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Childhood cancer survival and avoided deaths in Australia, 1983–2016

Danny R. Youlden[1,2] | Peter D. Baade[1,2,3] | Andrew S. Moore[4,5] | Jason D. Pole[6] | Patricia C. Valery[7] | Joanne F. Aitken[1,8,9]

[1]Cancer Council Queensland, Brisbane, Queensland, Australia

[2]Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland, Australia

[3]School of Mathematical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia

[4]Oncology Service, Queensland Children's Hospital, Children's Health Queensland Hospital and Health Service, Brisbane, Queensland, Australia

[5]Child Health Research Centre, The University of Queensland, Brisbane, Queensland, Australia

[6]Centre for Health Services Research, The University of Queensland, Brisbane, Queensland, Australia

[7]Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia

[8]Institute for Resilient Regions, University of Southern Queensland, Brisbane, Queensland, Australia

[9]School of Public Health, The University of Queensland, Brisbane, Queensland, Australia

Correspondence
Danny R. Youlden, Cancer Council Queensland, 553 Gregory Tce Spring Hill 4001, Brisbane, Qld, Australia.
Email: dannyyoulden@cancerqld.org.au

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Abstract

Background: Large improvements in childhood cancer survival have been reported over recent decades. Data from cancer registries have the advantage of providing a 'whole of population' approach to gauge the success of cancer control efforts.

Objectives: The aim of this study was to investigate recent survival estimates for children diagnosed with cancer Australia and to examine the extent of changes in survival over the last 35 years. For the first time, we also estimated the number of deaths among Australian children that were potentially avoided due to improvements in survival.

Methods: A retrospective, population-based cohort study design was used. Case information was extracted from the Australian Childhood Cancer Registry for 1983–2016, with follow-up to 31 December 2017. Eligible children were aged 0–14 with a basis of diagnosis other than autopsy or death certificate only. Five-year relative survival was calculated using the semi-complete cohort method for three diagnosis periods (1983–1994, 1995–2006 and 2007–2016), and changes in survival over time were assessed via flexible parametric models. Avoided deaths within 5 years for those diagnosed between 1995 and 2016 were estimated under the assumption that survival rates remained the same as for 1983–1994.

Results: Overall 5-year survival within the study cohort (n = 20,871) increased from 72.8% between 1983 and1994 to 86.1% between 2007 and 2016, equating to an adjusted excess mortality hazard ratio of 1.82 (95% confidence interval 1.67, 1.97). Most cancers showed improvements in survival; other gliomas, hepatoblastoma and osteosarcoma were exceptions. Among children diagnosed between 1995 and 2016, 38.7% of expected deaths within 5 years of diagnosis (n = 1537 of 3970) were avoided due to temporal improvements in survival.

Conclusions: Survival for childhood cancer has continued to improve over recent years, thanks mainly to ongoing progress in treatment development combined with improved supportive care. Providing innovative measures of survival, such as avoided deaths, may assist with understanding outcome data produced by cancer registries.

KEYWORDS
Australia, avoided deaths, cancer, child, registries, survival

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1 | BACKGROUND

Trends in cancer survival at a population level provide an important benchmark for gauging improvement in cancer control.[1] Results from hospital-based registries or clinical trials are usually limited to a select group of patients, making estimates susceptible to bias and unable to fully evaluate survival rates at the population level. Data from population-based registries are therefore essential to evaluating the effectiveness of cancer control strategies for all cancer patients.[2]

Interpretation of cancer survival statistics is complex, and the use of different prognostic measures can aid understanding.[3] Relative survival is the most commonly reported outcome using cancer registry data. It is based on the hypothetical situation where all deaths are assumed to be due to the cancer of interest,[3,4] making it difficult to adequately explain from a 'real-world' perspective. Alternative measures of survival, such as the number of deaths avoided over time due to increases in survival rates,[5,6] may be more relatable to a wider audience.

Information from the Australian Childhood Cancer Registry has previously demonstrated that survival for children diagnosed with cancer increased over the period between 1992 and 1998 to the period between 1999 and 2006, particularly for leukaemia.[7] The availability of another decade of data provides the opportunity to calculate survival for more recently diagnosed children in Australia and to examine the impact of changes in survival over the last 35 years. We also report on the estimated number of deaths among children that were potentially avoided due to improvements in survival.

Synopsis

Study question

How has survival for childhood cancer in Australia changed over the last four decades, and how many deaths have been potentially avoided due to improvements in survival?

What's already known

Survival following a diagnosis of cancer during childhood depends on several factors, including the patient's age, type of cancer, how far cancer has spread at diagnosis and access to high-quality care.

What this study adds

After adjusting for these key factors, the risk of death within 5 years of diagnosis has almost halved since the early 1980s. Furthermore, using baseline information from 1983 to 1994, it was estimated that 1537 of 3970 expected deaths (38.7%) were potentially avoided for Australian children diagnosed with cancer between 1995 and 2016.

2 | METHODS

Notification of new cancer diagnoses (excluding squamous and basal cell carcinomas of the skin) is required under legislation from hospitals and pathology laboratories to one of Australia's eight state and territory cancer registries. The Australian Institute of Health and Welfare asserts that all cases of cancer diagnosed nationwide are captured as part of this process.[8] Details of cancer incidence pertaining to children aged under 15 at the time of diagnosis are then forwarded to the Australian Childhood Cancer Registry.

Australia provides a free public hospital system for residents. Most Australian children with cancer receive specialised treatment at one of nine public paediatric oncology centres. Further clinical information for each child is obtained via review of the hospital records for each patient by an experienced coder. Cases in the Australian Childhood Cancer Registry are also annually matched against the National Death Index, which contains a record of all deaths in Australia since 1980, to ensure that current mortality status is maintained.

De-identified unit record data were extracted from the Australian Childhood Cancer Registry. The study cohort comprised children diagnosed between 1983 (the start of the Australian Childhood Cancer Registry) and 2016, inclusive. Follow-up on mortality was available to 31 December 2017; survival for those who were still alive was censored at that end date or 5 years after diagnosis, whichever occurred first. Patients whose cancer diagnosis was based on death certificate or autopsy only were excluded as were those whose date of diagnosis and date of death coincided, as per the commonly accepted practice when calculating survival using cancer registry data.[9,10] For patients with more than one cancer, only the first primary cancer was included.

Childhood cancers differ from adult cancers in their biology and behaviour. Consequently, the classification for children is primarily based on morphology rather than anatomic site. Furthermore, non-malignant intracranial and intraspinal tumours are included for children. The International Classification of Childhood Cancer (version 3)[11] incorporates these criteria and was used to categorise patients into diagnostic groups (12 categories) and subgroups (47 categories). The 16 most heterogeneous subgroups are broken down further into finer divisions. A combination of all three levels of the International Classification of Childhood Cancer classification was used for the reporting of results.

Remoteness of residence for each patient was assigned according to the Australian Statistical Geography Standard Remoteness Structure[12] and area-based socioeconomic status was defined using the Index of Relative Socioeconomic Advantage and Disadvantage.[13] Mortality data for all causes of death among children in Australia, used as the numerator in the calculation of life tables, were sourced from the General Record of Incidence of Mortality published by the Australian Institute of Health and Welfare.[14] Estimates of the

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resident population were obtained from the Australian Bureau of Statistics[15] and formed the denominator for the life tables.

2.1 | Statistical analysis

The main outcome of interest was 5-year relative survival, which is typically used when estimating disease-specific survival from population-based cancer registries because information is only required on the mortality status of the patient rather than the exact cause of death.[16] Relative survival compares the observed survival of children with cancer against the expected survival of children from the general population, matched by age group, sex and calendar year. A semi-complete cohort method was used for this analysis to enable comparison of survival outcomes between distinct groups of patients based on when they were diagnosed (1983–1994, 1995–2006 and 2007–2016), with a minimum of 1 year of follow-up available for the most recently diagnosed patients.

We applied a life table method for calculating observed survival. This approach involves dividing the total period of observation into a series of discrete-time intervals. The survival probabilities are then calculated for each interval and multiplied together to obtain the estimate for observed survival. Expected survival was calculated based on the Ederer II method,[17] with 3-year averages used to minimise the effects of year-to-year variation.

Changes in survival over the three time periods were compared using flexible parametric survival models. Unlike traditional Cox proportional hazards modelling, this technique does not assume that hazard rates are proportional over the follow-up interval, but instead fits the baseline cumulative hazard using restricted cubic splines.[18] The models for individual cancers included sex, age group, remoteness of residence, area-based socioeconomic status, type of treatment (curative surgery, chemotherapy and/or radiotherapy, as relevant) and metastatic status at diagnosis (except for blood cancers) as covariates. The model for all cancers combined was further adjusted for diagnostic group. Results for each time period were expressed in terms of the excess mortality hazard ratio (HR) within 5 years of diagnosis, using 2007–2016 as the reference group. For those cancers where there were a sufficient number of cases, changes in survival over time period were additionally stratified by metastatic status. Time period was also fitted as an ordinal variable in the models to determine the significance of trends in survival.

The avoided number of cancer deaths within 5 years of diagnosis was defined as the difference between the expected and observed number of cancer deaths. Calculating the number of expected deaths was based on the hypothetical premise that survival rates do not change over time. Specifically, for children diagnosed between 1995–2006 and 2007–2016, the expected number of deaths was calculated by assuming that relative survival rates were the same as for 1983–1994. Note that observed deaths for the period 2007–2016 accounted for censoring of patients who were still alive at the study end date but who had survived for less than 5 years from the time of diagnosis.

All analyses were conducted using Stata/SE (version 16.1; StataCorp LLC, College Station, Texas).

2.2 | Missing data

The study cohort did not contain any missing values for key variables of interest.

2.3 | Ethics approval

The Australian Childhood Cancer Registry operates with ethics approval from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (reference HREC04/QRCH/18) along with numerous HRECs representing each of the state/territory cancer registries and major paediatric treating hospitals throughout Australia (full details are available on request).

3 | RESULTS

A total of 21,068 Australian children aged 0–14 were diagnosed with cancer between 1983 and 2016. Of these, 136 (0.6%) were excluded from the study because their basis of diagnosis was either autopsy or death certificate only and a further 61 (0.3%) were excluded because their date of death was the same as their date of diagnosis.

The remaining 20,871 patients (99.1%) formed the study cohort, comprising a combined 84,457 years of follow-up within 5 years of diagnosis. Boys (n = 11,484, 55.0%) outnumbered girls (n = 9387, 45.0%), and the overall median age at diagnosis was 5 years (interquartile range = 2 to 10 years). Lymphoid leukaemia (n = 5386, 25.8%), astrocytoma (n = 2133, 10.2%) and neuroblastoma and ganglioneuroblastoma (n = 1304, 6.2%) were the most common diagnostic subgroups. A minority (n = 2645, 12.7%) of children resided in outer regional, remote or very remote areas at the time of diagnosis and 21.1% (n = 4409) lived in the most socioeconomically disadvantaged areas. There were no differences in the distribution of remoteness of residence or area-based socioeconomic status by type of cancer.

Five-year relative survival estimates by type of cancer for patients diagnosed between 2007 and 2016 are presented in Table 1. Children with acute myeloid leukaemia had poorer survival compared with those with lymphoid leukaemia. Survival was high (around 90% or greater) for each of the main diagnostic subgroups of lymphoma. There were no differences in survival by sex for either leukaemia or lymphoma.

Around three-quarters (76.7%) of patients with a central nervous system (CNS) tumour remained alive at 5 years after diagnosis (Table 1). Survival was highest for children with astrocytoma (85.4%) and lowest for the diagnostic subgroup of other gliomas (48.2%). No differences in survival by sex were found for any type of CNS tumour.

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TABLE 1 Relative survival for childhood cancers in Australia by ICCC-3 classification and time from diagnosis, 2007-2016[a]

			1 year	5 years
ICCC-3 classification	***n***	**% of diagnostic group**	**Survival % (95% CI)**	**Survival % (95% CI)**
I. Leukaemias, myeloproliferative diseases and myelodysplastic diseases	2313	100.0	95.5 (94.6, 96.3)	90.3 (89.0, 91.5)
Ia. Lymphoid leukaemia	1829	79.1	97.2 (96.4, 97.9)	93.0 (91.6, 94.2)
Ia1. Precursor cell leukaemia	1811	78.3	97.4 (96.5, 98.0)	93.1 (91.7, 94.3)
Ib. Acute myeloid leukaemia	306	13.2	86.3 (82.0, 89.7)	76.9 (71.7, 81.3)
Ic. Chronic myeloproliferative diseases[b]	73	3.2	97.3 (89.6, 99.4)	93.8 (83.9, 97.8)
Id. Myelodysplastic syndrome and other myeloproliferative diseases[c]	72	3.1	93.2 (84.2, 97.2)	83.7 (72.2, 90.7)
Ie. Unspecified and other specified leukaemias	33	1.4	87.9 (70.9, 95.3)	72.6 (51.9, 85.5)
II. Lymphomas and reticuloendothelial neoplasms	763	100.0	97.0 (95.5, 98.0)	95.2 (93.3, 96.6)
IIa. Hodgkin lymphoma	251	32.9	99.6 (97.2, 99.9)	99.7 (97.3, 100)
IIb. Non-Hodgkin lymphoma (except Burkitt lymphoma)	245	32.1	93.9 (90.1, 96.3)	90.4 (85.9, 93.6)
IIIb1. Precursor cell lymphoma	91	11.9	96.7 (90.2, 99.0)	91.1 (82.9, 95.5)
IIIb2. Mature B-cell lymphoma (except Burkitt lymphoma)	78	10.2	94.9 (86.9, 98.1)	92.2 (83.4, 96.5)
IIIb3. Mature T-cell and NK-cell lymphoma	67	8.8	91.1 (81.2, 95.9)	89.3 (78.7, 94.8)
IIc. Burkitt lymphoma	147	19.3	96.6 (92.0, 98.6)	93.2 (87.1, 96.5)
IId. Miscellaneous lymphoreticular neoplasms	116	15.2	98.4 (93.4, 99.6)	98.4 (93.4, 99.7)
III. CNS and miscellaneous intracranial and intraspinal neoplasms	1683	100.0	89.0 (87.4–90.4)	76.7 (74.5–78.7)
IIIa. Ependymoma and choroid plexus tumour	184	10.9	96.3 (92.3, 98.2)	77.3 (69.5, 83.3)
IIIa1. Ependymoma	135	8.0	96.3 (91.4, 98.5)	74.1 (64.3, 81.5)
IIIa2. Choroid plexus tumour	49	2.9	96.0 (84.8, 99.1)	85.3 (71.5, 92.8)
IIIb. Astrocytoma	696	41.4	94.6 (92.6, 96.0)	85.4 (82.4, 88.0)
IIIc. Intracranial and intraspinal embryonal tumours	319	19.0	80.3 (75.5, 84.3)	60.5 (54.6, 65.9)
IIIc1. Medulloblastoma	220	13.1	86.8 (81.6, 90.7)	72.7 (65.9, 78.4)
IIIc2. Primitive neuroectodermal tumour (PNET)	54	3.2	77.8 (64.2, 86.8)	39.2 (26.0, 52.2)
IIIc4. Atypical teratoid/rhabdoid tumour	45	2.7	51.2 (35.8, 64.6)	27.8 (15.0, 42.1)
IIId. Other gliomas	204	12.1	66.6 (59.7, 72.6)	48.2 (40.8, 55.1)
IIId1. Oligodendroglioma	18	1.1	100 (100, 100)	87.1 (56.9, 96.7)
IIId2. Mixed and unspecified gliomas	183	10.9	63.9 (56.4, 70.4)	45.1 (37.5, 52.5)
IIIe Other specified intracranial and intraspinal neoplasms	213	12.7	98.6 (95.7, 99.6)	94.8 (90.5, 97.3)
IIIe2. Tumours of the sellar region (craniopharyngioma)	45	2.7	95.6 (83.4, 98.9)	93.3 (80.5, 97.9)
IIIe3. Pineal parenchymal tumour	19	1.1	94.8 (68.2, 99.3)	73.5 (40.9, 90.0)
IIIe4. Neuronal and mixed neuronal-glial tumours	128	7.6	100 (100, 100)	97.4 (91.8, 99.2)
IIIf Unspecified intracranial and intraspinal neoplasms	67	4.0	89.6 (79.4, 94.9)	88.0 (77.2, 93.9)
IV. Neuroblastoma and other peripheral nervous cell tumours	476	100.0	95.1 (92.7, 96.7)	77.9 (73.6, 81.6)
IVa. Neuroblastoma and ganglioneuroblastoma	474	99.6	95.1 (92.7, 96.7)	77.8 (73.5, 81.6)
V. Retinoblastoma	188	100.0	99.6 (96.4, 100)	98.9 (95.1, 99.9)
VI. Renal tumours	360	100.0	96.7 (94.3, 98.2)	91.6 (87.9, 94.3)
VIa. Nephroblastoma and other nonepithelial renal tumours	345	95.8	96.6 (94.0, 98.1)	92.3 (88.7, 94.9)
VIa1. Nephroblastoma	325	90.3	98.2 (96.0, 99.2)	93.7 (90.0, 96.0)
VIb. Renal carcinomas	14	3.9	100 (100, 100)	78.0 (46.0, 92.4)
VII. Hepatic tumours	107	100.0	88.9 (81.2, 93.6)	79.3 (69.9, 86.1)

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TABLE 1 (Continued)

ICCC-3 classification	*n*	% of diagnostic group	1 year Survival % (95% CI)	5 years Survival % (95% CI)
VIIa. Hepatoblastoma	95	88.8	90.6 (82.7, 95.1)	83.2 (73.5, 89.7)
VIIb. Hepatic carcinomas	11	10.3	81.8 (44.8, 95.1)	54.6 (22.9, 78.0)
VIII. Malignant bone tumours	268	100.0	93.7 (90.0, 96.0)	77.4 (71.2, 82.4)
VIIIa. Osteosarcoma	126	47.0	91.3 (84.8, 95.1)	66.2 (55.8, 74.7)
VIIIc. Ewing tumour and related sarcomas of bone	124	46.3	95.2 (89.6, 97.8)	86.4 (78.3, 91.7)
VIIIc1. Ewing tumour and Askin tumour of bone	122	45.5	95.1 (89.4, 97.8)	86.2 (77.9, 91.6)
IX. Soft tissue and other extraosseous sarcomas	406	100.0	91.4 (88.3, 93.8)	76.3 (71.5, 80.3)
IXa. Rhabdomyosarcoma	200	49.3	94.5 (90.3, 97.0)	75.6 (68.5, 81.4)
IXb. Fibrosarcomas, peripheral nerve sheath tumours and other fibrous neoplasms	38	9.4	94.8 (80.6, 98.8)	88.8 (72.5, 95.8)
IXb1. Fibroblastic and myofibroblastic tumours	20	4.9	100 (100, 100)	94.7 (66.8, 99.4)
IXb2. Nerve sheath tumours	18	4.4	88.9 (62.4, 97.1)	82.4 (54.4, 94.0)
IXd. Other specified soft tissue sarcomas	128	31.5	88.4 (81.4, 92.8)	74.6 (65.4, 81.6)
IXd2. Peripheral primitive neuroectodermal tumour (pPNET) of soft tissue	24	5.9	100 (100, 100)	77.9 (54.5, 90.3)
IXd3. Extrarenal rhabdoid tumour	18	4.4	33.4 (13.7, 54.7)	27.9 (10.1, 49.0)
IXd5. Fibrohistiocytic tumour	28	6.9	100 (100, 100)	100 (100, 100)
IXd7. Synovial sarcomas	23	5.7	95.7 (73.0, 99.4)	70.7 (41.6, 87.2)
IXe. Unspecified soft tissue sarcomas	40	9.9	82.6 (66.8, 91.3)	71.9 (54.8, 83.4)
X. Germ cell tumours, trophoblastic tumours and neoplasms of gonads	279	100.0	98.7 (96.3, 99.6)	96.8 (93.9, 98.4)
Xa. Intracranial and intraspinal germ cell tumours	102	36.6	99.1 (93.3, 99.9)	96.1 (89.8, 98.6)
Xa1. Intracranial and intraspinal germinomas	57	20.4	100 (100, 100)	98.3 (88.1, 99.8)
Xa2. Intracranial and intraspinal teratomas	38	13.6	97.5 (82.9, 99.8)	94.9 (80.5, 98.9)
Xb. Malignant extracranial and extragonadal germ cell tumours	65	23.3	98.7 (89.8, 100)	97.1 (88.2, 99.5)
Xb2. Malignant teratomas of extracranial/extragonadal sites	39	14.0	97.7 (83.4, 100)	95.0 (80.5, 99.0)
Xb4. Yolk sac tumour of extracranial and extragonadal sites	21	7.5	100 (100, 100)	100 (100, 100)
Xc. Malignant gonadal germ cell tumours	100	35.8	100 (100, 100)	100 (100, 100)
Xc1. Malignant gonadal germinomas	23	8.2	100 (100, 100)	100 (100, 100)
Xc2. Malignant gonadal teratomas	33	11.8	100 (100, 100)	100 (100, 100)
Xc4. Gonadal yolk sac tumour	25	9.0	100 (100, 100)	100 (100, 100)
XI. Other malignant epithelial neoplasms and malignant melanomas	319	100.0	97.8 (95.5, 99.0)	95.8 (92.7, 97.6)
XIb. Thyroid carcinoma	69	21.6	100 (100, 100)	100 (100, 100)
XId. Malignant melanoma	82	25.7	98.8 (91.7, 99.9)	97.5 (90.0, 99.5)
XIf. Other and unspecified carcinomas	145	45.5	95.9 (91.0, 98.1)	93.5 (87.7, 96.6)
X1f1. Carcinomas of salivary glands	21	6.6	100 (100, 100)	100 (100, 100)
X1f3. Carcinomas of appendix	75	23.5	100 (100, 100)	100 (100, 100)
XIf10. Carcinomas of other specified sites	27	8.5	92.6 (73.5, 98.1)	88.6 (68.4, 96.2)
XII. Other and unspecified malignant neoplasms	23	100.0	95.7 (73.0, 99.5)	77.3 (53.6, 90.0)

Abbreviations: 95% CI, 95% confidence interval; ICCC-3, International Classification of Childhood Cancers, version 3.

[a]survival was calculated using the semi-complete cohort method with follow-up available to 31 December 2017.

[b]Includes chronic myeloid leukaemia, not otherwise specified (ICD-O-3 code 9863/3).

[c]Includes juvenile myelomonocytic leukaemia (ICD-O-3 code 9946/3).

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There were two distinct survival profiles among children with non-CNS solid tumours (Table 1). Five-year relative survival by diagnostic group was either above 90% (retinoblastoma, germ cell tumours, other malignant epithelial neoplasms and renal tumours) or between 70% and 80% (soft tissue sarcomas, bone tumours, neuroblastoma and hepatic tumours). No substantive differences in survival by sex for non-CNS solid tumours were observed.

Five-year relative survival for all children with cancer combined increased over time (Table 2). After adjusting for cancer diagnostic group and other patient and treatment characteristics, children diagnosed between 1983 and 1994 were estimated to have had an almost twofold risk of death within 5 years of diagnosis compared with those diagnosed between 2007 and 2016.

Improvements in survival over time were most pronounced among children with blood cancers. For example, children with Burkitt lymphoma in the earliest time period had an almost fivefold increased risk of death within 5 years of diagnosis in comparison with the 2007–2016 reference group. Changes in survival were more limited for children with central nervous system tumours. Five-year relative survival increased considerably for the diagnostic subgroup of intracranial/intraspinal embryonal tumours. In contrast, no improvements in survival were observed for other subtypes, particularly gliomas. Among children with non-CNS solid tumours, the largest changes in survival were for neuroblastoma and Ewing tumours of the bone. An improvement was also recorded for children with rhabdomyosarcoma; however, there was little change in survival over the study period for patients with nephroblastoma (Wilms tumour), hepatoblastoma or osteosarcoma.

Stratification of survival over time by metastatic status at diagnosis for selected solid tumours showed that 5-year relative survival increased sharply from 75.6% between 1983 and 1994 to 93.0% between 2007 and 2016 for non-metastatic neuroblastoma with a corresponding HR of 3.95 (95% confidence interval [CI] 2.03, 7.71) and from 38.8% to 63.1% for children with metastatic neuroblastoma (HR 2.26, 95% CI 1.70, 3.01; Figure 1B). An almost threefold improvement was recorded for children with either non-metastatic Ewing bone tumour (72.1% to 90.8%, HR 2.91, 95% CI 1.28, 6.61) or metastatic disease (44.3% to 69.8%, HR 2.65, 95% CI 1.07, 6.61; Figure 1E). No appreciable change in survival was recorded for children with non-metastatic rhabdomyosarcoma, whereas those with metastatic disease experienced an increase in survival from 35.4% to 54.6% (HR 2.56, 95% CI 1.41, 4.65; Figure 1F). Only minor changes in survival over time, irrespective of metastatic status, were recorded for intracranial/intraspinal embryonal tumours (Figure 1A), Wilms tumour (Figure 1C) or hepatoblastoma (Figure 1D).

It was estimated that 1537 potential deaths within 5 years of diagnosis were avoided in total among all children diagnosed with cancer between 1995 and 2016. Specifically, there were 1424 observed deaths within 5 years of diagnosis among children diagnosed between 1995 and 2006 compared with 2007 expected deaths (based on survival for the 1983–1994 period), resulting in 583 avoided deaths (29.0% of expected deaths). The number and percentage of avoided deaths increased further for children diagnosed between 2007 and 2016, among whom there were 1009 observed deaths within 5 years of diagnosis, compared with 1963 expected deaths, equating to 954 avoided deaths (48.6% of expected deaths).

Across the diagnosis periods 1995–2006 and 2007–2016 combined, the highest number of avoided deaths within 5 years of diagnosis was estimated to be among children with lymphoid leukaemia (540 avoided deaths, 35.1% of all avoided deaths), neuroblastoma (197, 12.8%) and acute myeloid leukaemia (174, 11.3%; Figure 2). During 2007–2016, the percentage of avoided deaths reached 78.8% for germ cell tumours. Only 3.4% of expected deaths among children diagnosed with intracranial/intraspinal embryonal tumours were avoided between 1995 and 2006, rising to 21.0% for those diagnosed between 2007 and 2016.

4 | COMMENT

4.1 | Principal findings

Our results establish that Australian children diagnosed with cancer between 1983 and 1994 were almost twice as likely to die within 5 years compared with children diagnosed between 2007 and 2016, with corresponding relative survival rates of 73% and 86%, respectively. Survival improved for many types of childhood cancer over the study period, although there were some exceptions, with little or no change in survival found for other gliomas, hepatoblastoma and osteosarcoma. Consequent to these gains in survival, we estimated that more than 1500 deaths following childhood cancer were avoided between 1995 and 2016, representing well over one-third of all expected deaths within 5 years of diagnosis.

4.2 | Strengths of the study

The Australian Childhood Cancer Registry has virtually complete population coverage and is one of the longest-running and most comprehensive national population-based databanks of childhood cancer in the world.

4.3 | Limitations of the data

It is possible that changes in coding practices and diagnostic technologies throughout the study period may have had some impact on the findings presented here. Also note that we were unable to apply stage at diagnosis as defined in the more detailed Toronto Paediatric Cancer Staging Guidelines[19,20] as this information is currently only available in the Australian Childhood Cancer Registry for children diagnosed from 2006 onwards. Details of household socioeconomic status, which have been shown to influence childhood cancer survival,[21] are not collected in the Australian Childhood Cancer Registry and so area-based socioeconomic status was used as a proxy. The vital status of children

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TABLE 2 Five-year relative survival and adjusted excess mortality hazard ratios for childhood cancer in Australia by selected ICCC-3 diagnostic subgroups and year of diagnosis, 1983–2016

	Year of diagnosis					
	1983–1994		1995–2006		2007–2016	
ICCC-3 diagnostic subgroup	*n*	Estimate (95% CI)	*n*	Estimate (95% CI)	*n*	Estimate (95% CI)
Total childhood cancers						
5-year RS (%)[a]	6349	72.8 (71.6, 73.8)	7337	80.7 (79.8, 81.6)	7185	86.1 (85.2, 86.9)
Adjusted HR[b]		1.82 (1.67, 1.97)		1.35 (1.24, 1.46)		1.00 (reference)
Ia. Lymphoid leukaemia						
5-year RS (%)[a]	1670	75.6 (73.4, 77.6)	1887	87.3 (85.7, 88.8)	1829	93.0 (91.6, 94.2)
Adjusted HR[b]		3.07 (2.46, 3.84)		1.69 (1.34, 2.14)		1.00 (reference)
Ib. Acute myeloid leukaemia						
5-year RS (%)[a]	342	46.0 (40.7, 51.2)	378	67.0 (62.0, 71.5)	306	76.9 (71.7, 81.3)
Adjusted HR[b]		2.60 (1.94, 3.46)		1.51 (1.11, 2.05)		1.00 (reference)
IIb. Non-Hodgkin lymphoma (except Burkitt lymphoma)						
5-year RS (%)[a]	283	76.8 (71.4, 81.3)	261	83.2 (78.1, 87.3)	245	90.4 (85.9, 93.6)
Adjusted HR[b]		1.95 (1.17, 3.25)		1.68 (1.01, 2.82)		1.00 (reference)
IIc. Burkitt lymphoma						
5-year RS (%)[a]	89	73.1 (62.6, 81.2)	146	91.2 (85.3, 94.8)	147	93.2 (87.1, 96.5)
Adjusted HR[b]		4.75 (2.03, 11.1)		1.45 (0.59, 3.58)		1.00 (reference)
IIIa. Ependymoma and choroid plexus tumour						
5-year RS (%)[a]	148	66.4 (58.1, 73.4)	150	70.1 (62.1, 76.8)	184	77.3 (69.5, 83.3)
Adjusted HR[b]		1.25 (0.79, 1.98)		1.22 (0.77, 1.93)		1.00 (reference)
IIIb. Astrocytoma						
5-year RS (%)[a]	661	78.2 (74.8, 81.2)	776	79.2 (76.2, 81.9)	696	85.4 (82.4, 88.0)
Adjusted HR[b]		1.01 (0.75, 1.35)		1.28 (0.98, 1.66)		1.00 (reference)
IIIc. Intracranial/intraspinal embryonal tumours						
5-year RS (%)[a]	269	49.9 (43.8, 55.7)	322	51.6 (46.0, 56.9)	319	60.5 (54.6, 65.9)
Adjusted HR[b]		1.17 (0.89, 1.53)		1.33 (1.04, 1.70)		1.00 (reference)
IIId. Other gliomas						
5-year RS (%)[a]	177	48.1 (40.6, 55.3)	196	53.1 (45.9, 59.8)	204	48.2 (40.8, 55.1)
Adjusted HR[b]		0.83 (0.62, 1.12)		0.98 (0.73, 1.30)		1.00 (reference)
IVa. Neuroblastoma and ganglioneuroblastoma						
5-year RS (%)[a]	397	51.4 (46.3, 56.2)	433	67.9 (63.2, 72.1)	474	77.8 (73.5, 81.6)
Adjusted HR[b]		2.48 (1.91, 3.23)		1.64 (1.25, 2.15)		1.00 (reference)
VIa. Nephroblastoma and other nonepithelial renal tumours						
5-year RS (%)[a]	329	87.8 (83.7, 90.9)	375	88.9 (85.3, 91.7)	345	92.3 (88.7, 94.9)
Adjusted HR[b]		1.48 (0.86, 2.54)		1.42 (0.83, 2.43)		1.00 (reference)
VIIa. Hepatoblastoma						
5-year RS (%)[a]	45	82.6 (67.9, 91.1)	94	84.3 (75.2, 90.4)	95	83.2 (73.5, 89.7)
Adjusted HR[b]		1.35 (0.52, 3.58)		1.75 (0.70, 4.38)		1.00 (reference)
VIIIa. Osteosarcoma						
5-year RS (%)[a]	108	67.7 (58.0, 75.6)	138	71.1 (62.7, 77.9)	126	66.2 (55.8, 74.7)
Adjusted HR[b]		1.46 (0.88, 2.42)		1.28 (0.79, 2.09)		1.00 (reference)
VIIIc. Ewing tumour and related sarcomas of bone						
5-year RS (%)[a]	152	63.9 (55.7, 71.0)	148	72.4 (64.4, 78.9)	124	86.4 (78.3, 91.7)
Adjusted HR[b]		2.74 (1.50, 4.99)		2.05 (1.10, 3.83)		1.00 (reference)
IXa. Rhabdomyosarcoma						
5-year RS (%)[a]	231	64.2 (57.6, 70.0)	202	70.9 (64.1, 76.6)	200	75.6 (68.5, 81.4)
Adjusted HR[b]		1.81 (1.21, 2.68)		1.41 (0.94, 2.14)		1.00 (reference)

Abbreviations: CI, confidence interval; ICCC-3, International Classification of Childhood Cancers; HR, hazard ratio; RS, relative survival.

[a]survival was calculated using the semi-complete cohort method with follow-up available to 31 December 2017.

[b]Excess mortality hazards ratios were adjusted for sex, age group at diagnosis, remoteness of residence, area-based socioeconomic status and metastases present at diagnosis (where applicable).

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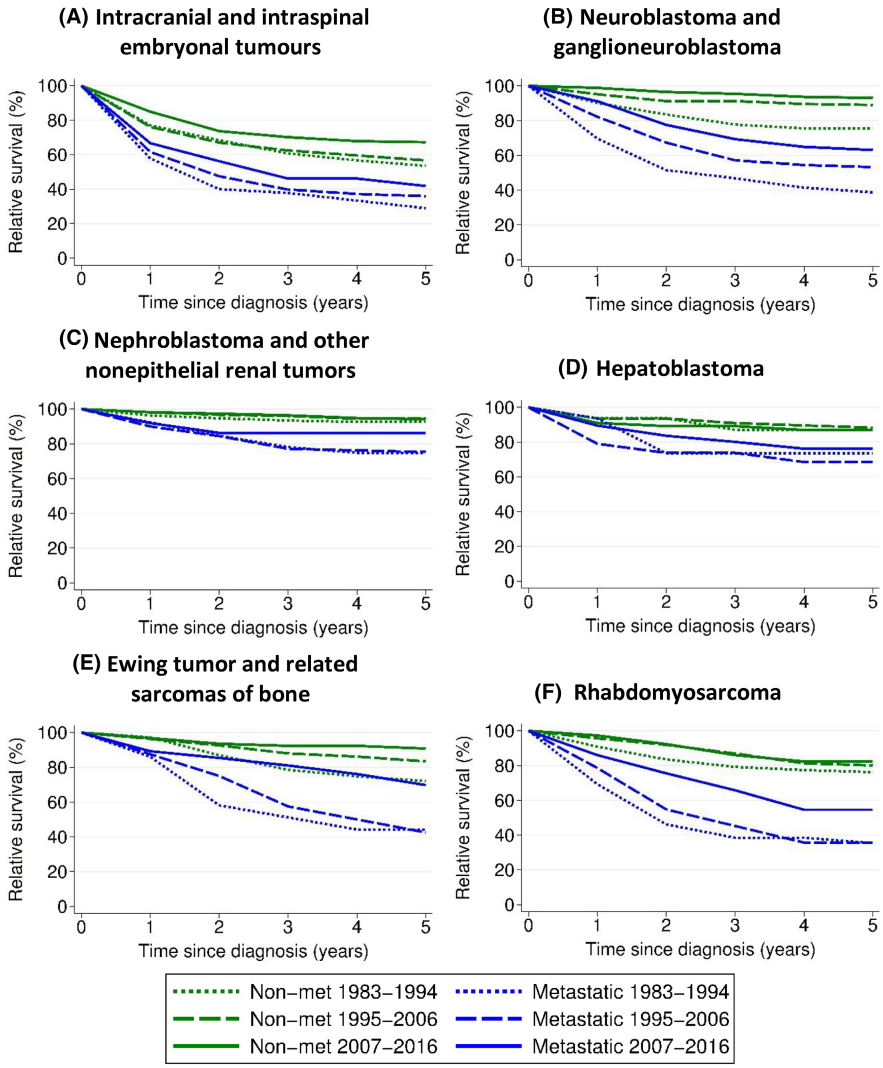

FIGURE 1 Relative survival curves for childhood cancer in Australia by selected ICCC-3 diagnostic subgroups, year of diagnosis and metastatic status, 1983–2016

who emigrated overseas within 5 years of their cancer diagnosis would not be recorded in the National Death Index, although we expect this would have minimal impact on our results due to the low proportion of children involved.[22]

4.4 | Interpretation

Survival following a diagnosis of cancer during childhood depends on a number of factors such as the patient's age, type of malignancy, extent of disease (or stage) at diagnosis and other clinical characteristics.[23] Health-system factors, including the availability of contemporary, high-quality medical and supportive care, are also crucial to the outcome.[24] Ongoing progress in the development of multimodal treatments and improved supportive care has led to large improvements in survival for many types of childhood cancer over the last few decades,[23,25] as evidenced by our findings. These advances have largely come about as a direct result of international collaborative clinical trials.[23,26,27]

A key evolution in the management of childhood leukaemia has involved refinements in molecular classification,[28,29] allowing the development of chemotherapy regimens that are more targeted. Treatment protocols for children with various solid tumours have retained similarities over time.[30] Adjuvant radiotherapy following surgery has, however, been phased out for some cancers and replaced by a multimodal approach centred around chemotherapy,[23] while innovative approaches for delivering radiotherapy to reduce long-term effects (such as proton beam therapy[31]) have developed for situations where irradiation remains necessary. The recent introduction of immunotherapy has also proven successful across a range of childhood cancers.[32]

In contrast, little or no improvement in outcomes was observed for some childhood cancers including osteosarcoma, hepatoblastoma and certain CNS tumours. Ongoing international collaborative efforts aim to improve the prognosis of these cancers through better understanding of their biology and genomics, identification of novel agents and implementation of clinical trials.[33–35]

Overall survival for childhood cancer in Australia generally compares well with outcomes from countries in North America and Europe. For example, the latest 5-year survival rates reported for all childhood cancers combined were 85% in the United States (2011–2017)[36] and 84% in England (2011–2015),[37] compared with 86% in Australia (2007–2016). Comparisons of overall survival should be

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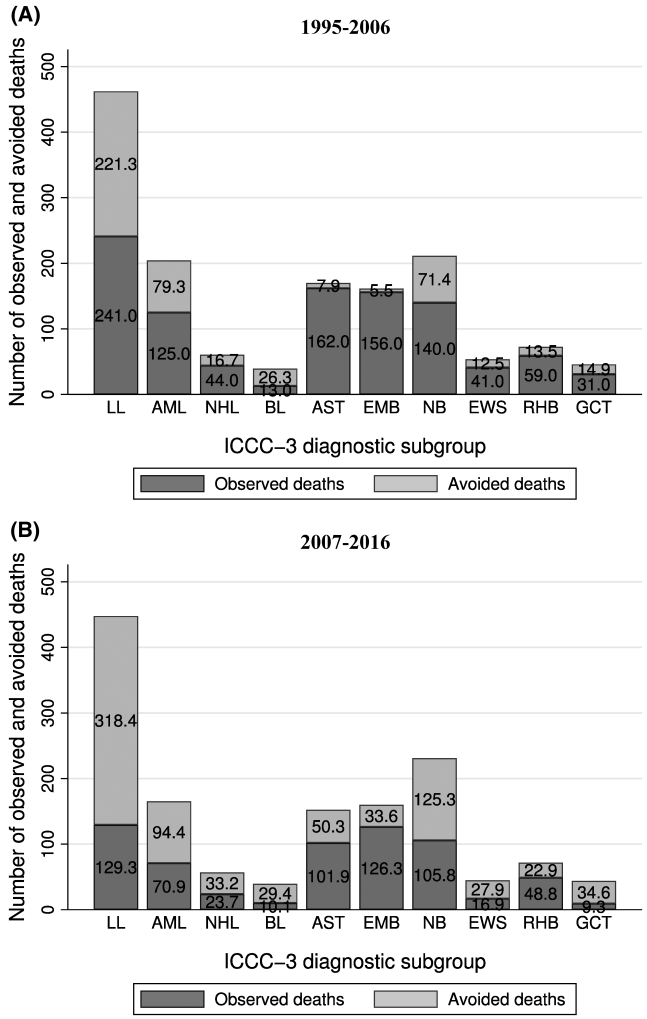

FIGURE 2 Number of observed and 'avoided' deaths within 5 years after diagnosis by period and selected ICCC-3 diagnostic groups/subgroups, Australia, 1995–2016. LL, 01a—lymphoid leukaemia; AML, 01b—acute myeloid leukaemia; NHL, 02b—Non-Hodgkin lymphoma (excluding Burkitt); BL, 02c—Burkitt lymphoma; AST, 03b—Astrocytoma; EMB, 03c—intracranial/intraspinal embryonal tumours; NB, 04b—neuroblastoma and ganglioneuroblastoma; EWS, 08c—Ewing tumour and related sarcomas of bone; RHB, 09a—rhabdomyosarcoma; GCT, 10—germ cell tumours, trophoblastic tumours and neoplasms of gonads

interpreted with caution, however, as they do not account for differences in the mix of cancers between countries.

Australian children with acute myeloid leukaemia or Ewing tumour and related sarcomas of the bone tend to have considerably better survival (77% and 86% after 5 years, respectively) than reported elsewhere. The finding for acute myeloid leukaemia compares favourably to population-based survival estimates for children in England (71%, 2011–2015),[37] the United States (68%, 2011–2017)[36] and Canada (61%, 2001–2016),[38] but was similar to the result from a recent Dutch study (74% for the period 2010–2015).[39] Reported 5-year survival varied widely for children with Ewing bone tumours living in other high-income countries, from 80% in Canada (2001–2016)[38] and 76% in the United States (2011–207)[36] to 66% in Germany (2002–2006)[40] and England (2011–2015),[37] all lower than the outcome recorded in Australia.

Comparisons between Australia and overseas were mixed for some childhood tumours of the central nervous system, particularly the diagnostic subgroups of intracranial and intraspinal embryonal tumours and other gliomas. Children with embryonal CNS tumours in Australia recorded 61% relative survival 5 years after diagnosis, lower than the corresponding result of 68% in both the United States (2011–2017) and Canada (2001–2016),[36,38] but higher than published by the French National Registry of Childhood Solid Tumors (54% for the period 2000–2008).[41] Five-year relative survival following other glioma was 48% as reported here, compared with 56% for children in the United States[36] but only 25% for Canada[38] and 35% for France.[41] There are no clear reasons for these variations in survival among children from Australia in relation to international data, with further consideration warranted.

Importantly, we were able to show that more than a third of expected deaths within 5 years of diagnosis were potentially avoided among Australian children with cancer between 1995 and 2016. Presenting cancer survival information in terms of potentially avoided deaths provides a different metric for quantifying the large gains in childhood cancer survival that have been observed over the last few decades. While restricting our estimates to within 5 years of diagnosis may underestimate the total number of deaths avoided among children, our previous work has shown that for most childhood cancer types, conditional 5-year survival in Australia is over 95%.[42] This is suggestive of 'population cure' among these children, so the number of additional deaths after 5 years would be expected to be low. It must also be acknowledged that the positive finding of avoiding deaths also brings implications in terms of ongoing health issues, given childhood survivors are known to experience excess morbidity related to late effects stemming either directly from their cancer or the treatments received.[23,43–45]

5 | CONCLUSIONS

Our findings provide evidence of the ongoing progress in survival for children with cancer. Over the 35 years of the study, the risk of mortality within 5 years of diagnosis for all childhood cancers combined has decreased, resulting in hundreds of young lives in Australia being preserved over the last two decades. In the face of this good news a few exceptions remain, with little or no headway observed for some childhood solid tumours. The intention of this study is to continue to spur efforts towards ensuring that all children diagnosed with cancer can look to the future with hope.

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Institute of Health and Welfare and the Medical Records Department at each of the major paediatric oncology treating hospitals throughout Australia.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Conception and design of the work - DRY, PDB, JFA; Data analysis - DRY; Interpretation of findings - PDB, ASM, JDP, PCV, JFA; Drafting the manuscript - DRY; Critical revision of the manuscript for important intellectual content - PDB, ASM, JDP, PCV, JFA; Final approval of the version to be published - All authors; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved - All authors. Open access publishing facilitated by Griffith University, as part of the Wiley - Griffith University agreement via the Council of Australian University Librarians. [Correction added on 06 July 2022, after first online publication: CAUL funding statement has been added.]

DATA AVAILABILITY STATEMENT

Unit record data that support the findings of this study are not publicly available through the Australian Childhood Cancer Registry due to privacy and ethical restrictions but may be requested directly from the state and territory data custodians (subject to ethical approval). Please contact statistics@cancerqld.org.au for further details.

ORCID

Danny R. Youlden https://orcid.org/0000-0002-2721-9083
Peter D. Baade https://orcid.org/0000-0001-8576-8868

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