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by Larry F. Ellison

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Increasing survival from leukemia among adolescents and adults in Canada: A closer look

by Larry F. Ellison

Abstract

Background: Survival from adult onset leukemia has increased substantially in Canada since at least the early 1990s. However, an analysis of the extent of this improvement by type of leukemia is lacking.

Data and methods: Data are from the Canadian Cancer Registry, with mortality follow-up through record linkage to the Canadian Vital Statistics Death Database. Increases in five-year relative survival ratios (RSRs) between 1992-to-1994 and 2006-to-2008 were calculated by age and sex for all leukemias combined and for each of the main types.

Results: Increases in five-year RSRs were significant for all leukemia types studied, ranging from 9.2 percentage units for acute myeloid leukemia (AML) to 24.9 percentage units for chronic myeloid leukemia (CML). For all leukemias combined, additional adjustment for case-mix reduced the increase in survival from 14.6 to 11.8 units; increases were significant among both sexes and each age group. Improvement in survival for chronic lymphocytic leukemia (CLL) was greater at older ages. For AML, improvements were greater among people younger than age 55; no significant change was detected among those diagnosed at ages 75 to 99. A significant survival advantage for women relative to men was apparent in the 2006-to-2008 period for all leukemias combined and for CLL and CML.

Interpretation: Despite recent significant gains in survival for each main type of leukemia, room remains for improvement.

Key words: Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphoblastic leukemia, chronic myeloid leukemia, neoplasms, population-based, registries, relative survival, survival analysis

In Canada, leukemia is diagnosed at a rate of 15 cases per 100,000 persons, and accounts for 3% of all new primary cancers (excluding non-melanoma skin).[1] Most cases can be classified into one of four main types: acute lymphocytic (ALL), chronic lymphocytic (CLL), acute myeloid (AML), and chronic myeloid (CML). Despite etiologic and epidemiologic differences in these types, leukemia is often presented in the collective for convenience in reporting.[2,3]

Population-based analyses using data from cancer registries can provide a more complete assessment of progress in survival than is available from clinical trials, which often preselect younger and generally healthier subjects and may not be representative of the average diagnosed individual.[4-6] Studying survival trends over time can provide information about cancer treatment and control efforts.[7]

Population-based studies—often using data from the United States or Sweden—have found improvements in survival that vary by the type of leukemia and the age at onset within specific leukemia types.[4,8-17] For Canada, a 15-percentage-unit increase between 1992-to-1994 and 2006-to-2008 was reported in five-year relative survival among people diagnosed with leukemia in adolescence or adulthood.[2] Among the cancers or cancer groups studied, this was the second-largest survival increase during the period, after non-Hodgkin lymphoma. However, information is lacking about the extent of the improvement by type of leukemia. The current paper addresses this gap in knowledge and presents outcomes for intermediate time-frames to offer a more complete picture of trends in survival by leukemia type.

Methods

Data sources

Cancer incidence data are from the October 2011 version of the Canadian Cancer Registry. The Canadian Cancer Registry is a dynamic, person-oriented, population-based database. Each provincial and territorial cancer registry supplies data on patients and tumours to Statistics Canada in a standard format, and has the ability to add, update and delete records. To build and maintain the database, Statistics Canada applies a series of core edits and an internal record linkage process that identifies duplicates.

A file was created using the multiple primary coding rules of the International Agency for Research on Cancer.[18] Cases were defined based on the *International Classification of Diseases for Oncology, Third Edition*[19] and classified using Surveillance, Epidemiology, and End Results (SEER) Program grouping definitions (Appendix, Table A).[20] Mortality follow-up through December 31, 2008 was carried out by record linkage to the Canadian Vital Statistics Death database (excluding deaths registered in the province of Quebec) and from information reported by the provincial/territorial cancer registries. For deaths reported by a provincial/territorial registry but not confirmed by the national record linkage, the date of death was assumed to be that submitted by the registry. Application of the multiple primaries rules and record linkage were completed by Statistics Canada before the data file was made available.

Expected survival, used in the calculation of relative survival ratios (RSR), was derived from sex-specific complete annual[21] provincial life tables. Detail is provided elsewhere.[22]

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Analytical techniques

Analyses were based on all primary leukemias.[23-25] Data from the province of Quebec were excluded because of issues in correctly ascertaining the vital status of cases and because the method of determining the date of diagnosis differed from that of the other provinces. Records were also excluded if: age at diagnosis was younger than 15 or older than 99; diagnosis had been established through autopsy only (0.2%) or death certificate only (2.7%); or the year of birth or death was unknown (both extremely rare).

Relative survival analyses were based on a publicly available algorithm[26] incorporating the Ederer II method,[27] with minor adaptations to increase precision. A five-year survival duration was used for all analyses. Three-month subintervals were used for the first year of follow-up, then 6-month subintervals for the remaining 4 years, for a total of 12 subintervals. Cases with the same date of diagnosis and death (not including those previously excluded because they were diagnosed through autopsy only or death certificate only) were assigned one day of survival (0.7%), because the program automatically excludes cases with zero days' survival. Exclusion of these cases would have biased RSRs upward.

Although the definition of relative survival stipulates that the population comparison group should be ". . . free of the specific disease under study . . .,"[28] the population life tables included people previously diagnosed with cancer. The bias introduced into estimates of five-year RSRs by such life tables is negligible for most individual cancers, including leukemia.[22,29,30]

Age-standardized five-year RSRs were calculated using the direct method by weighting age-specific estimates for a given cancer to the age distribution of people aged 15 to 99 diagnosed with that cancer from 2004 to 2008 (Appendix, Table B). In two instances—female ALL cases aged 75 to 99 in the 2006-to-2008 period and ALL cases aged 75 to 99 for both sexes combined in the 2005-to-2007 period—five-year RSRs were not available, as no survival data existed beyond the 3.0- to 3.5-year and 3.5- to 4.0-year intervals, respectively. To calculate standardized rates, the five-year RSR was presumed to be that of the last calculable value in each instance. The maximal biases introduced by these presumptions—assuming an actual five-year RSR of 0.0—were 1.8 and 1.4 percentage units, respectively, given the pertinent weight of 0.14148 (Appendix, Table B).

For all leukemias combined, RSRs for ages 15 to 99 were simultaneously standardized by age and case-mix to mitigate the effect of differences in the distribution of cases by leukemia type over time. They were obtained by weighting age- and leukemia type-specific estimates to the age and leukemia type case distribution of all persons aged 15 to 99 diagnosed with leukemia from 2004 to 2008. Age-specific estimates for all leukemias combined were similarly standardized by case-mix (Appendix, Table C). The 25 weights used for age- and case-mix-standardization can be derived by multiplying age-standardized weights by the weight associated with the corresponding leukemia type for ages 15 to 99 (Appendix, Table C, first column).

In this study, outcomes from the age- and case-mix-standardized analyses are the primary indicators for all leukemias combined; corresponding age-standardized results are presented for comparison.

Standard errors of RSRs were estimated by dividing the standard error of observed survival (determined by Greenwood's method)[31] by expected survival.[32] For age-standardized RSRs, they were estimated by taking the square root of the sum of the squared weighted age-specific RSR standard errors.

The percentage-unit increase in five-year RSRs between 1992-to-1994 and 2006-to-2008 was the measure of improvement in survival. Differences in RSRs were calculated before rounding to one decimal place. The statistical significance of between-time-period differences was determined via the Z test. RSRs for the 2006-to-2008 interval were calculated using the period method[33]; for 1992 to 1994, the cohort method was used.

To describe the pattern of change over time for each leukemia type in greater detail, age-standardized five-year RSRs were derived for successive three-year periods: cohort analysis was used between 1992-to-1994 and 2001-to-2003; mixed-analysis,[34] between 2002-to-2004 and 2005-to-2007; and period analysis, for 2006-to-2008. Mixed-analysis combines data from cohort and period analyses to derive survival estimates intermediate to those obtained from these methods separately.

The period method provides more timely estimates of survival for recent periods than do cohort methods.[35-37] Estimates derived using the period method reflect the cumulative survival that would be expected by newly diagnosed individuals in a recent period, assuming that the observed conditional survival probabilities within the pre-defined intervals of follow-up in this period are experienced by these individuals going forward. To the extent that these probabilities are, instead, increasing, the

Table 1
Number of cases eligible for survival analyses, case distribution, percentage male and age distribution at diagnosis, by leukemia type, ages 15 to 99, Canada excluding Quebec, 1992 to 2008

				Age group (years) %				
Leukemia type	Cases†	% of cases	Sex % male	15 to 44	45 to 54	55 to 64	65 to 74	75 to 99
All leukemias	**45,340**	**100.0**	**58.4**	**11.7**	**11.1**	**18.0**	**25.5**	**33.8**
Acute lymphocytic	2,070	4.6	59.5	48.8	12.9	12.1	12.7	13.5
Chronic lymphocytic	19,985	44.1	60.3	2.5	9.7	20.7	29.8	37.4
Acute myeloid	11,000	24.3	54.1	17.1	12.2	17.0	24.4	29.3
Chronic myeloid	5,575	12.3	59.0	18.4	12.5	16.3	21.2	31.8
Other leukemias	6,710	14.8	59.1	13.3	11.8	14.8	21.9	38.2

† case counts randomly rounded to base of five for confidentiality
Note: Because of rounding, leukemia type- and age-specific percentages may not sum to 100.
Source: Canadian Cancer Registry database.

period-based prediction of cumulative survival will underestimate what is eventually observed.[35,38]

Results

Distribution of cases

Among leukemia cases diagnosed at ages 15 to 99 from 1992 to 2008 and eligible for survival analysis, the most common type was CLL (44.1% of cases); ALL (4.6%) was the least common (Table 1). The percentage of cases diagnosed in men was highest for CLL (60.3%) and lowest for AML (54.1%).

The most skewed age distributions were for CLL and ALL. CLL was much more likely to be diagnosed at older ages, and was rarely detected at ages 15 to 44 (2.5% of CLL cases). By contrast, almost half (48.8%) of non-childhood ALL cases were diagnosed before age 45.

Increases in survival by leukemia type

The predicted five-year age- and case-mix-standardized RSR for all leukemias combined for 2006-to-2008 was 57.5% (Table 2). This figure, however, masked great diversity in prognosis among the individual types of leukemia. Predicted five-year age-standardized RSRs ranged from 22.8% for AML to 80.9% for CLL. The wide range of the survival estimates remained when they were age-standardized using a common standard (all leukemias combined, first row Appendix Table B), although the estimate associated with ALL decreased to 25.9% (data not shown). This difference reflects the age distribution for ALL, which was more skewed toward younger ages than was the age distribution for all leukemias combined.

Survival increased significantly for all main types of leukemia between 1992-to-1994 and 2006-to-2008, but the size of the increase varied. The five-year RSR for CML rose 24.9 percentage units from 36.0% to 60.9%, compared with 9.2 percentage units for AML. No statistically significant increase was observed for the all "other leukemias" category.

For all leukemias combined, the five-year age- and case-mix-standardized RSR rose 11.8 percentage units between 1992-to-1994 and 2006-to-2008. The additional adjustment for case-mix reduced the increase by 2.8 percentage units, or 19% of the originally noted increase in the age-standardized RSR.

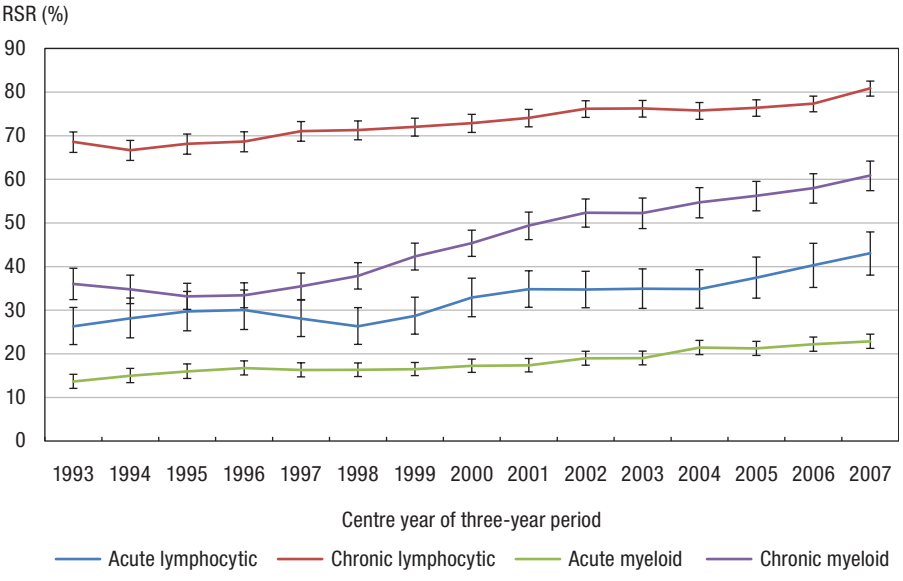
For the period studied, five-year RSRs for CML started to rise in the mid-to-late 1990s (Figure 1). The largest gains occurred between 1996-to-1998 and 2001-to-2003, although survival estimates after this period become increasingly predictive and possibly understated (see Methods). While improvements in ALL survival appear to date back to the late 1990s, relatively large increases totalling 8.2 percentage units were observed more recently (between 2003-to-2005 and 2006-to-2008). CLL and AML survival improved gradually over the study period with the possible exception of the mid-to-late 1990s for the latter type.

Table 2
Five-year age-standardized relative survival ratios (RSRs) and increases in survival, by leukemia type, ages 15 to 99, Canada excluding Quebec, 1992 to 2008†

	Time period						Increase in five-year RSR: 1992-1994 to 2006-2008			
	1992 to 1994			2006 to 2008						
	RSR	95% confidence interval		RSR	95% confidence interval		%	95% confidence interval		
Leukemia type	(%)	from	to	(%)	from	to	units	from	to	p-value
All leukemias‡	**45.7**	**44.4**	**47.1**	**57.5**	**56.4**	**58.6**	**11.8**	**10.1**	**13.5**	**< 0.0005**
All leukemias	**43.5**	**42.1**	**44.9**	**58.1**	**56.9**	**59.3**	**14.6**	**12.8**	**16.5**	**< 0.0005**
Acute lymphocytic	26.3	22.1	30.6	43.1	38.1	47.9	16.8	10.2	23.3	< 0.0005
Chronic lymphocytic	68.6	66.2	70.9	80.9	79.1	82.5	12.3	9.4	15.2	< 0.0005
Acute myeloid	13.6	12.1	15.3	22.8	21.2	24.5	9.2	6.9	11.5	< 0.0005
Chronic myeloid	36.0	32.4	39.6	60.9	57.4	64.2	24.9	19.9	29.8	< 0.0005
Other leukemias	36.7	33.5	39.9	40.1	37.2	43.0	3.4	-0.9	7.7	0.120

† period method of survival analysis used for 2006 to 2008; cohort method for 1992 to 1994
‡ RSRs simultaneously standardized by age and case-mix (primary result); age-standardized RSRs directly below for comparison
Sources: Canadian Cancer Registry database; life tables.

Figure 1
Five-year age-standardized relative survival ratios (RSR), by leukemia type, ages 15 to 99, Canada (excluding Quebec), 1992-to-1994 to 2006-to-2008



I = 95% confidence intervals
Sources: Canadian Cancer Registry; life tables.

Increases in survival by sex

For all leukemias combined and for each main type, increases in five-year relative survival were statistically significant among both men and women (Table 3). For "other leukemias," the significant increase was restricted to women. Point estimates of increases in RSRs were higher among women than men (13.3 versus 11.0 percentage units) for all leukemias combined. The largest difference in survival improvement between the sexes was among those diagnosed with CML (8.2 percentage-unit larger increase among women).

A significant survival advantage for women was observed in the 2006-to-2008 period for all leukemias combined, but only when RSRs were adjusted for both age and case-mix (statistical testing results not shown). Significant advantages for women were also observed among those diagnosed with CLL and CML, while a significant disadvantage was noted for "other leukemias."

Increases in survival by age group

For both types of acute leukemia, five-year RSRs for 2006-to-2008 were highest among people diagnosed at ages 15 to 44 (61% to 64%) and declined sharply with advancing age (Table 4). The importance of age at diagnosis as a predictor of prognosis for AML is underscored by the fact that none of the age-specific 95% confidence intervals overlapped.

Relative survival estimates for both types of chronic leukemia also declined with advancing age at diagnosis, although from a higher initial point (CLL 94.1%, CML 86.5%), and not until after age 54. The decline was generally steeper for CML than for CLL.

For all leukemias combined, increases in five-year relative survival between 1992-to-1994 and 2006-to-2008 were statistically significant in each age group. The previously noted large gains in relative survival associated with CML were evident in each of the five age groups, with increases ranging from 41.4 percentage units among people diagnosed at ages 45 to 54, to 17.1 units among those diagnosed at ages 75 to 99. As a result, by 2006-to-2008, five-year relative survival among those diagnosed at ages 45 to 54 (87.5%) matched that for the 15-to-44 age group (86.5%), whereas at the beginning of the study period, it was approximately 20 percentage units lower.

For CLL, improvements in five-year relative survival were greatest at age 65 or older. By contrast, for AML, the largest improvement—just over 20 percentage units—was among people younger than age 55, and survival remained below 5% among the most elderly. Significant improvement among those aged 65 to 74 at diagnosis meant that survival in this age group for 2006-to-2008 (11.7%) was superior to that of those aged 75 to 99 (3.8%), whereas the two estimates had been virtually identical in the early 1990s. For ALL, the largest improvements were at ages 15 to 44 (20.4 percentage units) and ages 55 to 64 (25.7 percentage units), although the precision of age-specific estimates was relatively poor for this cancer.

While improved survival for CML appeared to begin in the mid-to-late 1990s among most age groups, it was observed from the beginning of the study period among those aged 45 to 54, and was delayed until the turn of the century among the most elderly (data not shown). For those diagnosed at ages 75 to 99, five-year RSRs rose from 16.6% in 1999-to-2001 to 37.1% in 2006-to-2008.

Table 3
Five-year age-standardized relative survival ratios (RSRs) and increases in survival, by sex and leukemia type, ages 15 to 99, Canada excluding Quebec, 1992 to 2008†

	Time period						Increase in five-year RSR: 1992-1994 to 2006-2008			
	1992 to 1994			2006 to 2008						
	RSR	95% confidence interval		RSR	95% confidence interval		%	95% confidence interval		
Sex / leukemia type	(%)	from	to	(%)	from	to	units	from	to	p-value
Males										
All leukemias‡	**45.1**	**43.2**	**46.9**	**56.0**	**54.5**	**57.5**	**11.0**	**8.6**	**13.3**	**< 0.0005**
All leukemias	**44.0**	**42.0**	**45.9**	**57.7**	**56.1**	**59.3**	**13.8**	**11.2**	**16.3**	**< 0.0005**
Acute lymphocytic	25.3	20.1	30.7	40.9	34.4	47.4	15.7	7.2	24.1	< 0.0005
Chronic lymphocytic	66.3	63.0	69.5	77.9	75.4	80.1	11.5	7.5	15.6	< 0.0005
Acute myeloid	11.9	9.8	14.1	22.0	19.8	24.4	10.1	7.0	13.3	< 0.0005
Chronic myeloid	36.2	31.6	40.7	57.7	52.9	62.3	21.6	15.0	28.1	< 0.0005
Other leukemias	42.4	38.0	46.8	43.8	39.5	48.0	1.4	-4.7	7.5	0.658
Females										
All leukemias‡	**46.4**	**44.4**	**48.3**	**59.7**	**58.1**	**61.2**	**13.3**	**10.8**	**15.8**	**< 0.0005**
All leukemias	**42.8**	**40.7**	**44.9**	**58.6**	**56.8**	**60.4**	**15.8**	**13.0**	**18.6**	**< 0.0005**
Acute lymphocytic	28.6	21.5	36.2	47.9	40.2	55.2	19.2	8.7	29.8	< 0.0005
Chronic lymphocytic	71.8	68.3	75.1	85.0	82.3	87.3	13.1	8.9	17.4	< 0.0005
Acute myeloid	15.8	13.4	18.4	24.2	21.9	26.6	8.3	4.9	11.8	< 0.0005
Chronic myeloid	35.1	29.4	40.8	64.9	59.7	69.6	29.8	22.2	37.4	< 0.0005
Other leukemias	27.3	22.6	32.1	35.2	31.0	39.4	7.9	1.5	14.3	0.015

† period method of survival analysis used for 2006 to 2008; cohort method for 1992 to 1994
‡ RSRs simultaneously standardized by age and case-mix (primary result); age-standardized RSRs directly below for comparison
Sources: Canadian Cancer Registry database; life tables.

Discussion

This analysis of Canadian data indicates that previously identified significant increases in survival between 1992-to-1994 and 2006-to-2008 for all leukemias combined also apply among the main types of leukemia, both sexes, and all age groups studied. At the same time, stratum-specific differences in the magnitude of the improvements are evident. For example, five-year relative survival for CML increased 24.9 percentage units

from 36.0% to 60.9%. As well, a survival advantage for women relative to men emerged.

Large increases in relative survival for CML have been found in other population-based studies and have been attributed to advances in treatment.[8,14,17,39] In 2001, imatinib—the first targeted treatment for CML—was approved for use in a number of countries, including Canada.[14,39-41] Previously, interferon-α and hematopoietic stem cell transplantation had improved survival in some subpopulations.[14,39,40]

Table 4
Five-year relative survival ratios (RSRs) and increases in survival, by age group and leukemia type, ages 15 to 99, Canada excluding Quebec, 1992 to 2008†

	Time period						Increase in five-year RSR: 1992-1994 to 2006-2008			
	1992 to 1994			2006 to 2008						
		95% confidence interval			95% confidence interval			95% confidence interval		
Age group /Leukemia type	RSR (%)	from	to	RSR (%)	from	to	% units	from	to	p-value
15 to 44										
All leukemias‡	**54.7**	**51.3**	**57.9**	**69.7**	**66.7**	**72.4**	**15.0**	**10.7**	**19.4**	**< 0.0005**
All leukemias	**53.4**	**49.9**	**56.7**	**70.4**	**67.5**	**73.2**	**17.1**	**12.6**	**21.5**	**< 0.0005**
Acute lymphocytic	43.6	36.2	50.9	64.0	56.2	70.9	20.4	10.0	30.8	< 0.0005
Chronic lymphocytic	86.3	75.5	92.8	94.1	87.3	97.6	7.8	-1.9	17.4	0.114
Acute myeloid	40.2	34.7	45.7	61.1	55.6	66.1	20.8	13.2	28.4	< 0.0005
Chronic myeloid	66.3	58.6	72.9	86.5	80.4	90.8	20.2	11.4	29.0	< 0.0005
Other leukemias	65.0	55.1	73.3	63.6	56.2	70.1	-1.4	-12.9	10.1	0.807
45 to 54										
All leukemias‡	**57.3**	**54.0**	**60.5**	**72.7**	**70.1**	**75.2**	**15.4**	**11.3**	**19.5**	**< 0.0005**
All leukemias	**54.9**	**50.9**	**58.7**	**74.8**	**72.0**	**77.4**	**19.9**	**15.2**	**24.7**	**< 0.0005**
Acute lymphocytic	34.9	20.2	50.1	41.1	27.1	54.6	6.1	-14.7	27.0	0.564
Chronic lymphocytic	87.5	82.1	91.5	94.8	91.9	96.9	7.3	2.0	12.6	0.007
Acute myeloid	21.1	15.4	27.3	43.3	36.8	49.6	22.2	13.5	31.0	< 0.0005
Chronic myeloid	46.1	36.0	55.6	87.5	80.2	92.5	41.4	29.8	53.0	< 0.0005
Other leukemias	58.2	47.4	67.6	65.6	57.8	72.4	7.4	-5.1	20.0	0.245
55 to 64										
All leukemias‡	**57.2**	**54.6**	**59.8**	**68.7**	**66.6**	**70.7**	**11.4**	**8.1**	**14.7**	**< 0.0005**
All leukemias	**54.7**	**51.6**	**57.7**	**70.0**	**67.6**	**72.3**	**15.3**	**11.5**	**19.1**	**< 0.0005**
Acute lymphocytic	8.1	2.1	19.8	33.8	19.4	49.1	25.7	8.0	43.3	0.005
Chronic lymphocytic	81.4	77.4	84.9	89.2	86.6	91.5	7.8	3.3	12.3	0.001
Acute myeloid	14.3	10.4	18.7	25.6	21.1	30.2	11.3	5.1	17.5	< 0.0005
Chronic myeloid	47.1	37.8	56.1	77.1	69.5	83.4	30.0	18.5	41.6	< 0.0005
Other leukemias	52.8	44.1	60.9	60.7	53.0	67.6	7.9	-3.2	19.0	0.164
65 to 74										
All leukemias‡	**46.9**	**44.6**	**49.2**	**59.3**	**57.3**	**61.2**	**12.4**	**9.4**	**15.4**	**< 0.0005**
All leukemias	**44.2**	**41.6**	**46.8**	**60.3**	**58.0**	**62.6**	**16.1**	**12.6**	**19.6**	**< 0.0005**
Acute lymphocytic	5.9	1.1	17.4	16.0	6.3	30.0	10.1	-4.4	24.6	0.171
Chronic lymphocytic	73.2	69.4	76.9	86.8	84.0	89.4	13.6	9.0	18.2	< 0.0005
Acute myeloid	4.6	2.8	7.2	11.7	9.0	14.9	7.1	3.4	10.8	< 0.0005
Chronic myeloid	25.6	19.2	32.7	52.9	44.6	60.9	27.3	16.7	37.9	< 0.0005
Other leukemias	32.5	26.5	38.7	38.4	31.6	45.2	5.9	-3.3	15.0	0.210
75 to 99										
All leukemias‡	**33.4**	**30.7**	**36.1**	**43.1**	**40.9**	**45.2**	**9.7**	**6.2**	**13.2**	**< 0.0005**
All leukemias	**31.4**	**28.7**	**34.2**	**42.6**	**40.2**	**44.9**	**11.2**	**7.5**	**14.8**	**< 0.0005**
Acute lymphocytic	0.0	...	...	13.9	4.9	28.4	13.9	...	...	...
Chronic lymphocytic	53.5	48.7	58.3	68.5	64.9	72.1	15.0	9.0	21.0	< 0.0005
Acute myeloid	4.7	2.6	7.7	3.8	2.4	5.8	-0.8	-3.8	2.2	0.591
Chronic myeloid	20.0	13.7	27.5	37.1	30.1	44.4	17.1	7.1	27.0	0.001
Other leukemias	18.0	13.3	23.5	19.0	14.5	24.2	1.0	-6.0	8.1	0.771

... not applicable
† period method of survival analysis used for 2006 to 2008; cohort method for 1992 to 1994
‡ RSRs standardized by case-mix (primary result); unstandardized RSRs directly below for comparison
Sources: Canadian Cancer Registry database; life tables.

For all age groups, the current study reports significant survival improvements, the smallest of which (17.1 percentage units) was among people diagnosed at ages 75 to 99. Survival gains for this age group were somewhat later relative to younger age groups. In other studies, too, improvements in survival for the most elderly trailed those for younger age groups, a difference attributed, in part, to the delayed and less widespread use of imatinib in this population.[8,14]

For AML, the greater improvement in five-year relative survival in younger age groups in the present study is consistent with observations based on Swedish[11] and American SEER data.[4] Nonetheless, more than half of adult cases are diagnosed among people older than age 64, whose survival continues to be very poor. Improved survival in the "younger old"—here 65 to 74; up to age 80 elsewhere[11]—but not in the "older old" has been observed elsewhere,[4,11,15] and has been partially attributed to more aggressive treatment in the "younger old."[4,5,15,42] In general, overall gradual improvements in AML survival have been ascribed to a combination of a better understanding of how to diagnose and allocate individuals into different treatments, better and increased use of supportive care, intensified chemotherapy, and improvements in stem cell transplantation techniques.[4,11,15,43]

For ALL, recent increases in survival, such as those observed in this analysis, may be broadly explained by increasing use of targeted therapies and stem cell transplantation, introduction of pediatric-inspired protocols in young adults, and improvements in supportive therapy.[12,44-46] Improved CLL survival has been generally ascribed to more effective therapeutic approaches and better supportive care.[9,10,13,47] However, lead-time bias may have played a part.[9,10] The effect of treatment on survival outcomes could not be gauged directly in the current study, because the Canadian Cancer Registry does not contain clinical data.

Attenuation of the overall increase in five-year RSRs after adjustment for case-mix highlights the importance

What is already known on this subject?

- Substantial improvements in survival among adults diagnosed with leukemia have been reported, primarily based on data from the United States and Sweden.
- The extent of improvements varied by the type of leukemia and the age at onset.
- A 15% increase in the five-year age-standardized relative survival ratio (RSR) has been noted among adults in Canada diagnosed with leukemia between 1992-to-1994 and 2006-to-2008.
- Canadian estimates of age-standardized five-year relative survival for all leukemias combined do not differ significantly by sex.

What does this study add?

- Between 1992-to-1994 and 2006-to-2008, survival improved significantly for the main types of leukemia.
- The largest gain—24.9 percentage points—was among people diagnosed with chronic myeloid leukemia; survival improved substantially in each age group.
- For acute myeloid leukemia, improvements in survival were greater among people diagnosed before age 55; no significant change was detected among those diagnosed at ages 75 to 99.
- Additional adjustment for case-mix reduced the magnitude of the increase in five-year relative survival for all leukemias combined, and revealed a significant survival advantage for women relative to men.
- An advantage for women was also noted among those diagnosed with chronic myeloid and chronic lymphocytic leukemia.

of this factor in comparative analyses of leukemia survival. Between 1992 and 2008, the percentage of CLL cases among all leukemia cases diagnosed rose from 39.9% to 47.9%, while the percentage of AML cases fell from 26.0% to 21.7% (data not shown). The relative increase in CLL, the leukemia with the best prognosis, and the simultaneous relative decrease in AML, the leukemia with the poorest prognosis, over the study period led to an artificial advantage in survival that was not accounted for in the age-standardized results.

The current study found a significant survival advantage for women relative to men for all leukemias combined and for CLL and CML specifically. This contrasts with the results of a recent study that found leukemia to be one of the few cancers not associated with a survival advantage for women.[48] The earlier study, however, did not consider case-mix for individual cancers or for cancer groups such as leukemia, and information on specific types of leukemia was not presented. A survival advantage for women with CML has also been observed in data from Sweden, the United States, and Germany.[14,39] For CLL, the current analysis supports the 29% lower excess mortality for women compared with men reported by Kristinsson et al.[10] In two other studies, however, greater improvements in five-year RSRs among men for cases diagnosed up to 2004 negated previously observed sex-specific differences.[9,13]

The use of period survival analysis in this study revealed recent improvements in RSRs among people with leukemia. Nonetheless, some of the predictions of five-year relative survival for the most recent years—particularly for ALL and CML—may underestimate what will eventually be observed. This is because predictions of survival based on period analysis tend to be conservative to the extent that survival appears to have been increasing in the most recent years.

This can be illustrated by applying the period method to the 2001-to-2003 interval (the last three-year period for which an estimate exclusively based on the cohort method can be derived) and comparing the predicted estimate to the actually observed estimate. The cohort-based five-year RSR for CML was 52.3%, but the period-based estimate—using follow-up data only to the end of 2003—was 45.0%. On the other hand, for AML where survival was fairly stable directly before 2001-to-2003, the difference (0.2 percentage units) between the period and cohort-based estimates was negligible.

Conclusion

Gains in survival between 1992-to-1994 and 2006-to-2008 for each of the main types of leukemia have been significant, although five-year relative survival for adult ALL and AML remains below 50% and 25%, respectively. However, advancements in treatment for leukemia—including second-generation targeted therapies[49]—are ongoing. ■

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Appendix

Table A
Classification of leukemia cases

Leukemia type	Site	Morphology[§]
Acute lymphocytic		9826, 9835-9837
Chronic lymphocytic	C420, C421, C424	9823
Acute myeloid		9840, 9861, 9866, 9867, 9871-9874,9895-9897,9910,9920
Chronic myeloid		9863, 9875, 9876, 9945, 9946
Other leukemias		9733, 9742, 9800, 9801, 9805, 9820, 9831-9834, 9860, 9870, 9891, 9930, 9931, 9940, 9948, 9963, 9964
	C420, C421, C424	9827

[§] malignant cases only

Table B
Age-specific weights used for age-standardization of relative survival ratios, by leukemia type

	Age group				
Leukemia type	15 to 44	45 to 54	55 to 64	65 to 74	75 to 99
All leukemias	**0.098**	**0.109**	**0.182**	**0.244**	**0.367**
Acute lymphocytic	0.443	0.145	0.138	0.133	0.141
Chronic lymphocytic	0.021	0.093	0.205	0.280	0.401
Acute myeloid	0.149	0.122	0.175	0.235	0.319
Chronic myeloid	0.152	0.123	0.170	0.208	0.347
Other leukemias	0.129	0.117	0.145	0.197	0.411

Note: Because of rounding, row totals may not sum to 1.

Table C
Case-mix-specific weights used for case-mix-standardization of relative survival ratios, by age group

	Age group					
Leukemia type	15 to 99	15 to 44	45 to 54	55 to 64	65 to 74	75 to 99
Acute lymphocytic	0.041	0.182	0.054	0.031	0.022	0.016
Chronic lymphocytic	0.468	0.100	0.399	0.526	0.539	0.512
Acute myeloid	0.234	0.355	0.263	0.224	0.226	0.204
Chronic myeloid	0.109	0.168	0.124	0.101	0.093	0.103
Other leukemias	0.148	0.194	0.160	0.118	0.120	0.166

Note: Because of rounding, column totals may not sum to 1.