Running Head: Incidence, mortality and survival in young people

Cancer incidence, mortality and survival for children, adolescents and young adults in Queensland between 1987 and 2016

Lucy R. Holland (BSc (hons), MSc, MSWQ, PhD Cand) **Corresponding author*
Institute of Health and BioMedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia.
The University of Newcastle, Newcastle, NSW, Australia
E: lucy.holland@health.qld.gov.au
P: +64 414 756 228

Natalie K. Bradford (Bnur, MPH, PhD)
Institute of Health and BioMedical Innovation at Centre for Children's Health Research, Queensland University of Technology, Brisbane, QLD, Australia.
E: natalie.bradford@qut.edu.au

Youl, P. (MPH, PhD)
Cancer Alliance Queensland, Metro South Hospital and Health Service, Princess Alexandra Hospital, 2 Burke St, Woolloongabba, QLD, Australia
E: Phillipa.youl@health.qld.gov.au

Cossio, D. (BBsMn - Health Information Management)
Cancer Alliance Queensland, Metro South Hospital and Health Service, Princess Alexandra Hospital, 2 Burke St, Woolloongabba, QLD, Australia
E: danica.cossio@health.qld.gov.au

Dunn, N.
Cancer Alliance Queensland, Metro South Hospital and Health Service, Princess Alexandra Hospital, 2 Burke St, Woolloongabba, QLD, Australia
E: Nathan.dunn@health.qld.gov.au

Tran, N. (Bachelor of Applied Science - Mathematics)
Cancer Alliance Queensland, Metro South Hospital and Health Service, Princess Alexandra Hospital, 2 Burke St, Woolloongabba, QLD, Australia
E: Nancy.tran@health.qld.gov.au

Rick Walker (BMedSc, MBBS, GCert (Adol.Health), FRACP)
Cancer Alliance Queensland, Metro South Hospital and Health Service, Princess Alexandra Hospital, 2 Burke St, Woolloongabba, QLD, Australia
Queensland Youth Cancer Service, Children's Health Queensland, Brisbane, QLD, Australia.
Princess Alexandra Hospital, Brisbane, QLD, Australia.
School of Medicine, University of Queensland, QLD, Australia.
E: rick.walker@health.qld.gov.au

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Abstract

Purpose: Cancer remains the most common cause of disease-related death among young people and carries a significant burden. In the absence of prior state-based Australian epidemiological studies, this retrospective cohort study reviewed all cases of invasive cancer diagnosed in Queensland children, adolescents and young adults (0-39 years) from 1987-2016 using the Queensland Oncology Repository (QOR).

Methods: Cancers were classified according to SEER AYA site recode. Age-standardised rates (ASR) were calculated. JoinPoint regression examined trends in ASRs across three age cohorts, for three decades (1987-1996, 1997-2006 and 2007-2016).

Results: In total, 3,576 children aged 0-14 years (ASR=15.2/100,000), 6,441 aged 15-24 years (ASR=39.3/100,000) and 29,923 (ASR=122.6/100,000) aged 25-39 years were diagnosed. Incidence increased for female children and leukaemia was the most common diagnosis. For those 15-24 years, incidence increased initially before decreasing and was higher than other nationally reported rates. For those 25-39 years, incidence increased. For the older cohorts, the most common diagnosis was melanoma. All cohorts demonstrated a decline in mortality and improvement in five-year relative survival, with those 0-14 years demonstrating the greatest gains. The lowest survival for all cohorts was associated with CNS tumours.

Conclusion: These results highlight areas in need of further investigation to improve survival, reduce the burden of cancer for young people and aid service delivery. Future studies should focus on cancer biology, early detection, barriers in access to clinical trials, innovative models of care, improved data collection and patient reported outcomes.

Cancer incidence, mortality and survival for children, adolescents and young adults in Queensland between 1987 and 2016

Compared to other nations, Australia reports a higher incidence of cancer among children 0-14 years old and adolescents and young adults (AYAs) 15-39 years old (1-3). While mortality is low in high income countries, cancer remains the most common cause of disease-related death among children and AYAs (4, 5). Research also highlights the lack of gain in survival for certain cancers in those aged 15-24 years, compared to children or older adults (5). This is due to several factors that can include: distinct clinical and pathological features; distinct tumour distribution; delayed diagnosis or presentation; barriers in access to clinical trials, appropriately trained healthcare professionals and access to age specific services and; a predominant focus to date on childhood cancer research (4, 6-12). For cancer survivors, the number of life-years affected is also greatest in young people, leading to this cohort to have the greatest burden of disease (4).

Clear understanding of the epidemiology of childhood and AYA cancer incidence and mortality is hindered by variation in age definitions (13). Additionally, there are few state-based epidemiological studies described for Australian AYAs, which limits the planning and delivery of age-appropriate services. Queensland is the third largest Australian state or territory by population, with an ethnic composition of English (37.6%), Australian (36.7%), Irish (11.2%) and Aboriginal or Torres Strait Islander (3.6%) people (14). Queensland is geographically large with a total land area of 1,729,742 km^2 (15). This has specific implications for the delivery of healthcare with health services spread diversely across public and private sectors, throughout metropolitan, regional and rural areas. To aid the development of services, reporting of incidence and mortality within and between different age groups is important. This study therefore aimed to describe the incidence, mortality

and survival of invasive cancer in Queensland in three age cohorts (0-14 years, 15-24 years and 25-39 years) over a 30-year period between 1987 and 2016.

Methods

Study Population

This retrospective cohort study included all cases of invasive cancer diagnosed in individuals aged 0-39 years from 1987 to 2016 in Queensland. Data were extracted from the Queensland Oncology Repository (QOR). QOR collates and matches patient-level administrative and clinical data from the Queensland Cancer Register (QCR), together with public and private hospital admissions, pathology, radiology, treatment and mortality data The QCR is population-based and maintains a register of all cases of cancer (excluding basal and squamous cell carcinoma of the skin) and tumours of uncertain behaviour that have been diagnosed in Queensland since the beginning of 1982. Death data were obtained from the Register of Births, Deaths and Marriages with cause of death coded by the Australian Bureau of Statistics. Cancers were categorised according to the Surveillance, Epidemiology and End Results (SEER) AYA site recode (7). While cancer in children is generally reported using the International Classification of Childhood Cancers, we elected to use the SEER site AYA recode system to allow for comparison across groups and with other studies (16-18). The recode includes relevant morphology information from the International Classification of Childhood Cancers, including specific childhood cancers, as well as relevant topographical information for AYAs (7).

Variables Included and Age Group Definition

Variables included age at diagnosis, date of diagnosis, date of death, age at death, primary site, morphology, area-level socioeconomic status at diagnosis and remoteness of residence at diagnosis. Age groups included 0-14 years, 15-24 years

and 25-39 years. To allow for comparisons with published international data we also combined the 15-24 and 25-39 year cohorts into one group aged 15-39 years (4).

Analysis

Age-standardised rates (ASR) per 100,000 population were directly standardised to the 2001 Australian population (19). JoinPoint regression package version 4.7.0.0 (20) was used to examine trends in ASRs from 1987-2016 for all invasive cancers across the three cohorts. A maximum of three joinpoints were specified with a minimum of 6 years between joinpoints. The model that provided the best fit was selected. Monte Carlo Permutation method was used to test for significant trends. Results were expressed as annual percentage change (APC) with 95% confidence intervals. We additionally calculated ASRs for each of the three ten-year time periods (1987-1996, 1997-2006 and 2007-2016) for the five most common cancers in each age cohort with differences across time or between sexes expressed as relative change. Five-year relative survival was calculated for four time periods (1997-2001, 2002-2006, 2007-2011 and 2012-2016) from the date of diagnosis and censored at 31 December 2018. Relative survival estimates were produced using the period method.

Results

Incidence

0-14 years

From 1987-2016 a total of 3,576 children were diagnosed with an invasive cancer in Queensland (53.7% male, ASR 15.2/100,000). In males, the ASR for incidence remained stable with no significant change (APC; +0.3%, p=0.53). For females, ASR increased by 1.2% annually (p=0.001) (Figure 1a). Table 1 presents the most common cancers in children over three ten-year time-periods (1987-1996, 1997-2006 and 2007-2016). Leukaemia was the most common cancer, with rates

about 10% higher in males than females (5.1/100,000 and 4.8/100,000, respectively in the most recent period). ASRs for lymphoma were more than double in males compared to females (2.3/100,000 and 1.0/100,000 from 2007-2016, respectively, Table 1).

15-24 years

Over the same time-period, 6,441 individuals aged 15-24 years were diagnosed with an invasive cancer (49.7% male) (ASR=39.3/100,000). Incidence increased by 4.2% from 1987-1996 for males (p=0.07) before decreasing by 1.3% annually from1996-2016 (p=0.002) (Figure 1c). A similar pattern was observed for females. The most common cancer in this cohort was melanoma (Table 2). For males, ASR for 1987-1996 was 15.9/100,000 and 7.6/100,000 for 2007-2016 (52% decrease). A similar magnitude of change was observed in females with ASR from 1987-1996 being 19.2/100,000 and 10.6/100,000 from 2007-2016 (45% decrease). In females, thyroid cancer rates more than doubled from 2.2/100,000 in 1987-1996 to 5.1/100,000 from 2006-2016 (132% increase) (Table 2). Rates of germ cell tumours were significantly higher in males compared to females for each three-time period, driven mostly by gonadal tumours. There was a 140% increase in ASRs for appendiceal tumours in females from 1987-1996 to 2007-2016 (1.5/100,000 and 3.6/100,000, respectively) (Table 2).

25-39 years

From 1987-2016, 29,923 young adults aged 25-39 were diagnosed with an invasive cancer (41.1% male) (ASR=122.6/100,000). For females, incidence increased by 0.3% per year (p=0.002) from 1987-2016 (Figure 1e). The most common cancer in those aged 25-39 years was melanoma, with rates decreasing by about 14% in males and 7% in females over time (Table 3). In females, breast was the second most common cancer, with little difference in ASRs over time. Rates of

cervical cancer decreased by about 23% from 17.6/100,000 for 1987-2006, to 13.6/100,000 from 2007-2016. Thyroid cancer rates were about 340% higher in females compared to males for 2007-2016. ASRs for thyroid cancer in females more than doubled over time (1987-1996 ASR=7.4/100,000 and ASR 18.0 from 2007-2016).

15-39 years

From 1987-2016, 36,365 cancers (ASR=91.1/100,000) were diagnosed in this cohort. For females, incidence increased by 0.2% annually from 1987-2016 (p=0.03) (Figure 5).

Mortality

0-14 years

In total, 714 children died in the period 1987-2016 and the mortality rate was 3.0/100.000. As the number of deaths per year were relatively few, 3-year moving ASRs were used in the JoinPoint models. Mortality decreased by 4.5% per year (p=0.04) for males from 1987-1999, before stabilising from 1999 onwards. For females, mortality decreased by 2.8% per year (p <0.001) from 1987-2016 (Figure 1b). In males, mortality from leukaemia decreased from 1.9/100,000 in 1987-1996, to 0.5/100,000 from 2006-2016 (74% decrease) with a similar magnitude of decrease observed for females. Mortality rates decreased by 44% for CNS tumours in females over time (0.9/100,000 from 1987-1996 and 0.5/100,000 from 2007-2016).

15-24 years

From 1987-2016, 707 deaths occurred in those aged 15-24 years (57.1% male, ASR=4.3/100,000). We found no statistically significant changes in rates over time for males. For females, mortality decreased by 2.2% per year (p=0.01) from 1987-2016 (Figure 1d). The highest mortality was observed for leukaemia in males and females, with a reduction of about 50% for both sexes combined over time

(Table 2). Mortality decreased over time for melanoma, lymphoma and germ cell tumours. However, it remained relatively stable for CNS and bone cancers.

25-39 years

Overall, 3,701 deaths occurred (46.0% male) and the mortality rate was 15.2/100,000. There was a 1.9% ($p < 0.001$) and 1.6% ($p < 0.001$) annual decrease in mortality for males and females respectively over the 30-years of data (Figure 1f). Mortality rates decreased across several cancers including melanoma, lymphoma, female breast carcinoma and germ cell tumours (Table 3). For 2007-2016, the highest mortality was observed for melanoma (1.7/100,000) and CNS cancers (1.6/100,000). The greatest reduction in mortality over time was found for lymphoma with a 76% reduction (1.7/100,000 from 1987-1996 and 0.4/100,000 from 2007-2016).

15-39 years

Mortality in males decreased by 1.8% annually from 1987-2016 ($p<0.001$). A similar magnitude of decrease was observed for females (APC= -1.5%) ($p<0.001$) (Figure 5).

Five-year relative survival

0-14 years

For both sexes combined, 5-year relative survival (RS) was 77.5% (95%CI=73.9-81.1) for 1997-2001 and 86.1% (95%CI=83.6-88.6) for 2012-2016 ($p=0.01$) (Figure 2). For all cancers combined, RS increased over time by about 6.5% in females and 15.0% in males. Across selected cancers, improvements in 5-year RS were observed for leukaemia in males and females. Children with CNS tumours had the lowest survival, however a 22% and 18% absolute improvement in survival was observed over time for males and females respectively.

15-24 years

The 5-year relative survival for those diagnosed in the most recent period (2012-2016) was 90.3% for males and 91.6% for females. Survival in males increased by about 3% from the earlier period (1997-2001) to the most recent period (2012-2016). From 1997-2001 5-year RS for leukaemia was 54.4% for males and 52.9% for females and was 81.9% and 74.0% in the period 2012-2016 for males and females, respectively. Survival was lowest for CNS cancers (Figure 3).

25-39 years

Overall five-year RS increased from 85.4% to 88.8% for males and from 87.9% to 90.4% females for the time periods 1997-2001 and 2012-2016, respectively. Survival was highest for melanoma (95.7% and 98.3% for males and females, respectively) in the period 2012-2016. RS for leukaemia was 64.3% (males) and 66.9% (females) during 1997-2001 and 85.5% (males) and 71.8% (females) for 2012-2016 (Figure 4).

Discussion

This study provides a novel examination incidence, mortality and five-year-relative survival for Queensland children and AYAs.

Incidence

In children (0-14 years), the overall incidence of cancer we observed is similar to that reported in other developed nations (21). Trends in incidence varied by gender. While we observed increasing incidence for females, incidence for males was relatively stable. This aligns with an earlier Australian wide study that noted an increase in incidence for females but incidence plateauing among males from 1983-2006 (22). However, these differences may also reflect different tumour distribution, as outlined below. The higher incidence rates in the 15-24 year age group in this study compared to others are mainly driven by the higher rates of melanoma (23). However, the reduction in rates from 1994-2016 observed, aligns with a recent

Australian study that identified decreasing incidence rates from 2009 onwards (17). For the 25-39 age group, incidence remained relatively stable, with only a small annual percentage increase for females over time. This increase appears to be mainly driven by increasing rates of thyroid cancers. ASRs for 15-39 year age group reflects global data reporting increases in cancer incidence over time, particularly in young adult females (4, 13).

Mortality

A significant decline in mortality was observed for children over time. These reductions are similar to those reported elsewhere and likely reflect improvements in the treatment of leukaemia as the most common childhood malignancy (17). Significant mortality reductions were also evident for males and females 15-24 years and 25-39 years. These reductions are similar to those observed in other developed countries and again likely reflect improvements in treatment and management, as well as clinical trial access and multidisciplinary care (4, 13, 17, 24-26).

Survival

Significant improvements in five-year RS were observed over time, with the greatest gains found for children, although they demonstrated lower overall RS. For the AYA groups, RS also increased over the same period. In comparison to survival data recently published from New Zealand (80.6% for the period 2000-2009), the EUROCARE consortium (87% for the period 2000-2002) and Canada (85% for the period 2001-2005) (25, 27, 28), RS for AYAs in this study was superior (89.1%). This likely reflects the high proportion of treatable melanoma in the Queensland cohort.

Disease-Specific Sites

The distribution of cancers in children is similar to that previously reported, with leukaemias, neuroblastoma, rhabdomyosarcoma and CNS tumours most common (1, 10, 22, 26, 29, 30). While numbers were relatively small, a reduction in

incidence of melanoma in children was observed over time. A doubling in the incidence of appendiceal tumours in females was found. With changes in pathology practices, these tumours are now more likely to be reviewed (1, 31). In addition, a halving in mortality from leukaemia was observed over time which would be the main driver of reduction in mortality for the whole group. Smaller reductions were observed for lymphomas, paediatric and embryonal tumours. Cancers with the highest mortality among children were CNS cancers, leukaemias and paediatric tumours.

For 15-24 years, while melanoma was the most common cancer observed, a reduction in incidence and mortality over time were found. The timeline suggests that these results may be an encouraging reflection of well-established public health campaigns such as SunSmart in Australia, aimed at reducing sun exposure, as well as improved early detection (17, 32-34). Rates of thyroid cancers more than doubled over the study period and were 300% higher in young adult females than males. This is consistent with other national and international data (17). While the exact reasons for increasing incidence are unknown, increased incidental detection from ultrasound and imaging (35), leading to over diagnosis, is possible. While increasing incidence of colorectal cancers have been reported in national data (2), when we examined colorectal cancers by sub-site, we found the vast majority were from the appendix and is also likely reflective of incidental findings (1, 31). Unsurprisingly, rates of germ cell tumours were significantly higher in males, driven mostly by gonadal tumours. For 15-24 years, cancers of the bone, CNS and leukaemias were associated with the greatest mortality. However, a reduction in mortality for both males and females over time was found for leukaemias.

The data showed an increase in incidence of lymphomas in the 15-24 and 25-39-year cohorts. This may be attributable to changing diagnostic practices or

changes in known risk factors associated with viral infection and immunosuppression (17). The incidence of cervical cancers decreased dramatically over time for young adult females, aligning with other Australian and US data (36). This is likely the result of improved public sexual health campaigns and improved screening programmes. It is hoped that, with the introduction of Australia's Human Papilloma Virus (HPV) Vaccination Program in 2007, the incidence of cervical adenocarcinoma will decrease but further investigation is needed (17, 26). Germ cell tumours increased in males over time although a reduction in mortality was observed for 25-39 years, similar to findings from other recent Australian and US data (16, 17). For females, breast cancer was relatively prevalent in this cohort, with survival improving over time, as consistent with other recent Australian data (37). For 25-39 years, the highest mortality was found for melanoma and CNS tumours. Higher mortality for melanoma is due to the extremely high incidence in the Queensland population; with a mortality to incidence ratio (MIR) of 0.05, compared to a MIR for CNS cancers of 0.44. The most fatal diseases for all age groups remain those where there have been little advances in treatment and where there remains significant barriers in access to clinical trials (13, 16, 17, 26, 29).

Future Directions

Further effort is needed to understand the causes of cancer in children and young people with its unique biological and genetic features. Efforts targeted at early detection and prevention through public health campaigns and appropriate treatment measures have been demonstrated to be effective in the past and are paramount to further improve outcomes and reduce cancer burden in this population (4, 17, 25). Improvements in the treatment of leukaemia across all age groups has also led to overall reduction in mortality, however it also masks the lack of improvement in CNS and sarcomas across the age groups which should be the focus of future trials.

Improving availability of, and access to clinical trials and treatments for rare cancers, remains a priority if survival outcomes are to be improved over time, particularly for AYAs (13, 17). Within Australia, AYA care is complicated by treatment distribution across several healthcare settings (38, 39). Further research investigating the use of tele-health and technology to connect patients, specialist and primary care teams is therefore required that build upon national and international work to date focused on the development of specialist AYA services (25, 28, 38, 40, 41) (42). Improved consistency in data collection and capture is also required along with improved recording of Patient Reported Outcome Measures, to deepen our understanding of the experience, outcomes and burden of cancer for children, young people and their families (43).

Strengths and Limitations

As this was a state-based study, the number of cancers in some groups was relatively small. Caution should therefore be applied when examining trends over time. The use of Australian standard population figures may also limit comparison with international studies. For rare cancers with low incidence and mortality, trends are particularly subject to fluctuation. Additionally, the authors acknowledge that the application of the AYA SEER recode to paediatric data may not fully represent the presentation of some tumour types which only occur in childhood. The use of population-based verified, cancer registry data is a strength of this study. These results will aid cancer service planning and the delivery of paediatric and AYA cancer care. They also highlight important areas requiring further investigation to continue to improve services and outcomes for young people living with cancer.

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Conflict of interest statement

The authors declare no current or potential conflicts of interest.

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