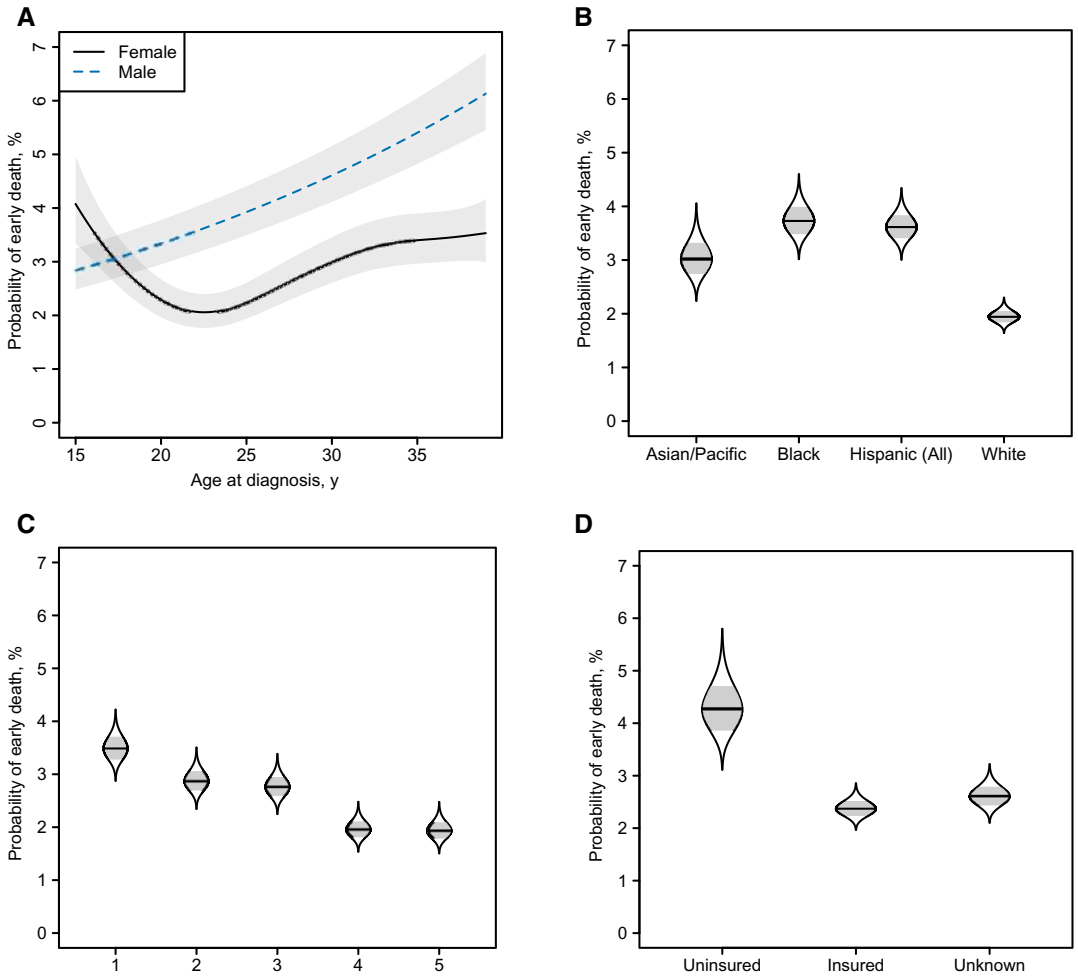

Figure 2. Early death in adolescent and young adult (AYA) patients with hematologic malignancies. Model-adjusted probability of early death by **A**) sex and age at diagnosis, **B**) race or ethnicity, **C**) socioeconomic status as defined by Yost quintile, and **D**) insurance status. A) shows the model-adjusted nonlinear relations between probability of early death and age at diagnosis by sex, with shaded ± standard error intervals, with other covariates held fixed at the mean year of diagnosis, nonrurality, Yost quintile 3, uninsured, and White race. B–D) show catseye plots illustrating the normal distributions of the model-adjusted means, with shaded ± standard error intervals; model-adjusted means are weighted proportionally to covariate marginal frequencies.

Among AYAs with solid tumors, certain less common tumors were associated with high risk of early death, particularly liver/biliary, gastric, lung/tracheal/bronchial, and pancreatic cancers, as well as osteosarcoma. Apart from osteosarcoma, these cancers are not common in AYAs and may be diagnosed at later stages (29-31). A recent analysis found a disproportionate increase in incidence of metastatic gastric cancer among AYAs (32,33). In this study, we found high percentages of distant disease at presentation among AYAs with these cancers. In older adults with pancreatic cancer, disease progression, infection, and thromboembolic events contribute to death within 3 months of diagnosis (34). Late stage at diagnosis and lack of treatment have been associated with early death (within 3 months of diagnosis) among older adult gastric and lung cancer patients (13,35,36). More data are needed to determine factors that increase risk of early death in AYAs with these cancer types.

Stage at diagnosis affected risk of early death among AYAs with solid tumors. Percentage of early death was over 7 in AYAs with distant disease and less than 1% for those with locoregional disease. Among AYAs, sociodemographic factors, including male sex, low SES, Black race, Hispanic ethnicity, rural residence, and no or public insurance, have all been associated with higher stage at presentation (32,37,38). Patients with higher disease burden are more likely to require emergent intervention, including surgical procedures and/or rapid initiation of chemotherapy. Efforts focused on earlier presentation to care, diagnosis, and treatment in these higher risk populations are needed.

We also found that male AYAs had increased risk of early death compared with females. In the AYA population, male sex consistently has been linked with worse outcomes, including lower 5-year and longer-term survival compared with females (1,39-41). Males are less likely to present for routine preventive care services and less likely to be insured (42), which may result in delayed diagnosis and suboptimal care. Sex-based differences in treatment response represent an emerging research field; however, to date, some studies show that females experience higher rates and more severe toxicities to many chemotherapy drugs than males do (43,44). This suggests that prognostic factors, including stage at diagnosis and health-care access and use factors, rather than treatment toxicity, may place male AYAs at higher risk of early death than females.

Older age at diagnosis was only associated with increased risk of early death among males. Insurance coverage may contribute to increased risk of early death among those diagnosed at older ages because insurance rates decrease with increasing age in the AYA population (45). The increasing number of comorbidities

Table 3. Model-adjusted odds ratios of early death among 268 501 AYAs diagnosed with cancer between 2000 and 2016 identified in SEER database by sex, race and ethnicity, rurality, SES, insurance status, and cancer stage at diagnosis

	Hematologic malignancies		CNS Tumors		Solid Tumors	
Characteristic[a]	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex						
Female	[b]		1.0		[b]	
Male	[b]		1.28 (1.02 to 1.61)	.04	[b]	
Race and ethnicity						
White	1.0		1.0			
Asian or Pacific Islander	1.57 (1.29 to 1.92)	<.001	1.20 (0.76 to 1.89)	.75	[b]	
Black	1.95 (1.69 to 2.23)	<.001	1.51 (1.02 to 2.23)	.11	[b]	
Hispanic	1.85 (1.66 to 2.16)	<.001	1.75 (1.33 to 2.30)	<.001	[b]	
Rurality						
Nonrural	1.0		1.0		1.0	
Rural	0.86 (0.70 to 1.07)	.16	0.94 (0.61 to 1.46)	.80	0.94 (0.79 to 1.12)	.50
Yost quintile						
1	1.0		1.0		1.0	
2	0.82 (0.71 to 0.94)	.02	0.93 (0.66 to 1.30)	.95	0.78 (0.68 to 0.89)	<.001
3	0.79 (0.68 to 0.91)	.007	0.87 (0.62 to 1.24)	.82	0.75 (0.65 to 0.86)	<.001
4	0.55 (0.46 to 0.66)	<.001	0.85 (0.60 to 1.21)	.75	0.64 (0.56 to 0.75)	<.001
5	0.55 (0.45 to 0.66)	<.001	0.57 (0.39 to 0.85)	.02	0.48 (0.40 to 0.57)	<.001
Insurance						
Uninsured	1.0		1.0		1.0	
Insured	0.55 (0.45 to 0.67)	<.001	0.52 (0.33 to 0.82)	.01	0.54 (0.46 to 0.65)	<.001
Unknown	0.60 (0.47 to 0.77)	<.001	0.99 (0.57 to 1.72)	>.99	0.63 (0.51 to 0.78)	<.001
Stage						
Locoregional	N/A		N/A		[b]	
Distant	N/A		N/A		[b]	
Year of diagnosis	0.95 (0.93 to 0.97)	<.001	1.00 (0.96 to 1.05)	.86	0.97 (0.96 to 0.99)	.002

[a] Proportion of early death by age at diagnosis for AYAs diagnosed with hematologic malignancies, CNS tumors, and solid tumors can be found in Figures 2, A, 3, B, and Supplementary Figure 2 (available online), respectively. AYA = adolescents and young adults; CI = confidence interval; CNS = central nervous system; OR = odds ratio; SEER = Surveillance, Epidemiology, and End Results; SES = socioeconomic status.

[b] The model of early death with relation to hematological malignancies included a nonlinear interaction between age at diagnosis and sex, and the model with relation to solid tumors included a nonlinear interaction between age at diagnosis and sex, race, and stage. Due to the presence of these nonlinear interactions, discrete estimates of odds ratios for sex in the case of hematological malignancies and for sex, race, and stage in the case of solid tumors are not estimable. Penalized spline regressions were used for these variables.

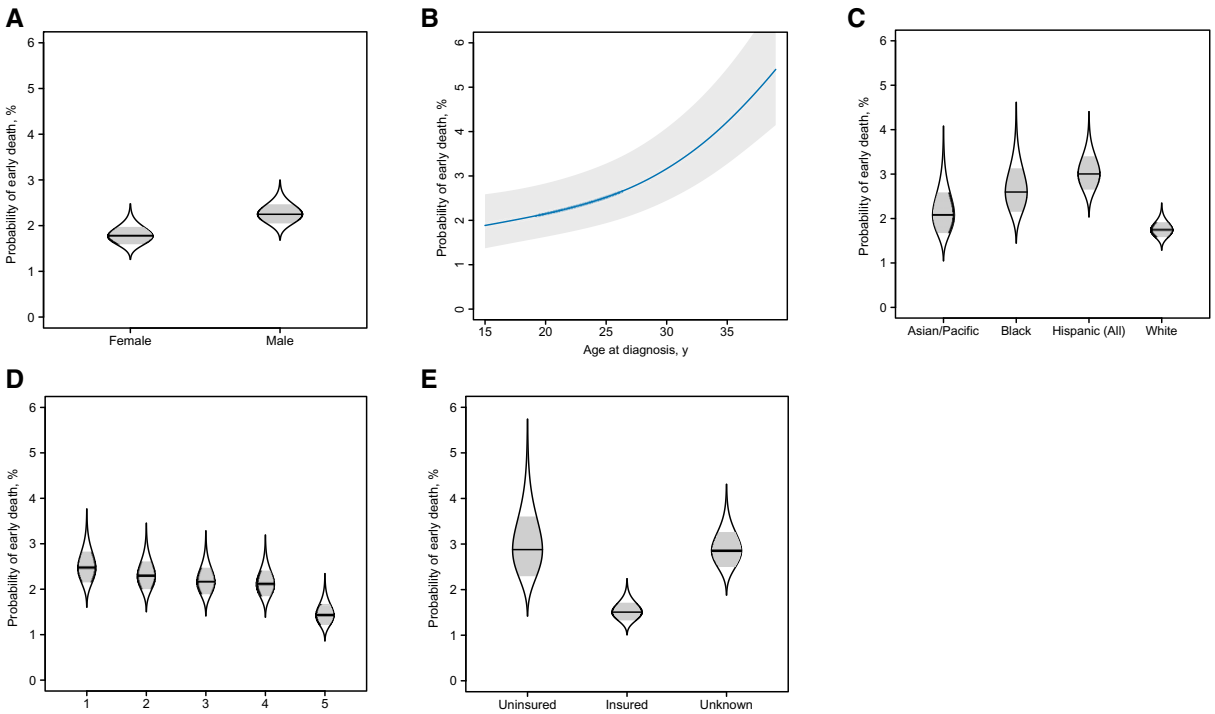

Figure 3. Early death in adolescent and young adult (AYA) patients with central nervous system (CNS) tumors. Model-adjusted probability of early death by **A**) sex, **B**) age at diagnosis, **C**) race or ethnicity, **D**) socioeconomic status as defined by Yost quintile, and **E**) insurance status. B) shows the model-adjusted nonlinear relations between probability of early death and age at diagnosis, with shaded ± standard error intervals, with other covariates held fixed at the mean year of diagnosis, male sex, nonrurality, Yost quintile 3, uninsured, and White race. A), C), D), and E) show catseye plots illustrating the normal distributions of the model-adjusted means, with shaded ± standard error intervals; model-adjusted means are weighted proportionally to covariate marginal frequencies.

that occur with age may also contribute because comorbidities are associated with treatment delay and toxicity risk (46). However, it is unclear why these factors would differentially impact males.

Racial and ethnic disparities in early death risk among female AYAs diminished with increasing age at diagnosis, and among male AYAs, Black and Asian patients had increased risk of early death compared with White and Hispanic patients across all ages at diagnosis. Prior studies have reported that Black patients are more likely than White and Asian patients to present with advanced-stage disease, and Black and Hispanic patients are less likely to receive definitive treatment (47,48), both of which may contribute to early death disparities. Better understanding of biological differences in AYA cancers by race and ethnicity (49,50) and differences in treatment toxicities (51) and elucidation of the ways that structural racism plays a role in timely diagnosis and access to and receipt of quality cancer care are needed.

AYAs living in lower SES census tracts and those without insurance coverage had increased risk of early death. In AYA cancer patients, lower SES and lack of insurance or public insurance are associated with higher stage at diagnosis and less optimal initial cancer treatment, including delays in treatment and cancer-directed surgery (37,39,52,53). In the childhood cancer population, low SES is associated with decreased adherence to care, increased abandonment of treatment, and lower rates of follow-up (54,55). These factors may contribute to the increased risk of early death in AYAs from socioeconomically disadvantaged areas and without private insurance.

There are limitations to this study. SEER is considered an authoritative source for US population–level data; however, certain data are unavailable, such as individual-level SES data and insurance status data before 2007. For the time period included in this study, census tract SES data are available, which more closely approximate individual level SES compared with other area-based measures (56). Detailed information on therapeutic exposures is also unavailable, limiting the ability to discern whether differences in early treatment regimens affect risk of early death. In addition, data on treatment setting, specifically whether patients received initial care at an academic or community site, are limited. Finally, SEER survival data are reported in integer months, whereas date of diagnosis is reported to the nearest year; thus, some individuals may have been diagnosed at time of death or died on the day of diagnosis. Strengths of this study include the very large sample size and use of a contemporary population-based cohort. With large sample sizes comes the ability to detect differences with smaller magnitudes, and, as demonstrated in this study, we found statistically significant differences in early death between groups by cancer type, sex, race and ethnicity, SES, and insurance status. In some cases, statistical significance does not necessarily reflect clinically meaningful differences.

Whereas previous studies among AYAs with cancer have focused on 5-year or longer survival, early death has been understudied. The percentage of early death in this population is clinically significant, particularly among common AYA hematologic malignancies such as AML, with early death close to 10% over this study period, as well as certain solid tumors such as liver and biliary, gastric, lung, and pancreatic cancers that are uncommon in AYAs. Knowledge of these risk factors for early death highlights the need to optimize and standardize supportive care early in treatment for AYAs with hematologic malignancies as well as focus on increasing access to care to support earlier diagnosis among AYAs with less common malignancies. Additionally, future research is needed to understand why certain AYA subgroups are at increased risk of death within 2 months of diagnosis, with a focus on AYAs with hematologic malignancies, Black males, and those who live in low-SES areas and/or lack private health insurance. Discerning the interplay of cancer-related factors such as tumor biology and stage at diagnosis, treatment-related factors including initial treatment type and risk of treatment toxicity, and health systems disparities that place certain groups of AYAs at higher risk for early death will be critical to address these disparities and improve outcomes.

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Data availability

The data underlying this article are available in the Surveillance, Epidemiology, and End Results Program (SEER), at https://seer.cancer.gov. The data sets were derived from sources in the public domain.

References

1. Berkman AM, Livingston JA, Merriman K, et al. Long-term survival among 5-year survivors of adolescent and young adult cancer. *Cancer*. 2020;126(16):3708-3718.
2. Anderson C, Smitherman AB, Nichols HB. Conditional relative survival among long-term survivors of adolescent and young adult cancers. *Cancer*. 2018;124(14):3037-3043.
3. Miller KD, Fidler-Benaoudia M, Keegan TH, et al. Cancer statistics for adolescents and young adults, 2020. *CA A Cancer J Clin*. 2020;70(6):443-459.
4. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials

between 1980 and 2002–Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol*. 2005;23(36):9219-9226.
5. Green AL, Furutani E, Ribeiro KB, et al. Death within 1 month of diagnosis in childhood cancer: an analysis of risk factors and scope of the problem. *J Clin Oncol*. 2017;35(12):1320-1327.
6. Pastore G, Viscomi S, Mosso ML, et al. Early deaths from childhood cancer. A report from the Childhood Cancer Registry of Piedmont, Italy, 1967-1998. *Eur J Pediatr*. 2004;163(6):313-319.
7. Hamre MR, Williams J, Chuba P, et al. Early deaths in childhood cancer. *Med Pediatr Oncol*. 2000;34(5):343-347.
8. Burke MJ, Devidas M, Chen Z, et al. Outcomes in adolescent and young adult patients (16 to 30 years) compared to younger patients treated for high-risk B-lymphoblastic leukemia: report from Children's Oncology Group Study AALL0232. *Leukemia*. 2022;36(3):648-655.
9. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from Children's Oncology Group Study AALL0232. *J Clin Oncol*. 2016;34(20):2380-2388.
10. Abrahao R, Keogh RH, Lichtensztajn DY, et al. Predictors of early death and survival among children, adolescents and young adults with acute myeloid leukaemia in California, 1988-2011: a population-based study. *Br J Haematol*. 2016;173(2):292-302.
11. Alvarez EM, Malogolowkin M, Li Q, et al. Decreased early mortality in young adult patients with acute lymphoblastic leukemia treated at specialized cancer centers in California. *J Oncol Pract*. 2019;15(4):e316-e327.
12. AYA SiteRecode/WHO 2008 definition. https://seer.cancer.gov/ayarecode/aya-who2008.html. Accessed April 1, 2022.
13. Grivaux M, Debieuvre D, Herman D, et al. Early mortality in lung cancer: French prospective multicentre observational study. *BMC Pulm Med*. 2016;16:45.
14. Alvarez EM, Malogolowkin M, Hoch JS, et al. Treatment complications and survival among children and young adults with acute lymphoblastic leukemia. *J Clin Oncol Oncol Pract*. 2020;16(10):e1120-e1133.
15. Yu M, Tatalovich Z, Gibson JT, et al. Using a composite index of socioeconomic status to investigate health disparities while protecting the confidentiality of cancer registry data. *Cancer Causes Control*. 2014;25(1):81-92.
16. Liu L, Deapen D, Bernstein L. Socioeconomic status and cancers of the female breast and reproductive organs: a comparison across racial/ethnic populations in Los Angeles County, California (United States). *Cancer Causes Control*. 1998;9(4):369-380.
17. Yost K, Perkins C, Cohen R, et al. Socioeconomic status and breast cancer incidence in California for different race/ethnic groups. *Cancer Causes Control*. 2001;12(8):703-711.
18. Creutzig U, Zimmerman M, Reinhardt D, et al. Analysis of the causes of deaths during the course of intensive initial chemotherapy in the AML-BFM 93 study. *Klin Pediatr*. 2003;215(3):151-158.
19. Prucker C, Attarbaschi A, Peters C, et al.; Austrian Berlin-Frankfurt-Münster (BFM) Study Group. Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of the Austrian Berlin-Frankfurt-Munster study group. *Leukemia*. 2009;23(7):1264-1269.
20. Valcarcel D, Montesinos P, Sanchez-Ortega I, et al.; CETLAM Group. A scoring system to predict the risk of death during induction with anthracycline plus cytarabine-based chemotherapy in patients with de novo acute myeloid leukemia. *Cancer*. 2012;118(2):410-417.
21. Rubnitz JE, Lensing S, Zhou Y, et al. Death during induction therapy and first remission of acute leukemia in childhood: the St. Jude experience. *Cancer*. 2004;101(7):1677-1684.
22. Klein K, van Litsenburg RRL, de Haas V, et al. Causes of early death and treatment-related death in newly diagnosed pediatric acute myeloid leukemia: recent experiences of the Dutch Childhood Oncology Group. *Pediatr Blood Cancer*. 2020;67(4):e28099.
23. O'Brien SN, Blijlevens NMA, Mahfouz TH, et al. Infections in patients with hematological cancer: recent developments. *Hematol Am Soc Hematol Educ Program*. 2003;2003(1):438-472. doi:10.1182/asheducation-2003.1.438:438-72.
24. Canner J, Alonzo TA, Franklin J, et al. Differences in outcomes of newly diagnosed acute myeloid leukemia for adolescent/young adult and younger patients: a report from the Children's Oncology Group. *Cancer*. 2013;119(23):4162-4169.
25. Creutzig U, Zimmermann M, Reinhardt D, et al. Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukemia: analysis of the multicenter clinical trials AML-BFM 93 and AML-BFM 98. *J Clin Oncol*. 2004;22(21):4384-4393.
26. Higdon ML, Atkinson CJ, Lawrence KV. Oncologic emergencies: recognition and initial management. *Am Fam Physician*. 2018;97(11):741-748.
27. Maertens JA, Girmenia C, Bruggemann RJ, et al.; European Conference on Infections in Leukaemia (ECIL), a joint venture of the European Group for Blood and Marrow Transplantation (EBMT), the European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and the European LeukemiaNet (ELN). European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J Antimicrob Chemother*. 2018;73(12):3221-3230.
28. Lehrnbecher T, Fisher BT, Phillips B, et al. Clinical practice guideline for systemic antifungal prophylaxis in pediatric patients with cancer and hematopoietic stem-cell transplantation recipients. *J Clin Oncol*. 2020;38(27):3205-3216.
29. Ren J, Tong YM, Cui RX, et al. Comparison of survival between adolescent and young adult vs older patients with hepatocellular carcinoma. *World J Gastrointest Oncol*. 2020;12(12):1394-1406.
30. Wong E, Goh W, Hong J, et al. Characteristics and prognosis of gastric cancer (GC) in adolescents and young adults (AYA) in Singapore. *Ann Oncol*. 2020;31:S918.
31. Waters AM, Maizlin II, Russell RT, et al. Pancreatic islet cell tumors in adolescents and young adults. *J Pediatr Surg*. 2019;54(10):2103-2106.
32. Bhutada JS, Hwang A, Liu LH, et al. Poor-prognosis metastatic cancers in adolescents and young adults: incidence patterns, trends, and disparities. *JNCI Cancer Spectrum*. 2021;5(3): pkab039.
33. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394-424.
34. Sgouros J, Maraveyas A. Excess premature (3-month) mortality in advanced pancreatic cancer could be related to fatal vascular thromboembolic events. A hypothesis based on a systematic review of phase III chemotherapy studies in advanced pancreatic cancer. *Acta Oncol*. 2008;47(3):337-346.
35. Yang Y, Chen ZJ, Yan S. The incidence, risk factors and predictive nomograms for early death among patients with stage IV

gastric cancer: a population-based study. *J Gastrointest Oncol*. 2020;11(5):964-982.
36. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol*. 2012;30(15):1829-1834.
37. Keegan THM, Parsons HM, Chen Y, et al. Impact of health insurance on stage at cancer diagnosis among adolescents and young adults. *J Natl Cancer Inst*. 2019;111(11):1152-1160.
38. Johnson KJ, Wang X, Barnes JM, et al. Associations between geographic residence and US adolescent and young adult cancer stage and survival. *Cancer*. 2021;127(19):3640-3650.
39. Berkman AM, Andersen CR, Puthenpura V, et al. Impact of race, ethnicity, and socioeconomic status over time on the long-term survival of adolescent and young adult Hodgkin lymphoma survivors. *Cancer Epidemiol Biomarkers Prev*. 2021;30(9):1717-1725.
40. Berkman AM, Andersen CR, Puthenpura V, et al. Disparities in the long-term survival of adolescent and young adult diffuse large B cell lymphoma survivors. *Cancer Epidemiol*. 2021;75:102044.
41. Bleyer A. Latest estimates of survival rates of the 24 most common cancers in adolescent and young adult Americans. *J Adolesc Young Adult Oncol*. 2011;1(1):37-42.
42. Burnside C, Hudson T, Williams C, et al. Sex differences in the use of healthcare services among US adults with and without a cancer diagnosis. *Turk J Urol*. 2018;44(4):298-302.
43. Lopes-Ramos CM, Quackenbush J, DeMeo DL. Genome-wide sex and gender differences in cancer. *Front Oncol*. 2020;10:597788.
44. Li CH, Prokopec SD, Sun RX, et al.; PCAWG Consortium. Sex differences in oncogenic mutational processes. *Nat Commun*. 2020;11(1):4330.
45. Henderson JR, Kiernan E, McNeer JL, et al. Patient-reported health-related quality-of-life assessment at the point-of-care with adolescents and young adults with cancer. *J Adolesc Young Adult Oncol*. 2018;7(1):97-102.
46. George M, Smith A, Sabesan S, et al. Physical comorbidities and their relationship with cancer treatment and its outcomes in older adult populations: systematic review. *JMIR Cancer*. 2021;7(4):e26425.
47. Hardy D, Du DY. Socioeconomic and racial disparities in cancer stage at diagnosis, tumor size, and clinical outcomes in a large cohort of women with breast cancer, 2007-2016. *J Racial Ethnic Health Disparities*. 2021;8(4):990-1001.
48. Zhang C, Zhang C, Wang Q, et al. Differences in stage of cancer at diagnosis, treatment, and survival by race and ethnicity among leading cancer types. *JAMA Netw Open*. 2020;3(4):e202950.
49. Holowatyj AN, Lewis MA, Pannier ST, et al. Clinicopathologic and racial/ethnic differences of colorectal cancer among adolescents and young adults. *Clin Transl Gastroenterol*. 2019;10(7):e00059.
50. Hurst Z, Liyanarachchi S, He H, et al. Risk haplotypes uniquely associated with radioiodine-refractory thyroid cancer patients of high African ancestry. *Thyroid*. 2019;29(4):530-539.
51. Han HS, Reis IM, Zhao W, et al. Racial differences in acute toxicities of neoadjuvant or adjuvant chemotherapy in patients with early-stage breast cancer. *Eur J Cancer*. 2011;47(17):2537-2545.
52. Smith EC, Ziogas A, Anton-Culver H. Association between insurance and socioeconomic status and risk of advanced stage Hodgkin lymphoma in adolescents and young adults. *Cancer*. 2012;118(24):6179-6187.
53. Abdelsattar ZM, Hendren S, Wong SL. The impact of health insurance on cancer care in disadvantaged communities. *Cancer*. 2017;123(7):1219-1227.
54. Petridou ET, Sergentanis TN, Perlepe C, et al. Socioeconomic disparities in survival from childhood leukemia in the United States and globally: a meta-analysis. *Ann Oncol*. 2015;26(3):589-597.
55. Syse A, Lyngstad TH, Kravdal O. Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study. *Int J Cancer*. 2012;130(8):1870-1878.
56. Moss JL, Johnson NJ, Yu M, et al. Comparisons of individual- and area-level socioeconomic status as proxies for individual-level measures: evidence from the Mortality Disparities in American Communities study. *Popul Health Metr*. 2021;19(1):1.