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Stomach cancer burden in Central and South America☆

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ABSTRACT

Rationale and objective: Stomach cancer mortality rates in Central and South America (CSA) are among the highest in the world. We describe the current burden of stomach cancer in CSA.
Methods: We obtained regional and national-level cancer incidence data from 48 population-based registries (13 countries) and nation-wide cancer deaths from WHO's mortality database (18 countries). We estimated world population age-standardized incidence (ASR) and mortality (ASMR) rates per 100,000 and estimated annual percent change to describe time trends.
Results: Stomach cancer was among the 5 most frequently diagnosed cancers and a leading cause of cancer mortality. Between CSA countries, incidence varied by 6-fold and mortality by 5–6-fold. Males had up to 3-times higher rates than females. From 2003 to 2007, the highest ASRs were in Chile, Costa Rica, Colombia, Ecuador, Brazil and Peru (males: 19.2–29.1, females: 9.7–15.1). The highest ASMRs were in Chilean, Costa Rican, Colombian and Guatemalan males (17.4–24.6) and in Guatemalan, Ecuadorian and Peruvian females (10.5–17.1). From 1997 to 2008, incidence declined by 4% per year in Brazil, Chile and Costa Rica; mortality declined by 3–4% in Costa Rica and Chile. 60–96% of all the cancer cases were unspecified in relation to gastric sub-site but, among those specified, non-cardia cancers occurred 2–13-times more frequently than cardia cancers.
Conclusion: The variation in rates may reflect differences in the prevalence of *Helicobacter* pylori infection and other risk factors. High mortality may additionally reflect deficiencies in healthcare access. The high proportion of unspecified cases calls for improving cancer registration processes.

1. Introduction

Stomach cancer is one of the most common malignant neoplasms worldwide [1–3]. In 2012, nearly 1 million new cancer cases and 723,000 deaths were estimated to occur globally in both males and females, making stomach cancer the fifth most common cancer diagnosis (after lung, breast, colorectal and prostate cancers) and the fourth leading cause of cancer death (after lung, breast and liver cancers) [4]. More than 70% of the total number of cases occurred in less developed regions of the world (677,000 new cases and 548,000 deaths) and less than 30% of the cases occurred in more developed regions (275,000 new cases and 175,000 deaths) [4]. The age-standardized incidence rates of stomach cancer vary by 5- to 10-fold through the world, and the male-to-female ratio is 2:1 [4,5]. Eastern Asia and South America have the highest incidence rates in the world, whereas North America, Western Africa and South-Central Asia have the lowest rates [6]. Mortality rates of stomach cancer in Central and South America (CSA) are highest along the Pacific coast, with the highest mortality rates (from 12.4 to 22.3 per 100,000) in the mountains of the Andes (from Chile to Venezuela) and the Sierra Madre Mountains in Central America (from Costa Rica to southern Mexico) [7]. The worldwide variation in stomach cancer incidence and mortality rates reflect differences in the distribution of the factors associated with this disease across the world [5,8]. Moreover, stomach cancer rates, within any population, tend to be higher in those who are relatively poorer and more socioeconomically deprived [9].

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The incidence and mortality of stomach cancer have been declining over the past decades in nearly all populations, regardless of the background risk of stomach cancer. The declines are thought to be due to declines in the prevalence of *Helicobacter pylori* (*H. pylori*) infection and improvements in sanitation and preservation and storage of foods and other dietary factors (high consumption of fruit and vegetables, reduced salt consumption). Changes in tobacco smoking may also play a role [8,10–12]. Despite the observed declines in incidence, the absolute burden of stomach cancer remains particularly high in several Asian and Central and South American (CSA) countries [5,8].

Although stomach cancer is usually reported as a single entity, it can be classified according to its anatomic location into cardia (CGC) and non-cardia (NCGC), and according to its histological pattern into intestinal (well-differentiated) and diffuse (undifferentiated) types [13–15]. These two classifications are currently used because their epidemiology, biology, clinical features, pathology, and precursor lesions are particular for each subtype [14–16]. Recent global estimates revealed that 87% of all stomach cancer cases diagnosed in 2012 were NCGC, with most of the cases occurring in Eastern Asia (61%) followed by Central Asia (10%), Eastern Europe (7.5%), and South America (7.0%) [3]. In 2012, the estimated incidence of CGC varied by about 3-fold in both males and females across world regions; the incidence of NCGC varied by nearly 8-fold in males and by 4.5 in females [17]. Global estimates indicate that 89% (774,000) of the NCGC cases that occurred in 2008 were attributable to *H. pylori* infection [18]. This is particularly concerning for CSA given the high prevalence of *H. pylori* infection, ranging from 50 to 95% [19–21].

Despite the reported declines in the incidence and (mainly) mortality of stomach cancer in CSA in the last few decades [1,2,12,22–28], CSA has some of the highest incidence and mortality rates in the world [4,29,30]. Recent projections indicate that the burden of stomach cancer in CSA will increase by approximately 80% by the year 2030 (102,000 new cases and 88,000 deaths); such increases are expected to be driven primarily by the growth and ageing of the population [4]. Given that the descriptive epidemiology of stomach cancer in many CSA countries is limited, we aim to describe the most current geographical and temporal trends in incidence and mortality of stomach cancer in the CSA region and present a description of the distribution of incident cases by anatomic site and histological subtype by sex. We interpret the results based on the known determinants of stomach cancer.

2. Methods

The present analysis includes stomach cancer (C16), 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 in an earlier article in this supplement (Sierra and Forman). 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 mortality database for 18 countries. We estimated age-standardized incidence (ASR) and mortality (ASMR) rates per 100,000 person-years using the direct method and the world standard population [31,32]. We estimated national ASRs by aggregating the data from the available cancer registries using a weighted average of local rates. To describe incidence and mortality time trends, we calculated the estimated annual percentage change (EAPC) for four countries (Table 1) using the method proposed by Esteve et al. [33]. 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 $\leq$0.05. We conducted all analyses in Stata version 12.1 (StataCorp) [34].

Table 1
Countries included in the analysis of time trends.

Country	Names 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

In addition, we estimated the incidence of stomach cancer by anatomic location as cardia (C16.0), non-cardia (fundus (C16.1), corpus (C16.2), antrum (C16.3), pylorus (C16.4), lesser curvature (C16.5), and greater curvature (C16.6), and other – overlapping lesions (C16.8) and unspecified (C16.9) – as classified in Cancer Incidence in Five Continents (CI5) [6]. We also evaluated the distribution of tumors by histological type [35] as intestinal (ICD-O-3 codes M8010, M8140, M8144, and M8211), diffuse (codes M8490, M8142, and M8145), and other epithelial (all other histology codes excluding M8800–M9759 and M8000–M8004) using the same classification as in other studies [36–38].

3. Results

3.1. Age-standardized incidence and mortality rates

During the most recent 5-year period evaluated, stomach cancer was one of the five most frequently diagnosed cancers in Argentina, Brazil, Bolivia, Chile, Colombia, Costa Rica, Ecuador, El Salvador, French Guyana, and Peru and one of the five leading causes of cancer death in most CSA countries (except for females in Argentina, Cuba, and Suriname). Overall, males had incidence and mortality rates 1.3–2.8 times higher than females (Table 2).

The incidence of stomach cancer varied by 6-fold across countries in CSA. In males, the highest incidence rates were observed in Chile (29.1) followed by Costa Rica, Colombia, Ecuador and Brazil, and Peru (ASRs ranging from 19.2 to 26.5) while the lowest rates were observed in Mexico, Bolivia and El Salvador (3.3–4.6). In females, the highest ASRs were seen in Peru, Costa Rica, Ecuador, Colombia, Chile and Brazil (9.7–15.1) and the lowest rates were in Mexico, Bolivia and El Salvador (ASRs $\leq$3.0) (Table 2).

Mortality rates of stomach cancer varied by 5–6-fold in CSA. In males, the highest mortality rates were observed in Chile and Costa Rica (ASMRs: 20.1–24.6) followed by Colombia and Guatemala (17.4–17.8) and the lowest rates were in Suriname, Cuba and Paraguay (5.0–7.1). In females, the highest ASMRs were seen in Guatemala (17.1) followed by Ecuador and Peru (10.5–11.2) and the lowest rates were in Paraguay, Argentina, Cuba and Suriname (2.9–3.9) (Table 2).

3.2. Age-specific rates

Stomach cancer incidence and mortality were strongly related to age. In the majority of CSA countries, 80–97% of all the stomach cancer cases were diagnosed in older men and older women ($\geq$50 years) and 3–18% were diagnosed in younger men and women ($<$50 years) in the most recent 5-year period. In Bolivia and Mexico, 21% and 19% of the cases, respectively, were diagnosed in younger men. In French Guyana, El Salvador, Mexico, and Costa Rica 20–25% of the cases were diagnosed in younger women. The mean age at diagnosis across CSA countries ranged from 61 to 68 years in males and from 59 to 73 years in females (data not shown).

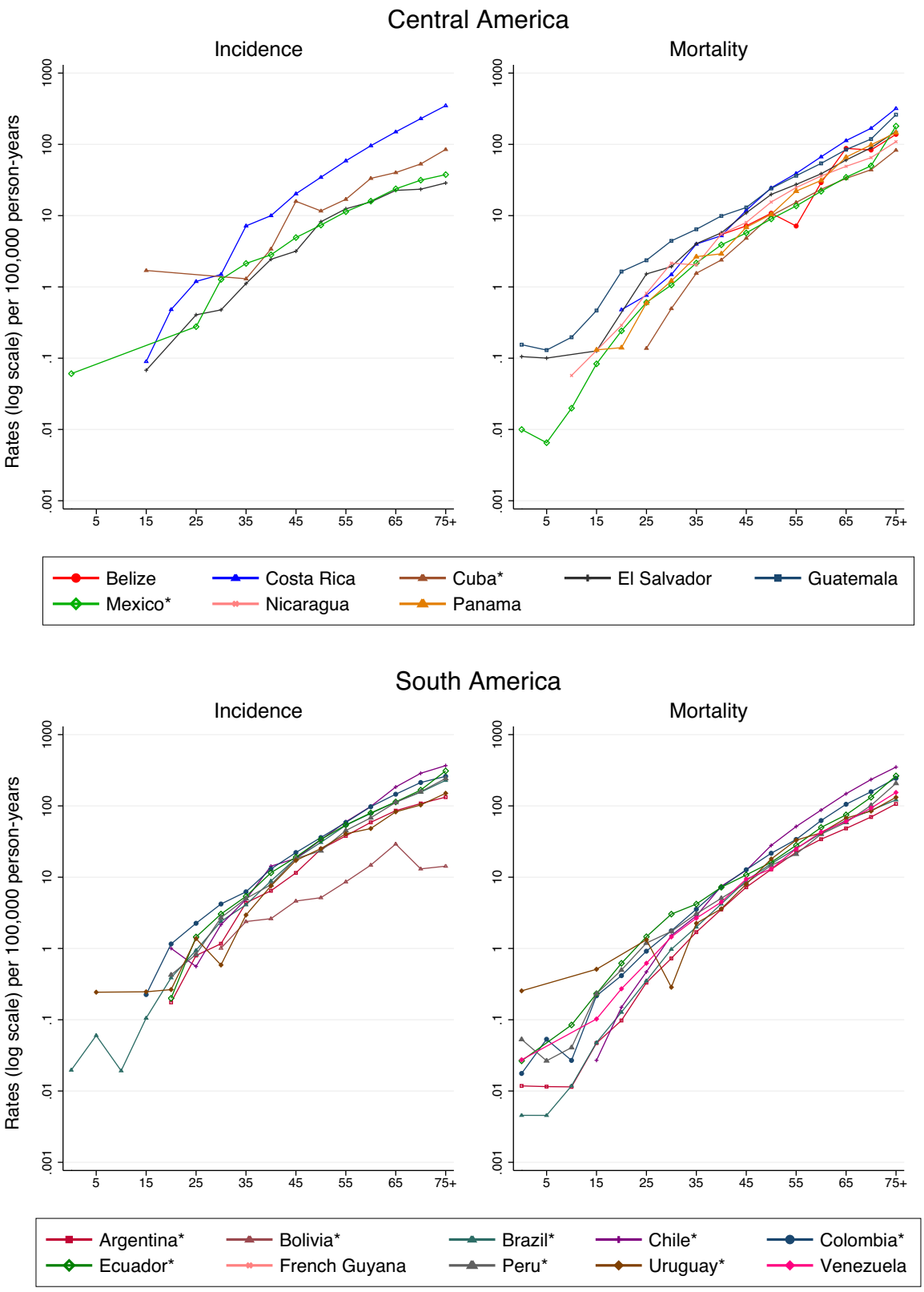
Incidence rates slowly increase after age 40–44 years and gradually increase with advanced age, reaching a peak around age $\geq$75 years (Figs. 1 and 2). Stomach cancer mortality rates followed a

Table 2
Age-standardized incidence and mortality rates (per 100,000) from stomach cancer in Central and South America, all ages.

Country (period)	Sex	Incidence						Mortality				
		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							38	5.5	9.8	1.6	3
	F							29	4.1	6.1		5
Costa Rica (2003–07)	M	2380	22.0	26.5	1.8	80	2	1866	17.1	20.1	2.1	1
	F	1512	14.4	15.0		80	2	995	9.4	9.4		2
Cuba[b] (2004–07)	M	206	12.6	8.0	2.0	67	7	1967	8.7	6.2	2.0	5
	F	119	7.4	4.0		60	11	1161	5.2	3.2		9
El Salvador[b] (1999–03)	M	369	2.8	3.7	1.8	86	1	1265	8.8	11.8	1.4	1
	F	252	1.8	2.0		88	2	1176	7.6	8.6		4
Guatemala (2003–07)	M							3234	10.4	17.4	1.0	1
	F							3636	11.2	17.1		1
Mexico[b] (2006–10)	M	643	3.8	4.6	1.5	100	5	14474	5.2	8.4	1.4	4
	F	482	2.7	3.0		100	11	12509	4.2	5.8		5
Nicaragua (2003–07)	M							726	5.4	9.3	1.6	2
	F							544	4.0	6.0		2
Panama (2003–07)	M							717	8.8	10.4	1.6	3
	F							494	6.2	6.4		3
South America												
Argentina[b] (2003–07)	M	1748	14.2	14.0	2.5	71	4	9564	10.1	8.7	2.6	4
	F	902	7.0	5.5		63	9	5088	5.2	3.3		7
Bolivia[b] (2011)	M	38	2.9	3.3	1.3	100	4					
	F	32	2.4	2.6		91	7					
Brazil[b] (2003–07)	M	8964	16.1	21.2	2.2	79	4	40343	8.8	10.5	2.4	3
	F	6065	9.8	9.7		78	7	21585	4.6	4.5		4
Chile[b] (2003–07)	M	623	26.6	29.1	2.8	82	3	10215	25.3	24.6	2.8	1
	F	262	11.8	10.3		78	6	5095	12.4	8.9		4
Colombia[b] (2003–07)	M	2028	22.4	25.3	2.0	85	2	13492	12.7	17.8	1.9	1
	F	1407	14.0	12.7		81	4	9072	8.3	9.3		4
Ecuador[b] (2003–07)	M	900	19.0	22.7	1.5	79	2	4262	12.7	15.8	1.4	1
	F	764	14.9	14.7		73	4	3406	10.2	11.2		1
French Guyana[b] (2003–08)	M	53	10.7	16.9	1.9	100	4					
	F	32	6.4	9.0		94	5					
Paraguay (2003–07)	M							716	4.8	7.1	1.7	3
	F							431	3.0	3.9		3
Peru[b] (2001–05)	M	1629	17.7	19.2	1.3	76	2	6110	9.1	12.4	1.0	1
	F	1492	15.5	15.1		71	3	6061	9.0	10.5		1
Suriname (2003–07)	M							49	3.9	5.0	1.4	4
	F							34	2.7	2.9		7
Uruguay (2005–07)	M	960	20.0	14.3	2.1	80	6	776	16.1	11.3	1.6	3
	F	648	12.6	6.7		77	9	487	9.4	4.5		5
Venezuela (2003–07)	M							5498	8.2	11.3	1.6	3
	F							3453	5.2	6.1		4

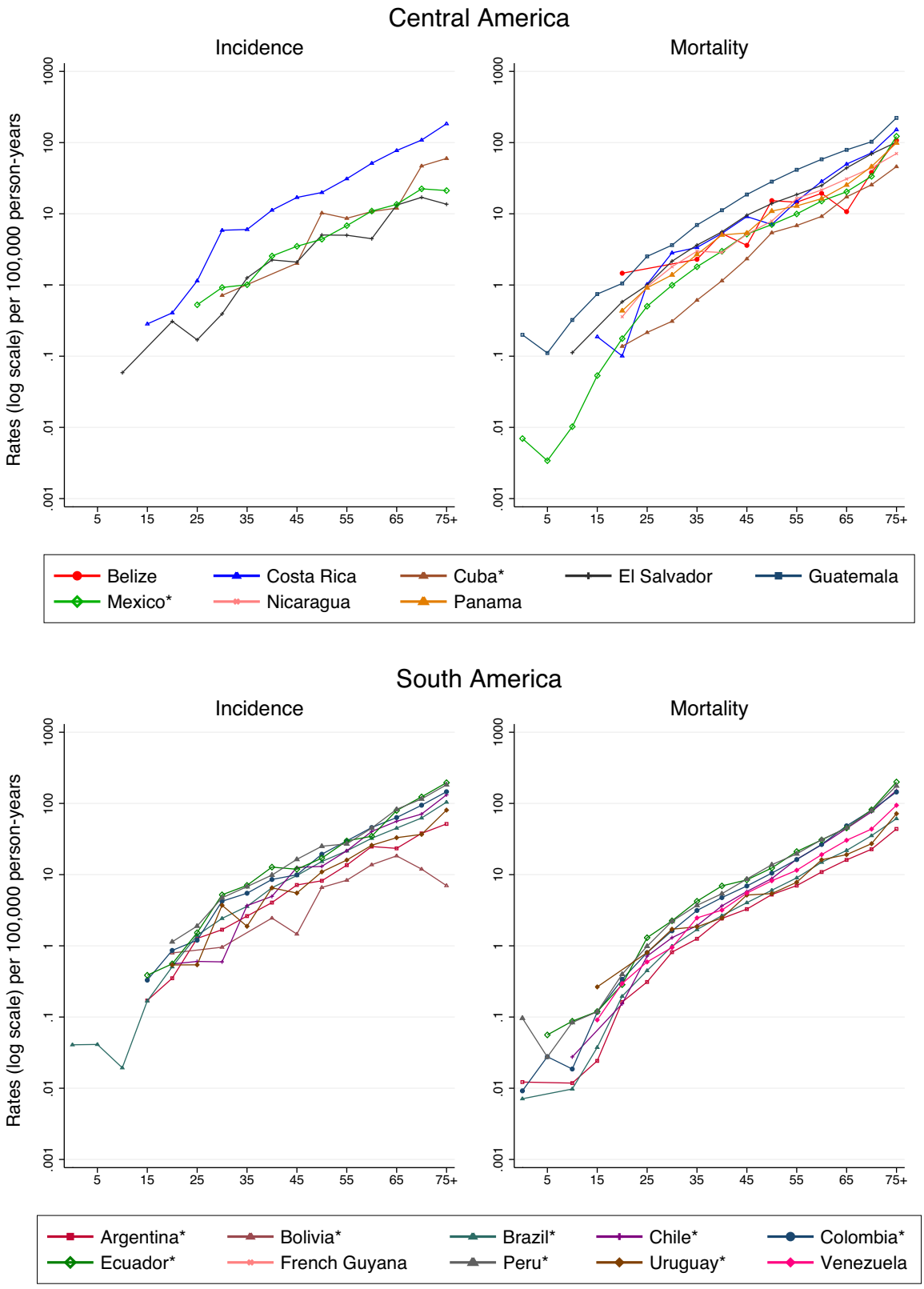
ASR (W), age-standardized (World population) rate per 100,000; M, males; F, females; M:F, male-to-female ratio (female, reference).
[a] Rank across cancer types, based on highest ASR excluding: all sites but C44 and all sites.
[b] Incidence rates were estimated using data from regional cancer registries.

similar pattern. Age-specific mortality rates began to increase after age 45 years in both sexes, followed by a sharp increase from ages 60–64 and 65–69 years, with the highest mortality rates observed among older age groups (Figs. 1 and 2). In general, incidence and mortality rates in males were higher than in females in most age groups, after the age of 35–39 years. The male-to-female (M:F) incidence and mortality ratios were 1:1 in young age groups (<40 years), then increased to 2–4:1 for ages 50–69 years, and then M:F ratios declined to about 2:1 after age 70+ years (Fig. 3).



*Incidence rates were estimated using aggregated data from regional cancer registries

Fig. 1. Male age-specific rates (per 100,000) of stomach cancer in Central and South America.



*Incidence rates were estimated using aggregated data from regional cancer registries

Fig. 2. Female age-specific rates (per 100,000) of stomach cancer in Central and South America.

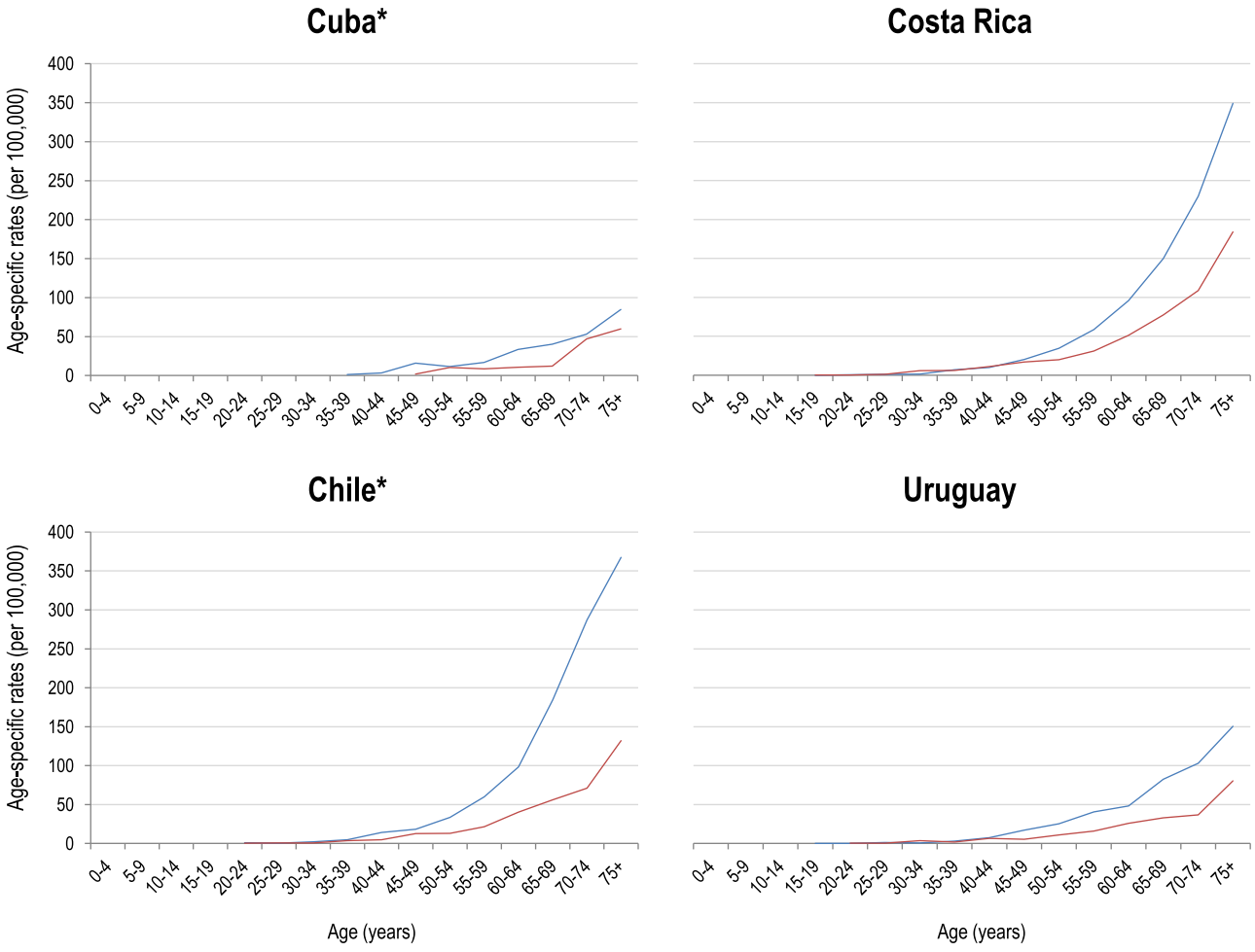


Fig. 3. Age-specific incidence rates (per 100,000) among males (blue) and females (red) for selected countries.

3.3. Time trends

In the four countries evaluated (Argentina, Brazil, Chile and Costa Rica), stomach cancer rates have been declining since the 1990s in both males and females (Fig. 4). In males, the incidence of stomach cancer declined, significantly, on average 3.9–4.4% per year in Costa Rica, Chile and Brazil for the period from 1997 to 2008; mortality rates declined on average 4.4% per year in Costa Rica and by 3.3% in Chile for the same time period (Fig. 5). Mortality rates among Argentinean males declined by 2% annually, although not significantly, whereas incidence rates remained constant. In females, the greatest declines in incidence and mortality for the period 1997–2008 were seen in Costa Rica (EAPC: −3.5% for incidence and EAPC: −4.6 for mortality) and Chile (EAPC: −3.4% for both incidence and mortality); rates also declined in Argentina and Brazil; however, the declines did not reach statistical significance (Fig. 5).

3.4. Distribution of gastric cancer cases by anatomic subsite

In the most recent 5-year period, about 80% of all the stomach cancer cases diagnosed in CSA were classified as other (C16.8–C16.9), ranging from 34 to 93% in males and 31–96% in females; 16% of the cases were classified as non-cardia gastric cancers (NCGC) and 5% were classified as cardia gastric cancers (CGC).

Table 3 shows the frequency distribution of CGC and NCGC in CSA. In general, NCGC was 2–7 times and 2–13 more frequently diagnosed in males and females, respectively, than CGC, except for males in Cuba, El Salvador, Chile, and Uruguay where a similar proportion of CGC and NCGC were diagnosed. In males, the proportion of CGC cases ranged from 12 to 58% (except in Mexico, 0%) and the proportion of NCGC cases ranged from 42% to 88% (except in Mexico, 100%). In females, the corresponding proportions for CGC and NCGC cancers were 7–40% (except in Mexico, 0%) and 60–93% (except in Mexico, 100%), respectively.

3.5. Distribution of gastric cancer cases by histology

Approximately 79% (range 65–80%) of all the stomach cancer cases diagnosed in CSA in the most recent 5-year period were classified as intestinal, diffuse, or other epithelial subtype, and about 21% (range 18–40%) corresponded to histology code 8000 (malignant tumor not otherwise specified) (data not shown). Table 4 shows the distribution of gastric cancers in CSA by histological type. The intestinal subtype was 2–7 times more common than the diffuse type. Approximately 50–80% of all the cases diagnosed in both sexes were of intestinal type, 8–35% were

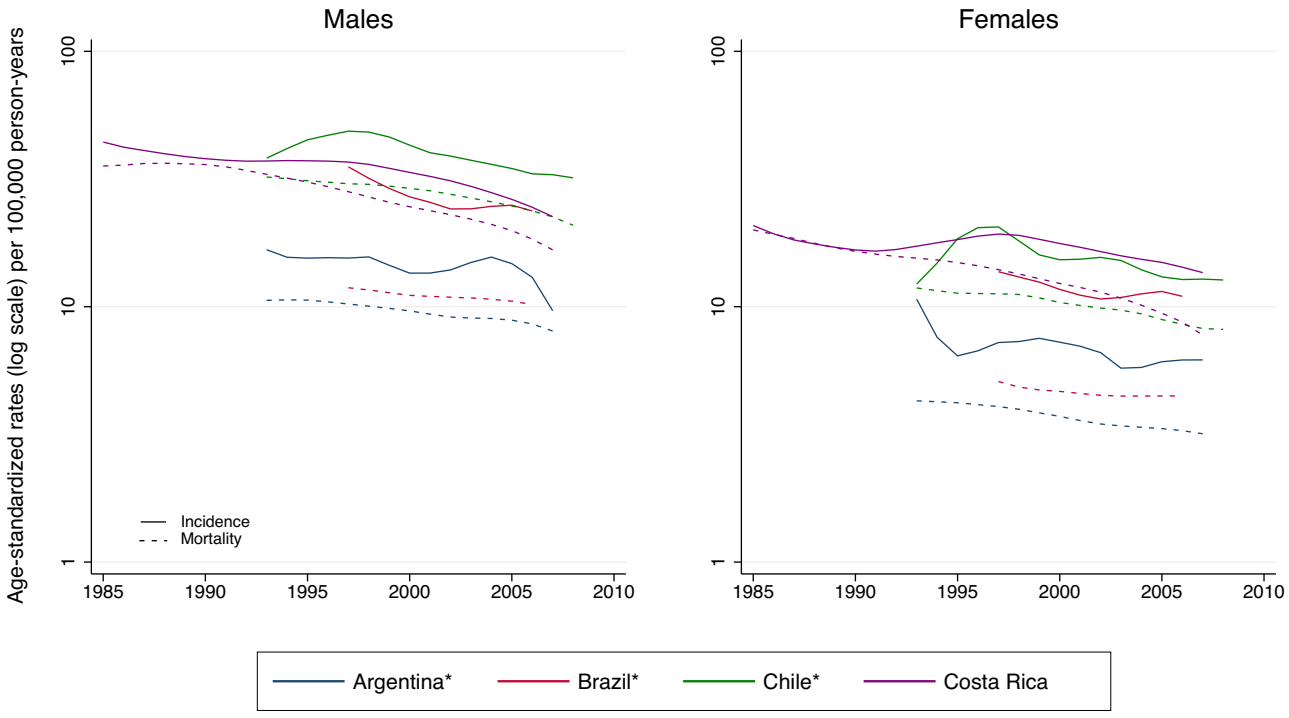


Fig. 4. Trends in cancer incidence and mortality from stomach cancer by sex, all ages.

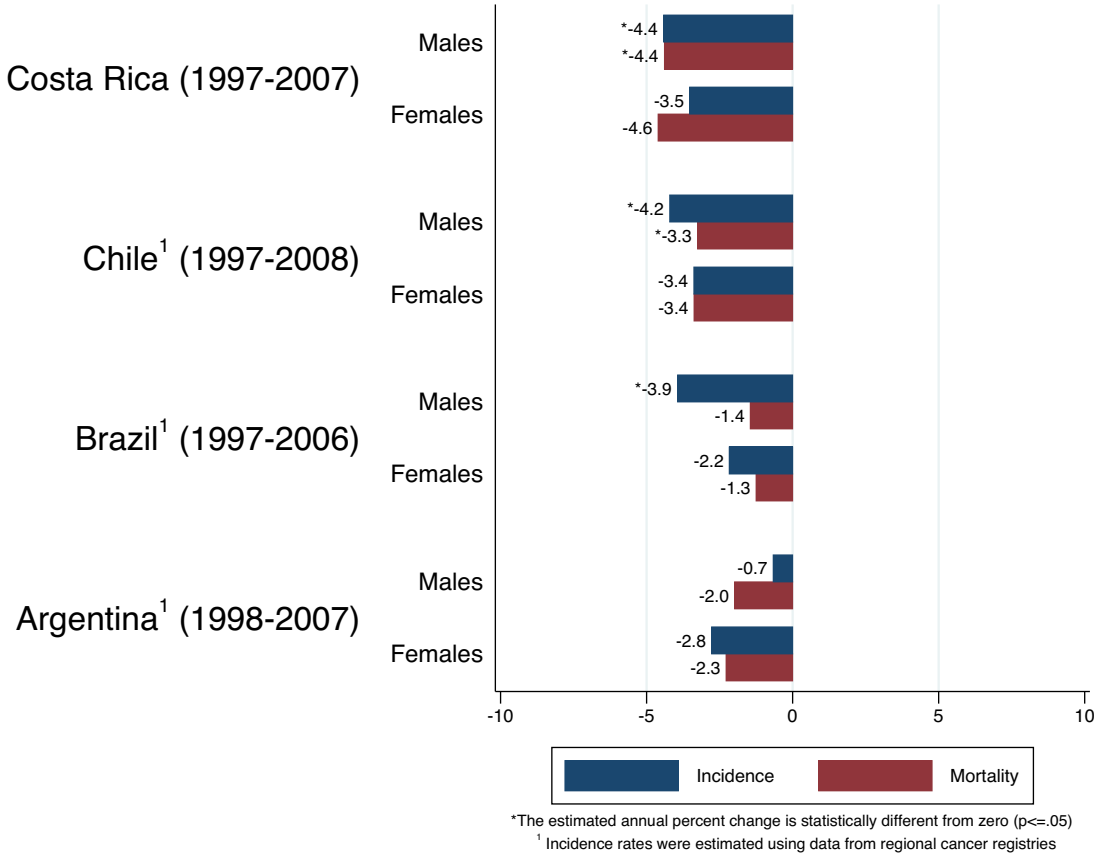


Fig. 5. Estimated annual percentage change in age-standardized incidence and mortality rates (per 100,000) of stomach cancer by sex.

Table 3
Distribution of cardia gastric cancers (CGCs) and non-cardia gastric cancers (NCGCs), by sex, in Central and South America.

Country (period)	Males			Females		
	CGC n(%)	NCGC n(%)	NCGC/CGC	CGC n(%)	NCGC n(%)	NCGC/CGC
Central America						
Costa Rica (2003–07)	182 (22)	659 (78)	4	54 (11)	447 (89)	8
Cuba† (2004–07)	8 (53)	7 (47)	1	2 (40)	3 (60)	2
El Salvador[a] (1999–03)	19 (58)	14 (42)	1	3 (14)	18 (86)	6
Mexico[a] (2005–10)	0 (0)	59 (100)	–	0 (0)	49 (100)	–
South America						
Argentina[a] (2003–07)	63 (28)	162 (72)	3	17 (16)	87 (84)	5
Bolivia[a] (2011)	4 (33)	8 (67)	2	3 (21)	11 (79)	4
Brazil[a] (2003–07)	525 (32)	1100 (68)	2	195 (20)	791 (80)	4
Chile[a] (2003–07)	47 (42)	66 (58)	1	13 (29)	32 (71)	2
Colombia[a] (2003–07)	198 (36)	350 (64)	2	76 (24)	245 (76)	3
Ecuador[a] (2003–07)	48 (17)	233 (83)	5	15 (7)	197 (93)	13
French Guyana[a] (2003–08)	5 (12)	36 (88)	7	2 (7)	25 (92)	13
Peru[a] (2001–05)	84 (16)	439 (84)	5	33 (8)	379 (92)	11
Uruguay (2005–07)	65 (53)	58 (47)	1	20 (35)	37 (65)	2

[a] Number of cases and percentages were estimated using aggregated data from regional cancer registries.

Table 4
Distribution of gastric cancers by histology in Central and South America.

	Males			Females		
	Intestinal n (%)	Diffuse n (%)	Other epithelial n (%)	Intestinal n (%)	Diffuse n (%)	Other epithelial n (%)
Central America						
Costa Rica (2003–2007)	1285 (54)	328 (14)	218 (9)	724 (48)	288 (19)	162 (11)
Cuba[a] (2004–2007)	115 (56)	0 (0)	8 (4)	60 (50)	1 (1)	4 (3)
El Salvador[a] (1999–2003)	234 (63)	56 (15)	13 (4)	156 (62)	50 (20)	6 (2)
Mexico[a] (2005–2010)	521 (67)	193 (25)	44 (6)	367 (62)	170 (29)	39 (7)
South America						
Argentina[a] (2003–2007)	999 (57)	241 (14)	104 (6)	435 (48)	136 (15)	61 (7)
Bolivia[a] (2011)	30 (79)	7 (18)	1 (3)	23 (72)	5 (16)	0 (0)
Brazil[a] (2003–2007)	5566 (62)	935 (10)	676 (8)	3456 (57)	863 (14)	467 (8)
Chile[a] (2003–2007)	336 (54)	85 (14)	82 (13)	126 (48)	54 (21)	23 (9)
Colombia[a] (2003–2007)	1248 (62)	350 (17)	56 (3)	739 (53)	317 (23)	34 (2)
Ecuador[a] (2003–2007)	513 (57)	180 (20)	12 (1)	387 (51)	161 (21)	2 (0)
French Guyana[a] (2003–2008)	33 (51)	23 (35)	6 (9)	16 (42)	12 (32)	6 (16)
Peru[a] (2001–2005)	765 (47)	340 (21)	131 (8)	554 (37)	397 (27)	97 (7)
Uruguay (2005–2007)	591 (62)	77 (8)	90 (9)	330 (51)	99 (15)	42 (6)

[a] Number of cases and percentages were estimated using aggregated data from regional cancer registries.

of diffuse type (except in Cuba, 0–1% diffuse type cases), and 0–13% were of other or epithelial type. Male-to-female ratios were 1–3:1 for intestinal type, 1–2:1 for diffuse type, and 1–6:1 for epithelial type.

4. Discussion

In this study we aimed to describe the current burden of stomach cancer in CSA. Stomach cancer continues to be one of the five leading causes of cancer diagnosis and cancer death in both males and females in most countries within the region. There was a remarkable variation in stomach cancer incidence and mortality rates across CSA (6-fold and 5–6-fold, respectively). Overall, males had incidence and mortality rates 1.3–2.8 times higher than those in females. The high incidence rates observed in Chile (males), Costa Rica, Colombia, Ecuador, Brazil (males) and Peru (females) were lower than the incidence rates reported in other regions of the world where the burden of stomach cancer remains very high, such as China (ASRs: 45–68 for 2003–2007), yet these rates were up to 3 times higher than the rates reported for Hispanics in the US (9.4 for males and 5.9 for females) [6].

Mortality rates of stomach cancer in CSA were among the highest in the world. Chilean males had the fourth highest mortality rates in the world for the period 2003–2007, following the Republic of Korea, the Russian Federation and Kazakhstan (ASMRs: 24.8–27.7) [29]. Guatemalan females had the highest mortality rates in the world between 2003 and 2007. Females in Ecuador, Peru, Colombia, and Costa Rica also had some of the highest mortality rates in the world, ranking third, sixth, seventh, and tenth, respectively [29]. The low mortality rates observed in Paraguay, Argentina, Cuba and Suriname were about twice as high as the mortality rates in the US (3.8 for males and 1.6 for females for the period 2003–2007) [29]. The extremely high mortality rates in CSA may reflect poor access to healthcare. A study from Chile showed that most stomach cancer cases are diagnosed late (12% identified via death certifications, 20% at an inoperable stage) and

only 6% were diagnosed early (stages I or II). These percentages were much lower that the proportion of cases diagnosed early in other regions (i.e. 37% in Florence, Italy and 31% in China) [39].

The incidence of stomach cancer observed in both males and females in CSA in the most recent 5-year period was lower than the incidence rates previously reported for Brazil, Colombia, Costa Rica, Ecuador, and Peru for earlier time periods (1998–2002) [1,40,41]. The observed mortality patterns of stomach cancer for both sexes were generally consistent with those in recent reports [24,42]; however, the observed rates were lower when compared with mortality rates from earlier periods (i.e. 1990s) [40,43,44]. The declines in the incidence and mortality of stomach cancer observed in Argentina, Brazil, Chile and Costa Rica in 1997–2008 coincide with declines in stomach cancer reported in other CSA regions in the last few decades [1,2,12,22–28] which may in part be explained by declines in the prevalence of *H. pylori* infection and by improvements in sanitation and in the preservation and storage of foods [1,2,8,10,11,45]. Death certifications for gastric cancer are "sufficiently reliable" particularly among those below 65 years of age [12,26,43]; thus the observed changes in mortality trends may not be impacted by the validity of death certifications [26].

It has been reported that Hispanics in the US are more frequently diagnosed with stomach cancer at younger ages (<50 years) than any other ethnic group (21% versus 7–16%) [46,47]. In the most recent 5-year period, a comparable proportion of cases were diagnosed in younger men in Bolivia and Mexico (19–21%) and in younger women in French Guyana, El Salvador, Mexico, and Costa Rica (20–25% diagnosed in young women); however, in most CSA countries the vast majority of the stomach cancer cases (80–97%) were diagnosed in older populations (≥50 years). Recent data from CI5 showed an age-specific incidence pattern across different ethnic groups in the US that is similar to the one described in the present report. Although Hispanics, Blacks and Asian-Pacific Islanders had higher stomach cancer rates than non-Hispanic Whites and Whites, stomach cancer was relatively rare in males and females under 45 years of age; incidence rates slowly increased with age and attained the highest rates at ages of 60 years and above [4].

Despite the geographic variation in stomach cancer rates, incidence and mortality rates were higher in males than females in most age groups after the age of 35–39 years. The general age-specific pattern of the M:F ratios was from low-to-high-to-low, which is consistent with other reports [9,48,49]. The widest gap between sexes was observed between the ages of 50 and 69 years (M:F incidence and mortality ratios of about 2–4:1). Although the reasons for the sex disparities in stomach cancer risk are unclear, it has been suggested that female sex-specific hormones may play a protective role [50]. The sex difference may also reflect the lag in age at intestinal type adenocarcinoma onset in females as compared to males [51].

Only a few established factors are known to increase the risk of stomach cancer; these include age, sex, family history of the disease, radiation, *H. pylori* infection and smoking [5,52]. Despite the high relative risk, family history and radiation may explain only a small proportion of the cases observed in CSA given their low prevalence in the general population [5,8].

Infection with *H. pylori*, a major determinant of stomach cancer, probably contributed to the high rates of stomach cancer observed in CSA [17,18]. The prevalence of *H. pylori* infection varies widely between and within countries and differs by age, race/ethnicity, migration from high-prevalence areas, and by indicators of low socioeconomic status (crowding, education level, lack of proper sanitation and safe drinking water, and poor diets) [53,54]. In South America, for example, the prevalence of *H. pylori* infection among adults ranges from 50% to 95% (50–90% in the developing world) [19–21].

It is possible that tobacco smoking contributed to some extent to the geographic variation in stomach cancer rates across CSA, and may partially explain the observed disparity in cancer rates between males and females [30,55]; however, Freedman et al. [56] suggested that the high rates of upper gastrointestinal cancers among males could not be explained by differences in smoking history. It has been estimated that approximately 10% (or more) of the stomach cancer deaths in parts of Latin America, the Western Pacific and Eastern Europe were due to smoking [57]. In Latin America (including the Caribbean), tobacco smoking has increased over the last few decades, particularly among females [58]. In CSA, the prevalence of any tobacco smoking in 2011 among males ranged between 20% (in Guatemala) and 44% (in Chile) and among females from 2% (in Guatemala and Belize) to 38% (in Chile) [59]. Moreover, smoking has been shown to "potentiate the carcinogenic effect of infection with cagA-positive *H. pylori*" [5].

Although we were unable to estimate the incidence of stomach cancer by anatomic location or histological type due to the large percentage of unspecified cases, we observed that NCGCs were 2–13 times more frequently diagnosed in most CSA countries than CGCs in both sexes. The consistent observation was the male predominance of any anatomic subtype as compared to females. Additionally, the distribution of NCGC was the highest in countries where the incidence of stomach cancer was also the highest, such as Chile, Costa Rica, Colombia, Ecuador, Brazil, and Peru. Given the high prevalence of *H. pylori* in CSA and the strong association between *H. pylori* and NCGC [60], we expected to see a higher proportion of incident NCGC cases than CGCs. Similarly, a high proportion of NCGC cases was reported in four Central American countries as well as Hispanics in the US, and Hispanics born in Central America (80–86%) [38]. Our observations were consistent with previous studies as well [12,17].

We also noted that intestinal subtype was the most frequent histological classification in CSA (representing about 50–80% of the total), being 2–7 times more common than the diffuse type in both sexes. Similarly, Corral et al. [38] reported that in four Central American countries 64% of the stomach cancer cases were of the intestinal subtype; in contrast, only 31% of cases diagnosed among Hispanics in the US were of the intestinal subtype. Both intestinal and diffuse types are also related to *H. pylori* infection [21]. Declines in the incidence of intestinal type and diffuse type have been reported in the US in recent years, which is consistent with the declines in *H. pylori* infection [61].

Limited evidence from intervention studies suggests that eradication of *H. pylori* infection may reduce the risk of developing gastric cancer [62,63]. *H. pylori* resistance to different antibiotics is a major concern in CSA given the widespread use of antibiotics in the region [64,65]. Currently, there are no national screening programs for the prevention of gastric cancer in CSA [66]. In 2006, the Chilean Ministry of Health initiated an opportunistic national screening program for gastric cancer, offering endoscopic examination to patients older than 40 years with dyspeptic symptoms and with an immediate family member with history of gastric cancer; *H. pylori* eradication therapy is recommended in any patient undergoing endoscopy with duodenal or stomach ulcers, atrophic gastritis, lymphoma, adenoma, gastric cancer, and family history of gastric cancer [66]. Two studies conducted in Costa Rica and Venezuela using x-rays for screening yielded contradictory results on its impact in reducing stomach cancer mortality [67,68]. The intervention study conducted in Cartago, Costa Rica, during 1998–2000 showed a reduction in gastric cancer mortality of about 50%, but the high cost of this intervention is an obstacle for its implementation on a larger scale [67]. In contrast, a case–control study of gastric cancer screening using X-rays conducted in Tachira, Venezuela, in 1980, revealed no changes in stomach cancer mortality [68].

Other factors possibly associated with an increased risk of stomach cancer are: alcohol consumption [30,69–71], salt and salt-preserved foods [30,72], consumption of processed meat [30,73], obesity [72,74–77], attained height [16,78–81], Epstein–Barr virus (EBV) [8,30,60,82], and pernicious anemia [8]. In contrast, factors probably inversely associated with stomach cancer are: non-starchy vegetables (allium vegetables) and fruits [72], increased physical activity [83] and non-steroidal anti-inflammatory drug use, including aspirin [30,82,84–86]. Moreover, diet, smoking and alcohol are related to NCGC, whereas obesity, gastroesophageal reflux, and Barrett's esophagus are associated with CGC [14–16]. However, the extent to which these factors contributed to the observed variation in stomach cancer rates in CSA remains uncertain.

The present study has several strengths and limitations. We used the most up-to-date available data to present a comprehensive description of the burden of stomach cancer in 13CSA countries (48 cancer registries), more than the data published in the latest volume of CI5 (eight countries, 22 cancer registries) [6] and national mortality data from 18 countries. However, our results should be interpreted with caution because in most countries cancer incidence data are represented by aggregated data from regional registries which do not cover the entire country (except for Costa Rica and Uruguay). Registrations may also differ in completeness and data quality due to the age and development in maturity of the registries, and this could explain the strikingly low incidence rates observed in Bolivia and El Salvador. We did not estimate incidence rates by anatomic site because the rates would have been underestimated due to the large percentage of cases (60–96% of the total) classified as unspecified (C16.9). Similarly, we did not estimate the incidence rates by histological type given that 18–40% of cases had histology code M8000, malignant tumor not otherwise specified. Disparities in the classification of tumors in the gastroesophageal region have been described in Sweden, a country with a high-quality cancer registry, because of the difficulty in distinguishing between whether the tumor originated from the gastric cardia or the esophagus [87], and such disparities in disease classification may bias the estimation of rates [88]. While the difficulties in classifying some of these tumors may persist, particularly by anatomic site, improvements in stomach cancer registrations of both histological type and anatomic sites in CSA are needed in order to minimize missing or incomplete data.

5. Conclusion

Stomach cancer is one of the most frequently diagnosed cancers and among the leading causes of cancer death in both males and females in several countries of CSA, after prostate, breast, cervix, colorectum and lung cancers. Stomach cancer rates varied widely across CSA (6-fold for incidence and 5–6-fold for mortality) and males had up to 3 times higher incidence and mortality rates than females. The highest incidence of stomach cancer was seen in Chile (males), Costa Rica, Colombia, Ecuador, Brazil (males) and Peru (females). Mortality rates in CSA were among the highest in the world, particularly among Guatemalan females (ranking first) and Chilean males (ranking fourth). From 1997 to 2008, incidence declined by about 4% per year in Brazil, Chile and Costa Rica in 1997–2008, and mortality declined by about 3–4% in Costa Rica and Chile, although statistically significant declines were seen for males but not for females. According to the anatomic site, NCGC were 2–13 times more frequently diagnosed in CSA than CGC. According to histological definition, 50–80% of the cases were of intestinal subtype, and this subtype was 2–7 times more common than diffuse type in both sexes. The overall geographic and temporal variation of stomach cancer rates observed in CSA may in part be explained by differences in the prevalence of *H. pylori* infection and by improvements in sanitation and the preservation and storage of foods. Smoking patterns could also explain some of the geographic variations and sex disparities. However, the extent to which other presumed factors contributed to the observed variation in stomach cancer rates in CSA remains uncertain. The extremely high mortality of stomach cancer may reflect deficiencies in access to healthcare in CSA and highlights the need to focus efforts on the prevention and management of this disease.

The large percentage of stomach cancer cases classified as unspecified (60–96% for anatomic site and 18–40% for histological subtype) highlights the need to improve cancer registration processes for both histological type and anatomic sites in CSA in order to minimize missing or incomplete data, allowing an understanding of the descriptive epidemiology of stomach cancers in more detail.

Conflicts of interest

None.

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Authors contribution

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

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