A Comparison of Late Mortality Among Survivors of Childhood Cancer in the United States and United Kingdom

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Abstract

Background: It is unclear whether late-effect risks among childhood cancer survivors vary internationally. We compared late mortality in the North American Childhood Cancer Survivor Study (CCSS) and British Childhood Cancer Survivor Study (BCCSS). **Methods:** Late mortality was assessed among 49 822 5-year survivors of childhood cancer diagnosed before 15 years of age from 1970 to 1999 (CCSS, $n = 31\,596$; BCCSS, $n = 18\,226$) using cumulative mortality probabilities (CM%) and adjusted ratios of the standardized mortality ratio. **Results:** The all-cause CM% at 10 years from diagnosis was statistically significantly lower in the CCSS (4.7%, 95% confidence interval [CI] = 4.5% to 5.0%) compared with the BCCSS (6.9%, 95% CI = 6.5% to 7.2%), attributable to a lower probability of death from recurrence or progression of the primary cancer, with statistically significant differences observed in survivors of leukemia, lymphoma, central nervous system tumors, and sarcoma. However, at 40 years from diagnosis, the CCSS had a greater CM% (22.3% vs 19.3%), attributable to a twofold higher risk of mortality from subsequent malignant neoplasms, cardiac and respiratory diseases, and other health-related causes. Differences increased when assessed by follow-up interval, with the CCSS faring worse as time-since-diagnosis increased. Finally, the gap in all-cause mortality widened more recently, with CCSS survivors diagnosed in 1990-1999 experiencing one-half the excess deaths observed in the BCCSS (ratios of the standardized mortality ratio = 0.5, 95% CI = 0.5 to 0.6). **Conclusions:** Our findings suggest that US survivors may have received more intensive regimens to achieve sustainable remission and cure, but the cost of this approach was a higher risk of death from late effects. Although the clinical impact of these differences is unclear, our results provide important evidence to aid the discussion of late effects management.

Survival from childhood cancer has increased substantially since the 1970s, with 80% of children diagnosed in Westernized countries now becoming 5-year survivors (1,2). Although the 5-year survival rate is encouraging, these individuals continue to experience clinically significant, long-term sequelae because of their cancer and its treatment (3,4), with previous studies reporting increased risks for late mortality (5-9), subsequent malignant neoplasms (SMNs) (10-12), and chronic health conditions (13,14) among other adverse outcomes. Although late effects have been assessed in a range of settings, it is unknown

whether risks differ between countries; indeed, even among the most developed countries, the risk of late effects could vary because of differences in treatment protocols, healthcare systems, and follow-up care recommendations. Thus, we compared for the first time, to our knowledge, the North American Childhood Cancer Survivor Study (CCSS) and British Childhood Cancer Survivor Study (BCCSS), 2 of the largest childhood cancer survivorship cohorts in the world, to assess whether risks for late mortality among 5-year survivors vary between the United States and United Kingdom.

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Methods

North American Childhood Cancer Survivor Study

The CCSS is a retrospective cohort study comprising 34 033 5-year survivors of cancer diagnosed at younger than 21 years of age from 1970 to 1999 in the United States or Canada (15). Participants were identified by each participating institution, and complete ascertainment was achieved for survivors meeting the eligibility criteria (15), with the exception of standard risk acute lymphoblastic leukemia (ALL) survivors diagnosed from 1987 to 1999 because these individuals were intentionally undersampled. The CCSS protocol was approved by the Human Subjects Committee at each participating institution.

British Childhood Cancer Survivor Study

The BCCSS is a retrospective cohort study comprising 34 489 5-year survivors of cancer diagnosed at younger than 15 years of age from 1940 to 2006 in Britain (16). The cohort was identified using the National Registry of Childhood Tumors, which has a high level of ascertainment (approximately 99%) (17) and is population based from 1962 onwards. Ethical approval was obtained from the National Research Ethics Service.

Study Population

Because the CCSS and BCCSS cohorts differ in their inclusion criteria, only survivors who fulfilled the following eligibility criteria were included: 1) diagnosis of a leukemia, central nervous system (CNS) tumor, lymphoma, Wilms tumor, neuroblastoma, rhabdomyosarcoma, or bone tumor (18); 2) age at diagnosis of younger than 15 years; and 3) diagnosis period of 1970-1999. Furthermore, the Canadian component of the CCSS was excluded ($n = 1141$) because of differences in healthcare systems between the United States and Canada, which could affect long-term outcomes. After all exclusions, 31 596 and 18 226 5-year survivors were included from the CCSS and BCCSS, respectively.

Death Ascertainment

All individuals in the CCSS who died or had an uncertain vital status were included in a National Death Index search to ascertain their vital status. Similarly, the BCCSS ascertained each survivor's vital and embarkation status by linking with National Health Service Digital. In both cohorts, the need for informed consent to link with the relevant death registry was waived by the ethics boards. The death certificate and primary underlying cause of death, as coded using the relevant *International Classification of Diseases* volume, were obtained for all deceased survivors and subsequently grouped into the following causes of death: recurrence or progression; SMNs, cardiac diseases, respiratory diseases, external causes, and other causes (5,7). There were no missing data of death or cause of death data in the BCCSS cohort. For CCSS participants with missing data regarding the date of death, we used the multiple-imputation method proposed by Taylor et al. (19).

Statistical Analyses

Time at risk began at 5-year survival, and individuals were censored at the first occurrence of emigration (for the BCCSS), death, or the study exit date; the study exit date was defined as

the date of the most recent vital status linkage for each cohort (CCSS: December 31, 2013; BCCSS: February 28, 2014). To account for the undersampling of ALL survivors in the CCSS, weights were applied to all analyses.

Mortality risks were calculated using standardized mortality ratios (SMRs), which is the ratio of the observed over expected number of deaths, and absolute excess risks (AERs), defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10 000. To determine the expected number of deaths used in the calculation of the SMR and AER, person-years for each sex-, age-, and calendar-year-specific stratum were multiplied by the corresponding mortality rate for the general population of US Whites (CCSS) (20) or England and Wales (BCCSS) (21). Because the mortality rate in the general population for recurrence or progression deaths is 0, SMRs were not calculated, but the AER corresponds to the crude mortality rate.

To compare late-mortality risks between cohorts, a cohort variable was included in the multivariable Poisson models that adjusted for sex, diagnosis group, age at cancer diagnosis, diagnosis period, and attained age to calculate the ratios of the SMRs (RSMR) and ratios of the AER, also known as the excess mortality ratios (EMR) (22), with corresponding 95% confidence intervals (CI). To assess for trend, we used likelihood ratio tests within Poisson regression models where the criteria for statistical significance was a 2-sided P value less than .05. Overall and cause-specific cumulative mortality probabilities (CM%) were calculated, by cohort, as a function of follow-up, where causes of death other than the one under study were treated as a competing risk. The 2-sample test of survival probabilities at fixed time points was used to compare the overall CM% between 2 cohorts at a specific follow-up time point (23).

Results

Of the 49 822 5-year childhood cancer survivors included in this study, 63.4% and 36.6% were from the CCSS and BCCSS, respectively (Table 1). No statistically significant differences in the cohort characteristics were observed, although the CCSS cohort had a slightly higher median time from follow-up and median attained age. In total, 6375 deaths were observed: 3924 from the CCSS (12.4% of CCSS) and 2451 from the BCCSS (13.4% of BCCSS).

Overall, the risk of all-cause mortality was statistically significantly lower in the CCSS compared with the BCCSS for the RSMR (0.8, 95% CI = 0.8 to 0.9) and EMR (0.9, 95% CI = 0.8 to 1.0) (Table 2). Indeed, the CM% was in excess for the BCCSS at 10 years postdiagnosis (CCSS = 4.7% vs BCCSS = 6.9%) as well as for the majority of the follow-up time, with the cohorts only becoming similar at 35-40 years postdiagnosis, at which point they intersect (Figure 1, A). Ultimately, the CCSS had a statistically significantly higher CM% at 40 years after diagnosis compared with the BCCSS (22.3% vs 19.3%, respectively). When assessed by diagnosis group, the results were less consistent; leukemia and CNS tumor survivors in the CCSS had statistically significantly lower risks of all-cause mortality compared with the BCCSS for the RSMR and/or EMR (Table 2; Supplementary Table 1, available online), whereas lymphoma survivors in the CCSS had a 60% greater risk of death compared with their British counterparts (RSMR and EMR = 1.6, 95% CI = 1.3 to 1.8).

To further explore these differences, we assessed the RSMR, EMR, and CM% by each cause of death and observed that the main contributor to the cohort differences was recurrence or progression deaths. Compared with the BCCSS, CCSS survivors

Figure 1. Observed and expected cumulative mortality probabilities for (A) all causes of death combined and (B) each cause-specific death, as a function of follow-up time, by cohort. BCCSS = British Childhood Cancer Survivor Study; CCSS = Childhood Cancer Survivor Study.

experienced statistically significantly less recurrence or progression deaths (EMR = 0.6, 95% CI = 0.6 to 0.7), with no evidence of variation with duration of follow-up (Table 2). This was clearly illustrated when we compared the contribution of recurrence or progression deaths with the overall CM% (Figure 1, B); at 20 years postdiagnosis, nearly 75% (8.1% and 10.9%) of the deaths in the BCCSS were due to recurrence or progression, whereas the corresponding percentage was only 57% (5.0% and 8.8%) in the CCSS. However, as postdiagnosis time increased, the CM% for the CCSS approached that observed for the BCCSS because the US survivors had a twofold increased risk of deaths from SMNs (RSMR = 2.1, 95% CI = 1.8 to 2.3), cardiac (RSMR = 1.7, 95% CI = 1.4 to 2.2) and respiratory (RSMR = 1.9, 95% CI = 1.5 to 2.6) diseases, external causes (RSMR = 1.5, 95% CI = 1.2 to 1.9), and other causes (RSMR = 2.5, 95% CI = 2.1 to 2.9) compared with British survivors.

When cause-specific late mortality was assessed by diagnosis group, the CM% for recurrence or progression deaths was consistently greater in the BCCSS compared with the CCSS (Figure 2), with statistically significant EMRs observed for

leukemia, lymphoma, CNS tumor, and sarcoma survivors (Table 2; Supplementary Table 1, available online). For SMN deaths, statistically significantly higher RSMRs were observed in the CCSS for leukemia, lymphoma, CNS tumor, sarcoma, and Wilms survivors compared with the BCCSS, with RSMRs ranging from 1.7- to 2.8-fold greater. Lymphoma survivors in the CCSS also experienced statistically significantly higher risks of cardiac (RSMR = 2.4, 95% CI = 1.6 to 3.6; EMR = 2.3, 95% CI = 1.4 to 3.7) and respiratory (RSMR = 6.5, 95% CI = 2.9 to 14.5; EMR = 5.4, 95% CI = 17.6) disease deaths, with very substantial increases in the CM% observed after 20 years from diagnosis (Supplementary Figure 1, available online). Finally, for all other health-related causes, the greatest discrepancies between the cohorts were observed for sarcoma, lymphoma, and CNS tumor survivors, with RSMR risks being 4.3-fold (95% CI = 2.1 to 8.8), 3.3-fold (95% CI = 2.2 to 4.9), and 3.0-fold (95% CI = 2.3 to 4.0) greater in the CCSS compared with the BCCSS, respectively. Again, when assessed using the CM%, the divergence between the 2 countries was noted around 20 years postdiagnosis for these diagnosis groups.

Table 1. Characteristics of the British Childhood Cancer Survivor Study (BCCSS), North American Childhood Cancer Survivor Study (CCSS), and pooled study population

Characteristic	BCCSS	CCSS	Total	p ^b
	No. (%)	No. (% ^a)	No. (% ^a)	
Overall	18 226 (100.0)	31 596 (100.0)	49 822 (100.0)	
Sex				
Male	10 215 (56.0)	17 650 (55.9)	27 865 (55.9)	.98
Female	8011 (44.0)	13 946 (44.1)	21 957 (44.1)	
Diagnosis				
Acute lymphoblastic leukemia	6676 (36.6)	12 042 (38.1)	18 718 (37.6)	.99
Acute myeloid leukemia	569 (3.1)	1013 (3.2)	1582 (3.2)	
Other leukemia	134 (0.7)	374 (1.2)	508 (1.0)	
Astrocytoma	2677 (14.7)	3284 (10.4)	5961 (12.0)	
Medulloblastoma	730 (4.0)	1227 (3.9)	1957 (3.9)	
Other central nervous system tumors	540 (3.0)	800 (2.5)	1340 (2.7)	
Hodgkin lymphoma	1459 (8.0)	2206 (7.0)	3665 (7.4)	
Non-Hodgkin lymphoma	1299 (7.1)	2141 (6.8)	3440 (6.9)	
Kidney (Wilms)	1595 (8.8)	2903 (9.2)	4498 (9.0)	
Neuroblastoma	942 (5.2)	2481 (7.9)	3423 (6.9)	
Soft tissue sarcoma	777 (4.3)	1420 (4.5)	2197 (4.4)	
Ewings sarcoma	354 (1.9)	680 (2.2)	1034 (2.1)	
Osteosarcoma	380 (2.1)	974 (3.1)	1354 (2.7)	
Other bone	94 (0.5)	51 (0.2)	145 (0.3)	
Age at diagnosis				
0-4 y	8410 (46.1)	15 738 (49.8)	24 148 (48.5)	.74
5-9 y	5323 (29.2)	8818 (27.9)	14 141 (28.4)	
10-14 y	4493 (24.7)	7041 (22.3)	11 534 (23.2)	
Year of diagnosis				
1970-1974	1838 (10.1)	2786 (8.8)	4624 (9.3)	.97
1975-1979	2450 (13.4)	4355 (13.8)	6805 (13.7)	
1980-1984	2812 (15.4)	5508 (17.4)	8320 (16.7)	
1985-1989	3076 (16.9)	5928 (18.8)	9004 (18.1)	
1990-1994	3779 (20.7)	6307 (20.0)	10 085 (20.2)	
1995-1999	4271 (23.4)	6712 (21.2)	10 983 (22.0)	
Follow-up from 5-y survival at exit				
Median	18.4	19.5	19.1	.93
0-4 y	1297 (7.1)	1492 (4.7)	2789 (5.6)	
5-9 y	1151 (6.3)	1949 (6.2)	3100 (6.2)	
10-14 y	4186 (23.0)	6840 (21.7)	11 026 (22.1)	
15-19 y	3496 (19.2)	6066 (19.2)	9535 (19.1)	
20-24 y	2845 (15.6)	5618 (17.8)	8463 (17.0)	
25-29 y	2343 (12.9)	4755 (15.1)	7098 (14.3)	
30+ y	2935 (16.1)	4876 (15.4)	7811 (15.7)	
Attained age at exit				
Median	30.0	30.6	30.5	.98
5-19 y	2686 (14.7)	3939 (12.5)	6625 (13.3)	
20-24 y	3066 (16.8)	5247 (16.6)	8313 (16.7)	
25-29 y	3377 (18.5)	5825 (18.4)	9202 (18.5)	
30-34 y	2963 (16.3)	5759 (18.2)	8722 (17.5)	
35-39 y	2209 (12.1)	4561 (14.4)	6770 (13.6)	
40-44 y	2113 (11.6)	3541 (11.2)	5654 (11.4)	
45+ y	1812 (9.9)	2724 (8.6)	4536 (9.1)	

^aCalculated using weights for the CCSS because of undersampling of acute lymphoblastic leukemia case patients.^bTwo-sided χ^2 tests were used to test for statistical significance.

Further stratification of these risks by follow-up time showed that the disparities between the CCSS and BCCSS widened over time for deaths from SMNs, cardiac and respiratory diseases, external causes, and other causes, with generally comparable risks at 5-14 years postdiagnosis increasing to statistically worse outcomes for the CCSS at 30+ years postdiagnosis (Table 2; Supplementary Table 1, available online). For example, overall, the CCSS had a 1.7-fold (95% CI = 1.4 to 2.1)

greater risk of a SMN death at 5-14 years postdiagnosis compared with the BCCSS (in terms of RSMR), which increased to a 2.8-fold (95% CI = 2.1 to 3.6) greater risk at 30+ years follow-up ($P_{\text{trend}} = .004$). This growing excess mortality in the CCSS compared with the BCCSS was generally consistent when assessed for each diagnosis group, though these findings were not always statistically significant because of low statistical power for certain stratifications.

Table 2. RSMRs and EMRs from multivariable analyses comparing cause-specific mortality in the North American Childhood Cancer Survivor Study (CCSS) with the British Childhood Cancer Survivor Study (BCCSS) overall and by follow-up time for all survivors and survivors of leukemia, lymphoma, and CNS tumors

CCSS											
Cause of death	BCCSS	RSMR (95% CI)				EMR (95% CI)					
		Overall ^a	5-14 y follow-up	15-29 y follow-up	30+ y follow-up	P _{trend} ^b	Overall ^a	5-14 y follow-up	15-29 y follow-up	30+ y follow-up	P _{trend} ^b
All survivors ^c											
All causes	1 (Referent)	0.8 (0.8 to 0.9)	0.5 (0.5 to 0.6)	1.4 (1.3 to 1.6)	2.5 (2.1 to 2.9)	<.001	0.9 (0.8 to 1.0)	0.7 (0.7 to 0.8)	1.4 (1.2 to 1.6)	2.7 (2.1 to 3.6)	<.001
Recurrence	1 (Referent)			—			0.6 (0.6 to 0.7)	0.6 (0.6 to 0.6)	0.8 (0.7 to 1.0)	0.8 (0.5 to 1.4)	.17
SMNs	1 (Referent)	2.1 (1.8 to 2.3)	1.7 (1.4 to 2.1)	2.0 (1.7 to 2.4)	2.8 (2.1 to 3.6)	.004	1.4 (1.2 to 1.6)	1.4 (1.1 to 1.7)	1.2 (0.9 to 1.5)	1.9 (1.3 to 2.8)	.47
Cardiac causes	1 (Referent)	1.7 (1.4 to 2.2)	1.3 (0.8 to 2.1)	1.6 (1.1 to 2.2)	2.5 (1.7 to 3.8)	.06	1.7 (1.3 to 2.3)	1.4 (0.8 to 2.5)	1.5 (1.0 to 2.2)	2.8 (1.5 to 5.3)	.19
Respiratory causes	1 (Referent)	1.9 (1.5 to 2.6)	1.3 (0.8 to 2.0)	2.6 (1.6 to 4.1)	2.5 (1.3 to 5.0)	.05	1.3 (0.9 to 1.7)	0.9 (0.6 to 1.5)	1.6 (0.9 to 2.7)	2.1 (0.8 to 5.6)	.11
Other health-related causes ^d	1 (Referent)	2.5 (2.1 to 2.9)	1.6 (1.2 to 2.0)	2.9 (2.2 to 3.7)	4.1 (2.9 to 5.9)	<.001	2.3 (1.8 to 2.9)	1.4 (1.1 to 1.9)	2.9 (1.9 to 4.6)	6.7 (2.5 to 18.0)	<.001
External causes	1 (Referent)	1.5 (1.2 to 1.9)	0.9 (0.7 to 1.3)	1.9 (1.4 to 2.6)	3.4 (1.7 to 7.0)	.001	NR	NR	NR	NR	—
Leukemia survivors ^e											
All causes	1 (Referent)	0.6 (0.5 to 0.6)	0.4 (0.4 to 0.5)	1.1 (0.9 to 1.3)	2.5 (1.8 to 3.6)	<.001	0.7 (0.6 to 0.7)	0.6 (0.6 to 0.7)	1.0 (0.8 to 1.4)	4.1 (1.6 to 10.4)	<.001
Recurrence	1 (Referent)			— ^a			0.5 (0.5 to 0.6)	0.5 (0.5 to 0.6)	0.6 (0.4 to 1.0)	1.7 (0.2 to 17.5)	.23
SMNs	1 (Referent)	1.7 (1.4 to 2.1)	1.8 (1.3 to 2.6)	1.3 (1.0 to 1.9)	2.4 (1.4 to 4.0)	.75	1.2 (1.0 to 1.6)	1.6 (1.1 to 2.3)	0.8 (0.5 to 1.1)	1.6 (0.8 to 3.5)	.21
Cardiac causes	1 (Referent)	1.3 (0.8 to 2.0)	0.8 (0.4 to 1.7)	0.9 (0.5 to 1.8)	12.9 (1.7 to 96.7)	.007	1.2 (0.7 to 2.2)	0.9 (0.4 to 2.1)	1.0 (0.4 to 2.5)	NR	.07
Respiratory causes	1 (Referent)	1.5 (0.9 to 2.4)	1.6 (0.8 to 3.4)	1.5 (0.7 to 3.5)	0.7 (0.2 to 3.2)	.58	1.0 (0.5 to 1.8)	1.1 (0.5 to 2.5)	1.0 (0.4 to 2.5)	NR	.49
Other health-related causes ^d	1 (Referent)	1.8 (1.4 to 2.4)	1.3 (0.9 to 1.8)	2.0 (1.2 to 3.3)	4.6 (2.1 to 9.8)	.002	1.5 (1.0 to 2.2)	1.1 (0.7 to 1.6)	2.7 (0.6 to 13.6)	NR	.08
External causes	1 (Referent)	1.6 (1.1 to 2.4)	1.3 (0.7 to 2.5)	1.8 (1.1 to 3.0)	2.3 (0.8 to 6.7)	.37	NR	NR	NR	NR	—
Lymphoma survivors ^e											
All causes	1 (Referent)	1.6 (1.3 to 1.8)	0.6 (0.5 to 0.8)	2.8 (2.1 to 3.6)	3.5 (2.5 to 4.9)	<.001	1.6 (1.3 to 1.9)	0.8 (0.6 to 1.0)	4.0 (2.3 to 6.8)	4.3 (2.3 to 8.3)	<.001
Recurrence	1 (Referent)			— ^a			0.7 (0.5 to 0.9)	0.5 (0.4 to 0.7)	1.6 (0.8 to 3.3)	1.4 (0.3 to 7.5)	.007
SMNs	1 (Referent)	2.8 (2.1 to 3.7)	1.8 (1.1 to 3.0)	3.1 (2.0 to 4.8)	3.6 (2.1 to 6.2)	.06	1.8 (1.3 to 2.5)	1.4 (0.8 to 2.3)	1.8 (1.0 to 3.3)	2.4 (1.1 to 5.1)	.16
Cardiac causes	1 (Referent)	2.4 (1.6 to 3.6)	0.9 (0.3 to 2.3)	3.4 (1.7 to 6.5)	2.5 (1.4 to 4.5)	.23	2.3 (1.4 to 3.7)	1.0 (0.3 to 3.1)	3.2 (1.3 to 7.6)	2.6 (1.2 to 5.7)	.20

(continued)

Table 2. (continued)

CCSS											
Cause of death	BCCSS	RSMR (95% CI)				EMR (95% CI)					
		Overall ^a	5-14 y follow-up	15-29 y follow-up	30+ y follow-up	P _{trend} ^b	Overall ^a	5-14 y follow-up	15-29 y follow-up	30+ y follow-up	P _{trend} ^b
Respiratory causes	1 (Referent)	6.5 (2.9 to 14.5)	3.0 (1.0 to 9.2)	9.8 (2.2 to 43.3)	14.5 (1.9 to 112.0)	.16	5.4 (1.6 to 17.6)	2.3 (0.6 to 8.7)	7.4 (0.7 to 75.6)	NR	.37
Other health-related Causes ^d	1 (Referent)	3.3 (2.2 to 4.9)	1.4 (0.8 to 2.6)	4.8 (2.4 to 9.4)	6.4 (2.5 to 16.3)	.003	3.9 (1.7 to 8.6)	1.3 (0.6 to 2.8)	NR	NR	.91
External causes	1 (Referent)	1.9 (1.1 to 3.1)	0.9 (0.5 to 1.9)	2.7 (1.3 to 5.9)	6.2 (0.8 to 48.4)	.02	NR	1.3 (0.2 to 10.0)	NR	NR	.94
CNS tumor survivors ^e											
All causes	1 (Referent)	0.9 (0.8 to 1.0)	0.6 (0.6 to 0.7)	1.2 (1.0 to 1.4)	2.4 (1.7 to 3.2)	<.001	1.0 (0.9 to 1.1)	0.9 (0.8 to 1.0)	1.1 (0.9 to 1.4)	2.1 (1.4 to 3.3)	<.001
Recurrence	1 (Referent)			— ^a			0.8 (0.7 to 0.9)	0.8 (0.7 to 0.9)	0.8 (0.6 to 1.1)	0.8 (0.4 to 1.5)	.41
SMNs	1 (Referent)	2.0 (1.6 to 2.6)	1.9 (1.3 to 2.7)	1.8 (1.3 to 2.7)	3.4 (1.7 to 6.5)	.16	1.3 (1.0 to 1.8)	1.5 (1.0 to 2.2)	1.0 (0.7 to 1.6)	2.6 (0.9 to 7.8)	.95
Cardiac causes	1 (Referent)	1.9 (1.1 to 3.3)	8.0 (1.0 to 65.0)	1.0 (0.5 to 2.2)	2.8 (1.0 to 7.7)	.91	2.6 (1.0 to 6.6)	NR	0.8 (0.3 to 2.2)	NR	.91
Respiratory causes	1 (Referent)	1.4 (0.8 to 2.4)	0.8 (0.3 to 1.9)	2.3 (1.0 to 5.2)	1.8 (0.5 to 5.9)	.10	0.9 (0.5 to 1.5)	0.5 (0.2 to 1.3)	1.3 (0.5 to 3.0)	1.3 (0.3 to 5.8)	.18
Other health-related causes ^d	1 (Referent)	3.0 (2.3 to 4.0)	2.6 (1.5 to 4.3)	2.8 (1.9 to 4.1)	4.7 (2.4 to 9.2)	.20	2.6 (1.8 to 3.8)	2.5 (1.3 to 4.8)	2.2 (1.3 to 3.7)	8.2 (1.3 to 52.9)	.38
External causes	1 (Referent)	1.5 (0.9 to 2.4)	0.8 (0.4 to 1.6)	2.0 (1.0 to 4.2)	2.4 (0.8 to 8.0)	.04	1.4 (0.3 to 5.5)	0.9 (0.1 to 7.0)	NR	NR	.18

^aResults additionally adjust for follow-up time (5-14 years, 15-29 years, 30+ years). RSMRs are not reported for deaths because of recurrence or progression of the first primary neoplasm as the expected mortality rate in the general population is 0.

^bP value for trend across follow-up time.

^cAdjusting for sex, first primary neoplasm type (leukemias, lymphomas, CNS tumors, sarcomas, Wilms tumors, neuroblastomas), age at diagnosis (0-4 years, 5-9 years, 10-14 years), and treatment period (1970-1974, 1975-1979, 1980-1984, 1985-1989, 1990-1994, 1995-1999).

^dAll causes of death except those from recurrence or progression, second primary neoplasms, cardiac diseases, respiratory diseases, and external causes.

^eAdjusting for sex, age at diagnosis (0-4 years, 5-9 years, 10-14 years), and treatment period (1970-1974, 1975-1979, 1980-1984, 1985-1989, 1990-1994, 1995-1999).

Figure 2. Observed and expected cumulative mortality probabilities by first primary neoplastic group for (A) recurrence or progression deaths, (B) subsequent primary neoplasm deaths, and (C) deaths from all other health-related causes, as a function of follow-up time, by cohort. All other health-related causes refers to all causes of death except those from recurrence or progression, second primary neoplasms, cardiac diseases, respiratory diseases, and external causes. BCCSS = British Childhood Cancer Survivor Study; CCSS = Childhood Cancer Survivor Study; CNS = central nervous system.

Finally, we investigated whether differences between the CCSS and BCCSS were diminishing among those more recently treated, ignoring follow-up beyond 25 years from diagnosis for comparability (Figure 3). Improvements were observed in the

CCSS for deaths from SMNs, cardiac diseases, and respiratory diseases, with US and British survivors diagnosed in 1990-1999 having comparable risks (Supplementary Table 2, available online). The CCSS and BCCSS also became more comparable for

Figure 3. RSMRs and EMRs from multivariable analyses comparing cause-specific mortality in the CCSS to the BCCSS by treatment decade. Data beyond 20 years from 5-year survival were excluded for comparability across the treatment eras. BCCSS = British Childhood Cancer Survivor Study; CCSS = Childhood Cancer Survivor Study; EMRs = excess mortality ratios; RSMR = ratios of the standardized mortality ratios.

other health-related deaths, though risks were still at least 60% greater in the CCSS (RSMR = 1.6, 95% CI = 1.1 to 2.3; EMR = 1.7, 95% CI = 1.0 to 2.6). For recurrence or progression deaths, the differences between the 2 cohorts remained static (EMR $P_{\text{trend}} = .89$), with an EMR of 0.6-0.7 observed for each decade. As a result, the gap between the CCSS and BCCSS for all-cause mortality widened statistically significantly with treatment decade (RSMR $P_{\text{trend}} = .04$), with US survivors experiencing 50% fewer deaths compared with British survivors (RSMR = 0.5, 95% CI = 0.5 to 0.6); this gap appeared to be driven by leukemia, CNS tumor, and sarcoma survivors, who, according to the RSMRs, experienced 40%-60% fewer deaths in the CCSS compared with the BCCSS (Supplementary Table 3, available online).

As the general population mortality rates for the United States and United Kingdom differed (Supplementary Figure 2, available online), we undertook sensitivity analyses using the UK rates for both cohorts. Although the RSMRs and EMRs were attenuated towards the null, we still observed a statistically significantly lower EMR for all-cause mortality in the CCSS, and statistically significantly greater risks (both RSMRs and EMRs) for deaths from SMNs, cardiac diseases, external causes, and other health-related causes compared with the BCCSS (Supplementary Table 4, available online).

Discussion

In this first-ever, to our knowledge, large-scale international comparative study of late mortality among childhood cancer survivors, we identified statistically significant differences in

overall and cause-specific long-term mortality depending on whether the individual was treated in the United States or the United Kingdom. These differences were driven by a lower risk of recurrence or progression deaths in the CCSS, though the 2 cohorts ultimately became more comparable with time because of a higher burden of late-effect deaths in the CCSS beyond 20 years from diagnosis. The results of this study provide novel international comparative evidence on the burden of late mortality in childhood cancer survivors based on pooling individual patient data from 2 of the largest cohorts available worldwide.

The differences observed may relate to treatment practices in the 2 countries. Although detailed treatment information is not available for the BCCSS and thus precluded its examination in this study, we explored the role of therapy by comparing trial protocols for childhood ALL because there was high trial enrollment in both countries during the study period (24,25). In brief, 7 ALL trials were conducted in the 1970s in the United Kingdom, but all observed worse outcomes than the US Children's Cancer Group (CCG) trials (26). Thus, in collaboration with the CCG, the United Kingdom introduced the UKALL VIII trial (1980-1984), which followed the CCG 162 trial and achieved the greatest survival improvement in the United Kingdom up to that time, with survival rates similar to those in the United States (26). Although the lessons from UKALL VIII encouraged a more intensive treatment approach in the United Kingdom, subsequent trials again lagged behind the United States, and ultimately the 2 countries collaborated again in 1999 to introduce US regimens to British ALL patients (27); this collaboration led to comparable rates of event-free survival, with insufficient intensification

phases identified as the main cause for poorer outcomes in the United Kingdom (24). This historical comparison highlights known disparities in childhood cancer survival between the United States and United Kingdom in relation to ALL treatment and suggests that UK trials were not sufficiently sustained and intensive and thus were less effective. This could explain the increased mortality burden observed in our study for the United Kingdom due to recurrence or progression deaths. Conversely, the use of more intensive regimens in the United States to achieve sustainable remission and cure likely increased the mortality burden from late effects, particularly SMNs and cardiac disease, which have known dose-response relationships with radiation and anthracycline dose, respectively (28,29). Although disparities in 5-year survival between the United States and the United Kingdom are documented for many childhood cancer diagnoses (30,31), it is uncertain whether the pattern observed for ALL applies to other cancer types. Nonetheless, our findings highlight the complexity of childhood cancer treatment in balancing cure with late-effect risks.

Another notable finding of this study was the increasingly poorer outcomes in US childhood cancer survivors as time since diagnosis increased. Previous studies have found suboptimal follow-up for survivorship care in the United States (32), with lack of insurance identified as an important predictor (32-35). Indeed, US adult survivors of childhood cancer were more frequently denied healthcare coverage, paid more out-of-pocket fees for care, and were more likely to borrow money because of healthcare costs compared with controls (36). Additionally, prior research found that CCSS survivors were more likely to miss a necessary medical test or treatment because of cost concerns (36). These examples highlight how childhood cancer survivors often lack access to consistent follow-up care in adulthood in the United States, a contrast to the United Kingdom where the National Health Service offers universal healthcare and facilitates survivor-focused care through its linked network of care providers. Thus, as the risk for serious medical problems increases, US childhood cancer survivors could be less likely to receive the recommended follow-up care, which may increase disparities compared with the United Kingdom with increasing time since diagnosis. Because the Affordable Care Act, which prohibited denying coverage or increasing insurance premiums of individuals with preexisting conditions, came into effect after our study exit date, it is unclear whether the observed disparities will persist, particularly as awareness of late effects among community providers and survivors in the United States is also increasing through the implementation of survivorship care plans.

Finally, we report that the late mortality gap is widening because of persisting disparities in recurrence or progression deaths, with a greater burden of years of life lost observed in the BCCSS. It remains unclear the degree to which these findings should cause public health or clinical concern however as the mortality risks in the CCSS, a hospital-based cohort, may not be representative of the entire US childhood cancer survivor population, in terms of age, sex, race or ethnicity, or tumor types, since the cohort is not population-based and thus is susceptible to bias due to the potential for differential participation of eligible study participants (37,38). In relation to this study, selection bias was suggested by the study of Mertens et al. (39), which found superior survival in the CCSS compared with population-based US data of childhood cancer survivors. Comparison of the BCCSS with the Surveillance, Epidemiology, and End Results Program, which collects population-based data on cancer case patients from various locations and sources throughout the

United States, would complement this study and further elucidate whether late mortality differs in childhood cancer survivors from the United States and the United Kingdom. However, we recognize that this proposed analysis would still be limited by the fact that ethnicities and environmental exposures differ between the countries, both of which affect the distribution of cancers and degree of late effects (40-43), and thus all potential confounders are unlikely to be accounted for.

A limitation of this study is that the death classification relied on the underlying cause of death as coded on the death certificate. Although this methodology is mandatory to make direct comparisons with the general population, it is known that death certificates are imperfect (44-48), and thus misclassification is inherent in our data. Currently, the degree of misclassification among childhood cancer survivors is unclear, and it is possible that misclassification could differ between the United States and the United Kingdom. Furthermore, as detailed treatment information is not available for the BCCSS, investigations into the relative importance of differences in treatment practices between countries were not feasible. We nonetheless attempt to draw hypotheses using historical treatment protocols for certain childhood cancer groups. Race and ethnic data were also not comprehensively collected in both cohorts, and thus we are unable to discuss the role of this potential confounder. Finally, we have purposefully excluded Canadian childhood cancer survivors from the CCSS because we suspected that late mortality risks in Canadians may differ from those in the United States because of the existence of a public healthcare system. Our suspicion was confirmed when we plotted the all-cause CM% for the 3 countries as the CM% in Canada was between that observed in the United States and the United Kingdom up to 20 years from diagnosis, after which it had the lowest CM% of the 3 countries (results not shown).

In conclusion, there are substantial differences in the risks for late mortality among 5-year childhood cancer survivors in the CCSS and BCCSS cohorts. In particular, our findings suggest that US survivors may have received more intensive regimens to achieve sustainable remission and cure. However, the cost of this approach was a higher risk of late-effect deaths. Although the reported statistically significant differences are open to interpretation in regards to their clinical meaningfulness, our results provide important evidence for clinicians, researchers, and survivors that will aid the discussion of late effects management and exemplify the complexities of childhood cancer treatment, notably the balance of maximizing cure while minimizing late effects.

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Data Availability

The data are not publicly available due to them containing semi-identifiable information that could compromise research participant privacy. Additional summary tables of count data or person-years are available from the corresponding author upon request.

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