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Population-based survival of children in New Zealand diagnosed with cancer during 1990–1993

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Abstract

In this study, we have aimed to characterise the survival of all 0–14 year-old New Zealand children who were diagnosed with cancer during 1990–1993. Four hundred and nine children were followed up using two largely independent sources. We calculated Kaplan–Meier survival probabilities and investigated various prognostic factors using the Cox model. Five-year survival for all cancers was 66% (95% confidence interval (CI) 62–71%) and for acute lymphoblastic leukaemia it was 70% (CI 62–79%). Cancers with particularly favourable prognoses (followed by their respective 5-year survival probabilities) included: retinoblastoma 100% (CI 74-100%), Hodgkin's disease 93% (CI 79–100%), non-Hodgkin's lymphoma 87% (CI 73-100%) and osteosarcoma 91% (CI 74–100%). Cancers with poor prognoses included: neuroblastoma 35% (CI 14–56%), rhabdomyosarcoma 42% (CI 14–70%) and central nervous system tumours 49% (CI 38–60%). Girls with any cancer had a significantly lower risk of death than boys. Generally, survival for childhood cancers in New Zealand increased greatly between 1961–1965 and 1990–1993. Nevertheless, outcomes for some cancers remained poor.

Keywords: Child; Neoplasms; Survival; Prognosis; New Zealand

1. Introduction

New Zealand is a developed but geographically isolated nation with fewer than 15 specialist paediatric oncologists covering our widely dispersed population. Here, cancer is newly diagnosed in approximately 130 children under the age of 15 years annually. It is the third most common cause of death in this age group [1].

The last national childhood cancer survival study reported in New Zealand investigated children diagnosed between 1961 and 1976 [2], the formative years of paediatric oncology services. Since that time, overseas population-based studies have demonstrated astounding increases in survival for most childhood cancers [3–6]; largely attributable to increased adoption of international therapeutic protocols.

In 1999, a visiting reviewer of the New Zealand childhood cancer service expressed his disappointment at the lack of dependable and recent data on childhood cancer survival in New Zealand. We aimed to address this paucity of information by reporting on the survival of a national sample of 0–14 year-old children diagnosed with cancer between the beginning of 1990 and the end of 1993. Additionally, we have investigated the effects of various prognostic factors on survival for all cancers combined, acute lymphoblastic leukaemia (ALL) and astrocytoma (the latter being the most numerous single diagnoses).

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2. Patients and methods

All 13 regional ethics committees in New Zealand approved this study.

2.1. Participants

The methods for accruing the children in this study and detailed information on their cancers are described elsewhere [7,8]. Multiple sources including the New Zealand Cancer Registry were used to ascertain all children aged 0–14 years who were diagnosed with a malignancy during the 4-year period 1990–1993. Ascertainment was virtually complete [7]. Of the 409 cancers identified, 398 (97.3%) were verified microscopically [8]. Five children (1.2%) received a diagnosis of an unspecified malignancy. All cancers were classified according to the International Classification of Childhood Cancer (ICCC) [9].

2.2. Follow-up

We followed the 409 children up until May 2003 using two major sources of survival data. Firstly, the New Zealand Health Information Service (NZHIS) provided vital status information from three distinct datasets: the Mortality Collection, the New Zealand Cancer Registry and the National Health Index. The sources of information for these datasets included New Zealand death certificates and admission/discharge systems from public hospitals throughout the country. Data provided included date and underlying cause of death or the last date each child could be confirmed to be alive and, for the purpose of controlling potential confounding in the comparative analyses, the ethnicity of each child. Secondly, we asked doctors throughout New Zealand to complete vital status question forms for each child in our study who had been under their care. Doing so provided an opportunity to detect overseas deaths as well as verify the data from the NZHIS.

In total, we received some survival data for all 409 (100%) of the children in our study. Seven (1.7%) of the children were lost to follow-up before accruing 5 years of observation whilst 63 (15.4%) were censored prior to accruing 10 years of follow-up. Three overseas deaths were detected. The mothers of 303 of the children in this study identified a single ethnic group for their children during an earlier case-control study [10]. When available, we used this ethnicity data from the mothers, otherwise we used "prioritised" ethnicity [11] from the National Health Index within the NZHIS (whereby any child identified as Maori in any of the three fields supplied was coded as Maori, any child with Pacific (Islander) in any of the three fields was coded as Pacific unless they also identified with Maori and all other ethnicities were identified as non-Maori non-Pacific (predominantly people of European descent)).

2.3. Statistical analyses

We calculated one-, three-, five- and ten-year survival probabilities using the Kaplan–Meier method [12] for all cancers combined and individual diagnostic groups. Two children died of causes unrelated to their cancer or its treatment and were censored at their deaths making the survival probabilities cause-specific. Access to health care and public attitudes influencing promptness of presentation to health care systems are crucial factors affecting population-based childhood cancer survival. Therefore, we included the one child identified by 'death certificate only' in survival analyses by assigning her a survival time of zero. Standard errors for all survival probabilities were calculated by logistic transformation and application of the standard binomial formula. Corresponding 95% confidence intervals were calculated with maximum bounds of 0% or 100%. In cases where survival was 100%, the binomial formula gives a standard error of zero. In these situations, we used exact confidence intervals from "Scientific Tables" [13].

The Cox proportional hazards model [14] was used to assess the influence of various prognostic factors on survival for all cancers combined, ALL and astrocytoma. The factors of particular interest were sex and age at diagnosis, although to prevent over-fitting, age at diagnosis was not included in the model for astrocytoma. We included place of treatment (Auckland hospitals or elsewhere) as a potential confounder in all models as studies have shown that survival for childhood cancer varies by type and size of treatment centre [15,16]. Ethnicity (Maori, Pacific, non-Maori non-Pacific) was also included in the model for all cancers combined since overseas research has demonstrated differences in survival according to ethnicity [3,17] and health disparities exist between ethnic groups in New Zealand [11]. Survival by ethnicity as well as an assessment of the accuracy of ethnicity data stored at the NZHIS will be reported in a separate paper. We tested the proportional hazards assumption for each variable in the Cox models using log-log plots. All statistical analyses were carried out using SPSS® for Windows®, release 11.5.0.

3. Results

3.1. Survival by diagnosis

Table 1 shows cause-specific survival probabilities by diagnosis. Overall, 5-year survival for children diagnosed with any cancer between 1990 and 1993 was 66% (95% confidence interval (CI), 62–71%) and at 10-years was 62% (CI 57–67%). For ALL, survival at 5 years from diagnosis was relatively favourable (70%,

Table 1
Cause-specific Kaplan–Meier survival for children aged 0–14 years diagnosed with cancer in New Zealand between 1990 and 1993

Diagnosis (ICCC category or code)	*n*	Survival probability (95% confidence interval), (%)			
		1-year	3-year	5-year	10-year
Leukaemia (I)	144	90 (85–95)	72 (65–79)	65 (57–73)	57 (49–65)
Acute lymphoblastic leukaemia (Ia)	111	94 (89–98)	77 (70–85)	70 (62–79)	60 (50–69)
Acute non-lymphoblastic leukaemia (Ib)	26	77 (61–93)	54 (35–73)	50 (31–69)	50 (31–69)
Lymphomas (II)	37	92 (83–100)	92 (83–100)	89 (79–99)	86 (75–98)
Hodgkin's disease (IIa)	14	100 (77–100)	100 (77–100)	93 (79–100)	86 (67–100)
Non-Hodgkin's lymphoma (IIb, IIc, IIe)	23	87 (73–100)	87 (73–100)	87 (73–100)	87 (73–100)
CNS malignancies (III)	80	62 (51–73)	52 (41–63)	49 (38–60)	45 (34–56)
Astrocytoma (IIIb)	44	66 (52–80)	59 (45–74)	55 (40–69)	52 (37–67)
Primitive neuroectodermal tumour (IIIc)	15	67 (43–91)	53 (28–79)	53 (28–79)	53 (28–79)
Sympathetic nervous system tumours (IV)	21	57 (36–78)	38 (17–59)	38 (17–59)	38 (17–59)
Neuroblastoma (IVa)	20	55 (33–77)	35 (14–56)	35 (14–56)	35 (14–56)
Retinoblastoma (V)	12	100 (74–100)	100 (74–100)	100 (74–100)	100 (74–100)
Renal tumours (VI)	25	92 (81–100)	80 (64–96)	80 (64–96)	80 (64–96)
Wilms' tumour (VIa)	24	96 (88–100)	83 (68–98)	83 (68–98)	83 (68–98)
Hepatic tumours (VII)	7	86 (60–100)	86 (60–100)	86 (60–100)	86 (60–100)
Hepatoblastoma (VIIa)	6	100 (54–100)	100 (54–100)	100 (54–100)	100 (54–100)
Malignant bone tumours (VIII)	20	95 (85–100)	95 (85–100)	79 (61–97)	79 (61–97)
Osteosarcoma (VIIIa)	12	100 (74–100)	100 (72–100)	91 (74–100)	91 (74–100)
Ewing's sarcoma of bone (VIIIc)	7	86 (60–100)	86 (60–100)	57 (20–94)	57 (20–94)
Soft tissue sarcomas (IX)	23	82 (66–98)	45 (25–66)	45 (25–66)	40 (19–61)
Rhabdomyosarcoma (IXa)	12	92 (76–100)	42 (14–70)	42 (14–70)	42 (14–70)
Germ cell, trophoblastic and other gonadal (X)	23	83 (67–98)	83 (67–98)	83 (67–98)	83 (67–98)
Carcinomas and other malignant epithelial (XI)	16	94 (82–100)	88 (71–100)	81 (62–100)	81 (62–100)
All cancers	409	83 (79–86)	70 (66–75)	66 (62–71)	62 (57–67)

n, number of cases; ICCC, International Classification of Childhood Cancer.

CI 62–79%), however late mortality led to noticeably lower 10-year survival (60%, CI 50–69%). Both Hodgkin's disease and non-Hodgkin's lymphoma had encouraging prognoses with 5-year survival probabilities of 93% (CI 79–100%) and 87% (CI 73–100%), respectively. Very high 5-year survival was also achieved for retinoblastoma (100%, CI 74–100%), hepatoblastoma (100%, CI 54–100%) and osteosarcoma (91%, CI 74–100%), although there were small numbers of children in each of these categories. In contrast, CNS malignancies, sympathetic nervous system tumours and soft tissue sarcomas carried poor prognoses with 5-year survival ranging between 38% and 49%.

3.2. Prognostic factors

Table 2 shows the risk of death (hazard ratio) for children in various prognostic groups who were diagnosed with any cancer, ALL or astrocytoma. The risk of death for girls with any cancer relative to boys was 0.71 (CI 0.52–0.98, $P = 0.04$). Although there were minor differences in prognosis for children with any cancer by age of diagnosis, none reached statistical significance. For ALL, female sex and age between 1 and 9 years were non-statistically significant beneficial prognostic indicators. For astrocytoma, girls had a non-significantly poorer prognosis than boys (hazard ratio 1.57, CI 0.65–3.80, $P = 0.32$).

4. Discussion

Overall, two thirds (66%) of the children in this study survived at least 5 years from diagnosis. Most haematopoietic and lymphoid cancers carried favourable prognoses whilst survival for tumours of the central and sympathetic nervous systems was poor. In general, girls had more favourable outcomes than boys.

Population-based childhood cancer survival probabilities relate to a range of factors including, but not limited to, the success of paediatric oncology services in the context of a population's social and economical milieu. Comparisons of such probabilities are fraught with issues of data comparability and cannot be used to directly assess the efficacy of particular cancer treatments. Before comparing our survival figures with those from other population-based studies, it is necessary to appraise our data quality and consider some important caveats.

A previous capture–recapture study showed that case accrual for the dataset of 409 children used in this study was essentially complete; probably only one child was missed [7]. Rigorous characterisation of the cancers and careful follow-up were important features of this and other recent population-based studies [5,18,19]. Nevertheless, this was a comparatively small study and hence the survival probabilities and comparisons, especially for rare cancers, were susceptible to chance varia-

Table 2
Multiple Cox regression analyses of the effects of prognostic factors on survival for children diagnosed with any cancer, ALL or astrocytoma in New Zealand between 1990 and 1993

	n	HR (95% CI)	*P*-value
All cancers[a]			
Sex			
Boys	216	1.00[b]	–
Girls	192	0.71 (0.52–0.98)	0.04
Age at diagnosis			
<1 year	41	1.23 (0.70–2.15)	0.50
1–4 years	143	1.00[b]	–
5–9 years	107	1.19 (0.80–1.78)	0.40
10–14 years	117	0.91 (0.60–1.36)	0.63
Acute lymphoblastic leukaemia			
Sex			
Boys	60	1.00[b]	–
Girls	51	0.82 (0.45–1.52)	0.54
Age at diagnosis			
<1 year	4	1.87 (0.44–7.88)	0.39
1–9 years	90	1.00[b]	–
10–14 years	17	2.05 (0.95–4.42)	0.07
Astrocytoma			
Sex			
Boys	31	1.00[b]	–
Girls	13	1.57 (0.65–3.80)	0.32

n, number of cases; HR, hazard ratio; CI, confidence interval.
All Cox models include confounder treatment centre (Auckland hospitals, elsewhere).
[a] Cox model includes confounder ethnicity (Maori, Pacific, non-Maori non-Pacific).
[b] Reference category.

tion. Any selection or information bias is likely to have been negligible, however confounders such as sex, age, stage and diagnosis could have affected the comparisons with other studies.

Between the two periods 1971–1976 and 1990–1993, 5-year survival for all childhood cancers diagnosed in New Zealand increased from 37% to 66% (Fig. 1) [2]. One can be confident that this reflects a true and significant improvement in childhood cancer services in New Zealand.

Our survival figures can be compared with data from whole countries (or aggregates of countries) in the EUROCARE-3 study whose registries reportedly had complete population coverage. Overall 5-year survival probabilities for such countries ranged from 44.9% (Estonia) to 90.1% (Iceland) for children diagnosed between 1990 and 1994 [18]. These probabilities were standardised to the age distribution of all children in the EUROCARE-3 database. Fortuitously, this distribution almost exactly matches our own (proportion of 0–4 year-old children in both studies = 45%) (Dr. G. Gatta, Istituto Nazionale Tumori, Italy). As a rule, survival probabilities for Eastern European countries were lower than New Zealand's whereas the British, Scandinavian, Western and Central European probabilities were higher. Speculative explanations for these differences include: chance variation, differences in the distribution of several important prognostic factors

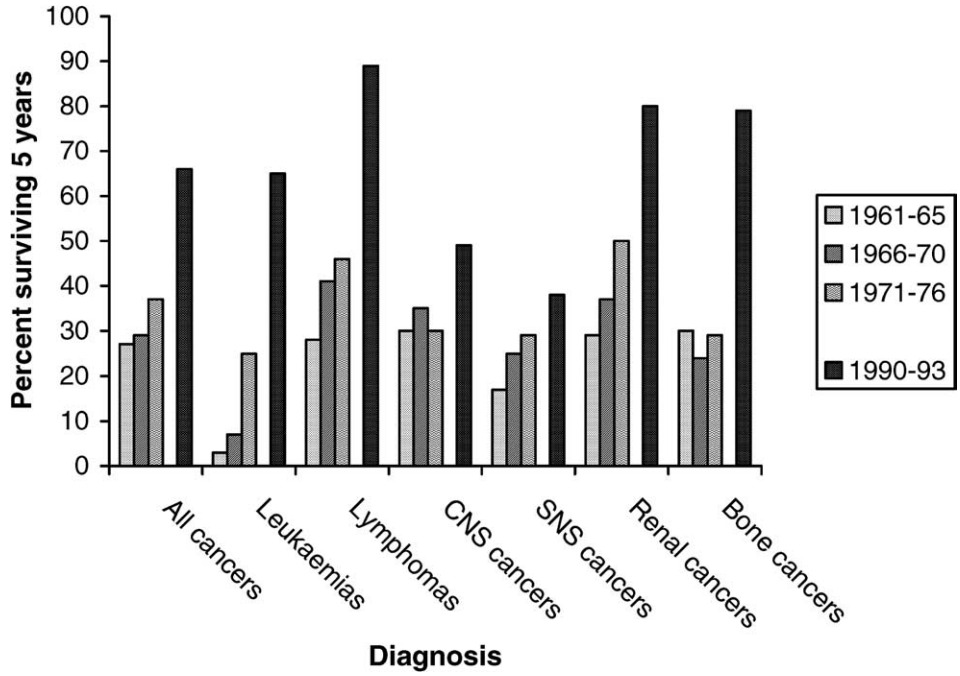

Fig. 1. Comparison of 5-year survival probabilities for childhood cancers in New Zealand diagnosed during the periods 1961–1965, 1966–1970, 1971–1976 and 1990–1993. CNS, central nervous system; SNS, sympathetic nervous system. Survival information for the earliest three periods was taken from an earlier study [2]. The cancers in the earlier study were coded according to the International Classification of Diseases (ICD) 7th and 8th revisions, whereas the cancers in this study were coded according to the International Classification of Childhood Cancer (ICCC). Cancers included in the above categories were: leukaemias (ICD 204-7; ICCC I), lymphomas (ICD 200-2; ICCC II), CNS cancers (ICD 191-2 minus 192.5 (cancers of the sympathetic nervous system); ICCC III), SNS cancers (ICD 192.5; ICCC IV), renal cancers (ICD 189; ICCC VI), bone cancers (ICD 170; ICCC VIII).

(including accrual period) or differences in paediatric oncology services.

Fig. 1 shows that since 1971–1976, survival for individual groups of cancers in New Zealand has reliably increased. For 'leukaemias combined', survival at 5 years improved almost 22-fold from 3% to 65% between 1961–1965 and 1990–1993 [2]. This undoubtedly reflects the delivery of more intensive chemotherapeutic protocols to a greater proportion of childhood leukaemia sufferers as well as the availability of bone marrow transplantation for acute non-lymphoblastic leukaemia and other high-risk subtypes. A large proportion of the children with ALL in this study was treated according to the Australia and New Zealand Children's Cancer Study Group (ANZCCSG) study V or VI protocols. The 5-year survival probability for ALL in this study (70%, CI 62–79%) was lower than the age-adjusted probabilities for several of the comparable countries in the EUROCARE-3 study (range from 84.8% (Nordic countries) to 80.3% (Denmark)) [18]. Chance and differences in the distribution of prognostic indicators such as white cell count and histological subtype may have contributed to this finding. However, differential age distribution is unlikely to have been important since the proportion of 1–9 year-olds in both studies was 81% (Dr. G. Gatta, Istituto Nazionale Tumori, Italy). One further speculative explanation for this finding is that salvage therapy for children relapsing multiple times may have been less aggressive in New Zealand than in many European countries. Our relatively substantial late mortality lends weight to this theory.

The improvement in outcomes for CNS tumours and sympathetic nervous system cancers in New Zealand has been less dramatic (Fig. 1). Other studies have also demonstrated comparatively modest progress for these cancers [20–22]. Nevertheless, the 5-year survival probabilities for CNS tumours (49%, CI 38–60%) and neuroblastoma (35%, CI 14–56%) were poor when compared to the probabilities achieved by countries with population-based childhood cancer registration in the EUROCARE-3 study (range for CNS tumours, 73.0% (Nordic countries) to 60.0% (United Kingdom) and for neuroblastoma, 62.1% (Germany) to 41.3% (Denmark)) [18]. During the early 1990s, paediatric oncologists were not always involved in managing the treatment of children with brain tumours in New Zealand. This situation has now been remedied and outcomes for these tumours have almost certainly improved as a result. Survival from neuroblastoma is heavily influenced by age at diagnosis with infants generally carrying much more favourable prognoses [22]. The proportion of children <1 year old in this study was 30% whilst in the EUROCARE-3 study it was 25% (Dr. G. Gatta, Istituto Nazionale Tumori, Italy). This skewed distribution would have tended to differentially inflate New Zealand's survival probability.

Survival for lymphomas, renal tumours and bone tumours has improved markedly over the last three decades [2]. During the early 1990s, non-Hodgkin's lymphoma carried an especially impressive prognosis when compared with most European countries [18]. New Zealand children with this disease were generally treated according to ANZCCSG protocols similar to the regimens used today.

Our finding that girls with any cancer had a better overall prognosis than boys is consistent with a previous Canadian study [23]. This may be partly due to a more favourable diagnostic distribution for girls. In this study, a greater proportion of CNS tumours was diagnosed in boys (64%) whilst a much greater proportion of renal tumours occurred in girls (72%). Many studies have shown that girls with ALL generally have a slightly better prognosis than boys with this disease [5,24,25]; possibly due to a different immunophenotype distribution [26]. Our results, although not statistically significant, confirm this prognostic effect. Other studies have shown that sex has little influence on outcomes for CNS cancers [21,27,28]. In this study, sex did not significantly affect prognosis for astrocytoma but, due to small numbers, even a large effect could not be ruled out.

The effects of age at diagnosis on prognosis for children with any cancer or ALL were not statistically significant. However, 1–9 year-olds with ALL did appear to have a better prognosis than both infants and 10–14 year-olds. A similar pattern has been found in other studies [5,23–25].

Survival studies are necessarily historical by the time they are published. The survival probabilities achieved in this study should be put in the context of a steadily decreasing childhood cancer mortality rate and a stable incidence rate in New Zealand between the early 1980s and 1997 [29]. Since the children in this study were diagnosed, New Zealand's childhood cancer services have become increasingly centralised. Currently there are three tertiary paediatric oncology centres, where previously there were five. A greater proportion of children are now treated on international trial-based protocols. This study shows that survival for childhood cancers in New Zealand uniformly increased between the early 1970s and early 1990s, though only to a comparatively modest extent for CNS and sympathetic nervous system tumours. Further improvement is likely to have occurred since then.

Conflict of interest statement

None declared.

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