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Incidence and mortality of myeloid malignancies in children, adolescents and Young adults in Brazil: A population-based study

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ABSTRACT

Background: Myeloid malignancies (MM) are heterogeneous when it comes to incidence rates and pathogenesis. These variation rates are important to generate hypotheses on causal aetiology. This study aimed to describe incidence and mortality patterns of MM among children, adolescents and young adults (cAYA) in Brazil and to evaluate trends in incidence and mortality rate overtime.

Methods: Data were extracted from a dataset of 15 Population-based Cancer Registries located in five Brazilian geographical regions and calculated by age-specific, crude, and age-standardized incidence (ASR) and mortality rates per million persons. Joinpoint regression analyses were performed for trends evaluations, regionally. Annual Percent Change (APC) and Average Annual Percent Change (AAPC) were also estimated.

Results: The overall ASR for incidence and mortality of MM in Brazil was 14.57 and 8.83 per million, respectively. The AML (non-APL AML and APL) incidence rate is 8.18 per million, whereas other MM subtypes altogether have an incidence rate of 2.62 per million, and not otherwise specified (NOS) is 3.70 per million. The analysis of incidence trends (AAPC) showed a significant decline in Manaus (-5.6%) and São Paulo (-4.7%), and a significant increase was observed in Fortaleza (5.8%). Mortality trends steadily declined in all registries, with significant declines occurring in Goiânia (-1.5%), Belo Horizonte (-2.3%), São Paulo (-2.5%), Curitiba (-2.8%)

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and Porto Alegre (-4.1%).
Conclusion: Our findings showed differences in the incidence and mortality rates of MM in cAYA in Brazil, geographically. Infants-AML have the highest incidence within the cAYA population (17.42 per million). There was a substantial decrease in mortality rate observed, which was interpreted as an improvement in MM recognition and therapeutic approach.

1. Introduction

Myeloid malignancies (MM), which include acute myeloid leukaemia (AML), are heterogeneous diseases. Classification is based on the cytomorphology, immunophenotyping and cytogenetics subtypes according to World Health Organization (WHO) recommendations to predict clinical relevance in outcome [1,2]. The late ICD edition (ICD-O-3) proposed by WHO is very important added terms and code changes for haematological diseases, mainly leukaemias in the activities of Population-Based Cancer Registry (PBCR), necessary to monitor status and changes at the population level of such malignancies associated with environmental factors [3,4]. All PBCR cancer control programs are under constant scrutiny to avoid inaccurate population data and all the consequences of country economic instability and population movements. The interpretation of such variables is particularly critical in low and middle-income countries (LMIC) [5,6].

In Europe the incidence of all MM is approximately 10 cases per million in children under 15 years of age at diagnosis and 12 cases per million in adolescents and young adults [7]. Meanwhile, in the United States (US) a small difference in incidence rates was found between Hispanic (8.2 per million) and non-Hispanic white (7.7 per million) children in California [8]. Variations in AML incidence rates ranging from 1 to 15 cases per million have been reported around the world [9]. These variations rates are important to generate hypotheses for causal aetiology and carcinogenesis [6]. Recently, two population-based studies in Brazil have demonstrated incidence rate variations in MM according to regional areas and age range strata, and these data continue to be interpreted with caution because of regional socioeconomic inequalities would compromise health access care and correct diagnosis given that these variables would effected PBCR information [10,11]. For instances, in a recent case-cohort study, childhood AML was strongly associated with occupational maternal exposures during pregnancy agricultural or petrol chemicals (adjOR, 2.18) in Brazil [12]. Herein, we aimed to critically revisit the incidence and mortality rates among children, adolescents and young adults (cAYA), as well as to evaluate trends in incidence and mortality rates of MM in Brazil. There is no doubt that, to accurately ascertain cancer incidence, constant monitoring and research is required.

2. Material and methods

2.1. Study Population, data sources and extraction

Incidence and mortality data on Brazilian children (age 0–14 years), adolescents (age 15–19 years) and young adults (age 20–29 years) diagnosed with MM during the 10-year time frame (2000–2009) were obtained from the databases of 15 PBCRs, as shown in Fig. 1. Brazilian cancer registries correspond to local records by state, located in capitals and metropolitan regions, which gather information on diagnosed incident cancers in the contributing registration areas. The PBCRs are located in five different geographical regions of Brazil distributed as follows: two cities in the North region (Belém and Manaus), four in the Northeast (Aracaju, Fortaleza, João Pessoa and Recife), two in the Middlewest (Cuiabá and Goiânia), five in the Southeast (Barretos, Belo Horizonte, Espírito Santo, Jahu and São Paulo) and two in the South (Curitiba and Porto Alegre) region. The coverage areas per Brazilian region with contributing PBCRs are shown in Table 1. For the incidence and mortality rates, the same 10-year period was used. Patient information in each registry was collected according to standardized criteria recommended by the International Agency for Research on Cancer (IARC) for Cancer Registries [13]. Data were collected by uniformly trained personnel in each coverage PBCR area. Data evaluated for this study include cases collected as microscopically verified (MV), and the also those identified from death certificate only (DCO). Only datasets with high-quality data were eligible for inclusion in the analyses. Incidence data were extracted from the website of Instituto Nacional de Cancer (INCA) (https://www.inca.gov.br/BasePopIncidencias/Home.action), mortality data from the databases of the Brazilian Health Mortality Information System (from the complete calendar, spanning from 1979 to 2015) for the respective PBCR coverage areas, extracted from the On-Line Mortality Atlas (https://www.inca.gov.br/app/mortalidade), and population data from the databases of the Brazilian Institute of Geography and Statistics (http://www.datasus.gov.br).

This study design was reviewed and approved by INCA's Ethics Committee on February 7th, 2018#CAAE Nº: 81841718.1.0000.5274.

2.2. Case definition and variables

The information on leukaemia cases included coded data on age, date of birth, date of diagnosis, tumour sequence number, morphology, and the currently valid leukaemia basis of diagnosis. Incidence cases of MM were classified using the revised version of ICD-O-3 accordingly [1]. Cases in which the ICD-O 2nd Edition codes were used were converted to ICD-O-3 codes, as shown in Supplementary Table 1. The AML cases were divided into two subgroups, non-acute promyelocytic leukaemia AML (non-APL AML) and APL, because APL cases have unique characteristics regarding cytogenetics, treatment and clinical outcomes. Myeloproliferative neoplasms (MPN), myelodysplastic syndrome (MDS) and myelodysplastic and myeloproliferative neoplasms (MDS/MPN) cases were grouped together as Others, due to the small number of cases. Cases of mortality due to MM were classified using the International Classification of Diseases, ICD-10 [14]: myeloid leukaemia (C92), monocytic leukaemia (C93), other leukaemia of specified cell type (C94), leukaemia of unspecified cell type (C95) and myelodysplastic syndromes (D46).

2.3. Statistical methods

Incidence and mortality rates of all MM were calculated as annual number of cases per million person-years, grouped by the 15 PBCR cities in representative geographical regions (North, Northeast, Middlewest, Southeast and South) of Brazil, and in five age groups strata (< 1 year, 1–4 years, 5–9 years, 10–19 years and 20–29 years). The 10-year period from 2000 to 2009 was harmonized with available information for each PBCR shown in Table 1. The incidence was calculated as the number of cases divided by the number of person-years in the categories of geographical area, age, and diagnostic group for the given 10-year period and expressed per million person-years. Mortality was calculated as the number of deaths divided by the number of person-years in the categories of geographical area and age, for the given 10-year period and expressed per million person-years. Age-standardized incidence and mortality rates (ASR) per million person-years were calculated using the World Standard Population as proposed by Segi [15] and modified by Doll and colleagues [16]. The 95% confidence intervals (CI) for incidence and mortality age-standardized rates

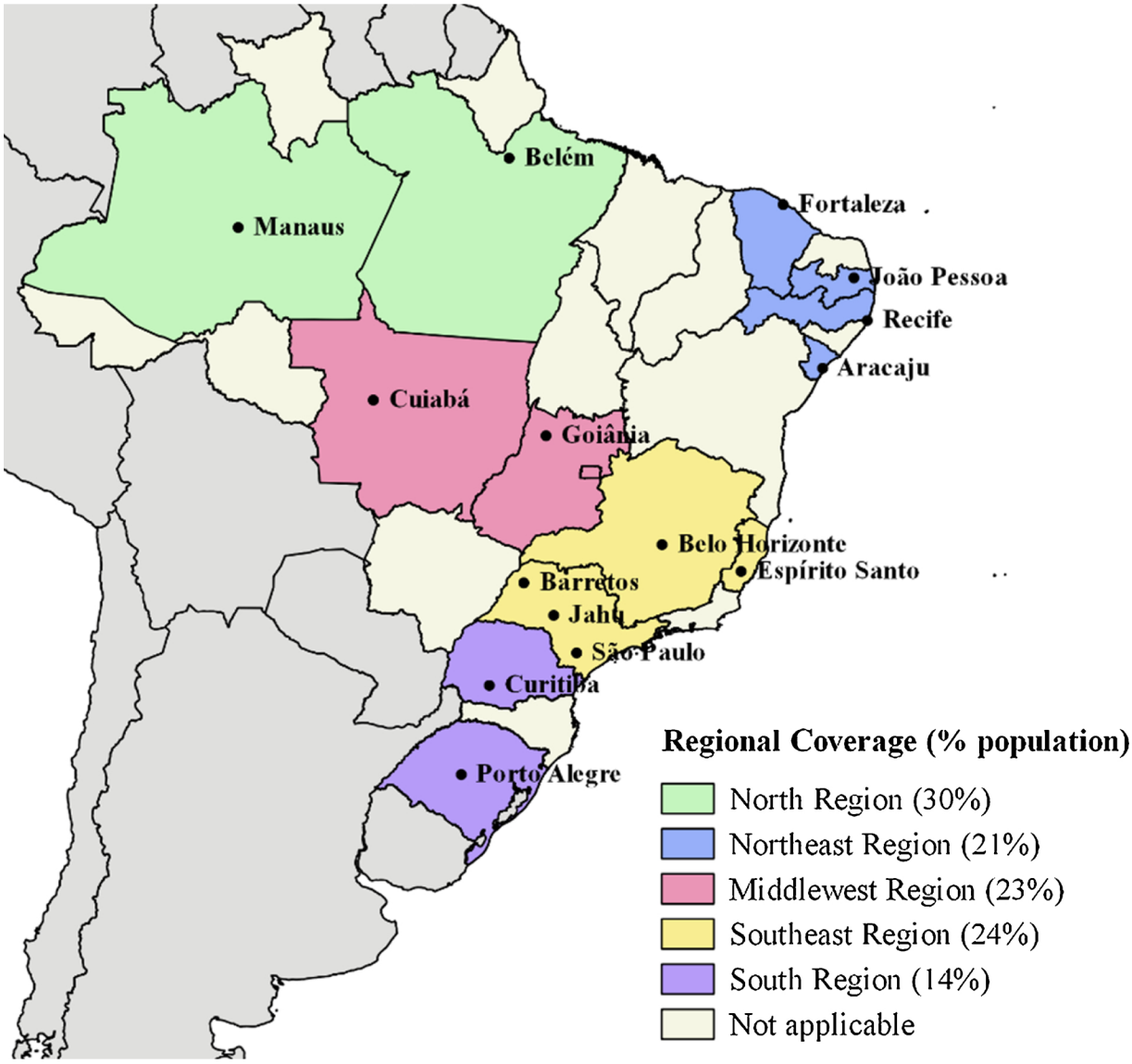

Fig. 1. Percentual Coverage of populations of children, adolescents and young adults (0–29 years old) in the Population-Based Cancer Registries (PBCRs).

were calculated using the Poisson approximation [13].

Joinpoint regression (JR) model was performed to identify changes in the trends for MM incidence and mortality rates [17]. The software was provided by the Surveillance Research Program of the US National Cancer Institute, version 4.6.0.0 (https://surveillance.cancer.gov/joinpoint). To minimize the variability inherent in the small number of observations, the logarithm of the rates was used in the total dataset, for each PBCR and by region. To describe linear trends by period, annual percent changes (APC) and average annual percent ranges (AAPC) were estimated with corresponding 95% CIs for each of the linear segments identified between two joinpoints. Significance was determined using the Monte Carlo Permutation method. This method is useful to identified changes in time trends directions.

3. Results

3.1. Incidence

The estimated Brazilian population covered by this study was 23%, varying between 14% and 30%, as shown in Fig. 1. The coverage area of PBCR, time trends, number of cases and sex ratio for incidence and mortality rates that contributed to these analyses are shown in more detail in Table 1. The proportion of microscopic verification was 80%, death certificate was 18.3% and the not-otherwise-specified (NOS) subtype accounts for 24.9% of cases. A total of 2,297 incident MM cases in cAYA from 15 Brazilian PBCR were observed. Among the total MM accrued non-APL AML and APL (55.8%), MPN, MDS and MDS/MPN (19.3%) and NOS (24.9%). The increased proportion of AML cases was observed among males in most of the regions in Brazil, ranging from 54.6% to 59.5%, with the exception of the Northeast region (48.2%).

The age-specific, crude and age-standardized (ASR) incidence rates for all MM by PBCR and Brazilian region coverage are shown in Table 2. The crude and ASR incidence for both males and females in Brazil was 15.11 and 14.57 per million, respectively. In general, the highest age-specific incidence rates were observed in infants (17.42 per million) and in young adults (20–29 years, 17.29 per million). The lowest were observed in children in the age strata 5–9 years of age (11.34 per million). The age-specific incidence rates have a similar pattern in all of the regions, however, the age-specific incidence rates in Northeast in infants (15.57 per million), 1-4 years of age (16.41 per million) and young adults (15.44 per million), are similar and all high. The ASR for the incidence of non-APL AML, APL, Others and NOS by geographical region in Brazil is shown in Fig. 2. The AML/APL incidence rate was 8.18 per million and Others MM subtypes have 2.62 per million. Among

Table 1
The coverage area by Brazilian region with contributing registries by period and constitution of datasets for various analyses.

			Incidence										Mortality			
Region	Registry	Coverage	Times trends	N	Range*	N*	M, %	F, %	M/F	MV, %	DCO, %	NOS, %	Times trends	N	Range*	N*
North	Belém	Capital city and County[a]	1996-2014	279	2000-2009	159	57.2	42.8	1.3	76.7	22.0	33.3	1979-2015	384	2000-2009	121
	Manaus	Capital	1999-2009	175	2000-2009	153	52.3	47.7	1.1	81.7	17.6	17.6	1979-2015	282	2000-2009	108
				454	2000-2009	312	54.8	45.2	1.2	79.2	19.9	25.6		666	2000-2009	229
Northeast	Aracaju	Capital city	1996-2013	55	2000-2009	27	48.1	51.9	0.9	88.9	11.1	7.4	1979-2015	103	2000-2009	18
	Fortaleza	Capital city	1990-2009	297	2000-2009	190	45.8	54.2	0.8	74.2	25.3	25.3	1979-2015	417	2000-2009	120
	João Pessoa	Capital city	1999-2013	103	2000-2009	61	59.0	41.0	1.4	93.4	3.3	45.9	1979-2015[e]	130	2000-2009	28
	Recife	Capital city	1995-2013	214	2000-2009	112	46.4	53.6	0.9	83.0	13.4	23.2	1979-2015 [e]	289	2000-2009	60
				669	2000-2009	390	48.2	51.8	0.9	80.8	17.4	26.7		939	2000-2009	226
Middlewest	Cuiabá	Capital city and County[b]	2000-2009	69	2000-2009	69	69.6	30.4	2.3	82.6	17.4	34.8	1979-2015	129	2000-2009	44
	Goiânia	Capital city	1988-2011	222	2000-2009	128	51.6	48.4	1.1	NA	NA	21.9	1979-2015	269	2000-2009	66
				291	2000-2009	197	57.9	42.1	1.4	82.6	17.4	26.4		398	2000-2009	110
Southeast	Barretos	Metropolitan area[c]	2000-2015	29	2000-2009	17	64.7	35.3	1.8	100.0	0.0	11.8	1979-2015	63	2000-2009	15
	Belo Horizonte	Capital city	2000-2012	201	2000-2009	156	59.0	41.0	1.4	72.4	23.7	16.0	1979-2015	516	2000-2009	94
	Jahu	County	1996-2015	21	2000-2009	11	45.5	54.5	0.8	100.0	0.0	9.1	1979-2015	17	2000-2009	3
	Espírito Santo	Metropolitan area[d]	1997-2012	143	2000-2009	84	57.1	42.9	1.3	78.6	17.9	22.6	1979-2015	245	2000-2009	72
	São Paulo	Capital city	1997-2013	1454	2000-2009	903	53.5	46.5	1.2	NA	NA	28.7	1979-2015	1888	2000-2009	511
South				1848	2000-2009	1171	54.6	45.4	1.2	77.2	19.4	26.1		2729	2000-2009	695
	Curitiba	Capital city	1998-2014	223	2000-2009	131	58.8	41.2	1.4	94.7	5.3	7.6	1979-2015	323	2000-2009	94
	Porto Alegre	Capital city	1993-2011	183	2000-2009	96	60.4	39.6	1.5	65.6	32.3	21.9	1979-2015	264	2000-2009	49
				406	2000-2009	227	59.5	40.5	1.5	82.4	16.7	13.7		587	2000-2009	143
Brazil			1988-2015	3,668	2000-2009	2,297	54.3	45.7	1.2	80.0	18.3	24.9	1979-2015	5,319	2000-2009	1,403

Note. N, total number cases; PBCR, Population-Based Cancer Registry; M, male; F, female; MV, microscopically verified cases; DCO, death certificate only; NOS, not otherwise specified; *Last 10 years period. [a]Belém (Capital) and Ananindeua; [b]Cuiabá (Capital) and Várzea Grande; [c]DRS Barretos (Altair, Barretos, Bebedouro, Cajobi, Colina, Colômbia, Guaíra, Guaraci, Jaborandi, Monte Azul Paulista, Olímpia, Severínia, Taiaçu, Taiúva, Taquaral, Terra Roxa, Viradouro and Vista Alegre do Alto; [d]Vitória (Capital), Cariacica, Vila Velha, Fundão, Guarapari. Serra and Viana; [e]Analyzed two periods:1979–2005 and.2007–2015.

Table 2
Age-specific, crude and age-standardized incidence rates of all myeloid malignancies in children, adolescents and young adults according PBCR coverage, geographic region, Brazil.2000–2009.

PBCR	Number of cases	Age-specific incidence rates					CR	ASR	
		< 1 year	1–4 years	5–9 years	10–19 years	20–29 years	00–29 years	00–29 years	95% CI
North									
Belém	159	9.10	14.04	12.00	15.88	14.89	22.04	14.30	14.26-14.33
Manaus	153	22.91	15.03	9.79	14.01	17.80	14.97	14.90	14.86-14.93
Total	312	16.20	14.54	10.90	14.99	16.25	17.89	14.60	14.56-14.63
Northeast									
Aracaju	27	11.71	2.89	6.92	8.01	13.99	9.43	8.80	8.78-8.83
Fortaleza	190	14.63	18.88	11.90	11.93	15.42	14.03	14.23	14.19-14.26
João Pessoa	61	18.75	20.86	29.90	9.25	16.72	16.67	17.47	17.50-17.43
Recife	112	17.17	14.88	8.89	14.33	15.41	14.02	13.89	13.86-13.92
Total	390	15.57	16.41	12.88	11.86	15.44	13.90	14.00	13.97-14.03
Middlewest									
Cuiabá	69	44.77	21.66	12.48	9.55	17.75	15.33	16.00	15.97-16.03
Goiânia	128	21.81	17.18	16.54	14.91	25.57	19.56	18.93	18.90-18.97
Total	197	31.51	19.09	14.81	12.69	22.55	17.83	17.79	17.75-17.82
Southeast									
Barretos	17	0.00	12.09	3.00	5.42	13.16	8.25	8.11	8.09-8.14
Belo Horizonte	156	11.31	10.43	11.63	13.16	13.85	12.81	12.54	12.51-12.56
Jahu	11	0.00	0.00	32.20	19.11	18.85	18.25	17.28	17.25-17.31
Espírito Santo	84	25.13	8.95	7.24	9.53	9.45	9.56	9.67	9.64-9.69
São Paulo	903	15.72	16.53	11.40	14.17	19.79	16.11	15.75	15.72-15.78
Total	1171	15.67	14.55	10.89	13.28	17.61	14.69	14.41	14.38-14.44
South									
Curitiba	131	23.94	12.38	12.30	12.19	17.74	14.57	14.33	14.30-14.36
Porto Alegre	96	20.00	13.56	4.76	17.70	14.54	14.15	13.87	13.84-13.90
Total	227	22.19	12.89	9.04	14.57	16.38	14.39	14.14	14.11-14.17
Brazil	2,297	17.42	15.03	11.34	13.34	17.29	15.11	14.57	14.54-14.61

Note. PBCR, Population-Based Cancer Registry; CR, Crude rates; ASR, Age-standardized 0–29 years (world standard population) incidence rates; CI, confidence interval.

the AML group, non-APL AML and APL subgroups presented ASR with incidences of 7.77 and 0.41 per million, respectively. The APL ASR incidence varied from 0.19 to 1.36 per million in the North and South regions, respectively. In the South region were observed the lowest ASR rate for NOS subtype code (2.01 per million), North, Northeast, Southeast (3.79-3.85 per million) whereas in the Middlewest regions, the ASR rates (4.75 per million) accounting for two-fold higher than South region.

3.2. Mortality profile

The crude and ASR mortality of all MM rates in cAYA for both sexes in Brazil according to PBCR coverage was 9.23 and 8.83 per million, respectively (Table 3). Overall, the highest age-specific mortality rates were observed in young adults (10.60 per million), in infants (9.14 per million) and in 10–19 year (8.74 per million), with children aged 5–9 years old (6.31 per million). The North and South regions have the highest mortality rates among infants 14.73 per million and 13.32 per million, respectively. When analysed by PBCR, cities such as Manaus, Cuiabá, Curitiba and Recife presented the highest mortality rate among infants with 22.91 per million, 22.38 per million, 19.95 per million and 17.17 per million, respectively.

3.3. Trends

The incidence and mortality trends in age-standardized 0–29 years for all MM cases in the Brazilian PBCRs are shown in Fig.3a and 3b. The JR analysis of incidence trends were stable during the full period for Belém, Aracaju, Recife, Cuiabá, Goiânia, Barretos, Belo Horizonte, Espírito Santo, Jahu, Curitiba and Porto Alegre. Mortality trends are stable for Belém, Manaus, Aracaju, Fortaleza, João Pessoa, Recife, Cuiabá, Barretos, Espírito Santo. Incidence trends showed a significant decline in Manaus (AAPC: -5.6%, $p < 000.1$) and São Paulo (AAPC: -4.7%, $p < 000.1$), and a significant increase was observed in Fortaleza (AAPC: 5.8%, $p < 000.1$), as shown in Fig.4a. Mortality trends steadily declined in all cities, with significant declines in Goiânia (AAPC: -1.5. $p < 000.1$), Belo Horizonte (AAPC: -2.3%, $p < 000.1$), São Paulo (AAPC: -2.5%, $p < 000.1$), Curitiba (AAPC: -2.8%, $p < 000.1$) and Porto Alegre (AAPC: -4.1%, $p < 000.1$), as shown in Fig.4b.

4. Discussion

4.1. Incidence trends over time

In this large population-based study about MM (by subtypes) we have described the incidence and mortality rates in cAYA in Brazil. One strong motivation for this investigation was the variations in leukaemia incidences reported internationally, which lacked information concerning MM patterns in Brazil. The fact that the quality of the information from the PBCRs in Brazil has improved in the last two decades allows for consistent information and interpretation of the childhood AML (c-AML) profile [18,19]. A population coverage with 15 PBCRs encompassing about 30% of the country's population can be sufficiently representative of Brazil as a whole.

Another motivation was to explore the epidemiological data from previous reports and update them [10,11]. In the former report we evaluated trends in incidence rates of childhood leukaemia (of patients up to 14 years of age) from PBCRs with at least 8 years of consolidated data. In those studies we found increased incidence rates of MM in Brazilian cities compared with acute lymphoblastic leukaemia (ALL) incidence rates. In those studies point out the necessity of continuing to improve the quality of information in the PBCRs in order to accurately ascertain incidence rates of MM overtime in at-risk populations in different age strata. We raised a hypothesis that those differences concern environmental factors highly associated with c-AML, especially if in utero or before conception expositions would occur.

In the present study we found that ASR incidence rates for AML (including APL subgroup) in Brazil are among the highest in the world

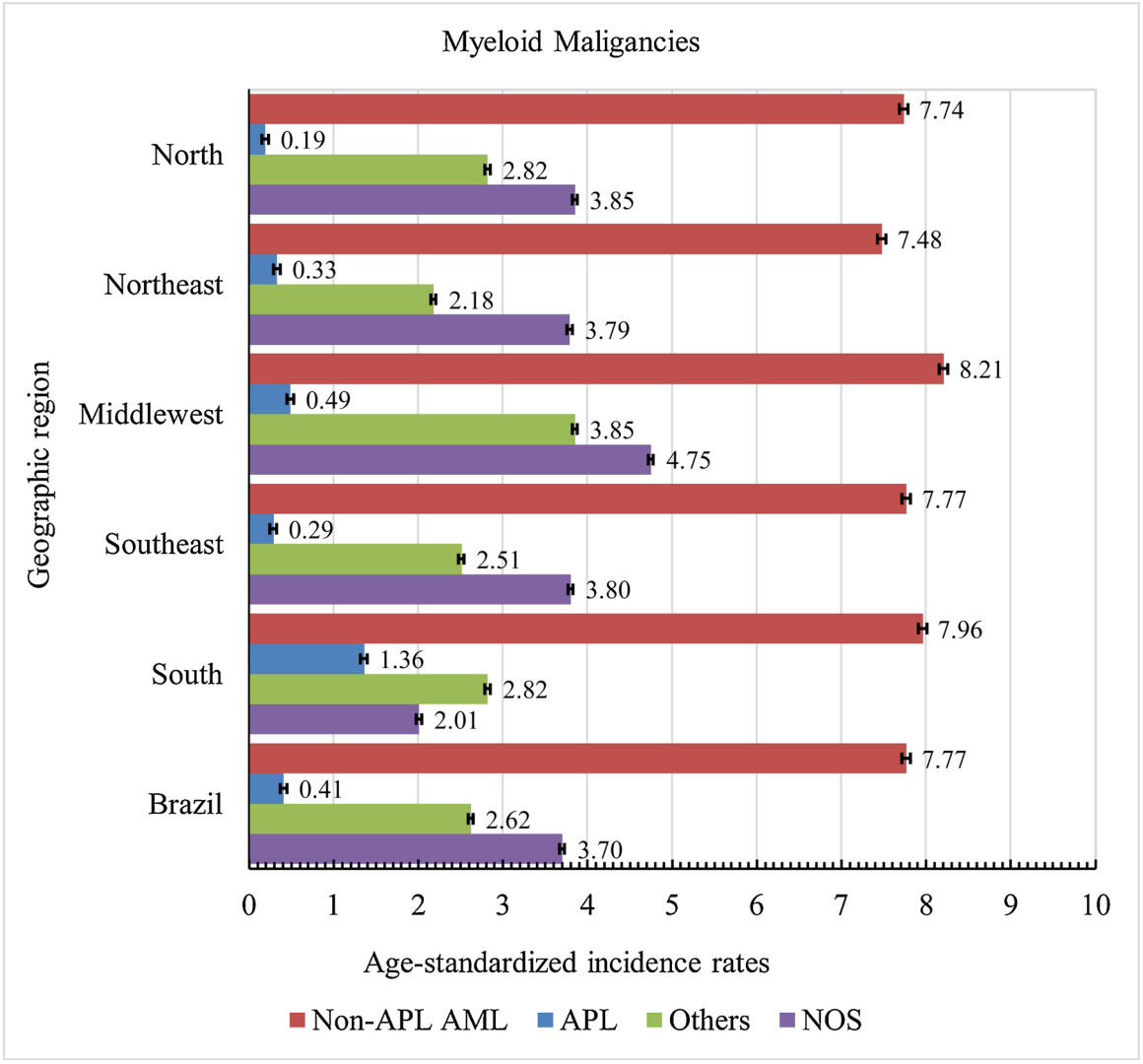

Fig. 2. Estimated age-standardized incidence per million people for each myeloid malignancy among children, adolescents and young adults according geographical region, Brazil 2000–2009. Note. PBCR, Population-Based Cancer Registries; AML, acute myeloid leukaemia; APL, acute promyelocytic leukaemia; NOS, not otherwise specified; Others included: MPN, MDS and MDS/MPN cases. Error bars represent 95% confidence intervals.

and overall MM incidence rates have a bimodal age pattern [19,20]. An initial peak occurs in infants (aged < 1 year), followed by a decline in childhood (aged 5–9 years), then an exponential rise in incidence rates in young adults. This bimodal pattern is similar to the population-based analysis of MM in the US [20]. However, we observed higher incidence rates by age-strata in children (older than 1–4 years) than AMLs analysed in Surveillance, Epidemiology and End Results (SEER) in the US [20] It is worth noting that the present results validate previous studies of incidence rates verifying geographical differences within Brazil [10,11].

The major differences in age-specific incidene rates observed in infants and in young adults in the North, Middlewest and South (16.20–31.51 per million) corroborates the assumption that region-specific environmental exposures might be associated with underlying causal factors. It is important to emphasize that these cities are in Brazilian geographic regions where the agribusiness and oil and gas industries are the predominant economic activities. Activities that involve the use of environmental toxicants have been found to be associated with infant AML [21–23]. In a previous Brazilian study exploring mother and child characteristics at birth, the record linkage of registries have assessed 11 out 15 PBCR described herein and the results demonstrated a strong risk association between maternal occupational exposures at work (agricultural, petrol) and AML in their offspring's [12]. The value of these results could be a warning to continue searching for parental risk factors associated with c-AML and young adult exposures. The consistency of findings that early-age leukaemias (EAL) development occurs *in utero* associated with inadvertent maternal chemical exposure during pregnancy can explain the high incidence rates in some Brazilian regions [11,24].

Overall the incidence rate of MM in Brazil (15.03 per million) is approximately 50% higher than in the US (9.9 per million) in children up to 4-years of age, presumably because the pesticide use in Brazil differs to the use in US [20,22]. It is biologically plausible that maternal occupational pesticide exposure could increase the risk of AML in the offspring as there is evidence that some benzene metabolites cross the placental blood barrier resulting in foetal exposure [23,24]. The same environmental exposures can be observed directly in adolescents and young adults. The overall ASR incidence of AML (0–19 years) in our study is 7.97 per million in cAYA, which is only slightly higher than US and European rates of 7.0 per million [7,25], while the estimated ASR incidence for AML including APL in cAYA (0-29 years) is 8.18 per million. It would be of great value to test how this observed variations in AML subtypes incidence rate associated with age strata.

In series of AML cases recruited from a large population-based study

Table 3
Age-specific, crude and age-standardized mortality rates of all myeloid malignancies in children, adolescents and young adults according PBCR coverage, geographic region, Brazil.2000–2009.

PBCR	Number of cases	Age-specific mortality rates					CR	ASR	
		< 1 year	1-4 years	5-9 years	10-19 years	20-29 years	00-29 years	00-29 years	95% CI
North									
Belém	121	6.06	12.56	8.57	11.11	11.97	16.78	10.93	10.91-10.96
Manaus	108	22.91	9.31	6.91	9.63	12.67	10.56	10.53	10.50-10.55
Total	229	14.73	10.91	7.74	10.41	12.30	13.13	10.74	10.72-10.77
Northeast									
Aracaju	18	0.00	2.89	2.31	8.01	7.99	6.28	5.77	5.75-5.79
Fortaleza	120	9.75	7.08	6.41	9.21	10.28	8.86	8.67	8.65-8.70
João Pessoa	28	9.38	6.95	8.79	6.94	7.96	7.65	7.67	7.65-7.69
Recife	60	17.17	5.31	4.85	7.53	8.60	7.51	7.39	7.37-7.41
Total	226	10.78	6.15	5.88	8.31	9.24	8.05	7.88	7.85-7.90
Middlewest									
Cuiabá	44	22.38	12.64	6.93	7.64	11.18	9.78	10.01	9.99-10.04
Goiânia	66	0.00	11.89	8.27	8.59	12.37	10.08	9.81	9.78-9.84
Total	110	9.45	12.21	7.70	8.19	11.91	9.96	9.91	9.88-9.94
Southeast									
Barretos	15	0.00	16.12	3.00	4.07	10.24	7.28	7.53	7.51-7.55
Belo Horizonte	94	8.48	8.34	7.20	7.80	7.60	7.72	7.76	7.73-7.78
Jahu	03	0.00	0.00	10.73	4.78	4.71	4.98	4.80	4.78-4.82
Espírito Santo	72	14.36	3.58	5.79	7.56	11.14	8.20	7.87	7.85-7.90
São Paulo	511	4.66	8.12	6.16	9.27	10.96	9.11	8.80	8.78-8.83
Total	695	6.19	7.78	6.22	8.67	10.39	8.72	8.46	8.44-8.49
South									
Curitiba	94	19.95	17.14	5.79	6.26	13.46	10.46	10.68	10.66-10.71
Porto Alegre	49	5.00	3.70	2.86	10.36	7.48	7.22	6.82	6.80-6.85
Total	143	13.32	11.28	4.52	8.03	10.92	9.07	9.01	8.99-9.04
Brazil	1,403	9.14	8.58	6.31	8.74	10.60	9.23	8.83	8.80-8.85

Note. PBCR, Population-Based Cancer Registry; CR, Crude rates; ASR, Age-standardized 0–29 years (world standard population) mortality rates; CI, confidence interval.

and in which the diagnostic karyotype groups were well defined (numerical abnormalities, translocations and deletions) the results have shown that age-dependent incident patterns in AML are consistent with cytogenetic abnormalities. These findings may define disease entities with different etiologies and support differences in the mechanisms by which these abnormalities develop [26,27]. The most common chromosomal abnormality in c-AML up to 5 years of age at diagnosis is translocation involving the *MLL* gene (*MLL*-r or 11q23 region abnormalities), highly prevalent in infants, whereas the chromosomal translocation t(15;17)*/PML-RARA* is exclusive to APL, which is an AML subtype with constant incidence rates across all age strata [19,28]. It is recognised that acute leukaemia with *MLL*-r has causal relationship with substances that lead to DNA damage [21,24]. APL with *PML-RARA* has been a reference model for cancer treatment because of the effective target therapy, which changed dismal outcomes to high cure rates [27,28].

Because variation in APL incidence rates among ethnic groups have been described and comprises about 7% of AML cases worldwide [19,27,28] we have investigated if the incidence rate of APL would be an impact on MM incidence across Brazilian geographical areas. APL incidence rates are different across PBCRs and Brazilian regions, although with inconsistencies. The majority of the PBCR ascertainment data were codified by ICD-O-3 codes and the MM subtypes were grouped according to WHO classification criteria [1]. In the PBCRs quality assessments, the NOS category remains a major concern because it gathers the AML heterogeneity and the APL registry is underspecified. For instances, we have tested the NOS incidence rate time trend and geographical pattern analysis using MM subtypes, as well as all MM combined and fluctuations were found in all Brazilian regions, although the trend in whole country was stable in 2005-2009 period (shown in Supplementary Table 2). In a recent Brazilian hospital-based cancer analysis with data extracted from 239 cancer centers (90% of the hospitals with oncological assistance in Brazil), the APL subgroup was the main MM subtype specified in the Brazilian series, even considering the high rates of AML-NOS [28]. The distribution of AML subgroups found in those hospital-based analysis corroborates the population-based study carried out in the US studies [20]. Interestingly, when we compared the proportion of NOS and APL rates in different Brazilian regions, we found a directly proportional low incidence rate of APL and higher NOS in the Middlewest cities (0.49 versus 4.75 per million), whereas in South the comparison between APL and NOS decreased (APL, 1.36; NOS, 2.01 per million), which led us to conjecture that APL cases might be included in the group of NOS in the majority of Brazilian PBCR.

Overall, the proportion of NOS was more than 20% within Brazilian regions, although the NOS category declined significantly from 2000 to 2005 (ASR: 5.06 to 2.40 per million) and from 2007 to 2009 (ASR: 3.77 to 3.44 per million). We suspect that the lack of AML coded by subtypes in the PBCR reflects the absence of record in the patient's chart, rather than a lack of diagnosis access. In Japan, Korea, and in Costa Rica the reported incidence rates for NOS were similar to what we found [29,30].

The low incidence rates observed for MPN, MDS and MDS/MPN were not very different from rates observed in Europe [7] and the MDS/MPN rates could be due to the application of ICD-O classification before the adoption of ICD-O-3. Until recently these entities were not considered malignant and not reportable to cancer registries [31].

The incidence rate of MM trends seems to be stable over time, although in some PBCRs, such as Manaus and São Paulo, a decrease was observed. However, the MM ASR did increase in Fortaleza. The interpretation of this finding is the expansion and distribution of oncological centres in Brazil with modernizing areas in the AML treatments have changed health-care specialised patients in all geographical regions overtimes [32].

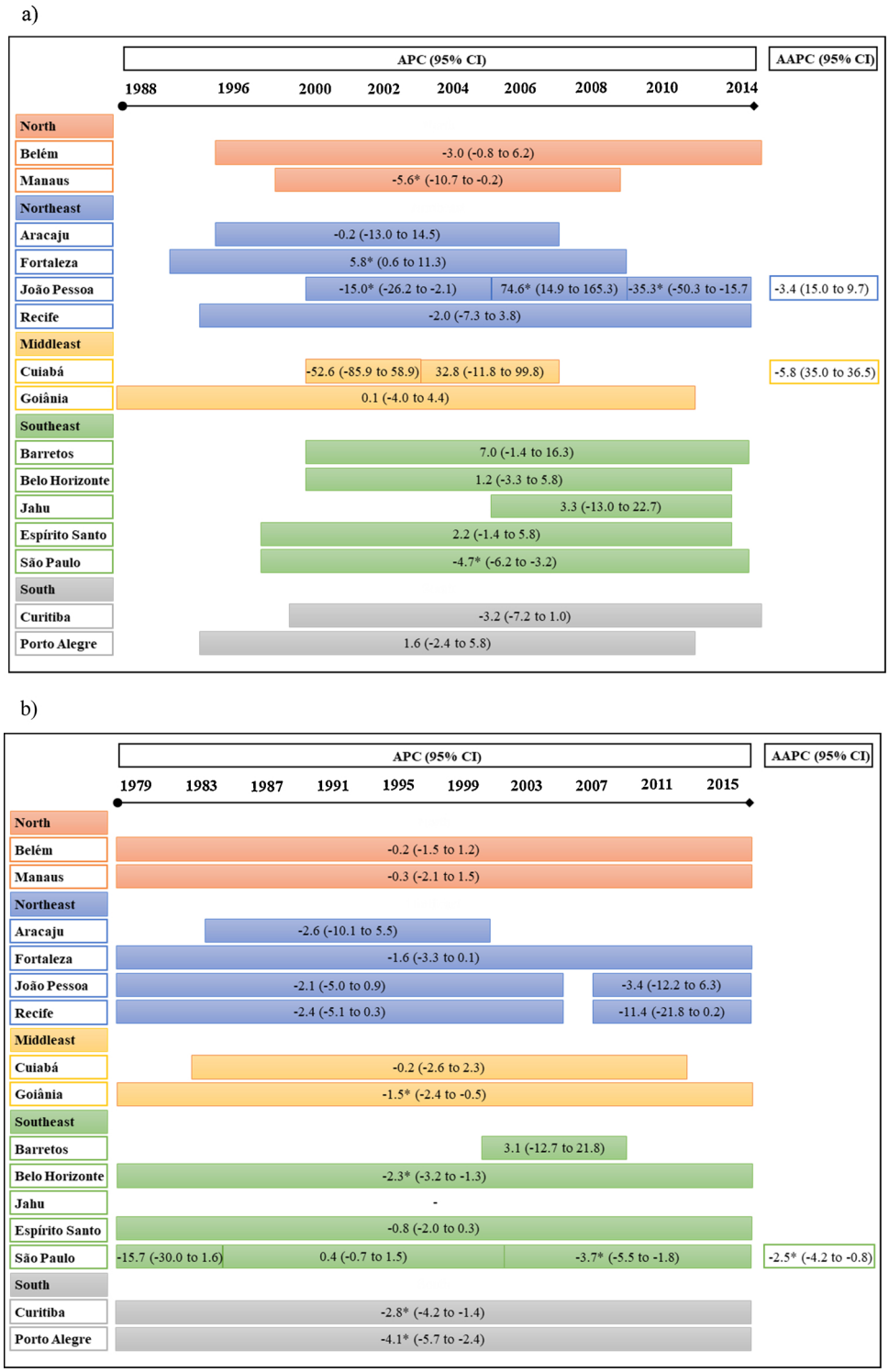

Fig. 3. Incidence and mortality trends among children, adolescents and young adults with all myeloid malignancies in Brazilian PBCR. a) Incidence trends (2000–2009); b) Mortality trends (1979–2015).
Note. APC, Annual Percent Change; AAPC, Average Annual Percent Change. *APC or AAPC statistically significant (P-values < 0.05). For João Pessoa and Recife the year 2006 death rates were not computed because there were zero occurrence; - Rates were not computed because there were zero occurrence for many years. Single bar indicates that join point was identified for a given category.

4.2. Mortality trends over time

Most mortality studies are performed in overall acute leukaemia – i.e. including ALL and AML. The GLOBOCAN 2018 report, for example, estimates the overall ASR mortality of leukaemia, in ages 0–29, was 15.00 per million worldwide [19]. The discrimination of mortality rate by leukaemia subtypes is rare, especially in cAYA. We found the major differences in mortality rates were observed in children < 1-year-old that presented high rates (> 20 per million) in Manaus, Cuiabá and Curitiba, and were similar to those observed in the incidence rates. Compared to previous studies, the current update of geographic patterns and temporal trends in MM mortality in various Brazilian PBCRs

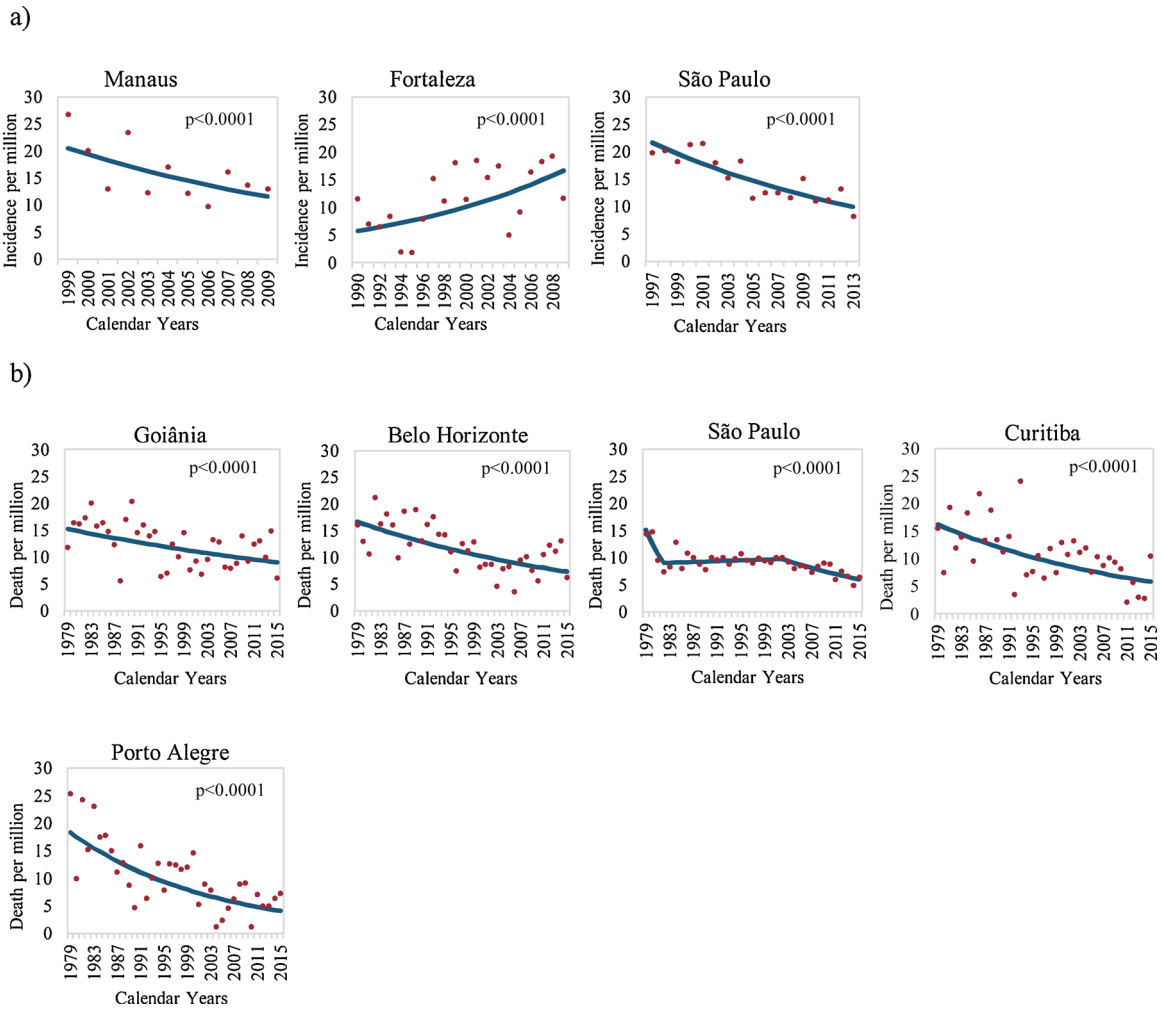

Fig. 4. Joinpoint analysis for age-standardized 0–29 years (world standard population) from all myeloid malignancies in Brazilian PBCR, 1979-2015. a) Incidence rates; b) Mortality rates. Solid circles indicate data for observed age-adjusted rate; Solid line indicate data for modeled age-adjusted rate. These cities were shown because of the significant trend. These cities were shown because of the significant trend.

reveals that mortality declined significantly over time [33]. In the less Brazilian developed regions, like North and Northeast regions, the high mortality rates and unfavorable trends observed demonstrate the need for continuous efforts to improve treatment and the quality of the information gathered. MM mortality rates are similar across regions with poverty and unfavorable socioeconomic conditions. The declining trends in mortality in more developed cities (Belo Horizonte, São Paulo, Goiânia, Curitiba and Porto Alegre) were caused by better management in the quality of health care, including the adoption of effective multidrug chemotherapy protocols and bone marrow transplantation assessment; supportive measures to overcome toxicity and the practice guidelines for the use of antimicrobial agents in neutropenic patients with leukaemia; hospital environmental precautions; advancements in radiotherapy; and improved diagnostic techniques. In summary, the MM mortality rate did not decrease equally in all regions, although age-adjusted mortality rates were similar across the five Brazilian regions, for period 2000 to 2009.

4.3. Strengths and limitations

In addition to the previous report, which focused on childhood leukaemia at a very early age, our present investigation accrued a large number of MM cases in cAYA. It is the first report on MM in a South American country to calculate incidence and mortality rates by MM subtypes. The statistical power assessed by age strata, over time, explored new group such as young-adults that was not previously reported. Our results found high incidence of MM in the Middlewest and South regions, mainly among infants, which showed an a priori hypothetical evidence of a causal association with the environmental exposures. Given that in both regions have as their main economic activity agriculture and livestock, to explore parental risk factors can be an important determinant to conduct environmental ecological studies. The incidence rates of AML (paediatric and in adulthood) have been associated with SES, as well as parental smoking or alcohol consumption (in paediatric cases) and activities in the oil and gas industries [34–36].

The most notable limitation of our analysis was the lack of a centralized hematopathology expert review to decrease the NOS subtype rate. Hematological disorders are different from solid tumors in the assessment of malignancies in so far as the former requires cytological, immunophenotype and karyotype diagnosis, as recommended the WHO criteria [2]. The European Network of Cancer Registries (ENCR) have recommended to update the WHO classification periodically, because MM diagnoses are subject to modification overtime, such as MDS to AML or transformations in secondary leukaemia. The guidelines of the ENCR recommendation provide precise information to improve PBCR data regarding haematological malignancies such as, the multiple data sources register linkage, the registration of multiple notifications (ei. same tumour, but with a more specific or revised diagnosis, transformation and new tumour registration), the basis of cytological diagnosis

reviewed by an expert haemato-pathologist [37,38]. We recognised that there is still a possibility of under-ascertainment or underreporting of MM, particularly among young children where diagnostic evaluation might not be as aggressively pursued as in other younger patients. In a recent report, Craig et al call attention to the impact of MM underreporting in SEER [39].

5. Conclusion

The incidence and mortality rates of myeloid malignancies in cAYA in Brazil is very high compared with patterns already described in US and European countries. Infants have the highest incidence rate of AML within the cAYA population, suggesting that infant-AML is a malignancy subtype with a distinct biology originating during foetal development and reflecting important transplacental exposures. Mortality rate decreased in some Brazilian cities, based on two decades of improvements of heath care assessment services and PBCR qualities.

A better understanding of age-dependent associations in the geographical differences in Brazil would help investigations of environmental exposures and causal effects in myeloid malignancies as well as contribute to the improvement of regional health care services. Further studies examining the distribution of MM in PBCRs should be carried on.

Authors' contributions

SVMF, MOS and MSPO developed the concept and study design, and analysed interpreted data. SVMF, MOS conducted the statistical data analyses with advice from MSPO. SVMF drafted the manuscript, and MSPO critically reviewed and edited the manuscript for important intellectual content. JAPA, TAA, MMUA, BNA, AMC, LACF, CAL, CAL, NCM, JCO, LDAP, AS, CMAS, PCFS, and DBV contributed to this work collecting patients' data and inserting the data into the PBCR. SVMF, MOS and MSPO provided critical feedback, revised the manuscript for intellectual content and approved the final version.

Declaration of Competing Interest

No conflict of interest is declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101583.

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