Population-based Risks of Specific Causes of Death up to 55 Years after Childhood Cancer: The British Childhood Cancer Survivor Study

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Abstract

Context Survivors of childhood cancer are at increased risk of premature mortality compared to 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 the background mortality in the general population starts to increase substantially.

Objective To investigate long-term cause-specific mortality in a cohort with over three times the number of person-years and deaths beyond 25 years from diagnosis than previously available.

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.

Main outcome measures Cause-specific standardized mortality ratios (SMR) and absolute excess risks (AER).

Results Overall, 3,049 deaths were observed, which was 11-times (SMR=10.7; 95%CI: 10.3-11.1) the number expected. The SMR declined with follow-up, but was still 3-fold expected (SMR=3.1, 95%CI: 2.5-3.9) 45 years from diagnosis. The AER for deaths from recurrence declined from 97 extra deaths (per 10,000 per year) at 5-14 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 cancer and circulatory causes increased from 8 and 2 extra deaths to 58 and 29 extra deaths, respectively. Beyond 45 years from diagnosis recurrence only accounts for 7% of the excess number of deaths observed whilst second primary cancer and circulatory deaths together account for 77%.

Conclusion These results indicate that considerable numbers of survivors are dying prematurely from second primary cancer and circulatory disease beyond 25 years from diagnosis. Survivors should therefore be able to access health care programmes even decades from treatment.

Introduction

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 five-year survival compared to the general population.[1] Previous studies have shown that the leading cause of death following five-year survival is recurrence or progression of the original tumor, followed by second primary cancer and non-neoplastic conditions such as cardiac disease.[2-8] Although studies have shown that the risk of death from recurrence decreases with increasing time since five-year survival, the uncertainty about the long-term risks of death from other causes remains. Investigations into long-term cause specific mortality are important as any excess mortality may be related to long-term complications of treatment. Strongly elevated mortality risks related to second primary cancer and non-neoplastic disease, when compared to 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 the background mortality in the general population starts to increase substantially. Previous studies had insufficient person-years and observed deaths beyond 25 years from diagnosis to satisfactorily investigate long-term cause-specific mortality. 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 population-based cohort with more than four times the number of person-years and three times the number of deaths beyond 25 years from initial cancer diagnosis than previously available to the largest of all previous studies.[2] We report mortality risks up to 55 years after diagnosis of the initial childhood cancer; 20 years longer than previously reported by any other large-scale study.

Subjects and 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 five-year survivors of childhood cancer diagnosed under the age of 15 years between 1940 and 1991 in Britain.[9] 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. Information on type of childhood cancer, initial treatment (i.e., radiotherapy, chemotherapy), and demographics were provided by CCRG. Ethical approval was obtained from the relevant Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain (212 in total).

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 when each survivor dies. 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 other available sources 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 five-year

survival beyond the time of initial childhood cancer diagnosis. The cohort exit date was 31 December 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.[10] 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 AER is a useful measure for determining the additional mortality burden beyond the background mortality as it reflects the number of excess deaths per 10,000 persons per year. To derive the expected number of deaths used in the calculation of the SMR and AER, person-years for each sex, age (5-year bands) and calendar year (1-year bands) specific stratum were multiplied by the corresponding mortality rate for the England & Wales population and then summed across the strata.[11] 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, 10-14 yr), treatment with radiotherapy (yes/no), treatment with chemotherapy (yes/no), years from diagnosis (5-14, 15-24, 25-34, 35-44 and ≥45 yr) and attained age (0-19, 20-29, 30-39, 40-49, and ≥50 yr).To evaluate the simultaneous effect of the above-mentioned factors on the SMR and AER, special multivariable Poisson regression models were used to derive relative risks (RR) and excess mortality ratios (EMR) (see online Appendix).

Derivation of SMRs for deaths due to recurrence would not be appropriate because the corresponding mortality rate in the general population would be zero. 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 (0-4, 5-9, 10-14 yr), treatment with radiotherapy (yes/no), treatment with chemotherapy (yes/no), years from diagnosis (5-14, 15-24, 25-34, 35-44 and ≥45 yr) and attained age (0-19, 20-29, 30-39, 40-49, and ≥50

yr). The simultaneous effects of these factors on the mortality rate were evaluated by employing a multivariable Poisson regression model (see online Appendix).

Cumulative mortality, as a function of years since diagnosis, for death causes exceeding 100 deaths was estimated by means of the stcompet command in Stata.[12] Causes of death other than the one under study were treated as competing risks. Stata statistical software was used for all analyses.[13] The criterion for statistical significance was a two-sided p-value of less than 0.05.

Results

Cohort characteristics

Of the 17,981 five-year survivors in the cohort, 3,049 (17.0%) had died, 245 (1.4%) were lost to follow-up, and 14,687 (81.7%) were alive at the study exit date. Death certificates were obtained for 3,035 out of the 3,049 (99.5%) deaths. Nearly half of the cohort (47.4%) had survived 25 years or more from diagnosis of their childhood cancer, with 32% having survived more than 30 years. Survivors were followed-up for a total of 370,025 person-years from 5-year survival with a mean follow-up of 20.6 years. 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.

Overall observed and expected number of 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 absolute excess risk, survivors were most at risk of dying of recurrence (AER=51.8), second primary cancer (AER=11.3), circulatory disease (AER=3.4) and respiratory disease (AER=2.5).

All causes of death combined – potential risk factors

Overall, survivors experienced 11 times the number of deaths expected from the general population (SMR=10.7, 95% confidence interval [CI] = 10.3-11.1) and 75 additional deaths per 10,000 per year in excess of that expected (Table 2). The SMR declined significantly with increasing follow-up and attained age (P_{trend}<.0001); nonetheless, significant excess mortality remained even after 45 years from diagnosis (SMR=3.1, 95%CI=2.5-3.9). There was evidence of non-linearity in AERs by follow-up ($P_{non\text{-}lineaity}$<.0001); with the variation in the AER resembling a U-shaped curve. The AER was 115 over the first 10 years after 5-year

171 survival, declined to roughly 40 between 15 and 35 years after diagnosis, and then
172 increased back up to 114 beyond 45 years after diagnosis. All types of childhood cancer
173 were associated with significantly increased mortality relative to the general population, with
174 the greatest SMRs observed among survivors of primitive neuroectodermal tumor (PNET)
175 and leukemia. The AER was 192 after PNET and also exceeded 100 after CNS tumors other
176 than PNET and after leukemia (other than AML).
177
178 **Specific causes of death - potential risk factors**
179 The crude mortality rate for recurrence, which may be interpreted as an AER, decreased
180 rapidly from almost 100 at 5-14 years from diagnosis to less or equal to 11 deaths per
181 10,000 survivors per year beyond 25 years from diagnosis (Table 2). Mortality due to
182 recurrence or progression of the original disease was greatest among PNET survivors.
183 Females were at significantly lower risk than males (RR=0.8, 95%CI= 0.8-0.9) (eTable1).
184 The SMR for a second primary cancer declined sharply up to 35 years after
185 diagnosis, but thereafter remained at a roughly constant level (Table 2). Even after 45 years,
186 the SMR was still 3.6-fold (95% CI=2.6-4.9). Similarly, the SMR decreased significantly with
187 attained age (P_{trend}<.0001), but still was elevated 3-fold beyond age 50. In contrast, the AER
188 increased with time since diagnosis and attained age reaching 58 beyond 45 years from
189 diagnosis and 39 beyond age 50. Beyond 45 years, over 51% of the total absolute excess
190 risk could be attributed to deaths due to a second primary cancer (Table 3). The SMR was
191 significantly elevated for all types of childhood cancer, but greatest among survivors of
192 PNET and heritable retinoblastoma. Treatment with radiotherapy increased both the RR and
193 EMR 2-fold (eTable 1).
194 The SMR for circulatory deaths, which includes cardiac and cerebrovascular deaths,
195 was 11-fold over the first 10 years of follow-up and then declined to a plateau and remained
196 roughly at 2 to 3-fold beyond 25 years from diagnosis (Table 4). On the other hand, the AER
197 for circulatory deaths increased steadily with follow-up (P_{trend}<.0001) reaching 29 beyond 45
198 years from diagnosis. Nearly 26% of all excess deaths beyond 45 years from diagnosis were

attributed to circulatory causes (Table 3). All survivors, apart from retinoblastoma and bone tumor survivors, exhibited significantly elevated SMRs for circulatory disease. The AER exceeded 10 for survivors of AML. 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 in terms of both RR and EMR (eTable 2).

The SMR for cardiac disease declined with increasing follow-up, but remained 2-fold elevated 45 years after diagnosis (Table 4). The AER increased significantly (P_{trend}=.01) with follow-up, reaching 15 beyond 45 years from diagnosis. The SMR and AER was greatest for survivors of AML. 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 (Table 4). In contrast, the AER increased significantly with increasing time since diagnosis to an AER of 8.5 beyond 45 years from diagnosis. Survivors of all cancer types, apart from those with non-heritable (NH) retinoblastoma or a bone tumor, exhibited significantly elevated SMRs for respiratory disease. Survivors treated with chemotherapy were at 3-fold increased risk versus those not treated with chemotherapy, in terms of both RR and EMR (eTable 2).

The SMR for external causes of death increased slightly with follow-up, to an SMR of 3.0 beyond 45 years from diagnosis (Table 4). The AER also increased slightly with follow-up.

Cumulative mortality

The cumulative mortality (CM) from all death causes, other than recurrence, was 28.0% at 55 years from initial diagnosis whereas 8.7% was expected based on rates from the general population (Figure 1). The CM of death due to recurrence increased rapidly with time from diagnosis to 8.9% by 15 years; but then leveled off reaching 12.4% by 50 years (Figure 1). The CM of second primary cancer increased gradually with time from diagnosis reaching 2.4% by 30 years, but then increased rapidly up to 13.4% by 55 years (Figure 1). For

226 circulatory deaths, the CM was low by 30 years (CM=0.8%), but increased substantially up
227 to 6.1% by 55 years from diagnosis (Figure 1).
228
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Discussion

Previously no study has satisfactorily investigated the cause-specific mortality of survivors of childhood cancer beyond 25 years after the initial cancer diagnosis. This study, the largest ever in terms of accumulated person-years and number of deaths, identified that there is a persistence of an elevated risk of mortality due to second primary cancer, circulatory, and pulmonary disease beyond 25 years from diagnosis relative to the general population. As a result of this elevated relative risk, the absolute excess risk of mortality due to second primary cancer, circulatory disease, and pulmonary disease increases rapidly with increasing time from diagnosis. The AER for deaths from recurrence declined from 97 extra deaths (per 10,000 per year) at 5-14 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 only amounts for 7% of the excess number of deaths observed whilst second primary cancers and circulatory deaths together account 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 1,507 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 two 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 three studies, however, the cumulative mortality of second primary cancer by 25 years from diagnosis was low (<3.5%); but in the current study it increased substantially (>13%) in the subsequent years of follow-up and such older survivor experience is only available to the current study. The AERs by follow-up for second primary cancer, cardiac, 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. Whilst 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. Second primary cancers are a recognized late complication of childhood cancer[14-16] 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.[17] Evidence is also emerging that treatment of childhood cancer increases the risk of circulatory disease.[18] More specifically, exposure to cranial irradiation increases the risk of stroke[19-20] and exposure to chest irradiation has been associated with heart disease[18], but also exposure to high cumulative doses of specific chemotherapeutic agents, principally the anthracyclines, may induce cardiotoxicity.[18, 21-23]

A potential limitation of our study includes the lack of detailed data on radiotherapy and chemotherapy exposures 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 anti cancer therapy, may not be applicable to survivors treated with modern therapy including, for example, 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 diseases 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 the most at risk of dying of a second primary cancer or circulatory disease, yet these survivors are much less likely to be on active hospital follow-up than those diagnosed more recently [24]. The findings of this study suggest that survivors should be able to access health care intervention programmes even many years after survival from their first cancer.

In conclusion, the findings from this largest ever population-based study of its kind indicate that the absolute excess risk and cumulative mortality related to second primary tumors, circulatory, and respiratory disease increases 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 programmes even decades post 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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Author Contributions: Drs Reulen and Hawkins had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hawkins, Reulen, Winter, Lancashire, Jenney, Stevens, Stiller

Acquisition of data: Hawkins, Winter, Stiller

Analysis and interpretation of data: Reulen, Hawkins

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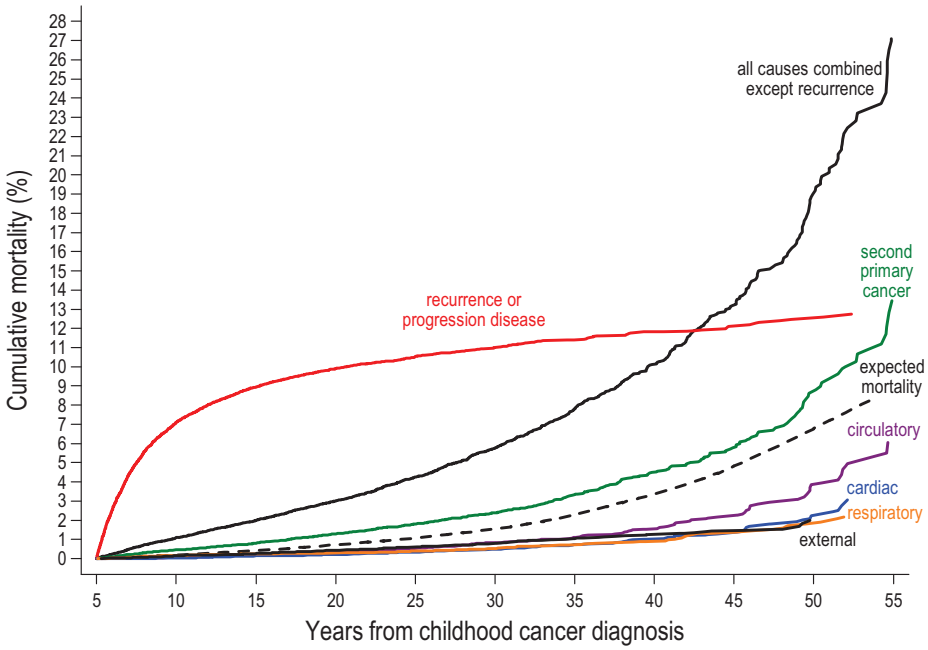

Figure 1. Cumulative mortality for each cause of death taking into account other causes of death as a competing risk

Table 1. Observed and expected deaths, standardized mortality ratio (SMR), and absolute excess risk (AER) of specific causes of death

	Observed	Expected	SMR	95%CI	AER*
All causes	3049	284.8	10.7	(10.3, 11.1)	74.9
Recurrence/progression disease	1918	0	NA	NA	51.8
All causes except recurrence	1117	284.8	3.9	(3.7-4.1)	22.4
Second primary cancer	483	66.4	7.3	(6.7, 8.0)	11.3
All non-neoplastic causes	634	218.4	2.9	(2.7-3.1)	11.1
Infections	44	5.9	7.5	(5.4,10.0)	1.0
Blood disease	7	1.3	5.4	(2.2,11.2)	0.2
Endocrine disease	24	6.2	3.9	(2.5, 5.7)	0.5
Mental disorders	7	8.5	0.8	(0.3, 1.7)	0.0
Nervous system disease	55	13.5	4.1	(3.1, 5.3)	1.1
Circulatory (all) disease	170	43.0	4.0	(3.4, 4.6)	3.4
--Cardiac disease	105	29.9	3.5	(2.9, 4.2)	2.0
--Cerebrovascular disease	48	9.0	5.2	(3.9, 6.9)	1.0
--Circulatory disease other	17	4.0	4.3	(2.7, 6.9)	0.4
Respiratory disease	106	13.3	8.0	(6.6, 9.7)	2.5
Digestive disease	30	14.3	2.1	(1.4, 3.0)	0.4
Skin and musculoskeletal disease	5	1.5	3.3	(1.1, 7.6)	0.1
Genitourinary disease	21	2.0	10.6	(6.6, 16.3)	0.5
Pregnancy and childbirth	17	6.5	2.6	(1.5, 4.2)	0.3
External causes	138	99.6	1.4	(1.1, 1.6)	0.9
--Suicide	37	37.6	1.0	(0.7-1.4)	0.0
Other	10	2.7	3.7	(2.0, 6.8)	0.2

* Per 10,000 survivors per year
NA, Not applicable

Table 2. Standardized mortality ratio (SMR) and absolute excess risk (AER) 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		
		PYRS	Obs/Exp	SMR (95%CI)	AER*	Obs	Crude rate (95%CI)*†	Obs/Exp	SMR (95%CI)	AER*
Overall		370025	3049/284.8	10.7 (10.3-11.1)	74.9	1918	51.8 (49.4-54.1)	483/66.4	7.3 (6.7-8.0)	11.3
Sex	males	200422	1808/195.7	9.2 (8.8-9.7)	80.4	1126	56.2 (53.0-59.6)	282/34.4	8.2 (7.3-9.2)	12.4
	females	169603	1241/89.1	13.9 (13.2-14.7)	67.9	792	46.7 (43.6-50.1)	201/32.0	6.3 (5.5-7.2)	10.0
	$P_{heterogeneity}$			<0.0001	<0.0001		<0.0001		0.003	0.04
Type of childhood cancer	CNS tumor (excl PNET)	74958	879/67.9	12.9 (12.1-13.8)	108.2	574	76.6 (70.6-83.1)	89/17.6	5.1 (4.1-6.2)	9.5
	PNET	11210	224/8.8	25.5 (22.3-29.0)	192.0	147	131.1 (111.6-154.1)	46/1.8	25.1 (18.8-33.5)	39.4
	Leukemia (excl AML)	74730	797/37.1	21.5 (20.0-23.0)	101.7	640	85.6 (79.3-92.5)	61/5.8	10.5 (8.2-13.5)	7.4
	Acute Myeloid leukemia	5342	45/2.8	15.8 (11.8-21.2)	78.9	28	52.4 (36.2-75.9)	7/0.5	15.2 (7.3-31.9)	12.2
	Hodgkin's lymphoma	27232	251/28.4	8.8 (7.8-10.0)	81.8	144	52.9 (44.9-62.3)	46/6.1	7.5 (5.6-10.0)	14.6
	Non-Hodgkin's lymphoma	18527	84/18.5	4.5 (3.7-5.6)	35.3	32	17.3 (12.2-24.4)	18/4.3	4.2 (2.6-6.6)	7.4
	Neuroblastoma	16970	92/9.9	9.3 (7.5-11.4)	48.4	49	28.9 (21.8-38.2)	16/2.1	7.5 (4.6-12.2)	8.2
	NH-retinoblastoma	18394	21/14.2	1.5 (1.0-2.3)	3.7	0	0.0	11/3.6	3.0 (1.7-5.5)	4.0
	H-retinoblastoma	15160	100/11.1	9.0 (7.4-11.0)	58.7	19	12.5 (8.0-19.6)	67/2.7	24.7 (19.4-31.3)	42.4
	Wilms' tumor	34301	122/21.0	5.8 (4.9-6.9)	29.4	41	12.0 (8.8-16.2)	35/4.4	8.0 (5.8-11.2)	8.9
	Bone tumor	12915	116/13.1	8.9 (7.4-10.6)	79.7	78	60.4 (48.4-75.4)	24/3.6	6.7 (4.5-10.0)	15.8
	Soft tissue sarcoma	26680	161/23.6	6.8 (5.9-8.0)	51.5	98	36.7 (30.1-44.8)	26/5.9	4.4 (3.0-6.5)	7.5
	other	33607	157/28.5	5.5 (4.7-6.4)	38.2	68	20.2 (16.0-25.7)	37/8.0	4.6 (3.4-6.4)	8.6
	$P_{heterogeneity}$			<0.0001	<0.0001		<0.0001		<0.0001	<0.0001
Age at diagnosis	0-4 yrs	174166	1129/99.7	11.3 (10.7-12.0)	59.1	676	38.8 (36.0-41.9)	217/20.2	10.7 (9.4-12.3)	11.3
	5-9 yrs	96304	921/74.2	12.4 (11.6-13.2)	87.9	632	65.6 (60.7-70.9)	109/15.9	6.9 (5.7-8.3)	9.7
	10-14 yrs	99555	999/110.9	9.0 (8.5-9.6)	89.2	610	61.3 (56.6-66.3)	157/30.3	5.2 (4.4-6.1)	12.7
	P_{trend}			<0.0001	<0.0001		<0.0001		<0.0001	0.50
Radiotherapy	No	91386	560/77.8	7.2 (6.6-7.8)	52.8	355	38.8 (35.0-43.1)	81/19.6	4.1 (3.3-5.1)	6.7
	Yes	207172	2047/173.4	11.8 (11.3-12.3)	90.4	1254	60.5 (57.3-64.0)	357/40.9	8.7 (7.9-9.7)	15.3
	$P_{heterogeneity}$			<0.0001	<0.0001		<0.0001		<0.00001	<0.0001
Chemotherapy	No	157185	1328/164.2	8.1 (7.7-8.5)	74.0	741	47.1 (43.9-50.7)	264/45.6	5.8 (5.1-6.5)	13.9
	Yes	128761	1198/75.8	15.8 (14.9-16.7)	87.2	827	64.2 (60.0-68.8)	165/12.3	13.4 (11.5-15.6)	11.9
	$P_{heterogeneity}$			<0.0001	0.0002		<0.0001		<0.0001	0.16
Years from cancer diagnosis	5-14 yrs	166059	1970/69.1	28.5 (27.3-29.8)	114.5	1604	96.6 (92.0-101.4)	145/9.3	15.5 (13.2-18.3)	8.2
	15-24 yrs	120182	535/78.4	6.8 (6.3-7.4)	38.0	227	18.9 (16.6-21.5)	136/12.1	11.3 (9.5-13.3)	10.3
	25-34 yrs	57900	304/61.8	4.9 (4.4-5.5)	41.8	64	11.1 (8.7-14.1)	99/16.0	6.2 (5.1-7.5)	14.3
	35-44 yrs	21028	159/49.8	3.2 (2.7-3.7)	51.9	19	9.0 (5.8-14.2)	64/18.1	3.5 (2.8-4.5)	21.8
	45+ yrs	4855	81/25.8	3.1 (2.5-3.9)	113.7	4	8.2 (3.1-22.0)	39/10.8	3.6 (2.6-4.9)	58.0
	P_{trend}			<0.0001	<0.0001		<0.0001		<0.0001	<0.0001
Attained age	0-19 yrs	139996	1629/49.5	32.9 (31.3-34.5)	112.8	1343	95.9 (90.9-101.2)	124/6.9	18.1 (15.1-21.5)	8.4
	20-29 yrs	125988	744/78.5	9.5 (8.8-10.2)	52.8	422	33.5 (30.4-36.8)	126/9.8	12.8 (10.8-15.3)	9.2
	30-39 yrs	69696	374/62.4	6.0 (5.4-6.6)	44.7	119	17.1 (14.3-20.4)	117/14.1	8.3 (6.9-10.0)	14.8
	40-49 yrs	26171	184/51.2	3.6 (3.1-4.2)	50.7	28	10.7 (7.4-15.5)	66/17.2	3.8 (3.0-4.9)	18.6
	50+ yrs	8173	118/43.2	2.7 (2.3-3.3)	91.6	6	7.3 (3.3-16.3)	50/18.4	2.7 (2.1-3.6)	38.6
	P_{trend}			<0.0001	<0.0001		<0.0001		<0.0001	<0.0001

*Per 10,000 survivors per year; †may be interpreted as an AER

Abbreviations: PYRS, Person-years; Obs, Observed; Exp, Expected; CNS, Central Nervous System; PNET, Primative Neuroectodermal Tumor; AML, Acute Myeloid Leukemia; NH, Non-Heritable; H, Heritable

Table 3. Absolute excess risk (AER) by years from diagnosis as a proportion of total absolute excess risk

Cause of death	Years from diagnosis (yrs) 5-14 AER	15-24 AER	25-34 AER	35-44 AER	45+ AER
Recurrence*	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†	113.9	37.8	41.5	51.9	113.7

* Expected number for deaths due to recurrence assumed to be zero

† Small inconsistency of total AER with AER from Table 2 is due to unknown causes of death amongst 14 survivors.

Table 4. Standardized mortality ratio (SMR) and absolute excess risk (AER) for deaths due to circulatory, cardiac, respiratory and external causes by potential explanatory factors.

		Circulatory deaths			Cardiac deaths			Respiratory deaths			External deaths		
Total		**Obs/Exp**	**SMR (95%CI)**	**AER***	**Obs/Exp**	**SMR (95%CI)**	**AER***	**Obs/Exp**	**SMR (95%CI)**	**AER***	**Obs/Exp**	**SMR (95%CI)**	**AER***
Sex	males	170/43.0	4.0 (3.4-4.6)	3.4	105/29.9	3.5 (2.9-4.2)	2.0	106/13.3	8.0 (6.6-9.7)	2.5	138/99.6	1.4 (1.1-1.6)	0.9
	females	104/31.3	3.3 (2.7-4.0)	3.6	66/23.7	2.8 (2.2-3.5)	2.1	65/8.3	7.8 (6.1-9.9)	2.8	94/80.8	1.2 (1.0-1.4)	0.7
	$P_{heterogeneity}$	66/11.7	5.6 (4.4-7.2)	3.2	39/6.3	6.2 (4.5-8.5)	1.9	41/4.9	8.3 (6.1-11.3)	2.1	44/18.8	2.3 (1.7-3.1)	1.5
Type of Childhood cancer	CNS tumor (excl PNET)		0.001	0.54		0.0001	0.74		0.75	0.21		0.0003	0.19
	PNET	40/11.6	3.4 (2.5-4.7)	3.8	12/8.2	1.5 (0.8-2.6)	0.5	44/3.3	13.2 (9.8-17.8)	5.4	47/21.3	2.2 (1.7-2.9)	3.4
	Leukemia (excl AML)	10/1.3	7.9 (4.3-14.7)	7.8	4/0.9	4.5 (1.7-12.0)	2.8	11/0.4	28.0 (15.5-50.6)	9.5	3/3.4	0.9 (0.3-2.8)	0.0
	Acute Myeloid leukemia	15/3.1	4.8 (2.9-7.9)	1.6	12/2.0	6.1 (3.5-10.8)	1.3	10/1.4	7.0 (3.8-13.0)	1.1	24/17.3	1.4 (0.9-2.1)	0.9
	Hodgkin's lymphoma	6/0.3	21.3 (9.5-47.3)	10.7	5/0.2	27.0 (11.3-65.0)	9.0	1/0.1	8.9 (1.3-63.5)	1.7	1/1.3	0.8 (0.1-5.6)	0.0
	Non-Hodgkin's lymphoma	25/4.8	5.2 (3.5-7.7)	7.4	19/3.5	5.4 (3.4-8.5)	5.7	5/1.3	3.9 (1.6-9.4)	1.4	11/10.2	1.1 (0.6-1.9)	0.3
	Neuroblastoma	17/3.2	5.2 (3.3-8.4)	7.4	11/2.4	4.6 (2.6-8.4)	4.7	5/0.9	5.8 (2.4-14.0)	2.2	5/6.3	0.8 (0.3-1.9)	0.0
	NH-retinoblastoma	6/1.3	4.6 (2.1-10.2)	2.8	5/0.9	5.6 (2.3-13.4)	2.4	5/0.5	10.6 (4.4-25.5)	2.7	8/3.7	2.2 (1.1-4.4)	2.5
	H-retinoblastoma	1/2.3	0.4 (0.1-3.1)	0.0	1/1.6	0.6 (0.1-4.4)	0.0	1/0.7	1.4 (0.2-10.0)	0.2	3/4.5	0.7 (0.2-2.1)	0.0
	Wilms' tumor	4/1.6	2.5 (0.9-6.6)	1.6	3/1.1	2.7 (0.9-8.3)	1.2	3/0.6	5.4 (1.7-16.8)	1.6	2/3.7	0.5 (0.1-2.1)	0.0
	Bone tumor	14/2.5	5.5 (3.3-9.3)	3.3	12/1.7	7.1 (4.0-12.5)	3.0	6/0.9	6.3 (2.8-14.1)	1.5	14/8.2	1.7 (1.0-2.9)	1.7
	Soft tissue sarcoma	3/2.4	1.3 (0.4-4.0)	0.5	2/1.7	1.2 (0.3-4.8)	0.3	0/0.6	0.0	0.0	5/3.8	1.3 (0.5-3.1)	0.9
	other	10/4.0	2.5 (1.3-4.7)	2.3	9/2.8	3.2 (1.6-6.1)	2.3	7/1.1	6.2 (2.9-12.9)	2.2	6/7.6	0.8 (0.4-1.8)	0.0
	$P_{heterogeneity}$	19/4.5	4.2 (2.7-6.6)	4.3	10/3.0	3.3 (1.8-6.1)	2.1	8/1.4	5.7 (2.8-11.4)	2.0	9/8.5	1.1 (0.6-2.0)	0.2
Age at diagnosis	0-4 yrs		0.0001	<0.0001		<0.0001	0.0005		<0.0001	<0.0001		0.04	0.02
	5-9 yrs	51/11.9	4.3 (3.3-5.6)	2.2	39/8.1	4.8 (3.5-6.6)	1.8	41/4.5	9.1 (6.7-12.3)	2.1	53/39.3	1.3 (1.0-1.8)	0.8
	10-14 yrs	45/10.2	4.4 (3.3-5.9)	3.6	26/7.0	3.7 (2.5-5.4)	2.0	28/3.3	8.5 (5.9-12.3)	2.6	35/28.3	1.2 (0.9-1.7)	0.7
	P_{trend}	74/20.8	3.5 (2.8-4.5)	5.3	40/14.9	2.7 (2.0-3.7)	2.5	37/5.5	6.8 (4.9-9.3)	3.2	50/32.0	1.6 (1.2-2.1)	1.8
Radiotherapy	No		0.27	0.0004		0.009	0.30		0.19	0.12		0.47	0.22
	Yes	27/12.4	2.2 (1.5-3.2)	1.6	22/8.6	2.6 (1.7-3.9)	1.5	23/3.7	6.2 (4.1-9.3)	2.1	31/25.2	1.2 (0.9-1.7)	0.6
	$P_{heterogeneity}$	127/27.5	4.6 (3.9-5.5)	4.8	70/19.3	3.6 (2.9-4.6)	2.4	68/8.2	8.3 (6.5-10.5)	2.9	88/59.5	1.5 (1.2-1.8)	1.4
Chemotherapy	No		0.0001	0.0002		0.14	0.15		0.21	0.25		0.37	0.34
	Yes	101/30.9	3.3 (2.7-4.0)	4.5	56/22.1	2.5 (2.0-3.3)	2.2	53/8.4	6.3 (4.8-8.2)	2.8	65/46.3	1.4 (1.1-1.8)	1.2
	$P_{heterogeneity}$	45/7.3	6.1 (4.6-8.2)	2.9	34/4.7	7.2 (5.1-10.1)	2.3	33/3.0	11.1 (7.9-15.6)	2.3	46/34.5	1.3 (1.0-1.8)	0.9
Years from cancer diagnosis	5-14 yrs		0.0008	0.06		<0.0001	0.85		0.01	0.44		0.79	0.69
	14-24 yrs	39/3.7	10.7 (7.8-14.6)	2.1	25/2.2	11.3 (7.7-16.8)	1.4	44/3.2	13.7 (10.2-18.4)	2.5	47/36.8	1.3 (1.0-1.7)	0.6
	25-34 yrs	42/7.1	5.9 (4.4-8.0)	2.9	27/4.4	6.1 (4.2-8.9)	1.9	19/3.0	6.3 (4.0-9.9)	1.3	46/38.2	1.2 (0.9-1.6)	0.7
	35-44 yrs	38/11.3	3.4 (2.4-4.6)	4.6	25/7.8	3.2 (2.2-4.7)	3.0	22/2.6	8.5 (5.6-12.9)	3.4	31/17.3	1.8 (1.3-2.5)	2.4
	45+ yrs	29/13.2	2.2 (1.5-3.2)	7.5	15/9.8	1.5 (0.9-2.5)	2.5	15/2.6	5.8 (3.5-9.6)	5.9	10/6.0	1.7 (0.9-3.1)	1.9
	P_{trend}	22/7.7	2.9 (1.9-4.3)	29.4	13/5.7	2.3 (1.3-3.9)	15.1	6/1.9	3.2 (1.5-7.2)	8.5	4/1.3	3.0 (1.1-8.1)	5.5
Attained age	0-19 yrs		<0.0001	<0.0001		<0.0001	0.01		0.0001	0.03		0.07	0.03
	20-29 yrs	24/2.3	10.6 (7.1-15.8)	1.6	17/1.4	12.0 (7.4-19.2)	1.1	33/2.5	13.5 (9.6-18.9)	2.2	30/25.7	1.2 (0.8-1.7)	0.3
	30-39 yrs	40/5.4	7.4 (5.4-10.0)	2.7	25/3.2	7.9 (5.4-11.7)	1.7	26/2.9	8.9 (6.1-13.1)	1.8	55/43.2	1.3 (1.0-1.7)	0.9
	40-49 yrs	43/9.3	4.6 (3.4-6.2)	4.8	28/6.1	4.6 (3.2-6.7)	3.1	22/2.6	8.4 (5.5-12.8)	2.8	32/20.9	1.5 (1.1-2.2)	1.6
	50+ yrs	30/13.1	2.3 (1.6-3.3)	6.5	17/9.6	1.8 (1.1-2.8)	2.8	13/2.3	5.6 (3.3-9.7)	4.1	17/7.6	2.2 (1.4-3.6)	3.6
	P_{trend}	33/12.9	2.6 (1.8-3.6)	24.6	18/9.7	1.9 (1.2-3.0)	10.2	12/3.0	4.0 (2.3-7.1)	11.1	4/2.2	1.8 (0.7-4.9)	2.2
			<0.0001	<0.0001		<0.0001	0.001		<0.0001	0.05		0.05	0.01

*Per 10,000 survivors per year

Abbreviations: Obs, Observed; Exp, Expected; CNS, Central Nervous System; PNET, Primative Neuroectodermal Tumor; AML, Acute Myeloid Leukemia; NH, Non-Heritable; H, Heritable