Cancer Epidemiology 56 (2018) 21–30

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Incidence of childhood cancer in Costa Rica, 2000–2014: An international perspective

Friederike Erdmann[a,b,*], Tengfei Li[c], George Luta[c], Brenda M. Giddings[d], Guillermo Torres Alvarado[e], Eva Steliarova-Foucher[f], Joachim Schüz[a], Ana M. Mora[g]

[a] Section of Environment and Radiation, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372, Lyon, France
[b] Childhood Cancer Research Group, Danish Cancer Society Research Center, Strandboulevarden 49, 2100, Copenhagen, Denmark
[c] Department of Biostatistics, Bioinformatics, and Biomathematics, Georgetown University, 4000 Reservoir Rd NW, Washington DC, 20057, USA
[d] California Cancer Reporting and Epidemiologic Surveillance (CalCARES) Program, UC Davis Health, Institute for Population Health Improvement, 1631 Alhambra Boulevard, Suite 200, Sacramento, CA, 95816, USA
[e] National Cancer Registry, Ministry of Health, San José, Costa Rica
[f] Section of Cancer Surveillance, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69372, Lyon, France
[g] Central American Institute for Studies on Toxic Substances (IRET), Universidad Nacional, P.O. Box 86-3000, Heredia, Costa Rica

ARTICLE INFO

Keywords:
Childhood cancer
Childhood leukemia
Incidence
Incidence trends
Costa Rica
Geographical differences

ABSTRACT

Background: Estimating childhood cancer incidence globally is hampered by a lack of reliable data from low- and middle-income countries. Costa Rica is one of the few middle-income countries (MIC) with a long-term high quality nationwide population-based cancer registry.

Methods: Data on incident cancers in children aged under 15 years reported to the Costa Rica National Cancer Registry between 2000 and 2014 were analyzed by diagnostic group, age, sex, and geographical region and compared with incidence data for Hispanic and Non-Hispanic White (NHW) children in California, USA.

Results: During the 15-year period, 2396 cases of childhood cancer were reported in Costa Rica, resulting in an overall age-standardized incidence rate (ASR) of 140/million. Most frequent cancer types were leukemias (40.5%), malignant central nervous system (CNS) tumors (13.9%), and lymphomas (12.7%). The observed ASR of lymphoid leukemia (46.9/million) ranked high globally. Low rates were found for most solid tumors including malignant CNS tumors, sympathetic nervous system tumors, and soft tissue sarcomas. There was almost no change in incidence rates over time, while geographical variations were observed within Costa Rica. The overall cancer rate in Costa Rica was lower compared to NHW (176.1/million) and Hispanic (161.7/million) children in California.

Conclusion: Based on the longstanding registration system, the childhood cancer incidence rates were similar to those observed in other Latin American countries. While a degree of under-ascertainment of cases cannot be excluded, the markedly high leukemia rates, in particular of the lymphoid sub-type deserves further study in this population.

1. Introduction

Little is known about the aetiology of childhood cancers. Many studies targeted lifestyle factors or environmental pollutants as possible risk factors but with inconsistent results [1,2]. To date, a few genetic conditions, exposure to high-dose ionizing radiation and prior chemotherapy, and high or low birth weight have been confirmed as risk factors [1], but only explain a small percentage (< 10%) of all cases [1,2]. Early age at diagnosis indicates that childhood cancer might originate *in utero* and that prenatal, including preconception, factors or early-life environmental exposures may be important determinants [3,4].

Population-based cancer registries around the world report incidence rates in children under the age of 15 years that vary between less than 70 to more than 200/million per year [5] for all cancers. Describing incidence patterns and identifying geographical differences, especially in genetically-related populations may provide useful indications for possible aetiological associations and observed geographical incidence differences have been used to support several hypotheses of the association between exposures related to modern

* Corresponding author at: Childhood Cancer Research Group, Danish Cancer Society Research Center, Strandboulevarden 49, DK-2100, Copenhagen, Denmark.
E-mail address: erdmann@cancer.dk (F. Erdmann).

https://doi.org/10.1016/j.canep.2018.07.004
Received 30 April 2018; Received in revised form 9 July 2018; Accepted 10 July 2018

lifestyle and the risk of childhood cancer, particularly leukemia [3].

However, estimating childhood cancer incidence globally is hampered by a lack of reliable data, especially marked in low- and middle-income countries (LMIC), including in Latin American countries. Incidence patterns are relatively consistent and well described for economically developed countries [6], with recent age-standardised incidence rates of 168, 176, and 155/million children being reported for Germany [7], US Non-Hispanic Whites (NHW) [5], and Australia [5], respectively. In contrast, childhood cancer rates of 46, 111, and 129/million have been reported for South Africa [8], Thailand [5], and Argentina [9], respectively, with a variation in the distribution of cancer types across these middle-income countries (MIC) and in comparison to high-income countries (HIC). Reported incidence rates for leukemia, the most common childhood cancer type in HICs [5], and for cancer in infants are considerably lower in many LMICs compared to HICs [5,10]. Simultaneously, some Latin American cancer registries including Costa Rica, consistently report very high incidence rates of leukemia [5].

Geographical variations in incidence rates may indeed indicate differences in genetic or environmental exposures that affect the risk of childhood cancers (or certain types of childhood cancer). However, evidence from Brazil [11], India [12], and South Africa [8] suggest that incidence differences across countries may also reflect under-diagnosis and/or under-reporting of cases in LMICs.

Costa Rica is an upper-middle income country [13] with a nationwide population-based cancer registry that has provided internationally comparable data for more than four decades and is also home to an ethnically homogenous population (i.e., most Costa Ricans are considered mestizos) [14]. Moreover, Costa Rica has a national public health care system (funded by employer, employee, and government) that provides free access to primary, secondary, and tertiary public health care for children until the age of 18 years [15]. This health care system gives every child with cancer the possibility to get diagnosed and treated for free. The National Children's Hospital situated in the capital San Jose is the only public specialized pediatric oncology treatment center in Costa Rica (see Fig. 1). In this report, we provide the first comprehensive description and interpretation of the incidence of childhood cancers diagnosed between 2000 and 2014 in Costa Rica by cancer type, age, sex, and place of residence. Furthermore, we discuss our findings in a global perspective and compare our results with data for Hispanics and NHW children in California, USA. Comparing the incidence of Costa Rica with the genetically-related population of Hispanics provides the basis for considering the potential impact of differences in diagnosis, reporting, and potential environmental risk factors, while comparison with NHW may suggest differences in genetic susceptibility.

2. Material and methods

2.1. Costa Rica National Cancer Registry

The Costa Rica National Cancer Registry (RNT, for its acronym in Spanish) was founded in 1976 and reached nationwide coverage in 1980 [16]. Reporting each diagnosed cancer case to the RNT is mandatory for all public and private hospitals and clinics, health care units, and clinical and pathology laboratories in Costa Rica. In addition, the RNT reviews all death certificates at the Central Bureau of Statistics and Census on a yearly basis. Cases notified from death certificates are traced back to medical records and if their diagnosis is supported clinically or microscopically, the registry record is updated; otherwise it stays death certified only (DCO). The DCO cases represented 1.7% of the childhood cancer cases diagnosed between 2000 and 2014, while 91.5% of diagnoses were confirmed microscopically (histology or cytology). Diagnoses are coded based on primary organ site and morphological type according to the International Classification of Diseases for Oncology, third edition (ICD-O-3) [17].The RNT registers only tumors of malignant behaviour (or in situ), not benign tumors. Each multiple primary cancer is recorded as an additional case.

2.2. California Cancer Registry

The California Cancer Registry (CCR) is a state-wide population-based registry that collects information on incident cancers diagnosed among California residents since 1988. State law requires any hospital or other health care facility that diagnoses or treats cancer patients to report the cancer case to the registry. The CCR collects information on all primary malignant and *in situ* cancers (except certain carcinomas of the skin) and benign and borderline tumors of the brain and central nervous system [18]. The CCR follows the National Cancer Institute Surveillance Epidemiology and End Results (SEER) Program's multiple primary rules to distinguish a single primary from multiple primary tumors at the time of diagnosis [19]. Cancers in the CCR are classified according to ICD-O-3. Each year, the CCR performs a record linkage with a file of all deaths in the state. If a cancer death does not link to an existing cancer registry case, and no additional information on the cancer is found through follow-back to medical facilities, the case is added to the registry and designated as a DCO case. Less than one percent (0.03%) of childhood cancer cases diagnosed in California between 2000 and 2014 were DCO cases, whereas 92.7% were microscopically confirmed.

Demographic information for cases in the CCR, including a patient's ethnicity and race, come mainly from medical records. This information may be based on self-report by the patient or their family or on assumptions made by medical personnel. The CCR uses various methods to enhance the identification of a patient's ethnicity and race and may infer this information based on birthplace, maiden name, surname, or parents' race [20]. In the CCR data Hispanics may be of any race, however 97.9% of cases identified as Hispanic are racially White.

The CCR was chosen as a reference registry because of the similarities in the genetic make-up between Costa Rican [21] and Californian Hispanic children [22].

2.3. Case definition

All malignant neoplasms diagnosed in patients younger than 15 years of age during the period 2000–2014 were obtained from the RNT and recoded into 12 major diagnostic groups and 47 subgroups according to the International Classification of Childhood Cancer 3rd edition (ICCC-3) [23]. Only one cancer case registered by the RNT during the period of interest had a combination of morphology and topography codes that did not correspond to a specific ICCC-3 group and was retained in the analyses as unclassified.

2.4. Definition of geographical regions in Costa Rica

The territory of Costa Rica is divided into seven provinces which are subdivided into 82 counties (also called cantons), and these are further subdivided into districts. Districts have also been grouped into six geographical regions (i.e., Central, Chorotega, Pacífico Central, Brunca, Huetar Atlántica, and Huetar Norte) that were established by the Costa Rican Ministry of Planning and Economic Policy (MIDEPLAN) in 1978 (Fig. 1). These geographical regions were defined based on social, political, and economic characteristics such as population homogeneity, availability of natural resources, and predominant productive activities [24], and are commonly used for periodical statistical reports, including population counts.

Each MIDEPLAN region is comprised of multiple districts that do not necessarily belong to the same county. This is a challenge when classifying the residences of the cases reported to the RNT into MIDEPLAN regions because counties are commonly used to record these residences in the registry and access to the exact addresses is not permitted. There are three counties (i.e., Alajuela, San Ramón, and Grecia)

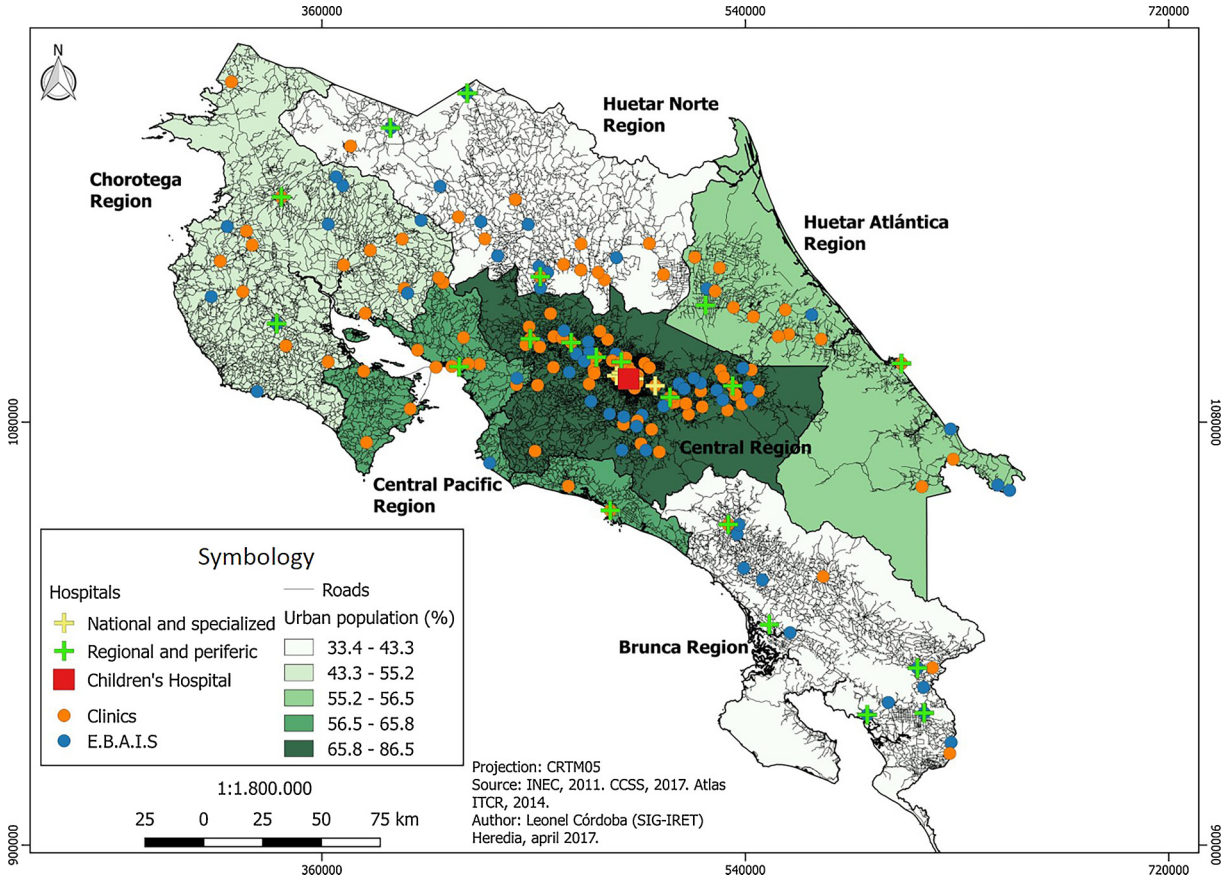


Fig. 1. MIDEPLAN regions, roads, health care facilities, and distribution of urban vs rural population in Costa Rica. Degree of urbanisation was defined by the total of individuals living in defined urban areas divided by the total population in that region. EBAIS is short for Equipos Básicos de Atención Integral en Salud and is the first level of care in Costa Rica, providing health care services to all of the individuals in a community.

that belong to two different MIDEPLAN regions (i.e., Central and Huetar Norte regions). One district in each of these counties (i.e., Sarapiqui, Rio Cuarto, Peñas Blancas) is part of the Huetar Norte Region and the remaining districts belong to Central Region. Other than these three specific counties all other counties correspond to district borders (as used by the RNT). To be able to match correctly the incident cases classified by county of residence with the resident population of MIDEPLAN regions, the 209 childhood cancer cases from the Alajuela, San Ramón, and Grecia counties were randomly assigned to either the Central or Huetar Norte Region, weighted by probabilities proportional to the population size of the respective districts in those two MIDEPLAN regions (having the conservative assumption of similar rates in both regions).

2.5. Population estimates

Mid-year population estimates from National Institute for Census and Statistics of Costa Rica were used as the denominator for calculating incidence rates for Costa Rica. In 2014 Costa Rica had a childhood population of about 1,120,000 children, which had gradually decreased from 1,230,000 children in the year 2000 (Table S1). Population estimates for California by race/ethnicity, sex, and age were obtained from the National Center for Health Statistics [25,26] and originated from the United States Census Bureau. The last decennial census was conducted in 2011 in Costa Rica and in 2010 in the USA.

2.6. Statistical methods

Frequencies, sex ratios, incidence rates, standardized rate ratios (SRRs), and (age-standardized) incidence rate proportions were used to describe and compare the incidence of childhood cancer in Costa Rica. The incidence rates were calculated per 1,000,000 children, by age (age-specific) and overall (crude and age-standardized). The age-standardized rates (ASRs) were calculated using weights (by age groups: 0, 1–4, 5–9, and 10–14 years) of the Segi 1960 World Standard Population [26]. For Supplementary Table S2 additional ASRs based on the WHO World Standard Population [27] were calculated. Subgroup analyses were conducted by ICCC-3 main groups and subgroups [23], age (categories: < 1, 1–4, 5–9, and 10–14 years), and geographical region of residence at the time of diagnosis (i.e., Central, Chorotega, Pacífico Central, Brunca, Huetar Atlántica, and Huetar Norte). Differences by geographical region were evaluated by calculating SRRs and their corresponding 95% confidence intervals (CI).

For time-trend analyses, a moving average of ASRs for 3-year periods was plotted for all cancers combined and separately for (i) leukemia, (ii) lymphoma, and their subtypes as well as for (iii) malignant CNS tumors and (iv) non-CNS solid tumors. Average annual percentage changes (APCs) in ASR were modelled using the Joinpoint Trend Analysis Software [28]. Because of the unexpectedly low leukemia rate and high lymphoma rate observed in 2000, additional sensitivity analyses were conducted by excluding cases diagnosed during the year 2000.

Incidence rate proportions in Costa Rica compared to California were calculated to investigate differences for specific subgroups of childhood cancer. For this purpose, the ASRs by cancer type and age group in Californian Hispanics were set to 100% and compared to the observed rates in Costa Rica and Californian NHW. Childhood cancer incidence rates from California presented in this report were calculated by the CCR using the same methods and restriction criteria [i.e., same time period (2000–2014) and diagnoses (e.g., exclusion of benign brain

Table 1
Childhood cancer reported to the Costa Rican National Cancer Registry in 2000–2014 by major diagnostic group, sex ratio, and age-specific, crude, and age-standardized incidence rates compared to incidence rates from the California Cancer Registry.

	Costa Rica									California	
				Age specific incidence[c]						ASR[e]	
ICCC-3 diagnostic group[a]	n	%	M/F[b]	< 1 year	1–4 years	5–9 years	10–14 years	Crude incidence[d]	ASR[e]	Hispanic	Non-Hispanic White
All childhood cancers	2396	100%	1.2	126.8	184.1	116.6	122.7	136.5	140.0	161.7	176.1
Leukemias	970	40.5%	1.2	24.6	97.4	51.7	33.6	55.3	58.5	67.6	56.5
Lymphoid leukemias	771	32.2%	1.2	6.4	84.2	42.4	22.9	43.9	46.9	56.0	45.8
Acute myeloid leukemias	112	4.7%	1.3	12.8	9.0	5.0	4.7	6.4	6.7	9.2	8.3
Unspecified and other specified leukemias	87	3.6%	1.1	5.5	4.3	4.3	6.0	5.0	5.0	2.4	2.4
Lymphomas	304	12.7%	2.0	1.8	13.4	18.9	21.4	17.3	16.6	14.3	15.4
Hodgkin lymphomas	126	5.3%	1.6	0.9	2.2	9.8	9.4	7.2	6.7	5.4	5.2
Non-Hodgkin lymphomas (except Burkitt lymphoma)	103	4.3%	2.8	0	5.4	4.8	8.3	5.9	5.6	5.9	5.9
Burkitt lymphoma	56	2.3%	2.1	0	4.5	2.9	3.1	3.2	3.2	1.6	3.2
Unspecified and other specified lymphomas	19	0.8%	1.1	0.9	1.3	1.4	0.7	1.1	1.1	1.5	1.2
Malignant CNS tumors[f]	334	13.9%	1.1	14.6	22.2	22.0	14.8	19.0	19.4	26.9	39.3
Sympathetic nervous system tumors	64	2.7%	1.6	21.9	7.4	1.0	0.2	3.7	4.4	8.1	13.9
Retinoblastomas	79	3.3%	0.9	21.0	11.0	1.0	0.2	4.5	5.4	5.6	4.3
Renal tumors	94	3.9%	0.9	9.1	11.6	2.9	2.4	5.4	6.0	7.4	10.2
Hepatic tumors	45	1.9%	2.0	7.3	4.5	1.4	1.5	2.6	2.8	3.1	3.6
Malignant bone tumors	96	4.0%	0.9	0	0.9	3.4	11.7	5.5	4.8	6.3	7.1
Soft tissue sarcomas	108	4.5%	1.3	11.0	6.1	3.8	7.6	6.2	6.2	10.3	11.1
Germ cell tumors	84	3.5%	0.7	7.3	4.5	2.1	7.1	4.8	4.7	6.3	5.7
Malignant epithelial neoplasms	179	7.5%	1.2	3.7	2.7	6.7	20.1	10.2	9.1	5.2	8.0
Other & unspecified malignant tumors	38	1.6%	1.0	4.6	2.5	1.7	2.0	2.2	2.2	0.5	0.6
Uncoded	1	0.0%	NA	0	0	0	0.2	0.1	0.1	NA	NA

[a] Diagnostic groups defined using the International Classification of Childhood Cancer Third Edition (ICCC-3).
[b] M/F: sex ratio – male cases/female cases.
[c] Age specific incidence: age group specific incidence rates per 1,000,000 population.
[d] Crude incidence: crude incidence rate per 1,000,000 population aged 0–14 years.
[e] ASR: age-standardized incidence rate (using Segi World Standard Population) per 1,000,000 population aged 0–14 years.
[f] Malignant central nervous system tumors.

tumors which are not recorded in the RNT)].

Analyses were performed using SAS 9.4 and Microsoft Excel 2010.

3. Results

3.1. Childhood cancer incidence in Costa Rica

A total of 2396 newly diagnosed cancer cases under the age of 15 years were registered by the RNT during the period 2000–2014. The overall ASR was 140.0/million children, but incidence rates varied by age and diagnostic group (Table 1 and Table S2). The highest age-specific rate for all childhood cancers combined was observed in children aged 1–4 years (184.1/million), whereas the lowest rate was found in children aged 5–9 years (116.6/million). Most frequent cancer types were leukemias (40.5%), malignant CNS tumors (13.9%), and lymphomas (12.7%). The male-to-female ratio was 1.2 for all childhood cancers combined, but also varied by age group and cancer type.

A total of 970 children were diagnosed with leukemia, resulting in an overall ASR of 58.5/million and a male-to-female ratio of 1.2 (Table 1). The highest age-specific rate for leukemia was found in children aged 1–4 years (94.7/million), while a low rate was observed in infants (age < 1 year; 24.6/million). The observed pattern for overall leukemia rates was driven by the rates of lymphoid leukemia, including the low rate seen in infants. With an ASR of 46.9/million, lymphoid leukemia is the most frequent subtype accounting for one third of all childhood cancer cases and 80% of all leukemia cases in Costa Rica.

A total of 304 children were diagnosed with lymphoma between 2000 and 2014, yielding an ASR of 16.6/million (Table 1). The incidence of lymphoma was highest in children aged 5–9 (18.9/million) and 10–14 years (21.4/million). A total of 334 children were diagnosed with malignant CNS tumors, resulting in an ASR of 19.4/million, with the highest incidence rates in children aged 1–4 (22.2/million) and 5–9 years (22.0/million). Relatively low ASRs were also observed for some non-CNS solid tumors including sympathetic nervous system tumors (4.4/million), soft tissue sarcomas (6.2/million), and malignant bone tumors (4.8/million). The ASR for retinoblastoma was 5.4/million and for renal tumors it was 6.0/million. ASR for epithelial neoplasms and melanoma was relatively high (9.1/million) with the rate of 2.4/million for thyroid carcinoma and 2.3/million for nasopharyngeal carcinoma (Table S2).

3.2. Childhood cancer incidence in Costa Rica over time

Fig. 2a–c show the ASRs for all childhood cancers combined, leukemia, lymphoma, malignant CNS tumors, non-CNS solid tumors as well as of leukemia and lymphoma subtypes over time for the period 2000–2014; Table 2 shows the corresponding APCs. Although the results of the Joinpoint Trend Analysis showed no statistically significant trends over time for all cancers or by main diagnostic group (Table 2), a tendency of somewhat increasing incidence over time was observed for lymphoid leukemia rates (APC of 1.82; 95% CI: −0.40, 4.09; Fig. 2b), while a statistically significant decreasing tendency was observed for Hodgkin lymphomas (APC of −5.56; 95% CI: −10.66, −0.17; Fig. 2c). A tendency of decreasing rates was also observed for non-Hodgkin lymphomas (APC of −4.80; 95% CI: −9.69, 0.35; Fig. 2c).

Sensitivity analyses excluding the year 2000 showed a statistically significant increase in lymphoma rates until the year 2005 (APC of 21.77; 95% CI: 1.31, 46.35), followed by a decreasing trend (APC of −8.14; 95% CI: −12.84, −3.19; Table 2). However, no statistically significant trend was observed for ASRs for all childhood cancers combined, leukemias, or malignant CNS tumors for this restricted study period.

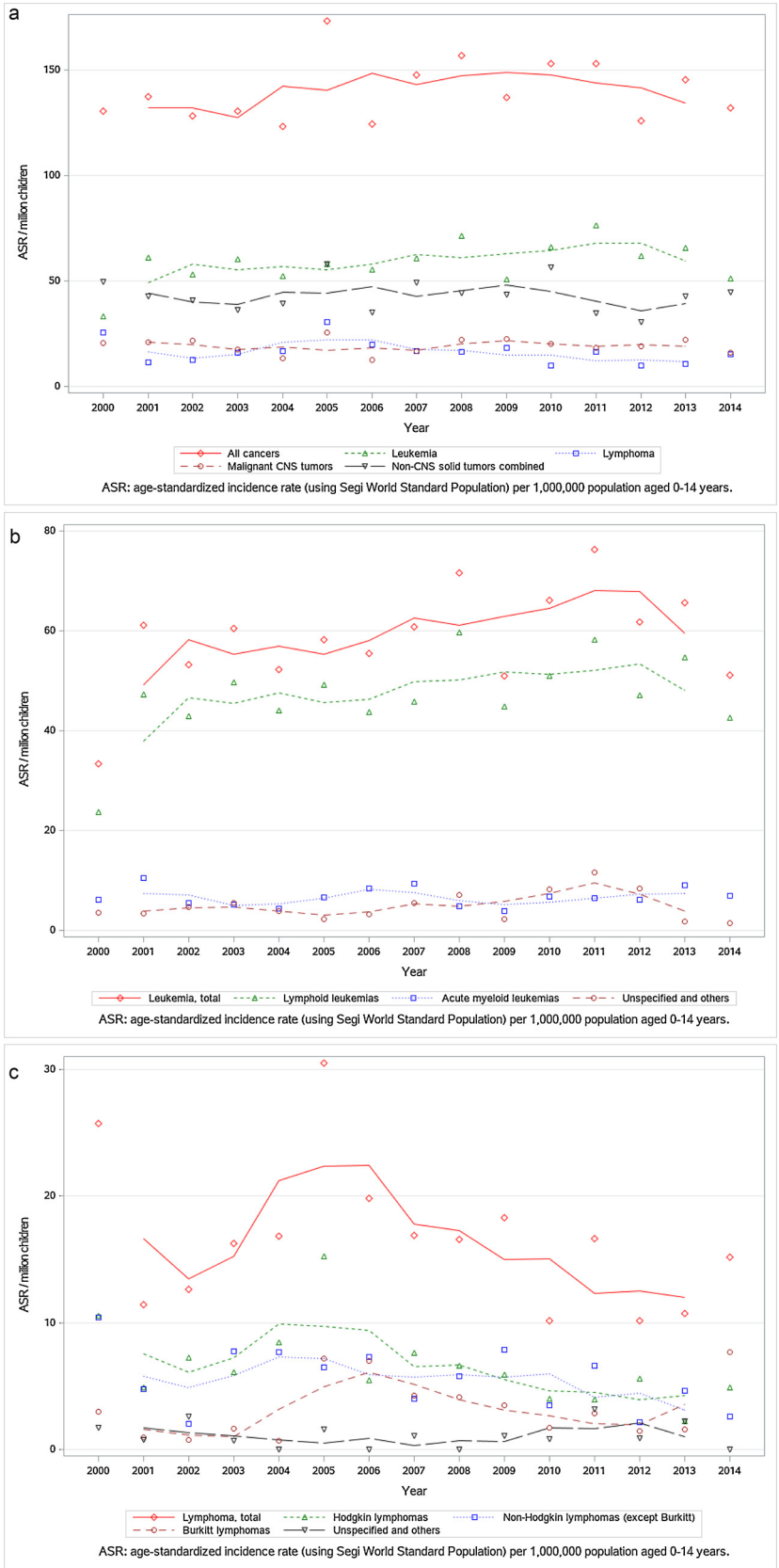


Fig. 2. (a) Incidence of leukemia, lymphoma, malignant CNS tumors, non-CNS solid tumors and all childhood cancers combined reported to the Costa Rican National Cancer Registry in 2000–2014 over time. A moving average of ASRs for 3-year periods was plotted. (b) Incidence of lymphoid leukemias, acute myeloid leukemias, unspecified and other leukemias and all leukemias combined reported to the Costa Rican National Cancer Registry in 2000–2014 over time. A moving average of ASRs for 3-year periods was plotted. (c) Incidence of Hodgkin lymphomas, Non-Hodgkin lymphomas, Burkitt lymphomas, unspecified and other lymphomas and all lymphomas combined reported to the Costa Rican National Cancer Registry in 2000–2014 over time. A moving average of ASRs for 3-year periods was plotted.

3.3. Geographical differences within Costa Rica

Some geographical variations in incidence rates of childhood cancer and cancer types were observed within Costa Rica (Table 3). The highest childhood cancer ASR was observed in children who lived in the Central (144.7/million) and Huetar Norte (140.2/million) Regions, whereas the lowest ASR for all childhood cancer was found in children from the Huetar Atlántica Region (120.1/million). For lymphomas, the

Table 2
Average annual percentage change in the age-standardized rates of childhood cancer reported to the Costa Rican National Cancer Registry in 2000–2014.

	Time period	APC[a]	95% CI[b]
All childhood cancers	2000–2014	0.49	−0.87; 1.88
Leukemia	2000–2014	1.77	−0.38; 3.96
Lymphoma	2000–2014	−3.29	−7.30; 0.91
Malignant CNS	2000–2014	−0.24	−2.60; 2.18
All childhood cancers	2001–2014	0.37	−1.21; 1.97
Leukemia	2001–2014	0.90	−0.92; 2.75
Lymphoma	2001–2005	21.77	1.31; 46.35
	2005–2014	−8.14	−12.84; −3.19
Malignant CNS	2001–2014	−0.09	−2.85; 2.75

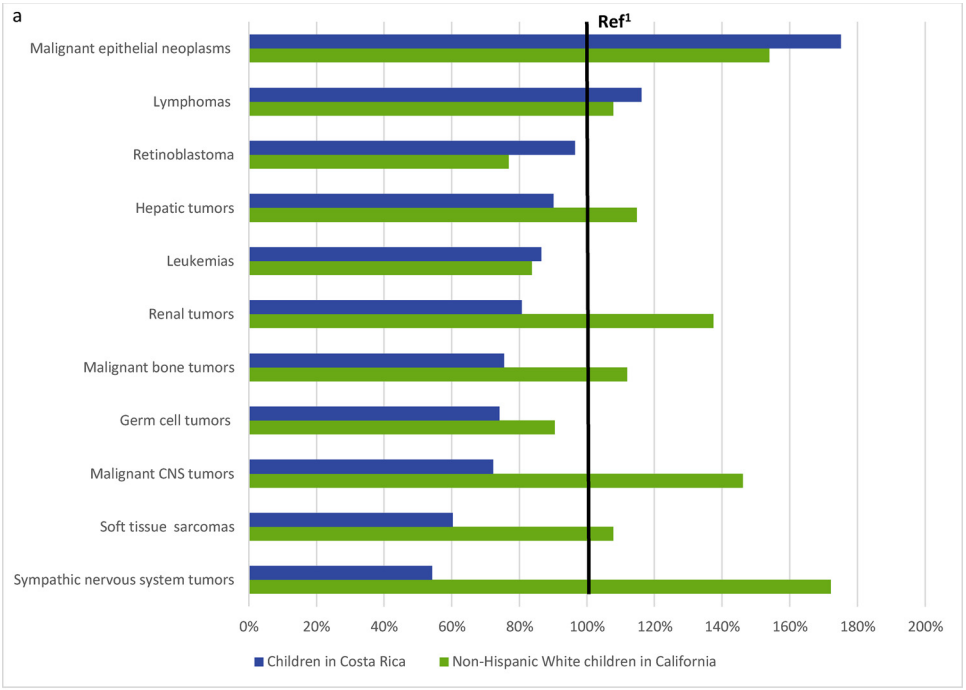
[a] Annual percentage change.
[b] 95% confidence interval.

incidence rate in the Huetar Atlántica (9.5/million) and Huetar Norte (11.8/million) Regions was markedly lower than in the rest of Costa Rica. In contrast, the Huetar Atlántica Region showed the highest ASR for leukemia (63.9/million). The most striking patterns of geographical variation were observed in infants; for instance, infants who lived in the Pacífico Central Region showed a particularly low rate of overall childhood cancer of 44.0/million in contrast to 140.7/million cases reported for the Central Region. Notably, the low incidence rate among infants in the Pacifico Region was not driven by a low number of leukemia cases but by a particularly low number of solid tumor cases including neuroblastoma and retinoblastoma (data not shown). The incidence of malignant CNS tumors in infants varied between the regions from no cases to 20.8/million and for other solid tumors in infants from no case to 103.5/million.

Table 3
Incidence of childhood cancer reported to the National Cancer Registry of Costa Rica in 2000–2014 by geographical region[a] and age group.

		Age specific incidence[c]					
Geographical Region at date of diagnosis[b]	N	< 1 year	1–4 years	5–9 years	10–14 years	ASR[d]	SRR (95% CI)[e]
All childhood cancers							
Central Region	1438	140.7	195.3	119.1	120.3	144.7	*Ref.*
Chorotega Region	168	124.5	147.2	103.0	128.7	125.8	0.87 (0.75, 1.01)
Pacífico Central Region	131	44.0	162.7	127.8	121.3	130.2	0.90 (0.76, 1.07)
Brunca Region	209	134.5	160.1	125.0	129.9	138.0	0.95 (0.83, 1.10)
Huetar Atlántica Region	215	101.3	170.9	92.8	101.2	120.1	0.83 (0.72, 0.95)
Huetar Norte Region	210	111.2	190.2	116.6	120.7	140.2	0.97 (0.84, 1.12)
Other[f]	*25*						
Leukemias							
Central Region	564	22.4	99.2	52.4	31.5	58.5	*Ref.*
Chorotega Region	68	22.6	93.4	35.8	37.1	53.0	0.91 (0.71, 1.16)
Pacífico Central Region	55	29.4	92.4	47.6	35.5	56.6	0.97 (0.73, 1.27)
Brunca Region	82	31.1	80.0	55.6	36.6	55.7	0.95 (0.76, 1.20)
Huetar Atlántica Region	112	33.8	106.3	53.7	37.9	63.9	1.09 (0.88, 1.35)
Huetar Norte Region	88	20.2	98.9	57.3	33.4	60.4	1.03 (0.82, 1.30)
Other[f]	*1*						
Lymphomas							
Central Region	184	1.6	15.1	19.0	21.7	17.2	*Ref.*
Chorotega Region	31	11.3	11.3	26.9	30.6	21.9	1.27 (0.84, 1.94)
Pacífico Central Region	17	0	11.1	26.8	14.8	16.4	0.95 (0.58, 1.55)
Brunca Region	30	0	7.7	25.8	25.6	18.2	1.05 (0.71, 1.57)
Huetar Atlántica Region	18	0	10.4	6.5	14.2	9.5	0.55 (0.37, 0.81)
Huetar Norte Region	18	0	15.2	11.9	11.1	11.8	0.68 (0.45, 1.04)
Other[f]	*6*						
Malignant CNS tumors							
Central Region	206	20.8	24.0	22.8	14.5	20.6	*Ref.*
Chorotega Region	17	11.3	11.3	15.7	10.9	12.6	0.61 (0.41, 0.92)
Pacífico Central Region	16	0	14.8	26.8	8.9	15.8	0.77 (0.48, 1.21)
Brunca Region	32	0	25.8	25.8	16.5	21.1	1.02 (0.70, 1.50)
Huetar Atlántica Region	29	16.9	16.7	14.7	15.8	15.8	0.77 (0.54, 1.09)
Huetar Norte Region	32	0	25.4	23.7	18.6	20.9	1.01 (0.69, 1.48)
Other[f]	*2*						
Other solid tumors							
Central Region	457	91.1	53.9	23.1	49.9	45.7	*Ref.*
Chorotega Region	48	79.2	31.1	20.2	45.8	35.6	0.78 (0.59, 1.02)
Pacífico Central Region	39	0	44.4	20.8	59.2	37.6	0.82 (0.61, 1.12)
Brunca Region	65	103.5	46.5	17.9	51.2	43.0	0.94 (0.73, 1.22)
Huetar Atlántica Region	55	50.6	35.4	17.9	33.2	30.3	0.66 (0.52, 0.85)
Huetar Norte Region	70	80.9	48.2	23.7	57.6	45.5	1.00 (0.77, 1.29)
Other[f]	15						

[a] Children from county Alajuela, San Ramón and Grecia in province Alajuela, were randomly assigned to either the Central or Huetar Norte Region , weighted by the childhood population size of the respective districts in the two MIDPLAN regions.
[b] Neither age specific incidence, nor ASR was calculated for unspecified geographical region.
[c] Age specific incidence: age group specific incidence rates per 1,000,000 population.
[d] ASR: age-standardized incidence rate (using Segi World Standard Population) per 1,000,000 population aged 0–14 years.
[e] SRR: standardized rate ratio between two ASRs, with 95% confidence intervals, using Región Central as the reference category.
[f] Children from provinces and/or counties unspecified.



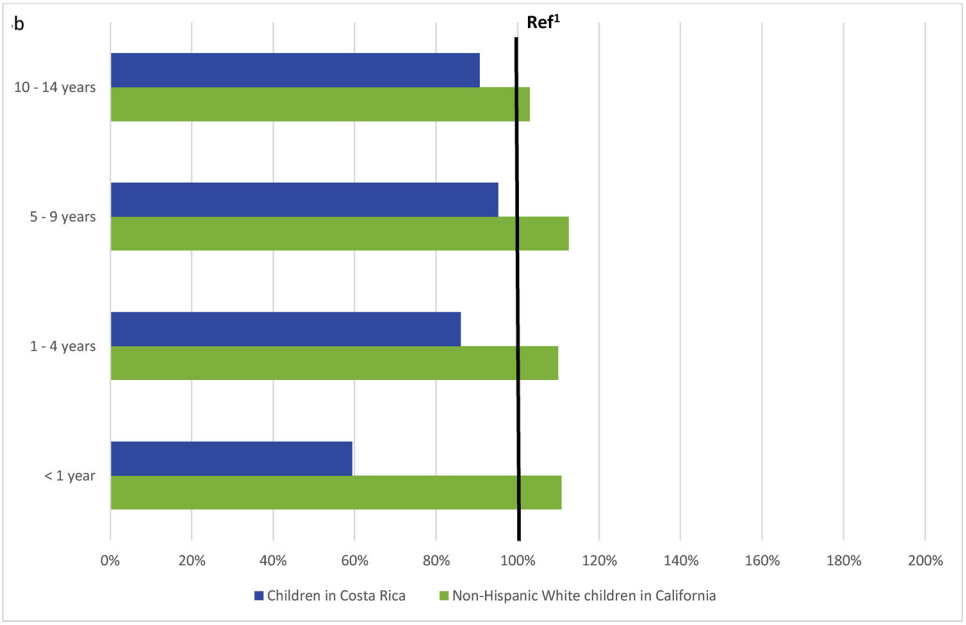


Fig. 3. a. Reported childhood cancer incidence of Californian Hispanics vs. Costa Rican and Californian Non-Hispanic White children. Age-standardized incidence rate proportions by major diagnostic group based on cases reported to the National Cancer Registry of Costa Rica and the California Cancer Registry (2000–2014). ASRs of Hispanic children from California were set to 100% as a reference point and serve as the base for this comparison. Bars are sorted from lowest to highest incidence rate proportion in Costa Rican children. 1ASRs of Hispanic children from California were set to 100% as a reference point. b. Reported childhood cancer incidence of Californian Hispanics vs. Costa Rican and Californian Non-Hispanic White children. Incidence rate proportions by age group based on cases reported to the National Cancer Registry of Costa Rica and the California Cancer Registry (2000-2014). Age-specific rates of Hispanic children from California were set to 100% as a reference point and serve as the base for this comparison. Bars are sorted by age at diagnosis. [1]Age-specific rates of Hispanic children from California were set to 100% as a reference point.

3.4. Comparison between Costa Rica, Hispanics in California, and Non-Hispanic Whites in California

Children in California had higher ASRs for all childhood cancers combined (176.1/million in NHW and 161.7/million in Hispanics) compared to Costa Rican children (140.0/million; Table 1), as well as for most solid tumors including malignant CNS tumors, sympathetic nervous system tumors, soft tissue sarcomas, and malignant bone tumors.

Fig. 3a and b show the age-standardized incidence rate proportions for Costa Rican children and Californian NHW children in comparison to the Hispanic children in California; the ASRs for the latter group were set to 100% as reference by (a) major diagnostic group and (b) age group. For most diagnostic groups including malignant CNS tumors, soft tissue sarcomas, sympathetic nervous system tumors, and renal tumors, the highest ASRs were found in NHW children in California (Fig. 3a). Leukemia and germ cell tumors incidence rates were highest in Hispanic children from California. Only the ASRs of malignant epithelial neoplasm and lymphomas in Costa Rican children exceeded those observed in Hispanic and NHW children in California. ASRs of childhood cancers combined were the highest in NHW children in California for all age groups (Fig. 3b).

4. Discussion

4.1. Key findings

In this report we provide the first comprehensive description and interpretation of the observed childhood cancer incidence in Costa Rica during the most recent 15-year period. Moreover, we compared the incidence rates from Costa Rica with those observed in two ethnic groups in California, including one genetically related to the studied population. ASRs in Costa Rica ranged in the upper third of rates observed in other Latin American countries and were closer to those

observed in HICs than found in many LMICs [5]. The incidence rate of lymphoid leukemia ranked among the highest in the world [5], whereas lower incidence rates were found for most solid tumors [5] including malignant CNS tumors, sympathetic nervous system tumors, soft tissue sarcomas, and malignant bone tumors; while retinoblastoma was in the expected range. No marked increases in childhood cancer incidence rates were noticed over time, but some noteworthy geographical variations were observed within Costa Rica. The direct comparison of incidence rates between Costa Rican and Californian children showed that, for most diagnostic groups, incidence rates were highest among NHW children in California; however, incidence rates for malignant epithelial neoplasm and lymphomas were highest in Costa Rican children. The leukemia incidence was the highest among Hispanic children in California.

4.2. International comparisons

Incidence patterns and the distribution of childhood cancer types differ across populations [5,10] but are relatively consistent and well described for economically developed countries [6]. Recent ASRs reported for HICs for overall childhood cancer ranged mainly between 150 and 180 per million [5], and between 45 and 56 per million for leukemia in children [5]. Reports from Latin-American countries including Chile, Peru, Ecuador and Mexico City [5] have described a somewhat similar picture to HICs, but with somewhat lower incidence rates of overall childhood cancer [5], mainly driven by low rates for solid tumors including CNS tumors, but high leukemia rates [5]. In contrast, in some other MIC, particularly in Sub-Saharan Africa or some parts of Asia where registry data is particularly limited, remarkably low leukemia and overall childhood cancer rates have been reported [5] [8].

In Costa Rica, a country with well-established pediatric oncology services, free access to public health care for children until the age of 18 years, and a longstanding nationwide high quality population-based cancer registry, the overall childhood cancer rate in Costa Rica of 140/million was just slightly lower than rates observed in Europe and North America [5], particularly when taking into account that the rate for Costa Rica only included malignant CNS tumors. However, the incidence rate of 56/million for leukemia in Costa Rica was similar or even higher to those seen in Europe, North America, and other Latin American countries [5]. The rate of lymphoid leukemia observed in Costa Rica (i.e., 47/million) ranked amongst the highest in the world [5]. Assuming incidence rates in Costa Rica were also impacted by a certain degree of under-ascertainment, like it has been postulated for some other LMICs [8,11,12], the true lymphoid leukemia rate would be even higher than observed. The low rates observed for most solid tumors in Costa Rica were similar to those reported in other Latin American countries [5], but could be also related to some under-ascertainment. The comparisons in our study may also be affected by possible overdiagnosis of certain cancers in California. The higher neuroblastoma rate in Californian Hispanic (compared to Costa Rican children) might potentially be a reflection of higher diagnostic awareness or even opportunistic screening and possible over-diagnosis in Californian (or children from the US) in general [29].

4.3. Incidence trends over time

Data from population-based cancer registries in HICs showed a modest increase in childhood cancer incidence rates during the last three decades of the 20th century, followed by a leveling off in the early 2000s [7,10]. Although this increase appeared to be largely driven by an increase in lymphoid leukemia [30,31], it remains unclear whether this trend is mainly the result of improved diagnosis and more complete reporting or the effects of changes in exposure to risk factors. The study period of our study started with the year 2000 and the trend analyses did not point towards a significant increase in incidence rates, which is consistent with reports from some HICs [7,10]. However, similar to the observation of a modest increase in the incidence of ALL (1.1%) among Hispanic children in California [32], we did note a tendency of a slightly increasing incidence of lymphoid leukemia.

4.4. Geographical differences within Costa Rica

Geographical differences in childhood cancer rates observed within the Costa Rican population could be due to several factors including differences in access to health care (e.g., poor transportation in rural areas) or modern diagnostic procedures, and region-specific environmental factors. The highest incidence rate of overall childhood cancer was found in children whose residence at the times of diagnosis was in the Central and Huetar Norte Regions. Proximity and accessibility of health care services and in particular to the Children's Hospital located in San Jose might explain the highest incidence rates seen for the Central Region. Families with sick children might have migrated from other regions to receive treatment at the Children's Hospital and could have provided the address of a relative who was living in the Central Region. The RNT has no means to assess the proportion of such children. In contrast, the Huetar Norte Region (represents ~19% of the national territory) is mainly rural and its main economic activities include agriculture (e.g., large pineapple and sugarcane plantations), livestock, and fishing [24], activities that involve the use of environmental toxicants (e.g., pesticides) that have been associated with increased risk of childhood cancer [33,34]. The high incidence rate of childhood cancer in the Huetar Norte Region could also be due to migration of Nicaraguan children who are looking for high-quality health care into Costa Rica.

In the present study, higher leukemia rates were observed in children from the Huetar Atlántica Region, which had at the same time the lowest incidence rates for overall childhood cancer and lymphomas. Large-scale banana and pineapple plantations constitute the main economic activity in the Huetar Atlántica Region (which represents ~18% of the national territory and also includes the counties with the lowest indices of social development in the country) [24]. Extensive agricultural pesticide use [33–35] and socio-demographic or lifestyle characteristics such as parental smoking [36,37] or alcohol consumption [36,38] could potentially be associated with the elevated leukemia rate found in the Huetar Atlántica Region. A previous study analyzing childhood leukemia cases diagnosed between 1981 and 1996 found highest rates of lymphoid leukemia in the western mountain chain of the Central Valley [39]. According to our classification system, the western mountain chain of the Central Valley would have been a small part of the Central Region for which we did not observe particularly high leukemia rates compared to other regions. However, a meaningful comparison between findings is challenging given the different geographical classifications used, time differences between studies, and small underlying numbers when looking at diagnostic subtypes.

The geographical differences seen in infants may be possibly explained by a diagnostic delay, varying by region, but as the numbers were low, the variations may also be a chance finding.

4.5. Strengths and limitations

In contrast to previous reports that have focused only on specific tumor types (leukemias [39] or CNS tumor [40]), our study presents the full picture by including all childhood cancer types, analyzing incidence data for a time period of 15 years, and including information on place of residence at the time of diagnosis. The latter strength allowed us to investigate differences by geographical residence, which is an important determinant of environmental exposures, socioeconomic background, and access to high-quality health care. Unfortunately the value of this information is somewhat limited by the circumstance that the cancer registry data contained only data on geographical region at the county level. As three counties included districts that belong to two

different MIDEPLAN regions, 209 cases could not be assigned explicitly to one MIDEPLAN region. Our approach to randomly assign those cases to either the Central or the Huetar Norte Region, weighted by the childhood population size of the respective districts in those two MIDEPLAN regions might have possibly biased towards the null the incidence differences between those two regions.

The second major strength of this study was the availability of directly comparable data from California. The CCR has a high level of childhood cancer ascertainment for Californian Hispanic children, who have a similar genetic make-up to Costa Rican children [22] and one of the highest leukemia rates in the world [5]. The registry was able to provide data in a structure comparable to that of the Costa Rican database with respect to the time period (2000–2014) and included diagnoses (e.g., exclusion of benign brain tumors not recorded in the RNT), making the comparison very meaningful.

For future studies it would be valuable to add clinical data, which might provide further insight into differences in stage at diagnosis and potential diagnostic delay by place of residence or age groups. Moreover, socioeconomic background is most likely related to access and utilization of health care services [41] and would be therefore interesting to study in relation to differences in incidence rates.

5. Conclusion

Based on the longstanding registration in Costa Rica, childhood cancer incidence patterns were similar to those observed in other Latin American countries. The low rates in infants and some solid tumors may suggest some underascertainment of cases. The markedly high leukemia rates, in particular of the lymphoid subtypes, in this population may be explained by both genetic and environmental factors. Further research should explore which factors may drive the high leukemia incidence rate, the low leukemia rate in infants, the low rates observed for some solid tumors, as well as the geographical differences within the country. Overall, our findings suggest using caution when interpreting global incidence differences, since our results from a MIC with well-established paediatric oncology services and a nationwide cancer registry showed only small differences to incidence patterns from HICs.

Authorship contribution statement

FE, JS and AMM developed the concept and study design. GTA, BMG, AMM and FE contributed to the data collection. TL conducted the statistical data analyses with advice from GL, JS and FE. FE drafted the manuscript. All authors participated in the interpretation of the results. All authors provided critical feedback, revised the manuscript for intellectual content and approved the final version.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Financial support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The work of the authors was supported by core funds of their respective institutions, namely the International Agency for Research on Cancer, Danish Cancer Society Research Centre, Georgetown University and Universidad Nacional, Costa Rica respectively.

Acknowledgements

The authors are grateful to O. M. Araya, M. Bolaños, N. Gómez, M. G. Mora-Mora, and A. Corrales for their help with the calculations of mid-year population estimates specifically for children younger than 1 year of age. The authors express their special appreciation to L. Córdoba for the preparation of the map of Costa Rica with the MIDEPLAN regions (Fig. 1).

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.2018.07.004.

References

[1] L.G. Spector, N. Pankratz, E.L. Marcotte, Genetic and nongenetic risk factors for childhood cancer, Pediatr. Clin. North Am. 62 (1) (2015) 11–25.
[2] J. Schuz, F. Erdmann, Environmental exposure and risk of childhood leukemia: an overview, Arch. Med. Res. 47 (8) (2016) 607–614.
[3] M. Greaves, Infection, immune responses and the aetiology of childhood leukaemia, Nat. Rev. Cancer 6 (3) (2006) 193–203.
[4] S. Savage, J. Schüz, Environmental chemicals and childhood cancer, in: J. Nriagu (Ed.), Encyclopedia of Environmental Health, Elsevier Science & Technology, Burlington, 2011, pp. 336–347.
[5] E. Steliarova-Foucher, M. Colombet, L. Ries, et al., International Incidence of Childhood Cancer, Volume III (electronic version), (2017) http://iicc.iarc.fr/results/.
[6] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, et al., International incidence of childhood cancer, 2001–10: a population-based registry study, Lancet Oncol. 18 (6) (2017) 719–731.
[7] P. Kaatsch, C. Spix, German Childhood Cancer registry – Annual Report 2016 (1980-2015), Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University, Mainz, 2016.
[8] F. Erdmann, D. Kielkowski, S.J. Schonfeld, et al., Childhood cancer incidence patterns by race, sex and age for 2000–2006: a report from the South African National Cancer Registry, Int. J. Cancer Suppl. 136 (11) (2014) 2628–2639.
[9] F. Moreno, D. Loria, G. Abriata, B. Terracini, R. Network, Childhood cancer: incidence and early deaths in Argentina, 2000–2008, Eur. J. Cancer 49 (2) (2013) 465–473.
[10] E. Steliarova-Foucher, A.L. Frazier, Chapter 1.3 childhood cancer, in: B. Stewart, P.W. Wild (Eds.), World Cancer Report 2014, International Agency for Research on Cancer, Lyon, 2014, pp. 69–76.
[11] F. Azevedo-Silva, S. Reis Rde, O. Santos Mde, R.R. Luiz, M.S. Pombo-de-Oliveira, Evaluation of childhood acute leukemia incidence and underreporting in Brazil by capture-recapture methodology, Cancer Epidemiol. 33 (6) (2009) 403–405.
[12] R. Swaminathan, R. Sankaranarayanan, Under-diagnosis and under-ascertainment of cases may be the reasons for low childhood cancer incidence in rural India, Cancer Epidemiol. 34 (1) (2010) 107–108.
[13] The World Bank, Countries and Economies, (2017) (Accessed 4 March 2015), http://data.worldbank.org/country.
[14] (INEC) INdEyC, X Censo Nacional de Población y VI de Vivienda 2011: Características Sociales y Demográficas Tomo II, Costa Rica: Instituto Nacional de Estadística y Censos, San José, 2011.
[15] Reglamento 8061: Reglamento del Seguro de Salud de la Caja Costarricense de Seguro Social. La Gaceta. Vol 1212006.
[16] A. Ortiz Barboza, R.M. Vargas Alvarado, G. Muñoz Leiva, Incidencia y Mortalidad Del Cáncer En Costa Rica 1990–2003, Ministerio De Salud, 2005.
[17] A. Fritz, C. Percy, A. Jack, et al., International Classification of Diseases for Oncology, third edition, World Health Organisation, Geneva, 2000.
[18] Registry CC, California Cancer Reporting System, M. Brant, D. Hansen (Eds.), Standards, Volume I: Abstracting and Coding Procedures, 17th ed., California Department of Public Health, Chronic Disease Surveillance and Research Branch, California Cancer Registry, 2017.
[19] C. Johnson, S. Peace, P. Adamo, A. Fritz, A. Percy-Laurry, B. Edwards, The 2007 Multiple Primary and Histology Coding Rules, National Cancer Institute, Surveillance, Epidemiology and End Results Program, Bethesda, MD, 2007.
[20] Hispanic and Asian/Pacific Islander Identification Algorithem Version 17.0, North American Association of Central Cancer Registries, 2018 (Accessed 1 April 2018, https://www.naaccr.org/?s=NHAPIIA.
[21] R. Campos-Sánchez, H. Raventós, R. Barrantes, Ancestry informative markers clarify &e regional admixture variation in &e Costa Rican population, Hum. Biol. Open Access Pre-Prints (2013) (Paper 34).
[22] E. González Burchard, L. Borrell, S. Choudhry, et al., Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research, Am. J. Public Health 95 (12) (2005) 2161–2168.
[23] E. Steliarova-Foucher, C. Stiller, B. Lacour, P. Kaatsch, International classification of childhood Cancer, third edition, Cancer 103 (7) (2005) 1457–1467.
[24] R. Alvarado Salas, Regiones y Cantones De Costa rica. Serie CANTONES DE COSTA RICA : N° 2, Dirección De Gestión Municipal Sección De Investigación y Desarrollo, Costa Rica, 2003.
[25] Intercensal Estimates of the Resident Population of the United States for July 1, 2000-July 1, 2009, by Year, County, Single Year of Age, Bridged Race, Hispanic Origin, and Sex, Prepared under a collaborative arrangement with the US Census Bureau, 2009 (Accessed 19 October 2012), http://www.cdc.gov/nchs/nvss/bridged_race.htm.
[26] Postcensal Estimates of the Resident Population of the United States for July 1, 2010-July 1, 2014 by Year, County, Single-year of Age, Bridged Race, Hispanic

Origin, and Sex (Vintage 2014), Prepared under a collaborative arrangement with the US Census Bureau, 2014 (Accessed 8 June 2015), http://www.cdc.gov/nchs/nvss/bridged_race.htm.
[27] O. Ahmad, C. Boschi-Pinto, A. Lopez, C. Murray, R. Lozano, M. Inoue, Age Standardization of Rates: a New WHO Standard. GPE Discussion Paper Series: No. 31, World Health Organization, Geneva, 2001.
[28] Joinpoint Regression Program, Version 4.5.0.1 [computer program]. Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute, 2017.
[29] M.K. Georgakis, N. Dessypris, M. Baka, et al., Neuroblastoma among children in Southern and Eastern European cancer registries: variations in incidence and temporal trends compared to US, Int. J. Cancer Suppl. 142 (10) (2018) 1977–1985.
[30] M.S. Linet, L.M. Brown, S.M. Mbulaiteye, et al., International long-term trends and recent patterns in the incidence of leukemias and lymphomas among children and adolescents ages 0–19 years, Int. J. Cancer Suppl. 138 (8) (2016) 1862–1874.
[31] J.W.W. Coebergh, A.M.J. Reedijk, E. de Vries, et al., Leukaemia incidence and survival in children and adolescents in Europe during 1978–1997. Report from the Automated Childhood Cancer Information System project, Eur. J. Cancer 42 (13) (2006) 2019–2036.
[32] B.M. Giddings, T.P. Whitehead, C. Metayer, M.D. Miller, Childhood leukemia incidence in California: high and rising in the Hispanic population, Cancer 122 (18) (2016) 2867–2875.
[33] H.D. Bailey, L. Fritschi, C. Infante-Rivard, et al., Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium, Int. J. Cancer 135 (9) (2014) 2157–2172.
[34] D.T. Wigle, M.C. Turner, D. Krewski, A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure, Environ. Health Perspect. 117 (10) (2009) 1505–1513.
[35] P. Monge, C. Wesseling, G. LicComp, et al., Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa rica, Scand. J. Work Environ. Health 33 (4) (2007) 293–303.
[36] J. Schüz, P. Kaatsch, U. Kaletsch, R. Meinert, J. Michaelis, Association of childhood cancer with factors related to pregnancy and birth, Int. J. Epidemiol. 28 (4) (1999) 631–639.
[37] E. Milne, K.R. Greenop, R.J. Scott, et al., Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia, Am. J. Epidemiol. 175 (1) (2012) 43–53.
[38] P. Latino-Martel, D.S. Chan, N. Druesne-Pecollo, E. Barrandon, S. Hercberg, T. Norat, Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis, Cancer Epidemiol. Biomark. Prev. 19 (5) (2010) 1238–1260.
[39] P. Monge, C. Wesseling, A.C. Rodríguez, et al., Childhood leukaemia in Costa rica, 1981–96, Paediatr. Perinat. Epidemiol. (16) (2002) 210–218.
[40] J. Reutfors, E. Kramárová, E. Weiderpass, P. Monge, C. Wesseling, A. Ahlbom, Central nervous system tumours in children in Costa rica, 1981–96, Paediatr. Perinat. Epidemiol. 16 (2002) 219–225.
[41] I. Magrath, E. Steliarova-Foucher, S. Epelman, et al., Paediatric cancer in low-income and middle-income countries, Lancet Oncol. 14 (3) (2013) e104–e116.