Original Article

Rare Cancers in Childhood and Adolescence in Brazil: First Report of Data From 19 Population-Based Cancer Registries

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BACKGROUND: Rare childhood cancer is challenging to define. The Italian Pediatric Rare Tumor (TREP) Study considers rare tumors to include solid malignancies characterized by an annual incidence rate of <2 cases per 1 million and not enrolled in clinical trials. The objective of the current study was to analyze the population incidence rate of rare tumors among children and adolescents (those aged birth-19 years) in Brazil. **METHODS:** Incidence data were obtained from 19 population-based cancer registries covering the 5 geographic regions in Brazil. Newly diagnosed cases were selected according to the TREP definition, using the *International Classification of Diseases for Oncology*. To calculate the crude incidence rate, the numbers of incident children and adolescents with a specific rare cancer were divided by the corresponding person-years lived for the population aged <20 years during the same period. **RESULTS:** Two tumors had an incidence rate that was >2 cases per 1 million (thyroid and skin cancers) in adolescents only. Several tumors demonstrated variations in incidence across the Brazilian regions. Adrenocortical carcinoma had a high incidence rate (4 cases per 1 million) in the south region among children aged <10 years. Thyroid and skin carcinoma had higher incidence rates in the midwest, southeast, and south regions. **CONCLUSIONS:** Due to the extraordinary rarity of these events, networking is important for improving basic research, clinical studies, and trials. Centralization of diagnosis is the only way to improve the diagnosis and treatment of children affected by these rare diseases. The registration and surveillance of rare pediatric cancers are crucial from a public health point of view, and therefore the quality of registration has to be improved. ***Cancer* 2019;125:2638-2646**. © *2019 American Cancer Society*.

KEYWORDS: adolescents, Brazil, childhood, population-based registries, rare tumors.

INTRODUCTION

Cancer in children and adolescents is a rare event, and a subset of such cancers are especially rare. The definition of rare childhood cancer includes both cancers that affect only children (eg, pancreatoblastoma, malignant rhabdoid tumors, and melanotic neuroectodermal tumors of infancy) as well as cancers that usually affect only adults (eg, cancers of the digestive system, thyroid, and adrenal gland).[1]

To the best of our knowledge, the first cooperative study of this group of rare tumors was undertaken in 2000 by the Italian Pediatric Rare Tumor Study (Tumori Rari in Eta Pediatrica [TREP]).[2] TREP defines this group of rare tumors as any solid malignancy characterized by an annual incidence rate of <2 cases per 1 million and the patients are not enrolled in clinical trials.[2,3] Groups from several other European countries (Italy, France, the United Kingdom, Poland, and Germany) later joined this initiative, and founded the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT).[2] EXPeRT defines rare childhood cancers not only based on incidence rates but also on a lack of registries and very limited clinical studies. Together, these tumors account for approximately 5% of all childhood cancers.[2,3]

The Children's Oncology Group (COG) in the United States defines rare tumors as those classified as other malignant epithelial neoplasms (including adrenocortical, thyroid, and nasopharyngeal carcinomas) and melanomas (subgroup XI from the International Classification of Childhood Cancer), predominantly adult cancers occurring in the pediatric age range, and other unspecified carcinomas. COG's Rare Tumor Committee also includes 3 other tumor types: retinoblastoma, liver tumors, and germ cell tumors. These 4 categories account for 15% to 20% of all childhood malignancies.[4,5]

Initiatives to study rare childhood tumors also include the creation of international disease-specific registries and clinics.[6] These include registries for pleuropulmonary blastoma,[7] pediatric adrenocortical carcinoma,[8] nuclear protein of the testis (NUT) midline carcinoma (http://www.nmcregistry.org/), and ovarian and testicular stromal tumors

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TABLE 1. Rare Cancers Studied With ICD-O-3 Topography and Morphology Codes

Rare Tumors in Childhood and Adolescents		
Tumor Group	ICD-O-3 Morphology Codes[a]	ICD-O-3 Topography Codes
Pancreatoblastoma	8971	All sites
Non-germ cell gonadal tumors	8600, 8620-8621, 8630, 8634, 8640	C56, C62
Pleuropulmonar blastoma	8973	All sites
Thymus tumors	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C379
Gastrointestinal stromal tumor	8936	All sites
Pheochromocytoma and paraganglioma	8680, 8700, 8711	All sites
Epithelial tumors of appendix	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C181
Breast cancer	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C50
Carcinoid tumors	8013, 8041, 8246	All sites, except C07.9, C08.9, C11, C18.1, C37.9, C44, C50, C73
Adrenocortical carcinoma	8370-8375	All sites
Salivary gland tumors	8010-8084, 8120-8157, 8190-8264, 8290, 8310, 8313-8315, 8320-8325, 8360, 8380-8384, 8430-8440, 8452-8454, 8480-8586, 8588-8589, 8940, 8941, 8983, 9000, 9010-9016, 9020, 9030	C079, C089
Renal carcinoma	8010-8589	C64
Nasopharyngeal carcinoma	8010-8041, 8050-8075, 8082, 8083, 8120-8122, 8130-8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244-8246, 8260-8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500-8576	C11
Skin tumors	8720-8780, 8790 (melanoma)	C44
	8010-8041, 8050-8075, 8078, 8082, 8090-8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390-8420, 8430, 8480, 8542, 8560, 8570-8573, 8940, 8941 (skin carcinoma)	C44
Thyroid carcinoma	8020-8022, 8050, 8260, 8330, 8345, 8346, 8430, 8480, 8510, 8588, 8589	C73

Abbreviation: ICD-O-3, *International Classification of Diseases for Oncology, 3rd Edition*.
[a]Included behavior recode 3 for all morphology codes.

(http://www.otstregistry.org/), as well as an annual centralized clinic for pediatric gastrointestinal stromal tumor (https://ccr.cancer.gov/gist).

The objective of the current study was to analyze the population incidence rate of rare tumors among children and adolescents (those aged birth-19 years) in Brazil, according to the TREP proposal.

MATERIALS AND METHODS

For the current study, rare tumors were defined according to the TREP definition,[9] using the *International Classification of Disease for Oncology, Third Edition* (ICD-O-3) (Table 1).[10] We included only malignant tumors (fifth digit of the morphological code equal to 3). Incidence data were obtained from 19 population-based cancer registries (PBCRs) covering the 5 geographic regions of Brazil: north (Belem, Roraima, Manaus, and Palmas), northeast (Fortaleza, Joao Pessoa, Recife, and Aracaju), midwest (Cuiaba, Goiania, and Campo Grande), southeast (Barretos, Sao Paulo, Jau, Grande Vitoria, Belo Horizonte, and Pocos de Caldas), and south (Curitiba and Florianopolis). These selected PBCRs cover approximately 23% of the total Brazilian population.

Figure 1 shows the period of coverage for each PBCR, the population coverage of children aged <20 years for each city providing PBCR data, and the distribution of skin color for each region. We did not evaluate skin color distribution according to individual PBCR due to the very high percentage of missing data. Skin color distribution from the 5 Brazilian regions was obtained from the Brazilian Institute of Geography and Statistics (https://sidra.ibge.gov.br) based on self-reported categorization as white, black, yellow, brown, and Indian.

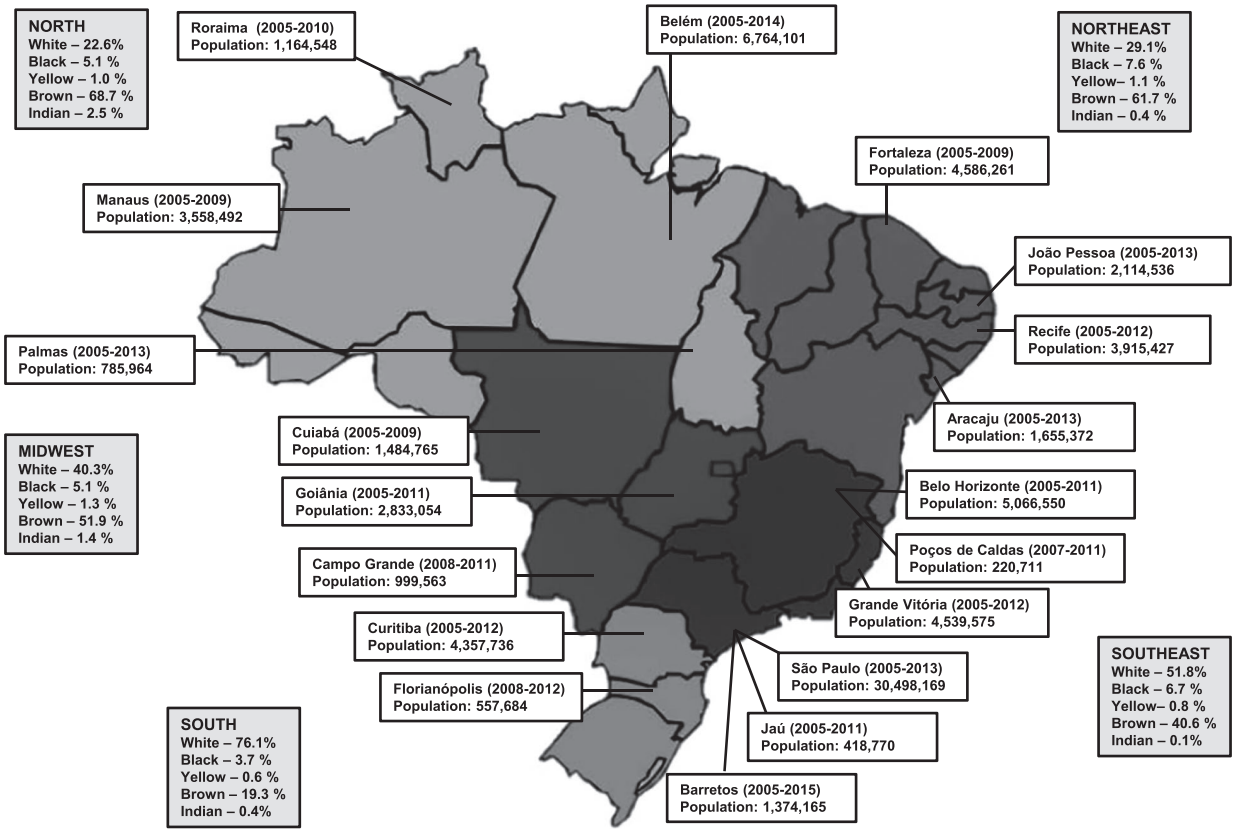

Figure 1. Map of Brazil showing the 5 different regions and their distributions of skin color as well as the cities, the period included in the study, and the respective populations of children and adolescents aged birth to 19 years.

Table 2 presents data quality indicators. Unspecified diagnoses and those with unspecified morphology codes (8000, 8800, 9800, etc) were divided into subgroups based on the *International Classification of Childhood Cancer, Third Edition*. Of the 19 PBCRs, all had 0% of their cases ascertained by death certificate only. The rate of microscopically verified cases was >80% in 18 PBCRs, and 1 PBCR had a rate <75%. To estimate crude incidence rates, we divided the numbers of incident cases for a given entity during the period of diagnosis by the corresponding person-years lived within the general population during the same period for each PBCR.

RESULTS

Table 3 presents the crude incidence rates for each different rare tumor according to TREP definition and region. Two tumors had an annual incidence rate of >2 cases per 1 million (thyroid and skin carcinoma). Several tumors demonstrated geographic variations in incidence. Thyroid carcinoma had higher incidence rates in the midwest, southeast, and south regions (>6 cases per 1 million per year). Skin carcinoma had higher incidence rates in the midwest and southeast (>5 cases per 1 million per year). Adrenocortical carcinoma had a higher incidence rate in the south region (2.2 cases per 1 million per year). Thyroid carcinoma, melanoma, and skin carcinoma had lower incidence rates in the north region. Some tumors demonstrated age-related variations in incidence (Table 4). Thyroid and skin carcinoma incidence rates increased with age, and were found to be highest among adolescents (those aged 15-19 years). The great majority of thyroid tumors included papillary carcinoma. Medullary carcinoma occurred in adolescents (5 cases) and in those aged 5 to 10 years (3 cases). Adrenocortical carcinoma had a higher incidence rate among children aged <10 years (Table 4). Figure 2 shows the annual incidence rates for the 4 major rare tumors according to patient sex and age. Skin and thyroid carcinomas had higher incidence rates in females, and nasopharyngeal carcinoma had a higher incidence rate among males. All 4 major rare

TABLE 2. Data Quality Indicators of Rare Tumors From 19 Brazilian PBCRs in Cases Aged <20 Years Who Were Diagnosed Between 2005 and 2015

Region	PBCR	No. of Cases	DCO, %	MV, %	NOS, %
North	Belem	36	0.0	100.0	14.1
	Manaus	13	0.0	92.3	16.6
	Palmas	7	0.0	100.0	10.2
	Roraima	3	0.0	100.0	20.3
Northeast	Aracaju	33	0.0	93.9	5.0
	Fortaleza	44	0.0	95.5	12.9
	Joao Pessoa	22	0.0	100.0	17.2
	Recife	42	0.0	92.9	10.9
Midwest	Campo Grande	19	0.0	94.7	11.0
	Cuiaba	14	0.0	100.0	13.2
	Goiania	61	0.0	72.1	3.2
Southeast	Belo Horizonte	99	0.0	100.0	11.8
	Barretos	22	0.0	100.0	3.4
	Grande Vitoria	16	0.0	100.0	10.1
	Jahu	7	0.0	85.7	0.0
	Pocos de Caldas	14	0.0	100.0	5.1
	Sao Paulo	616	0.0	100.0	22.6
South	Curitiba	54	0.0	100.0	3.5
	Florianopolis	24	0.0	100.0	4.1
Brazil		1146	0.0	99.5	15.2

Abbreviations: DCO, cases ascertained from death certificate only; MV, microscopically verified cases; NOS, cases not otherwise specified (*International Classification of Diseases for Oncology, 3rd Edition* morphology codes: 8000-8005); PBCR, population-based cancer registry.

TABLE 3. Number of Cases and CRs of Rare Tumors in 5 Brazilian Regions in Cases Aged <20 Years and Diagnosed Between 2005 and 2015

Tumor Group	No. of Cases	North CR	Northeast CR	Midwest CR	Southeast CR	South CR	Brazil CR
Pancreatoblastoma	0	0.00	0.00	0.00	0.00	0.00	0.00
Non-germ cell gonadal tumors	1	0.00	0.00	0.00	0.02	0.00	0.01
Pleuropulmonary blastoma	1	0.00	0.00	0.00	0.02	0.00	0.01
Thymus carcinoma	2	0.00	0.08	0.00	0.02	0.00	0.03
GI stromal sarcoma	3	0.00	0.08	0.00	0.02	0.20	0.04
Pheochromocytoma and paraganglioma	12	0.00	0.41	0.00	0.14	0.20	0.16
Carcinoid tumor	14	0.08	0.24	0.19	0.17	0.41	0.18
Neuroendocrine tumor	17	0.16	0.16	0.38	0.21	0.41	0.22
Breast cancer	24	0.16	0.49	0.38	0.31	0.20	0.31
Salivary gland tumor	35	0.24	0.57	0.56	0.47	0.41	0.46
Adrenocortical tumor	35	0.00	0.00	1.32	0.40	2.24	0.46
Renal cell carcinoma	39	0.33	0.33	0.38	0.55	1.22	0.51
Nasopharyngeal carcinoma	70	0.41	0.73	1.69	1.12	0.00	0.91
Melanoma	93	0.41	1.22	0.75	1.42	1.83	1.21
Nonmelanoma skin cancer	388	1.14	3.02	5.27	7.10	2.03	5.05
Thyroid carcinoma	412	1.87	4.07	6.39	6.48	6.51	5.36
All tumors	1146	4.81	11.41	17.30	18.47	15.66	14.90

Abbreviations: CR, crude incidence rates per 1 million; GI, gastrointestinal.

tumors had higher incidence rates among individuals aged >9 years.

DISCUSSION

To the best of our knowledge, there are few reports to date from PBCRs specifically regarding rare childhood tumors, and the current study is the first descriptive analysis of PBCR data regarding rare childhood cancers in Brazil, covering approximately 23% of a population of 62,923,165 Brazilian children and adolescents (https://censo2010.ibge.gov.br). The objective of the current study was to describe the incidence rates of rare childhood tumors in Brazil according to the TREP definition. We excluded several rare tumor types, including rhabdoid tumors, liver tumors, and malignant germ cell tumors, because these tumors currently are being studied in specific clinical trials.

TABLE 4. Number of Cases and CRs of Rare Tumors With a CR >0.45 According to Age Group and Brazilian Region

		Age Birth to 9 Years		Age 10 to 14 Years		Age 15 to 19 Years	
Region	PBCR	No.	Rate	No.	Rate	No.	Rate
Adrenocortical tumors	North	0	0.00	0	0.00	0	0.00
	Northeast	0	0.00	0	0.00	0	0.00
	Midwest	5	2.01	0	0.00	2	1.35
	Southeast	11	0.55	3	0.28	3	0.27
	South	9	3.99	0	0.00	2	1.44
	Brazil	25	0.69	3	0.15	7	0.34
Salivary gland tumors	North	0	0.00	1	0.32	2	0.62
	Northeast	0	0.00	3	0.95	4	1.18
	Midwest	0	0.00	1	0.74	2	1.35
	Southeast	2	0.10	10	0.92	8	0.71
	South	0	0.00	1	0.78	1	0.72
	Brazil	2	0.05	16	0.81	17	0.82
Renal carcinoma	North	2	0.34	1	0.32	1	0.31
	Northeast	0	0.00	1	0.32	3	0.88
	Midwest	0	0.00	2	1.49	0	0.00
	Southeast	5	0.25	6	0.55	12	1.07
	South	1	0.44	2	1.57	3	2.16
	Brazil	8	0.22	12	0.61	19	0.92
Nasopharyngeal carcinoma	North	0	0.00	0	0.00	5	1.55
	Northeast	0	0.00	3	0.95	6	1.77
	Midwest	0	0.00	3	2.23	6	4.06
	Southeast	0	0.00	19	1.75	28	2.49
	South	0	0.00	0	0.00	0	0.00
	Brazil	0	0.00	25	1.27	45	2.17
Melanoma	North	2	0.34	0	0.00	3	0.93
	Northeast	8	1.40	3	0.95	4	1.18
	Midwest	1	0.40	0	0.00	3	2.03
	Southeast	17	0.85	15	1.38	28	2.49
	South	1	0.44	2	1.57	6	4.33
	Brazil	29	0.80	20	1.01	44	2.12
Skin carcinoma	North	8	1.35	3	0.96	3	0.93
	Northeast	8	1.40	6	1.90	23	6.77
	Midwest	4	1.61	5	3.71	19	12.85
	Southeast	88	4.39	128	11.80	83	7.39
	South	4	1.77	2	1.57	4	2.88
	Brazil	112	3.07	144	7.30	132	6.37
Thyroid carcinoma	North	0	0.00	3	0.96	21	6.51
	Northeast	2	0.35	9	2.85	39	11.49
	Midwest	0	0.00	7	5.20	33	22.31
	Southeast	11	0.55	61	5.63	234	20.82
	South	0	0.00	11	8.63	25	18.02
	Brazil	13	0.36	91	4.61	352	16.98
All tumors with a CR >0.45	North	12	2.02	8	2.57	35	10.85
	Northeast	18	3.15	25	7.91	79	23.27
	Midwest	10	4.01	18	13.37	65	43.95
	Southeast	134	6.69	242	22.32	396	35.24
	South	15	6.66	18	14.12	41	29.56
	Brazil	189	5.19	311	15.60	616	29.72

Abbreviation: CR, crude incidence rate per 1 million; PBCR, population-based cancer registry.

Approximately 75% of rare tumors occur in adolescents (those aged 15-19 years).[11] In the current series, incidence rates generally increased according to age. Among thyroid carcinoma cases, approximately 56.4% involved patients aged >14 years. Within the adolescent group (those aged 15-19 years), thyroid carcinoma had the highest incidence rate, follow by skin carcinoma. It is interesting to note that adrenocortical carcinoma occurred with a high incidence rate of 4 cases per 1 million in the south region among children aged <10 years, constituting 51% of cases in all regions. Skin carcinoma also had a high incidence rate among children aged birth to 9 years.

Adrenocortical tumors represent approximately 0.2% of all pediatric tumors, with an annual incidence rate of 0.2 cases per 1 million children.[12] A previous study has demonstrated a higher rate of this tumor type in Brazil, with Sao Paulo showing an incidence

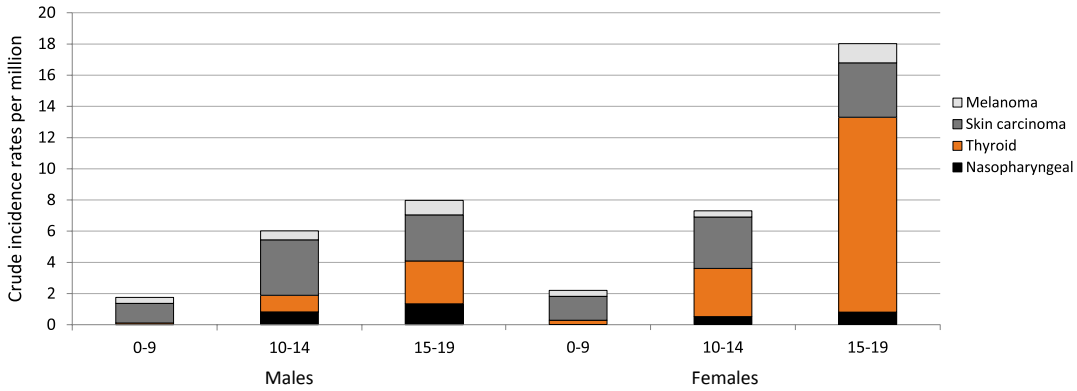

Figure 2. Crude incidence rates of the 4 major rare tumors in children and adolescents according to sex and age group. Data were obtained from 19 Brazilian population-based cancer registries for a period of diagnosis between 2005 and 2015.

rate of 1.5 cases per 1 million, which is >3 times the rate in most registries.[13] Since the 1980s, there has been a clear cluster of pediatric adrenocortical carcinoma cases in several southern states of Brazil.[14] In 1990, an International Pediatric Adrenocortical Tumor Registry was developed and 258 cases were registered in 11 years. The majority of these patients (79.5%) were from southern Brazil, whereas 13% were from the United States and 7.5% were from 9 other countries.[8] A unique constitutional *TP53* mutation (R337H) was identified in the Brazilian patients.[15] This mutation has been detected throughout a region of Brazil extending from the state of Minas Gerais (southeast region) to the state of Rio Grande do Sul (south region).[16] To the best of our knowledge, the origin of the R337H founder mutation is unknown and affected families are mostly distributed along a main route following the south, southeast, and midwest regions used by merchants of Portuguese origin in the 18th and 19th centuries.[17] A screening program was implemented to detect the *TP53* R337H mutation among newborns in Curitiba (south region), and this mutation was identified in 0.3% of all newborns.[18] In the current study, the incidence rate followed the same pattern. The south region presented with the highest incidence rate (2.2 cases per 1 million), followed by the midwest (1.05 cases per 1 million) and southeast (0.41 cases per 1 million) regions. More specifically, the highest incidence rate was noted among children aged <10 years in the south region (4 cases per 1 million). It is difficult to find definite histopathological criteria to differentiate adrenocortical carcinoma from adrenocortical adenoma, and the histopathological classification of adrenocortical carcinoma in pediatric patients remains controversial.[8,19] Unfortunately, in the current study, we did not have data regarding outcome, clinical characteristics, or pathological analysis. However, this is the first analysis, and the next steps will be to develop follow-up for these patients and revise the pathological reports from the PBCRs to improve the quality of registration and pathological reports.

The RARECAREnet database on the epidemiology of rare cancers in Europe provides incidence rates for many of the rare tumors reported in the current study; the youngest age categories were age <15 years and ages 15 to 29 years. For the majority of the rare entities in common with RARECAREnet, the Brazilian incidence rates (aged <20 years) are reported to be between age <15 years and ages 15 to 29 years.[20] RARECAREnet also estimated survival for these exceptional tumors and demonstrated a good prognosis for the majority of them, but with 5-year relative survival rates of <50% after 5 years for cases of adrenal gland carcinoma, some neuroendocrine tumors, and pancreatoblastoma. A comparative analysis between Brazilian and European data could be considered to enlarge the series of cases to study and to share the experience in treatment, protocols, and results.

Over the past decades, incidence rates for skin carcinoma have been rapidly increasing in all white populations worldwide. The risk of skin carcinoma increases with age but in the current series it was not clearly observed, especially in the southeast region, most likely due to the incomplete registration of skin cancers by all registries. A report from the Automated Childhood Cancer Information System (ACCIS) presented skin carcinoma incidence rates of 0.3 cases per 1 million and 3.7 cases per 1 million among children and adolescents, respectively.[21]

Skin cancer data have been collected in all Brazilian PBCRs and follow Surveillance, Epidemiology, and End Results (SEER) rules, in which different topographical codes are considered multiple primary tumors.[22] In a prior series of adolescents and young adults aged 15 to 29 years, the median incidence rate of skin carcinoma in Brazil was 18 cases per 1 million.[23] Among children and adolescents aged <20 years with xeroderma pigmentosum, the rate of skin carcinoma in sunlight-exposed areas is reported to be 10,000 times higher than in the general population.[24,25] A recent report has described a genetic cluster involving the *POLH* gene in families with xeroderma pigmentosum in a community in the state of Goias in the midwest region of Brazil.[26] In the current study, the incidence rate for skin carcinoma was highest in the midwest region, as has been previously reported among adolescents and young adults.[22] Further investigations are necessary.

The incidence of melanoma among children in the United States is rapidly increasing by an average of 2% per year.[27,28]According to the TREP definition, melanoma is rare in children but not in adolescents.[9] Several others countries also have reported increased incidence rates of melanoma, especially in adolescents aged 15 to 19 years and on sun-exposed areas of the body. Risk factors for pediatric melanoma include being white, being female, increasing age, and environmental ultraviolet radiation exposure.[28,29] Melanoma and skin carcinoma also demonstrated higher incidence rates in the south and southeast regions. The percentage of the population having white skin color is significantly higher in the south (76% of the population). Currently, improved education programs around the world are increasing awareness of the dangers of sun exposure among parents and adolescents.

Thyroid carcinoma has a low incidence rate among children aged <15 years (2.0 cases per 1 million).[30] However, over the last decades, the incidence of thyroid cancer has markedly increased, especially among children aged 15 to 19 years.[31-33] Moreover, thyroid cancer incidence rates are higher in white populations, at nearly twice those noted in black populations.[34,35] In the current study, the highest thyroid cancer incidence rates were observed in the midwest, southwest, and south regions of Brazil, which have the highest percentages of white residents. We also found a higher thyroid cancer rate among females, a finding that is in agreement with prior data.[31]

Nasopharyngeal carcinoma is very rare among children. Moreover, its incidence rates vary greatly in different populations, suggesting the influence of environmental factors such as exposure to Epstein-Barr virus.[36] The SEER database demonstrated an incidence rate of 0.5 cases per 1 million person-years among children and adolescents (aged birth-19 years).[37] In the European population, rates were 0.3 and 1.3 in those aged <15 years and 15 to 24 years, respectively, with large variations noted across European countries and a high incidence in the southern countries.[20] Single-institution data from Brazil have indicated that nasopharyngeal carcinoma accounts for 13% of head and neck tumors in children and adolescents (those aged birth-19 years).[38] However, in the European population, the corresponding percentage was higher (30%).[20] The incidence rate in the current study was 0.9 cases per 1 million, with the highest incidence noted in the midwest followed by the southeast region.

It is interesting to note that in the north region, which has the lowest percentage of white individuals, the incidence of these tumors is the lowest, suggesting that some preventative factors are present in this population or that a diagnosis is difficult to reach because of the low availability of good diagnostic centers.

One of the first hurdles to overcome in studying rare cancers is diagnostic accuracy. Unexpectedly, some entities such as pancreatoblastoma, non-germ cell gonadal tumors, and pleuropulmonary blastoma had no cases or only one case diagnosed in all the Brazilian regions covered. Collaboration with the pathologist and clinician and the relevance of obtaining a second opinion for a correct diagnosis are important issues that must be discussed and organized. Central pathology currently is considered essential in all clinical trials.[39] Unspecified cases are recorded in the registry in instances for which pathology reports could not be retrieved and no specific diagnosis could be made. A high percentage of unspecified neoplasms (not otherwise specified [NOS]) may distort the incidence rates in specific diagnostic groups or subgroups.[40] Institutions of reference should be offered centralized histological review and the identification of these centers also is important. The RARECARE project found that after the revision of both morphology and topography NOS codes by PBCRs, the percentage of NOS cases was reduced only marginally.[41] Microscopically verified cases were not 100% in 7 PBCRs but this is not a reason for their exclusion because quality criteria are captured for new cases in all sources, including clinical and imaging examinations, and not only pathology reports.

The concept of disease rarity is a matter of controversy. One objective of the TREP project is to create a network to enable the development of diagnostic and treatment recommendations for each rare

tumor.[2] The establishment of a network of specialists, including oncologists, pathologists, endocrinologists, dermatologists, and surgeons, is essential for clinical trials, pathology review, and biological studies. Partnerships with oncologists who treat adults are essential for developing new therapy. International collaboration is required to improve guidelines for diagnostic criteria, treatment, and research and trials performed among patients with rare tumors. It is well known that in patients with rare tumors, the diagnosis could improve after the establishment of such a group.

To the best of our knowledge, the current study is the first to report the incidence rates of this group of rare cancers in Brazil through population-based data to enlarge the collaboration with other Latin American countries. PBCRs can increase the robustness of the estimations and are useful to facilitate clinical collaborations. We believe the current study data can assist in the creation of a network of research groups to study rare tumors in children and adolescents, integrating specialists from different areas of Brazil. In addition, the collaboration between different cancer societies may improve the management of children with very rare cancers.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Nathalie V. Balmant: Data collection, analysis, and interpretation and final approval of the article. **Rejane de Souza Reis:** Study conception and design, data analysis and interpretation, and final approval of the article. **Marceli de Oliveira Santos:** Study conception and design, data analysis and interpretation, and final approval of the article. **Beatriz de Camargo:** Study conception and design, data analysis and interpretation, article writing, and final approval of the article. **Gemma Gatta:** Data analysis and interpretation, article writing, and final approval of the article.

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