Second primary cancers in people who had cancer as children: an Australian Childhood Cancer Registry population-based study

Author

Youlden, Danny R, Baade, Peter D, Green, Adèle C, Valery, Patricia C, Moore, Andrew S, Aitken, Joanne F

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Title: Second primary cancers following childhood cancer: a population-based study from the Australian Childhood Cancer Registry

Short title: Second primary cancers following childhood cancer

Abbreviations: ACCR - Australian Childhood Cancer Registry; CCSS – Childhood Cancer Survivor Study; CI - confidence interval; ICCC-3 International Classification of Childhood Cancers, 3rd edition; SIR – standardised incidence ratio.

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Abstract

Objective: Investigate second primary cancers in a contemporary cohort of childhood cancer survivors.

Design: Retrospective population-based study.

Setting: Australian Childhood Cancer Registry.

Participants: Cancer patients aged under 15 with a first primary diagnosis between 1983 and 2013. Follow-up was available to 31 December 2015.

Main outcome measures: Standardised incidence ratios (SIRs) were calculated to measure risk of a second primary cancer relative to the general population. Negative binomial models were used to assess differences in SIRs.

Results: Among 18,230 Australian childhood cancer survivors the risk of a second primary cancer was increased five-fold compared to cancer rates in the general population (SIR=5.13, 95% CI=4.65-5.67). Thirty-year cumulative incidence was 4.4% (95% CI=3.8%-5.0%). Relative risk of subsequent cancer was highest in the five years following first diagnosis and then decreased over time ($p<0.001$), although observed cancer incidence among survivors remained significantly elevated up to 30 years afterwards compared to expected incidence. Children diagnosed with a first primary rhabdomyosarcoma experienced the highest relative risk of second primary cancer (SIR=19.89, 95% CI=14.35-27.58). Mode of therapy was also a factor, with a combination of chemotherapy and radiotherapy incurring a ten-fold increased relative risk (SIR=9.80, 95% CI=8.35-11.49). Thyroid carcinomas (n=65, 17%) and acute myeloid leukaemias (n=57, 15%) were the most common types of second primary cancers.

Conclusions: Survivors of childhood cancer remain at increased risk of cancer well into adulthood. Given the likely contribution of late effects of cancer treatment, continued

research is required to refine treatments and reduce toxicity, while maintaining high rates of survival.

Twitter statement: Research from the Australian Childhood Cancer Registry shows that approximately 4% of survivors of childhood cancer will be diagnosed with a second cancer up to 30 years after their initial diagnosis, but the risk varies depending on the type of cancer and therapy received.

The known: Studies of childhood cancer survivors have commonly shown they are at increased risk of subsequent cancer but most previous studies have involved patients diagnosed two or more decades ago and/or have been limited to five-year survivors.

The new: Our results provide the first estimates at the national level of the risk of second cancers within a contemporary cohort of Australian childhood cancer survivors. Relative risk was highest within the five years following first diagnosis, and although remaining elevated, subsided as time passed.

The implications: Survivors of childhood cancer require ongoing monitoring for second primary cancers. Continued research is required to minimise late effects of cancer treatment early in life.

Introduction

Therapeutic advances for children with cancer over recent decades, commonly involving intensive chemotherapy often in combination with radiation therapy, have led to improved survival for many childhood malignancies.[1, 2] However, a large proportion of survivors suffer adverse health effects throughout their life-course due to either the cancer itself or the treatments received. These sequalae may include organ dysfunction (eg. cardiopulmonary, renal, gastrointestinal), impaired physical development, obesity, problems with vision or hearing, decreased fertility and neurocognitive deficits.[3, 4]

One of the most serious consequences can be the development of a second cancer. Although it is well established that childhood cancer survivors are at increased risk of being diagnosed with a subsequent cancer relative to cancer rates in the general population, much of the available information has come from studies comprising patients diagnosed prior to the introduction of modern treatment protocols and/or has been limited to second cancer diagnosed five or more years after the first diagnosis.[5, 6] The only data published for Australia comes from a single institution study in New South Wales that was restricted to five-year survivors of childhood cancer with a first diagnosis between 1972 and 1999.[7]

Here we investigate second primary cancers in a more contemporary national population-based cohort of childhood cancer survivors. For the first time in Australia we also examine risk in the years immediately following a patient's initial diagnosis.

Methods

Data

De-identified unit record data were sourced from the Australian Childhood Cancer Registry (ACCR) which contains details on all cancers diagnosed among children under 15 years of age. The ACCR operates under ethics approvals from the University of Queensland Behavioural and Social Sciences Ethical Review Committee (reference number 2004000302) and Human Research Ethics Committees representing each of the State/Territory cancer registries and major paediatric treating hospitals. Cases included in the ACCR cover the entire population of Australia and are ascertained from every state and territory cancer registry throughout the country on an annual basis.

Information on second primary cancers is obtained through regular matching of the ACCR with the comprehensive Australian Cancer Database, which holds data on all primary malignant cancers (excluding basal and squamous cell carcinomas of the skin) diagnosed in Australian residents at any age. The rules for defining second primary cancers are complex. Generally speaking, a new cancer was considered to be a second primary when it had a distinct morphology (Berg group)[8] compared to the first cancer, in contrast to a recurrence or relapse of the original primary when the second tumour had either the same or a related morphology.

Eligible patients were those with a first diagnosis of cancer between 1983 and 2013, with follow-up on second cancers available to 31 December 2015 (a minimum of 2 years and maximum of 33 years). The maximum attained age within the cohort was 47 (for a 14-year-old initially diagnosed in 1983 who was still alive at the end of the study period). Second primary cancers diagnosed within two months of the first cancer were excluded to minimise detection bias. For comparison with other studies, results were also calculated for the subgroup of five-year survivors only. Recurrences of the original cancer or progressive disease were not considered, nor were any additional cancer diagnoses that occurred subsequent to the second primary cancer.

Analysis

Standardised incidence ratios (SIRs) were used to estimate the risk of a childhood cancer survivor developing a second primary cancer relative to the incidence of cancer in the general population. Time at risk was accumulated from two months after first diagnosis until either 31 December 2015, date of diagnosis of a second primary cancer or date of death, whichever occurred first. The number of second primary cancers expected within the study cohort was obtained by applying the cancer incidence rate in the general population to the person-years at risk, matched by sex, five-year age group and calendar year. SIRs were then calculated by dividing the observed number of second primary cancers by the expected number. Differences between SIRs for characteristics of interest were assessed using an unadjusted negative binomial model with the observed number as the dependent variable offset by the log of the expected number and results were expressed in terms of the incidence rate ratio (IRR).

The “strate” command in Stata was used to calculate SIRs, with corresponding 95% confidence intervals calculated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.[9] Data were analysed by sex, age group at first diagnosis and type of first childhood cancer, defined in diagnostic groups/subgroups according to the International Classification of Childhood Cancer, third edition (ICCC-3).[10] SIRs by mode of treatment (chemotherapy only, radiotherapy only, both, neither) and changes in the SIR by time from first diagnosis (stratified as 0 to <2 years, 2 to <5 years, 5 to <10 years, 10 to <20 years and >=20 years) were examined. The latter was also modelled as an ordinal variable in a negative binomial model to examine the trend effect of time from first diagnosis.

Results

Of the 18,230 children aged under 15 who were diagnosed with cancer between 1983 and 2013 and survived for a minimum of two months, 388 (2%) were diagnosed with a second primary cancer during 228,411 person-years of follow-up (median=10.9 years, interquartile range=3.9-20.0 years) commencing from two months after first diagnosis through to 31 December 2015. Median time between first and second diagnosis was just under 10 years (interquartile range=4.0-16.4 years).

The study cohort experienced a five-fold increased risk of being diagnosed with a second primary cancer relative to the general population (SIR=5.13, 95% CI=4.65-5.67). Overall cumulative incidence of second primary cancers at 30 years after first diagnosis was estimated to be 4.4% (95% CI=3.8%-5.0%) and the absolute excess risk was 13.9 per 10,000 person-years at risk (95% CI=13.4-14.2 per 10,000 person-years at risk).

Among the 12,699 five-year survivors, the median follow-up from first diagnosis was 16.2 years (interquartile range=3.9-20.0 years). This subgroup accounted for 271 (70%) of the second primary cancers with a corresponding SIR of 4.29 (95% CI=3.81-4.83). Thirty-year cumulative incidence remained similar at 4.6% (95% CI=4.0%-5.3%).

For the entire cohort, little difference was found in the relative risk of second primary cancer by sex (p=0.18). Although the SIR remained elevated across all age groups, it was significantly higher for children aged 0-4 at first diagnosis compared to those aged 10-14 (IRR=1.52, 95% CI=1.21-1.92; p<0.001) – Table 1. SIRs by type of first childhood cancer varied from 1.90 for the diagnostic group 'other malignant epithelial neoplasms & melanoma' to 9.23 for children with 'soft tissue sarcomas'. Further analysis of the latter group revealed a 20-fold increased risk (SIR=19.89, 95% CI=14.35-27.58) following rhabdomyosarcoma, with 36 cases of second primary cancer diagnosed among 567 survivors. There were also approximately ten times as many second primary cancers compared to the background population following the diagnosis of a first cancer in the subgroups of 'intracranial and intraspinal embryonal tumours' (SIR=9.79, 95% CI=6.38-15.01) and 'Ewing tumours and related bone sarcomas' (SIR=11.36, 95% CI=7.25-17.82).

Mode of treatment received was strongly associated with the risk of development of a second primary cancer (Figure 1). While still elevated compared to the general population, patients who did not receive either chemotherapy or radiotherapy had the lowest relative risk (SIR=2.14, 95% CI=1.64-2.78) compared to a ten-fold increased risk (SIR=9.80, 95% CI=8.35-11.49) among those who received both of these treatments. This results in a nearly 5-fold incidence rate ratio (IRR=4.59, 95% CI=3.37-6.23; p<0.001) <u>for those receiving both chemotherapy and radiotherapy compared to those receiving neither chemotherapy nor radiotherapy</u>.

A clear pattern emerged in the relative risk of second primary cancers over elapsed follow-up time (Figure 2). The SIR was highest in the years immediately following first diagnosis, peaking at 10.32 (95% CI=8.20-12.98) between two to five years afterwards, before decreasing to 2.58 (95% CI=2.02-3.30) from 20 years onwards (p_{trend}<0.001).

The most common types of second primary cancer following any childhood cancer were thyroid carcinomas (n=65, 17%) and acute myeloid leukaemias (n=57, 15%) (Table 2). There were also 57 second primary cancers in the diagnostic group ‘other and unspecified carcinomas’, including 15 cases of female breast cancer. When only the follow up interval from five years after the first diagnosis was considered, thyroid carcinomas accounted for almost a quarter (n=63 of 271, 23%) of the second primary cancers diagnosed. In contrast, only 11 cases (4%) of therapy-related acute myeloid leukaemias occurred within this subgroup (data not shown), reflecting the respective median lag times of 14 years and 2 years between first and second diagnosis for these two types of second cancer.

Discussion

We present the first national data on second primary cancers among Australian childhood cancer survivors. Importantly, our results include outcomes within the first five years following initial diagnosis. Only one much smaller study in Australian children has previously investigated second primary cancers following childhood cancers. Wilson et. al.[7] investigated a cohort of 896 five-year survivors aged 0-14 who were treated for cancer at a single institution (the Sydney Children’s Hospital in New South Wales) between 1972 and 1999 with follow-up to 31 December 2004. The resultant SIR of 5.0 based on only 16 second primary cancers was of similar magnitude to the SIR of 5.1 among all survivors, and an SIR of 4.3 among five-year survivors, found here.

Among studies on second primary cancer following childhood cancer in other countries, SIRs ranging between 3 and 20 have been reported,[5, 6, 11-16] thereby placing our result at the lower end of the spectrum. The wide variation can, at least in part, be attributed to an array of factors, including length of follow-up, the time period of initial diagnosis, the mix of cancers being considered, the treatment regimen used for the first cancer, differences in the inclusion criteria by age at diagnosis, the incidence rates of cancer in the underlying population and population-based versus institutional studies. Differences in these attributes make direct comparison of outcomes across studies problematic. For example, in contrast to our work, five of the eight papers cited above solely comprised patients diagnosed prior to the year 2000 (and as early as the 1940s)[5, 6, 11-13], four considered five-year childhood cancer survivors only[5, 6, 12, 13] and five included patients first diagnosed up to 18 years of age or older[5, 12-14, 16]. There were a mix of institutional studies[5, 12, 15] and population-based series[6, 11, 13, 14, 16].

Overall cumulative incidence at 30 years for five-year survivors in our study appeared to be substantially lower than among five-year survivors in the CCSS in the United States[5] (4.6% versus 7.9%, respectively). Possible reasons for this disparity may include differences in the time period of first diagnosis (1983-2013 and 1970-1986, respectively); variation in eligibility by age at first diagnosis (0-14 here as opposed to 0-20 in the US study); and the somewhat shorter median follow-up in our study (16 years among five-year survivors in our study compared to 23 years in the CCSS).

By far the largest relative risk of second primary cancers found here was among survivors of rhabdomyosarcoma. Our result for second primary cancer associated with an initial diagnosis of rhabdomyosarcoma (SIR=19.9) appears to be much higher than the sixfold increased relative risk (SIR=5.7) from a study in the United States[17] that included rhabdomyosarcomas diagnosed between 1973-2010 at ages 0-19. However, Archer et. al.[17] note that the majority of second cancers in their cohort were observed following a first primary rhabdomyosarcoma diagnosed between 2000-2010 (SIR=21), closely in line with the current finding. Although the authors do not attempt to explain the sudden rise in relative risk for children diagnosed more recently, they suggest that childhood rhabdomyosarcoma survivors may have a genetic predisposition to cancer in addition to the effects of exposure to chemotherapy and radiotherapy at a young age.[17]

Endocrine-related second primary cancers featured heavily among longer-term survivors in our study, most notably thyroid and female breast cancers. Radiotherapy is the most important risk factor for the subsequent development of these two solid cancers with only weak evidence available for other possible influences.[18] Chemotherapy for childhood cancer is known to carry an increased risk, particularly for haematological malignancies,[19] with the most common form of subsequent disease being therapy-related acute myeloid leukaemia (t-AML).[20] It should be noted that around 80% of t-AMLs, and 30% of all second primary cancers, in our study were diagnosed within the initial five years, highlighting the importance of commencing follow-up time from close to the first diagnosis. While it is possible that lifestyle and environmental factors may also contribute to the excess risk of second cancers among childhood cancer survivors, they are reported to have similar health behaviours to their peers with the exception of generally being less physically active.[21]

Complementing our findings, data from elsewhere have shown that survivors of childhood cancer remain at increased risk of cancer many decades after the initial diagnosis,[14, 22] highlighting the importance of ongoing surveillance. Despite this reality, a recent Australian survey of long-term survivors of childhood cancer found that over 60% believed that they were not at risk of subsequent neoplasms,[23] indicating the difficulty of delivering appropriate and meaningful information to survivors.

A major strength of our study is the population-based cohort with national coverage of second primary cancers. All data used in this investigation have been independently recorded for administrative purposes at the time of diagnosis, removing the potential for information or recall bias. To reduce the possibility of increased medical surveillance of newly diagnosed cancer patients leading to detection bias, we only considered primary cancers that were not identified around the same time as the first cancer, with a minimum of two months between first and second diagnosis.

It is acknowledged that some second primary cancers diagnosed soon after the establishment of the QCR in 1983 may have been incorrectly classified as first primary cancers, but this is likely to have had only a minimal impact on the results. We were restricted in our abillity to report on second primary cancers following the administration of specific chemotherapeutic agents, as this level of detail for treatments is currently unavailable in the ACCR. Another limitation of the study was that the results were not adjusted for potential confounders; for example, cancer risk factors are not collected by the ACCR and stage at diagnosis was only assigned for a subset of more recent cases (2006 to 2014).

Second primary cancers continue as a lifelong hazard for survivors of childhood cancer and have been identified as a leading cause of treatment-related mortality among childhood cancer survivors.[24, 25] Whereas the size of the effect may vary depending on the study design, the finding that survivors of childhood cancer are at significantly increased relative risk of subsequent cancers appears to be universal, with the risk gradually diminishing over time from first diagnosis but never returning to the same level as that of the general population. Over past decades there have been advances in treatment for childhood cancer that have brought significantly improved survival for many childhood malignancies. The challenge remains to find ways of reducing treatment-associated morbidity while maintaining survival at equivalent levels.

Access to study data: The authors had full access to all of the data (including statistical reports and tables) in the study.

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

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