

Trends in childhood leukemia mortality over a 25-year period

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Abstract

Objective: To analyze trends in childhood leukemia mortality in the state of Rio de Janeiro, Brazil, between 1980 and 2006.

Method: Gender-stratified leukemia mortality data for children aged < 15 years from 1980 to 2006 were retrieved from the Brazilian Mortality Information System for the state of Rio de Janeiro. Data were stratified by place of death (city of Rio de Janeiro proper, the state capital; Rio de Janeiro Metropolitan Region, excluding the capital; and rest of the state). Leukemia deaths were defined according to death certificate ICD-9 and ICD-10 coding (for deaths occurring in 1980-1995 and 1996-2006, respectively). Leukemia mortality rates were calculated by age and calendar year and age-adjusted to a standard world population. Polynomial linear regression with a 5% significance level was used to evaluate mortality trends in the study regions.

Results: The three studied regions revealed similar trends, with a continuous downward pattern; the most substantial decline was detected in the municipality of Rio de Janeiro (city proper). In all studied areas, leukemia mortality was highest among males.

Conclusions: A downward trend in childhood leukemia mortality was detected throughout the state of Rio de Janeiro. The most pronounced reduction occurred in the state capital.

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Introduction

The leukemias are a heterogeneous group of hematological malignancies characterized by clonal proliferation of immature hematopoietic cells with aberrant differentiation.¹ They are the most common malignant neoplasms of childhood, and account for approximately 33% of all malignancies in children and adolescents under the age of 14 years worldwide.²

The incidence of childhood leukemia has been on the rise in several developed nations, such as the United States,³ England,⁴ and various European countries.⁵ This increase is partially explained by improvements in cancer registry systems and greater population-wide access to the healthcare system, which allows early diagnosis of malignancies. Reduced incidence rates have been reported in

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developing countries,⁶ although leukemia rates in the city of São Paulo are similar to those found in developed countries.⁷ In Goiânia, Goiás, childhood mortality rates declined between 1978 and 1996, significantly so for children aged 5 years or younger, as did leukemia mortality in patients under the age of 15 from 1979 to 1995.⁸

In developed countries, leukemia mortality rates in children under the age of 15 have declined significantly since the 1970s.⁹ This decrease is likely due to earlier diagnosis, standardization of treatment protocols, and subsequent improvement in the survival of children with leukemia.¹⁰

The demographic and epidemiologic transition observed over the past 20 years in several countries, as well as the magnitude of the incidence and prevalence of childhood leukemia, have attracted the interest of various researchers and been the subject of extensive epidemiological studies. In Brazil, however, childhood cancer statistics have not been analyzed in much depth in the literature, even though data are available, such as those collected in the Mortality Information System (Sistema de Informação sobre Mortalidade, SIM) maintained by the Brazilian Ministry of Health (Departamento de Informática do Sistema Único de Saúde - DATASUS, 1998)¹¹.

The present study sought to analyze mortality trends in childhood leukemia in the state of Rio de Janeiro from 1980 to 2006.

Methods

This was a descriptive, time-series study based on mortality data for boys and girls under the age of 15 living in the state of Rio de Janeiro between the years 1980 and 2006.

Data on childhood leukemia deaths were obtained directly from SIM, a public-domain, free and open-access Unified Health System database organized and maintained by the Brazilian Ministry of (DATASUS/MS).^{11,12} Mortality data were analyzed for the following geographic areas in the state of Rio de Janeiro: city of Rio de Janeiro proper (the state capital); Rio de Janeiro Metropolitan Region (excluding the state capital); and remainder of the state of Rio de Janeiro (total in-state deaths after exclusion of those recorded in the Metropolitan Region).

Leukemia deaths were defined as those with a proximate cause containing ICD-9 codes 202.4, 203.1, or 204-208 (for the 1980-1995 period) or ICD-10 codes C90.1 and C91-C95 (for the 1996-2006) period.

The period of analysis ranged from 1980 to 2006 and was subdivided into nine three-year periods. This strategy was adopted in an attempt to reduce the influence of random annual fluctuations in data.

First, childhood leukemia mortality rates were calculated for each region. Rates were age-standardized to the world

population proposed by Segi¹³ and modified by Doll¹⁴ with respect to the age range of interest (< 15 years). Scatter plots of mortality rates per calendar year were generated to provide a visual representation of rate distribution over time.

For model construction, age-standardized childhood leukemia mortality rates were analyzed as the dependent variable (y), and years of death (stratified into three-year periods), as an independent variable (x). Trend analysis was performed using linear regression, initially with a simple linear regression model ($Y = \beta_0 + \beta_1X$), followed by second- ($Y = \beta_0 + \beta_1X + \beta_2X^2$) and third-degree ($Y = \beta_0 + \beta_1X + \beta_2X^2 + \beta_3X^3$) polynomial models.

In order to avoid autocorrelation between points in the time series, the time variable was centered at the midpoint of the series, as suggested by Kleinbaum et al.¹⁵

Choice of the best model was based on significance level (p -value) and on residual analysis. Models were considered statistically significant when $p < 0.05$.

Models were constructed for overall mortality in children and adolescents under the age of 15, for mortality in males under the age of 15, and for mortality in females in the same age range.

Data analysis was carried out using the Microsoft Excel 2003 and SPSS version 15.0 software packages.

Results

Data on a total of 1,910 children were available for the entire study period (1980 to 2006), with 848 leukemia deaths in the city of Rio de Janeiro proper, 606 in the Metropolitan Region (excluding Rio de Janeiro proper), and 456 for the Rio de Janeiro countryside (total in-state deaths, except for those recorded in the Metropolitan Region).

Trend analyses for the three geographic areas showed similar patterns of a constant, downward trend (Figure 1).

Comparison of trends by geographic area showed that the city of Rio de Janeiro proper had the most marked decline in mortality rates (-1.79 per three-year period), the highest coefficient of determination ($R^2 = 82.1$), and the highest statistical significance ($p < 0.001$) (Table 1).

Analysis of mortality trends by gender showed a greater incidence in males as compared to females in all studied areas (Figure 2).

Fluctuations notwithstanding, mortality rates declined in both genders and in all three geographic areas throughout the series. In both genders, this decrease in mortality was greatest in the city of Rio de Janeiro proper (Table 2).

Discussion

The reduction in childhood leukemia mortality rates found in the state of Rio de Janeiro is consistent with similar

results reported in the literature. In economically developed regions, such as North America, Western Europe, Japan, and Oceania, a reduction in leukemia mortality rates in excess of 55% over the past three decades has been reported.¹⁰ In Brazil, a single study conducted in the city of Goiânia,

Goiás, also found a statistically significant decrease in leukemia mortality rates among children under the age of 15 between 1979 and 1995.⁸ This trend toward declining mortality in childhood leukemia may be due to advances in therapy, heralded by the standardization of treatment

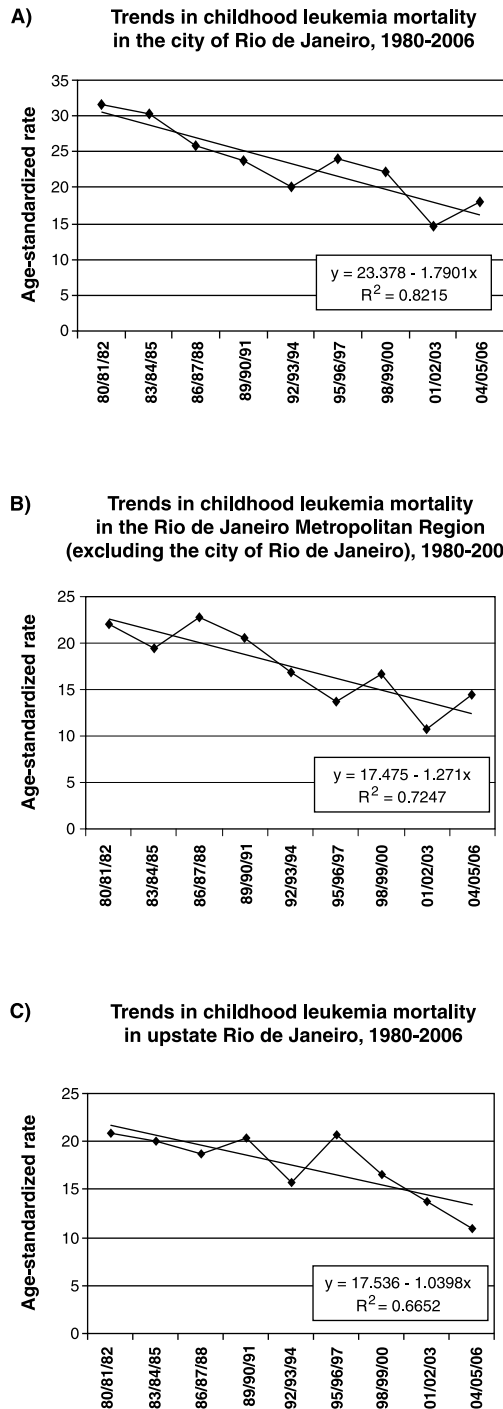


Figure 1 - Childhood leukemia mortality trends in the state of Rio de Janeiro. A) City of Rio de Janeiro; B) Metropolitan Region (except for the city proper); C) rest of state

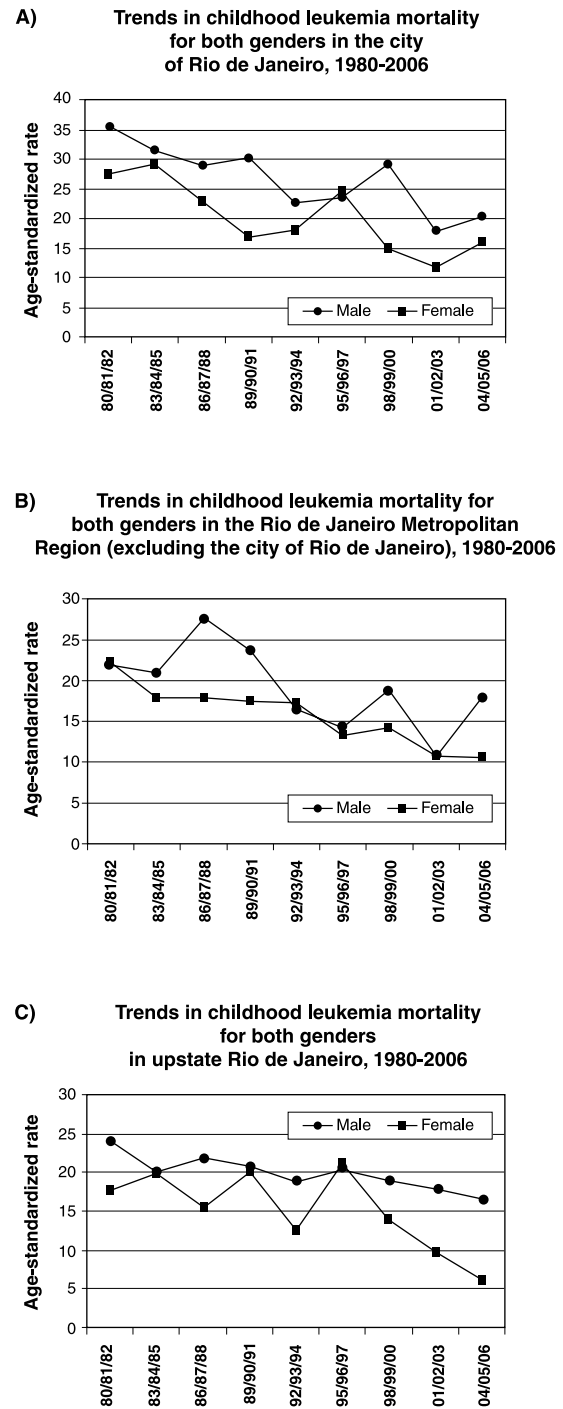


Figure 2 - Trends in childhood leukemia mortality by gender in the state of Rio de Janeiro. A) City of Rio de Janeiro; B) Metropolitan Region (except for the city proper); C) rest of state

Table 1 - Age-adjusted childhood leukemia mortality rates by region in the state of Rio de Janeiro, 1980–2006

Area	Model	R ² (%)	p	Trend	Rate reduction (%)
Capital (city proper)	$y = 23.378 - 1.7901x$	82.15	< 0.001	Constant downward	42.5
Metropolitan Region (except capital)	$y = 17.475 - 1.271x$	72.46	< 0.01	Constant downward	34.8
Rest of state	$y = 17.536 - 1.0398x$	66.52	< 0.01	Constant downward	47.4

p = significance level; R² = coefficient of determination.

Table 2 - Age-adjusted childhood leukemia mortality trends by gender in the state of Rio de Janeiro, 1980–2006

Area/gender	Model	R ² (%)	p	Trend	Rate reduction (%)
Rio de Janeiro proper (state capital)					
Male	$y = 26.548 - 1.8158x$	71.72	< 0.01	Constant downward	43.2
Female	$y = 20.137 - 1.7658x$	64.41	< 0.01		41.6
Metropolitan Region (except state capital)					
Male	$y = 19.192 - 1.2136x$	42.92	< 0.05	Constant downward	51.3
Female	$y = 15.716 - 1.3294x$	90.31	< 0.001		52.2
Rest of state					
Male	$y = 19.913 - 0.7073x$	77.92	< 0.01	Constant downward	30.8
Female	$y = 15.196 - 1.3165x$	50.00	< 0.05		45.7

p = significance level; R² = coefficient of determination.

protocols and the use of chemotherapeutic agents and combination regimens, which have substantially improved survival of pediatric cancer patients, particularly those with hematological malignancies.^{10,16}

Advances in treatment and improvements in diagnosis of leukemia have been increasing survival of affected children. In Recife (state of Pernambuco), overall five-year survival rates for childhood leukemia have risen from 32% (1980–1989) to 63% (1997–2002)¹⁷. Furthermore, treatment discontinuation and disease relapse rates on the order of 16 and 14%, respectively, were reported in the 1980s; between 1997 and 2002, these rates were 0.5 and 3.3% respectively.

A case series of all patients admitted to the São Paulo Cancer Hospital for treatment (including previously treated patients admitted for recurrent disease) also reported

improvement in five-year survival, which reached 55% between 1995 and 1999, up from 13% two decades before (1975–1979).¹⁸

In addition to increased survival, reductions in childhood cancer mortality rates have also been reported in various locations – evidence of improvement in diagnosis and treatment services for pediatric cancer patients. In the United States, childhood leukemia mortality rates fell roughly 50% between 1975 and 1995, for a statistically significant decrease of 3.4% per year, in both genders and across several age ranges.¹⁶ Considering the length of survival in pediatric leukemia patients in Brazil, mortality rates similar to those reported in developed nations may be found.¹⁹ This achievement may be ascribed to modern treatment of childhood cancer, with individualized, specific therapy – surgery, radiation therapy, chemotherapy, or

hematopoietic stem cell transplantation – depending on the type of neoplasm. These advances in treatment and the use of specific protocols have made cure rates of 75% possible in acute lymphoblastic leukemia (ALL).²⁰

A large study conducted in 17 European countries (European cancer registry-based study on survival and care of cancer patients – EUROCCARE) to assess the impact of novel diagnostic and treatment methods introduced between 1983 and 1995 found that leukemias and lymphomas had the longest survival of all childhood cancers. EUROCCARE concluded in favor of the efficacy of advances in childhood cancer treatment in the studied countries, as results indicated that, due to new treatment models, the prevalence of adults with a history of childhood cancer is likely to increase.²¹

Viana et al.²² noted that experience in the treatment of a complex illness such as leukemia, coupled with adoption of a unified treatment protocol such as the Berlin-Frankfurt-Münster (BFM) regimen, increases the possibility of prolonged remission in children with acute myeloid leukemia (AML). However, an assessment of the BFM protocol conducted in Brazil reported overall five-year survival rates of 50.8%, lower than those found in USA and European studies.²³

In several locations, the incidence of ALL is reportedly higher among male children than among girls.^{3,5,24} In Brazil, studies conducted in the city of São Paulo have also shown higher mortality rates in boys as compared to girls.⁷ The present study detected a similar pattern in mortality: through most of the series, childhood leukemia mortality rates were higher in male patients.

This study sought to characterize leukemia mortality trends in children and adolescents under the age of 15 in the state of Rio de Janeiro. Originally, data were to be analyzed at the municipal level; however, given the absence of leukemia deaths in many municipalities, the choice was made to group cases into eight predefined state health regions (Metropolitana, Serrana, Médio Paraíba, Norte, Baixada Litorânea, Noroeste, Centro-Sul, and Baía de Ilha Grande) for which data were available in the DATASUS system.¹¹ However, uneven population distribution across these existing health regions made reliable analysis impossible. We therefore chose to divide the state into three broad regions for analysis: the city of Rio de Janeiro proper (the state capital), the Rio de Janeiro Metropolitan Region (excluding the city of Rio de Janeiro), and the rest of the state.

Comparison between regions showed that childhood leukemia mortality rates declined most markedly in the city of Rio de Janeiro proper. Mortality declined 42.5% in the capital (from 31.55 per 1,000,000 in children under the age of 15 between 1980 and 1982 to 18.14 per 1,000,000 between 2004 and 2006), 34.8% in the Rio de Janeiro Metropolitan Region (from 22.11 to 14.41 per 1,000,000 respectively), and 47.4% in the remainder of the state (from 20.91 to 10.98 per 1,000,000 respectively).

Between 2001 and 2003, leukemia mortality rates in children under the age of 15 in the city of Rio de Janeiro (11.6 and 17.8 deaths per 1,000,000 in males and females respectively) were higher than those recorded in the USA (7.0 and 8.6 per 1,000,000 respectively) and Western Europe (6.3 and 9.9 per 1,000,000 respectively), whereas rates reported in Eastern Europe for the same period (13.8 and 17.6 per 1,000,000 respectively) were similar to those found in Brazil.²⁵

In short, the childhood leukemia mortality trends found by the present study in the state of Rio de Janeiro are likely due to improved access to healthcare allowing early diagnosis, which in turn translates to reduced mortality rates. Overall, the data presented herein are consistent with the current knowledge, as access to health services and early diagnosis are of the utmost importance in the prognosis of leukemia.

Although mortality rates are not directly representative of health care accessibility with respect to cancer treatment, analysis of childhood cancer mortality rates may serve as an indicator of the efficacy of cancer intervention strategies in the studied age range.¹⁰

One possible limitation of this study concerns quality of information, ranging from the quality of information collection and entry processes to the availability of data retrieved from the Mortality Information System. Furthermore, information is usually entered into the dataset by clerical staff and non-medical professionals, and the system is thus subject to error, misinformation, and even missing data. In the state of Rio de Janeiro, however, a highly qualified agency has standardized mortality information for several years; the percentage of overall deaths attributed to poorly defined causes has thus been low (3.75% of childhood deaths as 2007)¹¹ since the 1980s.²⁶⁻²⁸

Conclusions

We detected a downward trend in childhood leukemia mortality in the state of Rio de Janeiro, most prominently in the state capital. This mortality pattern is consistent with that described in the international literature, and may be due to improved population access to diagnostic services and earlier diagnosis and treatment of hematological malignancies.

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