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DOI:
10.1161/CIRCULATIONAHA.116.024811

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Fidler, M, Reulen, RC, Henson, KE, Kelly, J, Cutter, D, Levitt, GA, Frobisher, C, Winter, DL, Hawkins, M & British Childhood Cancer Survivor Study (BCCSS) Steering Group 2017, 'Population-based long-term cardiac-specific mortality among 34,489 five-year survivors of childhood cancer in Great Britain', *Circulation*, vol. 135, no. 10, pp. 951-963. https://doi.org/10.1161/CIRCULATIONAHA.116.024811

Population-Based Long-Term Cardiac-Specific Mortality Among 34 489 Five-Year Survivors of Childhood Cancer in Great Britain

BACKGROUND: Increased risks of cardiac morbidity and mortality among childhood cancer survivors have been described previously. However, little is known about the very long-term risks of cardiac mortality and whether the risk has decreased among those more recently diagnosed. We investigated the risk of long-term cardiac mortality among survivors within the recently extended British Childhood Cancer Survivor Study.

METHODS: The British Childhood Cancer Survivor Study is a population-based cohort of 34 489 five-year survivors of childhood cancer diagnosed from 1940 to 2006 and followed up until February 28, 2014, and is the largest cohort to date to assess late cardiac mortality. Standardized mortality ratios and absolute excess risks were used to quantify cardiac mortality excess risk. Multivariable Poisson regression models were used to evaluate the simultaneous effect of risk factors. Likelihood ratio tests were used to test for heterogeneity and trends.

RESULTS: Overall, 181 cardiac deaths were observed, which was 3.4 times that expected. Survivors were 2.5 times and 5.9 times more at risk of ischemic heart disease and cardiomyopathy/heart failure death, respectively, than expected. Among those >60 years of age, subsequent primary neoplasms, cardiac disease, and other circulatory conditions accounted for 31%, 22%, and 15% of all excess deaths, respectively, providing clear focus for preventive interventions. The risk of both overall cardiac and cardiomyopathy/heart failure mortality was greatest among those diagnosed from 1980 to 1989. Specifically, for cardiomyopathy/heart failure deaths, survivors diagnosed from 1980 to 1989 had 28.9 times the excess number of deaths observed for survivors diagnosed either before 1970 or from 1990 on.

CONCLUSIONS: Excess cardiac mortality among 5-year survivors of childhood cancer remains increased beyond 50 years of age and has clear messages in terms of prevention strategies. However, the fact that the risk was greatest in those diagnosed from 1980 to 1989 suggests that initiatives to reduce cardiotoxicity among those treated more recently may be having a measurable impact.

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Sources of Funding, see page 962

Key Words: mortality ■ neoplasms ■ pediatrics

Clinical Perspective

What Is New?

- We report for the first time risks of cardiac mortality among 5-year survivors of childhood cancer beyond 50 years of age.
- In particular, among those >60 years of age, subsequent primary neoplasms, cardiac disease, and other circulatory conditions accounted for 31%, 22%, and 15% of all excess deaths, respectively, providing clear focus for preventive interventions.
- The present study is also the first to show that the number of excess cardiac deaths, in particular cardiomyopathy/heart failure deaths, was greatest among those diagnosed in the 1980s.

What Are the Clinical Implications?

- Our findings suggest that cardiac disease becomes increasingly important as childhood cancer survivors reach mature adulthood, suggesting that initiatives aimed at preventing excess mortality and morbidity in survivors >50 years of age should be focused on both subsequent primary neoplasm and cardiac disease prevention, surveillance, and management.
- Nonetheless, efforts to reduce cardiotoxicity among those treated more recently appear to be having a measurable impact because the number of excess cardiac deaths was greatest among survivors diagnosed in the 1980s.

Treatment for childhood cancer has changed substantially over the past 50 years. In particular, since 1990, there have been attempts to reduce treatment intensity among children with relatively good-prognosis neoplasms with the aim of reducing the risk of treatment-related morbidity and mortality. Previous research has identified that thoracic radiotherapy and specific types of chemotherapy, particularly anthracyclines, which were introduced in the late 1970s, increase the risk of cardiac disease among survivors of childhood cancer.[1,2] Thus, it is important to assess whether there is evidence of a measurable decline in the risk of death from cardiac disease among those treated since 1990.

However, to date, only 2 studies have investigated the risk of cardiac mortality in relation to treatment era, both of which were restricted by narrow treatment era time spans.[3,4] For this reason, we have investigated the risk of cardiac mortality among nearly 35 000 survivors of childhood cancer included in the BCCSS (British Childhood Cancer Survivor Study), the largest study to assess mortality in survivors of childhood cancer.[5] Principal advantages of the BCCSS compared with previous studies are that it is large-scale and population based and includes survivors treated across almost 7 decades (1940–2006), enabling an assessment of the risk of cardiac mortality in relation to a wide span of treatment eras. Furthermore, because the BCCSS has an unrivaled number of survivors from earlier treatment decades, we have undertaken the most powerful investigation of excess cardiac mortality risks among childhood cancer survivors >50 years of age. As a result, the findings from this study provide new evidence with which to inform survivors of childhood cancer and clinicians and to update clinical follow-up guidelines.

METHODS

The BCCSS

The BCCSS comprises 34 489 five-year survivors of childhood cancer diagnosed under 15 years age from 1940 to 2006 in Britain. The cohort was the first national population-based study of survivors of childhood cancer to be untaken in Great Britain and was identified from the National Registry of Childhood Tumors, which has an ≈99% ascertainment rate.[6] The study is maintained at the Center for Childhood Cancer Survivor Studies, where research on a wide spectrum of possible adverse health outcomes of childhood cancer and its treatment is undertaken. Additional details relating to the study may be found online[7] and in the descriptive article concerned with methodological aspects underlying the BCCSS.[8] Ethics approval for the study was obtained from the National Research Ethics Service, and legal approval to process identifiable data without consent was approved by the Confidentiality Advisory Group. Descriptive characteristics of the BCCSS cohort can be found in Tables I–III in the online-only Data Supplement.

Death Ascertainment

Collaboration with the Health and Social Care Information Center (England and Wales) and National Health Service Central Register (Scotland) enabled us to ascertain each survivor's vital and residency/emigration status. 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 (England and Wales) and National Records of Scotland (Scotland) using the relevant *International Classification of Diseases*. *International Classification of Diseases* codes corresponding to a cardiac death were identified and subcategorized into clinically relevant groups for analysis, specifically ischemic heart disease (IHD), cardiomyopathy/heart failure (CM/HF), arrhythmias, pericardial disease, and valvular disease (Table IV in the online-only Data Supplement). Follow-up for cardiac mortality began at 5-year survival and continued until the first instance of emigration, death, or February 28, 2014.

Statistical Analyses

Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were calculated with standard cohort techniques.[9] The SMR was defined as the observed divided by the expected number of deaths. The AER was defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10 000. Expected numbers were calculated by multiplying the person-years within each sex-, age- (quinquennial), and calendar year- (single year) specific stratum by the

Circulation. 2017;135:951–963. DOI: 10.1161/CIRCULATIONAHA.116.024811

corresponding mortality rate for the population of England and Wales and then summing across the strata.[10]

Multivariable Poisson regression models for the SMRs and AERs were then fitted to evaluate the simultaneous effect of the following demographic- and cancer-related factors: sex, first primary neoplasm (FPN) type, age at cancer diagnosis, treatment era of diagnosis, and attained age. The results from the adjusted multivariable model were reported in terms of relative risks (which may be interpreted as the ratios of the SMRs adjusted for other factors fitted) and excess mortality ratios (EMRs; which may be interpreted as the ratios of the AERs adjusted for other factors fitted[9]; Table V in the online-only Data Supplement). To test for heterogeneity or linear trend, likelihood ratio tests within Poisson regression models were used. *P* for heterogeneity tests the null hypothesis that the relative risks or EMRs are equal across levels of the factor concerned, against the alternative hypothesis that the relative risks or EMRs vary across levels of the factor, having adjusted for other factors included within the model. *P* for trend tests the null hypothesis that the relative risks or EMRs are equal across levels of the factor concerned, against the alternative hypothesis that the relative risks or EMRs increase or decrease linearly across levels of the factor, having adjusted for other factors included within the model. Because we anticipated a priori that there might be evidence of risks increasing and then declining as treatment era became more recent, particularly in relation to anthracycline-related CM/HF, we also investigated for evidence of a quadratic relationship in risks with treatment era using likelihood ratio tests within multivariable Poisson regression models. *P* for quadratic tests whether there is evidence of such a specific type of systematic nonlinear variation in the relative risks or EMRs across levels of the factor concerned, having adjusted for other factors included within the model.

Cumulative mortality, as a function of follow-up, was estimated by use of the stcompet command in Stata.[11] Causes of death other than the one under study were treated as competing risks.[12,13] To test for heterogeneity among cumulative mortality curves, log-rank tests were used.

All analyses were completed with Stata 13.1,[11] for which the criterion for statistical significance was a 2-sided value of $P<0.05$.

Patient Involvement

Overall, survivors showed their support for the study by returning 10 488 BCCSS questionnaires, which represented 80% of those sent to survivors. Furthermore, almost all survivors completing the BCCSS questionnaire requested receipt of study newsletters, the means by which we inform survivors of the findings of the research. Last, 2 patient representatives attend the BCCSS Steering Group meetings and provide feedback on research priorities and research translation.

RESULTS

Study Characteristics

From 5-year survival, the cohort was followed up for a total of 620 753 person-years, with a mean follow-up of 18.0 years (range, 0.0–68.7 years) and to a mean attained age of 29.6 years (range, 5.5–85.6 years). By the study exit date, 4475 individuals (13.0%) in the cohort had died; of those deaths, 181 (4.0%) were attributed to cardiac causes (Table 1). The mean follow-up time from diagnosis and attained age at cardiac death were 31.4 and 39.2 years, respectively, which were greater than that observed for individuals who died of a noncardiac cause. Men accounted for approximately two thirds (63.5%) of the cardiac deaths, and survivors of central nervous system tumors (excluding primitive neuroectodermal tumor), Hodgkin lymphoma (HL), and Wilms accounted for nearly 50% of the cardiac deaths observed when combined.

Overall Cardiac Mortality

Survivors of childhood cancer experienced 3.4 times (95% confidence interval [CI], 2.9–3.9) the number of cardiac deaths expected from the general population, which equated to 2.1 (95% CI, 1.6–2.5) excess cardiac deaths per 10 000 person-years (Table 2). All FPN types with at least 5 observed cardiac deaths were at a statistically significant increased risk of cardiac death (Table 3). The SMR was substantially raised (SMR>5.0) for survivors of acute myeloid leukemia, Wilms, and HL at 23.5 (95% CI, 11.2–43.1), 6.5 (95% CI, 4.0–10.0), and 5.4 (95% CI, 3.7–7.6), respectively. From 5 to 19 to >60 years of age, the SMR declined from 9.7-fold (95% CI, 5.9–15.0) to 2.2-fold (95% CI, 1.3–3.5) that expected, respectively, whereas for the same age groupings the AER rose from 0.7 (95% CI, 0.4–1.1) to 23.7 (95% CI, 3.6–43.8) excess cardiac deaths per 10 000 person-years; both of these trends were statistically significant (SMR *P* for trend=0.0065; AER *P* for trend<0.0001). When assessed by treatment era, evidence of a quadratic relationship was identified for the SMRs (*P* for quadratic=0.0014) and AERs (*P* for quadratic=0.0072), where after adjustment the risk was higher among those treated in the 1980s than those treated in decades before or since (Table 4). Compared with those diagnosed before 1970, the relative risk for cardiac death was 1.6 times (95% CI, 1.1–2.5), 2.3 times (95% CI, 1.4–3.8), and 1.0 times (95% CI, 0.4–2.1) higher among those diagnosed in 1970 to 1979, 1980 to 1989, and 1990 to 2006, respectively, after adjustment for sex, FPN type, age at diagnosis, and attained age.

In Table 5, we provide the percentage contributions of specific causes of death to the total excess number of deaths observed at different attained ages. Among those >60 years of age, cardiac deaths accounted for 22% and 41% of all excess deaths and all excess nonneoplastic deaths, respectively. Of all excess deaths observed among those >60 years of age, 31%, 22%, and 15% were attributable to subsequent primary neoplasms (SPNs), cardiac disease, and other circulatory diseases, respectively, accounting for 68% of the excess number of deaths overall.

Table 1. Study Characteristics of the British Childhood Cancer Survivor Study

Patient Characteristic	Cardiac Deaths		Other Deaths		*P* Value	Total	
	n	%	n	%		n	%
Overall	181	100.0	4294	100.0		4475	100.0
Sex							
Male	115	63.5	2524	58.8		2629	58.7
Female	66	36.5	1780	41.5	0.182	1846	41.3
FPN type							
CNS (excluding PNET)	32	17.7	1302	30.3		1334	29.8
CNS PNET	5	2.8	336	7.8		341	7.6
Leukemia (excluding AML)	17	9.4	1086	25.3		1103	24.6
AML	10	5.5	72	1.7		82	1.8
HL	33	18.2	298	6.9		331	7.4
NHL	17	9.4	114	2.7		131	2.9
Neuroblastoma	4	2.2	140	3.3		144	3.2
Nonheritable retinoblastoma	2	1.1	29	0.7		31	0.7
Heritable retinoblastoma	4	2.2	134	3.1		138	3.1
Wilms	20	11.0	164	3.8		184	4.1
Bone sarcoma	9	5.0	189	4.4		198	4.4
Soft tissue sarcoma	12	6.6	241	5.6		253	5.7
Other	16	8.8	189	4.4	<0.001	205	4.6
Age at diagnosis, y							
Mean	7.8		7.3			7.3	
0–4	63	34.8	1598	37.2		1661	37.1
5–9	46	25.4	1306	30.4		1352	30.2
10–14	72	39.8	1390	32.4	0.099	1462	32.7
Treatment era							
1940–1969	79	43.6	1250	29.1		1329	29.7
1970–1979	48	26.5	1199	27.9		1247	27.9
1980–1989	43	23.8	898	20.9		941	21.0
1990–2006	11	6.1	947	22.1	<0.001	958	21.4
Years from diagnosis							
Mean	31.4		16.4			17.0	
5–9	10	5.5	2044	47.6		2054	45.9
10–19	31	17.1	1030	24.0		1061	23.7
20–29	42	23.2	505	11.8		547	12.2
30–39	45	24.9	372	8.7		417	9.3
40–49	34	18.8	243	5.7		277	6.2
50–59	17	9.4	86	2.0		103	2.3
≥60	2	1.1	14	0.3	<0.001	16	0.4
Attained age at exit, y							
Mean	39.2		23.7			24.3	
5–9	1	0.6	415	9.7		416	9.3

(*Continued*)

Table 1. Continued

Patient Characteristic	Cardiac Deaths		Other Deaths		*P* Value	Total	
	n	%	n	%		n	%
10–19	19	10.5	1812	42.2		1831	40.9
20–29	33	18.2	970	22.6		1003	22.4
30–39	42	23.2	493	11.5		535	12.0
40–49	36	19.9	328	7.7		364	8.1
50–59	32	17.7	206	4.8		238	5.3
≥60	18	9.9	70	1.6	<0.001	88	2.0

AML indicates acute myeloid leukemia; CNS, central nervous system; FPN, first primary neoplasm; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; and PNET, primitive neuroectodermal tumor.

Overall, the cumulative mortality for cardiac death was 5.0% at 60 years of follow-up compared with 3.5% expected (Figure I in the online-only Data Supplement). Among the FPN types, the cumulative mortality was greatest for survivors of Wilms and HL (Figure 1); the cumulative mortality for HL survivors began to increase at 20 years of follow-up compared with 25 years of follow-up in Wilms survivors and increased at a higher rate than that observed for Wilms survivors.

Cardiac-Specific Mortality

Of the 181 cardiac deaths observed, there were 96 IHD, 52 CM/HF, 8 valvular disease, 5 arrhythmia, 2 pericardial disease, and 18 other cardiac deaths (7 pulmonary heart disease, 4 acute/subacute infective endocarditis, 4 cardiovascular disease unspecified, 1 hypertensive heart and renal disease, 1 hypertensive heart disease without heart failure, 1 other ill-defined heart disease; Table 2). The SMRs for IHD, CM/HF, valvular, arrhythmia, pericardial, and other cardiac deaths were as follows: 2.5 (95% CI, 2.0–3.1), 5.9 (95% CI, 4.4–7.7), 3.6 (95% CI, 1.6–7.2), 3.4 (95% CI, 1.1–8.0), 8.0 (95% CI, 1.0–29.0), and 8.3 (95% CI, 4.9–13.1), respectively. Because IHD and CM/HF accounted for >80% of cardiac deaths overall, we consider only these 2 specific cardiac outcomes separately.

IHD Mortality

The cumulative mortality of IHD deaths increased steadily until ≈45 years of follow-up, at which point there was a steeper increase, ultimately reaching 3.8% at 65 years of follow-up, which was 1.0% higher than expected (Figure I in the online-only Data Supplement). The SMR for IHD death was highest for survivors of Wilms (SMR, 5.3; 95% CI, 2.7–9.5) and HL (SMR, 4.4; 95% CI, 2.7–6.8; Table 3). Survivors of central nervous system tumors (excluding primitive neuroectodermal tumor), non-Hodgkin lymphoma (NHL), and 'other' FPN types also had a statistically significant elevated risk of IHD death. As attained age increased, the SMR declined significantly (*P* for trend=0.0344) and AER increased significantly (*P* for trend<0.0001); beyond 60 years of age, survivors remained >2 times (SMR, 2.3; 95% CI, 1.3–3.8) more at risk than expected, which equated to 22.2 (95% CI, 3.2–41.1) excess IHD deaths per 10 000 person-years. There was no evidence of a relationship between treatment era and the excess risk (multiplicative or additive) of IHD deaths (Table 4).

CM/HF Mortality

At 65 years from diagnosis, the cumulative mortality of CM/HF deaths was 0.5% compared with 0.3% expected (Figure I in the online-only Data Supplement). All FPN types with at least 5 observed CM/HF deaths were found to be at a substantially higher risk than expected of CM/HF death (SMR>5.0; Table 3); survivors of acute myeloid leukemia, NHL, and Wilms were greatest at risk, with 66.0 times (95% CI, 28.5–130.0), 10.2 times (95% CI, 3.7–22.2), and 8.0 times (95% CI, 2.6–18.8) the number of expected CM/HF deaths, respectively. After adjustment, there was no evidence of

Table 2. Standardized Mortality Ratios and Absolute Excess Risks per 10 000 Person-Years for Deaths Resulting From All Cardiac Causes and Cardiac-Specific Causes

	O/E	SMR (95% CI)	AER (95% CI)
Overall	181/53.1	3.4 (2.9–3.9)	2.1 (1.6–2.5)
IHD	96/38.2	2.5 (2.0–3.1)	0.9 (0.6–1.2)
CM/HF	52/8.9	5.9 (4.4–7.7)	0.7 (0.5–0.9)
Valvular	8/2.2	3.6 (1.6–7.2)	0.1 (0.0–0.2)
Arrhythmia	5/1.5	3.4 (1.1–8.0)	0.1 (0.0–0.1)
Pericardial	2/0.2	8.0 (1.0–29.0)	0.0 (0.0–0.1)
Other cardiac	18/2.2	8.3 (4.9–13.1)	0.3 (0.1–0.4)

AER indicates absolute excess risk; CI, confidence interval; CM/HF, cardiomyopathy/heart failure; E, expected; IHD, ischemic heart disease; O, observed; and SMR, standardized mortality ratio.

Table 3. Standardized Mortality Ratios and Absolute Excess Risks per 10 000 Person-Years for Overall Cardiac Mortality, Ischemic Heart Disease Mortality, and Cardiomyopathy/Heart Failure Mortality, by Potential Explanatory Factors

		Overall Cardiac Mortality		
	Person-Years	O/E	SMR (95% CI)	AER (95% CI)
Overall	620 753	181/53.1	3.4 (2.9 to 3.9)	2.1 (1.6 to 2.5)
Sex				
Male	336 802	115/42.2	2.7 (2.2 to 3.3)	2.2 (1.5 to 2.8)
Female	283 951	66/10.9	6.0 (4.7 to 7.7)	1.9 (1.4 to 2.5)
P for heterogeneity			<0.0001	0.7771
FPN type				
CNS (excluding PNET)	124 750	32/13.9	2.3 (1.6 to 3.3)	1.5 (0.6 to 2.3)
CNS PNET	18 694	5/1.5	3.3 (1.1 to 7.6)	1.9 (–0.5 to 4.2)
Leukemia (excluding AML)	145 237	17/4.4	3.9 (2.3 to 6.2)	0.9 (0.3 to 1.4)
AML	13 029	10/0.4	23.5 (11.2 to 43.1)	7.3 (2.6 to 12.1)
HL	42 600	33/6.1	5.4 (3.7 to 7.6)	6.3 (3.7 to 9.0)
NHL	30 343	17/4.1	4.2 (2.4 to 6.6)	4.3 (1.6 to 6.9)
Neuroblastoma	28 500	4/1.7	2.4 (0.7 to 6.2)	0.8 (–0.6 to 2.2)
Nonheritable retinoblastoma	26 167	2/2.8	0.7 (0.1 to 2.6)	–0.3 (–1.4 to 0.8)
Heritable retinoblastoma	20 162	4/1.9	2.1 (0.6 to 5.4)	1.0 (–0.9 to 3.0)
Wilms	51 519	20/3.1	6.5 (4.0 to 10.0)	3.3 (1.6 to 5.0)
Bone sarcoma	21 798	9/3.1	2.9 (1.3 to 5.4)	2.7 (–0.0 to 5.4)
Soft tissue sarcoma	42 062	12/4.8	2.5 (1.3 to 4.3)	1.7 (0.1 to 3.3)
Other	55 891	16/5.3	3.0 (1.7 to 4.9)	1.9 (0.5 to 3.3)
P for heterogeneity			<0.0001	<0.0001
Age at diagnosis, y				
0–4	291 564	63/14.9	4.2 (3.2 to 5.4)	1.6 (1.1 to 2.2)
5–9	163 190	46/13.0	3.5 (2.6 to 4.7)	2.0 (1.2 to 2.8)
10–14	165 999	72/25.2	2.9 (2.2 to 3.6)	2.8 (1.8 to 3.8)
P for trend			0.0078	0.0211
Attained age, y				
5–19	243 030	20/2.1	9.7 (5.9 to 15.0)	0.7 (0.4 to 1.1)
20–29	195 584	33/4.2	7.8 (5.4 to 11.0)	1.5 (0.9 to 2.0)
30–39	108 573	42/8.5	5.0 (3.6 to 6.7)	3.1 (1.9 to 4.3)
40–49	51 869	36/15.4	2.3 (1.6 to 3.2)	4.0 (1.7 to 6.2)
50–59	17 552	32/14.8	2.2 (1.5 to 3.1)	9.8 (3.5 to 16.1)
≥60	4144	18/8.2	2.2 (1.3 to 3.5)	23.7 (3.6 to 43.8)
P for trend			0.0065	<0.0001

(*Continued*)

a linear increase or decrease in excess risk of CM/HF death with attained age (SMR *P* for trend=0.8121, AER *P* for trend=0.0591). However, with regard to treatment era, evidence of a quadratic relationship was found for both the SMRs (*P* for quadratic<0.0001) and AERs (*P* for quadratic<0.0001; Table 4). More specifically, the number of excess CM/HF deaths increased with treatment era beginning around 1970, peaked among those treated in the 1980s, and then subsequently declined among those treated more recently (Figure 2). After adjustment for sex, FPN type, age at diagnosis, and attained age, survivors diagnosed from 1970 to 1979, 1980 to 1989, and 1990 to 2006 had 13.9 times (95% CI, 1.1–168.5), 28.9 times (95% CI, 2.4–354.6), and 4.5 times (95% CI, 0.3–69.4) more excess CM/HF deaths, respectively, than survivors diagnosed before 1970 (Table 4).

Table 3. Continued

IHD Mortality			CM/HF Mortality		
O/E	SMR (95% CI)	AER (95% CI)	O/E	SMR (95% CI)	AER (95% CI)
96/38.2	2.5 (2.0 to 3.1)	0.9 (0.6 to 1.2)	52/8.9	5.9 (4.4 to 7.7)	0.7 (0.5 to 0.9)
70/31.6	2.2 (1.7 to 2.8)	1.1 (0.7 to 1.6)	27/6.6	4.1 (2.7 to 6.0)	0.6 (0.3 to 0.9)
26/6.6	4.0 (2.6 to 5.8)	0.7 (0.3 to 1.0)	25/2.3	10.9 (7.0 to 16.0)	0.8 (0.5 to 1.1)
	0.0091	0.2600		0.0002	0.2179
20/10.4	1.9 (1.2 to 3.0)	0.8 (0.1 to 1.5)	4/2.0	2.0 (0.5 to 5.0)	0.2 (–0.2 to 0.5)
4/1.1	3.7 (1.0 to 9.5)	1.6 (–0.5 to 3.7)	1/0.3	3.7 (0.1 to 20.5)	0.4 (–0.7 to 1.4)
3/2.2	1.4 (0.3 to 4.0)	0.1 (–0.2 to 0.3)	10/1.4	7.2 (3.5 to 13.3)	0.6 (0.2 to 1.0)
1/0.2	4.3 (0.1 to 24.0)	0.6 (–0.9 to 2.1)	8/0.1	66.0 (28.5 to 130.0)	6.0 (1.8 to 10.3)
20/4.6	4.4 (2.7 to 6.8)	3.6 (1.6 to 5.7)	6/0.9	6.7 (2.5 to 14.6)	1.2 (0.1 to 2.3)
8/3.1	2.6 (1.1 to 5.1)	1.6 (–0.2 to 3.4)	6/0.6	10.2 (3.7 to 22.2)	1.8 (0.2 to 3.4)
1/1.2	0.9 (0.0 to 4.8)	–0.1 (–0.7 to 0.6)	1/0.3	3.3 (0.1 to 18.1)	0.2 (–0.4 to 0.9)
2/2.1	0.9 (0.1 to 3.4)	–0.0 (–1.1 to 1.0)	0/0.4	-	-
4/1.4	2.9 (0.8 to 7.4)	1.3 (–0.6 to 3.2)	0/0.3	-	-
11/2.1	5.3 (2.7 to 9.5)	1.7 (0.5 to 3.0)	5/0.6	8.0 (2.6 to 18.8)	0.8 (–0.0 to 1.7)
5/2.4	2.1 (0.7 to 4.9)	1.2 (–0.8 to 3.2)	2/0.4	4.7 (0.6 to 16.9)	0.7 (–0.6 to 2.0)
7/3.6	1.9 (0.8 to 4.0)	0.8 (–0.4 to 2.0)	5/0.7	7.1 (2.3 to 16.7)	1.0 (–0.0 to 2.1)
10/3.9	2.6 (1.2 to 4.8)	1.1 (–0.0 to 2.2)	4/0.8	4.7 (1.3 to 12.1)	0.6 (–0.1 to 1.3)
	0.0412	0.0760		0.0003	0.0002
26/9.9	2.6 (1.7 to 3.9)	0.6 (0.2 to 0.9)	22/3.1	7.1 (4.4 to 10.7)	0.6 (0.3 to 1.0)
24/9.1	2.6 (1.7 to 3.9)	0.9 (0.3 to 1.5)	14/2.4	5.9 (3.2 to 9.9)	0.7 (0.3 to 1.2)
46/19.2	2.4 (1.8 to 3.2)	1.6 (0.8 to 2.4)	16/3.4	4.7 (2.7 to 7.6)	0.8 (0.3 to 1.2)
	0.5110	0.8914		0.0666	0.0986
1/0.1	8.0 (0.2 to 44.6)	0.0 (–0.0 to 0.1)	12/1.2	9.7 (5.0 to 16.9)	0.4 (0.2 to 0.7)
12/1.2	10.0 (5.2 to 17.5)	0.6 (0.2 to 0.9)	16/1.9	8.6 (4.9 to 14.0)	0.7 (0.3 to 1.1)
18/5.4	3.4 (2.0 to 5.3)	1.2 (0.4 to 1.9)	16/1.9	8.5 (4.9 to 13.8)	1.3 (0.6 to 2.0)
24/12.3	2.0 (1.3 to 2.9)	2.3 (0.4 to 4.1)	3/1.9	1.6 (0.3 to 4.6)	0.2 (–0.4 to 0.9)
25/12.4	2.0 (1.3 to 3.0)	7.2 (1.6 to 12.7)	4/1.3	3.0 (0.8 to 7.7)	1.5 (–0.7 to 3.8)
16/6.8	2.3 (1.3 to 3.8)	22.2 (3.2 to 41.1)	1/0.7	1.5 (0.0 to 8.3)	0.8 (–3.9 to 5.5)
	0.0344	<0.0001		0.8121	0.0591

AER indicates absolute excess risk; AML, acute myeloid leukemia; CI, confidence interval; CM/HF, cardiomyopathy/heart failure; CNS, central nervous system; E, expected; FPN, first primary neoplasm; HL, Hodgkin lymphoma; IHD, ischemic heart disease; NHL, Non-Hodgkin lymphoma; O, observed; PNET, primitive neuroectodermal tumor; and SMR, standardized mortality ratio. All *P* values were calculated with a multivariable Poisson regression model adjusted for sex, FPN type, age at diagnosis, treatment era, and attained age.

DISCUSSION

This largest ever study of cardiac mortality after childhood cancer within a cohort of 34 489 five-year survivors provides an unprecedented opportunity to investigate the impact of treatment era on the risk of cardiac death. Furthermore, with 73 565 person-years and 86 cardiac deaths among those >40 years of age and 21 696 person-years and 50 cardiac deaths among those >50 years of age, this is the first study to

Table 4. Standardized Mortality Ratios and Corresponding Relative Risks and Absolute Excess Risks per 10 000 Person-Years and Corresponding Excess Mortality Ratios for Each Treatment Era

Treatment Era	Overall Cardiac Mortality					IHD Mortality		
	O/E	SMR (95% CI)	RR (95% CI)	AER (95% CI)	EMR (95% CI)	O/E	SMR (95% CI)	RR (95% CI)
Before 1970	79/35.6	2.2 (1.8 to 2.8)	1 (Ref)	3.2 (1.9 to 4.5)	1 (Ref)	62/28.8	2.2 (1.7 to 2.8)	1 (Ref)
1970–1979	48/10.7	4.5 (3.3 to 5.9)	1.6 (1.0 to 2.5)	2.4 (1.6 to 3.3)	1.3 (0.7 to 2.4)	25/6.9	3.6 (2.4 to 5.4)	1.5 (0.9 to 2.6)
1980–1989	43/4.7	9.1 (6.6 to 12.3)	2.3 (1.4 to 3.9)	2.5 (1.6 to 3.3)	1.8 (0.9 to 3.5)	6/2.1	2.9 (1.1 to 6.2)	0.8 (0.3 to 2.0)
1990–2006	11/2.1	5.2 (2.6 to 9.4)	1.0 (0.4 to 2.1)	0.5 (0.1 to 0.9)	0.6 (0.2 to 1.5)	3/0.4	7.1 (1.5 to 20.6)	1.0 (0.3 to 3.8)
P for trend		0.1318		0.8583			0.9171	
P for quadratic		0.0014		0.0072			0.2518	

(*Continued*)

satisfactorily assess the pattern of excess cardiac deaths among survivors >50 years old. In doing so, this study adds 250 728 person-years and 76 cardiac deaths to our previous largest study assessing cardiac mortality.[14] Furthermore, this study expands on and addresses many of the limitations of previous work assessing mortality among childhood cancer survivors from the United States[3,4,15] and Nordic countries.[16,17]

Principal Findings and Comparisons With Other Studies

Although 2 previous studies have assessed trends in the risk of cardiac causes of death among 5-year survivors of childhood cancer in relation to treatment era,[3,4] this is the first study to provide evidence of a quadratic relationship for the excess risk of cardiac death overall and for CM/HF death in relation to treatment era, for which the number of excess deaths increases with treatment era, peaks among those treated in the 1980s, and then subsequently declines among those treated more recently. This relationship corresponds closely to the introduction of anthracycline chemotherapy, which has been shown to increase the risk of dilated cardiomyopathy[18–20] and congestive heart failure.[21] However, these results differ from a CCSS report[3] that found a significant decline in the adjusted relative rate of death resulting from cardiac causes with more recent treatment era. Although the CCSS has a more restricted diagnosis period (1970–1999, 30 years) compared with our study (1940–2006, 66 years), it is unlikely that this explains the difference observed because we did not observe a linear decline in excess cardiac deaths with treatment era after restricting our diagnosis period to match the CCSS (SMR *P* for trend=0.7687, AER *P* for trend=0.3521; Table VI in the online-only Data Supplement). In fact, a quadratic relationship between treatment era and excess cardiac deaths was observed in the BCCSS when the diagnosis period was restricted to 1970 to 1999 (SMR *P*

Table 5. Absolute Excess Risks for Recurrences/Progression, Subsequent Primary Neoplasms, Nonneoplastic, Cardiac, Other Circulatory, and Other Nonneoplastic Causes of Death, by Attained Age as a Proportion of Total Excess Risk

	Attained Age, y								
	5–19			20–29			30–39		
	O/E	AER	% Total	O/E	AER	% Total	O/E	AER	% Total
Recurrence/progression	1835/0.0	75.5	84.3	553/0.0	28.3	62.1	161/0.0	14.8	36.5
Subsequent primary neoplasms	184/10.1	7.2	8.0	184/13.7	8.7	19.1	163/20.2	13.1	32.3
Nonneoplastic	228/60.4	6.9	7.7	266/97.5	8.6	18.9	211/74.6	12.6	31.1
Cardiac	20/2.1	0.7	0.8	33/4.2	1.5	3.3	42/8.5	3.1	7.7
Other circulatory	10/1.4	0.4	0.4	23/3.4	1.0	3.2	21/5.1	1.5	3.7
Other nonneoplastic*	198/56.9	5.8	0.5	210/89.9	6.1	13.4	148/61.0	8.0	19.8
All causes	2247/70.5	89.6	100.0	1003/111.2	45.6	100.0	535/94.8	40.5	100.0

(*Continued*)

Table 4. Continued

IHD Mortality Continued		CM/HF Mortality				
AER (95% CI)	EMR (95% CI)	O/E	SMR (95% CI)	RR (95% CI)	AER (95% CI)	EMR (95% CI)
2.4 (1.3 to 3.6)	1 (Ref)	4/3.7	1.1 (0.3 to 2.7)	1 (Ref)	0.0 (–0.3 to 0.3)	1 (Ref)
1.2 (0.5 to 1.8)	1.0 (0.4 to 2.2)	16/2.4	6.5 (3.7 to 10.6)	8.9 (2.1 to 37.8)	0.9 (0.4 to 1.4)	13.9 (1.1 to 168.5)
0.3 (–0.1 to 0.6)	0.3 (0.1 to 1.4)	28/1.7	16.7 (11.1 to 24.1)	18.2 (3.9 to 84.2)	1.7 (1.0 to 2.4)	28.9 (2.4 to 354.6)
0.1 (–0.0 to 0.3)	0.4 (0.1 to 2.0)	4/1.0	3.9 (1.1 to 10.0)	3.7 (0.6 to 23.3)	0.2 (–0.1 to 0.4)	4.5 (0.3 to 69.4)
0.1098			0.1231		0.3453	
0.6850			<0.0001		<0.0001	

AER indicates absolute excess risk; CI, confidence interval; CM/HF, cardiomyopathy/heart failure; E, expected; EMR, excess mortality ratio; IHD, ischemic heart disease; O, observed; Ref, referent; RR, relative risk; and SMR, standardized mortality ratio. RR, EMRs, and all *P* values were estimated with a multivariable Poisson regression model adjusted for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age.

for quadratic=0.0024, AER *P* for quadratic=0.0019). A possible explanation for the difference observed between the BCCSS and CCSS would be differences in childhood cancer treatment exposures related to the development of cardiac diseases between the 2 studies. However, it is not possible to explore this hypothesis because of the lack of detailed treatment information for the BCCSS.

Overall, cardiac mortality estimates in this cohort were elevated at 3 times that expected. The risk of cardiac death remained elevated beyond 60 years of age, and the number of excess cardiac deaths was observed to increase significantly with age. Among those >60 years of age, cardiac deaths accounted for 22% and 41% of all excess deaths and all nonneoplastic excess deaths, respectively. This finding provides evidence that as survivors age beyond 60 years, circulatory deaths account for more excess deaths, 37% (60% of which was due to cardiac causes), than SPNs, 31%. With 31%, 22%, and 15% (in total 68%) of all excess deaths among those >60 years of age attributable to SPNs, cardiac disease, and other circulatory conditions, respectively, there is a clear message in terms of prevention of premature morbidity and mortality: Specific interventions, in terms of surveillance and treatment, that reduce SPNs and circulatory disease in survivors of childhood cancer are needed.

Another finding worth noting from our study relates to the risk of cardiac death by FPN type. Although HL survivors have long been recognized as having an increased risk of cardiac death, leading much research to focus on these survivors,[22–24] Wilms survivors were in fact found to have a greater risk of cardiac death than HL survivors. In particular, Wilms survivors were found to have the greatest risk of IHD death among all FPN types; this finding suggests that hypertension and having 1 kidney are strong risk factors in Wilms survivors for cardiac death because the cardiac radiotherapy exposure in these survivors would be expected to be much lower than that used for HL survivors.

Table 5. Continued

Attained Age, y Continued								
40–49			50–59			≥60		
O/E	AER	% Total	O/E	AER	% Total	O/E	AER	% Total
52/0.0	10.0	19.3	18/0.0	10.3	11.2	7/0.0	16.9	15.6
131/30.5	19.4	37.4	99/32.5	37.9	41.1	34/19.9	33.9	31.4
181/64.6	22.4	43.2	121/43.6	44.1	47.8	47/23.3	57.3	53.0
36/15.4	4.0	7.7	32/14.8	9.8	10.6	18/8.2	23.7	21.9
32/6.4	4.9	9.4	23/5.2	10.1	11.0	10/3.3	16.1	14.9
113/42.8	13.5	26.0	66/23.6	24.2	16.2	19/11.8	17.5	16.2
364/95.1	51.9	100.0	238/76.1	92.2	100.0	88/43.2	108.1	100.0

AER indicates absolute excess risk; E, expected; and O, observed.

*Includes the following causes of death: respiratory, nervous, infection, digestive, perinatal, endocrine, genitourinary, musculoskeletal, mental, blood, external, and other.

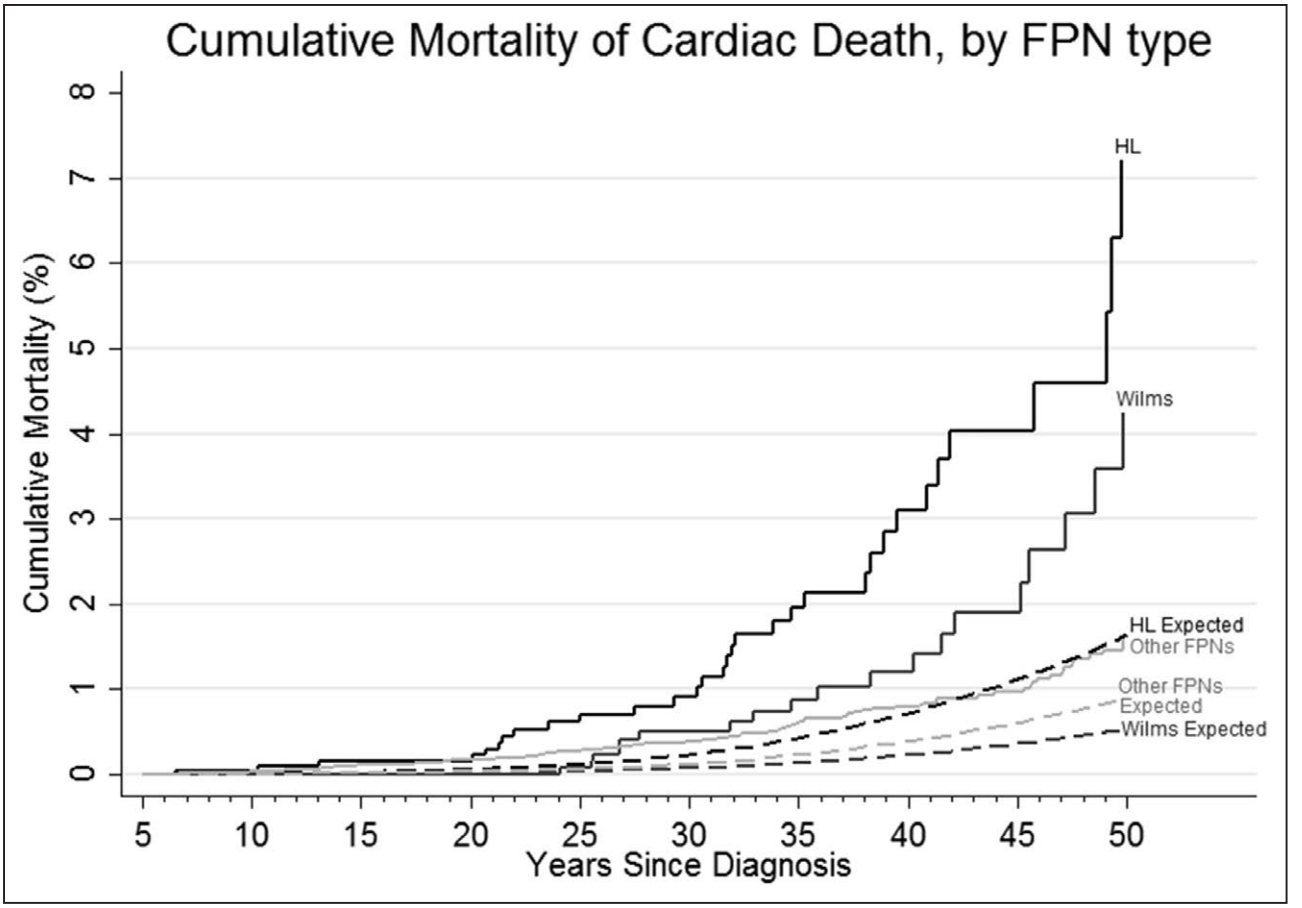

Figure 1. Cumulative mortality for cardiac death by first primary neoplasm (FPN) diagnostic groups, by follow-up (years since diagnosis), compared with that expected.

HL indicates Hodgkin lymphoma.

Special Consideration

Despite the increased risk of cardiac death reported in this study during the 1980s, it is important to recognize that many more children diagnosed with cancer in the 1980s have survived as a result of anthracycline chemotherapy than have died as a result of its late effects. Furthermore, the fact that the excess risk of cardiac death has subsequently declined in those diagnosed in the 1990s and 2000s suggests that measures to reduce cardiotoxicity through the use of alternative drugs, lower cumulative doses, and improved monitoring and intervention appears to be having a beneficial effect for those treated more recently.

Strengths and Weaknesses

The main strengths of our study are its large size, population-based design, wide diagnosis period, and long available follow-up time, which have provided an exceptional opportunity to assess cardiac mortality after childhood cancer. Through these strengths, we have been able to assess the impact of cancer treatment on cardiac mortality from prechemotherapy treatment eras to modern therapies and protocols. We have also been able to provide for the first time results on the risk of cardiac mortality among survivors of childhood cancer beyond 60 years of age. Because selection bias will be minimized through our population-based study design, these results are generalizable to survivors of childhood cancer in Great Britain, as well as other childhood cancer populations provided that they were treated with similar therapies. Therefore, the findings of this study provide useful evidence for survivors, clinicians, and clinical follow-up guidelines in Great Britain and potentially internationally.

A weakness of our study is the lack of detailed radiotherapy and chemotherapy information, which precluded any examination of dose-response patterns of treatment exposures in relation to cardiac mortality risk. However, the large-scale population-based design, wide spectrum of treatment eras, and very long follow-up available in this study provide opportunities not available in other cohorts. Another possible limitation of this study is that our classification of cardiac death relied on the underlying cause of death as listed on the death certificate, which has been previously shown to have imperfect accuracy.[25–28] Although there is possible misclassifica-

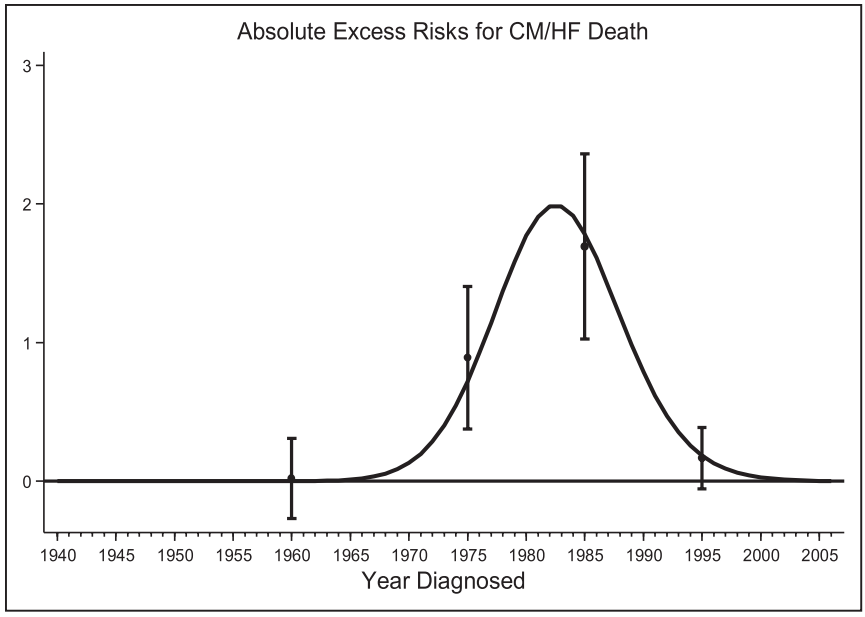

Figure 2. Absolute excess risk per 10 000 person-years for cardiomyopathy/heart failure (CM/HF) deaths for each calendar year of diagnosis.
The curve was produced by fitting a restricted cubic spline with the number of CM/HF deaths per 1 calendar year band as a weight. Point estimates of the absolute excess risk with corresponding 95% confidence intervals are plotted at the mean of the relevant treatment era (1940–1969, 1970–1979, 1980–1989, and 1990–2006).

tion, it is more likely that we have underascertained cardiac deaths and thus underestimated the risk of cardiac death among childhood cancer survivors because these individuals are more likely to be coded as having a neoplastic-related death resulting from their previous medical history.[16]

Reassessment of Findings

Over the treatment eras covered by this study, survival has improved substantially, and treatment regimens have changed markedly. Because of these evolving changes in survival and treatment exposures, reassessment of cardiac mortality after childhood cancer is crucial. For example, although we observed that the risk of cardiac death was greatest among those treated in the 1980s, it is important to determine whether with additional follow-up the more recently diagnosed survivors remain at a decreased risk or whether cardiac death has merely been delayed as a result of increased awareness, surveillance, and treatment of late effects after known cardiotoxic exposures. Similarly, we observed that cardiac death became one of the principal contributors to the excess number of deaths beyond 60 years of age. However, the survivors at least 60 years old at the time of our study are quite different from those more recently diagnosed in terms of both FPN types and treatment exposures. Therefore, a reassessment of the mortality risks in survivors >60 years of age is necessary in the future to determine the generalizability of our results for future childhood cancer survivors who reach 60 years of age.

Future Research

At present, the Center for Childhood Cancer Survivor Studies is involved in several investigations aimed at improving knowledge of the risks and causes of cardiovascular complications among childhood cancer survivors. In particular, the center is collaborating in PanCareSurFup[29] and PROCARDIO,[30] both European consortiums investigating the link between cardiovascular disease and exposure of the heart and major vessels to radiotherapy and chemotherapy. For these projects, detailed treatment records were collected, and cumulative doses of radiation from radiotherapy and of each anticancer drug are being calculated. The resultant case-control studies will enable investigation of the dose-response between radiation and chemotherapy exposure of the heart and the risk of heart disease. The BCCSS cohort has also been linked to the national database of Hospital Episode Statistics, which is an electronic health record system for all hospitalizations in England. Through this linkage, the BCCSS will be in a stronger position to understand cardiac morbidity, and its treatment, in childhood cancer survivors. As a result of such initiatives, the BCCSS will be able to provide further insight into cardiovascular late effects among childhood cancer survivors in the United Kingdom.

Conclusions and Implications

The greatest excess risks for deaths from CM/HF were observed among those treated between 1980 and 1989, which suggests that initiatives to reduce cardiotoxicity among those treated more recently may be having a measurable impact. Among those >60 years of age, SPNs, cardiac disease, and other circulatory conditions accounted for 31%, 22%, and 15% of all excess deaths, respectively, providing clear focus for preventive interventions. These findings provide important information for survivors, clinicians, and clinical guidelines, particularly in relation to preventing excess morbidity and mortality in survivors >60 years of age.

SOURCES OF FUNDING

This work was supported by grant number C386/A10422 from Cancer Research UK; PanCareSurFup, European 7th Framework Programme. Oxford funding was provided by Cancer Research UK (grant C8225/A21133) and by core funding to the Clinical Trial Service Unit (from Cancer Research UK, Medical Research Council, British Heart Foundation) and by the British Heart Foundation Centre for Research Excellence (grant RE/13/1/30181). No funder had a role in the study design, collection/analysis/interpretation of the data, writing of the report, or in the decision to submit the article for publication.

DISCLOSURES

All authors report no conflicts of interest in relation to this work. This report is independent research, and the views expressed in this article are not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health.

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FOOTNOTES

Received August 2, 2016; accepted January 3, 2017.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.116.024811/-/DC1.

Circulation is available at http://circ.ahajournals.org.

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Population-Based Long-Term Cardiac-Specific Mortality Among 34 489 Five-Year Survivors of Childhood Cancer in Great Britain

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On behalf of the British Childhood Cancer Survivor Study (BCCSS) Steering Group

Circulation. 2017;135:951-963; originally published online January 12, 2017;
doi: 10.1161/CIRCULATIONAHA.116.024811
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL:

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Acknowledgements: The British Childhood Cancer Survivor Study (BCCSS) is a national collaborative undertaking guided by a steering group that comprises Douglas Easton (chair), Michael Hawkins, Helen Jenkinson, Meriel Jenney, Raoul Reulen, Kathryn Pritchard-Jones, Elaine Sugden, Charles Stiller, Andrew Toogood, and Hamish Wallace. The BCCSS benefits from the contributions of the officers, centres, and individual members of the Children's Cancer and Leukaemia Group and the Regional Paediatric Cancer Registries. The BCCSS acknowledges the collaboration of the Office for National Statistics, the National Records of Scotland, the Welsh Cancer Intelligence and Surveillance Unit, the Health & Social Care Information Centre, the National Cancer Intelligence Network, and Public Health England. The BCCSS would not have been possible without the support of our funders: Cancer Research UK and the European Commission to whom we offer our profound thanks. The views expressed in this publication are those of the authors and not necessarily represent those of the funders or collaborators. Finally, thanks to all BCCSS staff who have given many years of dedicated work to bring the BCCSS to fruition.

Characteristic	No. Dead	%	No. Alive	%	P-value	Total No.	%
Overall	4475	13.0	30014	87.0		34489	100.0
Sex							
Male	2629	13.9	16310	86.1		18939	100.0
Female	1846	11.9	13704	88.1	<0.001	15550	100.0
First Primary Neoplasm Type							
CNS (excluding PNET)	1334	19.1	5636	80.9		6970	100.0
CNS PNET	340	28.4	858	71.6		1198	100.0
Leukemia (excluding AML)	1104	11.6	8398	88.4		9493	100.0
AML	82	8.4	899	91.6		981	100.0
Hodgkin Lymphoma	331	14.8	1903	85.2		2234	100.0
Non-Hodgkin Lymphoma	131	8.5	1418	91.5		1549	100.0
Neuroblastoma	144	9.4	1391	90.6		1535	100.0
Non-Heritable Retinoblastoma	31	3.1	975	96.9		1006	100.0
Heritable Retinoblastoma	138	18.4	612	81.6		750	100.0
Wilms	184	7.7	2204	92.3		1388	100.0
Bone Sarcoma	198	16.6	997	83.4		1195	100.0
Soft Tissue Sarcoma	253	11.8	1894	88.2		2147	100.0
Other	205	6.7	2838	93.3	<0.001	3043	100.0
Age at Diagnosis							
Mean	7.3		6.5			6.6	
0-4	1662	10.6	14035	89.4		15697	100.0
5-9	1351	14.6	7913	85.4		9264	100.0
10-14	1462	15.3	8066	84.7	<0.001	9528	100.0
Treatment Era							
1940-1969	1329	35.5	2417	64.5		3746	100.0
1970-1979	1247	23.2	4132	76.8		5379	100.0
1980-1989	942	13.2	6205	86.8		7147	100.0
1990-1999	703	7.0	9328	93.0		10031	100.0
2000-2006	254	3.1	7932	96.9	<0.001	8186	100.0
Years from Diagnosis							
Mean	17.0		23.9			23.0	
5-9 years	2054	37.9	3368	62.2		5422	100.0
10-19 years	1060	9.1	10561	90.9		11621	100.0
20-29 years	548	6.9	7352	93.1		7900	100.0
30-39 years	417	7.7	5026	92.3		5443	100.0
40-49 years	277	9.9	2529	90.1		2806	100.0
50-59 years	103	8.9	1052	91.1		1155	100.0
60+ years	16	11.3	126	88.7	<0.001	142	100.0
Attained Age at Exit							
Mean	24.3		30.4			29.6	
5-9 years	416	48.9	435	51.1		851	100.0
10-19 years	1831	21.7	6614	78.3		8445	100.0
20-29 years	1003	9.4	9730	90.7		10733	100.0
30-39 years	535	8.1	6083	91.9		6618	100.0
40-49 years	364	7.5	4486	92.5		4850	100.0
50-59 years	238	11.4	1859	88.7		2097	100.0
60+ years	88	9.8	807	90.2	<0.001	895	100.0

Supplemental Table I: Cohort characteristics of the British Childhood Cancer Survivor Study.

Abbreviations: CNS – central nervous system, PNET – primitive neuroectodermal tumor, AML – acute myeloid leukemia

Characteristic	Treatment Era							
	1940-1969		1970-1979		1980-1989		1990-2006	
	N	%	N	%	N	%	N	%
Overall	3746	10.9	5379	15.6	7147	20.7	18217	52.8
Sex								
Male	2019	53.9	2963	55.1	3941	55.1	10016	55.0
Female	1727	46.1	2416	44.9	3206	44.9	8201	45.0
First Primary Neoplasm Type								
CNS (excluding PNET)	1059	28.3	1094	20.3	1185	16.6	3632	19.9
CNS PNET	167	4.5	174	3.2	236	3.3	621	3.4
Leukemia (excluding AML)	168	4.5	1554	28.9	2206	30.9	5565	30.6
AML	10	0.3	68	1.3	193	2.7	710	3.9
Hodgkin Lymphoma	297	7.9	456	8.5	495	6.9	986	5.4
Non-Hodgkin Lymphoma	179	4.8	206	3.8	403	5.6	761	4.2
Neuroblastoma	217	5.8	153	2.8	307	4.3	858	4.7
Non-Heritable Retinoblastoma	255	6.8	195	3.6	160	2.2	396	2.2
Heritable Retinoblastoma	269	7.2	128	2.4	127	1.8	226	1.2
Wilms	324	8.7	480	8.9	515	7.2	1069	5.9
Bone Sarcoma	154	4.1	179	3.3	267	3.7	595	3.3
Soft Tissue Sarcoma	310	8.3	302	5.6	453	6.3	1082	5.9
Other	337	9.0	390	7.3	600	8.4	1716	9.4
Age at Diagnosis								
0-4	1727	46.1	2326	43.2	3317	46.4	8327	45.7
5-9	931	24.9	1567	29.1	1864	26.1	4902	26.9
10-14	1088	29.0	1486	27.6	1966	27.5	4988	27.4
Years from Diagnosis								
Mean	41.3		33.3		26.7		14.7	
5-9	458	12.2	524	9.7	459	6.4	3981	21.9
10-19	214	5.7	319	5.9	338	4.7	10750	59.0
20-29	166	4.4	243	4.5	4005	56.0	3486	19,1
30-39	202	5.4	2896	53.8	2345	32.8	0	0
40-49	1409	37.6	1397	26.0	0	0	0	0
50-59	1155	30.8	0	0	0	0	0	0
60+	142	3.8	0	0	0	0	0	0
Attained Age at Exit								
Mean	47.8		40.0		33.3		21.3	
5-9	86	2.3	105	2.0	95	1.3	565	3.1
10-19	405	10.8	478	8.9	429	6.0	7133	39,2
20-29	219	5.9	314	5.8	1474	20.6	8726	47.9
30-39	193	5.2	902	16.8	3730	52.2	1793	9,8
40-49	605	16.2	2826	52.5	1419	19.9	0	0
50-59	1343	35.9	754	14.0	0	0	0	0
60+	895	23.9	0	0	0	0	0	0

Supplemental Table II: Cohort characteristics of the British Childhood Cancer Survivor Study by treatment era.

Abbreviations: CNS – central nervous system, PNET – primitive neuroectodermal tumor, AML – acute myeloid leukemia

First Primary Neoplasm Type	Attained Age (years)													
	5-9		10-19		20-29		30-39		40-49		50-59		60+	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CNS (excluding PNET)	159	18.7	1553	18.4	2258	21.0	1196	18.1	977	20.1	559	26.7	268	29.9
CNS PNET	19	2.2	371	4.4	381	3.6	193	2.9	148	3.1	62	3.0	24	2.3
Leukemia (excluding AML)	285	33.5	2987	35.4	3092	28.8	1892	28.6	1102	22.7	126	6.0	9	1.0
AML	36	4.2	320	3.8	363	3.4	181	2.7	58	1.2	22	1.1	1	0.1
Hodgkin Lymphoma	3	0.4	248	2.9	705	6.6	471	7.1	497	10.3	228	10.9	82	9.2
Non-Hodgkin Lymphoma	14	1.7	217	2.6	457	4.3	417	6.3	255	5.3	123	5.9	66	7.4
Neuroblastoma	100	11.8	550	6.5	412	3.8	225	3.4	135	2.8	95	4.5	18	2.0
Non-Heritable Retinoblastoma	31	3.6	214	2.5	230	2.1	154	2.3	201	4.1	122	5.8	54	6.0
Heritable Retinoblastoma	51	6.0	151	1.8	148	1.4	127	1.9	142	2.9	97	4.6	34	3.8
Wilms	48	5.6	624	7.4	627	5.8	488	7.4	405	8.4	155	7.4	41	4.6
Bone Sarcoma	4	0.5	182	2.2	365	3.4	270	4.1	203	4.2	100	4.8	71	7.9
Soft Tissue Sarcoma	35	4.1	454	5.4	676	6.3	409	6.2	306	6.3	173	8.3	94	10.5
Other	66	7.8	574	6.8	1019	9.5	595	9.0	421	8.7	235	11.2	133	14.9

Supplemental Table III: First primary neoplasm diagnoses of the British Childhood Cancer Survivor Study by attained age.

Abbreviations: CNS – central nervous system, PNET – primitive neuroectodermal tumor, AML – acute myeloid leukemia

	International Classification of Diseases (ICD) revision (calendar years of death)					
Cause of Death	**ICD-5 (1940-49)**	**ICD-6 (1950-57)**	**ICD-7 (1958-67)**	**ICD-8 (1968-78)**	**ICD-9 (1979-2000)**	**ICD-10 (2001-09)**
All Cardiac	58a-c, 90a-b, 91a-c, 92-95, 111b-c, 199, 200a(1)	401, 402.1, 410-416, 420-422, 430-434, 440-443	401, 402.1, 410-416, 420-422, 430-434, 440-443	391, 392.0, 393-398, 402, 404, 410-414, 420-429	391, 392.0, 393-398, 402, 404, 410-414, 416.1-9, 420-429	I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-9, I30-I52
Cardiomyopathy/ Heart Failure	58c, 93a-b, 93c(2-3), 93d, 111b-c, 200a(1)	401.2, 415, 422.0, 422.2, 431, 434.1-2	401.2, 415, 422.0, 422.2, 431, 434.1-2	391.2, 422, 425, 427.0, 427.1, 428	391.2, 398.0, 422, 425, 428, 429.0, 429.1, 429.3	I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7
Valvular Heart Disease	92a, 92b(1), 92c	421	421	394.9, 395.9, 396.9, 397.0, 424	424	I34-I39
Rheumatic Valvular Heart Disease	58b, 92b(2)	401.1, 410-414	401.1, 410-414	391.1, 394.0, 395.0, 396.0, 397.9	391.1, 394-397	I01.1, I05-I08, I09.1
Ischemic Heart Disease	93c(1), 94a, 94b	420, 422.1	420, 422.1	410-414	410-414, 429.7	I20-I25
Arrhythmias	199	433.0-1	433.0-1	427.2-9	426-427	I44-49
Pericardial Disease	58a, 90a-b	401.0, 432	401.0, 432	391.0, 393, 420, 423	391.0, 393, 420, 423	I01.0, I09.2, I30-I32
Other Cardiac	91a-c, 95	401.3, 402.1, 416, 430, 433.2, 434.0, 434.3, 440-443	401.3, 402.1, 416, 430, 433.2, 434.0, 434.3-4, 440-443	391.9, 392.0, 398, 402, 404, 421, 426, 429	391.8-9, 392.0, 389.9, 402, 404, 416.1-9, 421, 429.2, 429.4-6, 429.8-9	I01.8-9, I02.0, 109.8-9, I11.9, I13.1, I13.9, I27.1-9, I33, I51.0-3, I51.6, I51.8-9, I52

Supplemental Table IV: International Classification of Diseases (ICD) categorizations and sub-categorizations for cardiac causes of death as used in the analysis.

	Overall Cardiac Mortality		Ischemic Heart Disease Mortality		Cardiomyopathy/Heart Failure Mortality	
	RR (95%CI)	**EMR (95%CI)**	**RR (95%CI)**	**EMR (95%CI)**	**RR (95%CI)**	**EMR (95%CI)**
Sex						
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	2.2 (1.6,3.0)	1.1 (0.7,1.6)	1.9 (1.2,3.0)	0.7 (0.4,1.3)	3.0 (1.7,5.2)	1.5 (0.8,2.9)
Pheterogeneity	<0.0001	0.7771	0.0091	0.2600	0.0002	0.2179
First Primary Neoplasm Type						
CNS (excluding PNET)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
CNS PNET	1.2 (0.5,3.2)	0.9 (0.2,5.4)	1.9 (0.6,5.5)	1.7 (0.3,12.5)	1.7 (0.2,15.0)	3.8 (0.2,61.0)
Leukemia (excluding AML)	0.7 (0.4,1.4)	0.8 (0.3,1.8)	0.4 (0.1,1.5)	0.2 (0.0,4.4)	1.7 (0.5,5.4)	3.2 (0.4,23.6)
AML	5.8 (2.8,12.1)	7.6 (3.2,18.1)	1.7 (0.2,12.6)	2.3 (0.2,23.5)	19.2 (5.7,64.8)	39.8 (5.5,289.6)
Hodgkin Lymphoma	2.7 (1.6,4.4)	4.0 (1.9,8.2)	2.4 (1.3,4.5)	3.6 (1.3,9.8)	3.8 (1.0,13.6)	4.9 (0.5,45.8)
Non-Hodgkin Lymphoma	2.0 (1.1,3.6)	3.0 (1.4,6.6)	1.4 (0.6,3.3)	2.1 (0.6,7.1)	5.4 (1.5,19.2)	13.8 (1.8,106.1)
Neuroblastoma	0.7 (0.2,2.1)	0.8 (0.2,3.0)	0.4 (0.1,3.2)	0.5 (0.0,9.1)	1.2 (0.1,10.7)	2.2 (0.1,38.4)
Non-Heritable Retinoblastoma	0.2 (0.1,1.0)	0.1 (0.0,3.2)	0.5 (0.1,2.1)	0.5 (0.0,5.0)	*NE*	*NE*
Heritable Retinoblastoma	0.7 (0.2,2.0)	0.4 (0.0,4.7)	1.4 (0.4,4.5)	1.5 (0.2,9.9)	*NE*	*NE*
Wilms	1.7 (0.9,3.1)	1.9 (0.8,4.3)	2.2 (1.0,5.1)	2.8 (0.8,9.5)	2.5 (0.7,9.9)	5.0 (0.6,41.7)
Bone Sarcoma	1.4 (0.6,2.9)	1.6 (0.5,4.9)	1.1 (0.4,3.0)	0.9 (0.1,8.6)	2.6 (0.5,14.2)	6.2 (0.5,71.1)
Soft Tissue Sarcoma	1.1 (0.5,2.1)	1.0 (0.3,2.9)	1.0 (0.4,2.4)	0.9 (0.2,4.5)	3.5 (0.9,13.2)	8.0 (1.0,65.0)
Other	1.1 (0.6,2.1)	1.0 (0.4,2.8)	1.2 (0.6,2.6)	1.2 (0.3,4.6)	2.1 (0.5,8.3)	3.6 (0.4,36.0)
Pheterogeneity	<0.0001	<0.0001	0.0412	0.0760	0.0003	0.0002
Age at Diagnosis						
0-4 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-9 years	0.7 (0.5,1.1)	0.7 (0.4,1.2)	0.9 (0.5,1.8)	1.0 (0.4,2.8)	0.7 (0.3,1.4)	0.7 (0.3,1.6)
10-14 years	0.5 (0.4,0.8)	0.5 (0.3,0.9)	0.8 (0.4,1.6)	1.0 (0.3,2.7)	0.5 (0.2,1.1)	0.5 (0.2,1.2)
Ptrend	0.0078	0.0211	0.5110	0.8914	0.0666	0.0986
Treatment Era						
<1970	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1970-1979	1.6 (1.0,2.5)	1.3 (0.7,2.4)	1.5 (0.9,2.6)	1.0 (0.4,2.2)	8.9 (2.1,37.8)	13.9 (1.1,168.5)
1980-1989	2.3 (1.4,3.9)	1.8 (0.9,3.5)	0.8 (0.3,2.0)	0.3 (0.1,1.4)	18.2 (3.9,84.2)	28.9 (2.4,354.6)
1990-2006	1.0 (0.4,2.1)	0.6 (0.2,1.5)	1.0 (0.3,3.8)	0.4 (0.1,2.0)	3.7 (0.6,23.3)	4.5 (0.3,69.4)
Ptrend	0.1318	0.8583	0.9171	0.1098	0.1231	0.3453
Pquadratic	0.0014	0.0072	0.2518	0.6850	<0.0001	<0.0001
Attained Age						
5-19 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-29 years	0.8 (0.5,1.5)	1.9 (1.0,3.7)	1.3 (0.2,10.0)	11.4 (1.3,102.2)	0.9 (0.4,2.0)	1.6 (0.7,3.6)
30-39 years	0.6 (0.3,1.0)	3.6 (1.8,7.2)	0.4 (0.0,3.1)	19.8 (2.2,182.6)	1.0 (0.4,2.3)	2.9 (1.2,7.2)
40-49 years	0.3 (0.2,0.7)	5.7 (2.5,13.0)	0.2 (0.0,1.8)	30.1 (3.0,298.5)	0.4 (0.1,1.4)	*NE*
50-59 years	0.4 (0.2,0.8)	17.1 (6.6,44.7)	0.2 (0.0,2.0)	93.2 (9.1,949.8)	2.2 (0.5,10.4)	21.3 (3.1,147.8)
60+ years	0.4 (0.2,1.0)	45.7 (14.5,144.1)	0.3 (0.0,2.6)	267.5 (23.9,2992.9)	2.0 (0.1,26.7)	*NE*
Ptrend	0.0065	<0.0001	0.0344	<0.0001	0.8121	0.0591

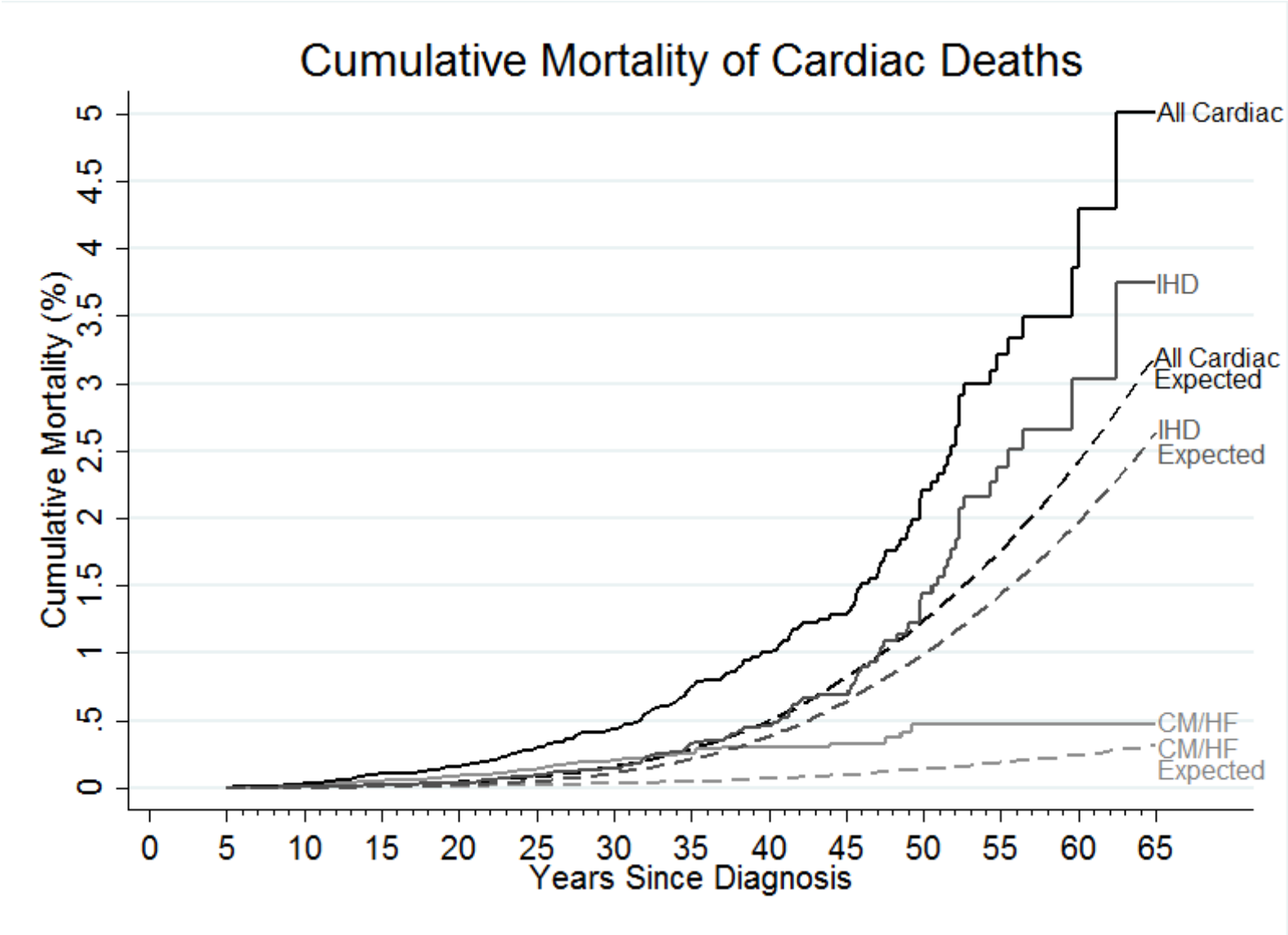
Supplemental Table V: Relative risks and excess mortality ratios per 10,000 person-years estimated using a multivariable model, adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age.

Abbreviations: CNS – central nervous system, PNET – primitive neuroectodermal tumor, AML – acute myeloid leukemia, RR – relative risks, EMR – excess mortality ratios, CI – confidence intervals, NE – not estimable

	Overall Cardiac Mortality	
	RR (95%CI)	**EMR (95%CI)**
Sex		
Male	1 (ref)	1 (ref)
Female	2.4 (1.6,3.7)	1.1 (0.7,1.9)
Pheterogeneity	<0.0001	0.5805
First Primary Neoplasm Diagnosis		
CNS (excluding PNET)	1 (ref)	1 (ref)
CNS PNET	0.4 (0.1,2.9)	0.4 (0.0,6.6)
Leukemia (excluding AML)	0.6 (0.3,1.2)	0.7 (0.3,1.7)
AML	4.9 (2.2,11.1)	6.7 (2.5,17.9)
Hodgkin Lymphoma	2.2 (1.1,4.4)	3.3 (1.3,8.3)
Non-Hodgkin Lymphoma	2.0 (0.9,4.5)	3.1 (1.2,8.4)
Neuroblastoma	0.3 (0.0,2.4)	0.4 (0.0,3.6)
Non-Heritable Retinoblastoma	0.3 (0.0,2.6)	0.4 (0.0,4.7)
Heritable Retinoblastoma	*NA*	*NA*
Wilms	1.2 (0.5,2.7)	1.4 (0.5,3.9)
Bone Sarcoma	1.8 (0.7,4.6)	2.5 (0.7,8.4)
Soft Tissue Sarcoma	1.2 (0.5,3.0)	1.6 (0.5,4.8)
Other	0.8 (0.3,2.0)	0.7 (0.2,2.9)
Pheterogeneity	0.0002	0.0001
Age at Diagnosis		
0-4 years	1 (ref)	1 (ref)
5-9 years	0.6 (0.4,1.1)	0.7 (0.4,1.2)
10-14 years	0.5 (0.3,0.9)	0.5 (0.2,0.9)
Ptrend	0.0216	0.0312
Treatment Era		
1970-1974	1 (ref)	1 (ref)
1975-1979	1.6 (0.9,2.9)	1.8 (0.8,4.2)
1980-1984	1.9 (1.0,3.5)	2.1 (0.9,4.8)
1985-1989	1.8 (0.9,3.7)	1.9 (0.7,4.6)
1990-1994	0.9 (0.4,2.4)	0.8 (0.3,2.7)
1995-1999	0.6 (0.2,2.1)	0.4 (0.1,2.4)
Ptrend	0.7687	0.3521
Pquadratic	0.0024	0.0019
Attained Age		
5-19 years	1 (ref)	1 (ref)
20-29 years	0.8 (0.4,1.4)	1.8 (0.9,3.7)
30-39 years	0.5 (0.2,0.9)	3.0 (1.4,6.3)
40-49 years	0.3 (0.2,0.8)	4.9 (1.8,13.5)
50+ years	0.3 (0.1,1.4)	15.8 (2.5,101.2)
Ptrend	0.0068	0.0004

Supplemental Table VI: Relative risks and excess mortality ratios per 10,000 person-years estimated using a multivariable model, adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age. For these analyses, the British Childhood Cancer Survivor Study was restricted to the diagnosis period to 1970-1999 in order to compare with the Childhood Cancer Survivor Study.

Abbreviations: CNS – central nervous system, PNET – primitive neuroectodermal tumor, AML – acute myeloid leukemia, RR – relative risks, EMR – excess mortality ratios, CI – confidence interval, NA – not applicable



Supplemental Figure I: Cumulative mortality of all cardiac causes, ischemic heart disease causes, and cardiomyopathy/heart failure causes among childhood cancer survivors compared to that expected in the general population, by follow-up (years since diagnosis).
Abbreviations: CM/HF – cardiomyopathy/heart failure, IHD – ischemic heart disease