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Hodgkin lymphoma burden in Central and South America☆

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ABSTRACT

Rationale and objective: Hodgkin lymphoma (HL) is largely curable owing to improvements in treatment since the 1960s; nevertheless, high mortality rates have been reported in Central and South America. We describe the current burden of HL in the Central and South American region.

Methods: We obtained regional- and national-level incidence data from 48 population-based cancer registries in 13 countries, and national-level mortality data from the WHO mortality database for 18 countries. We estimated world population age-standardized incidence rates (ASRs) and age-standardized mortality rates (ASMRs) per 100,000 person-years for 2003–2007 and present distributions by histological subtype.

Results: HL incidence rates varied 7-fold in males and 11-fold in females (male-to-female ratio 1:1–2.5:1). The highest ASRs were seen Argentina, Brazil, Costa Rica (males), Cuba (males) and Uruguay (females), whereas the lowest were in Bolivia and El Salvador. ASMRs varied by 4-fold in males and 6-fold in females (male-to-female ratio 1:1–4.3:1), with ASMRs <0.7 for most countries, except Cuba (≥ 1.0). In most countries, age-specific incidence rates of HL showed a bimodal pattern. Trends in HL in Argentina, Brazil, Chile, and Costa Rica remained stable in 1997–2008. Of all HL cases, 48% were unspecified as to histological subtype. Nodular sclerosis and mixed cellularity were the most frequent histologies.

Conclusion: The geographic variation in HL across the region may in part reflect differences in data quality and coverage, and differences in the adoption of modern therapies and healthcare access. Our results highlight the need for high-quality data and increased coverage in order to provide vital guidance for future cancer control activities.

1. Introduction

Despite Hodgkin lymphoma (HL) accounting for no more than 0.5% of the total cancer burden worldwide in 2012 [1], its unusual biology and epidemiology and positive response to treatment has drawn the attention of clinicians, pathologists and researchers [2]. HL is classified – on the basis of differences in histology, morphology and immunophenotype of the tumor cells – into two major types: classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL), accounting for 95% and 5% of all HL cases, respectively [3]. cHL is further subdivided into nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-rich, and lymphocyte-depleted types [4]. Initial treatment is based on histological characteristics, stage at diagnosis, and other prognostic factors [5]. HL is largely curable owing to improvements in treatment since the 1960s [6,7], with survival rates of 80.8% and 85.2% in Europe and in the United States, respectively [7,8]. Although the etiology of HL is complex and poorly understood, comparisons in age-specific incidence rates of HL, specific incidence patterns by sex and socioeconomic status for specific subtypes of HL have provided critical clues in the etiology of this disease [2,9–13]. For instance, age-specific incidence rates of HL are bimodal, with the first peak occurring at age 15–34 years and the second after age 60 years, specifically in European, American, Hispanic and Australian populations [14], whereas in developing countries the incidence of HL is characteristically high in early childhood and among the oldest age groups. Affluent standards of living during early

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childhood have been associated with an increased risk of young-adult HL, suggesting a delayed exposure to a common infectious agent, while the opposite is true for children living in less favorable living conditions [12,13,15].

GLOBOCAN estimates indicated that nearly 66,000 HL incident cases and more than 25,000 HL deaths occurred globally in 2012, with the vast majority (56% and 75%, respectively) occurring in less developed regions of the world. (Developed regions include all regions of Europe, Northern America, Australia/New Zealand and Japan. Less developed regions include: all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia.) Approximately 8–9% of the global burden of new HL cases and deaths were estimated to occur in the Central and South American region [1,16]. Recent predictions indicate an increase of 54% in the absolute number of HL cases in Central and South America for the year 2030, owing to growth and aging of the population [1,16].

Declines in HL mortality have been reported in Europe, the United States and Japan over the last few decades, largely because of the adoption of modern therapies [17,18]. Declines in HL mortality have also been described in several Latin American countries (including the Caribbean) in the past decade. In spite of the reported declines, elevated mortality rates occurred in Costa Rica, Cuba, Mexico and Venezuela, probably reflecting differences in healthcare access and management of this disease [6,19,20]. Unfortunately, HL incidence data in the Central and South American region are lacking given the small number of cancer registries that have met the data quality standards to be included in Cancer Incidence in Five Continents [21]. Statistics on incidence and mortality from HL are essential to identify disparities in cancer burden, to develop and evaluate cancer control policies and programs, as well as to guide future areas of research [22]. In this paper we describe the current burden of HL in the Central and South American region and interpret the data patterns in light of factors known to increase the risk of HL.

2. Methods

The present analysis includes Hodgkin lymphoma (C81), as coded by the 10th edition of the International Classification of Diseases for Oncology (ICD-10). The data sources and methods are described in detail elsewhere in this issue. In brief, we obtained regional- and national-level incidence data from 48 population-based cancer registries in 13 countries, and nationwide cancer deaths from the World Health Organization (WHO) mortality database for 18 countries. To facilitate data comparisons across countries, we used standard methods to check incidence data consistency and quality [23]. All incidence data were converted to the latest version of ICD-O (ICD-O-3) [24] and subsequently converted to the 10th edition of the International Classification of Diseases (ICD-10) [25]. Nationwide mortality data from the WHO systematically undergo data verification, and the data are coded in ICD-10 to avoid misclassification of cancer mortality over time [26]. We estimated age-standardized incidence rates (ASRs) and age-standardized mortality rates (ASMRs) per 100,000 person-years using the direct method and the World standard population [27,28]. We estimated national ASRs by aggregating the data from the available cancer registries using a weighted average of local rates. Trends in incidence were estimated for only four countries that provided written consent for the use of their data or submitted new data for about 10 years or more, and we matched mortality data to the same time-period (Table 1). To describe incidence and mortality time trends, we calculated the estimated annual percentage change (EAPC) for the most recent 10-year period using the method proposed by Esteve et al. [29]. To illustrate the direction of the trends in incidence and mortality rates by cancer site, locally weighted regression (LOWESS) curves were fitted to provide smoothed lines through the scatter plot of the annual age-standardized rates by calendar period. For this report, smooth lines were computed using a bandwidth of 0.5, which means that 50% of the annual time-series data was used to determine the LOWESS plotting position for each year. All of the EAPCs were tested for equality to zero by using the corresponding standard errors. We considered EAPCs statistically significant if the P-value ≤ 0.05. We conducted the data analysis in Stata version 12.1 (StataCorp) [30].

We present age-specific incidence and mortality patterns by country and sex. For comparative purposes, we selected the same age groups used by Hjalgrim et al. [31], except for the youngest age groups (0–14 years) where we divide the category into two (0–4 and 5–14 years) because the population in the region is relatively young [32].

We also present the distribution of HL by histological subtype, classified according to the revised WHO classification system [24] and used in Cancer Incidence in Five Continents [33].

3. Results

3.1. Age-standardized incidence and mortality rates

HL incidence rates varied 7-fold in males and 11-fold in females across Central and South America. Males generally had higher HL incidence rates than females: male-to-female (M:F) ratios ranging from 1.1 to 4.3:1.0, except in Chile (M:F ratio 1.0:1.0) (Table 2). In the most recent 5-year period, the highest incidence rates in males were observed in Argentina, Cuba, Brazil and Costa Rica (ASRs of about 2.0), whereas the lowest ASRs were in Peru, Bolivia and EL Salvador (range 0.4–0.9). Among females, the highest incidence rates were in Uruguay, Argentina and Brazil (ASRs ~1.5) and the lowest in Peru, French Guyana, Ecuador, El Salvador, and Bolivia (0.14–0.67).

Mortality rates varied 4-fold in males and 6-fold in females. Males had higher mortality than females (M:F ratios ranging from 1.1 to 2.5:1.0). Cuban males had the highest mortality rates of HL (ASMR: 1.0) followed by Costa Rica, Mexico and Venezuela (range 0.60–0.67), while the lowest were in Brazil (0.29). Females in Cuba, Costa Rica and Suriname had the highest mortality rates of HL (0.54–0.63), while Panama, Brazil, Nicaragua, Paraguay (0.13–0.20) had the lowest mortality (Table 2).

3.2. Age-specific rates

Age-specific incidence rates of HL seem to follow a bimodal pattern among males and females in most countries in the region, with the first peak seen around ages 15–24 years and the second

Table 1
Countries included in the analysis of time trends.

Country	Name of registries included	Period	% of the population covered
Argentina	Bahia Blanca	1993–2007	0.8
Brazil	Aracaju, Fortaleza, Goiania, Sao Paulo	1997–2006	8.0
Chile	Valdivia	1993–2008	2.2
Costa Rica	National registry	1985–2007	100.0

Table 2
Age-standardized incidence and mortality rates (per 100,000) of Hodgkin lymphoma in Central and South America by sex (all ages).

		Incidence						Mortality				
Country (period)	Sex	Cases	Crude rate	ASR (W)	M:F	MV%	Rank[a]	Deaths	Crude Rate	ASR (W)	M:F	Rank[a]
Central America												
Belize (2003–07)	M							2	*0.29*	*0.34*	1.2	16
	F							1	*0.14*	*0.29*		18
Costa Rica (2003–07)	M	205	1.9	1.9	1.3	100	19	65	0.59	0.67	1.2	18
	F	156	1.5	1.4		100	20	63	0.59	0.57		18
Cuba[b] (2004–07)	M	41	2.5	2.1	1.4	98	16	300	1.32	1.03	1.4	16
	F	30	1.9	1.4		100	20	220	0.98	0.73		20
El Salvador (1999–03)	M	49	0.37	0.40	1.3	88	14	59	0.41	0.49	1.2	16
	F	43	0.30	0.31		88	15	56	0.36	0.41		18
Guatemala (2003–07)	M							75	0.24	0.35	1.7	17
	F							50	0.15	0.21		18
Mexico[b] (2006–10)	M	231	1.3	1.4	1.3	100	15	1338	0.48	0.66	1.6	19
	F	192	1.1	1.0		100	19	936	0.31	0.40		21
Nicaragua (2003–07)	M							43	0.32	0.45	2.4	15
	F							22	0.16	0.19		20
Panama (2003–07)	M							24	0.29	0.32	1.6	19
	F							15	0.19	0.20		20
South America												
Argentina[b] (2003–07)	M	265	2.2	2.1	1.4	92	19	428	0.45	0.41	1.5	19
	F	212	1.6	1.5		93	22	366	0.37	0.28		22
Bolivia[b] (2011)	M	8	*0.61*	*0.60*	4.3	100	17					
	F	2	*0.15*	*0.14*		100	25					
Brazil[b] (2003–07)	M	1137	2.0	2.0	1.4	93	21	1268	0.28	0.29	1.5	17
	F	998	1.6	1.5		95	22	912	0.19	0.19		21
Chile[b] (2003–07)	M	28	1.2	1.1	1.0	100	22	126	0.31	0.31	1.3	20
	F	27	1.2	1.1		100	22	120	0.29	0.24		21
Colombia[b] (2003–07)	M	149	1.6	1.7	1.5	100	21	467	0.44	0.55	1.5	18
	F	115	1.1	1.1		100	23	368	0.34	0.37		22
Ecuador[b] (2003–07)	M	55	1.2	1.3	2.4	100	20	107	0.32	0.38	1.8	18
	F	29	0.56	0.52		100	23	69	0.21	0.22		20
French Guyana[b](2003–08)	M	8	*1.6*	*1.8*	3.1	88	20					
	F	3	*0.60*	*0.58*		100	23					
Paraguay (2003–07)	M							43	0.29	0.33	2.5	18
	F							17	0.12	0.13		21
Peru[b] (2001–05)	M	85	0.92	0.95	1.4	95	23	174	0.26	0.33	1.5	18
	F	68	0.71	0.67		94	22	124	0.18	0.22		20
Suriname (2003–07)	M							6	*0.48*	*0.57*	1.1	15
	F							6	*0.48*	*0.54*		13
Uruguay (2005–07)	M	89	1.9	1.8	1.1	100	20	28	0.58	0.48	2.2	19
	F	91	1.8	1.6		100	21	17	0.33	0.22		22
Venezuela (2003–07)	M							342	0.51	0.61	1.4	16
	F							257	0.39	0.42		20

ASR (W), age-standardized (world population) rate per 100,000; M, males; F, females; M:F, male-to-female ratio (female is the referent category). Numbers in *italics,* rates estimated with <10 cases which should be interpreted carefully.
[a] Rank based on highest ASR excluding: All sites but C44 and All sites.
[b] Incidence rates were estimated using data from regional cancer registries.

peak around ages ≥60 years. Age-specific incidence rates for males in Ecuador and Peru showed a slightly different pattern, with the first peak occurring at 5–14 years and the second peak at ages 50–59 years. Incidence rates in boys 5–14 years in Ecuador and Peru were 1.2 and 1.9 times higher than in young men (20–24 years), respectively. HL incidence rates displayed more than two peaks in males in Costa Rica and females in Chile, Colombia, Ecuador, and Peru: one at ages 15–19, the second in young adults (20–29), and the third in older adults (≥50 years). Females in Uruguay also showed more than two peaks: one at ages 15–19, the second at ages 30–49, and the third in older adults (≥60 years) (Fig. 1). HL mortality rates steadily increased with age, reaching a maximum in older males and females, around age ≥65 years (Fig. 2).

3.3. Time trends

Age-standardized incidence rates in the four countries evaluated did not reveal a clear pattern, with the exception of Costa Rica where incidence seemed stable. In contrast, age-standardized mortality rates tended to decline (Fig. 3). Trends analysis showed no statistically significant changes in age-standardized incidence and mortality rates from HL for the most recent 10-year period (1997–2008) (Fig. 4).

3.4. Histological distribution of HL incident cases in Central and South America

About half (48%) of the HL cases diagnosed in the region in both males and females were unspecified, while 49% were classified as classic HL (cHL) and 3% as nodular lymphocytic HL. Among the cHL, the most frequent tumors were nodular sclerosis (NS) and mixed cellularity (MC), accounting for 31% and 13% of all HL diagnoses respectively. In contrast, the least frequent cHL diagnosed were classic lymphocyte-rich and lymphocyte-depletion types, accounting for 3% and 2% of all HL tumors, respectively (Table 3).

The (median) age at diagnosis was 27 years (range 0–87) for nodular lymphocytic, 47 years (range 4–88) for classic lymphocyte-rich, 28 (range 1–90) for NS, 40 years (range 2–90) for MC,

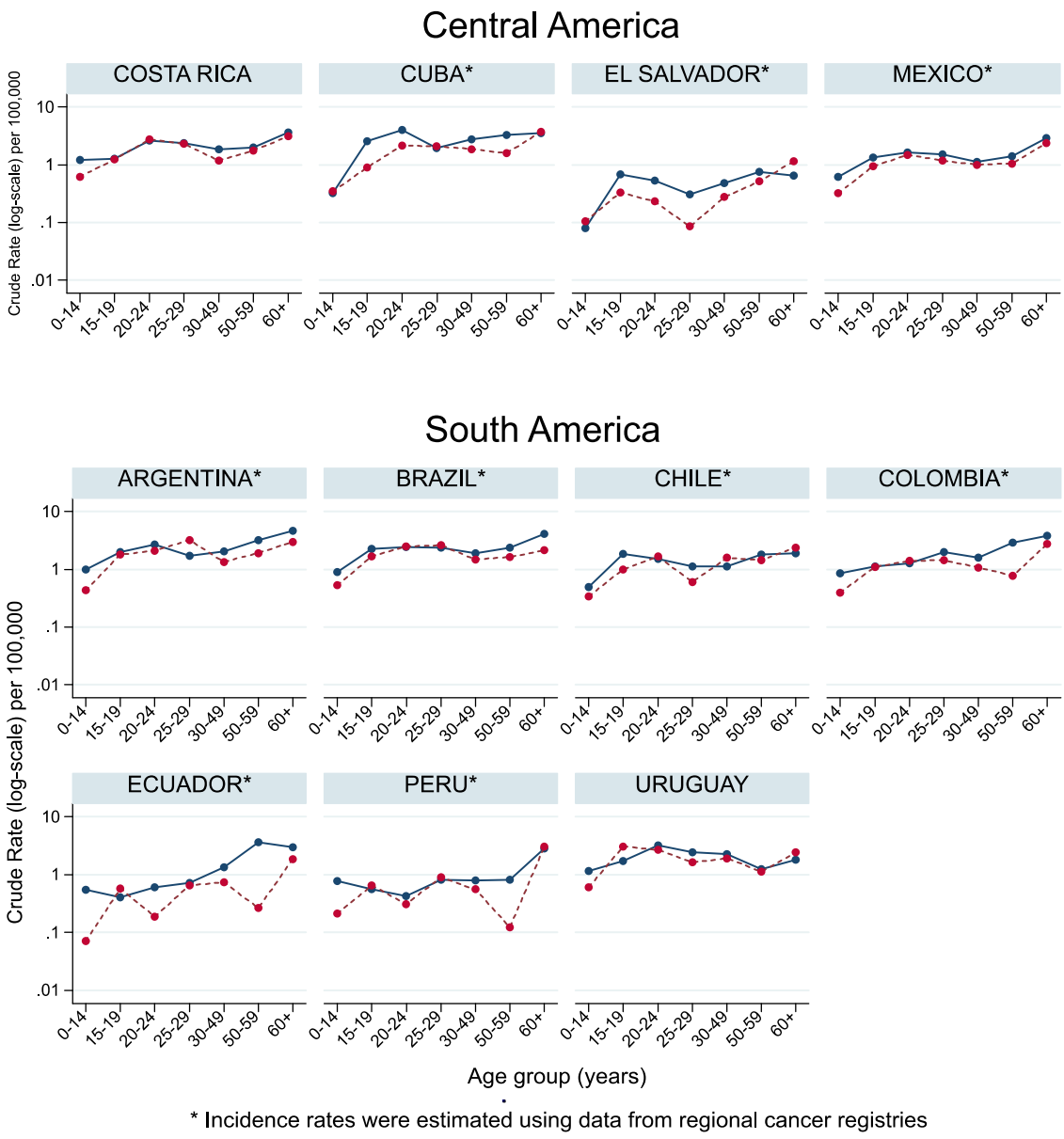

Fig. 1. Age-specific incidence rates (per 100,000) of Hodgkin lymphoma in males (solid blue line) and females (dashed red line).

47 years (range 2–87) for lymphocyte depletion, and 36 (range 2–100) for unspecified HL (Table 3).

4. Discussion

4.1. Patterns of HL incidence and mortality

This study showed a considerable variation in incidence (7-fold in males and 11-fold in females) and mortality (4-fold in males and 6-fold in females) of HL across the Central and South American region. In most countries, males had higher incidence and mortality rates than females (except in Chile and Uruguay). These geographical disparities may reflect differences in data quality and coverage within the region. Geographic differences in HL rates and sex disparity in HL rates have been documented around the world [34,35].

Cuba had one of the highest HL mortality rates in the world in both males and females (1.0 and 0.7, respectively), surpassed only by Greece (1.3 and 0.7) during 2003–2007. However, the mortality rates from Brazil, Belize, Chile, Ecuador, Guatemala, Peru, Paraguay, Panama, and Uruguay were comparable to the mortality rates reported in more developed areas of the world [26]. Such contrasts may reflect differences or inadequacies in the adoption of modern therapies across Central and South American countries, particularly among younger populations [6,19,36–39]. It is also possible that delays in HL diagnosis and disease stage [36,40–42] could have influenced the mortality patterns seen in the region. In Cuba, for example, a study conducted in Santa Clara revealed that 88% (84/96) of the HL adult patients were diagnosed at advanced stages, and 25% of them died (23/96) from this disease [40].

We observed a bimodal pattern in age-specific incidence rates of HL in most Central and South American countries, which is consistent with the patterns described for European, American, and Australian populations [9–11,14,43]. A similar pattern has been reported among Hispanics in the United States: one peak at ages 20–29 years followed by an exponential increase until another peak in the elderly (70–79 years) [9]. This pattern is known as the "third pattern" which is described in developed countries and patients with high socioeconomic status (SES). It is characterized by a low incidence in children, high incidence in young adults and a

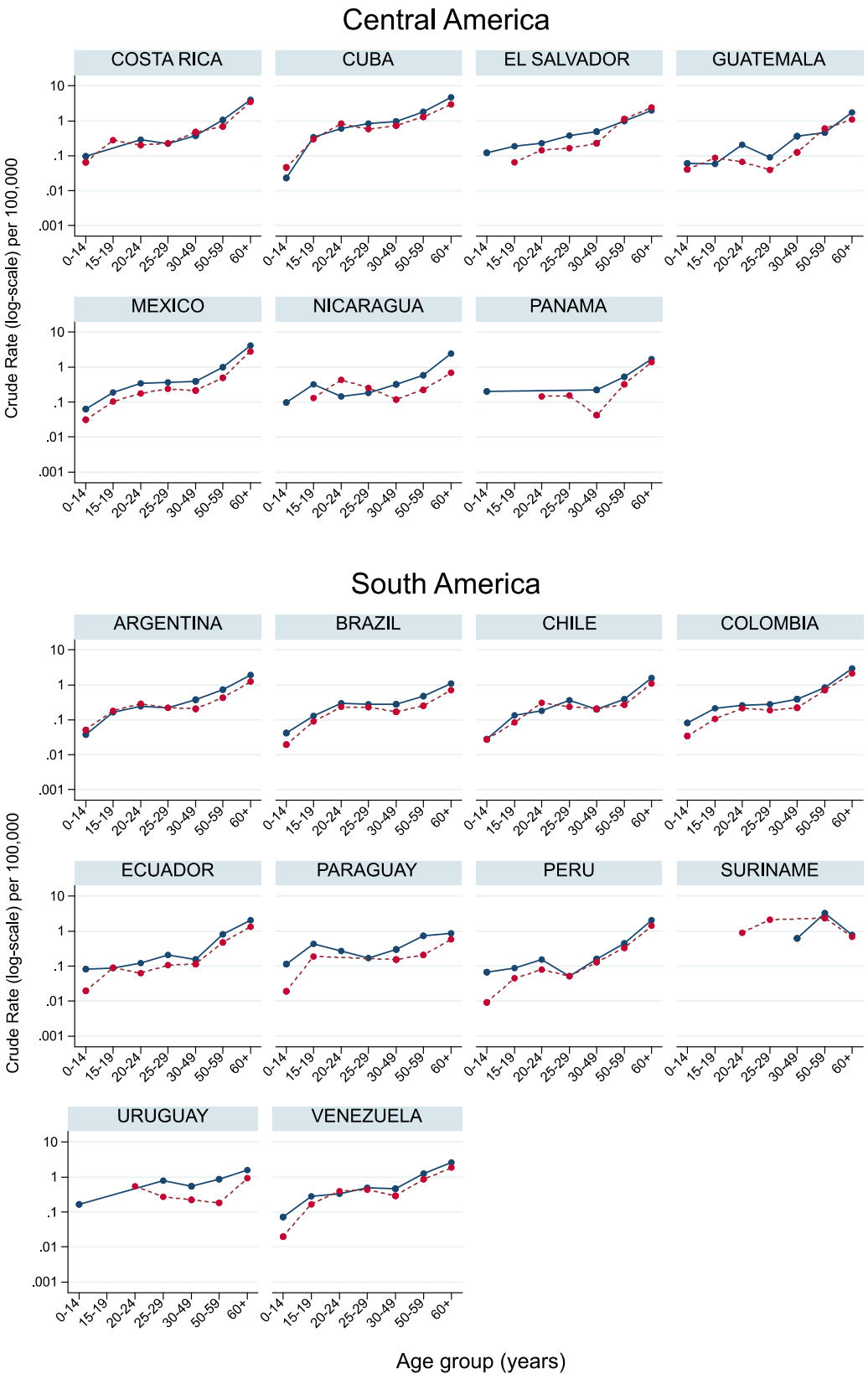

Fig. 2. Age-specific mortality rates (per 100,000) of Hodgkin lymphoma in males (solid blue lines) and females (dashed red lines).

second high incidence peak in older age groups, with tumors mainly of NS subtype and Epstein–Barr virus- (EBV-)negative tumors [13,14,43,44].

Interestingly, we observed higher incidence rates in boys (5–14 years) as compared to young men (20–24 years) in Ecuador and Peru, a finding more consistent with the "second pattern"

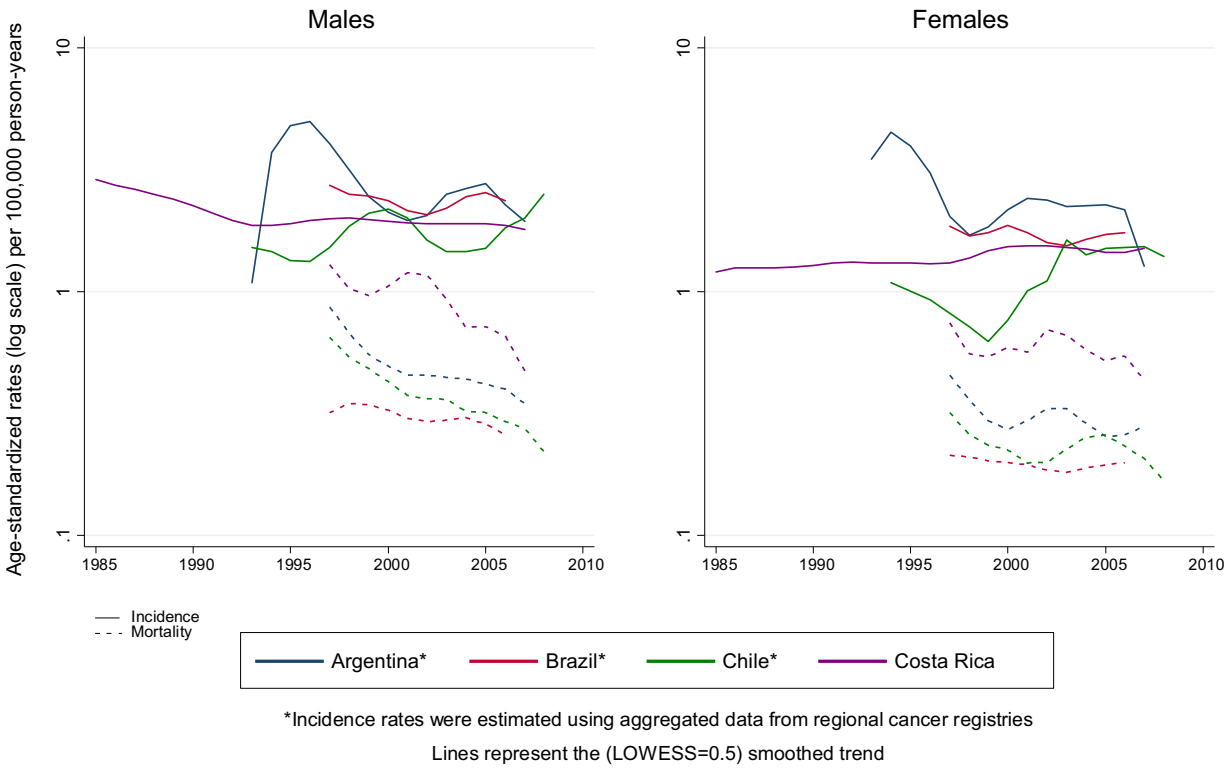

Fig. 3. Trends in age-standardized (world population) incidence and mortality from Hodgkin lymphoma, by country and sex, all ages.

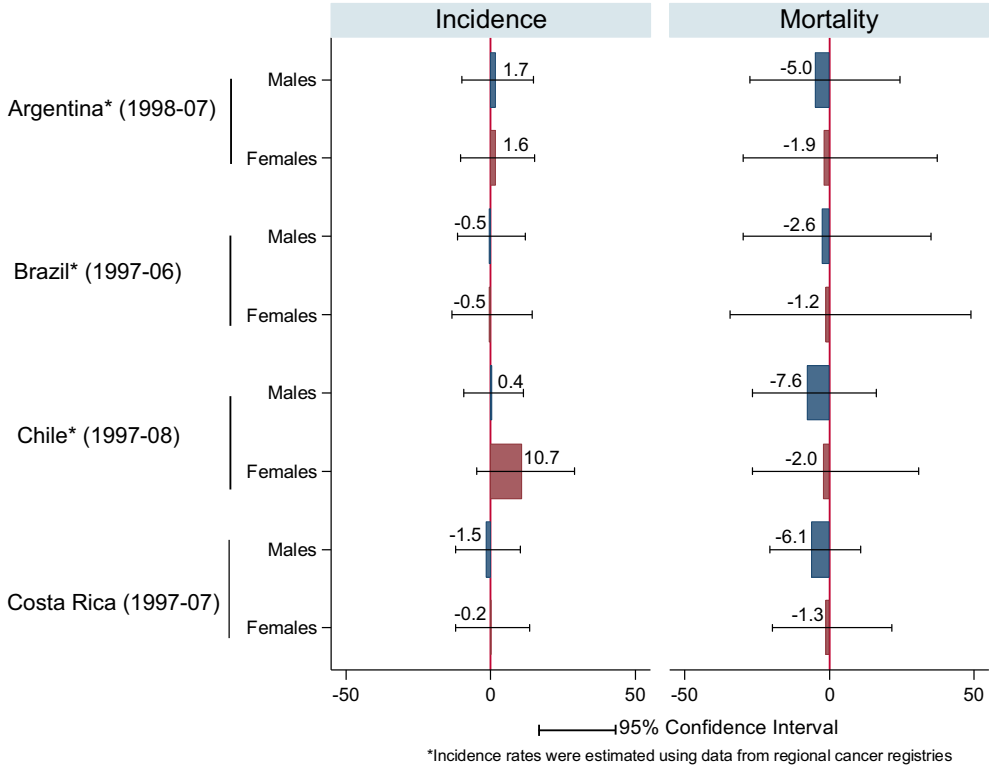

Fig. 4. Estimated annual percent change in age-standardized (world population) incidence and mortality rates (per 100,000) from Hodgkin lymphoma, by sex.

which is observed in countries with transitional economies and rural areas. In this pattern, the incidence of HL has peaks in childhood and then peaks again during the second decade of life. MC and NS subtypes are present in similar proportions in both age groups [13,14,43,44].

The bimodal age-specific incidence pattern was less evident in males in Costa Rica and females in Chile, Colombia, Ecuador, Peru,

Table 3
Distribution of Hodgkin lymphoma incident cases by histological subtype.

Country (period)	Classic Hodgkin lymphoma								Unspecified	
	Nodular lymphocytic		Classical lymphocyte-rich		Nodular sclerosis		Mixed cellularity		Lymphocyte depletion			
	n (%)	Age (range)	n (%)	Age (range)	n (%)	Age (range)	n (%)	Age (range)	n (%)	Age (range)	n (%)	Age (range)
CENTRAL AMERICA												
Costa Rica (2003–07)	28 (8)	18 (5–81)	22 (6)	46 (5–84)	208 (58)	27 (3–86)	35 (10)	52 (3–77)	11 (3)	51 (29–79)	57 (16)	41 (5–87)
Cuba[a] (2004–07)	1 (1)	70 (70–70)	0 (0)	–	5 (7)	41 (37–58)	1 (1)	57 (57–57)	1 (1)	72 (72–72)	63 (89)	42 (12–100)
El Salvador[a] (1999–03)	0 (0)	0 (–)	2 (2)	36 (18–54)	32 (35)	31 (12–84)	8 (9)	38 (13–66)	4 (4)	68 (18–81)	46 (50)	38 (13–94)
Mexico[a] (2006–10)	35 (8)	34 (9–87)	23 (5)	52 (4–88)	102 (24)	27 (4–86)	97 (23)	34 (5–82)	19 (4)	36 (5–66)	147 (35)	39 (7–87)
SOUTH AMERICA												
Argentina[a] (2003–07)	21 (4)	25 (6–69)	7 (1)	55 (21–82)	105 (22)	27 (5–87)	67 (14)	43 (4–85)	2 (0)	63 (61–65)	275 (58)	38 (2–89)
Bolivia[a] (2011)	0 (0)	–	1 (10)	75 (75–75)	0 (0)	–	1 (10)	32 (32–32)	0 (0)	–	8 (80)	59 (3–80)
Brazil[a] (2003–07)	20 (1)	31 (3–42)	36 (2)	44 (8–82)	641 (30)	27 (1–90)	220 (10)	36 (3–90)	28 (1)	47 (15–86)	1190 (56)	33 (2–98)
Chile[a] (2003–07)	0 (0)	–	0 (0)	–	15 (27)	35 (13–78)	1 (2)	16 (16–16)	3 (5)	41 (18–65)	36 (65)	45 (4–82)
Colombia[a] (2003–07)	18 (7)	31 (15–71)	16 (6)	38 (6–67)	113 (43)	31 (4–86)	48 (18)	45 (6–82)	3 (1)	42 (32–60)	66 (25)	42 (6–88)
Ecuador[a] (2003–07)	6 (7)	32 (5–62)	0 (0)	–	11 (13)	31 (14–76)	18 (21)	53 (3–84)	1 (1)	6 (6–6)	48 (57)	43 (5–85)
French Guyana[a] (2003–07)	1 (9)	14 (14–14)	1 (9)	66 (66–66)	5 (45)	16 (8–51)	2 (18)	48 (45–51)	1 (9)	9 (9–9)	1 (9)	49 (49–49)
Peru[a] (2001–05)	3 (2)	21 (14–79)	12 (8)	64 (25–78)	43 (28)	37 (3–84)	44 (29)	32 (2–83)	6 (4)	68 (36–87)	45 (29)	35 (5–92)
Uruguay (2005–07)	2 (1)	15 (6–24)	7 (4)	42 (11–80)	74 (41)	25 (3–79)	13 (7)	18 (7–85)	0 (0)	–	84 (47)	43 (3–96)
TOTAL	**135 (3)**	**27 (3–87)**	**127 (3)**	**47 (4–88)**	**1354 (31)**	**28 (1–90)**	**555 (13)**	**40 (2–90)**	**79 (2)**	**47 (2–87)**	**2066 (48)**	**36 (2–100)**

n, number of incident cases; NOS, not otherwise specified.
[a] Numbers of cases and percentages were calculated using aggregated data from regional cancer registries.

and Uruguay, a finding that is in line with previous reports [45]. We did not identify the "first pattern", usually seen in developing countries and patients of low SES, where the incidence of HL is characterized by a peak in early childhood, low incidence in the third decade and high incidence among the oldest age groups. These tumors are usually of the MC subtype, and a high proportion are EBV-positive [13,14,43,44]. This observation seems consistent with the hypothesis that the age-specific pattern in the region is becoming more like the pattern seen in economically developed countries [14]. Mortality rates did not display the same age-specific incidence pattern; instead mortality rates steadily increased with age, which is also consistent with other reports [6,19].

Trends in HL incidence and mortality in Argentina, Brazil and Chile did not reveal a clear pattern, whereas in Costa Rica rates seemed stable. The interpretation of incidence trends is challenging because of the evolving classification system, and improvements in disease detection and cancer registration over the past 20 years [46]. Moreover, given the rarity of this cancer, the observed fluctuations may reflect instability of rates due to low numbers. Mortality rates tended to decline or remained almost unchanged from 1997 to 2008 in the four countries analyzed. Small declines in HL mortality rates have also been described for males in Cuba and Mexico and females in Ecuador and Mexico, whereas in Colombian females HL mortality has increased from 1997 to 2008 [6]. The declines in HL mortality are probably due to therapeutic advancements; however, changes in diagnosis and classification may also have played a role [6].

We were unable to examine incidence rates by histological subtype in detail given that 48% of all the HL cases diagnosed in the region were unspecified. NS and MC subtypes accounted for 31% and 13%, respectively, of all HL cases diagnosed in the region. The high frequency of NS and MC, as compared to other subtypes, seem consistent with the histological subtypes found more frequently in populations of higher SES and with the second and third age-specific patterns described above [14,31]. In spite of the wide variation in age at diagnosis of HL subtypes, the (median) age of diagnosis of most subtypes observed in the region seem consistent with that in other reports [12,34]. For instance, NS patients are usually adolescents and young adults, while MC patients are usually children or older adults. Lymphocyte-rich HL usually occurs at ages $\geq$50 years. We observed that lymphocyte-depleted cases were diagnosed at (median) age 47 years (range 2–87), but this subtype usually occurs among elderly patients and in developing countries [12]; this discrepancy could be a reflection of the large proportion of unspecified cases.

4.2. Factors associated with HL risk

Explaining the geographical differences and age-specific patterns in HL rates is challenging given that the etiology of this disease remains largely unknown. Infections with EBV and human immune deficiency virus type 1 (HIV-1) are the only established agents with sufficient evidence to be classified as carcinogens in HL in humans [47]; differences in their prevalence could therefore, at least in part, explain some of the observed variations across Central and South America.

EBV has been associated mainly with cHL, and EBV-positive tumors tend to occur more frequently in children and the elderly [15,34]. Several studies conducted in the region have shown a wide variation in the prevalence of EBV positivity among patients with cHL: 45% in Argentina, 46–94% in Brazil, 69% in Colombia, 44% in Costa Rica, 100% in Honduras, 61–92% in Mexico, and 94% in Peru [48–50]. In Central and South America and the Caribbean, the prevalence of EBV positivity among men with cHL was 35% higher than in women with cHL (95% confidence interval, 0.89, 2.04) [48]. In 2008, 49% of the total number of HL incident cases estimated to

occur globally were attributed to EBV (33,000/68,000), 70% (23,000) of which were in less developed regions of the world [51]. In 2010, 44.7% of the total number of HL deaths estimated to occur worldwide were attributable to EBV (7917/17,718 cases) [52].

HIV-1 has been strongly associated with an increased risk of many cancers, including HL, mainly via immunodeficiency [47,53–55]. MC and lymphocyte-depleted subtypes are prevalent in patients with HIV infection and in developing countries [56]. In most Central and South American countries, the prevalence of HIV among 15–49-year-olds (≤0.6% in 2013) is lower than the global prevalence of HIV in 15–49-year-olds (0.8%) or in Africa (5.5%). In Belize and Guyana, however, the prevalence of HIV is higher than in most countries in the region (1.5% and 1.4%, respectively) [57]. This suggests that HIV infection probably plays a minor role in the observed geographic differences in HL rates in the region.

Twin and familial aggregation and population-based registry studies suggest that family history of HL may play a role in HL development [2,58–60]. Genome-wide association studies (GWAS) have identified 15 SNPs from nine different loci associated with HL, with the strongest associations reported for SNPs mapping to the human leukocyte antigen (HLA) class II [60]. HLA regions are associated with the development of several cancers and immunity disorders [61]. GWAS have also identified three single-nucleotide polymorphisms (SNPs) on chromosome 6p21.32 strongly associated with an increased risk of NS among adolescents and young adults of European origin [62].

Racial/ethnic disparities in HL rates have been reported in the United States [9]. Epidemiological studies have shown that some variability in HL rates across ethnic groups remains even after SES and environment-related factors are taken into account, suggesting possible differences in genetic susceptibility [9,63,64]. We were unable to evaluate whether such associations exist within the region because cancer registries do not systematically record this variable. In fact, we observed elevated incidence rates in regions with a large percentage of mostly White or European descendants or Mestizos (Argentina and Costa Rica) as well as in regions with a large percentage of Black populations (i.e. Brazil and Cuba) [65]. The study of race/ethnicity and HL risk in the region is very challenging given the racial heterogeneity of the population [66,67]. Racial categories are based on the subject's perception of skin color which are influenced by socioeconomic position [66]; this could in turn reflect differences in healthcare access and management of the disease.

Some studies among immigrant populations from Eastern Asia and China to North America revealed that the incidence of HL has increased in recent decades, probably due to the adoption of Western lifestyles and environmental exposures [2,9,31]. Epidemiological evidence is linking tobacco smoking with an increased risk of HL, although not consistently [68,69]. Specifically, smoking is associated with risk of EBV-positive HL but not with EBV-negative HL [68]. However, it remains unknown to what extent these factors could explain the observed variation in HL rates in Central and South America.

4.3. Strengths and weaknesses of the study

This study presents a comprehensive analysis of HL incidence and mortality rates in Central and South America. However, incidence data patterns must be interpreted with caution given that national data coverage was suboptimal, with the exception of that in Costa Rica and Uruguay. Cancer registries in Central and South America may differ in completeness and data quality which depend on the maturity of the cancer registry, and this could explain why some of the rates observed in Mexico, Bolivia and El Salvador were low. The estimation of HL mortality rates may be influenced by the quality of national registration of causes of death. In some Central and South American countries, mortality data may be considered of medium or low quality [70]. Moreover, incidence rates from Bolivia and French Guyana and mortality rates from Belize and Suriname must be interpreted with caution as they were estimated using less than ten cases and may not be stable.

Because we chose to present incidence rates by country rather than by cancer registry, our results do not depict possible within-country differences related to the catchment area of the population-based cancer registries. However, due to the rarity of HL, several cancer registries recorded less than ten cases by sex. The estimation of rates based on such low numbers of cases would have led to unstable age-standardized incidence rates and unclear age-specific patterns [71].

Regarding data quality indicators, the percentage of microscopically verified (MV) cases (validity of the diagnostic information) in most Central and South American countries was high (ranging from 98% to 100%) and comparable to the MV% observed across good-quality cancer registries in other parts of the world (i.e. North America, Africa, United Kingdom), where MV% ranged from 98% to 100% [71]. In Argentina, Brazil, El Salvador, French Guyana, and Peru, the MV% was lower than that in the rest of the countries in the region (ranging from 88% to 94%) (as shown in Table 2). Despite this, the MV% in our study is higher than that reported previously for Argentina, Brazil and Chile [6]. In contrast, all cancer registries across the region had poor diagnostic precision, as 48% of all HL incident cases were classified as unspecified by histological classification [72]. It is uncertain whether the observed geographic variation in HL rates is artefactual or not; however, our results highlight the need for high-quality data and increased coverage in order to provide vital guidance for future cancer control activities.

5. Conclusion

HL is a relatively rare cause of cancer incidence and mortality in the Central and South American region. Nevertheless, rates showed important geographic variations, perhaps reflecting differences in data quality and coverage within the region as well as differences or inadequacies in the adoption of modern therapies and healthcare access. This study revealed marked differences in age-specific rates. The most frequent age-specific pattern was consistent with the pattern observed in countries with transitional economies and rural areas. This study also revealed concerns regarding data quality of HL by histological classification, as 48% of the cases were unspecified; this underlines the need to improve the quality of registrations in the region.

Authors contribution

Study conception and design: DF, MS.
Acquisition of data: MS.
Analysis of data: MS.
Interpretation of data: GK, GA, MS, DF.
Writing the article: GK, MS.
Critical revision of the article: GK, GA, MS, DF.
Final approval of the article: GK, GA, MS, DF.

Conflict of interest

None.

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