Late mortality and second cancers in an Australian cohort of childhood cancer survivors

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ABSTRACT

Objective: The aim of this study was to characterise rates of late mortality and second cancers in an Australian cohort of childhood cancer survivors and compare these to rates observed in the New South Wales population.

Design, setting and participants: Records for 896 childhood cancer survivors treated at the Sydney Children's Hospital between 1972 and 1999 were linked to the National Death Index and NSW Central Cancer Registry to identify deaths and notifications of second cancers. Survivors were defined as those alive for at least 5 years after diagnosis and were followed until death or 31 December 2004, whichever occurred first.

Main outcome measures: Standardised mortality ratios (SMRs) and standardised incidence ratios (SIRs) were used as measures of relative risk. A Cox proportional hazard model was used to quantify the influence of demographic and disease-related characteristics on the risk of death and second cancers.

Results: The SMR and SIR were 7.46 and 4.98 times higher, respectively, among cancer survivors relative to the NSW population. Relative mortality was highest in survivors of soft-tissue sarcoma (SMR, 18.95 [95% CI, 6.88–40.81]) and central nervous system (CNS) malignancies (SMR, 16.78 [95% CI, 7.62–31.64]). The leading causes of death included recurrence of the primary childhood cancer (55%) and second cancers (12%), as well as treatment-related complications (17%) The most frequently observed second cancers were bone and thyroid cancers, melanoma, and CNS malignancies, and second cancers were most common among survivors of leukaemia, soft-tissue sarcoma and Hodgkin's lymphoma.

Conclusions: Compared with the general population, survivors of childhood cancer in Australia are at increased risk of late mortality and second cancers. These findings highlight a continuing need to assess health issues faced by childhood cancer survivors and develop strategies to minimise the adverse outcomes associated with treatment for childhood cancer.

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Survivors of childhood cancer are at increased risk of long-term sequelae and earlier death (compared with the general population) as a consequence of anticancer therapies received during childhood.[1,2] Death occurring more than 5 years after diagnosis of childhood cancer is often referred to as late mortality. Previous studies of childhood cancer survivors have shown an increased risk of mortality — eight to 17 times higher than in the general population.[3-7] While relapse of the primary childhood malignancy has been reported to account for about 57% to 75% of deaths, excess mortality due to cardiac and pulmonary complications has also been reported in survivors of childhood cancer followed for extended periods.[3-6]

Second cancers, defined as histologically distinct cancers that develop after the occurrence of a prior cancer, have also been reported to be a frequent cause of mortality in survivors of childhood cancer, with the most commonly occurring second cancers being thyroid, breast, bone and brain cancers.[6,8] Second cancers are largely thought to be direct consequences of anticancer therapies received during childhood, with solid tumours more prevalent in patients treated with radiation and secondary leukaemia more prevalent in those treated with epipodophyllotoxins and alkylating agents.[9] While radiation-associated second cancers are generally characterised by long latency periods following treatment during childhood, secondary leukaemias tend to arise early (1–3 years after treatment with epipodophyllotoxins and 5–10 years after treatment with alkylating agents).[10,11]

Studies from the United States and Europe have reported the overall cumulative incidence of second cancers in childhood cancer survivors to range from 2.5% to 4.2% at 25 years after diagnosis — three to six times higher than that observed in the general population.[8,12-16] However, few investigations have examined the rates of second cancers in Australian survivors of childhood cancer. These studies have been limited to pooled analyses of second cancers from 13 population-based cancer registries and did not report rates specific to Australia.[17,18] In addition, studies examining late mortality in Australian survivors of childhood cancer are lacking. Given that variable treatment protocols, as well as lifestyle, health care and ethnic diversity, are likely to differentially affect the occurrence of deaths and second cancers in childhood cancer survivors, it is important to characterise these long-term outcomes in the Australian context.

Here, we present findings from a hospital-based cohort study which characterised rates of death and second cancers in a cohort of childhood cancer survivors treated over three decades.

METHODS

Eligible for this study were individuals who were diagnosed with childhood cancer at age ⩽14 years, received anticancer treatment at the Sydney Children's Hospital between January 1972 and December 1999, and remained disease-free ⩾5 years after achieving remission. Analyses were restricted to patients who were residents of New South Wales at the time of diagnosis.

Data linkage with the Australian National Death Index (NDI) and NSW Central Cancer Registry (NCCR) and review of clinical records were undertaken to identify deaths and second cancers among the study cohort. Information on individuals originally diagnosed with a childhood cancer in NSW who developed a second cancer after relocating to another state or territory was also obtained from the NCCR.[19]

Rates of mortality and second cancers were calculated by dividing the number of deaths or cancers observed in the cohort by the total number of person-years at risk contributed by each cohort member. Person-years at risk were calculated from 5 years after the original diagnosis of a childhood cancer to death or 31 December 2004 for rates of mortality and to diagnosis of a second cancer or 31 December 2004 for rates of second cancers. Standardised mortality ratios (SMRs) and standardised incidence ratios (SIRs) were calculated with exact (Poisson) 95% confidence

intervals by dividing the observed number of incident cases by the expected number of incident cases. The expected numbers of cases were calculated by multiplying mortality and cancer rates for NSW — specific for sex, calendar year, and age (using 5-year groups) — by the person-years at risk. All subsequent malignancies were counted in the numerator of the SIR for patients who developed multiple malignancies following a previous diagnosis of cancer.[8] Second cancers that occurred within 5 years of the original diagnosis of childhood cancer were excluded from analyses. Absolute excess risk per 1000 person-years at risk was calculated by subtracting the expected number of second cancers or deaths from the observed number, dividing the difference by person-years at risk and multiplying the result by 1000.

A Cox proportional hazard model was used to assess the effects of patient characteristics such as childhood diagnosis, age at diagnosis and sex on risk of death and diagnosis of a second cancer, up to 31 December 2004. The Kaplan–Meier product limit method was used to estimate the cumulative incidence of second cancers and death, from 5 years after diagnosis.[20]

All calculations were performed using the statistical package Stata version 8 (Statacorp, College Station, Tex, USA). Full institutional ethics approval was obtained from the South Eastern Sydney and Illawarra Area Health Service Human Research Ethics Committee before commencing the study.

1 Risk of death among 5-year survivors of childhood cancer relative to the New South Wales population according to demographic and disease-related characteristics

	No. of individuals	No. of observed deaths*	No. of expected deaths	Standardised mortality ratio† (95% CI‡)	Absolute excess risk§
All survivors	896	42	5.63	7.46 (5.38–10.08)	3.41
Sex					
Male	502	25	4.28	5.84 (3.69–8.43)	3.48
Female	394	17	1.34	12.67 (7.39–20.31)	3.31
Age at diagnosis					
0–9 years	714	31	4.22	7.34 (4.99–10.43)	3.04
10–14 years	182	11	1.40	7.84 (3.92–14.06)	5.21
Childhood diagnosis					
Leukaemia	392	13	2.51	5.19 (2.76–8.86)	2.17
Central nervous system malignancy	123	9	0.54	16.78 (7.62–31.64)	8.34
Lymphoma¶	94	5	0.91	5.47 (1.78–12.82)	3.11
Soft-tissue sarcoma	45	6	0.32	18.95 (6.88–40.81)	9.87
Other solid tumour**	242	9	1.35	6.65 (3.05–12.66)	2.62
Length of follow-up					
5–9 years	201	20	0.13	156.17 (93.97–237.60)	38.82
10–14 years	197	12	0.44	27.20 (14.09–47.64)	7.89
15–19 years	183	6	0.99	6.08 (2.22–13.19)	2.19
⩾20 years	315	< 5	4.07	0.98 (0.27–2.52)	—

* To preserve confidentiality of participants and their data, numbers fewer than five cannot be specified. † Some standardised mortality ratios differ from those calculated using data shown in table due to rounding of numbers of expected deaths. ‡ Exact 95% confidence intervals were calculated using Poisson distribution. § Per 1000 person-years at risk. ¶ Lymphoma category includes both Hodgkin's and non-Hodgkin's lymphomas ** Childhood malignancies such as Wilms' tumour, neuroblastoma, retinoblastoma, hepatoblastoma, melanoma, germ cell tumours, bone tumours and carcinomas of the thyroid and nasopharynx. ◆

RESULTS

A total of 896 individuals diagnosed with cancer at ⩽14 years of age were eligible for the analyses. The median age at diagnosis was 4.7 years (range, 1 month to 14 years) and the median length of follow-up was 16.6 years (range, 5–32 years).

Late mortality

The cohort had accrued 10 648 person-years at risk by 31 December 2004. Data linkage to the NDI and review of clinical records identified 42 deaths. The leading cause of death was relapse of the primary childhood cancer (n = 23, 55%), followed by treatment-related complications (n = 7, 17%) and second cancers (n = 5, 12%). Motor vehicle accidents, accidental drug overdose and suicide collectively accounted for four deaths (10%). Causes of the remaining three deaths were not recorded. The proportion of deaths due to relapse was highest among survivors of central nervous system (CNS) malignancy (9/10, 90%) and acute lymphoblastic leukaemia (7/12, 58%). In the first 15 years after a diagnosis of a childhood cancer, 66% (21/32) of the deaths observed were the result of relapse of the primary malignancy, while relapse accounted for 20% (2/10) of deaths that occurred more than 15 years after diagnosis. Overall, cumulative mortality was 6.7% (95% CI, 4.8%–9.3%) 20 years after study entry.

Overall risk of death was 7.46 times higher in survivors of childhood cancer relative to the NSW population (Box 1). Risk of death was about double in females compared with males and was highest in survivors of soft-tissue sarcoma (SMR, 18.95 [95% CI, 6.88–40.81]) and CNS malignancy (SMR, 16.78 [95% CI, 7.62–31.64]).

Univariate analysis using a Cox proportional hazard model showed that age at diagnosis and sex were not significantly associated with an increased risk of death (P > 0.05; Box 2). However, an increase in the risk of death was observed in survivors of CNS malignancy (hazard ratio [HR], 3.30 [95% CI, 1.41–7.72]; P = 0.006) and soft-tissue sarcoma (HR, 3.69 [95% CI, 1.40–9.71]; P = 0.008) compared with survivors of leukaemia. This was confirmed in multivariate analysis, where the type of childhood cancer at diagnosis remained an independent predictor of death after adjusting for age at diagnosis and sex (Box 2).

Second cancers

At 10 559 person-years at risk, sixteen individuals were reported to have been diagnosed with second cancer, including one individual who developed two cancers following diagnosis of childhood cancer. The most common second cancers reported were bone sarcoma (n = 4), thyroid carcinoma (n = 3), melanoma (n = 3) and CNS malignancy (n = 2). Second cancers were most frequently observed following diagnoses of leukaemia, Hodgkin's lymphoma and soft-tissue sarcoma (Box 3). The median time to a second cancer was 13.8 years (range, 6–22 years), and the median age at diagnosis of a second cancer was 18.1 years (range, 8–35 years). The overall cumulative incidence of developing a second cancer was

3.5% (95% CI, 2.1%–6.0%) 20 years after study entry.

Survivors of childhood cancer had a 4.98-fold higher rate of second cancer relative to the NSW population (Box 3). The highest rates of second cancer were observed among survivors of soft-tissue sarcoma (SIR, 20.70 [95% CI, 5.74–53.90]) and Hodgkin's lymphoma (SIR, 29.51 [95% CI, 9.55–68.64]). Cox proportional hazard analysis also showed an increased risk of developing a second cancer in survivors of soft-tissue sarcoma (HR, 6.74 [95% CI, 1.51–30.15]; $P = 0.01$) and Hodgkin's lymphoma (HR, 11.16 [95% CI, 2.98–41.77]; $P < 0.001$) compared with survivors of leukaemia. However, the low incidence of second cancers observed in our cohort limited further analysis to adjust for potential confounders such as age at diagnosis or sex.

DISCUSSION

To our knowledge, this is the first study to specifically evaluate rates of both second cancers and late mortality in a cohort of Australian childhood cancer survivors. Overall, we found rates of death and second cancers to be elevated in survivors of childhood cancer relative to the general population. Rates of death were highest among survivors of a soft-tissue sarcoma and CNS malignancy, while the incidence of second cancers was highest in survivors of Hodgkin's lymphoma.

Survivors of childhood cancer treated at Sydney Children's Hospital had a 7.46-fold higher risk of death compared with the NSW population. This estimate of relative mortality is slightly lower than that reported by other studies, where SMRs have ranged from eight to 17 times higher than the general population.[3-6,21] However, differences in eligibility criteria — including age at diagnosis, length of follow-up, types of cancer studied and variable treatment regimens over different calendar years — are likely to have contributed to the variation between our results and those of other studies.[8]

We also found that relative mortality varied according to childhood cancer diagnosis, with the highest rates observed among survivors of CNS malignancies and soft-tissue sarcomas. Among survivors of CNS malignancies, most deaths were due to cancer recurrence; this may reflect failure of salvage therapies used to treat those who relapsed.[22]

Our finding of a 4.98-fold higher risk of a second cancer in survivors of childhood cancer compared with rates observed in the NSW population is consistent with results of previous studies,[8,12-15] and our observation that survivors originally diagnosed with a Hodgkin's lymphoma or a soft-tissue sarcoma were at increased risk of developing a second cancer also reflects previous findings.[8,14,15] However, the absence of an elevated rate of second cancers in survivors of leukaemia relative to the NSW population was unexpected and may have been due to the relatively small size of our cohort or the relatively short duration of follow-up. One previous report has shown

2 Cox proportional hazard model of risk of death among 5-year survivors of childhood cancer according to demographic and disease-related characteristics

	Mortality rate (95% CI)*	Univariate hazard ratio (95% CI)†	*P*	Multivariate hazard ratio (95% CI)‡	*P*
Sex					
Male§	4.22 (2.85–6.25)	1.0		1.0	
Female	3.59 (2.23–5.77)	0.85 (0.46–1.57)	0.60	0.82 (0.44–1.52)	0.52
Age at diagnosis					
0–9 years§	3.52 (2.58–5.01)	1.0		1.0	
10–14 years	5.93 (3.29–10.71)	1.72 (0.86–3.43)	0.12	1.55 (0.77–3.11)	0.22
Childhood diagnosis					
Leukaemia§	2.68 (1.56–4.62)	1.0		1.0	
Central nervous system malignancy	8.83 (4.59–16.97)	3.30 (1.41–7.72)	0.01	3.12 (1.32–7.37)	0.01
Lymphoma**	3.79 (1.58–9.12)	1.45 (0.52–4.07)	0.48	1.30 (0.46–3.71)	0.62
Soft-tissue sarcoma	10.39 (4.67–23.14)	3.69 (1.40–9.71)	0.01	3.56 (1.35–9.43)	0.01
Other solid tumour¶	3.10 (1.62–5.97)	1.14 (0.49–2.67)	0.78	1.12 (0.48–2.64)	0.80

* Per 1000 person-years at risk. † In the univariate analysis, each variable was fitted separately. ‡ In the multivariate analysis, variables were adjusted for childhood diagnosis, age at diagnosis and sex. § Reference category. ¶ Childhood malignancies such as Wilms' tumour, neuroblastoma, retinoblastoma, hepatoblastoma, melanoma, germ cell tumours, bone tumours and carcinomas of the thyroid and nasopharynx. ** Lymphoma category includes both Hodgkin's and non-Hodgkin's lymphomas. ◆

3 Risk of second cancers among 5-year survivors of childhood cancer relative to the New South Wales population according to demographic and disease-related characteristics

	No. of observed cancers*	No. of expected cancers	Standardised incidence ratio† (95% CI‡)	Absolute excess risk§
All survivors	17	3.41	4.98 (2.90–7.98)	1.29
Sex				
Male	7	1.84	3.80 (1.53–7.84)	0.88
Female	10	1.57	6.38 (3.05–11.71)	1.79
Age at diagnosis				
0–9 years	13	2.39	5.44 (2.90–9.30)	1.22
10–14 years	< 5	1.02	3.93 (1.07–10.04)	1.63
Childhood diagnosis¶				
Leukaemia	< 5	1.51	2.66 (0.72–6.78)	0.52
Hodgkin's lymphoma	5	0.17	29.51 (9.55–68.64)	9.46
Soft-tissue sarcoma	< 5	0.19	20.70 (5.74–53.90)	6.66
Other solid tumour**	< 5	1.28	3.12 (0.85–8.00)	0.70

* To preserve confidentiality of participants and their data, numbers fewer than five cannot be specified. † Some standardised incidence ratios differ from those calculated using data shown in table due to rounding of numbers of expected cancers. ‡ Exact 95% confidence intervals calculated using Poisson distribution. § Per 1000 person-years at risk. ¶ Survivors diagnosed with non-Hodgkin's lymphoma were excluded from this sub-analysis as no second cancers were observed in this group. ** Other solid tumour included malignancies such as Wilms' tumour, neuroblastoma, retinoblastoma, hepatoblastoma, melanoma, germ cell tumours, bone tumours, brain tumours, and carcinomas of the thyroid and nasopharynx. ◆

that survivors of childhood leukaemia are at a 6.1-fold increased risk of developing a second cancer relative to the general population.[17] However, this study observed rates of second cancers from diagnosis, rather than from 5 years after diagnosis — a more generally accepted definition for childhood cancer survivors. As a larger proportion of survivors in our study cohort were diagnosed in more recent decades compared with previous studies,[8,18] recent changes in treatment protocols, such as reduced use of prophylactic CNS irradiation, may have also influenced rates of second cancers observed among leukaemia survivors in our cohort.

Several studies have reported an increased risk of breast and thyroid carcinomas in female survivors of childhood cancer.[8,23,24] Although we observed thyroid cancers among female survivors, no cases of breast cancer were identified in our study. Although the risk of breast cancer among female survivors has been previously reported to be associated with exposure to mediastinal irradiation,[24] few female patients received mantle irradiation in our cohort due to the introduction of revised treatment protocols at the Sydney Children's Hospital in the 1980s in an effort to reduce the use of chest irradiation in female patients. Thus, the absence of breast cancer as a second cancer in our study may be attributable to differences in treatment practices at the Sydney Children's Hospital. Alternatively, the lack of breast cancers may have been influenced by the comparatively young age of female survivors at follow-up.

In our study, melanoma was among the most common second cancers observed in survivors of childhood cancer. Although one previous study has reported an increase in the risk of melanoma relative to population rates,[8] the most common second cancers reported among childhood cancer survivors have been cancers of the thyroid, breast, bone and brain.[12,15] In Australia, melanoma is the fourth most common cancer observed in the population and is the most common cancer diagnosed in individuals aged between 15 and 39 years.[19] Although we were unable to examine the melanoma-specific SIR in our cohort due to the small number of cases observed, coupling this finding with the high baseline risk of melanoma in the Australian population highlights the need for effective surveillance and routine screening for melanoma in Australian survivors of childhood cancer.

In summary, Australian survivors of childhood cancer are at increased risk of second cancers and late mortality compared with the general population. Identifying those at increased risk of second cancers or late mortality will assist in the modification of anticancer treatment regimens to minimise late complications, including second cancers, as well as the development of evidence-based long-term surveillance and prevention strategies.

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COMPETING INTERESTS

None identified.

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