

Childhood cancer mortality in Australia

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ABSTRACT

Aim: To determine current rates of childhood cancer mortality at a national level for Australia and to evaluate recent trends.

Methods: Using population-based data from the Australian Paediatric Cancer Registry, we calculated cancer-related mortality counts and rates for the 3-year period 2006-2008 and trends between 1998-2008 by sex, age group, and cause of death (defined according to the International Classification of Childhood Cancers, third edition). Rates were directly age-standardised to the 2000 World Standard Population, and linear regression was used to determine the magnitude and significance of trends. The standardized mortality ratio for non-cancer deaths among children with cancer was also estimated.

Results: A total of 282 children (23 per million per year) died from cancer in Australia between 2006-2008. Large decreases were observed in cancer mortality rates over the study period, particularly for boys (-5.5% per year; $p < 0.001$), children aged 10-14 years old (-5.5% per year; $p = 0.001$), and leukaemia patients (-9.4% per year; $p < 0.001$). However, there was no significant change in mortality due to tumours of the central nervous system. Children with cancer were twice as likely to die from non-cancer causes compared to other children (SMR=2.06; $p = 0.001$).

Conclusions: While ongoing improvements in childhood cancer mortality in Australia are generally encouraging, of concern is the lack of a corresponding decrease in mortality among children with certain types of tumours of the central nervous system during the past decade. The results also highlight the need for intensive monitoring of childhood cancer patients for other serious diseases that may subsequently arise.

Key words: childhood; cancer; mortality; trends; Australia.

Introduction

Approximately 620 children under the age of 15 are diagnosed with cancer in Australia each year, at an average annual rate of almost 160 per million population.¹ Incidence rate trends are stable for boys but steadily increasing by almost 1% per year among girls.¹ In conjunction with this, the last few decades have witnessed a significant and ongoing improvement in survival for childhood cancer patients in general, both in Australia² and elsewhere.³⁻⁵

Despite the positive news regarding survival, cancer remains the most common cause of disease-related death among children aged 1-14 years old in Australia, accounting for 17% of all deaths in this age group.⁶ The burden of childhood cancer mortality cannot be overstated. Each death represents at least 65 years of life lost from normal life expectancy and is associated with long-term distress and psychosocial problems for the families concerned.⁷⁻⁹ Parents of children who have died from cancer tend to experience higher levels of marital stress, depression and other health problems compared to the general community.¹⁰

Access to current, population-based mortality information is therefore useful for health planners to provide an indication of the resources required for services such as palliative care and bereavement counselling.¹¹ With such goals in mind, the purpose of this study was to quantify the recent rates of childhood cancer mortality at a national level for Australia as well as to investigate mortality trends.

Patients and Methods

De-identified data on all cases of cancer for children aged 0-14 years old who were diagnosed between 1983-2008 were accessed from the Australian Paediatric Cancer Registry (APCR), one of only a few national, population-based registries of childhood cancer in the world. Mortality status was determined by matching cases from the APCR against the National Death Index, which contains a record of all deaths in Australia. For the purposes of this study, deaths that occurred after a child turned 15 years of age were excluded. Further details regarding the operational procedures of the APCR are described elsewhere.¹

Previous studies on childhood cancer mortality trends have been based on deaths coded to the International Classification of Diseases,¹²⁻¹⁵ which primarily classifies cancers by body site. In the APCR, cancer-related deaths were coded according to the third edition of the International Classification of Childhood Cancers (ICCC-3),¹⁶ the internationally recognised standard, which defines 12 major groupings based on morphology. In accordance with the ICCC-3, this study included all deaths due to malignant neoplasms as well as those caused by intracranial and intraspinal tumours of benign or uncertain behaviour.

Cancer-related mortality counts and rates for the 3-year period 2006-2008 were generated by sex, age group at death and cause of death. Estimated resident population data was obtained from the Australian Bureau of Statistics¹⁷. Age-specific and directly age-standardised (2000 World Standard Population¹⁸) mortality rates were then derived and expressed per million population per year. Mortality rate ratios were calculated for the sex and age at death estimates, and differences were deemed to be statistically significant if the corresponding confidence interval did not include unity.

Trends were also investigated for all childhood cancer deaths from 1998-2008, again stratified by sex, age group at death, and major cause of death (categorised into leukaemias, tumours of the central nervous system, and other solid tumours). Data were further analysed within the subgroups of lymphoid and acute myeloid leukaemias, and trends were also calculated for the two largest subgroups for tumours of the central nervous system, namely astrocytomas and intracranial/intraspinal embryonal tumours. Since children diagnosed with cancer prior to 1983 were not included in the APCR, mortality data prior to 1998 would be incomplete. Hence, we only considered cancer-related deaths that occurred from 1998 onwards to ensure that the trend analyses were not biased by missing data.

Linear regression modeling was used to assess trends in the standardised mortality rates, with year of death the dependent variable. Results were reported in terms of an annual percentage change (APC) along with the associated 95% confidence interval (95% CI). Joinpoint models¹⁹ were also fitted to the data to determine whether there were any significant changes in the magnitude or direction of the trends over the 11 year period.

Finally, the relative risk of non-cancer deaths among children with cancer was approximated by calculating the standardised mortality ratio (SMR) for the period 1998-2008. This was done by generating sex- and age-specific non-cancer mortality rates for the general population of Australian children, and then applying these expected mortality rates to the summed years at risk for children with cancer within the corresponding age-sex strata, to determine the expected number of deaths from other causes. The SMR was obtained by dividing the observed number by the expected number of non-cancer deaths, with the 95% confidence interval calculated on the assumption of an underlying Poisson distribution.

Analyses were performed using the statistical software package Stata/SE version 11.2 for Windows (© 2009 StataCorp LP, College Station, USA) and the Joinpoint Regression Program version 3.4.3 (© 2010 Statistical Research and Applications Branch, National Cancer Institute, Silver Springs, USA). Approval for this work was obtained from the cancer registries in all Australian States and Territories and all hospitals that contributed to the data collection, as well as the ethics committees of the Queensland Institute of Medical Research and the University of Queensland.

Results

A total of 282 children died from cancer in Australia between 2006-2008, giving a mortality rate of 23.1 per million children per year (Table 1). There was no significant difference in the mortality rate by sex, with an age-adjusted rate ratio for boys:girls of 1.15 (95% CI = 0.91-1.46; $p = 0.220$). Cancer deaths were more common among children aged 0-4 years old (mortality rate ratio = 1.37, 95% CI = 1.02-1.83; $p = 0.038$) or 5-9 years old (mortality rate ratio = 1.36, 95% CI = 1.02-1.83; $p = 0.039$) than those in the 10-14 age group. Although the highest proportion of deaths occurred in the 0-4 age group for boys compared to the 5-9 age group for girls, there was no significant difference in the distribution of age at mortality by sex ($p=0.073$). Two out of five (40%) of all childhood cancer deaths were due to tumours of the central nervous system, followed by leukaemias (22%), neuroblastoma (11%) and soft tissue sarcomas (10%).

Cancer mortality decreased by an average of 5.5% per year for boys between 1998 and 2008 (Table 2 and Figure 1). Based on this trend, the mortality rate was estimated to be 43% lower in 2008 compared to 1998. There was some evidence that mortality rates for girls were also decreasing (annual percentage change = -3.2%, 95% CI = (-6.3%,+0.1%)), but the trend was only marginally significant ($p=0.055$).

Significant trends in cancer mortality rates were recorded for children in each age group, ranging from a decrease of 3.1% per year in the 5-9 age bracket (a cumulative decrease of 27% between 1998-2008) to an annual decrease of 5.5% among children aged 10-14 years old (corresponding to a 43% decrease over the 11 years - Table 2).

A sharp decline of 9.4% per year was observed in mortality due to leukaemia, resulting in an overall decrease of 63% between 1998-2008 (Table 2). Mortality rates also decreased by 2.9% per year (total of 25%) for the grouping of other solid tumours, but no significant trend was apparent for tumours of the central nervous system. The trends by type of cancer remained similar when stratified by sex (results not shown).

Analysis by cancer subgroup revealed significant decreases in mortality rate trends for lymphoid leukaemias (APC = -11.0%, 95% CI = (-14.9%,-7.0%); $p < 0.001$), acute myeloid leukaemias (APC = -7.4%, 95% CI = (-12.2%,-2.3%); $p = 0.010$) and astrocytomas (APC = -5.2%, 95% CI = (-9.2%,-1.1%); $p = 0.018$). In contrast, the trend for intracranial/intraspinal embryonal tumours was stable over the study period (APC = +1.5%, 95% CI = (-3.8%,+7.1%); $p = 0.548$).

The joinpoint models confirmed that simple linear regression provided the best fit for each of the trends described above (results not shown).

Twenty-four non-cancer deaths occurred among prevalent cases of childhood cancer between 1998-2008, of which 9 were caused by congenital or perinatal conditions and the remaining 15 were due to a variety of causes. This compared with a total of 11.7 expected deaths had the non-cancer mortality rate been the same as that for other children, giving a SMR of 2.06 (95% CI = 1.32-3.07; $p = 0.001$).

When repeated by age group, the number of excess deaths was only significant for children aged 10-14 years old, for whom there were 10 observed deaths compared with 2.2 expected deaths (SMR = 4.58; 95% CI = 2.20-8.42; $p < 0.001$). The non-cancer deaths in the 10-14 age group included 6 that were due to either diseases of the nervous system, circulatory system or digestive system.

Discussion

Our findings demonstrate significant decreases in childhood cancer mortality rates over the last 10 years throughout Australia, with the largest changes found among boys, children aged 10-14 years old and those diagnosed with leukaemia. The declines in cancer mortality have contributed to the downward trends for all causes of death that have been reported for children in Australia.⁶ However, the encouraging news is tempered by the lack of a significant change in mortality rates attributable to tumours of the central nervous system.

Cancer incidence rates for Australian children are relatively high when compared internationally¹, in line with the correlation that has been noted between childhood cancer and prosperity.²⁰ Conversely, mortality rates for childhood cancer in Australia are among the lowest reported in the world and similar to other developed countries.¹² As a comparison, childhood cancer mortality in the United States was also reported to be 23 deaths per million population per year between 2004-2008.²¹ This most likely reflects the use of standardised treatment regimens based on the newest therapies available combined with widespread participation in clinical trials in this country.²²

Steadily decreasing trends in childhood cancer mortality rates have been reported in many developed countries dating back to at least the early 1970s, including North America, most parts of Europe and Japan.¹²⁻¹⁵ In particular, Chatenoud et. al.¹² published yearly decreases in childhood cancer mortality rates in Australia of 2.7% for boys between 1970 and 2006 and 2.3% for girls between 1978 and 2006 using data obtained from the World Health Organization. Our estimates suggest that the decline in mortality rates among Australian boys may have accelerated recently, with an estimated annual decrease of 5.5% over the last decade.

The mortality trends reported here by sex and age at death are generally consistent with previously published variations in childhood cancer incidence and survival in Australia. For example, incidence rates have remained stable among boys since the mid-1990s but have continued to increase slowly among girls,¹ while there were significant improvements in survival for both sexes.² As a result of the convergence in incidence, the excess in mortality that existed for boys in the late 1990s has diminished and rates are now close to parity (Figure 1).

In regard to type of cancer, the large decreasing trend for leukaemia mortality among children in Australia occurred in the context of increases in the incidence of leukaemia during the study period,¹ which were offset by significant improvements in survival.² Comparable changes in incidence and survival for leukaemia have also been reported in the United States and Europe.^{21, 23} The key reason for the decreasing trends in childhood cancer mortality is improved treatment, particularly the introduction of more effective chemotherapy protocols and multimodal therapy.¹²⁻¹⁴ Children with haematological cancers (leukaemia and lymphoma) have benefitted most as a result of these therapeutic gains.²⁴

The lack of a significant decline in mortality for Australian children with tumours of the central nervous system was influenced by fluctuations in incidence¹ combined with stable survival rates.² Significant decreases in mortality for this type of cancer have, however, occurred for children in the United States, Canada, Italy and the United Kingdom from 1980 onwards.^{14, 15} In addition, the annual mortality rate for childhood tumours of the central nervous system in Australia is higher than in some of these other developed countries,^{14, 15} although this may be at least partly explained by the inclusion of intracranial and intraspinal tumours of benign or uncertain behavior in our cohort, whereas only malignant tumours were considered in the other studies. Closer inspection of the APCR data revealed that mortality rates due to astrocytomas were in fact decreasing, but there was no significant change for intracranial/intraspinal embryonal tumours. Further investigation is obviously warranted, with a focus on temporal patterns of treatment for tumours of the central nervous system by subgroup within Australia.

Our finding of a significant decrease in mortality caused by other solid tumours is consistent with a decline in the aggregated death rate of other solid tumours that was reported for children in the United States between 1990-2004.¹⁴ Decreasing mortality trends within selected developed countries for several other types of childhood cancers, such as lymphomas, renal tumours and bone tumours, have also been described by Yang et. al.¹⁵

Some children diagnosed with cancer are known to experience adverse health effects, either because of the cancer itself or as a result of the treatments that they receive. These effects can include an increased risk of subsequent cancer, organ dysfunction affecting the heart, kidneys or gastrointestinal system, impaired growth and development, neurological issues, and a decrease in fertility.^{25, 26} A study conducted in New South Wales, Australia, on 5-year survivors of childhood cancer reported a SMR of 7.46 compared to the general population.²⁷ Although the numbers in our study were too small to identify specific causes of death that occurred more often than expected, the overall inflated non-cancer mortality risk among children with cancer highlights the frequent occurrence of serious co-morbidities such as congenital anomalies, as well as the need to remain vigilant for signs of other potentially life-threatening diseases that may arise due to the late effect of treatment or as sequelae of the cancer itself.^{25, 26}

Due to the mandatory notification of cancer and complete death registration in Australia, we are confident that the results expressed here represent the mortality experience of virtually all children with cancer throughout the entire country during the study period. The quality of the data contained in the APCR is further underlined by the high rate of diagnostic histological verification (94% between 1997-2006).¹ We were, however, limited by the relatively small number of deaths, which resulted in wide confidence intervals for some of the rate estimates and the need to combine most of the cancer types when analysing mortality trends. We were also unable to assess whether the increased non-cancer mortality risk had changed over time. Finally, because deaths were only included in this study up to 14 years of age, it is possible that significant decreases in mortality may in part indicate improvements in the prolonging of life until after a child turns 15 years old rather than the achievement of a complete cure.

Although rates of cancer-related mortality are generally decreasing in Australia, there is still room for improvement. In particular, there has been no significant change in mortality rates for some tumours of the central nervous system, which also tend to have a worse prognosis compared to most other types of childhood cancer.² A greater focus on individualised therapies holds future promise of not only further reducing cancer-related mortality but also minimizing the consequences of adverse effects.^{22, 28} Continued monitoring of childhood cancer mortality rates is important given that some of the estimates were based on a relatively small number of deaths. Tracking of mortality trends at the population level, in conjunction with corresponding data on incidence and survival, will also help to complete the picture in regard to the effectiveness of existing and new treatments and thus ultimately assist in the continuing progress towards better outcomes for children with cancer and their families.

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Table 1. Childhood cancer mortality by sex, age at death and cancer type, Australia, 2006-2008

	All children			Boys			Girls		
	Number of cancer deaths	%	Average annual mortality rate per million children ^a (95% CI)	Number of cancer deaths	%	Average annual mortality rate per million children ^a (95% CI)	Number of cancer deaths	%	Average annual mortality rate per million children ^a (95% CI)
TOTAL	282	100.0	23.1 (20.5-25.9)	155	100.0	24.7 (21.0-28.9)	127	100.0	21.4 (17.8-25.4)
Age at death									
0-4 years	102	36.2	25.3 (20.7-30.8)	60	38.7	29.0 (22.2-37.4)	42	33.1	21.4 (15.5-29.0)
5-9 years	102	36.2	25.3 (20.6-30.7)	47	30.3	22.7 (16.7-30.2)	55	43.3	28.0 (21.1-36.4)
10-14 years	78	27.7	18.6 (14.7-23.2)	48	31.0	22.2 (16.4-29.5)	30	23.6	14.7 (9.9-20.9)
Cancer type^b									
Tumours of the CNS ^c	112	39.7	9.2 (7.6-11.1)	59	38.1	9.5 (7.2-12.2)	53	41.7	8.9 (6.7-11.7)
Leukaemias	63	22.3	5.1 (3.9-6.6)	33	21.3	5.2 (3.6-7.3)	30	23.6	5.0 (3.4-7.2)
Neuroblastoma	31	11.0	2.6 (1.8-3.7)	18	11.6	2.9 (1.7-4.6)	13	10.2	2.2 (1.2-3.8)
Soft tissue sarcomas	28	9.9	2.3 (1.5-3.3)	17	11.0	2.7 (1.6-4.3)	11	8.7	1.9 (0.9-3.3)
Other ^{c,d}	48	17.0	3.9 (2.9-5.2)	28	18.1	4.4 (3.0-6.4)	20	15.7	3.4 (2.1-5.2)

Abbreviations: 95% CI = 95% confidence interval; CNS = central nervous system.

Notes: a. Rates are age-standardised to the 2000 World Standard Population.

b. Cancer type defined using the International Classification of Childhood Cancers (ICCC-3).

c. Includes intracranial and intraspinal tumours of benign or uncertain behaviour.

d. "Other" includes lymphomas, retinoblastoma, renal tumours, hepatic tumours, malignant bone tumours, germ cell tumours, other malignant epithelial neoplasms and melanomas, and other and unspecified malignant neoplasms.

Table 2. Annual percentage change (APC) for childhood cancer mortality rates by sex, age at death and cancer type, Australia, 1998-2008

	n	APC^a (95% CI)	p
Sex			
Boys	709	-5.5 (-7.7,-3.3)	<0.001
Girls	544	-3.2 (-6.3,+0.1)	0.055
Age at death			
0-4 years	452	-4.9 (-8.8,-0.8)	0.026
5-9 years	440	-3.1 (-5.0,-1.1)	0.006
10-14 years	361	-5.5 (-8.2,-2.8)	0.001
Cancer type^b			
Leukaemias	373	-9.4 (-12.5,-6.3)	<0.001
Tumours of the central nervous system ^c	441	-1.2 (-3.2,+0.8)	0.205
Other solid tumours ^{c,d}	439	-2.9 (-5.7,-0.0)	0.050

Abbreviations: n = number of deaths; 95% CI = 95% confidence interval.

- Notes: a. Annual percentage change calculated using linear regression.
b. Defined using the International Classification of Childhood Cancers (ICCC-3).
c. Includes intracranial and intraspinal tumours of benign or uncertain behaviour.
d. Includes lymphomas, neuroblastoma, retinoblastoma, renal tumours, hepatic tumours, malignant bone tumours, soft tissue sarcomas, germ cell tumours, other malignant epithelial tumours and melanomas, and other and unspecified malignant neoplasms.

Figure 1. Mortality rate trends for childhood cancers by sex, age at death and cancer type, Australia, 1998-2008. Leuk = Leukaemias; CNS = Tumours of the central nervous system; Other = Other solid tumours.

