Title

Incidence of childhood cancer in Latin America and the Caribbean: coverage, patterns, and time trends

Short title

Childhood cancer in Latin America and the Caribbean

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Incidence of childhood cancer in Latin America and the Caribbean: coverage, patterns, and time trends

Abstract

Global childhood cancer control requires high-quality information, which is lacking particularly in low- and middle-income countries. We described geographical variations in 2001-2010 and incidence trends over 1993-2012 in the population of Latin America and the Caribbean (LAC) younger than 20 years using the database of the third volume of the International Incidence of Childhood Cancer study containing comparable data. Age-specific incidence per million person-years (ASR) was calculated for population subgroups and age-standardised (WSR) using the world standard population. Overall, 36 744 unique cases were included in this study. In 2001-2010 the overall WSR in age 0-14 years was 132.6. The most frequent were leukaemia (WSR 48.7), CNS neoplasms (WSR 23.0), and lymphoma (WSR 16.6). The overall ASR in age 15-19 years was 152.3 with lymphoma ranking first (ASR 30.2). Incidence was higher in males than in females, and higher in South America than in Central America and the Caribbean. Compared with global data LAC incidence was lower overall, except for leukaemia and lymphoma at age 0-14 years and the other and unspecified tumours at any age. Overall incidence at age 0-19 years increased by 1.0% per year (95%CI: 0.6,1.3) over 1993-2012. The included registries covered 16% of population aged 0-14 and 10% of population aged 15-19 years. The observed patterns provide a baseline to assess the status and evolution of childhood cancer occurrence in the region. Extended and sustained support of cancer registration is required to improve representativeness and timelines of data for childhood cancer control in LAC.

Keywords

Neoplasms, incidence, child, registries, Latin America, Caribbean region, cancer surveillance, time trends

Introduction

With improved control of communicable diseases, childhood cancer has gained relevance in low- and middle-income countries (LMIC) (1). Childhood cancers differ from those occurring in adults by biology, presentation, response to treatment and epidemiology. Aetiology of childhood cancers is poorly understood, which hampers their prevention. Causal evidence links to certain genetic conditions, high dose ionizing radiation, chemotherapy, and viral infections (2).

Geographical variations of cancer incidence indicate potential aetiological clues, implying further targeted studies. Incidence data are generated by population-based cancer registries, but these are sparse in many LMIC, including in Latin America and the Caribbean (LAC) (3). The reported incidence is often lower in the populations of LMIC than in the high-income countries (HIC) (3, 4).

LAC, with its 600 million inhabitants of Amerindian, European and African descendance, displays huge contrasts in socio-demographic, economic, and epidemiological patterns. In 2010, the size of national population ranged from 49 000 in Saint Kitts and Nevis to almost 200 million in Brazil (5), the gross domestic product per capita varied from 2 683 current international dollar (intl$) in Haiti to almost 31 000 intl$ in Puerto Rico while the life expectancy at birth ranged from 46 years in Haiti to 79 in Costa Rica, and the childhood mortality rate (under 5 years) varied from 6.4 per 1 000 live births in Cuba to 203.6 in Haiti according to the World Bank (databank.worldbank.org). Existing social inequalities are magnified by rapid urbanisation, internal and external migration, poverty, corruption and violence (6), all of which contribute to distortions in decisions that affect cancer control in many LAC countries. Cancer registration is often discontinued due to irregular funding and frequently changing policies (7).

Data generated by population-based cancer registries are vital for understanding of cancer burden and its control, and their production requires sustained commitment and funding (8, 9). Several LAC registries were established long ago and generate high quality data, including Puerto Rico in 1954, Kingston and St. Andrew, Jamaica in 1958, and Cali, Colombia in 1962. Others were discontinued or were unable to supply comparable data to international studies due to sub-optimal data quality (4, 10, 11). Although national cancer registration has developed in few countries, most registries have subnational coverage, meaning a lower informative potential compared with national registries (12). LAC, however, boasts two paediatric population-based cancer registries with national coverage of Argentina since 2000 (13) and Chile since 2007 (14). On the other hand, the regional childhood cancer registry, started in Mexico City in 1996 (15), vanished with the retirement of its founder, due to the lack of sustained support.

Using the most complete and up-to-date study, the International Incidence of Childhood Cancer, *volume* 3 (IICC-3, iicc.iarc.fr) (3, 11), we provide a unique comprehensive overview of geographical patterns (2001-2010) and time trends (1993-2012) of cancer incidence in children aged 0-19 in LAC and interpret the findings in the context of global patterns. We also share our views on the need for further development so that the countries in the region could join the WHO Global Initiative for Childhood Cancer (16).

Materials and Methods

Data sources and processing

Data were extracted from the database of individual cancer records of the IICC-3 study coordinated by the International Agency for Research on Cancer (3, 11). The LAC populations covered by the registries contributing to the IICC-3 are shown in Supplement, Figure S1.

Each cancer record contained information on sex, age, date of birth, date of incidence, tumour sequence, site, morphology, behaviour, laterality, and most valid basis of diagnosis. Cancers, originally coded by the registries according to the International Classification of Diseases for Oncology were first converted to its 3rd edition, 1st revision (17) and then to the International Classification of Childhood Cancer – 3rd edition, updated in 2017 (ICCC-3) (18). Data included in the IICC-3 database were quality controlled (3, 11). Quality indicators included the proportion of cases with microscopic verification, the proportion of cases retrieved from a death certificate only, the proportion of cases with morphology not otherwise specified and others. We constructed several datasets to utilise the maximum data available in each analysis.

Constitution of analytical datasets

All registered cancers diagnosed in residents younger than 20 years, obtained from the registries that provided data for each year of the entire decade 2001-2010, were eligible for inclusion in geographical analysis. Eligible paediatric registries covered populations aged 0-14 years. The reference period 2001-2010 contained the largest populations covered within LAC and within the IICC-3 database.

Geographical analyses for the age range 0-14 years were conducted using a *paediatric dataset*, which contained data from eligible paediatric registries, complemented by data from the eligible general registries that covered different, non-overlapping populations. The analyses for the age range 0-19 or 15-19 years were conducted using a *general dataset*, which included data only from the eligible general registries.

To compare cancer incidence within LAC, we have grouped registries into two sub-regions, Central America and the Caribbean (CAC) and South America (SA) as per the United Nations (UN) definition of world regions (unstats.un.org/sdgs/indicators/regional-groups).

We also compared incidence observed in LAC with that of North America (NA), as the region representative of incidence patterns in HIC, which hosts a large identifiable Hispanic population with a similar genetic background as the LAC population. LAC incidence was also compared with the global figures (which included LAC data) reported previously (3).

Incidence time trends were investigated over two decades, 1993-2012.

We examined the evolution of the coverage of childhood population of LAC by population-based cancer registries as reflected in the three IICC volumes (4, 10, 11) which included four decades of comparable global data.

Statistical analyses

Age-specific rates (ASR) were computed for five age groups (<1, 1-4, 5-9, 10-14, and 15-19 years) by dividing the number of cancer cases by the number of person-years at risk in the corresponding sex and age category. To enable comparisons between countries and world regions we adjusted overall incidence rates for the age ranges of 0-14 and 0-19 years, using the world standard population distribution (19) in 5-year age groups, and reported age-standardised rates (WSR). All incidence rates were expressed per million person-years at risk. We computed the 95% confidence intervals (CI) of the incidence rates according to standard methods (20). We assessed the male to female (M/F) sex ratio as the quotient of the rate in males to that in females.

To assess incidence time trends, we fit linear regression models weighted by the ratio of the squares of age-standardised rate and its standard error. The changes were reported as the average annual percentage change (AAPC) and corresponding 95% CI. Changes in trends during the study period were examined using Joinpoint software (21), allowing a maximum of 3 break points and using the permutation test method (22) to select the final model. In the subsets where at least one joinpoint was identified, we reported the overall AAPC and the annual percentage change with 95%CI for each time segment.

The population coverage was calculated by dividing the population covered by a registry in each IICC volume by the national population of the same country, year, and age range. For the first two IICC volumes (4, 10) we used the average annual population covered, while for the IICC-3 we used population covered in year 2010 or other closest available year (11). Countries with national cancer registries were assumed to have 100% coverage, using the population data provided by the registries. National populations for the countries with subnational coverage were retrieved from the UN estimates (5) for the calendar years most frequently represented in each volume, i.e. 1975, 1985 and 2010. The UN population estimates for the entire LAC region and its sub-regions in each reference year were used to calculate the overall coverage.

Unless stated otherwise, statistical analyses were performed using Stata/IC, version 14.2 (StataCorp, stata.com).

Results

Location and characteristics of all registries contributing to IICC-3 (11) are shown in the Supplement (Figure S1, Tables S1 and S2). Overall, 36 744 unique cancer cases, arising in 276 million person-years, excluding geographical and temporal overlap, were included in analyses of incidence presented below.

Childhood cancer incidence in LAC, 2001-2010

Overall WSR for the age range 0-14 years was 132.6, based on 24 556 cases and 191 million person-years and it ranged from less than 100 in Martinique and Jamaica, to 152.8 in Colombia. Overall WSR per million for the age range 0-19 years was slightly higher (139.0), and it remained at almost the same level as that for children under 15 years in Cuba (128.5) and in Jamaica (81.2) due to their low rates in the 15-19 years age group. The highest rate in the age group 15-19 years was observed in Chile (182.1). The paediatric cancer registries showed intermediate WSR of 130.1 in Argentina and 133.8 in Mexico City (Table 1). Using only data from general cancer registries, the incidence rate for the age range 0-14 years was 135.1 per million (95%CI 132.5-137.7), based on 11 099 cases. Incidence for all eligible registries is shown in Supplement, Table S3.

Figure 1 shows the ASR for main diagnostic groups by age, (see also Supplement, Table S4). Leukaemia was the most common diagnostic group in age 0-14 years, with the peak ASR=73.5 in age 1-4 years. Among children younger than 1 year, neuroblastoma (ASR=30.7) was almost as common as leukaemia.

Incidence of central nervous system (CNS) neoplasms was stable before age of 10 years (ASR around 24), after which it declined slightly. Incidence of lymphoma increased with age, from 7.8 at age under 1 year to 30.2 in age 15-19 years, in which it ranked first. The other most common were other carcinomas and melanoma (ASR=30.0), and leukaemia (ASR=27.6). Incidence rates for diagnostic groups and selected subgroups are compared in Figure 2 by age (see also Supplement, Tables S5A and S5B and Tables S6A and S6B).

Overall incidence was higher in males than in females (M/F=1.2). The M/F ratio was 2 or higher for lymphoma in age 0-14 years, for Non-Hodgkin & Burkitt lymphoma in age 0-19 years, and for lymphoid leukaemia, rhabdomyosarcoma, and gonadal tumours in age 15-19 years. Conversely, twice as many females than males had thyroid carcinoma before age 15 years and three times as many in age 0-19 and 15-19 years. Females with renal tumours were registered twice as often as males in the 15-19 years age group (Supplement, Figure S2 and Table S7).

Geographical variations in incidence, 2001-2010

Overall incidence for the age range 0-19 years was higher in South America (SA) (WSR=146.8) than in Central America and the Caribbean (CAC) (WSR=131.6), mostly due to rates of lymphoid leukaemia, and (gonadal) germ cell tumours in age 15-19 years (Supplement, Figures S3 and S4, Table S8). In children aged 0-14 years incidence was higher in SA than in CAC for leukaemia, CNS neoplasms, retinoblastoma, and rhabdomyosarcoma, while CAC showed higher incidence of non-Hodgkin combined with Burkitt lymphoma and the group of carcinomas and melanoma (Supplement, Figure S4 and Table S8). In each age category, CAC reported higher incidence of unspecified tumours (group XII).

The WSR for main diagnostic groups in the age range 0-14 years were compared between LAC, NA, and the world in Figure 3. LAC had the highest incidence of lymphoma and other and unspecified tumours. In contrast, incidence of CNS neoplasms, neuroblastoma, renal tumours, soft tissue sarcoma, and other carcinomas and melanoma were the lowest. LAC incidence of leukaemia was intermediate between the global and the NA rate. Incidence in age 0-19 and 15-19 years were lower in LAC than elsewhere except for other and unspecified tumours (Supplement, Table S9).

Incidence time trends in LAC for age 0-19 years, 1993-2012

Overall incidence increased by 1.0% per year on average with 95% CI (0.6-1.3) (Figure 4 and Supplement, Table S10). Incidence increased for CNS neoplasms (AAPC = 1.8%), retinoblastoma (1.7), hepatic tumours (4.9), bone tumours (1.4), germ cell tumours (2.0) and the group of carcinomas and melanoma (2.9); some changes were driven by a subpopulation defined by region or sex. For example, the AAPC of 4.3 in females with retinoblastoma in SA influenced the AAPC of 1.7% for the entire LAC. SA and CAC showed opposite trends of other and unspecified tumours, with a sharp decrease of 7.7% (95%CI -9.6, -5.7) per year in SA and a strong increase of 4.9% (95%CI 1.5, 8.4) per year in CAC (Supplement, Table S10). Joinpoint analysis revealed breaks in incidence time trends in some populations. In LAC, the time segments with variable time trends include those for leukaemia in males and for other and unspecified tumours in females. Variations were seen among females in CAC for lymphoma, germ cell tumours, and other carcinomas and melanoma and in the group of other and unspecified tumours (Supplement, Figure S5).

Evolution of the registration coverage in LAC

Coverage of the LAC population aged 0-14 years by internationally comparable data included in the three volumes of IICC has improved from 6.5% in 1975 to 16.4% in 2010, with a drop in 1985 (5.6%). The coverage of the population aged 15-19 years, which was included for the first time in IICC-3, was 9.8% (Supplement, Table S11).

Discussion

In this comprehensive overview of childhood cancer incidence in Latin America and the Caribbean (LAC), leukaemia was the leading diagnostic group, followed by CNS neoplasms and lymphoma in children aged 0-14 years. Compared with other world regions, LAC was shown to have a higher incidence of lymphoma and of other and unspecified tumours and intermediate rates of leukaemia. Incidence was lower for all diagnostic groups except for the unspecified tumours. We documented higher incidence in South America (SA) than in Central America and the Caribbean (CAC), especially in age 15-19 years. Increasing incidence and the expanding registration coverage mostly reflect the underlying changes in socio-political context.

Variations of childhood cancer incidence within LAC

The incidence variations within LAC likely reflect variable socio-economic development of individual countries and their income level, which has an impact on public health policies, including cancer registration. Low incidence of CNS neoplasms may be linked to inadequate diagnostic technology or access to health care (23), while high rates of thyroid carcinoma in HIC (France, Martinique, and USA, Puerto Rico) indicate a high level of medical vigilance, more affordable in affluent societies (24). The incidence variations thus likely reflect disparities in health services, care pathways, outcomes, and information systems, in addition to potential risk factors the role of which needs to be determined. The observed sex ratio variations are consistent with those observed on a global scale (3).

The larger intra-regional differences in incidence in the age group 15-19 years compared with age range 0-14 years is influenced by the composition of the analytical datasets. The paediatric dataset covered larger populations and had therefore more stable rates. The rates observed in paediatric cancer registries affected the overall rates in age 0-14 years: Argentinian national paediatric cancer registry contributed more than a half of the total person-years. Although some underrepresentation of tumours common in older children, noted in paediatric cancer registries (12), may draw down the combined rates, their quasi-complete registration of cancers characteristic of (early) childhood pulls the overall rate up. National coverage of high quality provides more reliable estimates than regional coverage because higher rates observed in urban areas even out with lower rates in rural areas. National registration is also more effective in using linked data sources, such as death certificates (12).

Comparison of incidence in LAC with other world regions

The low overall LAC incidence reflects the level of socio-economic development, as both tend to increase simultaneously (25). The low rates of CNS neoplasms, neuroblastoma, renal tumours, soft tissue sarcoma, and epithelial tumours and melanoma may be explained by lagging diagnostic capacity in LAC and will expectedly evolve over time towards those observed in NA. This assumption is further supported by the high proportion of unspecified cases in LAC, likely reflecting a sub-optimal capacity to provide precise diagnosis or inability of registries to obtain relevant records, although the absolute difference was smaller than for other tumour groups.

LAC leads the global incidence of lymphoma in the age range 0-14 years. Lymphoma is the prominent group also in African populations (4, 10, 11). In several LAC countries children are exposed to endemic forms of viral infections by Epstein-Barr virus, Kaposi sarcoma herpesvirus and human T-lymphotropic virus (HTLV-1), which may increase lymphoma rates in children, including in Amerindian populations (26).

The highest leukaemia rates worldwide are observed in Hispanic children in the USA (Supplement, Table S12) (3), which may be conditioned by the genome-wide Native American ancestry (27). However, the much lower rate in LAC, where the overwhelming majority are Hispanics, suggests that other environmental

and sociodemographic factors may modulate this risk (28). An additional component of the differences in incidence between genetically comparable populations living in different environment may be underdiagnosis or underreporting of childhood leukaemia (1) in LAC.

Incidence trends

The observed overall increase in incidence of approximately 1% per year was documented in other studies since several decades, and decelerated recently in high-income settings (29, 30). The modestly growing incidence rates may indicate changes in exposures, such as changing maternal and birth characteristics (31), or environmental risk factors (2). Nevertheless, improvements in the capacity to diagnose childhood cancer may have contributed to the increasing incidence of the CNS neoplasms, as diagnostic computed tomography and magnetic resonance imaging technology was introduced progressively in LAC during the study period (32). Surprisingly, the increasing incidence of CNS neoplasms in CAC was limited to males, which might indicate gender inequity in seeking care, similar to that seen in Indian populations (11) or, potentially, a sex-specific exposure factor. The increase in incidence of leukaemia over 1993-1998 in males, revealed in joinpoint analysis, may indicate sex-specific differences in seeking diagnosis (and treatment).

Increasing incidence of retinoblastoma observed in SA may reflect an improved registration by general cancer registries. Retinoblastoma is often diagnosed and treated in specialised (ophthalmology) clinics, which are sometimes missed as data sources. The increase in incidence of hepatic tumours among males has been described, however the reasons are unclear (33). The considerable increase in the incidence of bone tumours among males in SA may be the result of better diagnosis and would be consistent with the decreasing trend of unspecified tumour types and no increase seen in females, who also undergo growth spurt just before males.

Increase in the germ cell tumours incidence in males suggests environmental exposures, such as pollution or pesticides, which have an anti-androgen effect (34), although the evidence is ambiguous (35). The increasing incidence of other carcinomas and melanoma may be driven by a shift of diagnosis to an earlier age due to improved diagnostics (24) or changing exposures (2). As the available data were sparse, continued surveillance is needed to examine the evolution of these trends.

Finally, the opposed incidence trends of other and unspecified tumours in the two compared LAC regions suggest the need for improved diagnosis or registration techniques, and access to medical records in CAC.

Registration coverage in LAC

Of 91 invited population-based cancer registries representing 27 LAC countries 54 submitted data and 38 registries in 14 countries could contribute to IICC-3 (11). Among those included, 21 registries covered the entire decade 2001-2010. Several registries, contributing to the earlier IICC volumes (4, 10), were not included in IICC-3 because they ceased existing, did not have resources to submit data or did not provide comparable data. LAC countries need to expand cancer registration coverage, and strengthen quality of childhood cancer data, in support of a childhood cancer control strategy (8). Sharing data for research and surveillance is the best way to improve data quality (3, 11).

Strengths and limitations

The strength of this study is its large coverage and comprehensive underlying database which contains the most up-to-date internationally comparable and reliable information on childhood cancer incidence in LAC. This data resource would benefit from an update with more recent data, also embedding data on follow-up. Survival is the key outcome measure for the WHO Global Initiative for Childhood Cancer which aims to

achieve 60% survival of children with cancer by 2030 (16). The paucity of quality childhood cancer data in LAC is the limitation that highlights the need to scale up cancer registration.

Conclusions

In this study we showed the importance of international collaboration, which allows standardised data validation, customised data analyses and context-sensitive interpretation of global data. The LAC incidence rates likely reflect a combination of the status of diagnostic efficacy, completeness of registration and underlying risk factors. The slightly increasing incidence rates suggest improvement in access to care and cancer registration, as well as changing exposures, as countries pursue their overall socio-economic development. Coverage of childhood population of LAC by cancer registration is inadequate, and a long-term commitment is expected from governments to support production of data, to benefit current and future childhood cancer patients.

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Table 1: Overview of cancer incidence in children diagnosed in Latin America and the Caribbean, 2001-2010. Source: IICC-3 (11).

N, number of cases; WSR, age-standardised rate (world standard)(19); CI, confidence interval; ASR, age-specific rate; – not applicable.

	Paediatric dataset				General dataset							
	Age 0-14 years				Age 0-19 years				Age 15-19 years			
Country, registry	N	Person-years (thousands)	WSR per million	95% CI	N	Person-years (thousands)	WSR per million	95% CI	N	Person-years (thousands)	ASR per million	95% CI
Overall	24 556	191 186	132.6	130.9-134.3	15 832	116 078	139.0	136.8-141.2	4 733	31 070	152.3	148.0-156.6
ARGENTINA, paediatric	12 941	102 433	130.1	127.8-132.4	–	–	–	–	–	–	–	–
ARGENTINA, Entre Rios	–	–	–	–	521	4 184	126.2	115.3-137.1	138	1 029	134.2	111.8-156.6
BRAZIL, 4 registries	1 413	10 054	145.7	138.0-153.4	2 098	14 019	151.8	145.2-158.4	685	3 966	172.7	159.8-185.6
CHILE, Valdivia	119	932	140.5	114.8-166.2	182	1 278	149.9	127.5-172.3	63	346	182.1	137.1-227.1
COLOMBIA, 3 registries	1 381	9 258	152.8	144.6-161.0	1 925	12 517	156.0	148.9-163.1	544	3 259	166.9	152.9-180.9
COSTA RICA	1 591	11 856	138.0	131.1-144.9	2 341	16 142	146.3	140.3-152.3	750	4 286	175.0	162.5-187.5
CUBA	2 608	21 086	128.6	123.6-133.6	3 652	29 238	128.5	124.2-132.8	1 044	8 152	128.1	120.3-135.9
ECUADOR, 4 registries	1 355	10 285	136.1	128.8-143.4	1 892	13 829	139.6	133.2-146.0	537	3 544	151.5	138.7-164.3
FRANCE, Martinique	80	835	98.2	76.2-120.2	126	1 138	110.2	90.5-129.9	46	303	151.6	107.8-195.4
JAMAICA, Kingston & St. Andrew	139	1 743	82.9	68.9-96.9	187	2 379	81.2	69.3-93.1	48	635	75.5	54.1-96.9
MEXICO, Mexico City, paediatric	899	6 902	133.8	125.0-142.6	–	–	–	–	–	–	–	–
USA, Puerto Rico	988	8 216	124.3	116.4-132.2	1 453	11 172	131.7	124.8-138.6	465	2 956	157.3	143.0-171.6
URUGUAY	1 042	7 588	143.0	134.2-151.8	1 455	10 181	146.7	139.0-154.4	413	2 593	159.3	143.9-174.7

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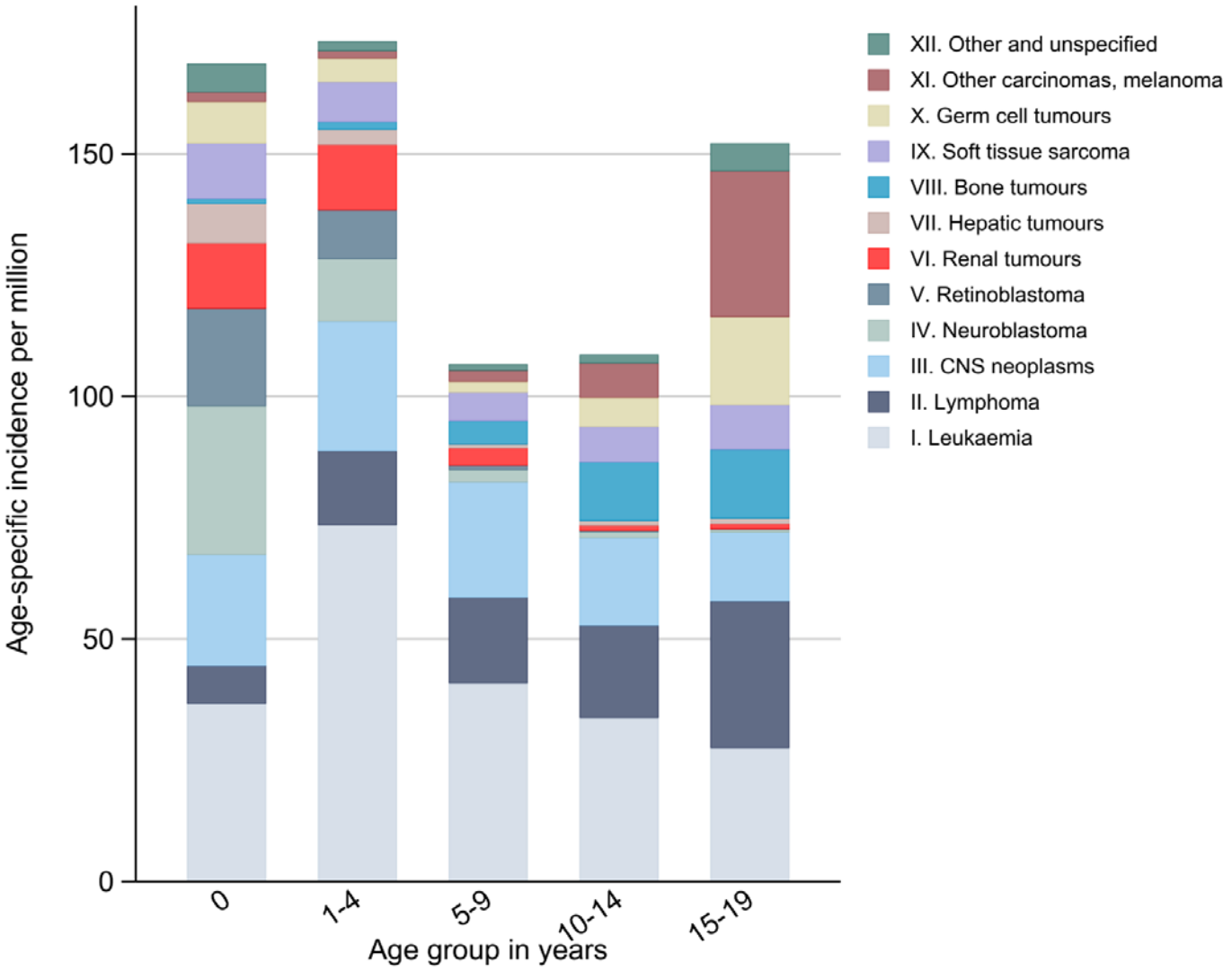

Figure 1: Age-specific cancer incidence by diagnostic groups of the International Classification of Childhood Cancer (18) in children diagnosed in 2001-2010 in Latin America and the Caribbean. Source: IICC-3 (11).

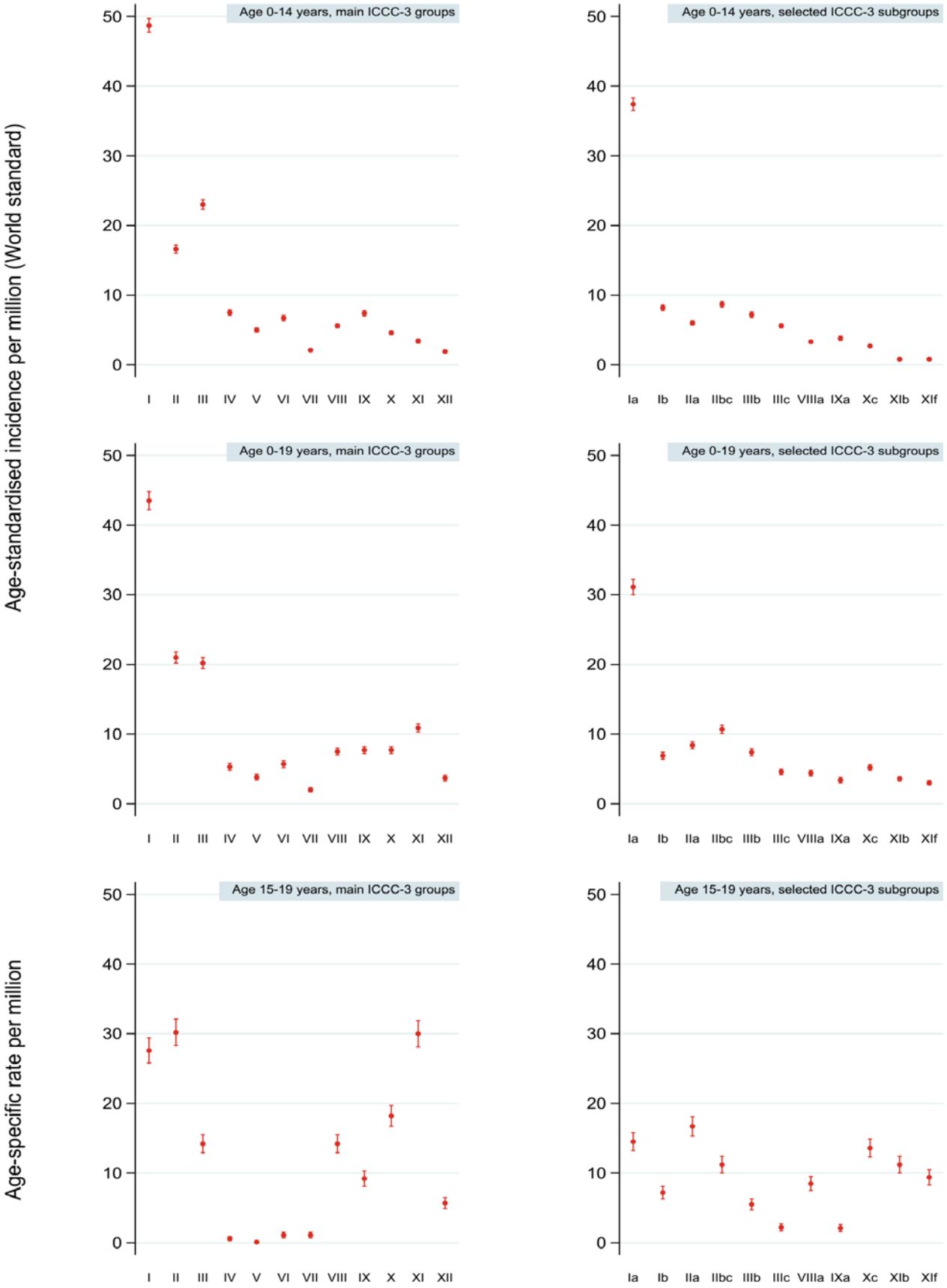

Figure 2: Childhood cancer incidence estimates and their 95% confidence intervals by categories of the International Classification of Childhood Cancer (ICCC-3) (18) in Latin America and the Caribbean, 2001-2010. Source: IICC-3 (11).

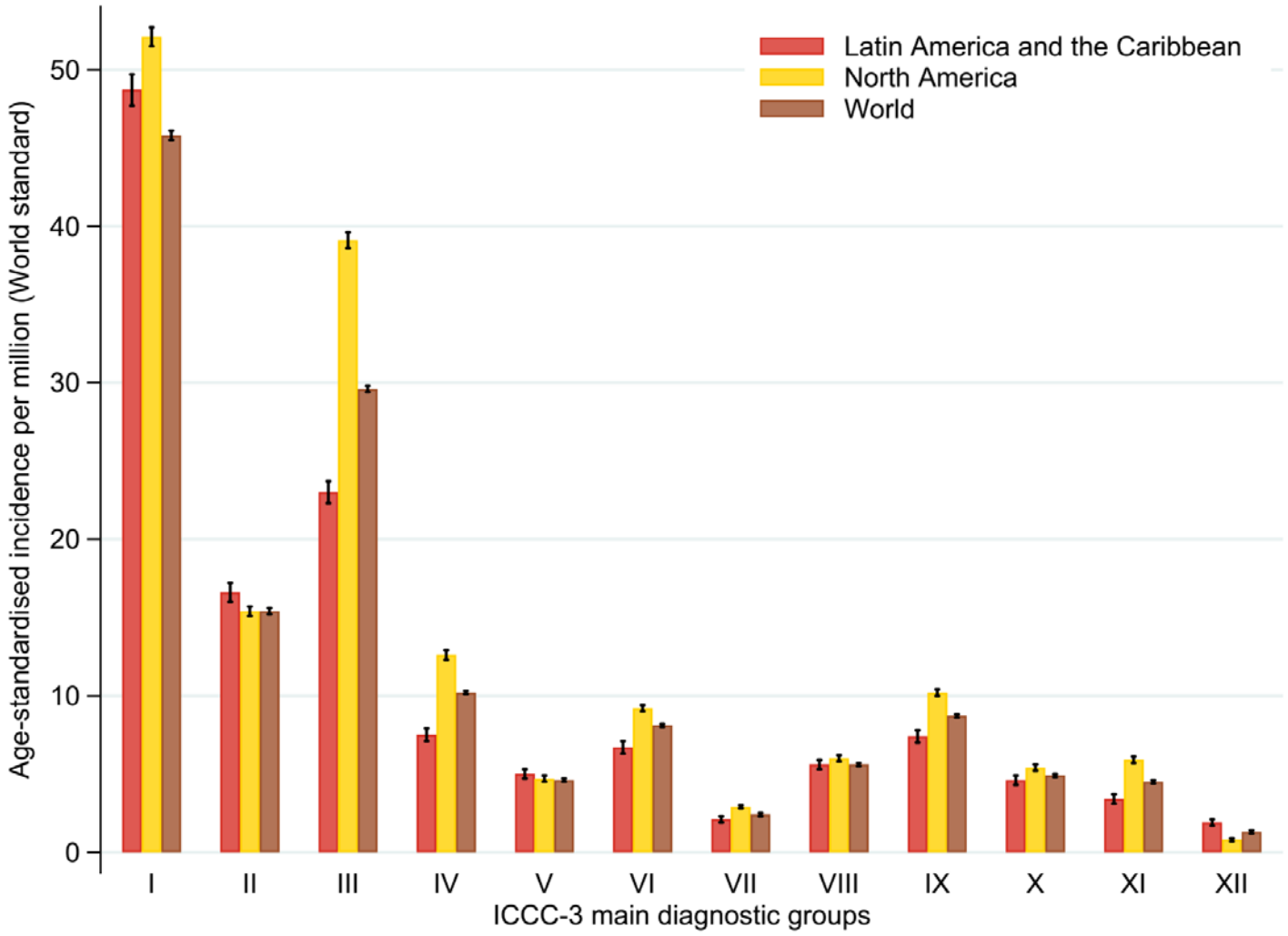

Figure 3: Cancer incidence estimates and their 95% confidence intervals in children aged 0-14 years in populations included in the IICC-3 study, 2001-2010. Diagnostic groups are defined according to the International Classification of Childhood Cancer (ICCC-3) (18). World includes Latin America and the Caribbean. Source: IICC-3 (11).

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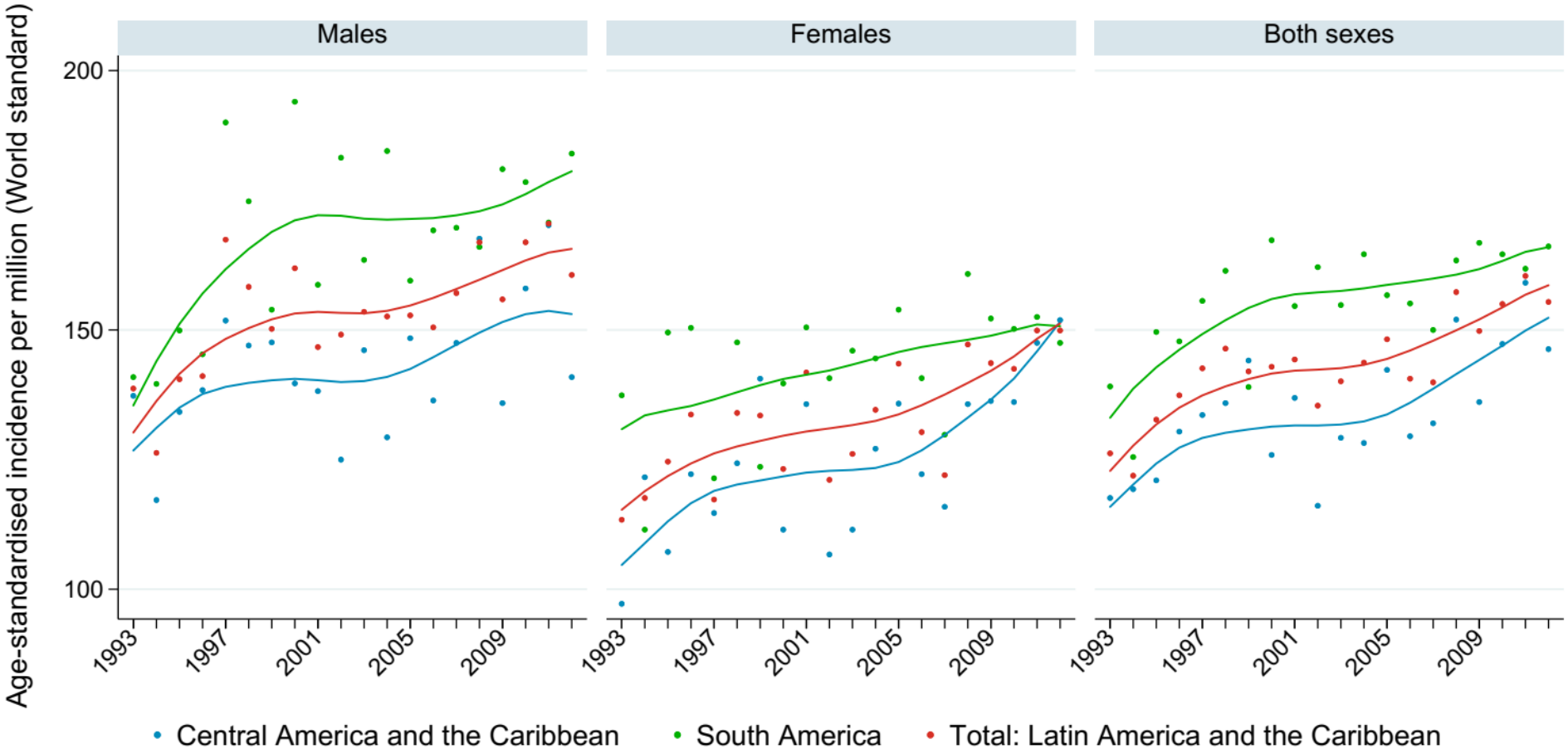

Figure 4: Cancer incidence trends in children aged 0-19 years in Latin America and the Caribbean, 1993-2012. Source: IICC-3 (11).

The dots represent the observed values, the trend curves were obtained from Poisson model.

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