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ORIGINAL ARTICLE

Geographic Distribution of Childhood Cancer in Brazil and the Time between the Diagnosis and the Start of Treatment: An Analysis of Hospital-Based Cancer Registries, 2010-2016

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ABSTRACT
Objective: To analyze the distribution of childhood cancer in Brazil and the time between the diagnosis and the start of treatment, according to hospital-based cancer registries (2010-2016). **Material and Methods:** This was an observational descriptive study using secondary data (36,187 records) from hospital databases of the National Cancer Institute (INCA) and the Onco-center Foundation of São Paulo (FOSP). Epidemiological data were obtained, and compliance with Federal Law 12,732/12 was verified, which establishes a maximum period of 60 days to start cancer therapy after the diagnosis. Absolute and percent frequencies, central tendency and dispersion measures, and the coefficient of prevalence of childhood cancer were calculated. **Results:** The mean age of the pediatric patients was 9.3 years (± 6.2); 54.1% (n=19,586) of them were males; 32.0% (n=11,440) were aged 0 to 4 years; and 43.4% (n=11,338) had a self-reported mixed-race skin color. The Southeast region of Brazil accounted for 40.2% (n=14,564) of the cases, of which 63.0% (n=9,178) corresponded to solid neoplasms, as opposed to the North region, where hematological neoplasms prevailed (53.9%, n=1,535). Most registered patients aged 0 to 19 years were treated in 60 days or less (77%, n=27,929). However, for 24.0% (n = 2,207) of adolescents (15 to 19 years) this time was more than 60 days after the diagnosis. **Conclusion:** The characteristics related to childhood cancer varied across the Brazilian geographic regions, and most patients were properly treated within the time enforced by law.

Keywords: Medical Oncology; Oncology Service, Hospital; Pediatrics; Hospital Information Systems.

Introduction

Cancer is the primary cause of death from illness in children and adolescents worldwide, with 300,000 new cases diagnosed each year [1]. However, when compared to neoplasms in adults, childhood cancer is considered a rare condition and accounts for only 1% to 3% of all malignant tumors in the general population [2].

The José Alencar Gomes da Silva National Cancer Institute (INCA) estimated for 2020 the occurrence of 8,460 new cases of cancer in children and adolescents up to 19 years of age, with an incidence rate of 138.44 per million inhabitants. As the second leading cause of death in the age group 0 to 19 years in most regions of Brazil, childhood cancer is considered a serious public health issue [3].

Neoplasms affecting children and adolescents have a different clinical behavior than those in adults. For instance, shorter latency periods, different primary sites and histological origins, and quick development and invasiveness, although with a better responsiveness to antineoplastic treatment [2,4]. The National Policy for the Prevention and Control of Cancer (PNPCC, in Portuguese) emphasizes the importance of an early diagnosis and access to healthcare services for a better prognosis, given that time is a critical factor for the patient with cancer [5].

A timely access to specialized healthcare services is decisive to increase patient survival and improve the prognosis of the disease, especially if the diagnosis is established early. Nevertheless, attending oncological centers on a frequent basis may drastically impact the quality of life of pediatric patients and their families in terms of distance, time, and financial costs [6].

The geographic inequality in cancer distribution in Brazil is an important aspect to consider. Given that childhood cancer is rarely associated with exposure to carcinogens, the distribution of cases was expected to be approximately even across the country. However, in 2008, a study mapped out the geographic variations of death and hospitalization rates and treatment modalities in pediatric cancer patients in 352 health regions of the Brazilian Healthcare System. The authors showed inequalities of access in the poorest regions of Brazil, with a small number of medical appointments in these populations. A lower cancer mortality rate and a high proportion of unknown death causes in children in most Northern and Northeastern areas support the hypothesis of inequality in geographic access, disorganization of health services, and poor-quality health assistance [7].

The start of cancer therapy can be delayed for various reasons, such as the time between the first symptoms and the search for medical assistance, the time between the first medical care until diagnosis, and/or from the diagnosis until the start of treatment. If the diagnosis is delayed, so will the treatment, which may result in several undesirable consequences for children and adolescents, including death [8].

Law 12,732/12, also known as the 60-day law, ensures access to the first treatment for cancer patients within 60 days after the diagnosis in a facility of the Brazilian Healthcare System. This law represents the legal basis for agility in the treatment of neoplasms in the healthcare system [9]. To guarantee the follow-up of patients with cancer and track the time elapsed in each stage of treatment, health information systems should be fully functional, and health professionals and managers should be trained accordingly.

Hospital-based Cancer Registries (HCR) have been installed in general hospitals and specialized oncology centers to monitor and evaluate cancer parameters in Brazil. The purpose of HCR is to collect data regarding the diagnosis, treatment, and evolution of malignant neoplasms treated in these institutions, whether public, private, philanthropic, or teaching-based/university [10]. The analysis of HCR contributes to providing better health care, supports cancer diagnosis and patient follow-up, and generates statistical data for planning, strategy development, and decision-making in the oncology care network [11]. Thus, this study aimed to determine the geographic distribution of childhood cancer in Brazil and the time between the diagnosis and the start of treatment based on the analysis of RHC from 2010 to 2016.

Material and Methods

Study Design and Data Collection

This was an observational descriptive study of HCR data from the Integrated HCR system (IHCR) developed and powered by the José Alencar Gomes da Silva National Cancer Institute (INCA), available from https://irhc.inca.gov.br/RHCNet/. The HCR data of the state of São Paulo were collected from the database of the *Fundação Oncocentro de São Paulo* (FOSP), available from www.fosp.saude.sp.gov.br. The data were collected on September 30, 2020, via Tabnet per Federation Unit and year of registration. The information has public access and users are not identified.

The study universe consisted of records of children and adolescents (0 to 19 years of age) who had their first consultation from 2010 to 2016 in reference hospitals for cancer therapy in Brazil and were monitored through the SISRHC (Hospital-based Cancer Registries System / *Sistema de Registros Hospitalares de Câncer*, in Portuguese). The study sample was selected using the following eligibility criteria: analytical cases, that is, patients who were presented at the referral service without previous treatment; with or without a diagnosis; first consultation between 2010 and 2016; complete data regarding the time of diagnosis and start of treatment, state of residence, and type of neoplasm.

The study variables were determined based on the required fields of the “tumor registration form” in the SISRHC, namely: patient identification (sex, age, place of residence, and skin color) and clinical variables (type of neoplasm, primary tumor location and histological type, date of diagnosis, and date of treatment start). Skin color is not a required field in the FOSP database; therefore, this variable was not considered in the samples obtained from the state of São Paulo.

Data Analysis

The data were entered into 2010 Microsoft Office Excel spreadsheets and analyzed in the software R (The R Project for statistical computing, 3.6.1 version). In the descriptive analysis, absolute and percent frequencies were calculated for categorical variables, whereas central tendency and dispersion measures were used for quantitative variables. The coefficients of prevalence of childhood cancer were calculated per year of first visit and geographic region. The population denominators used for this calculation were obtained from the estimates of the Brazilian Institute of Geography and Statistics (IBGE - *Instituto Brasileiro de Geografia e Estatística*, in Portuguese) between 2010 and 2016 [12], according to the population census conducted in 2010. The coefficients of prevalence were calculated per 1,000,000 inhabitants, considering the variables sex and age group.

Results

A total of 36,187 eligible records were included in the study. Of these, 26,126 were extracted from the HCR of the INCA and 10,061 from the FOSP. The mean age of pediatric patients with cancer was 9.3 years (± 6.2), with a median of 9 years; 54.1% (n = 19,586) of them were males and 32.0% (n = 11,440) were in the age group 0 to 4 years. Skin color information was available only in the INCA database and indicated that 43.4% (n = 11.338) of the patients self-reported a mixed-race skin color. Of the total sample, 59.0% (n = 21.423) presented solid neoplasms (Table 1).

Table 1. Time series of the number of first childhood cancer consultations by sex, age group, self-reported skin color, and type of neoplasm.

Variables	Categories	2010		2011		2012		2013		2014		2015		2016		Total	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sex	Male	2,732	54.3	2,882	55.3	2,674	52.6	2,822	53.0	2,909	55.1	2,740	53.8	2,827	54.8	19,586	54.1
	Female	2,302	45.7	2,334	44.7	2,413	47.4	2,499	47.0	2,372	44.9	2,351	46.2	2,330	45.2	16,601	45.9
	Total	5,034	100.0	5,216	100.0	5,087	100.0	5,321	100.0	5,281	100.0	5,091	100.0	5,157	100.0	36,187	100.0
Age Group	0 to 4 Years	1,599	31.8	1,569	30.0	1,624	32.0	1,677	32.0	1,661	32.0	1,623	32.0	1,687	33.0	11,440	32.0
	5 to 9 Years	962	19.1	1,033	20.0	939	18.0	975	18.0	1,002	19.0	1,013	20.0	973	19.0	6,897	19.0
	10 to 14 Years	1,158	23.0	1,179	22.5	1,056	21.0	1,134	21.0	1,124	21.0	1,019	20.0	995	19.0	7,665	21.0
	15 to 19 Years	1,315	26.1	1,435	27.5	1,468	29.0	1,535	29.0	1,494	28.0	1,436	28.0	1,502	29.0	10,185	28.0
	Total	5,034	100.0	5,216	100.0	5,087	100.0	5,321	100.0	5,281	100.0	5,091	100.0	5,157	100.0	36,187	100.0
Skin Color*	White	1,414	40.0	1,447	39.0	1,389	38.1	1,461	38.0	1,346	34.8	1,277	35.0	1,332	35.2	9,666	37.0
	Black	114	3.1	146	4.0	237	6.5	139	3.7	146	3.5	145	4.0	174	5.0	1,101	4.2
	Yellow	114	3.1	52	1.4	52	1.4	31	0.8	14	0.4	13	0.3	19	0.5	295	1.0
	Mixed-Race	1,532	42.3	1,583	42.6	1,502	41.3	1,691	44.0	1,699	44.0	1,528	41.7	1,803	48.0	11,338	43.4
	Indigenous	19	0.5	14	0.3	17	0.5	19	0.5	13	0.3	18	0.5	10	0.3	110	0.4
	No Information	424	12.0	471	12.7	442	12.2	500	13.0	654	17.0	684	18.5	441	12.0	3,616	14.0
	Total	3,617	100.0	3,713	100.0	3,639	100.0	3,841	100.0	3,872	100.0	3,665	100.0	3,779	100.0	26.126	100.0
Neoplasm	Solid	2,939	58.4	3,088	59.2	2,979	58.6	3,193	60.0	3,177	60.0	3,005	59.0	3,042	59.0	21,423	59.0
	Hematological	2,092	41.6	2,127	40.8	2,108	41.4	2,128	40.0	2,101	40.0	2,086	41.0	13	41.0	14,755	41.0
	No Information	03	0.0	01	0.0	-	-	-	-	03	0.0	-	-	02	0.0	09	0.0
	Total	5,034	100.0	5,216	100.0	5,087	100.0	5,321	100.0	5,281	100.0	5,091	100.0	5,157	100.0	36,187	100.0

Source: INCA- and FOSP-HCR databases from 2010 to 2016, accessed on September 30, 2020; *Variable not registered in the FOSP-HCR database.

The Southeast region of Brazil accounted for 40.2% (n = 14,564) of the registered cases, followed by the Northeast (28.9%), South (17.5%), North (7.9%), and Midwest (5, 5%). In the South, 83.6% (n = 5,222) of the children and adolescents declared their skin color white, whilst in the other regions of the country mixed-race skin color was predominant. The North region showed the greatest number of indigenous people with childhood cancer (2.8%). In the Southeast, 63.0% (n = 9,178) of the cases corresponded to solid neoplasms as compared to hematological neoplasms in the North (53.9%, n = 1,535). The time elapsed between the date of diagnosis and the start of treatment ranged from 0 to 4,257 days (median of 9 days). In 77.0% (n = 27,929) of the cases, the time between the diagnosis and the start of treatment was 60 days or less. In the Southeast region, 80.8% (n = 11,767) of the children and adolescents were treated within 60 days or less as compared to the North, where 23.2% (n = 661) of the patients underwent treatment more than 60 days after the diagnosis (Table 2).

Table 2. Distribution of childhood cancer cases by geographic region in Brazil, according to sex, age group, self-reported skin color, type of neoplasm, and time to treatment.

Variables		**North**	**Northeast**	**Midwest**	**Southeast**	**South**	**Total**
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total		2,849 (7.9)	10,435 (28.9)	1,998 (5.5)	14,564 (40.2)	6,341 (17.5)	36,187 (100.0)
Sex	Male	1,637 (57.5)	5,571 (53.4)	1,057 (52.9)	7,821 (53.7)	3,500 (55.2)	19,586 (54.1)
	Female	1,212 (42.5)	4,864 (46.6)	941 (47.1)	6,743 (46.3)	2,841 (44.8)	16,601 (45.9)
	Total	2,849 (100.0)	10,435 (100.0)	1,998 (100.0)	14,564 (100.0)	6,341 (100.0)	36,187 (100.0)
Age Group	0 to 4 Years	971 (34.0)	3,238 (31.0)	713 (36.0)	4,463 (30.6)	2,055 (32.0)	11,440 (32.0)
	5 to 9 Years	602 (21.0)	2,127 (20.4)	368 (18.0)	2,637 (18.1)	1,163 (19.0)	6,897 (19.0)
	10 to 14 Years	571 (20.0)	2,222 (21.3)	436 (22.0)	3,142 (21.6)	1,294 (20.0)	7,665 (21.0)
	15 to 19 Years	705 (25.0)	2,848 (27.3)	481 (24.0)	4,322 (29.7)	1,829 (29.0)	10,185 (28.0)
	Total	2,849 (100.0)	10,435 (100.0)	1,998 (100.0)	14,564 (100.0)	6,341 (100.0)	36,187 (100.0)
Skin Color*	White	244 (10.2)	1,641 (16.0)	348 (20.5)	2,211 (40.0)	5,222 (83.6)	9,666 (37.0)
	Black	38 (1.6)	470 (4.6)	43 (2.5)	422 (8.0)	128 (2.0)	1,101 (4.2)
	Yellow	09 (0.4)	229 (2.2)	05 (0.3)	30 (0.5)	22 (0.4)	295 (1.0)
	Mixed-race	1,650 (69.0)	5,998 (59.0)	784 (46.1)	2,512 (45.0)	394 (6.3)	11,338 (43.4)
	Indigenous	52 (2.8)	17 (0.2)	10 (0.6)	09 (0.2)	22 (0.3)	110 (0.4)
	No information	400 (17.0)	1,839 (18.0)	510 (30.0)	402 (7.3)	465 (7.4)	3,616 (14.0)
	Total	2,393 (100.0)	10,194 (100.0)	1,700 (100.0)	5,586 (100.0)	6,253 (100.0)	26,126 (100.0)
Neoplasm	Solid	1,314 (46.1)	5,944 (57.0)	1,226 (61.4)	9,178 (63.0)	3,761 (59.4)	21,423 (59.2)
	Hematological	1,535 (53.9)	4,491 (43.0)	772 (38.6)	5,386 (37.0)	2,571 (40.6)	14,755 (40.8)
	No information	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.0)	9 (0.0)
	Total	2,849 (100.0)	10,435 (100.0)	1,998 (100.0)	14,564 (100.0)	6,341 (100.0)	36,187 (100.0)
Time to Treatment	≤ 60 Days	2,009 (70.5)	7,561 (72.4)	1,574 (78.7)	11,767 (80.8)	5,018 (79.1)	27,929 (77.0)
	> 60 Days	661 (23.2)	1,737 (16.6)	297 (15.0)	1,988 (13.7)	719 (11.4)	5,402 (15.0)
	No information	179 (6.3)	1,137 (11.0)	127 (6.3)	809 (5.5)	604 (9.5)	2,856 (8.0)
	Total	2,849 (100.0)	10,435 (100.0)	1,998 (100.0)	14,564 (100.0)	6,341 (100.0)	36,187 (100.0)

Source: INCA- and FOSP-HCR databases from 2010 to 2016, accessed on September 30, 2020; *Variable not registered in the FOSP-HCR database.

The time to start treatment was 60 days or less in 34.0% (n = 9,407) of the children aged 0 to 4 years, whereas 76.0% (n = 2,207) of the patients aged 15 to 19 years had their treatment started after 60 days. When the type of neoplasm was considered in the analysis, 19.8% (n = 3,820) of the children and adolescents diagnosed with solid neoplasms started antineoplastic treatment after 60 days, which exceeds the time length enforced by law (Table 3).

Table 3. Distribution of childhood cancer cases by time to start the treatment, according to sex, age group, self-reported skin color, and type of neoplasm. Brazil, 2010-2016.

Variables		Time to Start the Treatment ≤ 60 Days N (%)	 > 60 Days N (%)	 Total N (%)
Sex	Male	15,422 (84.9)	2,741 (15.1)	18,163 (100.0)
	Female	12,507 (82.5)	2,661 (17.5)	15,168 (100.0)
Age Group	0 to 4 Years	9,407 (89.0)	1,168 (11,0)	10,575 (100.0)
	5 to 9 Years	5,561 (86.2)	892 (13.8)	6,453 (18.0)
	10 to 14 Years	5,959 (84.0)	1,135 (16.0)	7,094 (100.0)
	15 to 19 Years	7,002 (76.0)	2,207 (24.0)	9,209 (100.0)
Skin Color*	White	7,336 (84.3)	1,369 (15.7)	8,705 (100.0)
	Black	824 (82.4)	176 (17.6)	1,000 (100.0)
	Yellow	214 (84.3)	40 (15.7)	254 (100.0)
	Mixed-race	8,411 (81.4)	1,922 (18.6)	10,333 (100.0)
	Indigenous	90 (86.5)	14 (13.5)	104 (100.0)
Type of Neoplasm	Solid	15,462 (80.2)	3,820 (19.8)	19,282 (100.0)
	Hematological	12,467 (88.8)	1,580 (11.2)	14,047 (100.0)

Source: INCA- and FOSP-HCR databases from 2010 to 2016, accessed on September 30, 2020; *Variable not registered in the FOSP-HCR database.

When comparing the time to treatment by geographic region with the type of neoplasm, our findings showed that, in all regions, patients with solid neoplasms started treatment after 60 days more frequently. In contrast, the North region presented a higher frequency of hematological neoplasms (18.9%; n = 279) among patients who started treatment 60 days after the diagnosis (Table 4).

Table 4. Distribution of childhood cancer cases by geographic region and time to treatment, according to the type of neoplasm.

Region	Type of Neoplasm	Time to Start the Treatment ≤ 60 Days N	 %	 > 60 Days N	 %	 Total N	 %
North	Solid	813	68.0	382	32.0	1,195	100.0
	Hematological	1,196	81.1	279	18.9	1,475	100.0
Northeast	Solid	3,884	75.5	1,230	24.1	5,236	100.0
	Hematological	3,717	88.0	507	12.0	4,302	100.0
Midwest	Solid	907	80.6	218	19.4	1,125	100.0
	Hematological	667	89.4	79	10.6	746	100.0
Southeast	Solid	7,090	83.0	1,452	17.0	8,675	100.0
	Hematological	4,677	89.7	536	10.3	5,280	100.0
South	Solid	2,808	83.9	538	16.1	3,477	100.0
	Hematological	2,210	92.5	179	7.5	2,458	100.0

Source: INCA- and FOSP-HCR databases from 2010 to 2016, accessed on September 30, 2020.

The coefficients of prevalence of childhood cancer by year of the first medical consultation were higher among males and children aged 0 to 4 years during the years 2010 to 2016. In particular, the year 2014 registered a total of 90.4 cases per million inhabitants for males, whilst the years 2013 and 2016 had 115.0 cases per million inhabitants in the age group 0 to 4 years (Table 5). As for case distribution across the nation, the South region of Brazil showed a higher prevalence of childhood cancer among males (847.3 / million) and patients aged 0 to 4 years (1,051.8 / million) (Table 6).

Table 5. Coefficient of prevalence of childhood cancer by year of the first consultation, according to sex and age group. Brazil, 2010-2016.

Variables		Year of the First Consultation						
		Coefficient of Prevalence						
		2010	2011	2012	2013	2014	2015	2016
Sex	Male	82.3	87.5	81.8	87.0	90.4	86.0	89.2
	Female	72.0	73.3	76.5	80.0	77.0	76.5	77.0
	Total	77.0	80.5	79.2	84.0	84.0	81.2	83.0
Age Group	0 to 4 Years	108.0	107.0	111.0	115.1	114.0	110.5	115.0
	5 to 9 Years	61.0	66.2	61.0	64.1	67.0	68.3	66.3
	10 to 14 Years	66.5	68.5	62.5	69.0	70.0	64.3	64.0
	15 to 19 Years	76.4	83.2	85.0	88.2	86.0	83.0	87.5
	Total	77.0	80.5	79.2	84.0	84.0	81.2	83.0

Source: IBGE / Head of Research. Coordination of Population and Social Indicators, on July 1, 2010/2016; Coefficient of prevalence adjusted per 1,000,000 inhabitants.

Table 6. Coefficient of prevalence of childhood cancer by geographic region, according to sex and age group.

Variables		North	Northeast	Midwest	Southeast	South	Brazil
		Coefficient of Prevalence					
Sex	Male	474.5	591.7	428.5	639.8	847.3	618.1
	Female	366.0	536.6	397.3	574.9	718.3	545.6
	Total	421.4	564.7	413.2	608.0	784.2	1,105.5
Age Group	0 to 4 Years	600.4	776.8	596.7	772.0	1,051.8	777.4
	5 to 9 Years	362.2	484.1	320.9	470.1	627.7	470.3
	10 to 14 Years	334.0	467.7	361.1	531.0	649.3	492.1
	15 to 19 Years	397.8	551.2	373.9	650.4	800.1	593.7
	Total	421.4	564.7	413.2	608.0	784.2	1,105.5

Source: IBGE / Head of Research. Coordination of Population and Social Indicators, on July 1, 2010/2016; Coefficient of prevalence adjusted per 1,000,000 inhabitants.

Discussion

This study analyzed the distribution of childhood cancer across geographic regions of Brazil from 2010 to 2016 and the time between the diagnosis and the start of treatment. The data were analyzed according to region, sex, age group, and type of neoplasm. Our findings contributed to a better understanding of the epidemiological aspects of childhood cancer and access to antineoplastic treatment for greater patient survival.

The results obtained herein were consistent with international studies [13,14] and others conducted in Brazil based on the analysis of HCR [15,16]. A study carried out by the International Agency for Research on Cancer in collaboration with the International Association of Cancer Registries collected data from 153 population-based cancer registries in 62 countries across the five continents, including children and adolescents aged 0-19, from 2001 to 2010. The results showed that incidence rates were higher in males than in females (the sex ratio was 1.17 and 1.14 in the age groups 0-14 and 0-19, respectively) and varied with age, region, and diagnosis [13].

A study in the United States determined the incidence of childhood cancer from 2001 to 2009 by demographic and geographic variables. The results indicated an incidence rate of 171.01 per million people, with higher rates observed among males. Adolescents aged 15 to 19 years had a higher incidence rate than children aged 0 to 14, and white children had higher incidence rates than African-American ones. Northeastern United States showed the highest incidence rates nationwide [14].

Our results are in line with the literature findings indicating a higher frequency of cases in males (54.1%, n = 19,586), with regional differences in the distribution of HCR. The predominance of males was observed in the analysis of the year of registration and geographic region. This may be justified by a higher prevalence of male children and adolescents in the population aged 0 to 19 years in Brazil (51.0%), according to estimates of the IBGE for the year 2016 [12].

Another study carried out in Brazil using HCR data of childhood cancer from 2000 to 2015 found that 54.1% of the cases were in males, 32.0% were in the age group 0 to 4 years, and 40.4% were in self-reported mixed-race individuals [15]. A study in the state of Ceará, northeastern Brazil, analyzed the incidence of cancer from 2000 to 2012. According to the authors, 55.2% of the cases corresponded to males and 27.4% were aged 0 to 4 years [16].

A study performed in a referral public hospital in Northern Brazil analyzed records of childhood cancer from 2008 to 2014. The authors found a higher incidence of cancer in children up to 5 years of age (97%) and a predominance of males (64%). The average age at the start of treatment was 8.11 years [17]. Although studies [14-17] have revealed a greater number of cases affecting males, no biological reasons have been reasoned to explain their predisposition to develop neoplasms. However, the incidence ratio by sex may vary based on the type of neoplasm, and the previously mentioned study considering records from 62 countries showed that kidney, epithelial, germ cell, and gonadal tumors were more common in females than in males for the age group 0 to 14 years [13].

The analysis of the historical series of registered cases from 2010 to 2016 demonstrated a small variability in the number of records, specifically for the years 2010 (5,034 cases) and 2016 (5,157 cases). The INCA estimated for 2010 the occurrence of 9,386 new cases of cancer in children and adolescents up to 18 years of age [18], and for 2016, 12,600 new cases of cancer in individuals aged 0 to 19 years [2].

One important aspect to consider in our analysis is that HCR information is being constantly updated and that several cases may be underreported – especially in healthcare facilities located in resourceless areas such as in the North and Northeast regions of Brazil. Moreover, incomplete registration in the HCR database, lack of training of the professionals responsible for data entering and healthcare user coverage may altogether interfere with the accuracy of the data obtained from the SISRHC [19].

In our study, we determined the distribution of childhood cancer across Brazilian regions. Our findings showed a greater number of cases in the Southeast and Northeast regions considering all neoplasms from 2012 to 2016, which was consistent with the INCA data. Most cases were reported in the Southeast (n = 461,732), followed by Northeast (n = 220,637), South (n = 212,883), North (n = 36,902) and Midwest (n = 27,042). These figures are in line with the population density criterion, which indicates that the number of facilities specialized in oncological assistance is greater in more densely populated areas. Accordingly, some populations have a greater number of specialized centers and, consequently, have more HCR data and registered cases [20].

Previously, a study analyzed the number of pediatric oncology facilities based on the Outpatient Information System in 2014 (SIA/SUS - *Sistema de Informação Ambulatorial*, in Portuguese). The authors identified 71 accredited facilities, of which 26 were High Complexity Oncology Centers (CACONs, in Portuguese), followed by 13 High Complexity Oncology Units (UNACONs, in Portuguese) exclusive for pediatric oncology, and 12 UNACONs with radiotherapy, hematology, and pediatric oncology services. In the North region, there were only two accredited institutions (one CACON and one UNACON) with radiotherapy, hematology, and pediatric oncology services, while the Southeast concentrated approximately 50% (n = 35) of the accredited facilities. Of the 13 UNACONs qualified for pediatric oncology in the treatment of solid and hematological tumors, nine were located in the Southeast and South regions, whilst the other four were located in the Northeast region of Brazil [21].

An assessment of the medical assistance provided by cancer care facilities in Brazil showed that systemic cancer therapy varies significantly within the healthcare system in different regions or states, and within the same state, or even between public institutions in the same city [22]. A study reported an increase of 71.3% of referral centers in the last 15 years in Brazil, guaranteeing greater access of healthcare users to cancer therapy. This increase was different between the regions and ranged from 333% in the North to 50% in the Midwest. Between 2010 and 2017, the greatest increment in the number of chemotherapy and radiotherapy procedures was observed in the North (96%) and Northeast (60%), respectively [23].

Thus, despite regional, state, and municipal differences in the standard and quality of cancer therapy, the expansion of cancer care in the Brazilian healthcare system combined with the growth of primary care coverage has brought important advances in terms of access to health services [23]. The increasing number of chemotherapy procedures and the creation of a UNACON qualified for pediatric radiotherapy, hematology, and oncology in the North region support our findings showing a greater number of children and adolescents with hematological neoplasms in the North (53.9%; n = 1,535), while solid neoplasms predominated in other regions, mainly in the Southeast and Northeast.

Cancer patients living in the North are expected to have easier access to diagnosis and treatment of hematological neoplasms. This type of neoplasm triggers the abnormal proliferation of blood cells in the bone marrow, which can be observed with blood tests indicating the presence of anemia and/or leukopenia/leukocytosis, and/or thrombocytopenia. Early diagnosis of hematological neoplasms is reported to be easier since the pediatrician or family physician can readily detect blood cell alterations and refer the child to a specialized service in pediatric hematology-oncology for complementary laboratory tests, chest radiography, and abdomen ultrasound [24].

The diagnosis of solid neoplasms is performed through computed tomography (CT) scanning, nuclear magnetic resonance, and surgical planning for biopsies and identification of the lesion. Hence, a specialized team is required to decide the type of diagnostic test, and in the case of biopsy, the location and type of biopsy to be performed. Importantly, the referral service is expected to be the same that will start the treatment in order to accelerate the time between the diagnosis and the start of treatment [24].

Due to the complexity of diagnosis and antineoplastic therapy for solid neoplasms, the hypothesis that patients from the North reach out to UNACONs in other regions of the country for general or exclusive pediatric cancer therapy should be considered. Children and adolescents who were treated in other regions were registered in the HCR database as non-analytical cases, that is, they did not receive the diagnosis and treatment in the same hospital unit. These cases were not considered in our study.

The care flow data from the INCA regarding all types of cancer treated from 2012 to 2016 showed that most northern patients who were out of their home state were assisted in border states within the North region. Moreover, the data revealed a remarkable care flow of these patients to the state of São Paulo. In all states within the Northeast region, more than 90.0% of the patients were assisted in their home state. Relocation of southeastern and southern residents for cancer care in other states was not frequent, with the State of São Paulo being the main reference for all states. The proportion of cases treated in the state of residence varied from 41.7% in Goiás to 99.6% in São Paulo. Most of the patients assisted outside of Goiás went to São Paulo (51.0%) and the Federal District (5.3%) for treatment [20].

These findings corroborate the results of the present study showing a greater number of childhood cancer records in the Southeast (40.2%, n = 14.564) and Northeast (28.9%, n = 10.435) and a smaller number of cases in the North and Midwest. Therefore, patients from the North and Midwest regions possibly moved to the Southeast for cancer diagnosis and/or treatment.

A study evaluated the travel itinerary for medical care of children and adolescents with cancer between the places of residence and health institutions from 2000 to 2007. The results showed that most oncology centers in the North and Northeast regions were concentrated around state capitals and covered the entire state territory. Consequently, patients living in the North region possibly traveled great distances to have access to chemotherapy and/or radiotherapy services. Approximately 58% of the residents had to travel more than 1,000 km to reach the specialized center, and approximately 25% of them had to leave their region to receive treatment in places located beyond 1,600 km of their households [6].

Our findings indicated that children and adolescents from the North who were diagnosed with hematological cancer had their treatment started more frequently after 60 days (18.9%; n = 279). In contrast, this percentage was 12% or less in the other regions of the country. Aspects such as access issues, limited service in the Brazilian Healthcare System, excess of patients in large capitals, insufficient management, and underfunding should be considered, in addition to the need for a new structure in assistance policies [6]. The North region presents a poor distribution of pediatric oncology services, with the lowest number of accredited facilities in Brazil [21]. These regional differences in cancer therapy can negatively impact the patient's prognosis and decrease survival rates [22].

In our study, we also analyzed the distribution of childhood cancer cases in Brazil according to self-reported skin color. Our data revealed a greater concentration of white cancer patients in the Southeast and South, indigenous people in the North, and mixed-raced individuals in the Northeast and North. This is consistent with the data from the 2010 IBGE population census, which showed a predominance of mixed-raced individuals in the North and Northeast and white individuals in the Southeast and South [12].

The 2010 IBGE census indicated that black and mixed-race populations are the majority in Brazil (50.7%) [12]. An integrative literature review pointed out that racial and socioeconomic inequality negatively affect the accessibility to cancer care of the black population (black and mixed-race) in Brazil. Inarguably, black patients experience a critical difficulty in cancer care for social and economic reasons, regardless of the type of cancer, and diagnosis and/or treatment approaches [25]. This is historically related to the country's colonization background and the perpetuation of social inequality [26]. Consistent with this, pediatric cancer patients who self-reported mixed-race or black skin color were the majority in our study and frequently had their treatment started 60 days after the diagnosis.

A study with HCR data of 481 women from Minas Gerais with invasive breast cancer, diagnosed between 2003 and 2005, identified a worse prognosis for black women as compared to white ones. The authors reasoned this is because the diagnosis in the black population usually occurs at a late stage of the disease [27]. Therefore, skin color demonstrates to be a limiting factor for access to goods, and social and health resources, which also applies to children and adolescents with cancer.

The availability of specific services only in some Brazilian regions and the obstacles to diagnosis and treatment may delay cancer care in the Brazilian healthcare system. Early diagnosis and treatment are decisive for a favorable outcome (cure, prolongation of life, and improvement in the quality of life) in patients with childhood neoplasms. Thus, delayed attention is associated with poorer prognosis by reducing the chances of cure, requiring more invasive procedures, or even resulting in metastasis [28].

In 2012, Federal Law No. 12,732 established the 60-day limit after the diagnosis as the maximum period for starting cancer therapy [9]. According to the INCA's Integrated HCR System, 30% of the patients with childhood cancer were admitted to the reference service with a diagnosis, but without treatment, whilst 70% underwent treatment within 60 days, and only 30% within 15 days. As for the children and adolescents undiagnosed and untreated at admission, 80% started treatment 15 days after the diagnosis and 95% within 60 days [2].

Although 77.0% of the patients in our study started treatment before the time enforced by law, there were records of patients waiting 4,257 days before the start of antineoplastic therapy, with a median of 9 days. Such a large period between the diagnosis and the start of treatment may be related to the previously mentioned factors, such as difficulty in access to oncology care facilities, regional differences in the standard and quality of treatment in specialized services, and resource management issues in the Brazilian healthcare system.

In contrast with these results, a study analyzed the HCR of childhood cancer in Brazil from 2000 to 2015 and showed that the median time between the first consultation and the diagnosis in the hospital was six days, whereas the median time between the diagnosis and the start of treatment was two days [15]. The differences observed in the medians reported by these authors and those of our study may be related to continuous updating of HCR data and the time series analyzed (2000-2015 vs. 2010-2016, respectively).

Another study analyzed the itinerary of children and adolescents with suspected cancer who were referred by non-specialized health units in the city of Rio de Janeiro from October 2008 to June 2011. The time interval between the diagnostic confirmation and the start of treatment was five days in 8 cases (3 of them starting treatment the same day of diagnostic confirmation); between 10 and 15 days in 2 cases (awaiting catheter implantation); and between 15 and 35 days in 3 cases (19 days awaiting review of the biopsy report, 27 days to undergo the surgery, and 38 days to start radiotherapy) [29], with a median of only 5 days.

Thus, the lack of organization of the healthcare system, the need for more complex exams and treatments, and the type of neoplasm can altogether influence the time to diagnosis of childhood cancer and the adoption of appropriate therapeutic measures. The cases whose time to treatment exceeded what is enforced by law can be explained by other factors such as restricted access to treatment, absence of institutions qualified for pediatric treatment, difficulties in referrals, and need for long-distance travel to the reference oncology service.

The specificity of pediatric cancer requires that treatments be performed in qualified oncology institutions with a pediatric oncology service. However, in 2014, only 50% of oncology surgeries, 71% of pediatric chemotherapy procedures, and 53% of radiotherapy sessions were performed in healthcare facilities with this profile in Brazil [2]. Therefore, the absence of this type of institution, regional inequalities, and the lack of equipment, supplies, and specialists, may justify a time longer than 60 days to start the oncological treatment, mainly for solid neoplasms - which need surgical intervention.

Here, the prevalence rates of childhood cancer ranged from 82.3/million to 90.4/million among males and from 72.0/million to 80.0/million among females, according to HCR data from 2010 to 2016. In India, the incidence of childhood cancer among children aged 0 to 14 years ranged from 18.5 per million in the state of Nagaland to 235.3 per million in Delhi for males, and from 11.4 per million in the East Khasi Hill district to 152.3 per million in Delhi for females, according to secondary data of 2012-2014 [30]. These findings differ from those observed in Brazil, which showed a smaller variation between the sexes, although both are developing countries.

In Europe, a population-based study in 19 countries determined the incidence rate of childhood cancer in the period from 1991 to 2010. The mean annual incidence was 137.5 (95% CI 136.7-138.3) in children aged 0 to 14 years. In adolescents, the combined European incidence was 176.2 (174.4-178.0) per million people [13]. These incidence rates are similar to our results for the age group 0 to 4 years, with a coefficient of prevalence of 115.0/million in 2013 and 2016, and they differ from the findings corresponding to the age group 15 to 19 years, with coefficients of prevalence ranging from 76.4 to 88.2/million.

In Brazil, the incidence of childhood cancer is calculated based on the INCA's Population-Based Cancer Registries (RCBP, in Portuguese), which indicates the number of new cases, as well as their timeline and geographic distribution nationwide. Data extracted from a total of 25 RCBP in August 2015 indicated that the median of the average age-adjusted incidence rates was 126.65 per million for the age group 0-14 years and 139.99 per million from 0 to 19 years, with a higher incidence in the age groups 1 to 4 years (169.86/million) and 15 to 19 years (157.22/million) [2].

In Brazil, the South region showed the highest prevalence rates of cancer in males (847.3/million) and age group 0 to 4 years (1,051.8/million). Differing significantly from these results, the average incidence rate of the RCBP for childhood cancer in the South region was 255.53/million for patients aged 0 to 4 years and 229.33/million for those aged 15 to 19 years [2].

While the RCBP data differ from the coefficients of prevalence found in our study, the results are in line with the presence of higher rates in the age groups 0 to 4 years and 15 to 19 years. Of note, these rates were calculated based on the analysis of data from different sources. The HCR database presents the information of cases admitted to hospital units, while the RCBP registers new cancer cases in a specific geographic area. Moreover, the information extracted from both registry systems for calculations of incidence and prevalence was obtained in different periods and are being constantly updated.

One important aspect to consider is that the data in this study were obtained from a secondary source, limiting the analysis to the information available in the IRHC. The quality of the information depends essentially on a continuous data entering, periodic updating of the databases for public access, and an adequate, complete, and consistent filling of the patient's medical records in all levels of assistance. Likewise, it is important to train professionals who work with cancer registries to ensure that the information being entered is reliable [31].

The HCR database contains information of cases assisted mostly in accredited institutions for cancer therapy in Brazil. Therefore, it is an important reference source for the analysis of cancer care nationwide. Registered cases are uploaded into the HCR database within a maximum period of two years and are updated every six months to the public tab of the IRHC [3]. This study presents information extracted on September 30th, 2020; hence, the possibility of underreporting (non-registered patients), incomplete records, and data processing issues must be considered.

Collectively, our findings may assist in the identification of needs and definition of priorities in oncology care in Brazil, supporting health managers in decision-making for greater access to cancer therapy and promoting wellness among children and adolescents with cancer. The variability observed in the HCR data concerning geographic region, sex, age group, and type of neoplasm suggests that the data collection procedure should be improved and that health professionals should be trained accordingly.

Further research on childhood cancer and the time between the diagnosis and start of treatment is encouraged. As it is a rare disease with an invasive behavior, the time to start antineoplastic therapy is critical for patient survival.

Conclusion

The present study allowed us to perceive regional differences in childhood cancer care concerning skin color, time to treatment, and type of neoplasm, which are variables that may reflect geographic inequalities in terms of availability of resources and access to referral services for cancer treatment in Brazil. In compliance with Law 12,732, most pediatric cancer patients were treated within 60 days or less after the diagnosis, but there was a great variability of waiting days among those who remained untreated after the time limit determined by the law.

Authors' Contributions

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NNNL	https://orcid.org/0000-0002-6524-0908	Conceptualization, Methodology, Investigation, Formal Analysis and Writing - Review and Editing.
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AMGV	https://orcid.org/0000-0001-8460-3981	Conceptualization, Methodology, Formal Analysis and Writing -Review and Editing.

All authors declare that they contributed to critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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