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Gastric Cancer: Frequency and Trends

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A continued international decline in gastric cancer mortality is one of the most remarkable events in cancer epidemiology. This "unplanned triumph", however, is characterized by geographical differences in cancer frequency and trends, both between and within countries. The declining incidence of gastric carcinoma could be explained primarily by the decrease in the relative number of intestinal type cases, and the cancers of the cardia show increasing or stable trends.
The understanding of the site and histological type specific trends in each region, overcoming the methodological difficulties and the gaps in our knowledge of cancer aetiology, are essential to predict the future burden of gastric cancer.
Key-words: stomach neoplasms; cardia; histological type; trends.

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INTRODUCTION

A continued international decline in gastric cancer mortality is one of the most remarkable events in cancer epidemiology. It was first reported in the United States, with a decrease of 60% in white males and 72.1% in white females from 1930 to 1961 (1). By the 1950s this was experienced in all continents (Figure 1), although departure values, rates of decline, and the inflection points differed considerably across countries (2-5).

Mexico (6) may be an exception, although our interpretation of such trends is impaired by the scarcity and known limitations of frequency data in many American, African and Asian countries (7).

Despite the long lasting decreasing trend in gastric cancer incidence and mortality, the overall number of incident cases is increasing, and gastric cancer remains one of the most frequent malignancies worldwide, with 930,000 new cases and 700,000 deaths estimated for 2002 (7).

The age-standardised incidence rates of stomach cancer are on average twice as high in males compared to females, with ratios close to 1 in younger subjects, approaching 3 at the age of 60, and 1.5 to 2 in older age groups (8).

Gastric cancer frequency and its relative weight on the overall burden of malignant diseases differ considerably across geographical regions, being more frequent in Eastern and Southern Europe, South and Central America and in Eastern Asia (Table 1).

Gastric cancer incidence ranks fourth among males and fifth among females in developed countries, while it ranks second and third in developing countries, respectively. It is the third cause of cancer mortality in developing nations, and fourth in developed countries (Figure 2), being proportionally more frequent in the developing regions, where two thirds of the incident cases occur (7).

FREQUENCY AND TRENDS BY CANCER LOCATION

Despite the overall decline in stomach cancer frequency, most reports (9-25) showed increasing or stable trends in cardia cancers. Evidence of a decrease in cardia cancer frequency along the years is not so abundant (26-31). However, there is an ample opportunity for estimates of subsite-specific rates to be biased due to changes in tumour classification, variability in reporting subsites of origin, improvements in histological ascertainment and degree of accuracy in morphological diagnoses. The estimated trends and area-level differences must therefore be interpreted with caution.

Until the late 1980s, relatively little emphasis was placed on the distinction between cardia and distal gastric cancer, and the former was coded separately from other gastric cancers only after the 8th revision of the Interna-

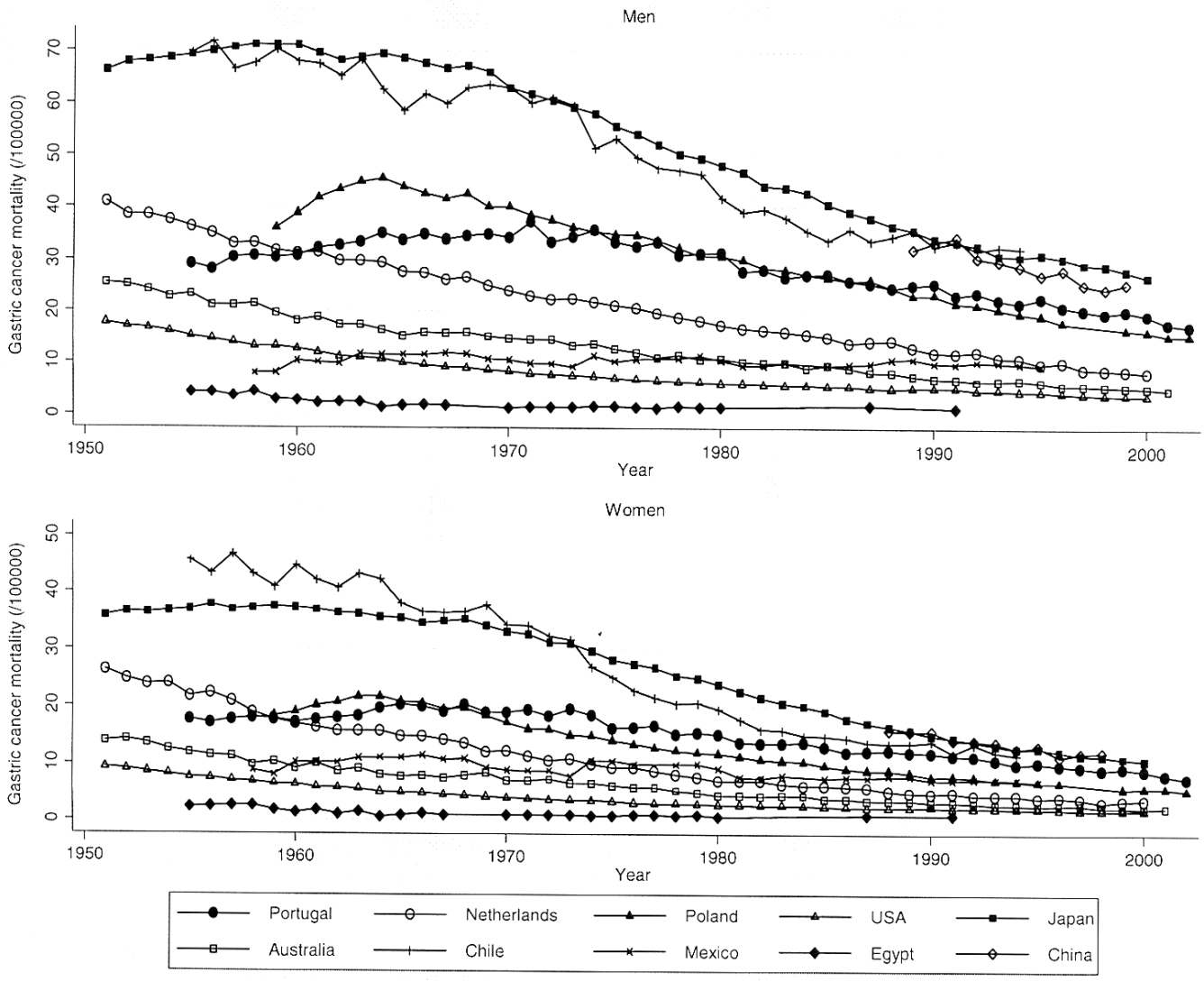

Fig. 1 - Trends in gastric cancer mortality, in men (top) and women (bottom), in selected countries (age-standardised mortality rates - world reference population).
Data source: World Health Statistics (5).

tional Classification of Diseases (32). To date there is still no consensus on the definition of the cardia area (33). These factors contribute to an incorrect classification of tumors, and the growing awareness of cardia cancer aetiological and clinical specificities may further contribute to its increasing misclassification.

In a Swedish population, Ekstrom et al. (32) uniformly classified all patients with newly diagnosed gastric adenocarcinoma (from 1989 through 1994) with respect to gastric subsite, and used this patient group as a gold standard. The completeness of the Swedish Cancer Registry in registering gastric adenocarcinomas, the completeness of cardia cancer registration and the rate of falsely included cases were evaluated to estimate the potential impact on observed incidence trends. The overall completeness of gastric cancer registration was 98%, but accuracy in registering cardia tumors was surprisingly low (the completeness of coding cardia cancer was only 69%, and the positive predictive value for cardia cancer was 82%, with no improvement over time). The authors estimated that the true cardia cancer incidence could be up to 45% higher or 15% lower than the reported in the Cancer Registry. This margin of error could accommodate the observed increase in cardia cancer in Sweden, bringing forward the need for caution in the interpretation of secular trends in cardia cancer incidence.

One American study estimated that if the unspecified gastric tumors were distributed anatomically in proportion to the relative frequencies of adenocarcinoma by known subsite, about one fourth of the observed increase in the incidence of gastric cardia cancer in the period 1976-1987 would have resulted from more specific diagnoses

Table 1 - **Cancer incidence estimated for 2002 (7).**

	Age-standardised rates, all ages (world reference population)			
	Stomach cancer incidence/100,000		Cancer (all sites but skin) incidence/100,000	
Region	**Men**	**Women**	**Men**	**Women**
Africa				
Eastern	7.4	5.5	158.7	156.7
Middle	13.4	12.6	141.9	121.5
Northern	4.4	2.5	99.0	85.2
Southern	8.2	3.7	213.7	163.2
Western	3.4	3.6	90.0	104.4
America				
Central	15.2	10.8	146.1	153.3
South	24.2	12.2	216.4	191.6
Northern	7.4	3.4	398.4	305.1
Asia				
Eastern	46.1	20.6	219.4	136.8
South-Eastern	8.5	4.5	130.4	120.9
South-Central	6.8	3.5	105.6	110.3
Western	11.6	6.4	149.5	125.7
Europe				
Eastern	29.6	12.8	257.7	175.1
Northern	12.4	5.9	283.1	252.3
Southern	18.0	8.7	299.4	208.1
Western	12.8	6.6	326.4	244.6
Australia/New Zealand	9.9	4.2	349.7	280.3

(19). A more recent study, also from the USA, showed a decrease in the proportion of all gastric cancers without a designated location from 38% in 1974-1976 to 17% in 1996-1998 (34), an observation compatible with the hypothesis that a substantial proportion of the recent purported increase in cardia cancer incidence is due to improvements in site classification of gastric carcinomas.

Incidence data published in Cancer Incidence in Five Continents VII, concerning observations in a single moment, shows substantial differences in cumulative cardia cancer rates according to gender and across countries, different ethnicities within the same country, and within the same ethnicity residing in different countries (35). Gender, ethnic (36), and regional (37) differences in cardia cancer incidence were also observed inside the USA.

Extending this analysis using data from the latest edition of Cancer Incidence in Five Continents (27), a wide intercountry variation in cardia cancer incidence is also observed in settings with similar overall gastric cancer incidence, both in males and females, although cardia cancer is proportionally more frequent in males. The incidence ratio antrum-pylorus/cardia cancer correlates positively with overall stomach cancer incidence (men: $r=0.60$, $p<0.001$; women: $r=0.52$; $p<0.001$), and negatively with oesophageal adenocarcinoma incidence (men: $r= -0.68$, $p<0.001$; women: $r= -0.61$; $p<0.001$) (Figure 3).

The higher relative frequency of cardia cancer, when the overall gastric cancer incidence is lower and when adenocarcinoma of the oesophagus is more frequent, may be explained by a specific association of cardia cancer with environmental factors different from those that drive the generalized gastric cancer decline, and eventually closer to those associated with the occurrence of oesophageal adenocarcinoma. These observations may also reflect that proximal tumours of the stomach and oesophageal adenocarcinomas are more likely to be classified as gastric cardia when the frequency of oesophageal adenocarcinoma is higher.

The large number of unspecified gastric tumours in many population-based cancer registries (27), and the many possibilities of misclassification of cancer location preclude a sound interpretation of trends in the frequency

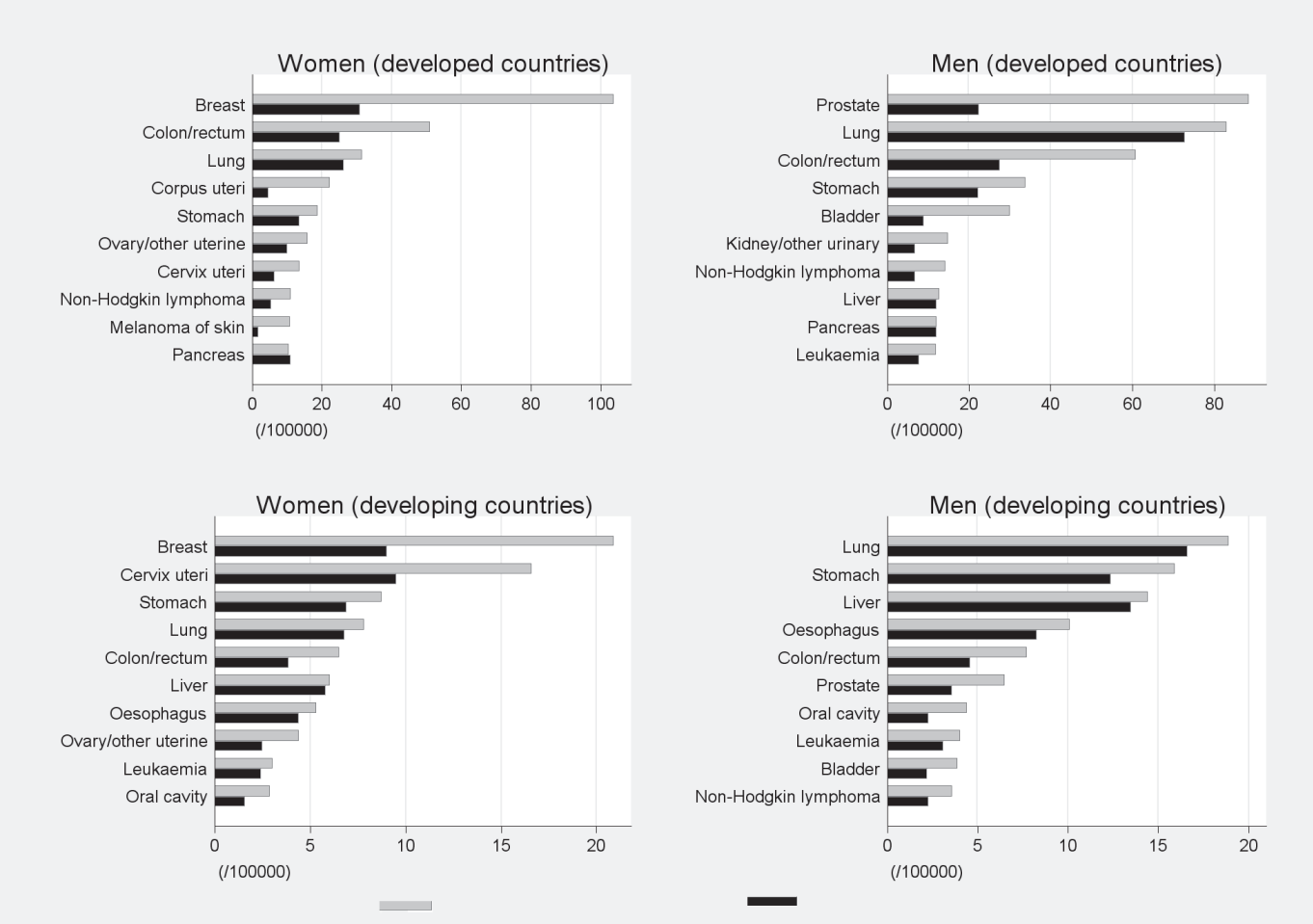

Fig. 2 - The 10 most frequent cancers in developed and developing countries in 2002. Data Source: GLOBOCAN 2002 (7).

of cancer of the cardia, and further work is needed to clarify location-specific time trends in gastric cancer. The evaluation of risk factor profiles for cardia versus distal gastric carcinomas may further clarify the biological differences between these sites.

FREQUENCY AND TRENDS BY HISTOLOGICAL TYPE

Laurén's classification of gastric carcinoma (38) has been shown to have prognostic value (39-41), and is the most frequently used in epidemiologic studies on stomach cancer aetiology (42-45). The intestinal type carcinoma is more frequent in elderly males, whereas the diffuse type tends to occur in younger individuals, mainly females (25,32,33). The intestinal type is more frequently observed in high-risk areas, also showing a wide inter-country variation in the intestinal/diffuse ratio, both in high- and low-risk areas and among regions with similar overall frequency of gastric cancer (45). Several case series and incidence studies supported the hypothesis that the declining incidence of gastric carcinoma could be explained primarily by the decrease in the number of intestinal type cases (10,13,45-47). Other studies observed parallel declines of both histological types (15,48,49). Ekstrom et al. (44) found no evidence of time decreasing ratios between the intestinal and diffuse types, in a study with a high proportion of specimens classified histologically and where a stratified analysis for tumour site was performed.

A matter of concern in time-trend studies is the fact that a less than optimal number of gastric cancers have a histological diagnosis, especially in the older age-groups, and as well the proportion of the histologically confirmed cases of gastric carcinoma has increased throughout the years (26,27,45,48,49). Histopathologic diagnosis has become more common with the increasing possibilities of surgical treatment of older patients, and with the possibility of obtaining gastric biopsies in subjects that are not considered for surgery. In the Portuguese cancer registry of Vila Nova de Gaia the proportion of stomach cancer cases with histological verification increased from 64% in males and 57% in Females 1983-1987 (49) to 82% and 71%, respectively, in 1993-1997 (27).

Differences in the interpretation of Laurén's classification must be considered when comparing frequencies. The omission of the group "unclassified" or the addition of one or more categories are common deviations from Laurén's original description (38), and other classifica-

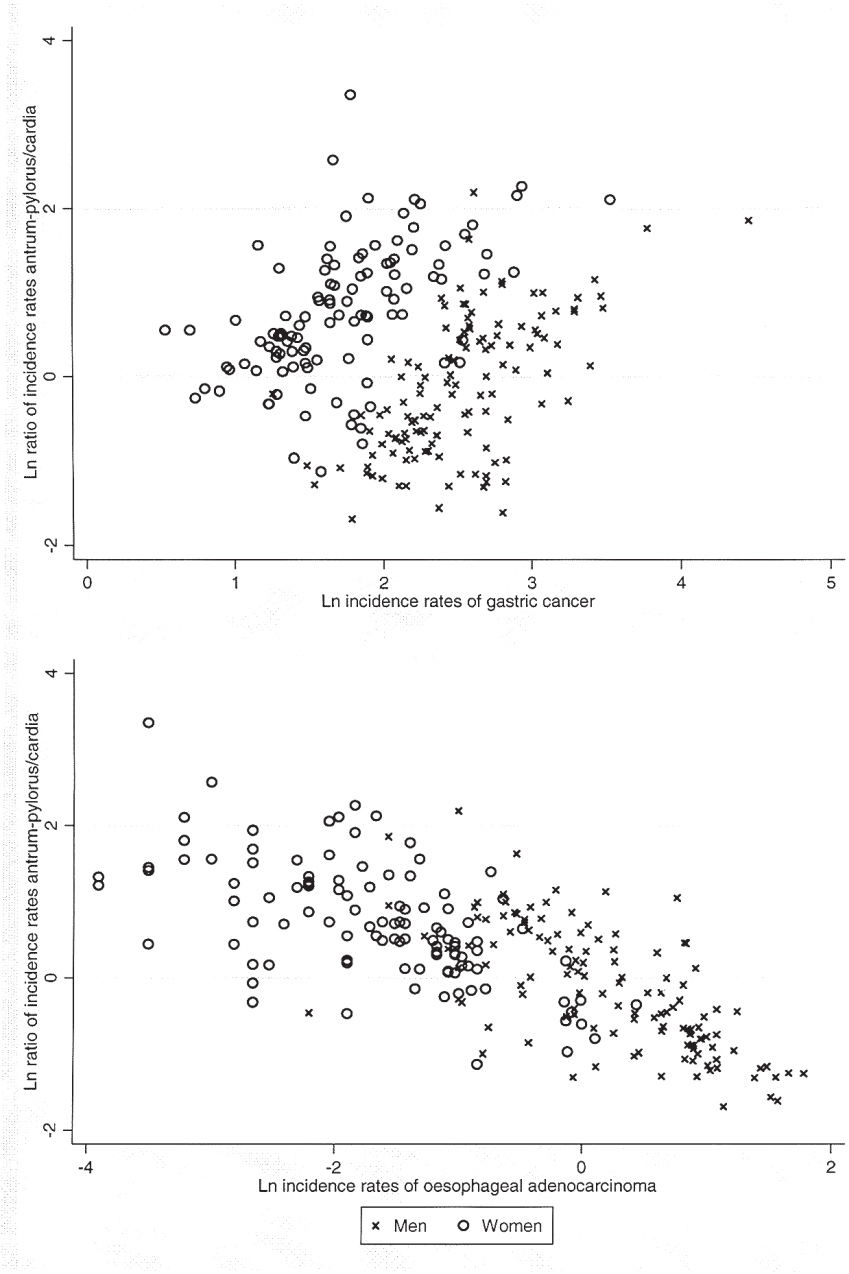

Fig. 3 - Scatterplots for the ratio of age-standardised (world population) incidence rates of antrum-pylorus/cardia cancer vs. age-standardised (world population) incidence rates of gastric cancer (top) or oesophageal adenocarcinoma (bottom).
Data Source: Cancer Incidence in Five Continents, Vol. VIII (27); cancer registries with less than 100 cases of gastric cancer were excluded.

tions have also been inserted into Laurén's (45). It is difficult to estimate the effect of these inaccuracies on the final proportion of the histological types.

The age distribution of the two main Laurén types of gastric carcinoma, their geographic distribution, and the selective decrease in incidence in those who migrate from high to low risk areas (38,45,50), has been taken as evidence of a relatively greater impact of environmental factors on the aetiology of intestinal type carcinoma. Correa et al. (9) proposed the intestinal type as an "epidemic type" of carcinoma, considering multiple sequential changes of the gastric mucosa preceding invasive neoplasia, dependent on environmental factors, and the diffuse type, more related to constitutional factors, proportionally less frequent in the low-risk populations, not preceeded by the above histomorphological changes. The genetic and epigenetic changes found in gastric carcinoma depend on its histological type, indicating different genetic pathways for the intestinal and diffuse types (51).

The association of distinct gastric cancer histological types with specific environmental factors may be expected, and may further contribute to understand its geographical distribution and trends.

CONCLUSION

Gastric cancer remains one of the most frequent causes of cancer and cancer mortality in the world, with a large heterogeneity in the population dynamics of the different nosological entities jointly designated as gastric cancer. The understanding of the site and histological-type specific trends in each region, overcoming the methodological difficulties and the gaps in our knowledge of cancer aetiology, are essential to predict the future burden of gastric cancer.

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