Long-term Cause-Specific Mortality Among Survivors of Childhood Cancer

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Context Survivors of childhood cancer are at increased risk of premature mortality compared with the general population, but little is known about the long-term risks of specific causes of death, particularly beyond 25 years from diagnosis at ages when background mortality in the general population starts to increase substantially.

Objective To investigate long-term cause-specific mortality among 5-year survivors of childhood cancer in a large-scale population-based cohort.

Design, Setting, and Patients British Childhood Cancer Survivor Study, a population-based cohort of 17 981 5-year survivors of childhood cancer diagnosed with cancer before age 15 years between 1940 and 1991 in Britain and followed up until the end of 2006.

Main Outcome Measures Cause-specific standardized mortality ratios (SMRs) and absolute excess risks (AERs).

Results Overall, 3049 deaths were observed, which was 11 times the number expected (SMR, 10.7; 95% confidence interval [CI], 10.3-11.1). The SMR declined with follow-up but was still 3-fold higher than expected (95% CI, 2.5-3.9) 45 years from diagnosis. The AER for deaths from recurrence declined from 97 extra deaths (95% CI, 92-101) per 10 000 person-years at 5 to 14 years from diagnosis, to 8 extra deaths (95% CI, 3-22) beyond 45 years from diagnosis. In contrast, during the same periods of follow-up, the AER for deaths from second primary cancers and circulatory causes increased from 8 extra deaths (95% CI, 7-10) and 2 extra deaths (95% CI, 2-3) to 58 extra deaths (95% CI, 38-90) and 29 extra deaths (95% CI, 16-56), respectively. Beyond 45 years from diagnosis, recurrence accounted for 7% of the excess number of deaths observed while second primary cancers and circulatory deaths together accounted for 77%.

Conclusion Among a cohort of British survivors of childhood cancer, excess mortality from second primary cancers and circulatory diseases continued to occur beyond 25 years from diagnosis.

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Over recent decades survival from childhood cancer has improved dramatically, yet mortality rates in childhood cancer survivors continue to be elevated for many years beyond 5-year survival compared with the general population.[1] Previous studies have shown that the leading cause of death following 5-year survival is recurrence or progression of the original tumor, followed by second primary cancers and nonneoplastic conditions such as cardiac disease.[2-8] Although studies have shown that the risk of death from recurrence decreases with increasing time since 5-year survival, uncertainty about the long-term risks of death from other causes remains.[2-9]

Investigations into long-term cause-specific mortality are important because any excess mortality may be related to long-term complications of treatment. Strongly elevated mortality risks related to second primary cancers and nonneoplastic disease, when compared with the general population, have been reported over the first 20 years after 5-year survival.[2-5] However, it is largely unknown whether these increased risks persist beyond 25 years from initial cancer diagnosis, at ages when background mortality in the general population starts to increase substantially. With increasing numbers of survivors now reaching mature adulthood, an elevated relative risk of common chronic diseases of mature adulthood sustained into old age would greatly increase the absolute number of survivors who ultimately die prematurely.

The main objective of this study was to investigate long-term cause-specific mortality within a large-scale

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population-based cohort with more than 4 times the number of person-years and 3 times the number of deaths beyond 25 years from initial cancer diagnosis than previously available in the largest previous studies.[2]

METHODS

British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study (BCCSS) is the largest population-based cohort study to comprehensively examine the late effects of childhood cancer and its treatment. The study comprises 17 981 5-year survivors of childhood cancer diagnosed before age 15 years between 1940 and 1991 in Britain.[10] The cohort was ascertained through the National Registry of Childhood Tumours, which is maintained by the Childhood Cancer Research Group (CCRG) at the University of Oxford. Ascertainment is thought to be very high because the registry receives notifications from multiple sources and cross-checks and validates reports with other sources. Information on type of childhood cancer, initial treatment (ie, radiotherapy, chemotherapy), and demographics was provided by the CCRG. Support to process data without individual consent and to obtain copies of death certificates was obtained from the Patient Information Advisory Group. We also obtained consent of the multicenter research ethics committee and every local research ethics committee in Britain.

Death Ascertainment

Deaths among childhood cancer survivors were ascertained by linking the BCCSS cohort with the National Health Service Central Registers. Such linkage of the entire population-based cohort with the national population-based death registration system provides a means of ascertaining each survivor's vital status and embarkations due to emigration. For each death, an attempt was made to obtain the death certificate and underlying cause of death as coded by the Office of National Statistics using the appropriate chronological revision of the *International Classification of Diseases*. The level of specificity used to classify underlying causes of death was determined a priori and corresponded to the principal sections of the relevant revisions of the *International Classification of Diseases*. Whenever the underlying cause of death was neoplastic, the death certificate and, if available, medical records were examined to decide whether the death was due to recurrence or progression of the original cancer, or in fact due to a second primary cancer. Follow-up of cohort members for mortality started at the date of 5-year survival beyond the time of initial childhood cancer diagnosis. The cohort exit date was December 31, 2006, with earlier exits at death or loss to follow-up.

Statistical Analysis

Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were calculated for each specific cause of death using standard cohort techniques.[11] The SMR was defined as the ratio of the observed over the expected number of deaths. The AER was defined as the observed minus the expected number of deaths divided by the number of person-years at risk multiplied by 10 000. The SMR is a useful multiplicative measure for determining the excess mortality relative to the background mortality, whereas the AER is a useful additive measure for determining the additional mortality burden beyond the background mortality, as it is the extra number of deaths observed, beyond that expected, per 10 000 person-years. To derive the expected number of deaths used in the calculation of the SMR and AER, person-years for each sex-specific, age-specific (5-year bands), and calendar year–specific (1-year bands) stratum were multiplied by the corresponding mortality rate for the population of England and Wales and then summed across the strata.[12] For causes of death that exceeded 100 observed deaths, SMRs and AERs were stratified by the following factors: sex, type of childhood cancer, age at childhood cancer diagnosis (0-4, 5-9, or 10-14 years), treatment with radiotherapy (yes/no), treatment with chemotherapy (yes/no), years from diagnosis (5-14, 15-24, 25-34, 35-44, or ≥45 years), and attained age (0-19, 20-29, 30-39, 40-49, or ≥50 years). To evaluate the simultaneous effect of these factors on the SMR and AER, special multivariable Poisson regression models were used to derive relative risks (RRs) and excess mortality ratios (EMRs), which are broadly adjusted ratios of AERs (see eAppendix, available at http://www.jama.com).

Derivation of SMRs for deaths due to recurrence would not be appropriate because the corresponding mortality rate in the general population would be 0. However, the AER corresponds to the crude mortality rate for recurrence, and we stratified these mortality rates by the factors sex, type of childhood cancer, age at diagnosis, treatment with radiotherapy, treatment with chemotherapy, years from diagnosis, and attained age. The simultaneous effects of these factors on the mortality rate were evaluated by using a multivariable Poisson regression model (eAppendix).

Cumulative mortality (CM), as a function of years since diagnosis, for death causes exceeding 100 deaths was estimated by means of the stcompet command in Stata (StataCorp, College Station, Texas).[13] Causes of death other than the one under study were treated as competing risks. Stata statistical software was used for all analyses. The criterion for statistical significance was a 2-sided $P < .05$. With regard to statistical power, if the true underlying SMR were to exceed at least 2.0 or 3.0, then the likelihood of detecting this with 9 and 3 expected deaths, respectively, would be 80%.[11]

RESULTS

Cohort Characteristics

Of the 17 981 5-year survivors in the cohort, 3049 (17.0%) had died, 245 (1.4%) were lost to follow-up, and 14 687 (81.7%) were alive at the study

Table 1. Observed and Expected Deaths, Standardized Mortality Ratio, and Absolute Excess Risk of Specific Causes of Death

	Observed	Expected	SMR (95% CI)	AER (95% CI)[a]
All causes	3049	284.8	10.7 (10.3-11.1)	74.7 (71.8-77.7)
Recurrent/progressive disease	1918	0	NA (NA)	51.8 (49.4-54.1)
All causes except recurrence	1117	284.8	3.9 (3.7-4.1)	22.5 (20.8-24.3)
Second primary cancer	483	66.4	7.3 (6.7-8.0)	11.3 (10.2-12.5)
All nonneoplastic causes	634	218.4	2.9 (2.7-3.1)	11.2 (10.0-12.6)
Infections	44	5.9	7.5 (5.4-10.0)	1.0 (0.7-1.4)
Blood disease	7	1.3	5.4 (2.2-11.2)	0.2 (0.1-0.4)
Endocrine disease	24	6.2	3.9 (2.5-5.7)	0.5 (0.3-0.8)
Mental disorders	7	8.5	0.8 (0.3-1.7)	0.0 (NA)
Nervous system disease	55	13.5	4.1 (3.1-5.3)	1.1 (0.8-1.6)
Circulatory (all) disease	170	43.0	4.0 (3.4-4.6)	3.4 (2.8-4.2)
Cardiac disease	105	29.9	3.5 (2.9-4.2)	2.0 (1.6-2.7)
Cerebrovascular disease	48	9.0	5.2 (3.9-6.9)	1.1 (0.7-1.5)
Other circulatory disease	17	4.0	4.3 (2.7-6.9)	0.4 (0.2-0.7)
Respiratory disease	106	13.3	8.0 (6.6-9.7)	2.5 (2.0-3.1)
Digestive disease	30	14.3	2.1 (1.4-3.0)	0.4 (0.2-0.8)
Skin and musculoskeletal disease	5	1.5	3.3 (1.1-7.6)	0.1 (0.0-0.3)
Genitourinary disease	21	2.0	10.6 (6.6-16.3)	0.5 (0.3-0.8)
Pregnancy and childbirth	17	6.5	2.6 (1.5-4.2)	0.3 (0.1-0.6)
External causes	138	99.6	1.4 (1.1-1.6)	1.0 (0.6-1.9)
Suicide	37	37.6	1.0 (0.7-1.4)	0.0 (NA)
Other	10	2.7	3.7 (2.0-6.8)	0.2 (0.1-0.5)

Abbreviations: AER, absolute excess risk; CI, confidence interval; NA, not applicable; SMR, standardized mortality ratio.
[a] Per 10 000 person-years.

exit date. Death certificates were obtained for 3035 of 3049 deaths (99.5%). Survivors were followed up for a total of 370 025 person-years from 5-year survival with a mean and median follow-up of 25.6 and 24.3 years (range, 5-66 years) since diagnosis, respectively. There were 134 727 and 83 783 person-years beyond 20 and 25 years from diagnosis, respectively, and 34 345 person-years beyond age 40 years.

Observed and Expected Deaths

The SMR was significantly increased for all causes of death, except for mental disorder–related deaths and suicide (TABLE 1). A substantial excess (SMR ≥5) was apparent for deaths due to genitourinary disease, respiratory disease, infection, second primary cancer, blood disease, and cerebrovascular disease. In terms of AER, survivors were most at risk of dying of recurrence (AER, 51.8; 95% confidence interval [CI], 49.4-54.1), second primary cancer (AER, 11.3; 95% CI, 10.2-12.5), circulatory disease (AER, 3.4; 95% CI, 2.8-4.2), and respiratory disease (AER, 2.5; 95% CI, 2.0-3.1).

All Causes of Death

Overall, survivors experienced 11 times the number of deaths expected from the general population (SMR, 10.7; 95% CI, 10.3-11.1) and 75 additional deaths (95% CI, 72-78) per 10 000 person-years in excess of that expected (TABLE 2). The SMR declined significantly with increasing follow-up and attained age ($P<.001$ for trend); nonetheless, significant excess mortality remained even after 45 years from diagnosis (SMR, 3.1; 95% CI, 2.5-3.9). There was evidence of nonlinearity in AERs by follow-up (nonlinearity $P<.001$); with the variation in the AER resembling a U-shaped curve. The AER was 115 (95% CI, 109-120) over the first 10 years after 5-year survival, declined to roughly 40 between 15 and 35 years after diagnosis, and then increased to 114 (95% CI, 83-157) beyond 45 years after diagnosis. All types of childhood cancer were associated with significantly increased mortality relative to the general population, with the greatest SMRs observed among survivors of primitive neuroectodermal tumor (PNET) and leukemia. The AER was 192 (95% CI, 168-220) after PNET and also exceeded 100 after central nervous system tumors other than PNET and after leukemia.

Specific Causes of Death

The crude mortality rate for recurrence, which may be interpreted as an AER, decreased rapidly from 97 (95% CI, 92-101) at 5 to 14 years from diagnosis to 11 or fewer deaths per 10 000 person-years beyond 25 years from diagnosis (Table 2). Mortality due to recurrence or progression of the original disease was greatest among PNET survivors. Females were at significantly lower risk than males (RR, 0.8; 95% CI, 0.8-0.9) (eTable 1).

The SMR for a second primary cancer declined sharply up to 35 years after diagnosis but thereafter remained at a roughly constant level (Table 2). Even after 45 years, the SMR was still 3.6-fold higher (95% CI, 2.6-4.9). Similarly, the SMR decreased significantly with attained age ($P<.001$ for trend) but still was elevated 2.7-fold (95% CI, 2.1-3.6) beyond age 50 years. In contrast, the AER increased with time since diagnosis and attained age reaching 58 (95% CI, 38-90) beyond 45 years from diagnosis and 39 (95% CI, 25-60) beyond age 50 years. Beyond 45 years, 51% of the total AER could be attributed to deaths due to a second primary cancer (TABLE 3). The SMR was significantly elevated for all types of childhood cancer but greatest among survivors of PNET and heritable retinoblastoma. Treatment with radiotherapy increased both the RR and EMR 2-fold (RR, 1.8; 95% CI, 1.4-2.3; EMR, 2.0; 95% CI, 1.5-2.8) (eTable 1).

The SMR for circulatory deaths, which includes cardiac and cerebrovascular deaths, was 10.7-fold (95% CI, 7.8-14.6) over the first 10 years of follow-up and then declined to a plateau and remained roughly at 2- to 3-fold beyond 25 years from diagnosis

Table 2. Standardized Mortality Ratio and Absolute Excess Risk for Deaths Due to All Causes Combined and Second Primary Cancer by Potential Explanatory Factors, and Crude Death Rates Due to Recurrence by Potential Explanatory Factors

	All Causes				Recurrence Deaths		Second Primary Cancer Deaths		
	Person-Years	Obs/Exp	SMR (95% CI)	AER (95% CI)[a]	Obs	Crude Rate (95% CI)[a,b]	Obs/Exp	SMR (95% CI)	AER (95% CI)[a]
Overall	370 025	3049/284.8	10.7 (10.3-11.1)	74.7 (71.8-77.7)	1918	51.8 (49.4-54.1)	483/66.4	7.3 (6.7-8.0)	11.3 (10.2-12.5)
Sex									
Male	200 422	1808/195.7	9.2 (8.8-9.7)	80.4 (76.4-84.7)	1126	56.2 (53.0-59.6)	282/34.4	8.2 (7.3-9.2)	12.4 (10.8-14.1)
Female	169 603	1241/89.1	13.9 (13.2-14.7)	67.9 (64.0-72.1)	792	46.7 (43.6-50.1)	201/32.0	6.3 (5.5-7.2)	10.0 (8.5-11.7)
$P_{heterogeneity}$			<.001	<.001		<.001		.003	.04
Type of childhood cancer									
CNS tumor (excluding PNET)	74 958	879/67.9	12.9 (12.1-13.8)	108.2 (100.7-116.2)	574	76.6 (70.6-83.1)	89/17.6	5.1 (4.1-6.2)	9.5 (7.4-12.3)
PNET	11 210	224/8.8	25.5 (22.3-29.0)	192.0 (167.5-220.0)	147	131.1 (111.6-154.1)	46/1.8	25.1 (18.8-33.5)	39.4 (29.2-53.2)
Leukemia (excluding AML)	74 730	797/37.1	21.5 (20.0-23.0)	101.7 (94.5-109.4)	640	85.6 (79.3-92.5)	61/5.8	10.5 (8.2-13.5)	7.4 (5.6-9.7)
AML	5342	45/2.8	15.8 (11.8-21.2)	78.9 (57.8-107.8)	28	52.4 (36.2-75.9)	7/0.5	15.2 (7.3-31.9)	12.2 (5.5-27.1)
Hodgkin lymphoma	27 232	251/28.4	8.8 (7.8-10.0)	81.8 (71.1-94.0)	144	52.9 (44.9-62.3)	46/6.1	7.5 (5.6-10.0)	14.6 (10.5-20.4)
NHL	18 527	84/18.5	4.5 (3.7-5.6)	35.3 (26.9-46.5)	32	17.3 (12.2-24.4)	18/4.3	4.2 (2.6-6.6)	7.4 (4.0-13.6)
Neuroblastoma	16 970	92/9.9	9.3 (7.5-11.4)	48.4 (38.5-60.8)	49	28.9 (21.8-38.2)	16/2.1	7.5 (4.6-12.2)	8.2 (4.6-14.4)
NH retinoblastoma	18 394	21/14.2	1.5 (1.0-2.3)	3.7 (1.0-13.8)	0	0.0	11/3.6	3.0 (1.7-5.5)	4.0 (1.7-9.7)
Heritable retinoblastoma	15 160	100/11.1	9.0 (7.4-11.0)	58.7 (47.1-73.1)	19	12.5 (8.0-19.6)	67/2.7	24.7 (19.4-31.3)	42.4 (33.0-54.4)
Wilms tumor	34 301	122/21.0	5.8 (4.9-6.9)	29.4 (23.8-36.5)	41	12.0 (8.8-16.2)	35/4.4	8.0 (5.8-11.2)	8.9 (6.1-13.0)
Bone tumor	12 915	116/13.1	8.9 (7.4-10.6)	79.7 (64.9-97.8)	78	60.4 (48.4-75.4)	24/3.6	6.7 (4.5-10.0)	15.8 (9.9-25.3)
Soft tissue sarcoma	26 680	161/23.6	6.8 (5.9-8.0)	51.5 (43.0-61.7)	98	36.7 (30.1-44.8)	26/5.9	4.4 (3.0-6.5)	7.5 (4.6-12.4)
Other	33 607	157/28.5	5.5 (4.7-6.4)	38.2 (31.6-46.3)	68	20.2 (16.0-25.7)	37/8.0	4.6 (3.4-6.4)	8.6 (5.7-13.0)
$P_{heterogeneity}$			<.001	<.001		<.001		<.001	<.001
Age at diagnosis, y									
0-4	174 166	1129/99.7	11.3 (10.7-12.0)	59.1 (55.4-63.0)	676	38.8 (36.0-41.9)	217/20.2	10.7 (9.4-12.3)	11.3 (9.8-13.1)
5-9	96 304	921/74.2	12.4 (11.6-13.2)	87.9 (82.0-94.3)	632	65.6 (60.7-70.9)	109/15.9	6.9 (5.7-8.3)	9.7 (7.8-12.0)
10-14	99 555	999/110.9	9.0 (8.5-9.6)	89.2 (83.2-95.7)	610	61.3 (56.6-66.3)	157/30.3	5.2 (4.4-6.1)	12.7 (10.5-15.4)
P_{trend}			<.001	<.001		<.001		<.001	.50
Radiotherapy									
No	91 386	560/77.8	7.2 (6.6-7.8)	52.8 (47.9-58.1)	355	38.8 (35.0-43.1)	81/19.6	4.1 (3.3-5.1)	6.7 (5.0-9.0)
Yes	207 172	2047/173.4	11.8 (11.3-12.3)	90.4 (86.3-94.8)	1254	60.5 (57.3-64.0)	357/40.9	8.7 (7.9-9.7)	15.3 (13.6-17.2)
$P_{heterogeneity}$			<.001	<.001		<.001		<.001	<.001
Chemotherapy									
No	157 185	1328/164.2	8.1 (7.7-8.5)	74.0 (69.6-78.7)	741	47.1 (43.9-50.7)	264/45.6	5.8 (5.1-6.5)	13.9 (12.0-16.1)
Yes	128 761	1198/75.8	15.8 (14.9-16.7)	87.2 (82.0-92.6)	827	64.2 (60.0-68.8)	165/12.3	13.4 (11.5-15.6)	11.9 (10.1-14.0)
$P_{heterogeneity}$			<.001	<.001		<.001		<.001	.16

(continued)

Table 2. Standardized Mortality Ratio and Absolute Excess Risk for Deaths Due to All Causes Combined and Second Primary Cancer by Potential Explanatory Factors, and Crude Death Rates Due to Recurrence by Potential Explanatory Factors (continued)

	All Causes				Recurrence Deaths		Second Primary Cancer Deaths		
	Person-Years	Obs/Exp	SMR (95% CI)	AER (95% CI)[a]	Obs	Crude Rate (95% CI)[a,b]	Obs/Exp	SMR (95% CI)	AER (95% CI)[a]
Years from cancer diagnosis, y									
5-14	166 059	1970/69.1	28.5 (27.3-29.8)	114.5 (109.4-119.8)	1604	96.6 (92.0-101.4)	145/9.3	15.5 (13.2-18.3)	8.2 (6.9-9.7)
15-24	120 182	535/78.4	6.8 (6.3-7.4)	38.0 (34.4-42.0)	227	18.9 (16.6-21.5)	136/12.1	11.3 (9.5-13.3)	10.3 (8.6-12.4)
25-34	57 900	304/61.8	4.9 (4.4-5.5)	41.8 (36.3-48.2)	64	11.1 (8.7-14.1)	99/16.0	6.2 (5.1-7.5)	14.3 (11.3-18.1)
35-44	21 028	159/49.8	3.2 (2.7-3.7)	51.9 (41.4-65.1)	19	9.0 (5.8-14.2)	64/18.1	3.5 (2.8-4.5)	21.8 (15.5-30.7)
≥45	4855	81/25.8	3.1 (2.5-3.9)	113.7 (82.6-156.5)	4	8.2 (3.1-22.0)	39/10.8	3.6 (2.6-4.9)	58.0 (37.5-89.6)
P_{trend}			<.001	<.001		<.001		<.001	<.001
Attained age, y									
0-19	139 996	1629/49.5	32.9 (31.3-34.5)	112.8 (107.3-118.6)	1343	95.9 (90.9-101.2)	124/6.9	18.1 (15.1-21.5)	8.4 (6.9-10.1)
20-29	125 988	744/78.5	9.5 (8.8-10.2)	52.8 (48.7-57.2)	422	33.5 (30.4-36.8)	126/9.8	12.8 (10.8-15.3)	9.2 (7.6-11.1)
30-39	69 696	374/62.4	6.0 (5.4-6.6)	44.7 (39.6-50.5)	119	17.1 (14.3-20.4)	117/14.1	8.3 (6.9-10.0)	14.8 (12.0-18.1)
40-49	26 171	184/51.2	3.6 (3.1-4.2)	50.7 (41.5-62.0)	28	10.7 (7.4-15.5)	66/17.2	3.8 (3.0-4.9)	18.6 (13.4-25.8)
≥50	8173	118/43.2	2.7 (2.3-3.3)	91.6 (68.9-121.7)	6	7.3 (3.3-16.3)	50/18.4	2.7 (2.1-3.6)	38.6 (24.9-59.9)
P_{trend}			<.001	<.001		<.001		<.001	<.001

Abbreviations: AER, absolute excess risk; AML, acute myeloid leukemia; CI, confidence interval; CNS, central nervous system; Exp, expected; NH, nonheritable; NHL, non-Hodgkin lymphoma; Obs, observed; PNET, primitive neuroectodermal tumor; SMR, standardized mortality ratio.
[a] Per 10 000 person-years.
[b] May be interpreted as an AER.

Table 3. Absolute Excess Risk by Years From Diagnosis as a Proportion of Total Absolute Excess Risk

Cause of Death	AER (%) by Years From Diagnosis				
	5-14 y	15-24 y	25-34 y	35-44 y	≥45 y
Recurrence[a]	96.6 (84.9)	18.9 (50.1)	11.1 (26.7)	9.0 (17.3)	8.2 (7.2)
Second primary cancer	8.2 (7.2)	10.3 (27.3)	14.3 (34.5)	21.8 (42.0)	58.0 (51.0)
Circulatory	2.1 (1.9)	2.9 (7.4)	4.6 (11.1)	7.5 (14.5)	29.4 (25.9)
Cardiac	1.4 (1.2)	1.9 (4.8)	3.0 (7.2)	2.5 (4.8)	15.1 (13.3)
Respiratory	2.5 (2.2)	1.3 (3.5)	3.4 (8.2)	5.9 (11.4)	8.5 (7.4)
External	0.6 (0.3)	0.7 (1.9)	2.4 (5.8)	1.9 (3.7)	5.5 (4.8)
Other	3.9 (3.4)	3.7 (9.8)	5.7 (13.7)	5.8 (11.1)	4.1 (3.6)
All deaths[b]	113.9	37.8	41.5	51.9	113.7

Abbreviation: AER, absolute excess risk.
[a] Expected number for deaths due to recurrence assumed to be 0.
[b] Small inconsistency of total AER with AER from Table 2 is due to unknown causes of death among 14 survivors.

(eTable 2). On the other hand, the AER for circulatory deaths increased steadily with follow-up ($P<.001$ for trend), reaching 29 (95% CI, 16-56) beyond 45 years from diagnosis (increasing from 2; 95% CI, 2-3, in the first 10 years of follow-up). Nearly 26% of all excess deaths beyond 45 years from diagnosis were attributed to circulatory causes (Table 3). All survivors, apart from survivors of retinoblastoma and bone tumor, exhibited significantly elevated SMRs for circulatory disease. The AER exceeded 10 for survivors of acute myeloid leukemia (AER, 10.7; 95% CI, 4.6-24.8). Multivariable analyses revealed that survivors treated with radiotherapy were at a 2-fold significantly increased risk of dying of circulatory disease relative to survivors not treated with radiotherapy (RR, 1.9; 95% CI, 1.2-3.0; EMR, 2.2; 95% CI, 1.2-3.9) (eTable 3).

The SMR for cardiac disease declined with increasing follow-up but remained 2-fold (SMR, 2.3; 95% CI, 1.3-3.9) elevated 45 years after diagnosis (eTable 2). The AER increased significantly ($P=.01$ for trend) with follow-up, reaching 15 (95% CI, 6-40) beyond 45 years from diagnosis. The SMR and AER were greatest for survivors of acute myeloid leukemia. Thirteen percent of all excess deaths beyond 45 years from diagnosis were attributed to cardiac causes (Table 3).

The SMR for respiratory disease declined with increasing follow-up but remained significantly elevated even 45

years after the initial cancer diagnosis (eTable 2). In contrast, the AER increased significantly with increasing time since diagnosis to an AER of 9 (95% CI, 3-27) beyond 45 years from diagnosis. Survivors of all cancer types, apart from those with nonheritable retinoblastoma or a bone tumor, exhibited significantly elevated SMRs for respiratory disease. Survivors treated with chemotherapy were at 3-fold increased risk vs those not treated with chemotherapy (RR, 3.1; 95% CI, 1.7-5.7; EMR, 2.9; 95% CI, 1.5-5.8) (eTable 3).

The SMR for external causes of death increased slightly with follow-up, to an SMR of 3.0 (95% CI, 1.1-8.1) beyond 45 years from diagnosis (eTable 2). The AER also increased slightly with follow-up ($P = .03$ for trend).

Cumulative Mortality

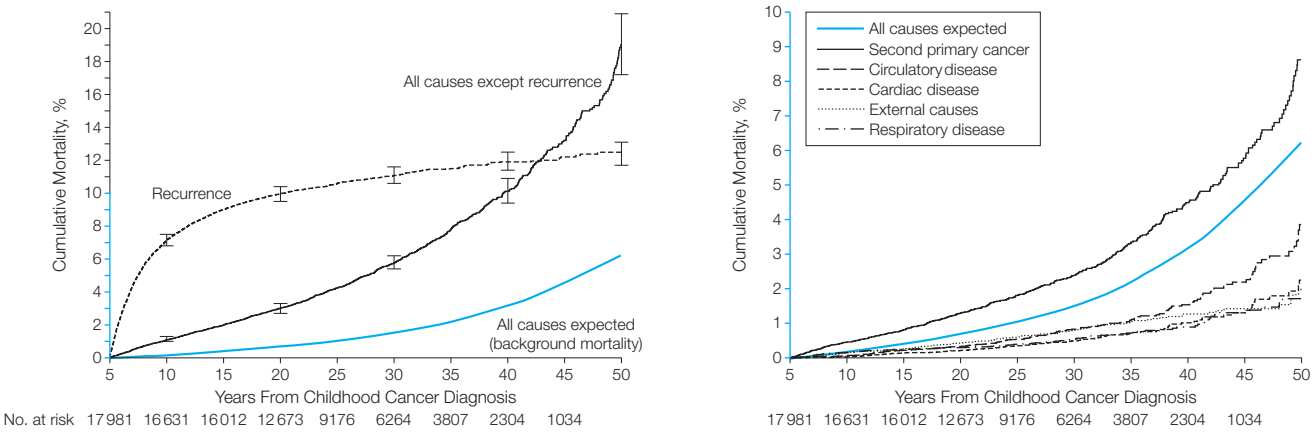
The CM from all death causes other than recurrence was 19.0% (95% CI, 17.2%-20.9%) at 50 years from initial diagnosis whereas 6.3% was expected based on rates from the general population (FIGURE). The CM of death due to recurrence increased rapidly with time from diagnosis to 8.9% (95% CI, 8.5%-9.4%) by 15 years but then leveled off, reaching 12.4% (95% CI, 11.7%-13.1%) by 50 years. The CM of second primary cancer increased gradually with time from diagnosis, reaching 2.4% (95% CI, 2.1%-2.7%) by 30 years, but then increased rapidly to 8.6% (95% CI, 7.4%-10.0%) by 50 years. For circulatory deaths, the CM was low by 30 years (CM, 0.8%; 95% CI, 0.7%-1.0%) but increased to 3.9% (95% CI, 3.0%-4.9%) by 50 years from diagnosis (Figure).

COMMENT

This study identified a persistence of an elevated risk of mortality due to second primary cancer, circulatory disease, and pulmonary disease beyond 25 years from the diagnosis of childhood cancer relative to the general population. As a result of this elevated RR, the AER of mortality due to second primary cancer, circulatory disease, and pulmonary disease increased rapidly with increasing time from diagnosis. The AER for deaths from recurrence declined from 97 extra deaths (per 10 000 person-years) at 5 to 14 years from diagnosis to 8 extra deaths beyond 45 years from diagnosis. In contrast, during the same periods of follow-up, the AER for deaths from second primary tumor, circulatory deaths, and cardiac deaths increased from 8, 2, and 1 extra deaths to 58, 28, and 15 extra deaths, respectively. Beyond 45 years from diagnosis, recurrence accounted for 7% of the excess number of deaths observed while second primary cancers and circulatory deaths together accounted for 77%.

Previously, we have reported the risks of specific causes of death after childhood cancer within the same cohort,[3,5] but the current study adds 16 years of follow-up and 1507 deaths for analysis. The Childhood Cancer Survivor Study (CCSS)[2] and a cohort from the Nordic countries[4] were of similar size as the current cohort but had fewer person-years and observed deaths, particularly beyond 25 years from diagnosis. Compared with these 2 studies, our SMRs by follow-up were generally consistent although somewhat higher than those in the Nordic Country Study and marginally lower than observed in the non–population-based CCSS. In all 3 studies, however, the CM of second primary cancer by 25 years from diagnosis was low (<3.5%), but in the current study it increased substantially in the subsequent years of follow-up and such older survivor experience is only

Figure. Cumulative Mortality of Causes of Death Among Survivors of Childhood Cancer



Observed cumulative mortality of all causes of death other than recurrence was 19.0% at 50 years from initial diagnosis, whereas 6.3% was expected based on rates from the general population. Cumulative mortality of death due to recurrence increased rapidly with time from diagnosis to 8.9% by 15 years but then leveled off to 12.4% by 50 years. Cumulative mortality for each cause of death takes into account other causes of death as a competing risk. For second primary cancer, cumulative mortality increased gradually with time to 2.4% by 30 years but then increased rapidly to 8.6% by 50 years. For circulatory disease, the cumulative mortality was low by 30 years (0.8%) but increased to 3.9% by 50 years. Segment of y-axis shown in blue indicates cumulative mortality range of 0% to 10%. Error bars indicate 95% confidence intervals.

available in the current study. The AERs by follow-up for second primary cancer, cardiac causes, and respiratory causes were comparable between the CCSS and BCCSS. If the AER in the CCSS were to increase over the next few decades in a similar fashion as in the current cohort, a substantial number of survivors would die prematurely.

It is interesting to note that there was no increase in deaths from suicide or other mental disorders. Although there are concerns about long-term psychological problems for some survivors of childhood cancer, this does not appear to lead to an excess of deaths from these causes.

The excess mortality due to second primary cancer and circulatory disease is likely attributable to late complications of treatment.[14,15] Second primary cancers are a recognized late complication of childhood cancer,[16-18] largely due to exposure to radiation during treatment, but specific cytotoxic drugs also have been implicated in the development of second primary cancers. In addition, a small proportion of all second primary cancer deaths might be related to familial cancer syndromes, such as Li-Fraumeni and heritable retinoblastoma.[19] Evidence is also emerging that treatment of childhood cancer increases the risk of circulatory disease.[20] More specifically, exposure to cranial irradiation increases the risk of stroke[21,22] and exposure to chest irradiation has been associated with heart disease,[20] but also exposure to high cumulative doses of specific chemotherapeutic agents, principally the anthracyclines, may induce cardiotoxicity.[20,23-25]

A potential limitation of our study includes the lack of detailed data on radiotherapy and chemotherapy exposures, missing data (approximately 30%) on treatment, and lack of data on treatment intensity, which precluded any examination of dose-response patterns of treatment exposures in relation to mortality risk. It is further important to acknowledge that survivors included in the current cohort were treated between 1940 and 1991; consequently, findings may not be translatable to survivors treated in more recent years. Also, the mortality risks we provide for survivors followed up for more than 30 years, and who were thus treated prior to the introduction of modern anticancer therapy, may not be applicable to survivors treated with modern therapy, including, for example, modern chemotherapy. Further follow-up is necessary to address with more certainty the mortality risk of survivors treated in more recent decades.

The large-scale population-based ascertainment of deaths in this cohort ensures provision of unbiased and reliable risk estimates of late mortality among survivors of childhood cancer. Such risk estimates are useful for informing survivors and clinicians regarding the risk of late death. In light of the rapid and progressive increase in AER by time since diagnosis, continued monitoring of mortality patterns among long-term survivors of childhood cancer would be prudent, particularly as increasing numbers of survivors reach an age at which the risk of mature-onset disease increases substantially in the general population. There is clearly potential for an increasingly substantial number of premature deaths among survivors.

In terms of absolute risk, survivors diagnosed more than 25 years ago are currently most at risk of dying of a second primary cancer or circulatory disease, yet these survivors are much less likely to be actively followed up than those diagnosed more recently.[26] The findings of this study suggest that survivors should be able to access health care intervention programs even many years after survival from their first cancer.

In conclusion, the findings from this large-scale population-based study indicate that the AER and CM related to second primary tumors, circulatory disease, and respiratory disease increase rapidly beyond 25 years from diagnosis, which suggests a substantial number of survivors are dying prematurely. These findings confirm the importance of very long-term outcome data and that survivors should be able to access health care programs even decades after treatment. Finally, the principal clinical message from these data is straightforward; 77% of the excess number of deaths observed among those surviving beyond 45 years from diagnosis of childhood cancer in Britain are due to second primary cancers and circulatory deaths. Finding ways to successfully intervene to reduce these potentially preventable premature deaths will be complex.

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Study concept and design: Winter, Lancashire, Stiller, Jenney, Skinner, Stevens, Hawkins.
Acquisition of data: Winter, Stiller, Lancashire, Hawkins.
Analysis and interpretation of data: Reulen, Frobisher, Stiller, Skinner, Stevens, Hawkins.
Drafting of the manuscript: Reulen, Frobisher, Stiller, Skinner, Stevens, Hawkins.
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Administrative, technical, or material support: Winter, Lancashire.
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REFERENCES

1. Mertens AC. Cause of mortality in 5-year survivors of childhood cancer. *Pediatr Blood Cancer*. 2007; 48(7):723-726.
2. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2008;100(19):1368-1379.
3. Hawkins MM, Kingston JE, Kinnier Wilson LM. Late deaths after treatment for childhood cancer. *Arch Dis Child*. 1990;65(12):1356-1363.
4. Möller TR, Garwicz S, Barlow L, et al; Association of the Nordic Cancer Registries; Nordic Society for Pediatric Hematology and Oncology. Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries. *J Clin Oncol*. 2001;19(13): 3173-3181.
5. Robertson CM, Hawkins MM, Kingston JE. Late deaths and survival after childhood cancer: implications for cure. *BMJ*. 1994;309(6948):162-166.
6. Cardous-Ubbink MC, Heinen RC, Langeveld NE, et al. Long-term cause-specific mortality among five-year survivors of childhood cancer. *Pediatr Blood Cancer*. 2004;42(7):563-573.
7. Dama E, Pastore G, Mosso ML, et al. Late deaths among five-year survivors of childhood cancer: a population-based study in Piedmont Region, Italy. *Haematologica*. 2006;91(8):1084-1091.
8. MacArthur AC, Spinelli JJ, Rogers PC, Goddard KJ, Abanto ZU, McBride ML. Mortality among 5-year survivors of cancer diagnosed during childhood or adolescence in British Columbia, Canada. *Pediatr Blood Cancer*. 2007;48(4):460-467.
9. Yeh JM, Nekhlyudov L, Goldie SJ, Mertens AC, Diller L. A model-based estimate of cumulative excess mortality in survivors of childhood cancer. *Ann Intern Med*. 2010;152(7):409-417, W131-8.
10. Hawkins MM, Lancashire ER, Winter DL, et al. The British Childhood Cancer Survivor Study: objectives, methods, population structure, response rates and initial descriptive information. *Pediatr Blood Cancer*. 2008;50(5):1018-1025.
11. Breslow NE, Day NE. *Statistical Methods in Cancer Research: Volume II, The Design and Analysis of Cohort Studies.* Lyon, France: IARC Scientific Publications; 1987.
12. Office of National Statistics. *Mortality Statistics.* London, England: Office of National Statistics; 2006.
13. Coviello V, Bogges M. Cumulative incidence estimation in the presence of competing risks. *Stata J*. 2004;4:103-112.
14. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA*. 2007;297(24):2705-2715.
15. Oeffinger KC, Mertens AC, Sklar CA, et al; Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355(15):1572-1582.
16. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *J Natl Cancer Inst*. 2001;93(8):618-629.
17. Olsen JH, Moller T, Anderson H, et al. Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. *J Natl Cancer Inst*. 2009;101(11):806-813.
18. Jenkinson HC, Hawkins MM, Stiller CA, Winter DL, Marsden HB, Stevens MC. Long-term population-based risks of second malignant neoplasms after childhood cancer in Britain. *Br J Cancer*. 2004;91(11): 1905-1910.
19. Yu CL, Tucker MA, Abramson DH, et al. Cause-specific mortality in long-term survivors of retinoblastoma. *J Natl Cancer Inst*. 2009;101(8): 581-591.
20. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606.
21. Morris B, Partap S, Yeom K, Gibbs IC, Fisher PG, King AA. Cerebrovascular disease in childhood cancer survivors: a Children's Oncology Group report. *Neurology*. 2009;73(22):1906-1913.
22. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2006; 24(33):5277-5282.
23. Lipshultz SE, Alvarez JA, Scully RE. Anthracycline associated cardiotoxicity in survivors of childhood cancer. *Heart*. 2008;94(4):525-533.
24. Lipshultz SE, Lipsitz SR, Mone SM, et al. Female sex and drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med*. 1995;332(26):1738-1743.
25. van Dalen EC, van der Pal HJ, Kok WE, Caron HN, Kremer LC. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. *Eur J Cancer*. 2006;42(18):3191-3198.
26. Taylor A, Hawkins M, Griffiths A, et al. Long-term follow-up of survivors of childhood cancer in the UK. *Pediatr Blood Cancer*. 2004;42(2):161-168.