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ORIGINAL REPORT

Temporal Trends in Cause-Specific Late Mortality Among 5-Year Survivors of Childhood Cancer

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ABSTRACT

Purpose
Five-year survival rates for childhood cancer have improved over the past four decades. However, it is unknown whether changes in primary cancer therapy have improved rates of long-term (> 5 years from diagnosis) durable remissions and reduced treatment-related deaths. We investigated changes in patterns of late mortality over time and cause-specific attribution of late-mortality among 5-year survivors.

Patients and Methods
Using data from the Surveillance, Epidemiology and End Results (SEER) population-based registry, we assessed all-cause and cause-specific (recurrence/progression of primary disease, external cause, and nonrecurrence/nonexternal cause) late mortality during four consecutive time periods from 1974 through 2000 among 26,643 5-year survivors of childhood cancer.

Results
All-cause late mortality improved during more recent eras, dropping from 7.1% (95% CI, 6.4% to 7.8%) among children diagnosed during 1974 to 1980 to 3.9% (95% CI, 3.3% to 4.4%) among children diagnosed during 1995 to 2000 ($P < .001$), largely because of reduced mortality from recurrence or progression. While there was no significant reduction in mortality attributable to other health conditions (including treatment-related health conditions), analysis controlling for demographic characteristics identified a trend toward reduced risk during more recent eras ($P = .007$). Disparity by race/ethnicity was identified, with higher mortality among non-Hispanic blacks than among non-Hispanic whites for all-cause and nonrecurrence/nonexternal -cause late mortality.

Conclusion
While overall patterns of mortality from other health conditions do not differ over time, adjustment for demographic characteristics provides evidence that risk of treatment-related mortality may be lower in more recent eras. Disparities in health care utilization among survivors should be explored.

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INTRODUCTION

Improvements in therapies for childhood cancer over the last four decades have resulted in significant increases in 5-year survival rates for most malignancies. The 5-year overall relative survival rate is 79.4% for patients diagnosed between 1999 and 2005.[1] However, long-term survivors of childhood cancer are also at risk of late (> 5 years from diagnosis) mortality.[2-8] During more recent decades, risk stratification of therapeutic intensity has guided primary therapy. In general, primary therapeutic regimens have been intensified for patients with poor prognoses in an attempt to reduce recurrence or progression of primary disease and thus improve long-term survival. Likewise, among patients identified as having a good prognosis, efforts have been directed toward reduction in intensity to prevent long-term morbidity and mortality from toxicity.

While detailed assessments of late mortality have been performed in selected cohorts of 5-year survivors, it remains unknown whether late mortality has declined among survivors of childhood cancer treated during more recent eras.[3-5] Furthermore, assessment of cause-specific attribution of late mortality may be able to identify specific underlying etiologies of late mortality that have changed during more recent eras. Improvement in late mortality attributable specifically to progression of primary disease versus health conditions, including sequelae of cancer therapy, across consecutive time periods has not been assessed. To evaluate these questions,

we used population-based data to describe temporal trends in late mortality over a 27-year period (1974 through 2000). We also report cause-specific mortality in an attempt to explain the contributions of treatment changes to changes in late mortality over time.

PATIENTS AND METHODS

We used data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (http://seer.cancer.gov) for the period 1974 through 2000. Eligibility criteria for inclusion in this analysis were a diagnosis of a malignant neoplasm before age 21 years and survival for 5 years after diagnosis. Diagnostic categories were defined according to the International Classification of Childhood Cancer (ICCC-3). Vital status (as of December 31, 2005) was determined by the National Center for Health Statistics and provided by the SEER program. Underlying cause of death was identified and classified as (1) recurrence/progression of primary malignancy, (2) external causes (eg, injuries, suicide, self-inflicted injury), or (3) nonrecurrence/nonexternal causes (ie, other health conditions, including treatment-related health conditions such as subsequent neoplasms, cardiac conditions, and pulmonary conditions). All cancer deaths were attributed to either primary or subsequent neoplasm. For cumulative mortality analysis, the 27-year period of evaluation was segmented into four consecutive time periods based on date of diagnosis (1974 to 1980, 1981 to 1987, 1988 to 1994, 1995 to 2000). We used Gray's method of accounting for competing risks of death to compare mortality by era.[9] To further explore the effect of race/ethnicity on cumulative mortality, multiple pair-wise comparisons were conducted with Bonferroni correction in two-sided tests ($P \leq .005$ indicated statistical significance). The effects of covariates such as age, sex, and race on the outcome of interest (all-cause mortality, recurrence/progression, or nonrecurrence/nonexternal cause) were estimated by using Fine and Gray's proportional hazards methods, an extension of the Cox proportional hazards model, to account for competing risks.[10] Trend tests were used to assess the change of hazards by consecutive treatment era by incorporating treatment era as a covariate in the model and testing the significance of the regression coefficient. Standardized mortality ratios (SMRs) for 5-year age groups were calculated by using the expected number of deaths based on age-, year-, sex-, and race-specific US mortality rates and the corresponding person-years at risk observed, and then a test of heterogeneity of SMRs was performed.[11] Statistical analyses were performed by using SAS 9.1.3 (SAS, Cary, NC) and R 2.8.0 software packages. All statistical tests were two-sided, and $P \leq .05$ indicated statistical significance.

RESULTS

Among 26,643 eligible 5-year survivors (Table 1), there were 2,076 deaths, resulting in 10-, 15-, 20-, and 25-year all-cause cumulative mortality rates of 5.0%, 7.8%, 10.4%, and 13.7%, respectively. The SMR for all-cause mortality was 8.89 (95% CI, 8.52 to 9.29) (Table 2). All-cause mortality at 10 years from diagnosis declined over time from 7.1% (95% CI, 6.4% to 7.8%) among children diagnosed from 1974 through1980 to 3.9% (95% CI, 3.3% to 4.4%) among children diagnosed from 1995 through 2000 ($P < .001$: Table 3, Fig 1). This improvement in long-term survival by treatment era was true when the primary diagnosis was acute lymphoblastic leukemia (ALL; $P < .001$), Hodgkin's lymphoma ($P < .001$), non-Hodgkin's lymphoma ($P = .006$), or rhabdomyosarcoma ($P = .05$). In contrast, among long-term survivors of osteosarcoma, Ewing sarcoma, or ependymoma, late-mortality rates appear to have increased over time, although changes were statistically significant only for Ewing sarcoma (Fig 1; Data Supplement).

There were 1,147 deaths attributable to primary disease recurrence/progression, 139 deaths from external causes, and 613 deaths from nonrecurrence/nonexternal causes. The 10-year cumulative incidence of mortality attributable to recurrence/progression across treatment eras was 5.1%, 4.1%, 2.8%, and 2.8% ($P < .001$; Table 3). Five-year survivors of ALL or Hodgkin's lymphoma experienced a statistically significant reduction in death rates due to primary malignancy across these time periods (Table 3). The cumulative incidence of mortality attributable to recurrence/progression of primary disease increased over the same periods for patients with osteosarcoma, Ewing sarcoma, ependymoma, and neuroblastoma, although this increase was statistically significant only in Ewing sarcoma ($P = .01$).

Table 1. Life Status of 5-Year Survivors of Childhood Cancer

Status	No. of Patients		
	Eligible Cohort	Alive	Dead
All patients	26,643	24,567	2,076
Sex			
Male	13,754	12,540	1,214
Female	12,889	12,027	862
Treatment era			
1974-1980	4,631	3,806	825
1981-1987	5,284	4,667	617
1988-1994	7,310	6,891	419
1995-2000	9,418	9,203	215
Race/ethnicity			
Non-Hispanic white	18,365	16,881	1,484
Non-Hispanic black	2,331	2,106	225
Hispanic	3,818	3,596	222
Non-Hispanic Asian or Pacific Islander	1,673	1,549	124
Non-Hispanic American Indian/Alaskan native	233	216	17
Age at diagnosis, years			
0-4	7,633	7,196	437
5-9	4,227	3,869	358
10-14	4,565	4,194	371
15-19	8,064	7,341	723
> 19	2,154	1,967	187
Survival after diagnosis, years			
5-9	—	—	1,125
10-14	—	—	406
15-19	—	—	254
20-24	—	—	180
25-29	—	—	104
30-34	—	—	7
Diagnosis			
Acute lymphoblastic leukemia	4,970	4,570	400
Acute myelogenous leukemia	592	549	43
Hodgkin's lymphoma	3,124	2,767	357
Non-Hodgkin's lymphoma	1,505	1,430	75
Astrocytoma	2,241	2,048	193
Medulloblastoma	743	643	100
Ependymoma	274	226	48
Osteosarcoma	643	567	76
Ewing sarcoma	392	333	59
Rhabdomyosarcoma	616	574	42
Neuroblastoma	1,024	973	51
Hepatic tumor	174	165	9
Renal tumors	1,242	1,203	39
Retinoblastoma	637	613	24
Thyroid carcinoma	1,401	1,369	32
Other cancers	7,065	6,537	528

Table 2. All-Cause and Cause-Specific Standardized Mortality Ratios in 5-Year Survivors of Childhood Cancer

Characteristic	All Causes				Subsequent Malignancy				Cardiac Causes				Pulmonary Causes			
	No. of Deaths	SMR	95% CI	P*	No. of Deaths	SMR	95% CI	P*	No. of Deaths	SMR	95% CI	P*	No. of Deaths	SMR	95% CI	P*
All patients	2,076	8.89	8.52 to 9.29		205	8.02	6.96 to 9.19		103	6.05	4.94 to 7.34		29	7.32	4.90 to 10.51	
Sex				< .001				.19				.89				.03
Male	1,214	7.64	7.22 to 8.08		104	8.81	7.20 to 10.68		68	6.12	4.75 to 7.75		21	10.10	6.25 to 15.43	
Female	862	11.57	10.81 to 12.37		101	7.33	5.97 to 8.91		35	5.93	4.13 to 8.25		8	4.25	1.83 to 8.38	
Year of diagnosis				< .001				.04				.03				.83
1974-1980	825	7.52	7.02 to 8.05		121	8.18	6.79 to 9.77		46	4.65	3.40 to 6.20		16	7.70	4.40 to 12.51	
1981-1987	617	8.82	8.14 to 9.54		42	6.29	4.53 to 8.51		40	8.72	6.23 to 11.88		8	7.18	3.09 to 14.15	
1988-1994	419	10.32	9.36 to 11.36		37	11.63	8.19 to 16.04		15	7.47	4.18 to 12.32		3	5.04	1.01 to 14.72	
1995-2000	215	16.35	14.24 to 18.69		5	5.40	1.74 to 12.60		2	3.77	0.42 to 13.63		2	11.47	1.29 to 41.41	
Race/ethnicity				< .001				< .001				.15				.19
White	1,699	8.92	8.50 to 9.36		156	7.12	6.05 to 8.33		87	6.41	5.13 to 7.91		22	7.27	4.55 to 11.00	
Black	229	6.67	5.84 to 7.59		29	10.72	7.18 to 15.40		11	3.71	1.85 to 6.65		4	5.01	1.35 to 12.83	
Asian, Pacific Islander, American Indian, Alaskan native	144	16.60	14.00 to 19.55		20	20.73	12.66 to 32.02		4	8.31	2.24 to 21.28		3	22.25	4.47 to 65.02	

NOTE. As of December 31, 2005. All SMRs were age-, sex-, and race-standardized according to the US mortality rates from the SEER Program. "Subsequent malignancy" refers to a new neoplasm. Cancer deaths resulting from progression of the original cancer are not included in the observed number of events.
Abbreviations: SMR, standardized mortality ratio; SEER, Surveillance, Epidemiology, and End Results.
*P from test for heterogeneity.

No significant decline in late mortality attributable to nonrecurrence/nonexternal causes was identified either in the overall survivor population (1.0%, 1.0%, 0.7%, and 0.8%; $P = .45$) or in any specific diagnostic group (Table 3). While monotonic trends in nonrecurrence/nonexternal cause mortality were seen for survivors of ALL (1.1%, 0.8%, 0.8%, and 0.5%; $P = .28$) or Hodgkin's lymphoma (1.4%, 1.2%, 0.8%, and 0.7%; $P = .48$), these improvements did not reach statistical significance.

Multivariable analyses incorporating demographic factors that may be associated with mortality were conducted (Table 4). Male sex was associated with an increased absolute risk of all-cause mortality (hazard ratio [HR], 1.43; 95% CI, 1.31 to 1.56) and of death from both recurrence/progression (HR, 1.34; 95% CI, 1.19 to 1.51) and nonrecurrence/nonexternal causes (HR, 1.36; 95% CI, 1.16 to 1.60). Compared with non-Hispanic whites, non-Hispanic blacks had an almost two-fold increased risk of death due to nonrecurrence/nonexternal causes (HR, 1.88; 95% CI, 1.49 to 2.37) but not for recurrence/progression (HR, 1.12; 95% CI, 0.91 to 1.37), resulting in an increased all-cause mortality for blacks (HR, 1.38; 95% CI, 1.20 to 1.59). Older age at diagnosis conferred greater risk of mortality from any cause. No interaction between treatment era and race, sex, or age at diagnosis was identified, with the exception of a significant interaction between age at diagnosis and treatment era for recurrence/progression-related mortality ($P = .01$). Of note, however, when treatment era was included in the multivariable model, there was evidence of a decreasing hazard with more modern treatment eras not only for all-cause and recurrence/progression mortality (P for trend $< .001$) but also for nonrecurrence/nonexternal cause mortality (P for trend $= .007$).

Males had a significantly greater cumulative incidence of all-cause and recurrence/progression mortality than did females ($P < .001$). At 10 years from diagnosis, there was no obvious difference between males and females in the incidence of nonrecurrence/nonexternal-cause mortality; however, with continued follow-up, males showed an increasing and significantly greater risk (Appendix Fig A1 and Table A1, online only). Within specific diagnostic groups, no statistically significant sex differences were identified, but sample sizes were small for many assessments. Additionally, non-Hispanic blacks showed increased all-cause and nonrecurrence/nonexternal-cause mortality at 25 years from diagnosis (Fig 2; Table 5). When standardized for the background rate of death in the general population, whites had a higher all-cause SMR than did blacks (8.92 *v* 6.67; Table 2) but a lower SMR for deaths attributable to subsequent malignant neoplasms (7.12 *v* 10.7; $P < .001$), the most common type of nonrecurrence/nonexternal-cause death.

DISCUSSION

These population-based analyses demonstrate a decrease in the cumulative incidence of all-cause mortality over time among children who survive 5 years after their original cancer diagnosis. These findings are consistent with three previous investigations[3,5,8] that explored late mortality in earlier treatment eras (1960-1995). In a population-based study in five Nordic countries, Möller et al[5] reported that patients diagnosed between 1980 and 1989 were at less risk of late mortality (HR, 0.61; 95% CI, 0.54 to 0.70) than those diagnosed between 1960 and 1979. Likewise, in an institution-based study, Hudson et al[3] noted higher mortality rates at 15 years after diagnosis among children diagnosed between 1962 and 1970 compared with those diagnosed between 1971 and 1983 (19.6% *v* 10.5%). Our data add to this evidence and further suggest that modern therapy has improved late mortality for children with the most common cancer types (ALL,

Table 3. 10-Year Cumulative Incidence of Mortality Among 5-Year Survivors of Childhood Cancer

	1974-1980			1981-1987			1988-1994			1995-2000			
Diagnosis	No.	Cumulative Incidence	95% CI	No.	Cumulative Incidence	95% CI	No.	Cumulative Incidence	95% CI	No.	Cumulative Incidence	95% CI	*P**
All-cause													
All diagnoses	4,266	7.1	6.4 to 7.8	4,958	5.8	5.2 to 6.5	6,809	4.0	3.6 to 4.5	2,311	3.9	3.3 to 4.4	< .001
All leukemias	673	15.1	12.6 to 17.6	920	9.7	7.9 to 11.5	1,535	5.0	4.0 to 6.1	543	4.1	3.0 to 5.2	< .001
Acute lymphoblastic leukemia	555	14.8	12.0 to 17.5	805	8.7	6.8 to 10.6	1,306	4.8	3.7 to 5.9	467	4.2	3.0 to 5.4	< .001
Acute myeloid leukemia	59	10.5	3.1 to 17.9	72	10.1	3.4 to 16.8	153	4.9	1.6 to 8.2	59	4.7	0.8 to 8.6	.19
Hodgkin's lymphoma	661	8.4	6.3 to 10.4	647	5.1	3.5 to 6.8	762	3.7	2.4 to 5.0	220	1.5	0.5 to 2.4	< .001
Non-Hodgkin's lymphoma	177	5.9	2.5 to 9.2	300	3.6	1.5 to 5.7	399	1.5	0.3 to 2.7	145	1.2	0.0 to 2.4	.006
All CNS tumors	539	9.0	6.7 to 11.3	679	7.6	5.6 to 9.5	1,040	5.4	4.1 to 6.7	348	7.1	5.0 to 9.2	.17
Astrocytoma	339	6.3	3.8 to 8.8	411	5.1	3.0 to 7.2	631	2.8	1.5 to 4.0	198	5.9	3.0 to 8.7	.13
Medulloblastoma	80	17.6	9.9 to 25.2	112	12.7	6.8 to 18.5	185	7.5	3.8 to 11.2	58	8.7	4.2 to 13.2	.11
Ependymoma	28	10.1	0.0 to 21.2	40	16.9	6.1 to 27.6	66	13.9	6.2 to 21.5	35	13.4	4.8 to 21.9	.61
Osteosarcoma	98	4.8	0.7 to 8.9	108	8.4	3.4 to 13.5	166	11.3	6.7 to 15.9	59	12.3	6.0 to 18.6	.71
Ewing sarcoma	52	7.1	0.3 to 13.8	73	16.5	8.5 to 24.4	104	8.6	3.5 to 13.7	26	8.9	2.9 to 14.9	.03
Rhabdomyosarcoma	96	6.8	1.9 to 11.7	126	6.6	2.4 to 10.8	165	1.8	0.0 to 3.8	61	3.7	0.7 to 6.7	.05
Neuroblastoma	160	4.1	1.1 to 7.1	191	3.5	1.0 to 6.1	284	3.6	1.5 to 5.7	91	4.9	1.9 to 7.9	.65
Hepatic tumors	12	7.1	0.0 to 21.1	36	5.5	0.0 to 13.0	47	2.0	0.0 to 5.8	16	2.6	0.0 to 7.6	.70
Renal tumors	202	1.0	0.0 to 2.3	263	1.1	0.0 to 2.4	348	1.6	0.3 to 2.9	89	1.6	0.0 to 3.2	.49
Retinoblastoma	105	1.9	0.0 to 4.5	120	4.0	0.5 to 7.4	176	1.0	0.0 to 2.5	47	0.9	0.0 to 2.8	.75
Recurrence/progression													
All diagnoses	4,266	5.1	4.5 to 5.8	4,958	4.1	3.5 to 4.6	6,809	2.8	2.4 to 3.2	2,311	2.8	2.3 to 3.3	< .001
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Medulloblastoma	80	13.4	6.6 to 20.3	112	11.1	5.6 to 16.6	185	7.5	3.8 to 11.2	58	6.8	2.9 to 10.8	.18
Ependymoma	28	6.7	0.0 to 15.7	40	12.6	3.1 to 22.2	66	10.1	3.4 to 16.8	35	10.1	2.7 to 17.5	.56
Osteosarcoma	98	2.9	0.0 to 6.1	108	5.9	1.6 to 10.1	166	7.5	3.7 to 11.3	59	8.0	3.2 to 12.9	.78
Ewing sarcoma	52	1.8	0.0 to 5.3	73	14.1	6.7 to 21.6	104	6.0	1.7 to 10.4	26	6.9	1.5 to 12.3	.01
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Neuroblastoma	160	1.8	0.0 to 3.7	191	2.0	0.1 to 4.0	284	2.9	1.0 to 4.8	91	4.9	1.9 to 7.9	.06
Hepatic tumors	12	7.1	0.0 to 21.1	36	2.7	0.0 to 8.0	47	2.0	0.0 to 5.8	16	2.6	0.0 to 7.6	.30
Renal tumors	202	1.0	0.0 to 2.3	263	0.7	0.0 to 1.8	348	1.4	0.2 to 2.6	89	1.3	0.0 to 2.8	.58
Retinoblastoma	105	0.0		120	1.6	0.0 to 3.8	176	0.0		47	0.0		.29
Nonrecurrence/nonexternal cause													
All diagnoses	4,266	1.0	0.7 to 1.3	4,958	1.0	0.8 to 1.3	6,809	0.7	0.5 to 0.9	2,311	0.8	0.5 to 1.0	.45
All leukemias	673	1.1	0.4 to 1.9	920	1.0	0.4 to 1.6	1,535	0.9	0.4 to 1.3	543	0.6	0.2 to 1.0	.39
Acute lymphoblastic leukemia	555	1.1	0.3 to 1.9	805	0.8	0.2 to 1.4	1,306	0.8	0.3 to 1.3	467	0.5	0.1 to 0.9	.28
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Hodgkin's lymphoma	661	1.4	0.5 to 2.3	647	1.2	0.4 to 2.0	762	0.8	0.2 to 1.4	220	0.7	0.0 to 1.4	.48
Non-Hodgkin's lymphoma	177	0.5	0.0 to 1.6	300	1.0	0.0 to 2.1	399	1.2	0.2 to 2.3	145	0.5	0.0 to 1.1	.93
All CNS tumors	539	1.9	0.8 to 3.0	679	1.7	0.7 to 2.6	1,040	0.5	0.1 to 1.0	348	1.2	0.5 to 2.0	.94
Astrocytoma	339	1.1	0.0 to 2.2	411	1.6	0.4 to 2.8	631	0.2	0.0 to 0.4	198	1.0	0.2 to 1.9	.80
Medulloblastoma	80	3.1	0.0 to 6.6	112	1.6	0.0 to 3.8	185	0.0		58	1.4	0.0 to 3.5	.76
Ependymoma	28	3.5	0.0 to 10.2	40	0.0		66	2.5	0.0 to 5.8	35	3.3	0.0 to 8.0	.82
Osteosarcoma	98	1.0	0.0 to 2.8	108	2.6	0.0 to 5.4	166	1.1	0.0 to 2.6	59	1.5	0.0 to 4.5	.97
Ewing sarcoma	52	1.8	0.0 to 5.2	73	1.2	0.0 to 3.5	104	1.7	0.0 to 4.1	26	1.2	0.0 to 3.6	.90
Rhabdomyosarcoma	96	1.9	0.0 to 4.6	126	1.5	0.0 to 3.5	165	0.6	0.0 to 1.8	61	0.0		.42
Neuroblastoma	160	1.8	0.0 to 3.8	191	1.0	0.0 to 2.4	284	0.7	0.0 to 1.6	91	0.0		.31
Hepatic tumors	12	0.0		36	2.8	0.0 to 8.2	47	0.0		16	0.0		.34
Renal tumors	202	0.0		263	0.0		348	0.0		89	0.3	0.0 to 0.9	.21
Retinoblastoma	105	0.9	0.0 to 2.8	120	0.8	0.0 to 2.3	176	0.5	0.0 to 1.5	47	0.9	0.0 to 2.8	.76

*Based on the comparison of cumulative mortality curves for the four time periods.

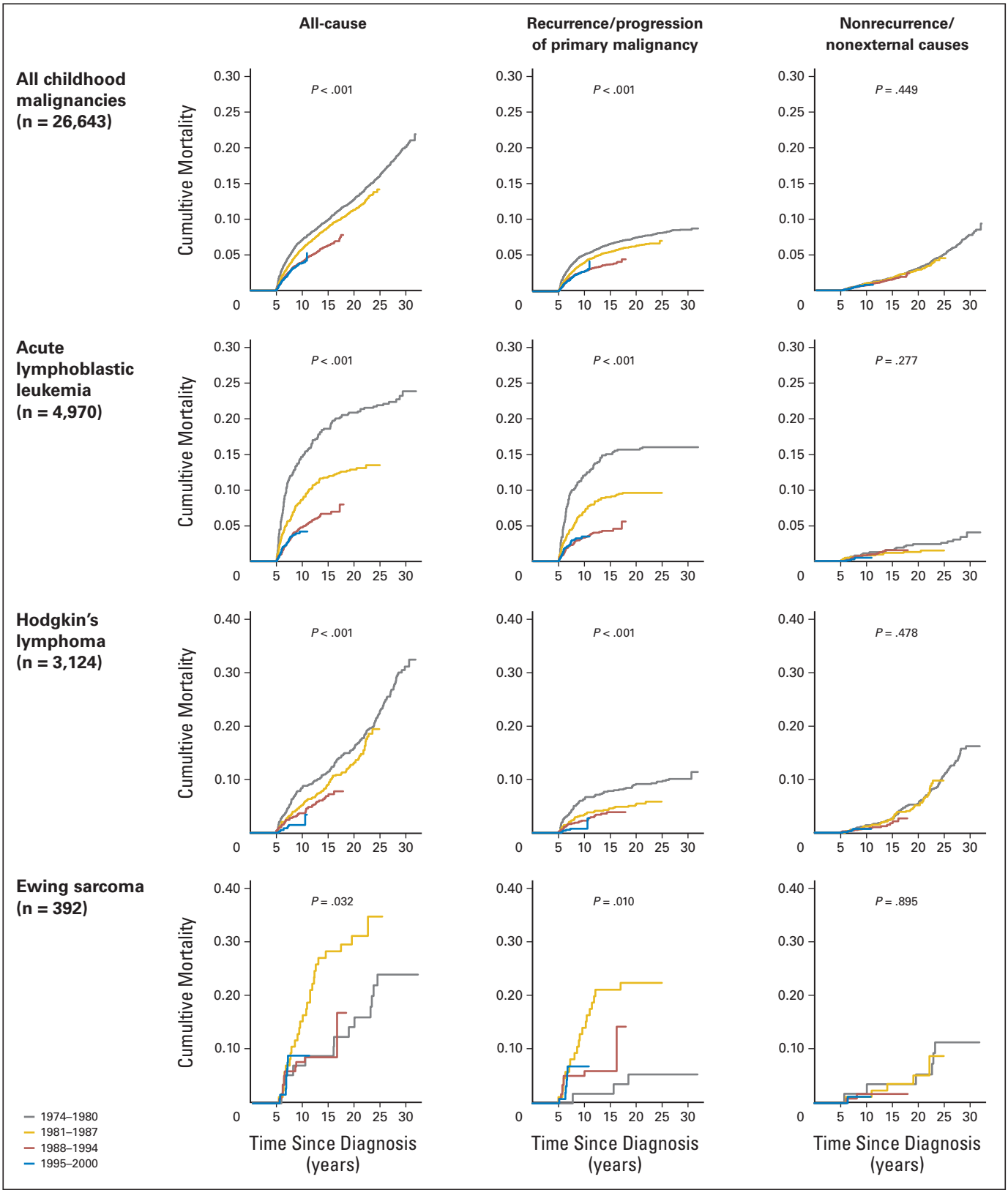

Fig 1. Cumulative incidence of all-cause late mortality, recurrence/progression-related late mortality, and nonrecurrence/nonexternal-cause late mortality for all 5-year survivors and for 5-year survivors of acute lymphoblastic leukemia, Hodgkin's lymphoma, or Ewing sarcoma.

Table 4. Hazard Ratios for Mortality Among 5-Year Survivors of Childhood Cancer

Characteristic	All Cause		Recurrence/Progression of Primary Malignancy		Nonrecurrence/Nonexternal Cause	
	HR	95% CI	HR	95% CI	HR	95% CI
Age*	1.02	1.01 to 1.02	1.00	1.00 to 1.01	1.04	1.03 to 1.05
Sex						
Female	1.0		1.0		1.0	
Male	1.43	1.31 to 1.56	1.34	1.19 to 1.51	1.36	1.16 to 1.60
Race/ethnicity						
Non-Hispanic white	1.0		1.0		1.0	
Non-Hispanic black†	1.38	1.20 to 1.59	1.12	0.91 to 1.37	1.88	1.49 to 2.37
Non-Hispanic American Indian/Alaskan native†	1.08	0.67 to 1.74	1.18	0.65 to 2.13	0.71	0.23 to 2.17
Non-Hispanic Asian or Pacific Islander†	1.20	1.00 to 1.44	1.11	0.87 to 1.42	1.42	1.02 to 1.97
Hispanic†	1.27	1.10 to 1.47	1.30	1.08 to 1.55	1.09	0.81 to 1.48
Year of diagnosis						
1974-1980	1.0		1.0		1.0	
1981-1987	0.80	0.76 to 0.84	0.78	0.73 to 0.83	0.87	0.79 to 0.96
1988-1994	0.64	0.58 to 0.70	0.61	0.54 to 0.69	0.76	0.63 to 0.93
1995-2000	0.51	0.44 to 0.59	0.48	0.40 to 0.57	0.67	0.50 to 0.89
Treatment era test for trend, *P*	< .001		< .001		.007	

*Age is a continuous variable and hazard ratios are based on 1-year increase in age.
†Reference group is non-Hispanic white.

Hodgkin's and non-Hodgkin's lymphoma, rhabdomyosarcoma) but not for children with osteosarcoma, Ewing sarcoma, or ependymoma.

Reduction in late mortality appears to be largely due to reduction in deaths attributable to recurrence/progression of primary disease. This fact suggests that treatments that have improved 5-year survival in more recent eras have also improved durable remission of primary disease beyond the 5-year time point. However, notable exceptions exist. Patients with osteosarcoma, Ewing sarcoma, ependymoma, or neuroblastoma experienced worsening late mortality rates attributable to their primary malignancy over time. It is possible that more intensive primary therapy prolongs initial disease control or that improvements in salvage (after primary progression) therapy may have extended survival beyond the 5-year time point, thus delaying, but not preventing, death resulting from primary disease.

In recent decades, the general philosophy in the design of treatment regimens for many pediatric malignancies has been to reduce the potential for long-term toxicities while not compromising therapeutic benefit. Examples of this approach include reduction in CNS-directed radiation for ALL,[12,13] multimodal therapy with generalized reduction in radiation doses for patients with Hodgkin's lymphoma, and lower cumulative doses of anthracycline to reduce cardiac toxicity.[14,15] Given these changes, one would anticipate that more recently treated patient populations should experience a lower rate of late treatment–related mortality. In the current analysis, we did not observe a significant difference by treatment era when assessing cumulative incidence of mortality attributed to nonrecurrence/nonexternal causes (Fig 1). However, analyses controlling for demographic characteristics of the treatment era cohorts did provide results showing a reduction

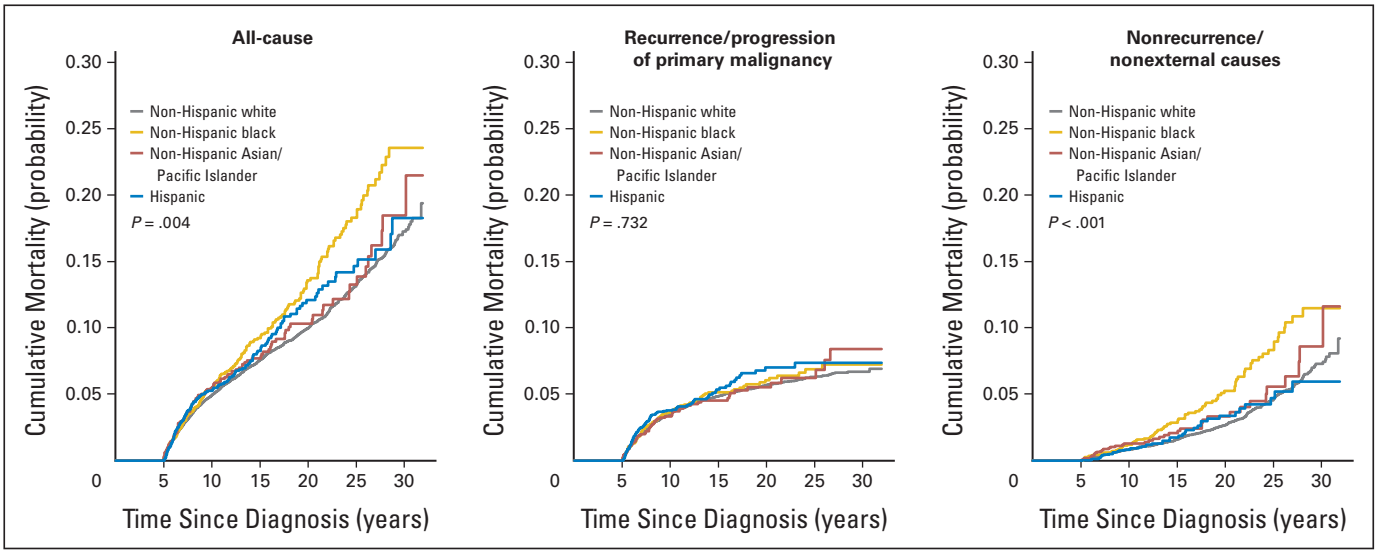

Fig 2. Cumulative all-cause and cause-specific mortality by race/ethnicity; non-Hispanic white (n = 18,365), non-Hispanic black (n = 2,331), non-Hispanic Asian/Pacific Islander (n = 1,673), and Hispanic (n = 3,818).

Table 5. Mortality Among 5-Year Survivors of Childhood Cancer by Ethnicity

Mortality by Ethnicity	Years After Diagnosis 10	20	30
All cause			
White			
Cumulative incidence	5.0	10.0	17.3
95% CI	4.6 to 5.3	9.4 to 10.5	16.1 to 18.5
Black			
Cumulative incidence	5.5	13.6	23.6
95% CI	4.5 to 6.5	11.6 to 15.6	19.6 to 27.5
American Indian			
Cumulative incidence	4.6	9.5	18.0
95% CI	1.6 to 7.6	4.5 to 14.5	5.7 to 30.2
Asian			
Cumulative incidence	5.5	10.3	18.5
95% CI	4.3 to 6.7	8.3 to 12.4	13.4 to 23.5
Hispanic			
Cumulative incidence	5.3	12.1	18.3
95% CI	4.4 to 6.1	10.1 to 14.1	13.8 to 22.7
Recurrence/progression			
White			
Cumulative incidence	3.6	5.7	6.7
95% CI	3.3 to 3.9	5.3 to 6.1	6.2 to 7.2
Black			
Cumulative incidence	3.7	6.1	7.2
95% CI	2.9 to 4.5	4.8 to 7.3	5.6 to 8.9
American Indian			
Cumulative incidence	3.1	6.0	10.1
95% CI	0.6 to 5.6	2.3 to 9.7	1.3 to 18.9
Asian			
Cumulative incidence	3.3	5.5	8.4
95% CI	2.4 to 4.3	4.1 to 7.0	5.4 to 11.4
Hispanic			
Cumulative incidence	3.8	7.0	7.4
95% CI	3.1 to 4.5	5.6 to 8.5	5.8 to 9.0
Nonrecurrence/nonexternal cause			
White			
Cumulative incidence	0.8	2.7	7.3
95% CI	0.7 to 1.0	2.4 to 3.0	6.4 to 8.2
Black			
Cumulative incidence	1.2	5.3	11.5
95% CI	0.7 to 1.7	3.9 to 6.6	8.5 to 11.4
American Indian			
Cumulative incidence	0.5	2.0	6.3
95% CI	0 to 1.6	0 to 5.0	0 to 15.2
Asian			
Cumulative incidence	1.3	3.3	8.6
95% CI	0.7 to 1.9	2.0 to 4.6	4.5 to 12.7
Hispanic			
Cumulative incidence	0.8	3.4	6.0
95% CI	0.5 to 1.2	2.2 to 4.6	3.5 to 8.4

in the HRs, with a statistically significant test for trend ($P = .007$). Thus, the strategy of reducing late toxicity seems to be having an effect because a 33% reduction in risk of death due to nonrecurrence/nonexternal causes was present when comparing the 1974 to 1980 cohort with the 1995 to 2000 cohort. The contrasting conclusions between the cumulative incidence and the adjusted risk estimates may well be related to the changing demographics of the SEER population between 1974 and 2000 (eg, 20% non-white and 52% female in 1974-1980 *v* 40% non-white and 47% female in 1995-2000), coupled with the observed demographic-specific risks for late mortality (eg, higher late mortality in non-whites and higher mortality in females). While the observed lower mortality in the more recently treated cohorts is encouraging, it will be important to continue to follow this trend and document that changes in therapy are preventing the occurrence of late mortality, as opposed to delaying the occurrence of fatal late toxicities.

In a population-based study, Howell et al[16] demonstrated higher mortality rates for blacks than for whites at an early time period following treatment (median follow-up, 25 months). In addition to previous analyses of SEER data showing lower 5-year survival rates for blacks than whites,[1] several studies[17-20] have established a worse survival rate for blacks with ALL or acute myeloid leukemia. However, we have now shown that beyond the 5-year time point, blacks are at a greater absolute risk of mortality than are whites. This difference is not due to recurrence/progression of primary disease. Rather, blacks have significantly higher mortality from nonrecurrence/nonexternal causes. This diagnostic group represents medical causes of death largely due, in this young age group, to complications of cancer therapy.[21] We speculate that these findings may suggest disparity in access to, utilization of, and knowledge about long-term medical care after cancer within the black population. Such disparities are well established in the general population.[22-29] It has been demonstrated that given equal access to effective antileukemic therapy, black and white children can expect the same event-free and overall survival rates.[30] Previous assessment of health care utilization by minority cancer survivors has not shown major disparities; however, these data were collected from a large retrospective cohort study (the Childhood Cancer Survivor Study [CCSS]), which may have lower rates of minority participation and thus may be biased toward lower mortality rates among participating minorities.[31,32]

Sex-based differences in mortality have been previously reported. Males have a greater absolute risk of death, but when data are standardized for the background rate of mortality in the population, female survivors of childhood cancer have a higher standardized mortality rate than males.[2,4,5,33] Our population-based analysis has identified a higher incidence of mortality among males similar to that identified by the CCSS,[4] with one exception. While our study identified greater male risk of nonrecurrence/nonexternal-cause death beyond the 10-year time point, the CCSS identified females as being at higher risk, likely because of high rates of breast cancer in the 1970 to 1986 time period. The rates of breast cancer may have been lower in patients treated during the more recent period of our study.

One limitation of this population-based study is that there is insufficient information on cause of death among those in the nonrecurrence/nonexternal-cause category to further classify them as treatment-related or nontreatment-related. Nontreatment-related causes of death in this population may include HIV, diabetes, influenza, and asthma, among other diagnoses. However, in this cohort with a median age of 24.5 years at the time of ascertainment of vital status, it is likely that the majority of medical deaths are attributable to treatment-related causes, as was demonstrated in the CCSS.[21] In addition, because SEER does not have complete and detailed information on cancer treatment, it is not possible to accurately evaluate associations between specific treatment exposures and late mortality. Therefore, we can only hypothesize that improved rates of mortality attributable to recurrence/progression of primary disease are due to increased intensity of treatment regimens among high-risk patients,

while improved rates of mortality from nonrecurrence/nonexternal causes are associated with decreased exposure among low-risk populations. However, use of the SEER population-based data set for this analysis provides mortality data on a population diagnosed across a broader time range (1974-2000) than that of the CCSS (1970-1986), thus improving the ability to assess temporal trends in mortality. In addition, findings from this population-based study may be more generalizable to the broad population of cancer survivors than those from the CCSS, which is a hospital-based cohort with a narrower spectrum of diagnoses. Future investigations using established cohorts with comprehensive assessment of therapy, such as the CCSS,[32] will allow more detailed assessment of relationships between radiation therapy, chemotherapy doses, and mortality, providing increased sensitivity to determine whether reductions in dose and intensity of therapies over time improve late mortality. The current expansion of the CCSS cohort will ultimately include patients diagnosed between 1970 and 1999, thus allowing a comprehensive assessment of these remaining questions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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