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ABSTRACT

Background

While impressive gains in childhood cancer survival have been reported both in Canada and internationally, it has been almost 15 years since the last comprehensive evaluation of Canadian data.

Data and methods

Data are from the population-based Canadian Cancer Registry, record-linked to the Canadian Vital Statistics Death database. Children aged 0 to 14 diagnosed with new primary malignant cancers from 1992 to 2017 in Canada except Quebec were included. Overall survival was measured using observed survival proportions (OSPs). Estimates for the 2013-to-2017 period were predicted using the period method; otherwise, the cohort method was used.

Results

For the 2013-to-2017 period, five-year OSPs were at least 90% for 10 of 24 individual cancer groups or subgroups reported. Survival was highest for thyroid carcinomas (100%) and Hodgkin lymphomas (99%) and lowest for other gliomas (42%). A significant increase in the five-year OSP from the 1992-to-1996 period (77%) to the 2013-to-2017 period (84%) was observed for all childhood cancers combined, but not since the 2003-to-2007 period. The greatest increase was for chronic myeloproliferative diseases (35.4 percentage points); for lymphoid leukemias, survival increased from 85% to 93%. Survival was relatively poor at baseline for hepatic tumours, malignant bone tumours, and soft tissue and other extraosseous sarcomas, and it remained virtually unchanged. Once children survived five years, the probability of surviving another five years exceeded 95% across most diagnoses.

Interpretation

Significant improvements in both short- and long-term paediatric cancer survival have been made in Canada since the early to mid-1990s. These findings are clinically meaningful and are likely to be reassuring to families.

Keywords

conditional survival, malignant neoplasms, paediatrics, population surveillance, prognosis, registries, survival analysis

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What is already known on this subject?

- Much of what is known about expected outcomes for children diagnosed with cancer has been derived from clinical trials. However, these results may not be generalizable to children not enrolled in clinical trials and, therefore, may not reflect outcomes at the population level.
- While impressive gains in childhood cancer survival have been reported both in Canada and internationally, it has been almost 15 years since the last comprehensive evaluation of Canadian data.
- Conditional survival, or the probability of continued survival given an initial survival period, has not been well described for paediatric cancer.

What does this study add?

- Five-year observed survival was at least 90% in Canada for the 2013-to-2017 period for over 40% of the diagnostic groups or subgroups reported.
- Childhood cancer survival in Canada was highest for thyroid carcinomas and Hodgkin lymphomas, and lowest for other gliomas, a subgroup of the central nervous system neoplasms diagnostic group.
- Both short- and long-term survival for all childhood cancers combined has significantly increased in Canada from the 1992-to-1996 period to the 2013-to-2017 period. Survival increased the most over this period for chronic myeloproliferative diseases. However, there has been little improvement over time for some cancer types with poor prognosis, including hepatic tumours, malignant bone tumours, and soft tissue and other extraosseous sarcomas.
- The long-term survival of children persisting through the first few years after diagnosis was very favourable. Once children survived five years, the probability of surviving another five years exceeded 95% across most diagnoses.

Each year in Canada, approximately 1,000 children aged 0 to 14 years are diagnosed with cancer, and 110 die from the disease.[1] Worldwide, impressive gains in survival have been made over time.[2-4] These advances can primarily be attributed to a deeper understanding of paediatric cancer biology, combined with successive, multi-institutional clinical trials.[5] As a result, much of what is known about expected outcomes and risk factors is derived from clinical trials. Clinical trials provide excellent insight into how regimens perform within the context of close monitoring, strict application of eligibility criteria and adherence to protocol therapy. However, these results may not be generalizable to children not enrolled in clinical trials. For example, observational studies have suggested that children enrolled in clinical trials differ in terms of demographic characteristics and cancer-specific features from those not enrolled. Consequently, clinical trial results may not reflect outcomes at the population level.[6,7]

One way to overcome the limitation of generalizability is through the use of population-based cancer registries such as the Canadian Cancer Registry (CCR). A previous analysis using the CCR found that paediatric cancer incidence rates were stable while rates of death decreased after 1985.[8] While this baseline evaluation provided important information from a national perspective, several important questions remain. Gaps include the description of population-based survival for a contemporary cohort—the last comprehensive evaluation was published in 2007[2]—and the evaluation of whether improvement in survival has been constant over time and by diagnosis. In addition, conditional survival, or the probability of continued survival given an initial survival period, has not been well described for paediatric cancer, whereas such analysis has been performed for adult cancer.[9] Such a description would be meaningful to both patients and health care providers.

Consequently, the objectives of this study were to describe survival, improvement in survival over time and conditional survival for paediatric cancer patients in Canada. Using data from the CCR, the study presents short- and long-term predicted survival estimates for the five-year period from 2013 to 2017, for all childhood cancer diagnostic groups and for selected subgroups. Trends in survival, including those for all childhood cancers combined, are examined from the 1992-to-1996 period to the 2013-to-2017 period. Five-year survival estimates conditional on having already survived 1 to 10 years are also provided.

Data and methods

Data sources and definitions

The data source was a pre-existing analytic file created by linking CCR cases diagnosed from 1992 to 2017 to mortality information complete through December 31, 2017, via Statistics Canada's Social Data Linkage Environment.[10] The CCR is a population-based database composed of cases diagnosed among Canadian residents since 1992. Each provincial and territorial

Table 1
Number of childhood cancer cases eligible for survival analyses and case distribution, by selected variables, ages 0 to 14, Canada excluding Quebec, 1992 to 2017

	Number	Percent
Age at diagnosis in years		
0 to 4	8,244	45.7
5 to 9	4,731	26.2
10 to 14	5,081	28.1
Sex		
Male	9,714	53.8
Female	8,342	46.2
Geographic area of diagnosis		
British Columbia	2,809	15.6
Alberta	2,572	14.2
Saskatchewan	791	4.4
Manitoba	871	4.8
Ontario	9,382	52.0
New Brunswick	512	2.8
Nova Scotia	613	3.4
Prince Edward Island	84	0.5
Newfoundland and Labrador	338	1.9
Territories	84	0.5
Method of diagnosis		
Histology	15,623	86.5
Radiology	482	2.7
Other	443	2.5
Unknown	1,508	8.4
ICCC category and description		
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	6,029	33.4
a. Lymphoid leukemias	4,673	25.9
b. Acute myeloid leukemias	868	4.8
c. Chronic myeloproliferative diseases	196	1.1
II. Lymphomas and reticuloendothelial neoplasms	2,133	11.8
a. Hodgkin lymphomas	731	4.0
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	713	3.9
c. Burkitt lymphoma	288	1.6
d. Miscellaneous lymphoreticular neoplasms	263	1.5
III. CNS and miscellaneous intracranial and intraspinal neoplasms	3,524	19.5
a. Ependymomas and choroid plexus tumour	339	1.9
b. Astrocytomas	1,600	8.9
c. Intracranial and intraspinal embryonal tumours	851	4.7
d. Other gliomas	532	2.9
IV. Neuroblastoma and other peripheral nervous cell tumours	1,230	6.8
a. Neuroblastoma and ganglioneuroblastoma	1,211	6.7
V. Retinoblastoma	411	2.3
VI. Renal tumours	955	5.3
a. Nephroblastoma and other nonepithelial renal tumours	904	5.0
VII. Hepatic tumours	282	1.6
VIII. Malignant bone tumours	794	4.4
a. Osteosarcomas	406	2.2
c. Ewing tumour and related sarcomas of bone	311	1.7
IX. Soft tissue and other extraosseous sarcomas	1,139	6.3
a. Rhabdomyosarcomas	572	3.2
d. Other specified soft tissue sarcomas	335	1.9
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	595	3.3
b. Malignant extracranial and extragonadal germ cell tumours	147	0.8
c. Malignant gonadal germ cell tumours	240	1.3
XI. Other malignant epithelial neoplasms and malignant melanomas	728	4.0
b. Thyroid carcinomas	275	1.5
f. Other and unspecified carcinomas	259	1.4
XII. Other and unspecified malignant neoplasms	209	1.2

Notes: CNS = central nervous system; ICCC = International Classification of Childhood Cancer. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. All estimates are based on invasive behaviour cases only. Percentages may not sum to 100% because of rounding.

Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

cancer registry provides demographic and cancer-specific information to Statistics Canada in a standard format. Annual submissions by jurisdictions include additions and revisions to data submitted in previous years.[11] The mortality information was obtained from the Canadian Vital Statistics Death database (CVSD), whose scope is all deaths in Canada,[12] and from the

T1 personal master file (as reported on tax returns). The use of death information from tax returns facilitated the identification of additional death events of patients in the CCR that may not have been included in the CVSD, such as out-of-country deaths. This source was also used to validate the date of death when discrepancies arose between dates in the CCR and the CVSD. The analytic file followed the multiple primary coding rules of `the International Agency for Research on Cancer.[13] Survival time was measured in days. More information on the linkage process and on the resulting death-linked analytic file is available upon request.

Cancers in children aged 0 to 14 years were classified according to the Surveillance, Epidemiology, and End Results (SEER) Program update[14] of the International Classification of Childhood Cancer, Third Edition (ICCC-3).[15] The update was in response to new morphology codes introduced by the World Health Organization.[16] For 19 cases with a histology code of 8963 (malignant rhabdoid tumour) and a topography code of C71 (brain) that would otherwise not have been mapped to a diagnostic group, the histology code was edited to 9508 (atypical teratoid/rhabdoid tumour) and the cases included in diagnostic subgroup IIIc.

Inclusion and exclusions

New malignant primary cancers diagnosed in children aged 0 to 14 years were initially included. Cases from Quebec were excluded because cancer incidence data from this province had not been submitted to the CCR since the 2010 data year. Exclusions then proceeded in a stepwise manner, starting with cases for which the diagnosis was established through autopsy only or death certificate only (0.5% excluded). The year of death, if applicable, was known in each case. The dataset was further restricted to first primary cancers per person per diagnostic subgroup diagnosed from 1992 to 2017 (0.4%

Table 2
Predicted observed survival proportions by diagnostic group and selected subgroup, selected survival durations, ages 0 to 14 at diagnosis, Canada excluding Quebec, 2013 to 2017

	Survival duration											
	1 year			3 years			5 years			10 years		
		95% CI			95% CI			95% CI			95% CI	
Diagnostic group / subgroup	OSP (%)	from	to	OSP (%)	from	to	OSP (%)	from	to	OSP (%)	from	to
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	95	93	96	89	88	91	88	87	90	87	85	89
a. Lymphoid leukemias	97	96	98	94	92	95	93	92	95	92	90	94
b. Acute myeloid leukemias	81	74	86	66	59	73	65	57	71	63	55	69
c. Chronic myeloproliferative diseases	97	87	99	93	83	97	90	79	95	86	73	93
II. Lymphomas and reticuloendothelial neoplasms	96	94	97	94	91	96	92	89	94	90	88	93
a. Hodgkin lymphomas	99	95	100	99	95	100	99	95	100	99	95	100
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	93	89	96	88	82	92	84	78	89	80	74	86
c. Burkitt lymphoma	97	89	99	96	87	99	94	84	98	94	84	98
d. Miscellaneous lymphoreticular neoplasms	96	90	98	95	89	98	94	88	97	94	88	97
III. CNS and miscellaneous intracranial and intraspinal neoplasms	84	81	87	75	71	78	72	69	75	69	66	72
a. Ependymomas and choroid plexus tumour	96	88	99	84	74	91	78	67	86	68 [E]	56	78
b. Astrocytomas	88	84	91	83	78	87	82	78	86	82	77	85
c. Intracranial and intraspinal embryonal tumours	85	79	90	75	68	81	71	64	78	66	58	73
d. Other gliomas	64	54	72	44	34	53	42	33	51	40	31	49
IV. Neuroblastoma and other peripheral nervous cell tumours	96	92	97	90	85	93	84	79	88	80	75	85
a. Neuroblastoma and ganglioneuroblastoma	95	92	97	89	85	93	84	79	88	80	75	85
V. Retinoblastoma	100	..	..	94	85	98	94	85	98	93	84	97
VI. Renal tumours	98	95	99	96	92	98	96	91	98	94	89	96
a. Nephroblastoma and other nonepithelial renal tumours	98	95	99	97	92	98	96	92	98	95	90	97
VII. Hepatic tumours	84 [E]	71	92	72 [E]	58	82	72 [E]	58	82	72 [E]	58	82
VIII. Malignant bone tumours	97	92	99	76	68	82	72	64	78	67	59	74
a. Osteosarcomas	95	87	98	70 [E]	59	79	65 [E]	53	74	59 [E]	48	69
c. Ewing tumour and related sarcomas of bone	98	88	100	82	70	90	79 [E]	66	87	75 [E]	62	84
IX. Soft tissue and other extraosseous sarcomas	90	85	93	75	69	80	70	64	76	69	63	74
a. Rhabdomyosarcomas	92	85	96	74	65	81	69	60	77	68	59	76
d. Other specified soft tissue sarcomas	87	77	93	75	64	84	71 [E]	60	80	68 [E]	56	77
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	92	86	96	91	85	95	91	85	95	91	85	95
b. Malignant extracranial and extragonadal germ cell tumours	91	75	97	91	75	97	91	75	97	91	75	97
c. Malignant gonadal germ cell tumours	97	83	100	97	83	100	97	83	100	97	83	100
XI. Other malignant epithelial neoplasms and malignant melanomas	96	92	98	93	88	96	92	86	95	91	86	94
b. Thyroid carcinomas	100	..	..	100	..	..	100	..	..	100	..	..
f. Other and unspecified carcinomas	97	90	99	92	84	97	88	78	94	86	74	93
XII. Other and unspecified malignant neoplasms	80 [E]	55	92	80 [E]	55	92	80 [E]	55	92	80 [E]	55	92

.. not available for a specific reference period

E use with caution

Notes: OSP = observed survival proportion; CI = confidence interval; CNS = central nervous system. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. All estimates are based on invasive behaviour cases only. The use of caution is suggested in the interpretation of estimates associated with an unrounded standard error > 0.05 and ≤ 0.10.

Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

excluded).[17-20] For children with multiple primary cancers within the same diagnostic group, only the first cancer was included in analyses at the diagnostic group level (0.1% excluded). These exclusions were incorporated to avoid including two deaths for a single person in the same survival analysis.[20] Finally, 15 remaining malignant cancer cases that did not map to a diagnostic group were excluded.

Diagnostic group and subgroup reporting

Results were reported for all 12 ICCC-3 diagnostic groups and for 21 of the 47 diagnostic subgroups, because of the rarity of diagnoses in many subgroups. Specifically, results were reported for subgroups when the standard error associated with their five-year observed survival proportion (OSP) for 2013 to 2017 was equal to or less than 0.05 (rounded), and the total number of cases diagnosed from 2008 to 2017 was at least 50. Consequently, in addition to the total cohort that included all eligible cancer cases, results for 24 independent individual ICCC-3 groups or subgroups were provided (i.e., the 21 subgroups plus 3 groups for which no subgroups were reported).

Statistical analysis

OSPs were derived using an algorithm developed by Dickman[21] and reported as percentages. Cases with the same date of diagnosis and death (excluding those diagnosed through autopsy only or death certificate only) were assigned one day of survival so they would be included in the survival estimates. Standard errors of OSP estimates were determined using Greenwood's method.[22] OSPs for all childhood cancers combined were calculated as a weighted average of sex- and diagnostic-group-specific estimates. The weights used were based on the sex and diagnostic group case-mix distribution of people aged 0 to 14 diagnosed with cancer in Canada, excluding Quebec, from 2010 to 2014 (see Appendix Table A1 for weights). Standard errors for estimates of this index were estimated by taking the square root of the sum of the squared, weighted, diagnostic-group-specific OSP standard errors. The most recent five-year period for which actual estimates can be calculated depends on the follow-up duration being examined (e.g., 2003 to 2007 for 10-year survival).

To describe changes in survival over time, survival estimates for three periods were presented: 1992 to 1996, 2003 to 2007 and 2013 to 2017. The period method[23] was used to predict OSPs for 2013 to 2017, while non-predictive (actual) estimates for 1992 to 1996 and 2003 to 2007 were calculated using the cohort method. Actual long-term survival estimates for people diagnosed in the most recent period will not be known for some time. The most recent cohort of cancer patients with complete five-year survival information was diagnosed in the 2008-to-2012 period. Empirical evaluations of period analysis have shown that this method provides estimates that closely predict the survival that is eventually observed for people diagnosed in the period of interest, particularly when survival is fairly constant.[24-26] When survival is generally increasing (or decreasing), a period estimate tends to be a conservative prediction of the survival that is eventually observed.[25,27]

The underlying methodology of both the cohort and the period methods is essentially the same, except the follow-up information used in the period method necessarily does not relate to a fixed cohort of people. Rather, estimates of period survival are based on the assumption that people diagnosed in the period of interest will experience the most recently observed conditional probabilities of OSPs.

The percentage point increase in five-year OSPs was used as the measure of improvement in survival. Differences in OSPs were calculated before rounding to one decimal place. The Z-test was used to determine P-values for between-time-period differences; the standard errors of differences were estimated by the square root of the sum of the variances associated with the two OSP estimates. P-values correspond to two-sided tests of the null hypothesis that the change in OSPs is zero, with a significance level of 0.05.

Five-year observed conditional survival proportions (OCSPs) were calculated as per five-year OSPs using only the data of people who had survived given selected times.[9,28] That is, they are the survival estimates for an additional 5 years among people who had already survived 1, 3, 5 or 10 years.

Results

Distribution of cases

From 1992 to 2017, 18,056 new cancer cases diagnosed in children 0 to 14 years of age were eligible and included in the survival analyses. Table 1 describes the demographics of the cohort and distribution of cases by ICCC-3 diagnostic group and selected subgroup. More boys (54%) than girls were diagnosed, slightly less than half of the children were diagnosed before the age of 5 (46%), and most of the cases were diagnosed in Ontario (52%). Among eligible cases, 87% were histologically verified, as were 94% of eligible cases for which the method of diagnosis was known. The most common diagnostic group was leukemias, myeloproliferative diseases and myelodysplastic diseases (33%), and the most common subgroup was lymphoid leukemias (26%).

Survival varied by cancer type

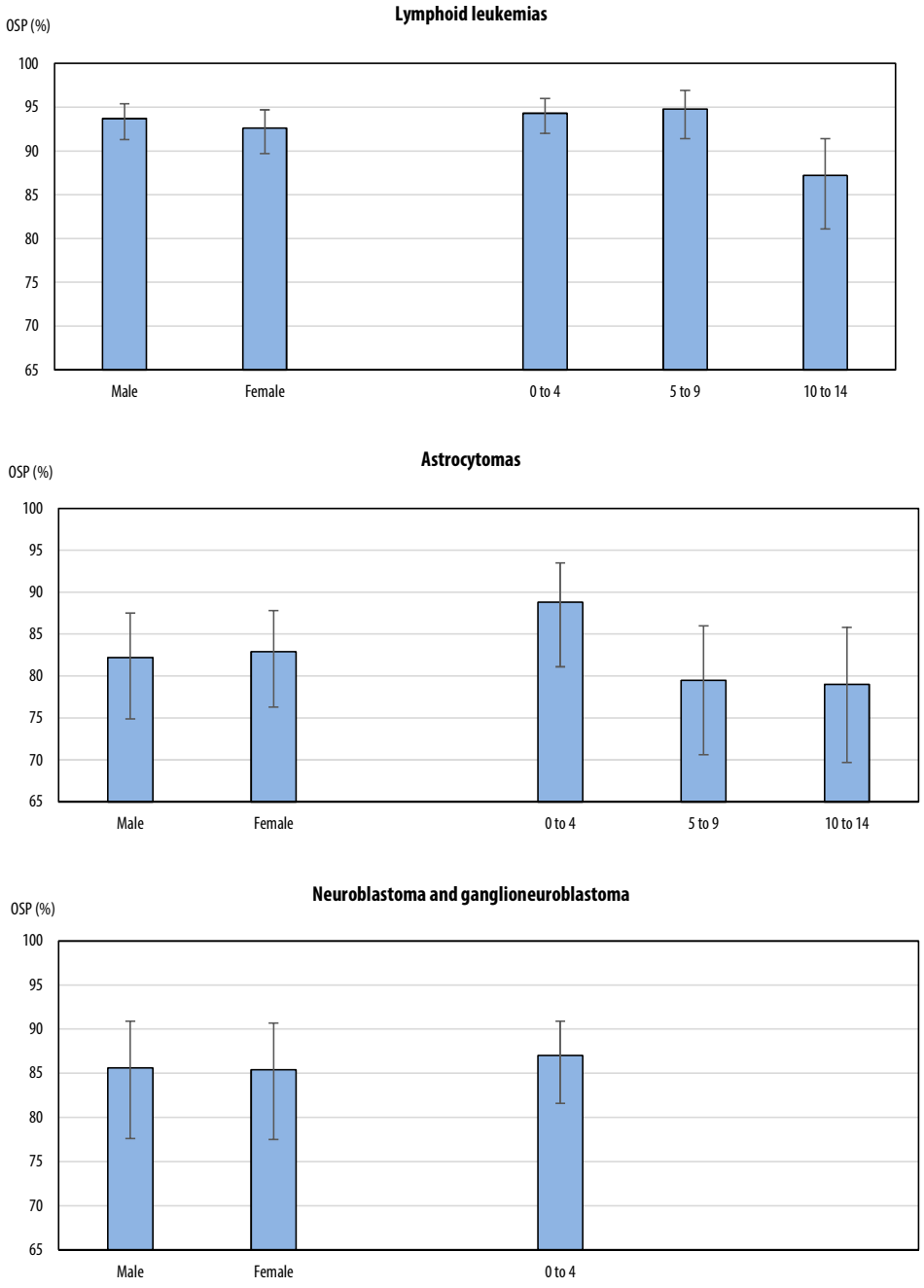
Table 2 presents 1-, 3-, 5- and 10-year predicted survival for cases diagnosed from 2013 to 2017. Five-year OSPs were at least 90% for 10 of the 24 individual ICCC-3 diagnostic groups or subgroups reported, and less than 80% for 9 others. Five-year survival was highest for thyroid carcinomas, at 100% (95% confidence interval [CI] undefined). This was followed by Hodgkin lymphomas, at 99% (95% CI = 95 to 100); malignant gonadal germ cell tumours, at 97% (95% CI = 85 to 100); and nephroblastoma and other nonepithelial renal tumours, at 96% (95% CI = 92 to 98). It was lowest for other gliomas, at 42% (95% CI = 33 to 51), followed by acute myeloid leukemias

(AMLs), at 65% (95% CI = 57 to 71), and osteosarcomas, at 65% (95% CI = 53 to 74). Median diagnostic-group-level OSPs were 95.5% (1-year), 88.5% (3-year), 84.0% (5-year) and 81.0% (10-year).

Survival did not vary by sex among leading cancer types

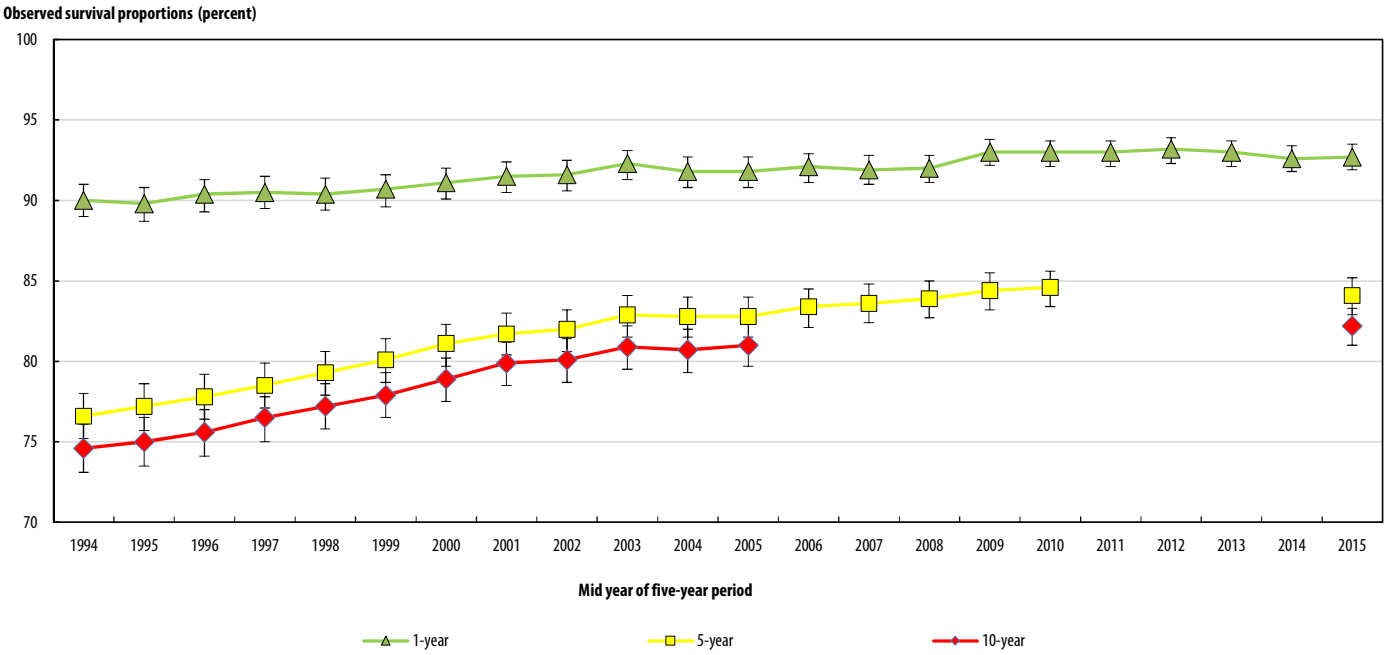
No significant sex-specific differences in five-year survival were observed among any of the three most commonly diagnosed cancer subgroups (Figure 1). For lymphoid leukemias, astrocytomas, and neuroblastoma and ganglioneuroblastoma, corresponding survival estimates among males and females differed by 1 percentage point or less. For lymphoid leukemias, five-year survival was higher among children diagnosed before the age of 10 than among those diagnosed between the ages of 10 and 14.

Figure 1
Five-year predicted observed survival proportions by sex and age group, selected cancers, ages 0 to 14, Canada excluding Quebec, 2013 to 2017



Notes: OSP = observed survival proportion. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. Results are not displayed for categories where the standard error of the point estimate exceeds 0.05. Vertical bars denote 95% confidence intervals.
Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

Figure 2
One-, 5- and 10-year observed survival proportions for all childhood cancers combined by overlapping 5-year period, ages 0 to 14, Canada excluding Quebec, 1992-to-1996 period to 2013-to-2017 period



Notes: Observed survival proportions (OSPs) were calculated as a weighted average of sex- and diagnostic-group-specific estimates. OSPs for the 2013-to-2017 period were predicted using period analysis. Vertical bars overlaid on the trend lines denote 95% confidence intervals. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry.
Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

Survival improved over time both overall and for selected cancers

Figure 2 depicts changes over time in 1-, 5- and 10-year OSPs for all childhood cancers combined, after adjustment for changes over time in the sex and diagnostic group distribution of cancer cases. Predicted OSPs for all childhood cancers combined for 2013 to 2017 were 93% (1-year), 84% (5-year) and 82% (10-year). Increases in the 5- and 10-year OSPs were virtually the same from the 1992-to-1996 period to the 2013-to-2017 period (7.5 to 7.6 percentage points), and 2.7 percentage points for 1-year survival. Increases were statistically significant for all three durations ($p < 0.001$).

A statistically significant increase in the five-year OSP from the 1992-to-1996 period to the 2013-to-2017 period was observed for 8 of the 24 individual ICCC-3 groups or subgroups reported (Tables 3-1 and 3-2). Diagnostic groups or subgroups experiencing the largest increases over time were chronic myeloproliferative diseases (35.4 percentage point increase), and ependymomas and choroid plexus tumour (32.1 percentage point increase).

Improvement in survival greatest in earliest period

For all childhood cancers combined, much of the 7.5 percentage point improvement in five-year survival occurred in the first half of the study period. The 1.3 percentage point increase from the 2003-to-2007 period to the 2013-to-2017 period was not statistically significant ($p = 0.134$). A similar pattern was also noted for six of the eight individual cancers exhibiting an increase over the entire period, including all three subgroups in the leukemias, myeloproliferative diseases and myelodysplastic diseases diagnostic group. The split was particularly noteworthy for AMLs, for which a 23.5 percentage point increase from the 1992-to-1996 period to the 2003-to-2007 period was followed by a non-significant 7.0 percentage point decrease from the 2003-to-2007 period to the 2013-to-2017 period. Conversely, all of the 9.5 percentage point increase for nephroblastoma and other nonepithelial renal tumours, and three-quarters of the 16.6 percentage point increase for intracranial and intraspinal embryonal tumours, occurred in the most recent period. A statistically significant increase since 2003 to 2007 was observed only for one other category (miscellaneous lymphoreticular neoplasms). For the other gliomas subgroup, a significant decrease since 2003 to 2007 followed a very similar significant increase from the 1992-to-1996 period to the 2003-to-2007 period.

Favourable prognoses for those surviving early years

The five-year OCSP among children surviving the first year after their diagnosis met or exceeded 95% in 9 of the 24 individual ICCC-3 groups or subgroups reported (Table 4). When the analysis is restricted to those surviving the first five years after diagnosis, all cancers achieved this standard, with

the exception of ependymomas and choroid plexus tumour, at 88% (95% CI = 74 to 94); osteosarcomas, at 91% (95% CI = 79 to 96); and intracranial and intraspinal embryonal tumours, at 92% (95% CI = 84 to 96). While the five-year OSP for other gliomas of 42% (95% CI = 33 to 51) was the lowest observed from diagnosis, the five-year OCSP among children surviving this cancer for three years was 92% (95% CI = 81 to 96). Similarly, the five-year outlook after three years among those diagnosed with AMLs was 95% (95% CI = 88 to 98), whereas at diagnosis it was 65% (95% CI = 57 to 71).

Discussion

In Canada, five-year predicted OSPs for the period from 2013 to 2017 were at least 90% for 10 of the 24 childhood cancer diagnostic groups or subgroups reported. A significant 7.5% increase in the five-year OSP from the 1992-to-1996 period to the 2013-to-2017 period was observed for all childhood cancers combined. The greatest increase was for chronic myeloproliferative diseases, at 35.4 percentage points. However, no improvement in five-year survival was observed for a number of diagnostic groups with relatively poor prognoses at baseline. Once children survived five years, the

Table 3-1
Changes in five-year observed survival proportions over time by diagnostic group and selected subgroup, ages 0 to 14 at diagnosis, Canada excluding Quebec, 1992-to-1996 period to 2013-to-2017 period — Part 1

	Time period								
	1992 to 1996			2003 to 2007			2013 to 2017		
		95% CI			95% CI			95% CI	
Diagnostic group / subgroup	OSP (%)	from	to	OSP (%)	from	to	OSP (%)	from	to
All groups	**77**	**75**	**78**	**83**	**82**	**84**	**84**	**83**	**85**
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	78	75	80	87	85	89	88	87	90
a. Lymphoid leukemias	85	83	87	91	89	93	93	92	95
b. Acute myeloid leukemias	48	40	55	72	64	78	65	57	71
c. Chronic myeloproliferative diseases	55 E	35	71	87 E	66	96	90	79	95
II. Lymphomas and reticuloendothelial neoplasms	84	80	88	91	88	94	92	89	94
a. Hodgkin lymphomas	90	83	94	99	95	100	99	95	100
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	77	67	84	90	82	94	84	78	89
c. Burkitt lymphoma	92	80	97	88	76	95	94	84	98
d. Miscellaneous lymphoreticular neoplasms	F	F	F	73 E	50	87	94	88	97
III. CNS and miscellaneous intracranial and intraspinal neoplasms	67	63	70	71	68	75	72	69	75
a. Ependymomas and choroid plexus tumour	46 E	33	58	66 E	52	76	78	67	86
b. Astrocytomas	83	79	87	84	79	87	82	78	86
c. Intracranial and intraspinal embryonal tumours	55	47	62	59	51	67	71	64	78
d. Other gliomas	45 E	34	55	60 E	49	69	42	33	51
IV. Neuroblastoma and other peripheral nervous cell tumours	65	59	71	79	73	84	84	79	88
a. Neuroblastoma and ganglioneuroblastoma	65	58	71	79	73	84	84	79	88
V. Retinoblastoma	99	93	100	94	84	98	94	85	98
VI. Renal tumours	87	81	91	85	79	90	96	91	98
a. Nephroblastoma and other nonepithelial renal tumours	86	81	91	86	79	90	96	92	98
VII. Hepatic tumours	70 E	56	81	71 E	56	81	72 E	58	82
VIII. Malignant bone tumours	73	65	79	68	60	75	72	64	78
a. Osteosarcomas	66 E	55	75	70 E	58	79	65 E	53	74
c. Ewing tumour and related sarcomas of bone	76 E	61	86	64 E	51	74	79 E	66	87
IX. Soft tissue and other extraosseous sarcomas	70	64	76	68	61	74	70	64	76
a. Rhabdomyosarcomas	67	59	75	63	53	72	69	60	77
d. Other specified soft tissue sarcomas	80 E	66	88	77 E	65	86	71 E	60	80
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	87	79	92	91	84	95	91	85	95
b. Malignant extracranial and extragonadal germ cell tumours	88 E	66	96	96	76	99	91	75	97
c. Malignant gonadal germ cell tumours	94	83	98	96	83	99	97	83	100
XI. Other malignant epithelial neoplasms and malignant melanomas	86	78	91	94	88	97	92	86	95
b. Thyroid carcinomas	97	83	100	100	..	..	100	..	..
f. Other and unspecified carcinomas	77 E	61	87	83 E	65	92	88	78	94
XII. Other and unspecified malignant neoplasms	91 E	74	97	93	82	97	80 E	55	92

.. not available for a specific reference period
E use with caution
F too unreliable to be published

Notes: OSP = observed survival proportion; CI = confidence interval; CNS = central nervous system. OSPs for all groups combined were calculated as a weighted average of sex- and diagnostic-group-specific estimates. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. All estimates are based on invasive behaviour cases only. OSPs for the 2013-to-2017 period were predicted using the period method. The use of caution is suggested in the interpretation of estimates associated with an unrounded standard error > 0.05 and ≤ 0.10.; if > 0.10, estimates were considered too unreliable to be published. Differences in survival over the full period may not equal the sum of differences for the subperiods because of rounding.

Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

Table 3-2
Changes in five-year observed survival proportions over time by diagnostic group and selected subgroup, ages 0 to 14 at diagnosis, Canada excluding Quebec, 1992-to-1996 period to 2013-to-2017 period — Part 2

	Time period											
	1992-to-1996 to 2013-to-2017				1992-to-1996 to 2003-to-2007				2003-to-2007 to 2013-to-2017			
	Change	95% CI			Change	95% CI			Change	95% CI		
Diagnostic group / subgroup	(% points)	from	to	P-value	(% points)	from	to	P-value	(% points)	from	to	P-value
All groups	**7.5**	**5.6**	**9.3**	**< 0.001**	**6.2**	**4.3**	**8.1**	**< 0.001**	**1.3**	**-0.4**	**3.0**	**0.134**
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	10.3	7.3	13.3	< 0.001	9.4	6.2	12.5	< 0.001	0.9	-1.7	3.6	0.484
a. Lymphoid leukemias	8.0	5.1	10.8	< 0.001	6.1	3.0	9.1	< 0.001	1.9	-0.5	4.3	0.126
b. Acute myeloid leukemias	16.6	6.4	26.8	0.001	23.5	13.2	33.9	< 0.001	-7.0	-16.9	2.9	0.167
c. Chronic myeloproliferative diseases	35.4	15.7	55.0	< 0.001	32.5	9.9	55.1	0.005	2.9	-12.5	18.2	0.714
II. Lymphomas and reticuloendothelial neoplasms	7.5	2.9	12.1	0.001	7.1	2.3	12.0	0.004	0.4	-3.3	4.1	0.839
a. Hodgkin lymphomas	9.4	4.1	14.7	< 0.001	9.5	4.3	14.8	0.000	-0.1	-2.1	1.9	0.934
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	7.0	-2.8	16.8	0.159	12.8	2.8	22.9	0.012	-5.8	-13.6	2.0	0.143
c. Burkitt lymphoma	1.6	-7.9	11.1	0.746	-3.8	-15.2	7.6	0.515	5.4	-5.2	16.0	0.321
d. Miscellaneous lymphoreticular neoplasms	..	..	..	..	..	..	..	..	20.6	2.0	39.3	0.030
III. CNS and miscellaneous intracranial and intraspinal neoplasms	5.2	0.4	10.1	0.034	4.4	-0.5	9.4	0.079	0.8	-4.1	5.6	0.750
a. Ependymomas and choroid plexus tumour	32.1	16.3	47.8	< 0.001	19.8	2.4	37.3	0.026	12.3	-2.9	27.4	0.112
b. Astrocytomas	-0.8	-6.6	5.0	0.784	0.4	-5.5	6.3	0.897	-1.2	-7.3	4.9	0.700
c. Intracranial and intraspinal embryonal tumours	16.6	6.5	26.7	0.001	4.1	-6.8	15.0	0.457	12.5	1.8	23.1	0.021
d. Other gliomas	-2.8	-16.7	11.1	0.694	15.3	0.6	29.9	0.041	-18.1	-31.8	-4.3	0.010
IV. Neuroblastoma and other peripheral nervous cell tumours	18.8	10.9	26.7	< 0.001	13.5	5.1	21.9	0.002	5.3	-1.7	12.3	0.137
a. Neuroblastoma and ganglioneuroblastoma	19.4	11.5	27.3	< 0.001	13.8	5.3	22.3	0.001	5.6	-1.4	12.7	0.119
V. Retinoblastoma	-4.8	-10.8	1.2	0.116	-5.1	-11.3	1.1	0.110	0.3	-7.8	8.4	0.942
VI. Renal tumours	8.7	3.1	14.2	0.002	-1.9	-8.9	5.2	0.603	10.6	4.4	16.7	0.001
a. Nephroblastoma and other nonepithelial renal tumours	9.5	3.8	15.1	0.001	-0.7	-7.9	6.6	0.856	10.1	4.0	16.3	0.001
VII. Hepatic tumours	2.0	-15.5	19.4	0.826	0.5	-17.0	17.9	0.957	1.5	-16.1	19.1	0.870
VIII. Malignant bone tumours	-0.9	-11.1	9.2	0.858	-4.9	-15.3	5.4	0.352	4.0	-6.2	14.2	0.445
a. Osteosarcomas	-1.3	-16.0	13.5	0.865	3.7	-10.8	18.3	0.616	-5.0	-19.7	9.7	0.503
c. Ewing tumour and related sarcomas of bone	2.6	-13.4	18.5	0.753	-12.1	-28.9	4.6	0.156	14.7	-0.7	30.1	0.061
IX. Soft tissue and other extraosseous sarcomas	0.0	-8.3	8.2	0.991	-2.1	-10.8	6.6	0.638	2.1	-6.6	10.7	0.641
a. Rhabdomyosarcomas	1.6	-10.1	13.4	0.785	-4.3	-17.0	8.4	0.508	5.9	-7.0	18.8	0.367
d. Other specified soft tissue sarcomas	-8.2	-22.9	6.6	0.277	-2.2	-17.1	12.8	0.774	-6.0	-20.5	8.5	0.418
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	4.9	-3.2	13.0	0.238	4.8	-3.6	13.1	0.262	0.1	-7.3	7.5	0.975
b. Malignant extracranial and extragonadal germ cell tumours	3.3	-13.0	19.6	0.690	8.5	-6.6	23.5	0.270	-5.1	-17.4	7.1	0.410
c. Malignant gonadal germ cell tumours	3.2	-4.8	11.2	0.431	1.3	-7.5	10.0	0.775	1.9	-5.8	9.7	0.626
XI. Other malignant epithelial neoplasms and malignant melanomas	5.9	-1.7	13.6	0.129	7.9	0.1	15.7	0.047	-2.0	-7.9	4.0	0.517
b. Thyroid carcinomas	2.6	..	..	..	2.6	..	..	..	0.0	..	..	..
f. Other and unspecified carcinomas	11.9	-3.0	26.8	0.117	6.2	-11.7	24.1	0.500	5.8	-9.1	20.6	0.447
XII. Other and unspecified malignant neoplasms	-10.9	-31.2	9.5	0.296	2.1	-10.2	14.3	0.743	-12.9	-31.9	6.1	0.182

.. not available for a specific reference period

E use with caution

F too unreliable to be published

Notes: OSP = observed survival proportion; CI = confidence interval; CNS = central nervous system. OSPs for all groups combined were calculated as a weighted average of sex- and diagnostic-group-specific estimates. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. All estimates are based on invasive behaviour cases only. OSPs for the 2013-to-2017 period were predicted using the period method. The use of caution is suggested in the interpretation of estimates associated with an unrounded standard error > 0.05 and ≤ 0.10.; if > 0.10, estimates were considered too unreliable to be published. Differences in survival over the full period may not equal the sum of differences for the subperiods because of rounding.

Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

probability of surviving another five years exceeded 95% across most diagnoses.

Overall, reasons behind increases in survival are likely multifactorial and include factors such as better supportive care, improved treatment protocols derived from successive randomized trials and better risk stratification. The biggest increase in survival occurred in chronic myeloproliferative diseases. This finding is likely attributable to the development of targeted therapy with tyrosine kinase inhibitors,[29,30] which has enabled better survival, combined with a substantial reduction in the intensity of therapy, including the use of hematopoietic stem cell transplantation. The improvement in ependymoma and choroid plexus tumour survival may be attributable to better surgical and radiotherapy approaches.[31,32]

Significant progress in survival was observed for children diagnosed with AMLs in Canada, though the five-year estimate remained relatively poor, at 65%. However, the progress appeared entirely limited to the first half of the study period. Similar results were reported in the United States, except progress appeared more consistent over time.[33] Improvements in survival for children with AMLs have been attributed to better supportive care,[34] including routine

Table 4

Predicted five-year observed conditional survival proportion given selected time already survived, by diagnostic group and selected subgroup, ages 0 to 14 at diagnosis, Canada excluding Quebec, 2013 to 2017

	Time already survived (years)												
	0		1			3			5			10	
			95% CI			95% CI			95% CI			95% CI	
Diagnostic group / subgroup	OCSP (%)	OCSP (%)	from	to	OCSP (%)	from	to	OCSP (%)	from	to	OCSP (%)	from	to
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	88	93	91	94	98	97	98	98	97	99	99	98	100
a. Lymphoid leukemias	93	95	94	97	98	97	99	99	98	99	99	98	100
b. Acute myeloid leukemias	65	79	72	85	95	88	98	97	92	99	100	..	..
c. Chronic myeloproliferative diseases	90	93	83	97	92	80	97	95	82	99	96	72	99
II. Lymphomas and reticuloendothelial neoplasms	92	95	93	97	97	95	98	99	97	99	100	98	100
a. Hodgkin lymphomas	99	100	..	..	100	..	..	100	..	..	100	..	..
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	84	89	83	93	93	87	96	96	90	98	100	..	..
c. Burkitt lymphoma	94	97	87	99	98	87	100	100	..	..	100	..	..
d. Miscellaneous lymphoreticular neoplasms	94	98	93	100	99	94	100	100	..	..	100	..	..
III. CNS and miscellaneous intracranial and intraspinal neoplasms	72	85	82	88	94	92	96	96	93	97	97	95	99
a. Ependymomas and choroid plexus tumour	78	81	70	88	89	78	95	88	74	94	97	82	100
b. Astrocytomas	82	93	89	95	99	97	100	99	97	100	99	97	100
c. Intracranial and intraspinal embryonal tumours	71	84	77	89	91	84	95	92	84	96	92	85	96
d. Other gliomas	42	65[E]	53	74	92	81	96	95	86	98	98	85	100
IV. Neuroblastoma and other peripheral nervous cell tumours	84	86	81	90	89	85	93	95	91	97	100	..	..
a. Neuroblastoma and ganglioneuroblastoma	84	86	81	90	90	85	93	95	91	97	100	..	..
V. Retinoblastoma	94	94	85	98	99	92	100	99	92	100	99	91	100
VI. Renal tumours	96	97	92	98	98	94	99	98	94	99	99	95	100
a. Nephroblastoma and other nonepithelial renal tumours	96	98	94	99	99	95	100	99	95	100	99	94	100
VII. Hepatic tumours	72[E]	86[E]	71	93	100	..	..	100	..	..	100	..	..
VIII. Malignant bone tumours	72	73	65	79	90	83	95	93	87	97	99	94	100
a. Osteosarcomas	65	67[E]	55	76	87	75	94	91	79	96	100	..	..
c. Ewing tumour and related sarcomas of bone	79	78[E]	66	87	92	79	97	95	83	99	98	84	100
IX. Soft tissue and other extraosseous sarcomas	70	77	71	82	92	87	95	98	94	99	99	94	100
a. Rhabdomyosarcomas	69	75	65	82	92	85	96	99	92	100	100	..	..
d. Other specified soft tissue sarcomas	71	79	68	87	90	78	95	95	84	98	97	83	100
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	91	99	94	100	100	..	..	100	..	..	99	93	100
b. Malignant extracranial and extragonadal germ cell tumours	91	100	..	..	100	..	..	100	..	..	95	69	99
c. Malignant gonadal germ cell tumours	97	100	..	..	100	..	..	100	..	..	100	..	..
XI. Other malignant epithelial neoplasms and malignant melanomas	92	95	90	98	98	94	99	99	95	100	98	93	100
b. Thyroid carcinomas	100	100	..	..	100	..	..	100	..	..	100	..	..
f. Other and unspecified carcinomas	88	89	77	95	93	80	98	97	83	100	97	82	100
XII. Other and unspecified malignant neoplasms	80[E]	100	..	..	100	..	..	100	..	..	98	85	100

.. not available for a specific reference period

E use with caution

Notes: OCSP = observed conditional survival proportion; CI = confidence interval; CNS = central nervous system. Quebec is excluded because cases diagnosed in Quebec from 2011 onward had not been submitted to the Canadian Cancer Registry. All estimates are based on invasive behaviour cases only. Five-year observed conditional survival represents the probability of surviving an additional five years. The use of caution is suggested in the interpretation of estimates associated with an unrounded standard error > 0.05 and ≤ 0.10.

Source: Statistics Canada, Canadian Cancer Registry death linked file (1992 to 2017).

administration of prophylactic antibacterial[35-37] and antifungal therapy,[38,39] as well as better approaches to allogeneic hematopoietic stem cell transplantation. However, these approaches should have been similar in Canada and the United States. The different patterns seen in the two countries may be spurious or may also be related to the use of therapy based on the United Kingdom Medical Research Council in some Canadian centres[40] during the earlier period, which was associated with very good outcomes.[41-43]

There are two broad reasons why some diagnostic groups or subgroups may not have experienced significant increases in survival over time. Some paediatric cancers were associated with high survival during the baseline period (i.e., 1992 to 1996), making it difficult to achieve and demonstrate significant increases over time. For example, while no significant increases in five-year survival were observed for either germ cell tumour subgroup, the five-year OSP for 2013 to 2017 exceeded 90% for both. However, failure to observe increases in survival may also mean that research has not translated into better outcomes for paediatric patients with relatively poor survival. For example, patients diagnosed with hepatic tumours, malignant bone tumours, and soft tissue and other extraosseous sarcomas all had relatively poor prognoses at baseline that remained virtually unchanged 20 years later. Future research should focus on identifying innovative approaches for diagnoses with poor outcomes and in which progress has been stalled. This highlights the importance of this study.

It has been emphasized that the characteristics of childhood cancer, including low incidence rates and favourable prognosis, argue for collecting paediatric cancer data separately from adult

cancer data.[44] Therefore, some may be concerned that estimates of paediatric cancer incidence may be biased in the CCR. However, paediatric cancer incidence rates in the CCR closely approximate those in Cancer in Young People in Canada, a paediatric-cancer-specific national population-based cancer registry,[45] suggesting that biased ascertainment of paediatric cancer in the CCR is not a concern. Another issue is that registries differ in their inclusion of non-malignant tumours, thus raising questions about comparability. The present study focused only on malignant cancers and classified cancers according to the SEER update of the ICCC-3, thus improving interpretability of the data. Lastly, this study did not include patients aged 15 and older. Future efforts could focus on evaluation of adolescent and young adult cancer patients.

During the COVID-19 pandemic, diagnosis of cancer in children may be delayed.[46] Parents may be less likely to engage with the health care system for cancer-like symptoms in their children. Delays in investigating symptoms not initially thought to be related to cancer may also be an issue, as children can be diagnosed with cancer incidentally. Children diagnosed with cancer during the pandemic, and those diagnosed shortly before, may also experience atypical delays in receiving treatment.[46,47] The impact of delays in the diagnosis and treatment of childhood cancer is unclear,[48,49] but delays are likely to have an emotional impact on the family, particularly where outcomes are poor. While the results of this study are based on data collected prior to the pandemic, they provide a baseline against which the impact of the pandemic on childhood cancer survival outcomes can eventually be gauged.

Strengths and limitations

Strengths of this study include its population-based nature, which reduces the possibility of selection bias. Furthermore, the ability to ascertain almost all deaths irrespective of time from diagnosis provides confidence in the long-term survival estimates. This aspect is particularly important since clinical trials and institutional reports may be limited in their ability to identify late deaths, particularly after children transition to adult institutions or if they move to other jurisdictions. Lastly, the description of conditional survival is clinically meaningful and will be useful for reassuring and counselling families. However, the data from this study should be interpreted in light of its limitations. The CCR lacks detailed diagnostic and treatment information; therefore, possible factors associated with both survival and improvements in survival over time could not be evaluated. More annotated databases, such as the Cancer in Young People in Canada registry,[45] could potentially be used to evaluate factors such as treatments associated with improvements in survival or worsening outcomes. Finally, the absence of cases diagnosed in the province of Quebec is an important limitation that should be addressed in future research.

Conclusion

Significant improvements in both short- and long-term paediatric cancer survival have been made in Canada since the early to mid-1990s. However, there has been little improvement over time for some cancer types with poor prognosis, including hepatic tumours, malignant bone tumours, and soft tissue and other extraosseous sarcomas. For children who survived the initial few years after diagnosis, the subsequent long-term outlook was very favourable. This finding is clinically meaningful and will be useful for reassuring and counselling families.

Appendix

Table A1
Weights used in the case-mix standardization of survival estimates for all childhood cancers combined

	Sex	
Diagnostic group	**Male**	**Female**
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases	0.18618	0.16142
II. Lymphomas and reticuloendothelial neoplasms	0.08484	0.04719
III. Central nervous system and miscellaneous intracranial and intraspinal neoplasms	0.09541	0.08845
IV. Neuroblastoma and other peripheral nervous cell tumours	0.03507	0.03326
V. Retinoblastoma	0.01109	0.00670
VI. Renal tumours	0.02192	0.02527
VII. Hepatic tumours	0.00877	0.00413
VIII. Malignant bone tumours	0.01831	0.02166
IX. Soft tissue and other extraosseous sarcomas	0.03610	0.02991
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	0.01444	0.01831
XI. Other malignant epithelial neoplasms and malignant melanomas	0.01444	0.02888
XII. Other and unspecified malignant neoplasms	0.00387	0.00438

Note: Weights are based on the sex- and diagnostic-group-specific proportion of cases diagnosed in Canada (excluding Quebec) from 2010 to 2014.
Source: Statistics Canada, Canadian Cancer Registry tabulation file (1992 to 2015), International Agency for Research on Cancer multiple primary rules version, released Janauary 29, 2018.

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