

Childhood cancer mortality trends in Brazil, 1979 – 2008

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OBJECTIVES: Childhood cancer mortality has substantially declined worldwide as a result of significant advances in global cancer care. Because limited information is available in Brazil, we analyzed trends in childhood cancer mortality in five Brazilian regions over 29 years.

METHODS: Data from children 0-14 years old were extracted from the Health Mortality Information System for 1979 through 2008. Age-adjusted mortality rates, crude mortality rates, and age-specific mortality rates by geographic region of Brazil and for the entire country were analyzed for all cancers and leukemia. Mortality trends were evaluated for all childhood cancers and leukemia using joinpoint regression.

RESULTS: Mortality declined significantly for the entire period (1979-2008) for children with leukemia. Childhood cancer mortality rates declined in the South and Southeast, remained stable in the Middle West, and increased in the North and Northeast. Although the mortality rates did not unilaterally decrease in all regions, the age-adjusted mortality rates were relatively similar among the five Brazilian regions from 2006-2008.

CONCLUSIONS: Childhood cancer mortality declined 1.2 to 1.6% per year in the South and Southeast regions.

KEYWORDS: Mortality Rate; Childhood Cancer; Leukemia; Trends.

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■ INTRODUCTION

Although mortality rates due to childhood leukemia and other cancers have substantially declined in several parts of the world, significant differences in specific patterns have been observed in certain regions (1-3). Favorable trends are less pronounced in less-developed regions, including Latin America (1,4,5). Cancer mortality statistics in low- and middle-income countries suffer from predictable sources of error, including inaccurate death certificates, misdiagnosis, and underreporting (1,5,6). Brazil demonstrates great heterogeneity in cultural and socioeconomic patterns across five geographic regions. In the 1970s, death certification quality, completeness, and reporting of ill-defined deaths differed among the five regions, with adequate coverage in the Southeast and South and poor coverage in the North and Northeast. National government agencies have exerted

continuous efforts to improve death certification quality, and the proportion of ill-defined deaths has achieved acceptable quality in all regions since 2006 (6).

The objectives of this study were to describe childhood cancer and leukemia mortality in the five geographic regions of Brazil and to evaluate trends in mortality over 29 years (1979-2008) using joinpoint regression analysis (7).

■ METHODS

Brazil was divided into five geographic regions: North, Northeast, Southeast, South, and Middle West (Table 1). Data from children 0-14 years old were extracted from the databases of the Brazilian Health Mortality Information System for the years 1979 to 2008. (<http://www.datasus.gov.br>) The age range of 0-14 years was chosen based on the criteria used by SEER (Surveillance, Epidemiology and End results; [www.http://seer.cancer.gov](http://seer.cancer.gov)) and IARC (International Agency for Research in Cancer; <http://www.iarc.fr>) in their international monographs.

Death-related information was organized according to gender, age group, state (place of residence), and cause of death (malignant neoplasm according to the International Classification of Diseases and Related Health Problems, ICD-9 (1979-95) and ICD-10 (1996-2008)) (8,9). The analysis

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Table 1 - Socioeconomic characteristics of Brazil and its regions.

	Brazil	North	Northeast	Middle West	Southeast	South
Total Population (2008)	189,612,814	15,142,684	53,088,499	13,695,944	80,187,717	27,497,970
Population 0-14 years (2008)	49,476,645	4,956,629	15,375,104	3,623,141	19,056,866	6,464,905
GNP* per capita	14,056.27	8,706.43	6,663.58	17,457.89	18,615.63	16,020.11
Income less than 1/4 minimum wage per family (%)	11.33	15.49	23.10	6.80	5.50	4.84
Illiteracy Rate (% population 15 and more years old)						
Male Population	10.16	11.21	21.06	8.24	5.25	5.00
Female Population	9.78	10.26	17.89	8.12	6.32	5.87
Total	9.96	10.73	19.41	8.18	5.81	5.45
Under 5 year Mortality Rate (2007)	24.07	26.32	35.2	20.18	17.08	15.11

Source: MS/SVS/DASIS/CGIAE/Indicators and Health Information (IDB), 2009. North Region: Acre, Amapá, Amazonas, Pará, Rondônia, Roraima, and Tocantins. Northeast Region: Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Rio Grande do Norte, and Sergipe. Southeast Region: Espírito Santo, Minas Gerais, Rio de Janeiro, and São Paulo. South Region: Paraná, Rio Grande do Sul, and Santa Catarina. Middle West Region: Brasília, Goiás, Mato Grosso, and Mato Grosso do Sul. GNP: Gross National Product.

included examination of the number of deaths, age-adjusted mortality rates (AAMRs), crude mortality rates, and age-specific mortality rates (ASMRs) by geographic region and for the entire country. AAMRs were calculated according to all cancer deaths and leukemia, gender, and time period via a direct method using the proposed world population in age groups less than 14 years old (10). For ASMRs, gender and time period were calculated by age groups defined as less than 1, 1-4, 5-9, and 10-14 years. To identify significant changes in the trends for all childhood cancers and leukemia, we performed joinpoint regression analysis to establish the best cut-point period for measuring the trends described elsewhere (www.srab.cancer.gov/joinpoint) (7). Significance was determined with the Monte Carlo Permutation method. The models either incorporated the estimated variation for each point when the responses were AAMRs or used a Poisson model of variation. In addition, the models could also be linear on the log of the response to calculate the annual percentage rate change. Because the proportion of ill-defined deaths achieved a quality control standard (less than 10% in all five Brazilian regions) in 2006-2008, the age-specific mortality rate was analyzed for this period (Supplemental Table 1).

RESULTS

Figure 1 depicts the trends in AAMR from all childhood cancers and from leukemia for 1979-2008 in the entire country and according to the five major regions. The AAMRs showed a trend toward stability in the entire country (36.91 deaths per million in 1979 and 39.83 deaths per million in 2008) for all cancers and a slight decrease for leukemia (14.33 deaths per million in 1979 and 13.83 deaths per million in 2008). The North and Northeast regions experienced increased mortality rates, while the rates decreased in the South and Southeast and were stable in the Middle West (Figure 1).

The joinpoint analysis of the AAMR (ages 0-14 years) for all childhood cancers and leukemia according to gender and region is shown in Table 2. Mortality from all childhood cancers from 1979-2008 demonstrated a slight but significant decline in boys of almost 0.5% per year (average annual percent change (AAPC) = -0.34) and was stable in girls (AAPC = -0.03). In the North and Northeast regions, there was a significant increase of 2 to 3% per year (boys and girls). In the Middle-West, South, and Southeast, the

mortality rate decreased significantly from 0.5 to 1.5% per year for boys and girls (Table 2).

A significant decline in leukemia of about 1% per year was observed in both genders (AAPC = -0.98 and -0.81 for boys and girls, respectively). Mortality due to childhood cancers declined over the entire period, with AAPCs of -1.41 for boys and -1.21 for girls in the Southeast and AAPCs of -1.57 for boys and -1.21 for girls in the South. The North (AAPC = +2.09 boys, +2.07 girls) and Northeast (AAPC = +2.52 boys, +2.80 girls) regions experienced significant increases of 2% per year in mortality rates. For leukemia, the same pattern of mortality decline occurred in the South and Southeast, but the mortality rates increased in the North and Northeast. A stable mortality rate was recorded in the Middle-West region except for boys, who experienced a significant decline for leukemia (AAPC -1.41).

Table 3 contains the AAMR data for all childhood cancers and for leukemia for 2006-2008. Similar mortality rates were recorded for all cancers among the five geographic regions of Brazil. The only difference was observed in some age groups among the regions; higher mortality rates were reported for the 0-year and 1-4-year groups in the Northeast and Middle West regions. Leukemia AAMRs were higher for boys in the North region (data not shown). During the first year of life, lower mortality rates were observed in the Southeast, while the mortality rate in the North was the highest.

DISCUSSION

Childhood cancer mortality rates have decreased significantly in recent decades and have remained fairly constant since 1997 (11). Less-developed countries, including many countries in South America, have experienced less favorable outcomes. However, a major limitation of mortality rate analyses is the availability of high-quality vital statistics (1,12). Mortality rates should be analyzed with caution because they are affected by the quality of diagnosis data, quality of death certification, socioeconomic characteristics, and medical facilities specializing in pediatric oncology.

Since 1988, a complex health system (the Unified Health System) has been under development in Brazil and has substantially improved access to health care. Infant mortality decreased from 114 per 1,000 live births in 1970 to 19.3 per 1,000 live births in 2007 (13). Although the disparity is decreasing, geographic and social inequalities still exist; in

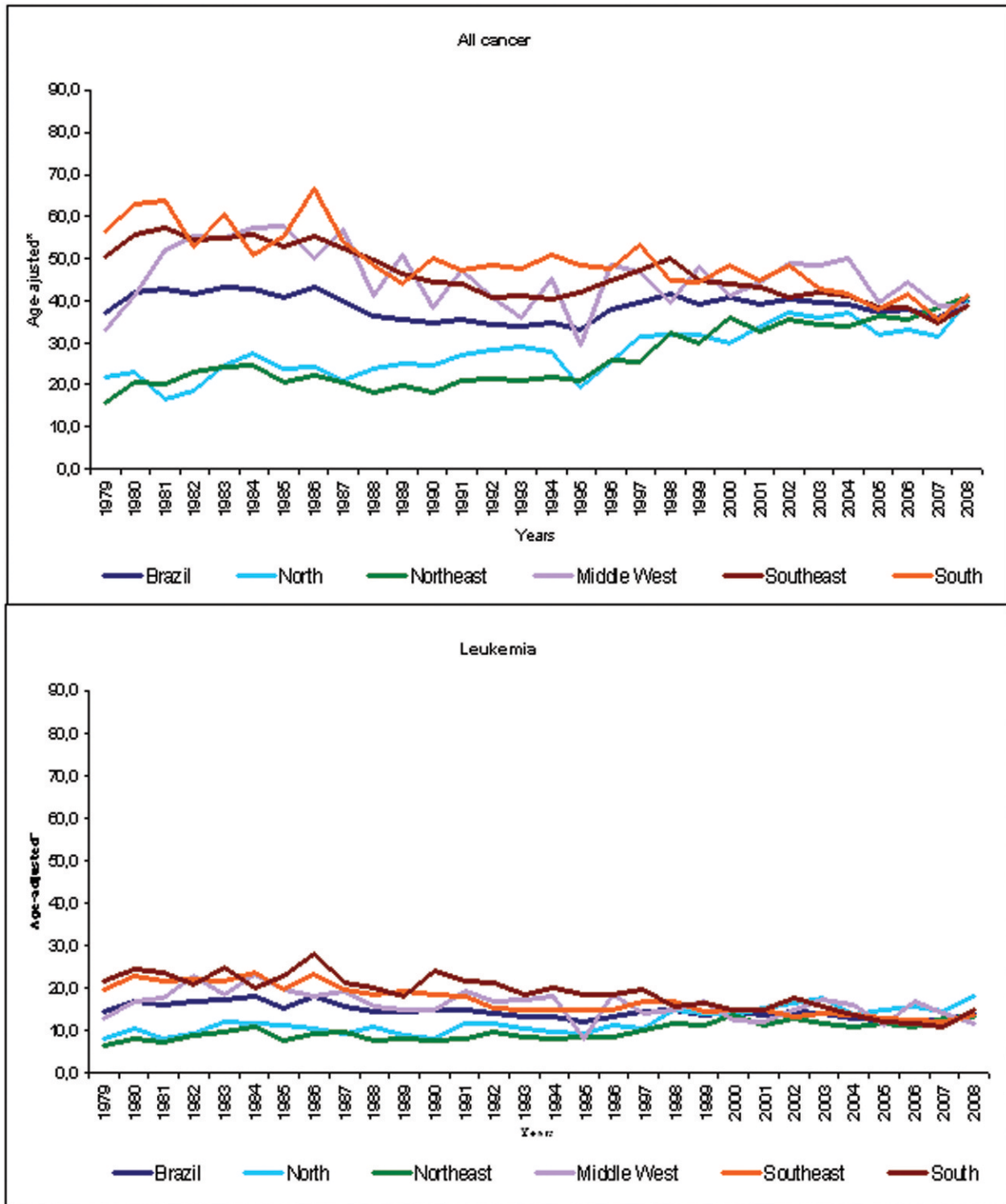


Figure 1 - Trends in age-standardized 0-14 years mortality rates for all childhood cancers and leukemias in Brazil and its 5 different regions.

the Northeast region, the infant mortality rate is 2.24 times higher than that in the South region (14). Pneumonia mortality for children aged 4 years and younger decreased significantly from 1991 to 2007 in all regions of Brazil, but the smallest decrease occurred in the North and Northeast regions in children younger than one year (15). Several

initiatives have contributed to this decline, including promotion of breastfeeding, oral rehydration, and immunizations. Malnourishment in children less than 5 years old has significantly decreased in the past 17 years, from 7.1% to 1.8% for low-weight children and 19.6% to 6.8% for low-height children (16). Vaccination reached universal coverage



Table 2 - Joinpoint analysis for all childhood cancers and leukemia mortality in boys and girls.

	GIRLS																	
	BOYS						GIRLS											
	Trend 1		Trend 2		Trend 3		Trend 4		Trend 1		Trend 2		Trend 3		Trend 4			
Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	Period	APC	
All cancers																		
Brazil	1979-1984	2.03	1985-94	-3.08*	1995-97	7.36	1998-08	-0.59	1979-81	11.21	1982-1993	-2.44*	1994-98	4.77	1999-08	-0.84	-0.03	
North	1979-2008	2.09*						1979-08	2.07*								2.07*	
Northeast	1979-1983	10.09*	1984-94	-1.99*	1995-98	12.65*	1999-08	1.95*	1979-82	13.23*	1983-1988	-5.51	1989-08	4.60*				2.80*
Middle West	1979-1984	13.07*	1985-90	-7.79	1991-08	0.25			1979-08	-0.22								-0.22
Southeast	1979-1986	0.21	1987-93	-4.75*	1994-97	4.09	1998-08	-2.06*	1979-81	11.34	1982-1994	-3.03*	1995-98	5.73	1999-08	-3.28*		-1.21*
South	1979-2008	-1.57*							-1.57*	1979-08	-1.21*							-1.21*
Leukemia																		
Brazil	1979-1984	4.01	1985-88	-5.96	1989-08	-0.55*			1979-08	-0.81*								-0.81*
North	1979-2008	2.02*						1979-08	2.50*									2.50*
Northeast	1979-1983	18.36*	1984-88	-7.24	1989-08	2.73*			1979-08	1.83*								1.83*
Middle West	1979-2008	-1.41*						1979-08	-0.86									-0.86
Southeast	1979-2008	-2.12*						1979-08	-2.21*									-2.21*
South	1979-2008	-2.45*						1979-08	-2.45*									-2.45*

APC indicates estimated annual percent change; AAPC, average annual percent change. * Significantly different from 0 ($p < 0.05$).

in the 1980s and is provided by the government. Poliomyelitis was eliminated from Brazil in 1989, and the last autochthonous case of measles occurred in 1999 (14).

Awareness of childhood cancer has increased since the 1980s, and several government and nongovernment initiatives have been implemented. In 1997, the Brazilian Ministry of Health and the Bank of Brazil Foundation together with the Brazilian Pediatric Oncology Society (SOBOPE) developed a program to promote early recognition of childhood cancer with better diagnostic procedures, better adherence to treatment protocols, and extensive pediatric oncology training. There has been a clear improvement in recognition and classification of leukemia with this approach (17). An early diagnosis program supported by a nongovernment organization was implemented in 2008. Its main objective is to train health family teams in the early recognition of signs and symptoms of cancer and to contribute to the organization of a network for referrals in various regions of the country.

Despite heterogeneity among the regions in Brazil, the AAMRs were similar from 2006-2008, and over 29 years, a slightly decreasing trend was observed in the Southeast and South regions. Several isolated institutions have significantly improved the treatment of childhood cancer. Following adherence to treatment protocols, children treated in specialized centers experienced a dramatic improvement in survival. In Recife, a city in the Northeast, a significant improvement in survival for children with acute lymphoblastic leukemia was reported following the establishment of a twinning program (16). The Pediatric Department of the Hospital A. C. Camargo in São Paulo, an isolated specialized cancer center, analyzed 3,827 children and adolescents 0-18 years old with cancer and leukemia and reported a significant decrease in mortality rates from 1975-1999 (from 81% to 33%; $p < 0.001$) (18). The Instituto Nacional de Câncer in Rio de Janeiro assessed 163 patients with rhabdomyosarcoma over 18 years and reported that 39.3% of the patients had metastatic disease at diagnosis, and the overall survival rates for clinical groups I+II, III, and IV were 79.6%, 68.3%, and 17.8%, respectively ($p < 0.001$). Low weight (body mass index $< 10^{\text{th}}$ percentile at diagnosis) emerged as an independent adverse prognostic factor (19).

Outcomes in children with cancer are much better following treatment by a multidisciplinary team in a pediatric cancer center (20,21). SOBOPE has established cooperative groups with planned clinical trials, which may potentially impact survival and mortality rates. The Brazilian Cooperative Group for Treatment of Childhood Acute Lymphocytic Leukemia (ALL) reported a 5-year overall survival of 92.5% among 544 children with low-risk ALL in several Brazilian centers (22). A recent study from the Osteosarcoma Brazilian Group indicated an overall survival of 60% for patients with nonmetastatic disease; a large tumor size was observed in 43% of the cases and was not associated with longer lag time (23). After the introduction of a standard protocol, the five-year overall survival for high-risk patients with germ-cell tumors was 83.3%, which is particularly relevant to the treatment protocols in small institutions with limited experience in the treatment of this rare disease (24).

An impressive decrease in mortality from ill-defined causes in all regions was observed from 1979-2008. The Mortality Information System was created in 1975 in Brazil, and since that time, steps have been taken to improve the

**Table 3** - Age-adjusted* and crude (0-14 years) mortality rates for all cancers and leukemia by age group in Brazil and its regions (2006-2008) per million children.

		Age	Brazil	North	Northeast	Middle West	Southeast	South
All cancer	Specific rates	0	40.43	33.59	49.55	45.13	36.60	32.60
		1-4	40.09	39.33	41.24	46.09	38.14	40.39
		5-9	36.61	30.34	34.86	36.95	39.15	37.86
		10-14	36.17	34.93	35.45	38.25	34.71	41.71
	Rates per million	Crude	37.62	34.49	37.68	40.35	37.21	39.52
		*Age-adjusted	37.86	34.71	38.15	40.79	37.35	39.36
Leukemia	Specific rates	0	11.43	14.93	13.49	14.60	8.19	11.37
		1-4	12.57	16.28	11.18	12.57	12.73	12.37
		5-9	13.10	14.62	12.11	14.37	13.73	11.76
		10-14	13.38	17.37	12.89	15.56	12.51	12.97
	Rates per million	Crude	12.95	15.99	12.22	14.31	12.70	12.31
		*Age-adjusted	12.89	15.96	12.15	14.18	12.64	12.27

*World Standard Population, modified by Doll et al. (1966).

quality of mortality data. In 2005, a thorough and careful supervision effort was performed to improve the quality of death certification in the Northeast and North. Fewer than 10% of ill-defined causes were recorded in the Southeast since 1979. This benchmark was reached in the South and Middle West regions in 1988 and in the Northeast and North in 2006. This change may underlie the documented increased cancer mortality rates in the North and Northeast regions. A consistent decrease in mortality rates due to childhood leukemia in Brazil and greater decreases in the South and Southeast were observed from 1980 to 2002. These decreases included a higher mortality rate for boys compared with girls, as confirmed by our data for 2006 to 2008. The leukemia mortality rate in the state of Rio de Janeiro declined during 1980 and 2006 and was also more pronounced in boys (25).

Correlations have been noted between social inequality and changes in mortality, with more pronounced decreases in mortality in the Brazilian regions with better socioeconomic conditions (5). Socioeconomic status plays a key role in health care due to factors such as access to health care services and specialized centers, availability of hospital beds, physician density, adherence and abandonment of treatment, early diagnosis, and clinician-parent communication. Despite improvements in childhood cancer survival in specialized centers, these improvements did not translate into a significant decline in mortality in Brazil or its regions. Socioeconomic inequalities may explain the divergence between hospital data and population-based registry data (26,27). According to a population-based registry study in São Paulo, the probability of survival for 60 months was 40% for patients 0-14 years of age with cancer (27).

The year 2006 may be considered a starting point for regional monitoring because quality control standards were achieved in the five geographic regions of Brazil and ill-defined deaths represented less than 10% of all deaths. During this period, the mortality rates were similar among all the regions, regardless of socioeconomic characteristics; the curves for the North and Northeast may still be climbing, or competitive risks of death may be masking mortality rates from cancer. The assessment period here was short, and longer periods will be necessary to evaluate comprehensive trends.

These observations need to be explored in further studies, including population-based cancer survival studies. Surveillance of childhood cancer mortality should be well

maintained as a major resource for health planning and as a base to monitor the effectiveness of implemented strategies. Substantial challenges remain, and socioeconomic issues and adoption of integrated treatment strategies should be addressed to improve mortality rates due to childhood cancers in Brazil. This study is consistent with previous studies from Brazil showing that the magnitude of cancer mortality rates is generally lower than that observed in developed countries (28-30).

AUTHOR CONTRIBUTIONS

Ferman S, Santos MO, and Camargo BD reviewed and discussed the data. Ferreira JM, Oliveira JF, and Santos MO analyzed the data, and Oliveira MS, Ferman S, and Camargo BD contributed to the writing of the manuscript. All the authors participated in the interpretation of results and read and approved the final manuscript.

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Supplemental Table 1 - Percentage of ill-defined mortality in children (0-14 years old) in Brazil and its regions (1979-2008).

Years	BRAZIL	NORTH	NORTHEAST	MIDDLE-WEST	SOUTHEAST	SOUTH
1979	24.4	25.0	53.1	13.4	6.4	15.0
1980	26.4	25.5	54.6	12.5	5.7	14.5
1981	24.7	21.9	52.1	12.9	4.7	14.6
1982	22.4	23.0	47.7	12.5	4.6	13.0
1983	23.8	23.6	47.3	13.3	4.9	12.8
1984	25.6	26.1	50.1	12.8	4.6	12.6
1985	23.9	24.7	45.6	11.9	7.5	11.9
1986	24.2	26.2	45.8	12.7	7.1	11.1
1987	23.5	25.4	45.1	12.6	6.6	11.2
1988	22.4	25.0	44.7	10.9	5.8	10.3
1989	20.7	24.3	41.6	9.0	5.7	10.8
1990	19.7	27.9	40.2	9.4	5.7	10.3
1991	19.6	25.6	39.3	9.2	6.7	8.5
1992	18.5	24.1	36.3	8.4	7.0	8.3
1993	19.2	23.6	38.0	8.3	7.0	7.8
1994	16.9	22.7	32.9	8.2	7.0	7.9
1995	14.3	18.3	27.8	7.4	6.3	7.3
1996	12.9	17.5	25.5	6.1	5.9	6.3
1997	11.8	17.3	23.1	5.1	5.2	5.1
1998	12.7	16.9	23.0	6.4	5.8	6.3
1999	12.2	15.8	21.2	5.2	6.6	5.3
2000	12.5	16.8	21.3	4.4	6.4	4.8
2001	10.8	14.6	17.7	3.8	5.8	4.6
2002	9.9	15.5	15.2	3.6	5.2	4.5
2003	9.4	14.8	14.2	3.0	5.2	4.9
2004	8.0	13.6	11.8	3.0	4.6	3.7
2005	6.3	11.3	7.8	3.1	4.5	4.0
2006	5.4	9.8	5.0	3.5	5.0	3.9
2007	4.8	8.9	4.2	2.6	4.6	4.0
2008	4.9	8.4	4.5	3.0	4.7	3.9

Source: MS/SVS/DASIS/CGIAE/Sistema de Informação sobre Mortalidade – SIM.