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Disparities in survival improvement for U.S. childhood and adolescent cancer between 1995 and 2019: An analysis of population-based data

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ABSTRACT

Background: Although treatment advances have increased childhood and adolescent cancer survival, whether patient subgroups have benefited equally from these improvements is unclear.
Methods: Data on 42,865 malignant primary cancers diagnosed between 1995 and 2019 in individuals ≤ 19 years were obtained from 12 Surveillance, Epidemiology, and End Results registries. Hazard ratios (HRs) and 95 % confidence intervals (CIs) for cancer-specific mortality by age group (0–14 and 15–19 years), sex, and race/ethnicity were estimated using flexible parametric models with a restricted cubic spline function in each of the periods: 2000–2004, 2005–2009, 2010–2014 and 2015–2019, versus 1995–1999. Interactions between diagnosis period and age group (children 0–14 and adolescents 15–19 years at diagnosis), sex, and race/ethnicity were assessed using likelihood ratio tests. Five-year cancer-specific survival rates for each diagnosis period were further predicted.
Results: Compared with the 1995–1999 cohort, the risk of dying from all cancers combined decreased in subgroups defined by age, sex and race/ethnicity with HRs ranging from 0.50 to 0.68 for the 2015–2019 comparison. HRs were more variable by cancer subtype. There were no statistically significant interactions by age group ($P_{interaction}$=0.05) or sex ($P_{interaction}$=0.71). Despite non-significant differences in cancer-specific survival improvement across different races and ethnicities ($P_{interaction}$=0.33) over the study period, minorities consistently experienced inferior survival compared with non-Hispanic Whites.
Conclusions: The substantial improvements in cancer-specific survival for childhood and adolescent cancer did not differ significantly by different age, sex, and race/ethnicity groups. However, persistent gaps in survival between minorities and non-Hispanic Whites are noteworthy.

1. Introduction

Cancer is the leading cause of disease-related death among U.S. children and adolescents [1,2]. Monitoring cancer survival over time is an essential part of cancer control. It includes assessing the presence of survival disparities, shifts in stage at diagnosis, and evaluating the effect of new therapies. During the past few decades, the overall five- and ten-year survival rates for childhood and adolescent cancer have increased to approximately 86 % and 82 %, respectively, largely due to the substantial improvements in cancer treatment, supportive care, and high clinical trial participation rates [3]. Treatment successes for childhood and adolescent cancer can be partly attributed to the use of integrated, multimodality treatment approaches that include surgery, radiation, and combination chemotherapy, which has become the standard treatment for most childhood solid tumors, as well as to the development and use of novel biologically-based approaches (e.g., immunotherapy) and agents (e.g., bevacizumab and bortezomib) [4,5]. However, the benefits of these advances for cancer patients are determined by many factors, including demographics, socioeconomic status, and access to care [2,6–10].

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Table 1
Demographic characteristics of children and adolescents with cancer according to year of diagnosis in 12 SEER registries, 1995–2019 (N = 42,865).

Characteristics	Year of diagnosis				
	1995–1999 N (%)	2000–2004 N (%)	2005–2009 N (%)	2010–2014 N (%)	2015–2019 N (%)
Age					
< 1 year	520 (7.0)	591 (7.1)	638 (7.3)	655 (7.1)	579 (6.3)
1–4 years	1961 (26.5)	2038 (24.6)	2133 (24.3)	2213 (24.1)	2145 (23.3)
5–9 years	1340 (18.1)	1432 (17.3)	1458 (16.6)	1590 (17.3)	1580 (17.2)
10–14 years	1405 (19.0)	1624 (19.6)	1707 (19.4)	1763 (19.2)	1915 (20.8)
15–19 years	2177 (29.4)	2602 (31.4)	2858 (32.5)	2952 (32.2)	2989 (32.5)
Sex					
Female	3421 (46.2)	3758 (45.3)	4027 (45.8)	4295 (46.8)	4272 (46.4)
Male	3982 (53.8)	4529 (54.7)	4767 (54.2)	4878 (53.2)	4936 (53.6)
Race/ethnicity					
Non-Hispanic White	4152 (56.1)	4320 (52.1)	4298 (48.9)	4174 (45.5)	4088 (44.4)
Non-Hispanic Black	592 (8.0)	684 (8.3)	735 (8.4)	778 (8.5)	751 (8.2)
Non-Hispanic Asian or Pacific Islander	546 (7.4)	731 (8.8)	888 (10.1)	1045 (11.4)	1069 (11.6)
Non-Hispanic American Indian/Alaska Native	73 (1.0)	85 (1.0)	87 (1.0)	79 (0.9)	85 (0.9)
Non-Hispanic Unknown Race	70 (0.9)	63 (0.8)	78 (0.9)	103 (1.1)	183 (2.0)
Hispanic	1970 (26.6)	2404 (29.0)	2708 (30.8)	2994 (32.6)	3032 (32.9)
County-level median household income					
<$65,000	3015 (40.7)	3517 (42.4)	2460 (28.0)	4569 (49.8)	2066 (22.4)
$65,000 - $74,999	1730 (23.4)	1608 (19.4)	3397 (38.6)	1873 (20.4)	3923 (42.6)
$75,000 +	2658 (35.9)	3162 (38.2)	2937 (33.4)	2731 (29.8)	3219 (35.0)
Rural/urban residence					
Metropolitan area > 1 million population	4974 (67.2)	5140 (62.0)	5705 (64.9)	6004 (65.5)	6014 (65.3)
Metropolitan area ≤ 1million population	1610 (21.7)	2370 (28.6)	2383 (27.1)	2456 (26.8)	2475 (26.9)
Non-metropolitan area	819 (11.1)	777 (9.4)	706 (8.0)	713 (7.8)	719 (7.8)
Cancer type[a]					
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	2073 (28.0)	2266 (27.4)	2450 (27.9)	2465 (26.9)	2450 (26.6)
Lymphomas and reticuloendothelial neoplasms	1024 (13.9)	1154 (13.9)	1224 (13.9)	1548 (16.9)	1470 (16.0)
CNS and miscellaneous intracranial and intraspinal neoplasms	1252 (16.9)	1470 (17.8)	1447 (16.5)	1460 (15.9)	1389 (15.1)
Neuroblastoma and other peripheral nervous cell tumors	372 (5.0)	386 (4.7)	399 (4.5)	397 (4.3)	395 (4.3)
Retinoblastoma	160 (2.2)	188 (2.3)	172 (2.0)	161 (1.8)	153 (1.7)
Renal tumors	307 (4.2)	276 (3.3)	322 (3.7)	310 (3.4)	309 (3.4)
Hepatic tumors	101 (1.4)	119 (1.4)	149 (1.7)	151 (1.6)	156 (1.7)
Malignant bone tumors	358 (4.8)	416 (5.0)	457 (5.2)	404 (4.4)	468 (5.1)
Soft tissue and other extraosseous sarcomas	526 (7.1)	563 (6.8)	603 (6.9)	584 (6.4)	579 (6.3)
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	523 (7.1)	615 (7.4)	663 (7.5)	648 (7.1)	604 (6.6)
Other malignant epithelial neoplasms and malignant melanomas	665 (9.0)	801 (9.7)	876 (10.0)	1007 (11.0)	1190 (12.9)
Other and unspecified malignant neoplasms	30 (0.4)	27 (0.3)	23 (0.3)	27 (0.3)	39 (0.4)

Abbreviations: CNS: central nervous system; SEER: Surveillance, Epidemiology, and End Results.
[a] Categorized based on the International Classification of Childhood Cancer third edition (ICCC-3), 44 cases were not classified by ICCC or were in situ.

Research on demographic differences in survival improvement is limited, particularly concerning whether disparities have decreased over time. It has been reported that younger adult cancer patients experienced greater benefits from recent oncology advances than elderly patients overall over the past two decades [11]. In childhood and adolescent cancers, several studies have reported increased survival over time [12–14]. However, there are pronounced differences in survival across various age, sex, race, and ethnicity groups for many cancers, with relatively poorer survival for racial/ethnic minorities, adolescents, and males [9,13,15–19]. One study reported a greater increase of five-year survival among White children and adolescents than Blacks and the lowest significant improvement among infants for the diagnostic period 1975–1999 [6]. Two recent studies among patients with acute lymphocytic leukemia observed a narrowed gap in survival between Black and White children [2], but a wider gap in survival between children and adolescents/young adults [20].

None of these studies to our knowledge has reported statistical evidence for how temporal trends in cancer survival for U.S. children and adolescents with different demographic characteristics affect the relative magnitude of these survival disparities, which might reflect a potential unequal benefit from medical advances [21]. In the current study, our objective was to examine differences in cancer-specific survival improvement in U.S. childhood and adolescent cancer patients diagnosed between 1995 and 2019 across various age, sex and race/-ethnicity groups.

2. Material and methods

Population. Data for primary cancers diagnosed in individuals ≤ 19 years old from 1995 to 2019 were obtained from 'Incidence - SEER Research Data, 12 Registries, Nov 2021 Sub (1992–2019)' database using SEER*Stat 8.4.1 [22]. This database includes 12 population-based cancer registries: Atlanta, Connecticut, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, and the Alaska Native Tumor Registry [23], covering 12.2 % of the U.S. population [24]. We excluded individuals whose death was reported by autopsy or death certificate only (0.2 %), whose cause of death were missing (0.5 %), or who were missing data on county-level median household income and rural/urban residence (1.2 %).

Variables. The primary outcome was death caused by cancer, defined using the 'SEER cause-specific death classification' variable [25]. Survival months were defined as the months from the initial diagnosis to the earliest date of death, last known contact, or the end of the observation (December 31, 2019) using the 'Survival months' variable. Because survival time was recorded in months and cases with less than one month of follow-up were coded as 0, an average survival time of 0.5 months was added to those cases to retain these cases in the analyses. The following 5-year periods were used to define our primary variable of interest, 1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2019. Potential confounders were identified based on the satisfaction of the back-door criterion in a directed acyclic graph (DAG),

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Table 2
Hazard ratios and 95 % CIs of cancer-specific mortality associated with diagnosis year period according to age at diagnosis by cancer type*.

Cancer types	N	Year of diagnosis				$P^{a}_{interaction}$
		2000–2004	2005–2009	2010–2014	2015–2019	
Cancers overall						0.050
Children	29,287	0.85 (0.78, 0.92)	0.74 (0.68, 0.80)	0.62 (0.57, 0.68)	0.58 (0.53, 0.65)	
Adolescents	13,578	0.96 (0.85, 1.08)	0.75 (0.67, 0.85)	0.61 (0.53, 0.69)	0.50 (0.43, 0.59)	
Leukemias, myeloproliferative diseases, and myelodysplastic diseases						0.148
Children	9673	0.83 (0.72, 0.96)	0.61 (0.52, 0.71)	0.52 (0.44, 0.62)	0.48 (0.39, 0.59)	
Adolescents	2031	0.81 (0.65, 1.02)	0.49 (0.38, 0.62)	0.46 (0.37, 0.59)	0.32 (0.24, 0.44)	
Lymphomas and reticuloendothelial neoplasms						0.129
Children	3418	0.71 (0.49, 1.03)	0.56 (0.38, 0.84)	0.40 (0.27, 0.60)	0.23 (0.13, 0.42)	
Adolescents	3002	1.24 (0.88, 1.74)	0.81 (0.56, 1.18)	0.51 (0.33, 0.78)	0.54 (0.33, 0.88)	
CNS and miscellaneous intracranial and intraspinal neoplasms						0.496
Children	5815	0.98 (0.84, 1.13)	0.94 (0.80, 1.09)	0.85 (0.72, 0.99)	0.89 (0.74, 1.07)	
Adolescents	1203	1.05 (0.75, 1.49)	0.83 (0.57, 1.19)	0.83 (0.57, 1.19)	0.64 (0.41, 1.02)	
Neuroblastoma and other peripheral nervous cell tumors						0.386
Children	1894	0.63 (0.48, 0.83)	0.68 (0.51, 0.90)	0.48 (0.35, 0.65)	0.42 (0.28, 0.63)	
Adolescents	55	1.39 (0.34, 5.67)	0.73 (0.16, 3.28)	1.55 (0.43, 5.55)	0.48 (0.05, 4.37)	
Renal tumors						0.796
Children	1442	0.50 (0.29, 0.84)	0.74 (0.47, 1.17)	0.45 (0.26, 0.78)	0.56 (0.31, 1.02)	
Adolescents	82	0.77 (0.15, 3.89)	1.33 (0.32, 5.46)	0.98 (0.21, 4.48)	0.40 (0.04, 3.98)	
Hepatic tumors						0.534
Children	589	0.75 (0.46, 1.22)	0.60 (0.36, 0.98)	0.38 (0.22, 0.65)	0.35 (0.19, 0.63)	
Adolescents	87	0.98 (0.45, 2.14)	0.39 (0.18, 0.84)	0.43 (0.17, 1.13)	0.56 (0.23, 1.40)	
Malignant bone tumors						0.740
Children	1211	0.87 (0.63, 1.20)	0.72 (0.51, 0.99)	0.86 (0.62, 1.19)	0.73 (0.49, 1.09)	
Adolescents	892	0.80 (0.58, 1.10)	0.70 (0.51, 0.96)	0.63 (0.43, 0.90)	0.71 (0.47, 1.07)	
Soft tissue and other extraosseous sarcomas						0.099
Children	1853	0.90 (0.67, 1.20)	1.01 (0.76, 1.33)	0.81 (0.60, 1.09)	0.98 (0.70, 1.37)	
Adolescents	1002	1.12 (0.80, 1.57)	0.89 (0.63, 1.24)	0.67 (0.46, 0.98)	0.58 (0.37, 0.93)	
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads						0.795
Children	1128	0.95 (0.53, 1.72)	0.71 (0.37, 1.37)	0.80 (0.42, 1.53)	0.46 (0.18, 1.15)	
Adolescents	1925	0.82 (0.50, 1.33)	0.91 (0.56, 1.48)	0.68 (0.41, 1.15)	0.63 (0.34, 1.18)	
Other malignant epithelial neoplasms and malignant melanomas						0.784
Children	1297	0.92 (0.53, 1.61)	0.67 (0.37, 1.22)	0.69 (0.39, 1.22)	0.25 (0.10, 0.61)	
Adolescents	3242	0.84 (0.57, 1.23)	0.79 (0.54, 1.15)	0.50 (0.33, 0.77)	0.22 (0.11, 0.41)	

Abbreviations: CI: confidence interval; CNS: central nervous system.
*All hazard ratios were calculated using period 1995–1999 as the reference (hazard ratio=1) and adjusted for sex, race/ethnicity, county level median household income and rural/urban residence; results for retinoblastoma and other and unspecified malignant neoplasms are not shown due to small number of cases and events.
[a] Computed using the likelihood ratio test.

visualized in DAGitty v3.0 [26], which included age at diagnosis, sex, race/ ethnicity, county-level median household income and rural/urban residence (Supplementary Figure 1). Age at diagnosis was categorized as < 1 year, 1–4 years, 5–9 years, 10–14 years, and 15–19 years for model adjustment and further dichotomized into children (<15 years) and adolescents (15–19 years) for subgroup analyses using the 'Age at diagnosis' variable. Sex was defined as male and female using the 'Sex' variable. Race and ethnicity were defined using 'Race and origin recode (NHW, NHB, NHAIAN, NHAPI, Hispanic)' variable as non-Hispanic White, non-Hispanic Black, non-Hispanic Asian or Pacific Islander, non-Hispanic American Indian/Alaska Native, non-Hispanic unknown race and Hispanic. Due to the small number of death events among non-Hispanic unknown race cases (12 events out of 497 unknown race cases), we only included this category for model adjustment. County-level median household income was defined using 'Median household income inflation adj to 2019′ [27] and classified into <$65, 000, $65,000 - $74,999, $75,000+. Rural/urban residence was defined using 'Rural-Urban Continuum Code' [28] and grouped as metropolitan area >1 million population, metropolitan area ≤1million population and nonmetropolitan area. Cancer types were defined using the 'ICCC site recode 3rd edition/IARC 2017′ variable, which was based on the third edition of International Classification for Childhood Cancer (ICCC-3) [29]. A total of 44 individuals reported as 'Not classified by ICCC or in situ', together with retinoblastoma and other and unspecified malignant neoplasms, were included in overall analyses but not cancer-specific analyses due to small numbers of cancer cases and death events.

Statistical analyses. Age-adjusted incidence rates for each age, sex and race/ethnicity category and cancer type in each diagnosis period were calculated in SEER*Stat 8.4.1 [22] Rate Session; corresponding 95 % confidence intervals (CIs) were calculated using Tiwari modification [30]. Hazard ratios (HRs) and 95 % CIs for cancer-specific mortality by age at diagnosis, sex, and race/ethnicity were calculated using flexible parametric models with a restricted cubic spline function [31] and covariate adjustment for patients diagnosed during 2000–2004, 2005–2009, 2010–2014, and 2015–2019 compared with those diagnosed at 1995–1999 for cancer overall and by cancer type. The proportional hazards assumption was examined by fitting a Cox proportional hazard model followed by the 'estat phtest' test based on Schoenfeld residuals. Violations of the PH assumption were attributable to age, sex and/or rural/urban residence depending on cancer type. Four to six degrees of freedom were used for the fixed effects in the flexible parametric model depending on cancer type and three degrees of freedom were used for the time-varying effect (i.e., age groups, sex and/or rural/urban residence to account for the non-proportional hazards) based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC) values. Interactions between calendar periods of diagnosis and age at diagnosis (children vs. adolescents), sex, and race/ethnicity were assessed using the likelihood ratio test that compared flexible parametric models with and without the interaction term. Population average five-year cancer-specific survival probability and 95 % CIs for each age, sex and race/ethnicity category in each diagnosis period were further estimated based on flexible parametric models. A two-sided *P* value of 0.05 was considered statistically significant. All statistical analyses were conducted in Stata (Version 17, StataCorp) and scatterplots were generated using R (Version 4.0.5).

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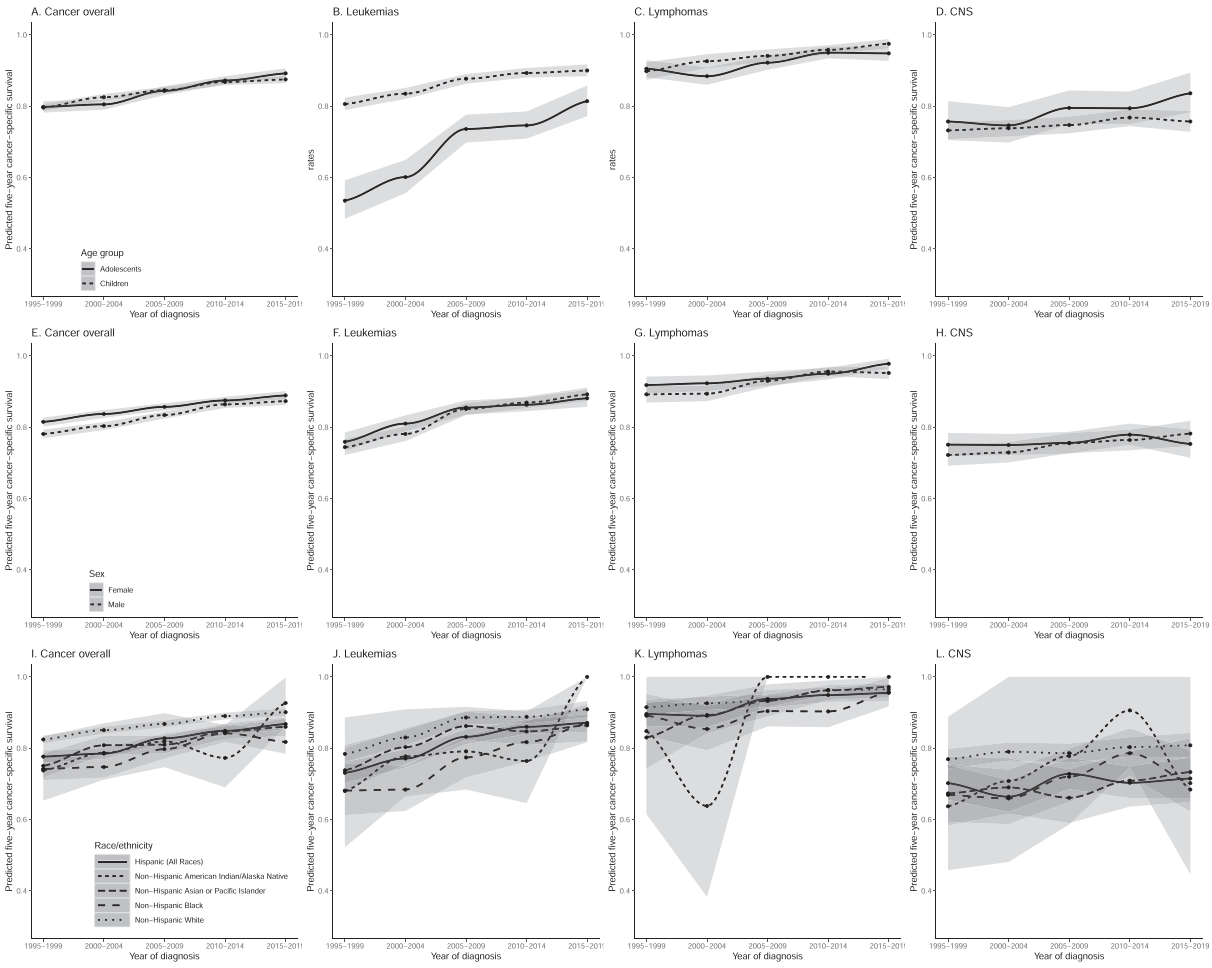

Fig. 1. Five-year cancer-specific survival probabilities by year of diagnosis according to age at diagnosis, sex, and race/ethnicity for childhood and adolescent cancer overall, leukemias, myeloproliferative diseases, and myelodysplastic diseases, lymphomas and reticuloendothelial neoplasms, and CNS and miscellaneous intracranial and intraspinal neoplasms. A-D. Five-year cancer-specific survival probabilities by age group. E-H. Five-year cancer-specific survival probabilities by sex. I-L. Five-year cancer-specific survival probabilities by race/ethnicity. Survival probabilities and 95 % confidence intervals (shaded areas) were estimated from the flexible parametric models with a restricted cubic spline function and visualized in scatterplots with locally weighted scatterplot smoothing (LOESS). Of note, survival probabilities for non-Hispanic American Indian/Alaska Native were largely unstable due to the small number of cases and should be interpreted with caution. Abbreviation: CNS: central nervous system.

3. Results

A total of 42,865 children and adolescents diagnosed with primary cancer from 1995 through 2019 were included in the analyses. From the earliest (1995–1999) to the latest (2015–2019) period, the percentage of cases diagnosed at ages 1–4 years slightly declined from 26.5 % to 23.3 %, while adolescent cases (15–19 years old) increased from 29.4 % to 32.5 %. The percentage of non-Hispanic White cases decreased from 56.1 % to 44.4 % and Hispanic cases steadily increased from 26.6 % to 32.9 %. Cases with county-level median household income below $65,000 decreased from 40.7 % to 22.4 %, while those with median household income between $65,000 and $74,999 increased from 23.4 % to 42.6 %. No specific patterns were found for sex, rural/urban residence, and cancer types (Table 1). The age-adjusted incidence rates generally increased over the study period across most demographic groups and cancer types. Incidence rates for cancers with localized stage increased over time, while incidence rates for cancers with distant stage decreased (Supplementary Table 1).

The cancer-specific mortality decreased significantly over time for both children and adolescents with cancer as shown by decreasing hazard ratios over time with significant mortality reduction in the 2015–2019 vs. the 1995–1999 cohort. Specifically, compared with the 1995–1999 cohort, children and adolescents in the 2015–2019 cohort experienced a 42 % (HR=0.58, 95 %CI: 0.53–0.65) and 50 % (HR=0.50, 95 %CI: 0.43–0.59) mortality reduction (Table 2). These reductions were observed across most cancer types including leukemias, myeloproliferative diseases, and myelodysplastic diseases; lymphomas, and reticuloendothelial neoplasms; and other malignant epithelial neoplasms and malignant melanomas for both children and adolescents diagnosed in the latest period between 2015 and 2019 vs. between 1995 and 1999 (Table 2). Among those with neuroblastoma and other peripheral nervous cell tumors and hepatic tumors, children but not adolescents experienced significant mortality reductions in the 2015–2019 vs. the 1995–1999 diagnosis cohorts. However, this finding is subject to small numbers of adolescent cases and might be unstable. The opposite findings were observed among those with soft tissue and other extraosseous sarcomas, where only adolescents had a significant mortality reduction in the 2015–2019 diagnosis cohort vs. the 1995–1999 cohort. Despite not finding significant differences in mortality reductions between children and adolescents for all cancers combined ($P_{interaction}$=0.05) and across cancer types (all $P_{interaction}$>0.05, Table 2), evidence for closing gaps in survival between children and adolescents with leukemias, myeloproliferative diseases, and myelodysplastic diseases is emerging (Fig. 1 & Supplementary Table 2). Of note, the

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Table 3
Hazard ratios and 95 % CIs of cancer-specific mortality associated with year of diagnosis according to sex by cancer type*.

Cancer types	N	Year of diagnosis				$P^{a}_{interaction}$
		2000–2004	2005–2009	2010–2014	2015–2019	
Cancers overall						0.713
Male	23,092	0.88 (0.81, 0.97)	0.73 (0.67, 0.80)	0.59 (0.54, 0.65)	0.55 (0.49, 0.62)	
Female	19,773	0.87 (0.78, 0.96)	0.75 (0.67, 0.83)	0.64 (0.58, 0.72)	0.57 (0.49, 0.65)	
Leukemias, myeloproliferative diseases, and myelodysplastic diseases						0.429
Male	6603	0.83 (0.71, 0.97)	0.53 (0.47, 0.63)	0.46 (0.38, 0.55)	0.37 (0.30, 0.46)	
Female	5101	0.75 (0.62, 0.91)	0.55 (0.45, 0.68)	0.51 (0.42, 0.63)	0.44 (0.34, 0.57)	
Lymphomas and reticuloendothelial neoplasms						0.252
Male	3829	0.98 (0.72, 1.34)	0.63 (0.45, 0.90)	0.39 (0.27, 0.57)	0.43 (0.27, 0.66)	
Female	2591	0.94 (0.62, 1.43)	0.77 (0.49, 1.19)	0.59 (0.37, 0.94)	0.26 (0.13, 0.53)	
CNS and miscellaneous intracranial and intraspinal neoplasms						0.518
Male	3808	0.97 (0.81, 1.16)	0.86 (0.71, 1.04)	0.83 (0.68, 1.00)	0.75 (0.60, 0.95)	
Female	3210	1.00 (0.82, 1.23)	0.98 (0.79, 1.21)	0.87 (0.70, 1.08)	0.99 (0.77, 1.27)	
Neuroblastoma and other peripheral nervous cell tumors						0.025
Male	1031	0.87 (0.62, 1.23)	0.89 (0.63, 1.27)	0.50 (0.33, 0.75)	0.34 (0.19, 0.61)	
Female	918	0.46 (0.30, 0.72)	0.52 (0.34, 0.79)	0.51 (0.33, 0.78)	0.49 (0.29, 0.83)	
Renal tumors						0.354
Male	683	0.45 (0.20, 0.99)	1.05 (0.57, 1.93)	0.61 (0.30, 1.27)	0.67 (0.30, 1.51)	
Female	841	0.57 (0.30, 1.09)	0.54 (0.29, 1.01)	0.39 (0.19, 0.79)	0.37 (0.16, 0.85)	
Hepatic tumors						0.817
Male	387	0.76 (0.45, 1.29)	0.43 (0.26, 0.72)	0.34 (0.19, 0.62)	0.31 (0.16, 0.62)	
Female	289	0.98 (0.50, 1.92)	0.69 (0.33, 1.42)	0.43 (0.20, 0.92)	0.53 (0.25, 1.13)	
Malignant bone tumors						0.951
Male	1250	0.82 (0.61, 1.09)	0.71 (0.53, 0.94)	0.77 (0.56, 1.04)	0.76 (0.53, 1.09)	
Female	853	0.87 (0.60, 1.27)	0.71 (0.48, 1.04)	0.71 (0.47, 1.06)	0.65 (0.40, 1.06)	
Soft tissue and other extraosseous sarcomas						0.279
Male	1555	0.84 (0.62, 1.12)	0.85 (0.63, 1.14)	0.70 (0.51, 0.95)	0.86 (0.61, 1.22)	
Female	1300	1.19 (0.86, 1.64)	1.08 (0.79, 1.49)	0.81 (0.57, 1.15)	0.72 (0.46, 1.11)	
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads						0.553
Male	1942	0.75 (0.47, 1.19)	0.73 (0.45, 1.16)	0.56 (0.33, 0.94)	0.57 (0.31, 1.05)	
Female	1111	1.08 (0.57, 2.04)	1.03 (0.54, 1.97)	1.11 (0.58, 2.12)	0.61 (0.24, 1.58)	
Other malignant epithelial neoplasms and malignant melanomas						0.153
Male	1512	1.24 (0.78, 1.97)	0.99 (0.62, 1.59)	0.70 (0.42, 1.16)	0.39 (0.20, 0.76)	
Female	3027	0.66 (0.42, 1.03)	0.62 (0.40, 0.97)	0.49 (0.31, 0.78)	0.12 (0.05, 0.30)	

Abbreviations: CI: confidence interval; CNS: central nervous system.
*All hazard ratios were calculated using period 1995–1999 as reference (hazard ratio=1) and adjusted for age, race/ethnicity, county level median household income and rural/urban residence; results for retinoblastoma and other and unspecified malignant neoplasms were not shown due to small number of cases and events.
[a] Computed using likelihood ratio test.

absolute survival difference between children and adolescents was still apparent for leukemias, myeloproliferative diseases, and myelodysplastic diseases (Fig. 1 & Supplementary Table 2).

Both male and female children and adolescents had pronounced reductions in cancer-specific mortality over time for all cancers combined and most cancers, despite generally consistent lower five-year cancer-specific survival rates in males than females (Table 3 & Fig. 1 & Supplementary Table 3). The risk of cancer-specific death decreased 45 % (HR=0.55, 95 %CI: 0.49–0.62) for males and 43 % (HR=0.57, 95 %CI: 0.49–0.65) for females among those diagnosed during 2015–2019 vs. 1995–1999 (Table 3). These mortality reductions for both males and females were also found for leukemias, myeloproliferative diseases, and myelodysplastic diseases; lymphomas, and reticuloendothelial neoplasms; neuroblastoma and other peripheral nervous cell tumors; and other malignant epithelial neoplasms and malignant melanomas. No statistically significant differences were found in sex-associated mortality reductions based on the interactions between calendar periods of diagnosis and sex for cancers overall ($P_{interaction}$ =0.71) and across most cancer types (all $P_{interaction} > 0.1$). Exceptions include neuroblastoma and other peripheral nervous cell tumors, for which males experienced a steady mortality reduction over time, while females had a stagnant reduction in mortality since the 2000–2004 cohort ($P_{interaction}$ =0.025, Table 3). Specifically, male five-year cancer-specific survival steadily increased from 0.71 (95 % CI: 0.65–0.77) in the 1995–1999 cohort to 0.89 (95 %CI: 0.83–0.94) in the 2015–2019 cohort, while female five-year cancer-specific survival probabilities increased from 0.70 (95 % CI: 0.64–0.76) in the 1995–1999 cohort to 0.83–0.84 in the 2000–2004 cohort and onward (Supplementary Table 3).

The risk of dying from cancer for non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Asian/Pacific Islanders and Hispanics decreased 46 % (HR=0.54, 95 %CI: 0.47–0.62), 32 % (HR=0.68, 95 %CI: 0.53–0.87), 48 % (HR=0.52, 95 %CI: 0.41–0.67), and 44 % (HR=0.56, 95 %CI: 0.48–0.66) in the 2015–2019 vs. the 1995–1999 diagnosis cohorts, respectively (Table 4). Despite the significant mortality reduction in the 2015–2019 cohort vs. the 1995–1999 cohort in non-Hispanic American Indians/Alaska Natives (HR=0.25, 95 %CI: 0.09–0.71), these estimates should be interpreted cautiously due to small case numbers (ranging from 73 to 87 cases in each diagnosis period for all cancers combined). In addition, the survival gap between non-Hispanic Blacks and Whites seemed to be widening in the last diagnosis cohort, possibly attributed to CNS and miscellaneous intracranial and intraspinal neoplasms; neuroblastoma and other peripheral nervous cell tumors; renal tumors; malignant bone tumors; and soft tissue and other extraosseous sarcomas (Fig. 1 & Supplementary Table 4). However, we did not find significant differences in mortality reductions by race/ethnicity for all cancers combined ($P_{interaction}$ =0.33) and most cancer types (Table 4). We found significant effect modification by race/ethnicity for other malignant epithelial neoplasms and malignant melanomas ($P_{interaction}$ =0.028, Table 4), with non-significant differences in mortality for later periods vs. the earliest period in non-Hispanic Asians and Blacks. There were reductions in mortality in later periods vs. the earliest period for Non-Hispanic Whites and Hispanics. However, given the high survival probability for this tumor category (Supplementary Table 4), this finding should be interpreted cautiously regarding differences in survival improvement across time by race/ethnicity.

Despite the non-significant differences in mortality reductions across

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Table 4
Hazard ratios and 95 %CIs of cancer-specific mortality associated with year of diagnosis according to race/ethnicity by cancer type*.

Cancer types	N	Year of diagnosis				$P^{a}_{interaction}$
		2000–2004	2005–2009	2010–2014	2015–2019	
Cancers overall						0.332
Non-Hispanic White	21,032	0.84 (0.76, 0.92)	0.73 (0.66, 0.81)	0.60 (0.54, 0.67)	0.54 (0.47, 0.62)	
Non-Hispanic Black	3540	0.98 (0.80, 1.19)	0.76 (0.61, 0.93)	0.57 (0.46, 0.72)	0.68 (0.53, 0.87)	
Non-Hispanic Asian/Pacific Islander	4279	0.74 (0.59, 0.92)	0.73 (0.59, 0.91)	0.57 (0.46, 0.72)	0.52 (0.41, 0.67)	
Non-Hispanic American Indian/Alaska Native	409	0.78 (0.44, 1.40)	0.65 (0.35, 1.20)	0.83 (0.46, 1.51)	0.25 (0.09, 0.71)	
Hispanic	13,108	0.96 (0.85, 1.08)	0.74 (0.66, 0.84)	0.64 (0.57, 0.73)	0.56 (0.48, 0.66)	
Leukemias, myeloproliferative diseases, and myelodysplastic diseases						0.478
Non-Hispanic White	4894	0.76 (0.63, 0.92)	0.49 (0.39, 0.61)	0.47 (0.38, 0.60)	0.38 (0.28, 0.51)	
Non-Hispanic Black	758	0.99 (0.66, 1.47)	0.66 (0.42, 0.99)	0.51 (0.32, 0.81)	0.35 (0.20, 0.60)	
Non-Hispanic Asian/Pacific Islander	1231	0.71 (0.47, 1.07)	0.47 (0.31, 0.73)	0.53 (0.35, 0.79)	0.46 (0.29, 0.75)	
Non-Hispanic American Indian/Alaska Native	138	0.64 (0.24, 1.71)	0.59 (0.22, 1.58)	0.68 (0.25, 1.83)	-	
Hispanic	4574	0.82 (0.68, 0.99)	0.57 (0.47, 0.70)	0.46 (0.38, 0.57)	0.43 (0.33, 0.55)	
Lymphomas and reticuloendothelial neoplasms						0.690
Non-Hispanic White	3277	0.87 (0.60, 1.24)	0.78 (0.54, 1.14)	0.42 (0.27, 0.66)	0.40 (0.23, 0.69)	
Non-Hispanic Black	627	1.37 (0.66, 2.86)	0.88 (0.42, 1.84)	0.89 (0.42, 1.88)	0.38 (0.12, 1.19)	
Non-Hispanic Asian/Pacific Islander	618	0.61 (0.28, 1.34)	0.37 (0.15, 0.92)	0.21 (0.08, 0.85)	0.15 (0.04, 0.54)	
Non-Hispanic American Indian/Alaska Native	38	-	-	-	-	
Hispanic	1767	1.05 (0.66, 1.68)	0.58 (0.33, 1.02)	0.47 (0.28, 0.81)	0.42 (0.22, 0.82)	
CNS and miscellaneous intracranial and intraspinal neoplasms						0.645
Non-Hispanic White	3891	0.90 (0.74, 1.09)	0.92 (0.76, 1.12)	0.83 (0.68, 1.03)	0.81 (0.64, 1.04)	
Non-Hispanic Black	639	1.04 (0.69, 1.56)	0.81 (0.53, 1.26)	0.60 (0.37, 0.95)	0.88 (0.55, 1.39)	
Non-Hispanic Asian/Pacific Islander	593	0.94 (0.58, 1.51)	1.05 (0.66, 1.66)	0.87 (0.53, 1.41)	0.78 (0.46, 1.34)	
Non-Hispanic American Indian/Alaska Native	60	0.76 (0.20, 2.96)	0.56 (0.14, 2.15)	0.22 (0.03, 1.78)	0.84 (0.22, 3.26)	
Hispanic	1758	1.16 (0.90, 1.49)	0.90 (0.68, 1.18)	0.99 (0.77, 1.30)	0.95 (0.69, 1.29)	
Neuroblastoma and other peripheral nervous cell tumors						0.805
Non-Hispanic White	1042	0.57 (0.39, 0.83)	0.57 (0.39, 0.84)	0.39 (0.25, 0.61)	0.40 (0.23, 0.69)	
Non-Hispanic Black	212	0.59 (0.25, 1.42)	1.25 (0.62, 2.52)	0.60 (0.27, 1.32)	0.92 (0.27, 2.51)	
Non-Hispanic Asian/Pacific Islander	201	-	0.45 (0.07, 2.76)	0.58 (0.24, 1.38)	0.36 (0.13, 1.03)	
Non-Hispanic American Indian/Alaska Native	13	-	-	-	-	
Hispanic	459	0.76 (0.45, 1.29)	0.67 (0.38, 1.22)	0.66 (0.38, 1.17)	0.43 (0.20, 0.96)	
Renal tumors						0.510
Non-Hispanic White	756	0.35 (0.15, 0.78)	0.52 (0.26, 1.03)	0.46 (0.22, 0.99)	0.53 (0.23, 1.19)	
Non-Hispanic Black	223	0.70 (0.23, 2.09)	0.79 (0.29, 2.15)	0.41 (0.12, 1.35)	1.09 (0.36, 3.30)	
Non-Hispanic Asian/Pacific Islander	95	-	0.45 (0.07, 2.76)	0.71 (0.14, 3.56)	0.53 (0.07, 3.19)	
Non-Hispanic American Indian/Alaska Native	19	-	-	-	-	
Hispanic	418	0.92 (0.39, 2.19)	1.29 (0.60, 2.79)	0.55 (0.20, 1.50)	0.12 (0.02, 0.94)	
Hepatic tumors						0.108
Non-Hispanic White	289	0.88 (0.48, 1.61)	0.43 (0.23, 0.81)	0.26 (0.12, 0.54)	0.37 (0.17, 0.81)	
Non-Hispanic Black	51	6.34 (1.53, 26.3)	0.79 (0.22, 2.78)	0.85 (0.21, 3.46)	0.59 (0.14, 2.39)	
Non-Hispanic Asian/Pacific Islander	103	1.27 (0.47, 3.40)	0.33 (0.12, 0.90)	0.49 (0.16, 1.49)	0.08 (0.01, 0.65)	
Non-Hispanic American Indian/Alaska Native	10	0.53 (0.03, 9.17)	-	0.26 (0.12, 0.54)	-	
Hispanic	216	0.36 (0.14, 0.96)	0.58 (0.26, 1.28)	0.44 (0.19, 0.99)	0.61 (0.26, 1.41)	
Malignant bone tumors						0.530
Non-Hispanic White	1071	1.03 (0.75, 1.41)	0.79 (0.57, 1.09)	0.67 (0.47, 0.96)	0.63 (0.40, 0.99)	
Non-Hispanic Black	187	0.44 (0.20, 0.95)	0.38 (0.17, 0.85)	0.41 (0.17, 0.97)	0.70 (0.30, 1.68)	
Non-Hispanic Asian/Pacific Islander	219	0.94 (0.43, 2.08)	0.97 (0.45, 2.09)	1.03 (0.47, 2.22)	0.97 (0.42, 2.24)	
Non-Hispanic American Indian/Alaska Native	21	-	-	-	-	
Hispanic	597	0.71 (0.46, 1.10)	0.64 (0.42, 0.98)	0.87 (0.56, 1.34)	0.79 (0.48, 1.29)	
Soft tissue and other extraosseous sarcomas						0.580
Non-Hispanic White	1367	0.90 (0.65, 1.24)	0.92 (0.67, 1.26)	0.88 (0.62, 1.24)	0.76 (0.49, 1.18)	
Non-Hispanic Black	358	1.19 (0.66, 2.14)	0.97 (0.53, 1.77)	0.57 (0.27, 1.17)	1.04 (0.51, 2.12)	
Non-Hispanic Asian/Pacific Islander	263	0.85 (0.38, 1.92)	1.20 (0.61, 2.36)	0.65 (0.31, 1.36)	0.83 (0.38, 1.82)	
Non-Hispanic American Indian/Alaska Native	28	-	-	-	-	
Hispanic	814	0.96 (0.64, 1.44)	0.86 (0.57, 1.30)	0.68 (0.45, 1.05)	0.75 (0.46, 1.23)	
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads						0.196
Non-Hispanic White	1351	0.86 (0.46, 1.62)	0.93 (0.49, 1.77)	0.88 (0.43, 1.82)	1.40 (0.66, 2.96)	
Non-Hispanic Black	147	0.43 (0.13, 1.42)	0.13 (0.02, 1.02)	0.51 (0.15, 1.71)	0.26 (0.03, 2.11)	
Non-Hispanic Asian/Pacific Islander	385	0.50 (0.20, 1.26)	0.62 (0.26, 1.47)	0.52 (0.21, 1.26)	0.24 (0.05, 1.09)	
Non-Hispanic American Indian/Alaska Native	25	-	-	-	-	
Hispanic	1119	1.32 (0.72, 2.42)	0.99 (0.54, 1.86)	0.74 (0.38, 1.43)	0.47 (0.20, 1.10)	
Other malignant epithelial neoplasms and malignant melanomas						0.028
Non-Hispanic White	2678	0.88 (0.59, 1.32)	0.73 (0.48, 1.13)	0.38 (0.22, 0.65)	0.13 (0.05, 0.35)	
Non-Hispanic Black	230	1.59 (0.49, 5.15)	1.39 (0.42, 4.57)	1.11 (0.33, 3.73)	0.45 (0.08, 2.50)	
Non-Hispanic Asian/Pacific Islander	445	1.33 (0.32, 5.58)	2.68 (0.77, 9.37)	1.61 (0.44, 5.78)	1.15 (0.27, 4.82)	
Non-Hispanic American Indian/Alaska Native	40	-	-	-	-	
Hispanic	1043	0.88 (0.46, 1.67)	0.57 (0.29, 1.12)	0.55 (0.29, 1.04)	0.24 (0.10, 0.58)	

Abbreviations: CI: confidence interval; CNS: central nervous system.
*All hazard ratios were calculated using period 1995–1999 as the reference (hazard ratio=1) and adjusted for age, sex, county level median household income and rural/urban residence; results for retinoblastoma, other and unspecified malignant neoplasms and for non-Hispanic American Indian/Alaska Native population were not shown due to small number of cases and events.
[a] Computed using likelihood ratio test.

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cancer types, potential gaps for minority groups in a few cancer types are noteworthy. For example, non-Hispanic Blacks with hepatic tumors in general did not experience mortality reductions over time. However, these findings are subject to small numbers of cases and should be interpreted with caution. Importantly, despite declining mortality for all races and ethnicities, non-Hispanic Whites still had the highest survival rates compared to minorities over time for most cancer types (Fig. 1 & Supplementary Table 4).

4. Discussion

In children and adolescents diagnosed with cancer between 1995 and 2019, we observed substantial reductions in cancer-specific mortality across various age, sex and race/ethnicity groups for all cancers combined, with varying degrees for different cancer types. Although mortality reductions did not differ across these demographic groups, a substantial survival gap between non-Hispanic Whites and minorities is still noteworthy.

A previous comprehensive trend analysis in SEER 9 registries on childhood and adolescent cancer diagnosed between 1975 and 1999 observed a greater increase in five-year cancer survival in White than Black children and adolescents [6]. Another study using SEER 17 registries data reported a continued widened five-year survival gap between Black and White children in years 2001–2007 vs. 1992–2000 among those with acute myeloid leukemia and neuroblastoma [8]. Nevertheless, this finding was not replicated in treatment cohorts at St. Jude Children's Research Hospital, suggesting that the gap observed in SEER population-based data was possibly related to unequal access to comprehensive treatment and supportive care [8]. In contrast to the widened gap in acute myeloid leukemia, another study found that the gap in survival between Black and White children and adolescents with acute lymphocytic leukemia narrowed from a 21 % difference during 1980–1984 to a 6 % difference during 2003–2009 using data from SEER 9 database [2]. Another recent study documented greater five- and ten-year survival improvements among Black children with acute lymphocytic leukemia compared with White children (annual percent change $[APC]_{\text{five-year survival}}$=3.01 % vs. 1.37 %, $APC_{\text{ten-year survival}}$=3.91 % vs. 2.15 %) but the opposite findings in adolescents and young adults ($APC_{\text{five-year survival}}$=1.25 % vs. 3.13 %, $APC_{\text{ten-year survival}}$=−1.26 % vs. 3.74 %). Among those with acute myeloid leukemia, both White children and adolescents experienced greater five- and ten-year survival improvements than their Black counterparts. While for Hodgkin lymphoma cases, no apparent differences were observed in survival improvements between Blacks and Whites in general [20]. Using the most recent data, the current study provides statistical evidence for differences in cancer-specific mortality reductions in childhood and adolescent cancer by different demographics using data from SEER 12 registries. We observed improvement in survival among both non-Hispanic Whites and non-Hispanic Blacks for all cancers combined and most cancer types, including leukemias and lymphomas. We also observed a widening survival gap between these two groups in the last diagnosis cohort for all cancers combined, however it did not reach statistical significance.

The lack of improvement in cancer survival among adolescents and young adults compared with other age groups highlighted in the 2006 landmark report called for an action to *Close the Gap* [32]. Since this report, diverse efforts have been undertaken to improve the outcomes of this particular group, such as improvement of participation in clinical trials [33], advances in effective therapy [34], and establishment of the discipline for adolescent and young adult oncology [35]. Consequently, results from a California Cancer Registry-based study indicated that the improvement in cancer survival for adolescents and young adults had exceeded all other age groups between 1988 and 2014 [32]. Nevertheless, using the most recent data, our study found no statistically significant differences in survival improvements between the two age groups, suggesting modest or parallel survival advances between adolescents and children.

Despite the large and recent analysis of survival improvement disparities in childhood and adolescent cancer, several limitations should be taken into consideration when interpreting these results. First, 12 SEER registries cover a minority of the U.S. population, limiting the generalizability of our findings. In SEER, Hispanic ethnicity was coded based on the North American Association of Central Cancer Registries (NAACCR) Hispanic Identification algorithm by matching the surname and maiden name and tends to under-classify individuals as Hispanic compared to self-identifications [36]. Similarly, American Indian/-Alaska Native patients tend to be under-classified in non-purchased/referred care delivery areas (non-PRCDAs) [37]. The small sample size in this group might lead to statistically unstable estimates and should be interpreted with caution. The effect of registry was not taken into account because this information is not publicly available in the database. Additionally, relying on death certificate and cause of death (COD) can be problematic for cause-specific survival estimates, but it is of less concern in children and adolescents with cancer, given cancer is the leading cause of disease-related death among U.S. children and adolescents. Our findings may be sensitive to potential selection bias resulting from the exclusion of patients with missing data. Multiple hypotheses were also tested in this study, which can increase type 1 errors in interpretation of results. Lastly, the survival rates may be inflated due to the possibility of overdiagnosis and lead time bias for cancers given the generally elevated incidence rates for cancers with localized stage and reduced incidence rates for cancers with distant stage over time [38,39].

5. Conclusions

In conclusion, we observed substantial improvements in cancer-specific survival for childhood and adolescent cancer overall and majority cancer types, however, we did not find statistical evidence for differential improvements by age, sex and race/ethnicity group. Importantly, racial/ethnic disparities in cancer survival are still noted to be substantial. Further studies with large cohorts are warranted to evaluate the disparities in specific cancers and to elucidate their underlying causes.

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CRediT authorship contribution statement

Xiaoyan Wang: conceptualization, formal analysis, methodology, writing–original draft, and writing–review and editing; **Derek S. Brown:** methodology and writing–review and editing; **Yin Cao:** methodology and writing–review and editing; **Christine C. Ekenga:** methodology and writing–review and editing; **Shenyang Guo:** methodology and writing–review and editing; **Kimberly J. Johnson:** conceptualization, methodology and writing–review and editing, and supervision.

Declaration of Competing Interest

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102380.

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