

Title: Changes in cancer incidence and survival among Aboriginal and Torres Strait Islander children in Australia, 1997-2016

Running title: Cancer in Aboriginal and Torres Strait Islander children

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Abbreviations:

ACCR Australian Childhood Cancer Registry
APC annual percentage change
CI confidence interval
HR hazard ratio
TSI Torres Strait Islander

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Abstract

Background: This study reports cancer incidence and survival among Aboriginal and Torres Strait Islander children and other Australian children and assesses changes over time.

Procedure: Data were from the population-based Australian Childhood Cancer Registry. The study comprised children aged under 15 diagnosed between 1997 and 2016 and with mortality follow-up to 31 December 2017. Incidence trends were analysed using Joinpoint regression. Five-year cancer-specific survival was calculated using the semi-complete approach with survival comparisons made using multivariable flexible parametric models.

Results: Aboriginal and Torres Strait Islander children accounted for 506 of 13,299 eligible cases (3.8%). Incidence rates for Aboriginal and Torres Strait Islander children across the study period increased by 2.3% annually (95% CI +0.6%, +4.0%) and for other Australian children increased by 0.6% annually (95% CI +0.3%, +0.9%), $p=0.05$). Nonetheless, cancer incidence was consistently lower for Aboriginal and Torres Strait Islander children, with an incidence rate ratio of 0.73 (95% CI 0.62-0.85; $p<0.01$) between 2012-2016. Survival for Aboriginal and Torres Strait Islander children with solid tumours was 70.6% (95% CI 62.5%-77.3%) and for other Australian children was 83.5% (95% CI 82.3%-84.7%; $p<0.01$) with indications of this difference diminishing in recent years.

Conclusions: Improvements in identification, particularly in urban areas, most likely accounts for the greater increase in cancer incidence rates among Aboriginal and Torres Strait Islander children. Examination of data on stage at diagnosis and treatment may provide important insights into survival for children with solid tumours.

Introduction

Aboriginal and Torres Strait Islander peoples are Australia's First Nations peoples. There are hundreds of distinct sovereign groups that have their own dialects and cultural traditions.¹

Estimates from the 2016 Census indicate 3% of the Australian population identified as Aboriginal and/or Torres Strait Islander.² This increased to 6% for children under 15 years of age,² reflecting the much younger age distribution of Aboriginal and Torres Strait Islander peoples. Aboriginal and Torres Strait Islander children are also far more likely than other Australian children to live in remote and very remote localities, comprising 43% of the population aged under 15 living in those areas.²

Health disparities between Aboriginal and Torres Strait Islander peoples and other Australians are well-documented, involving a wide range of conditions.³⁻⁵ While Aboriginal and Torres Strait Islander adults are known to experience higher rates of death from cancer, available information previously indicated Aboriginal and Torres Strait Islander people had a lower overall incidence of cancers compared to other Australians.³ With progress in the ascertainment of Aboriginal and Torres Strait Islander identification in health and mortality datasets,^{6,7} contemporary data now suggest cancer incidence is actually equivalent or higher among Aboriginal and Torres Strait Islander peoples.⁸ It is unclear whether this relative change is because of improved data quality, a groundswell of pride and connectedness with Aboriginal and Torres Strait Islander heritage leading to advances in self-identification, a real increase in cancer incidence among Aboriginal and Torres Strait Islander people over time, or some combination of these and other factors.

It is currently unknown how childhood cancer estimates have been affected by these developments. Our aim in this study was to determine current rates of cancer incidence and survival among Aboriginal and Torres Strait Islander children and to describe trends over the last two decades.

Methods

Data

The study cohort included children aged under 15 who were diagnosed with cancer from 1997 to 2016 (inclusive). Data were sourced from the Australian Childhood Cancer Registry (ACCR) and relate to distinct primary cases of cancer rather than individual patients, as per international conventions for reporting incidence.⁹ Approval for operation of the ACCR is obtained from the University of Queensland Behavioural and Social Sciences Ethical Review Committee (reference number 2004000302) along with 15 additional human research ethics committees representing each of the State/Territory cancer registries and major paediatric treating hospitals.

The ACCR annually receives details of all notified cases of cancer in children from every population cancer registry in Australia, including the patient's demographic details, Aboriginal and/or Torres Strait Islander status, usual residential address at time of diagnosis, and fundamental information about the patient's cancer including date of diagnosis, morphology and body site. This information is supplemented with detailed clinical and treatment data collected from specialised paediatric hospitals.

Several cancer registries have implemented revised strategies over recent years to increase the completeness of data on identification of Aboriginal and/or Torres Strait Islander status. While the precise methods may vary, the broad technique is to combine data on self-reported Aboriginal and/or Torres Strait Islander identification from multiple health and administrative datasets. A multi-stage median approach¹⁰ is then used to derive the most plausible category for each patient, i.e. "Aboriginal and/or Torres Strait Islander", "other Australian" (which includes all children identified as not being Aboriginal and/or Torres Strait Islander,

irrespective of ethnicity) and “unknown”. Registries have applied this algorithm retrospectively, thus increasing the completeness and accuracy of the identifier in the current study cohort. The small minority of patients for whom Aboriginal and/or Torres Strait Islander status was recorded as “unknown” were excluded from this study.

Cancer type was defined according to the International Classification of Childhood Cancer, version 3.¹¹ Estimated resident population data by Aboriginal and/or Torres Strait Islander status produced by the Australian Bureau of Statistics were used in the denominator for the calculation of incidence and mortality rates.² Remoteness of residence and area-based socioeconomic status were based on place of residence at the time of diagnosis, and were defined according to the Australian Statistical Geography Standard (ASGS)¹² and the Index of Relative Socioeconomic Advantage and Disadvantage¹³, respectively.

Follow-up for the calculation of survival was available to 31 Dec 2017, with mortality status confirmed by annual linkage of the ACCR with the National Death Index.¹⁴ Patients diagnosed on the basis of autopsy or death certificate only, or where the date of death was the same as the date of diagnosis, were excluded from the survival portion of the study.

Analysis

The incidence distribution of key demographic characteristics and type of cancer for were compared using chi-squared tests. Incidence trends by Aboriginal and/or Torres Strait Islander status over the study period were estimated with JoinPoint software (v4.7.0.0, National Cancer Institute, Maryland, 2019).¹⁵ Results for the various trend segments were reported in terms of the annual percentage change (APC). In addition, incidence and mortality rates for the most recent five years of data (2012-2016) were calculated for both

Aboriginal and Torres Strait Islander children and other Australian children, with significance of the resulting rate ratios assessed using modified F-intervals.¹⁶

Survival estimates were calculated by applying a semi-complete cohort approach.¹⁷ Survival time was censored at either five years from the time of diagnosis, death due to a cause other than cancer, or the end of the follow-up period for patients who remained alive, whichever occurred first. Cancer-specific survival was used in the analysis rather than relative survival due to a lack of accurate life table information by Aboriginal and/or Torres Strait Islander status. It should be noted that the choice of survival indicator makes little difference in this age group, as relative and cause-specific survival estimates are very similar due to the low underlying mortality among children. Estimates were stratified by Aboriginal and/or Torres Strait Islander status, broad cancer group (“Blood cancers”, “Tumours of the central nervous system” and “Non-CNS solid tumours”) and either the period of diagnosis (1996-2005 versus 2006-2015) or remoteness category (defined as “Major city”, “Inner/Outer regional” and “Remote/Very remote”). The log-rank test was used to test for equality of the survivor functions across the variables of interest.

Adjusted excess mortality hazard ratios (HRs) by broad cancer groupings within five years of diagnosis were obtained from multivariable flexible parametric survival modelling.¹⁸

Covariates included were Aboriginal and/or Torres Strait Islander status, sex, age group, time period of diagnosis, cancer type, remoteness of residence and area-based socioeconomic status. Stage at diagnosis was not included in the modelling as this information is currently only available for patients diagnosed from 2006 onwards.

Results

Ascertainment of Aboriginal and/or Torres Strait Islander status was generally high, with “unknown” recorded for only 262 of 13 561 patients (1.9%) across the 20-year study period. After limiting eligibility to those with known status, Aboriginal and Torres Strait Islander children accounted for 506 of the remaining 13 299 patients (3.8%). The proportion of Aboriginal and Torres Strait Islander children in the cohort steadily increased from 2.7% (1997-2001) to 4.5% (2012-2016, $p<0.01$).

A large majority of cancers in the study cohort were histologically verified ($n=12\,358$ of 13 299, 92.9%). There was no significant difference in histological verification by Aboriginal and/or Torres Strait Islander status ($p=0.15$) nor by remoteness of residence ($p=0.06$).

Girls made up a higher proportion of Aboriginal and Torres Strait Islander children with cancer compared to other Australian children (51.0% versus 45.1%, $p<0.01$), but there was no difference in the age distribution ($p=0.21$, both groups with a median age at diagnosis of 5 years) – Table 1. There was also no significant variation by broad type of cancer ($p=0.13$), with leukaemia being the most common diagnostic group, accounting for 28.9% and 33.2% of cases among Aboriginal and Torres Strait Islander and other Australian children, respectively. Further examination revealed the proportion of leukaemia patients with acute myeloid leukaemia was considerably higher among Aboriginal and Torres Strait Islander children (34/146, 23.3%) than for other Australian children (627/4247, 14.8%; $p=0.01$).

Large variations were observed in the geographical distribution of residence. Proportionally, almost four times as many Aboriginal and Torres Strait Islander children lived in outer regional, remote or very remote localities (40.3% versus 11.0% for other Australian children,

$p<0.01$) – Table 1. There was also a more than two-fold difference in the proportion of childhood cancer patients from the most socioeconomically disadvantaged areas (42.8% versus 19.8%; $p<0.01$).

Incidence

Childhood cancer incidence rates remained lower for Aboriginal and Torres Strait Islander children across the study period, although the difference appears to be reducing (Fig. 1). Between 1997 and 2016, the overall childhood cancer incidence rate increased by a total of 53.9% among Aboriginal and Torres Strait Islander children (APC = +2.3%, 95% CI +0.6%,+4.0%; $p=0.01$) compared to 12.0% for other Australian children (APC = +0.6%, 95% CI +0.3%,+0.9%; $p<0.01$). These trends were not parallel ($p=0.05$), indicating incidence rates were increasing more rapidly for Aboriginal and Torres Strait Islander children.

Changes in the incidence rate ratio (IRR) over time also reflect the differing trends. Between 1997 and 2001, mean incidence rates per year were 77.0 (95% CI 60.9-96.0) and 156.6 (95% CI 151.0-162.4) cases per million population for Aboriginal and Torres Strait Islander and other Australian children, respectively, resulting in an IRR of 0.49 (95% CI 0.39-0.62; $p<0.01$). By comparison, in the most recent five-year diagnosis period (2012-2016), mean incidence rates per year were 123.9 cases per million population (95% CI 105.9-144.1) for Aboriginal and Torres Strait Islander children and 170.4 (95% CI 164.8-176.1) for other Australian children, giving an IRR of 0.73 (95% CI 0.62-0.85; $p<0.01$).

Further examination of incidence rate trends for Aboriginal and Torres Strait Islander children by remoteness of residence are shown in Supplemental Figure 1. Incidence rates for major cities and inner/outer regional areas were around half those for remote/very remote

regions at the start of the study period but were similar by the end date. A significant increase in cancer incidence rates was observed for Aboriginal and Torres Strait Islander children living in major cities at the time of diagnosis (APC = +3.9%, 95% CI +1.1%,+6.7%; $p<0.01$), with a smaller, non-significant increase recorded for those from inner/outer regional areas (APC = +2.2%, 95% CI -0.3%,+4.8%; $p=0.08$). In contrast, the trend was stable (APC = -0.4%, 95% CI -3.8%,+3.1%; $p=0.83$) in remote/very remote areas.

Mortality

A total of 2338 cancer-related deaths (17.6% of all 13 299 eligible cases in the study) were recorded up to 31 Dec 2017. Of these cancer-related deaths, 113 (4.8%) occurred among Aboriginal and Torres Strait Islander children. Approximately one-third of cancer-related deaths were caused by tumours of the central nervous system for both Aboriginal and Torres Strait Islander children (35.4%) and other Australian children (36.6%; $p=0.19$). The overall median time from diagnosis to death was 431 days (interquartile range 208-927 days), and this was similar for both groups ($p=0.34$). Mean annual mortality rates under 15 years of age for the five-year period 2012-2016 were 23.6 deaths per million population (95% CI 16.1-33.3) for Aboriginal and Torres Strait Islander children and 21.2 deaths per million population (95% CI 19.2-23.2) among other Australian children, equating to a non-significant standardised rate ratio of 1.11 (95% CI 0.75-1.60; $p=0.60$).

Survival

A total of 89 of the 13 299 patients (0.7%) were excluded from the survival analysis due to diagnosis occurring on or after their date of death. There was no difference in these exclusions between Aboriginal and Torres Strait Islander children and other Australian children ($p=0.37$). The remaining cohort ($n=13\ 210$) contributed a total of 52 959 person

years at risk. Median follow-up was 5 years for both Aboriginal and Torres Strait Islander children (interquartile range = 2.4-5.0 years) and other Australian children (3.1-5.0 years).

For all childhood cancers combined, five-year cancer-specific survival among patients diagnosed between 1997 and 2006 was 73.5% (95% CI 66.8%-79.1%) for Aboriginal and Torres Strait Islander children and 80.9% (95% CI 79.8%-81.8%) for other Australian children ($p<0.01$; Fig. 2). However, the difference in overall cancer survival appeared to diminish to some extent over time. Among children diagnosed between 2007 and 2016, total cancer-specific survival for Aboriginal and Torres Strait Islander children was 82.0% (95% CI 76.6%-86.2%) and 86.0% (95% CI 85.1%-86.9%) for other Australian children ($p=0.18$).

Multivariable modelling over the entire study period showed some equivalence in five-year survival among Aboriginal and Torres Strait Islander children and other Australian children when stratified by broad cancer type. For blood cancers (Table 2), five-year survival was 88.2% and 88.5%, respectively, giving an adjusted HR of 1.11 (95% CI 0.73-1.71; $p=0.62$). Survival was also similar for Aboriginal and Torres Strait Islander children (74.8%) and other Australian children (74.1%) for tumours of the central nervous system (Table 3), with a resultant HR of 0.93 (95% CI 0.66-1.32; $p=0.70$).

In contrast, there was a significant difference in survival for childhood solid tumours (Table 4). Aboriginal and Torres Strait Islander children were almost twice as likely to die from a solid tumour within five years of diagnosis compared to other Australian children across the study period as a whole (adjusted HR 1.84, 95% CI 1.35-2.50; $p<0.01$). This difference appeared to dissipate somewhat over time, however. Five-year survival was 61.1% (95% CI 48.9%-71.3%) for Aboriginal and Torres Strait Islander children diagnosed with a solid

tumour between 1997 and 2006 and 81.1% (95% CI 79.3%-82.8%) for other Australian children (adjusted HR 2.27, 95% CI 1.54-3.35; $p<0.01$). For those diagnosed during the period 2007 to 2016, survival was 78.5% (95% CI 67.0%-86.4%) and 85.7% (95% CI 84.1%-87.2%), respectively (adjusted HR 1.37, 95% CI 0.83-2.29; $p=0.22$). There was no interaction with age group ($p=0.76$) or area-based socioeconomic status ($p=0.53$) by Aboriginal and/or Torres Strait Islander status among patients with solid tumours, indicating that differences in survival were consistent across these covariates.

Discussion

The results presented here build on previous work from the Australian Childhood Cancer Registry. Earlier studies showed Aboriginal and Torres Strait Islander children were 36% less likely to be diagnosed with cancer compared to other Australian children¹⁹ but they were also 36% less likely to survive for five years.²⁰

In the current investigation, the incidence rate ratio of childhood cancer among Aboriginal and Torres Strait Islander children compared to other Australian children increased from 0.49 to 0.73 over the course of the last 20 years. It is unlikely this represents a disproportionately faster growth in cancer cases among Aboriginal and Torres Strait Islander children, although that is difficult to determine since little is known about the causes of most childhood cancers.^{21,22} A more plausible explanation may be that these changes reflect improvements in the identification of Aboriginal and Torres Strait Islander status in cancer registries and hospitals within Australia due to both improved systems and greater self-identification, as outlined above. For example, there was a 16% increase in the number of Aboriginal and Torres Strait Islander patients of all ages with cancer in the Victorian Cancer Registry between 2011 and 2015 as a direct result of this augmentation.²³

The higher proportion of leukaemia patients diagnosed with acute myeloid leukaemia amongst Aboriginal and Torres Strait Island children has been noted elsewhere,²⁴ likely reflecting a lower incidence of acute lymphoblastic leukaemia more so than an inflated incidence of acute myeloid leukaemia. Greaves theorised that exposure to recurrent infections early in life has a dual role in developing acute lymphoblastic leukaemia during childhood,²⁵ but results thus far appear inconclusive.²⁶

We also found that cancer incidence rate trends among Aboriginal and Torres Strait Islander children varied by remoteness of residence. Incidence rates increased significantly among those from major cities compared to a stable trend in remote/very remote areas. This differential fits with the perception that identification of Aboriginal and Torres Strait Islander people living in discrete and remote communities has generally been more accurate and consistent than in urban environments until quite recently.^{27,28}

There was also evidence of a narrowing of the difference in overall survival rates of cancer among Aboriginal and Torres Strait Islander children and other Australian children, with the margin reducing from 7 percentage points between 1997 and 2006 to 4 percentage points between 2007 and 2016. Our analysis revealed the survival differences were not consistent across cancer types. Whereas little difference was observed in survival for patients with either blood cancers or tumours of the central nervous system across the entire study period, survival for solid tumours was considerably lower among Aboriginal and Torres Strait Islander children. Even so, the survival difference for childhood solid tumours by Aboriginal and/or Torres Strait Islander status appears to be closing; the significant survival difference observed in the earlier years of the cohort (1997-2006) became a non-significant difference in the latter years (2007-2016).

It is unclear whether access to medical care has a role in the observed differences in survival for solid tumours. Australia has a free health care system which reduces barriers to access. Nearly all children with cancer in Australia receive the majority of their treatment at one of nine specialised paediatric oncology centres located in the capital city of each state. Aboriginal and Torres Strait Islander children receive the same treatment protocols as other Australian children. Enrolment on open clinical trials is also equally available. To the best of

our knowledge, there are no pharmacogenomic differences which require any alteration of therapy.

The centralisation of care model might not always be culturally appropriate, however, because Aboriginal and Torres Strait Islander children may be dislocated from their families and land for prolonged periods to receive necessary treatment.²⁹ Guidelines for optimal care specific to Aboriginal and Torres Strait Islander children with cancer are possibly required, similar to those published for adults.³⁰ We are in the process of expanding and refining details on treatment and stage at diagnosis in the ACCR; analysis of this information in the future may provide valuable insights. Collection of additional information on issues such as abandonment of treatment and co-morbidities may also be helpful.

Results from other countries are mixed. In New Zealand, children of Māori descent were reported to have an almost equivalent rate of cancer incidence compared to non-Māori children between 2010 and 2014 (158 and 170 cases per million population per year, respectively).³¹ Survival from cancer among Māori and non-Māori children in New Zealand was also estimated to be similar, even as far back as the early 1990s, although the number of cases available for analysis was small.³²

Cancer in Young People Canada reported First Nations children comprised just 2.4% of incident cases compared to 6.3% of the population between 2001 and 2006.³³ It was speculated this may reflect limitations in the recording of ethnicity in medical charts.³³ A population-based study from Canada found five-year event-free survival following cancer was lower for First Nations children (56%) compared to other children (73%) in the province

of Ontario between 1985 and 2011,³⁴ but there was no difference in event-free survival by ethnicity in a smaller study carried out in Manitoba.³⁵

Incidence rates of childhood cancer in the United States between 2001 and 2010 were estimated to be more than double among White non-Hispanics (196 cases per million population per year) compared to the group of American Indian/Alaskan Natives (93 cases per million population per year).³⁶ Siegel *et. al*³⁷ found American Indian/Alaska Native patients aged 0-19 had significantly worse five-year relative survival than their White non-Hispanic peers for the period 2008 to 2015 (82% versus 87%, respectively), which was thought to be intertwined with factors such as socioeconomic status and health insurance.

The current study includes one of the largest population-based cohorts of Indigenous children with cancer reported in the international literature to date. Despite this, there was considerable variation associated with many of the point estimates due to the relatively small number of Aboriginal and Torres Strait Islander patients, and results should be interpreted with due caution. Regular linkage of the ACCR with the National Death Index, which collates records of all deaths recorded in Australia since 1980,¹⁴ is crucial to ensure that details of subsequent mortality is virtually complete for all patients, regardless of where they live.

A potential limitation is that some discord is likely in the accuracy and completeness of Aboriginal and/or Torres Strait Islander status between the numerator (cancer cases or deaths) and the denominator (population) for the rate calculations. In contrast to current practice in cancer registries where identification of Aboriginal and/or Torres Strait Islander status is derived by combining self-reports collected in multiple primary datasets, corresponding

population estimates are derived from self-reported information collected in one dataset at one point in time (the Australian Census). While it is likely that a change in the propensity to self-identify as Aboriginal and/or Torres Strait Islander has contributed to recent increases in population counts,³⁸ it is not possible to quantify the effect of these differing methodologies on the results presented here.

In conclusion, observed cancer incidence rates have increased among Aboriginal and Torres Strait Islander children, at least in part due to improved ascertainment, whereas there has been a corresponding overall decrease in the survival difference compared to other Australian children. Moving forward, culturally appropriate solutions are required to further improve outcomes for Aboriginal and Torres Strait Islander children with cancer,^{29,39} particularly for those with solid tumours. Future examination of any variations in data on stage at diagnosis and treatment may provide important understandings.

Conflict of interest statement: The authors have no competing interests to disclose.

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Data availability: 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.

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Figure Legends

FIGURE 1 Childhood cancer incidence rate trends^{b,c} by Aboriginal and/or Torres Strait Islander status, Australia, 1997-2016.

Abbreviation: TSI – Torres Strait Islander; APC - annual percentage change.

Notes: a.) 95% confidence intervals are shown in brackets. b.) Rates were age-standardised to the 2001 Australian Standard Population. c.) Trends modelled using joinpoint regression (<http://surveillance.cancer.gov/joinpoint/>).

FIGURE 2 Kaplan-Meier cancer-specific survival curves for all childhood cancers combined by Aboriginal and/or Torres Strait Islander status and period of diagnosis, Australia, 1997-2016.

Abbreviation: TSI – Torres Strait Islander.

Notes: Survival was calculated using the cohort method, with follow-up on mortality status to 31 Dec 2017.

SUPPLEMENTAL FIGURE 1 Aboriginal and Torres Strait Islander childhood cancer incidence rate trends^{a,b} by remoteness of residence^c, Australia, 1997-2016

Abbreviations: APC - annual percentage change; 95% CI = 95% confidence interval.

Notes: a.) Rates were age-standardised to the 2001 Australian Standard Population. b.) Trends modelled using joinpoint regression (<http://surveillance.cancer.gov/joinpoint/>). c.) Remoteness categories were defined according to the Australian Standard Geographical Classification Remoteness Structure.