

# Model-based patterns in stomach cancer mortality worldwide

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The decrease in stomach cancer mortality was not because of specific interventions, and is likely that different countries follow a similar model of variation. Here, we aimed to identify model-based patterns in the time trends of stomach cancer mortality worldwide. Stomach cancer mortality rates were retrieved for 62 countries from the WHO mortality database. Sex-specific mixed models were used to describe time trends in age-standardized rates between 1980 and 2010 (age group 35–74 years; World standard population). Three patterns, similar for men and women, were identified through model-based clustering. Pattern 1 presented the highest mortality rates in 1980 (median: men, 81.5/100 000; women, 34.4/100 000) and pattern 3 the lowest ones (median: men, 24.4/100 000; women, 12.4/100 000). The decrease in mortality rates was greater in 1980–1995 than during 1996–2010. Assuming that the patterns characterized by the highest rates precede temporally those with lower mortality, the overlap of model predictions supports a 20-year lag between adjacent patterns. We propose a model for the variation

in stomach cancer mortality with three stages that develop sequentially through a period of ~70 years. The countries with the lowest mortality had the highest proportional decrease in mortality rates. *European Journal of Cancer Prevention* 23:524–531 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Stomach cancer mortality has been decreasing worldwide over the last decades (Levi *et al.*, 2004; Bertuccio *et al.*, 2009), although with heterogeneous country-specific trends (Bertuccio *et al.*, 2009). Gastric cancer is no longer among the most frequent cancers in Northern Europe, but in Eastern and in several Southern European countries the decrease started later and has been slower (Levi *et al.*, 2004). In Latin America, the decrease has also been less marked, and gastric cancer mortality is still relatively high in many Asian countries (Bertuccio *et al.*, 2009). It remains the fourth most common cancer and the second leading cause of cancer-related deaths (Ferlay *et al.*, 2010).

The decrease in gastric cancer rates was primarily attributed to factors related to the improvement in the populations' living conditions, a better diet and improved food preservation (Howson *et al.*, 1986; La Vecchia and Franceschi, 2000), reflecting the global changes in socioeconomic level across countries. This decrease is not attributable to interventions planned specifically to prevent and control gastric cancer. We may therefore hypothesize that almost all countries share the same overall pattern of variation. Previous attempts to describe stomach cancer patterns worldwide have based the grouping of the countries mostly on geographical criteria

(Levi *et al.*, 2004; Bertuccio *et al.*, 2009) or socioeconomic characteristics (Bray *et al.*, 2012), even when risk factors are also taken into account (Zhang *et al.*, 2012). Model-based clustering may allow a more meaningful grouping of the countries, according to the mortality rates at onset of the observation period, as well as the magnitude and slope of its variation, with no *a-priori* constraints.

We aimed to identify patterns in the time trends of stomach cancer mortality worldwide and to define how these patterns may relate with each other in an overall model of variation in the mortality rates.

## Methods

Death certification data from malignant neoplasm of the stomach were retrieved from the WHO cancer mortality database, assessed through the International Agency for Research on Cancer (IARC) (World Health Organization Statistical Information System, 2012). Data were collected from inception to the most recent data available for each country, up to 2010, after the 4 January 2012 update of the WHO database. During the period considered, different Revisions of the International Classification of Diseases (ICD) were used by the different countries, from the 7th to the 10th revision. As differences between various revisions were minor in cancer of the stomach (Janssen and Kunst, 2004), data were used as retrieved from the database, corresponding to the codes A046 (ICD-7), A047 (ICD-8), B091 (ICD-9) and C16 (ICD-10).

All supplementary digital content is available directly from Dr Bárbara Peleteiro (e-mail: barbarap@med.up.pt).

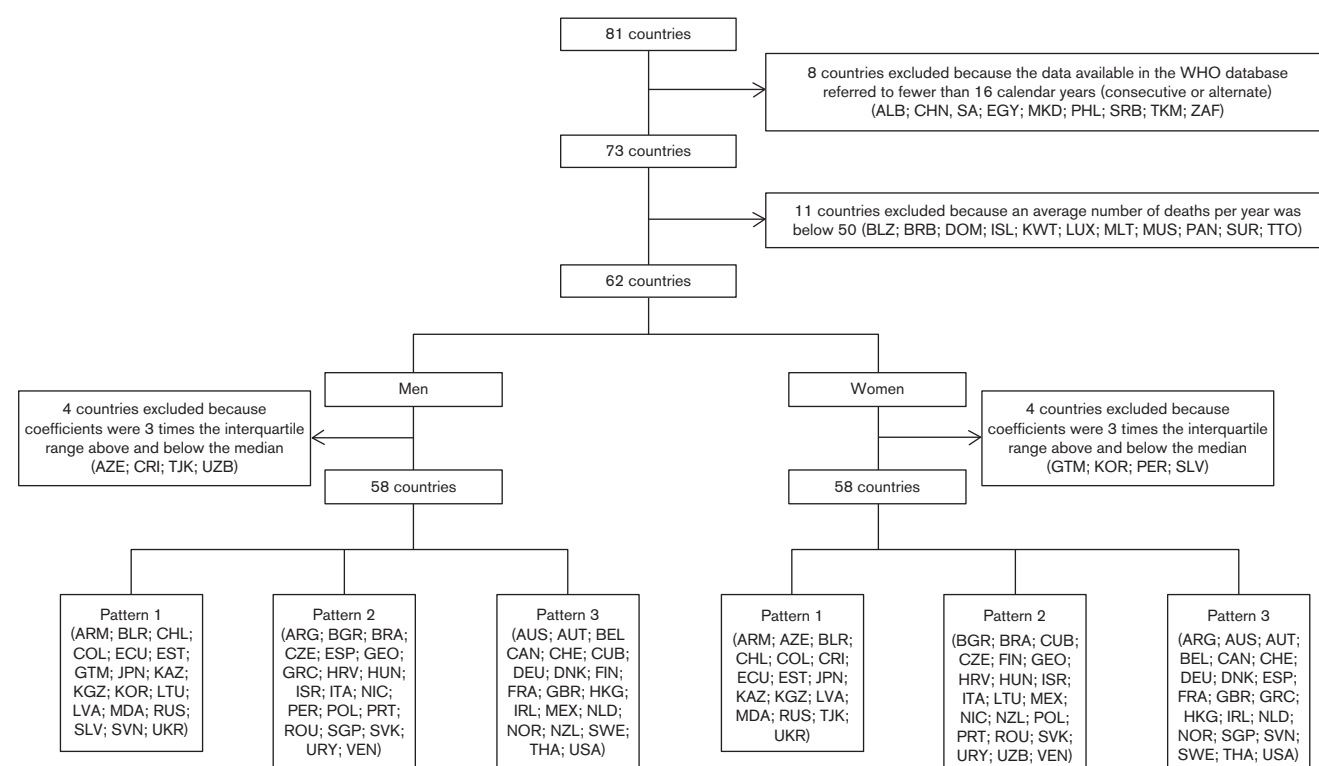
Age-standardized mortality rates (World standard population) for the age group 35–74 years were available for 86 countries. Although data were available for England and Wales, Northern Ireland and Scotland, we decided to use the mortality rates referring to the UK. For China, mortality rates could be retrieved for different regions (selected rural and urban areas), and we also opted for the more aggregated data (selected areas). As the data available for the special administrative region of Hong Kong were not aggregated to the other areas of China and corresponded to a different time series, this region was considered separately. For 38 countries, data were missing for one or more calendar years for the period between 1980 and 2010, and no interpolation was made for missing data. For 12 countries, the number of deaths for some calendar years was zero, and we treated these as years with missing data. Countries for which the data available in the WHO database referred to fewer than 16 consecutive or alternate calendar years ( $n = 8$ ) or having

an average number of deaths per year below 50 ( $n = 11$ ) were excluded from the analysis. After these exclusions, data were available for 62 countries (Fig. 1 and Supplementary Appendix 1).

Sex-specific mixed models (Pinheiro and Bates, 2000) were used to identify time trends in the age-standardized mortality rates (direct method, World standard population). All models included random terms by country for the intercept, slope, quadratic and cubic terms. Countries presenting values three times the interquartile range above and below the median were excluded from further analyses (Fig. 1). The observed mortality rates and the model predictions are presented in Supplementary Appendix 2.

Model-based clustering (Fraley and Raftery, 2002) was used to identify the patterns for the period between 1980 and 2010 for men and women (Supplementary Appendix 3). In this method, the clusters are considered to be ellipsoidal,

Fig. 1



Flowchart of the model-based approach used to identify stomach cancer mortality patterns for men and women. ALB, Albania; ARG, Argentina; ARM, Armenia; AUS, Australia; AUT, Austria; AZE, Azerbaijan; BEL, Belgium; BGR, Bulgaria; BLR, Belarus; BLZ, Belize; BRA, Brazil; BRB, Barbados; CAN, Canada; CHE, Switzerland; CHL, Chile; CHN, SA, China, selected areas; COL, Colombia; CRI, Costa Rica; CUB, Cuba; CZE, Czech Republic; DEU, Germany; DNK, Denmark; DOM, Dominican Republic; ECU, Ecuador; EGY, Egypt; ESP, Spain; EST, Estonia; FIN, Finland; FRA, France; GBR, United Kingdom; GEO, Georgia; GRC, Greece; GTM, Guatemala; HKG, Hong Kong Special Administrative Region; HRV, Croatia; HUN, Hungary; IRL, Ireland; ISL, Iceland; ISR, Israel; ITA, Italy; JPN, Japan; KAZ, Kazakhstan; KGZ, Kyrgyzstan; KOR, Republic of Korea; KWT, Kuwait; LTU, Lithuania; LUX, Luxembourg; LVA, Latvia; MDA, Republic of Moldova; MEX, Mexico; MKD, Macedonia (Former Yugoslav Republic of Macedonia); MLT, Malta; MUS, Mauritius; NIC, Nicaragua; NLD, The Netherlands; NOR, Norway; NZL, New Zealand; PAN, Panama; PER, Peru; PHL, Philippines; POL, Poland; PRT, Portugal; ROU, Romania; RUS, Russian Federation; SRB, Serbia; SGP, Singapore; SLV, El Salvador; SVK, Slovakia; SVN, Slovenia; SUR, Suriname; SWE, Sweden; THA, Thailand; TJK, Tajikistan; TKM, Turkmenistan; TTO, Trinidad and Tobago; UKR, Ukraine; URY, Uruguay; USA, United States of America; UZB, Uzbekistan; VEN, Venezuela; ZAF, South Africa.

centred at the means, and the covariances determine their other geometric features. Characteristics (orientation, volume and shape) of distributions are estimated from the data, and can be allowed to vary between clusters or constrained to be the same for all clusters (Fraley and Raftery, 2007). The most appropriate models for each sex were considered to be those allowing for the most homogeneous grouping of the countries in their patterns of variation, as assessed by visual inspection of the country-specific trends, selected among those with the lowest Bayesian information criterion (Schwarz, 1978) (Supplementary Appendix 3).

The reliability of the model-based clustering was evaluated by 10-fold cross-validation (Efron and Tibshirani, 1997). The sample was divided into 10 partitions, and each of the subsets of nine out of the 10 partitions was used to construct 10 different models. The agreement between the predictions from these models and those from the model constructed with the complete dataset was calculated; the overall  $\kappa$  coefficient was estimated by the mean of the  $\kappa$  coefficients referring to the agreement between each of the 10 subset models and the full model.

The patterns identified through the model-based approach were further characterized according to the gross national income *per capita*, Atlas method (current US\$), for 1980 and 2010; data were obtained from the World Bank database (The World Bank, 2012).

Assuming a temporal sequence across these patterns, the overlap of model predictions that describe trends in subsequent patterns was computed. The temporal relation between the patterns was validated using the relative squared error (RSE) method (Witten and Frank, 2005). In this method, the error associated with the model prediction is made relative to what it would have been if a simple predictor, such as the average of the actual values, had been used instead. The value obtained can be interpreted as the per cent decrease in error that is associated with the model prediction. For this model validation, stomach cancer mortality rates between 1950 and 1980 were retrieved, and sex-specific models similar to the ones constructed for data between 1980 and 2010 were computed. These two models were validated against the observed rates between 1950 and 1980, and the RSE for each model was computed.

Data analysis was carried out with the software R 2.14.1 using the packages nlme (Pinheiro *et al.*, 2007) and mcclust (Fraley *et al.*, 2012) for mixed-models analysis and model-based clustering, respectively.

## Results

Three clusters were identified in each sex for the variation in mortality between 1980 and 2010 corresponding to the same general patterns of variation both in men and in women, hereafter referred to as pattern

1, pattern 2 and pattern 3 (Fig. 2). The reliability of the model-based clustering was good (men:  $\kappa = 0.74$ ; women:  $\kappa = 0.70$ ).

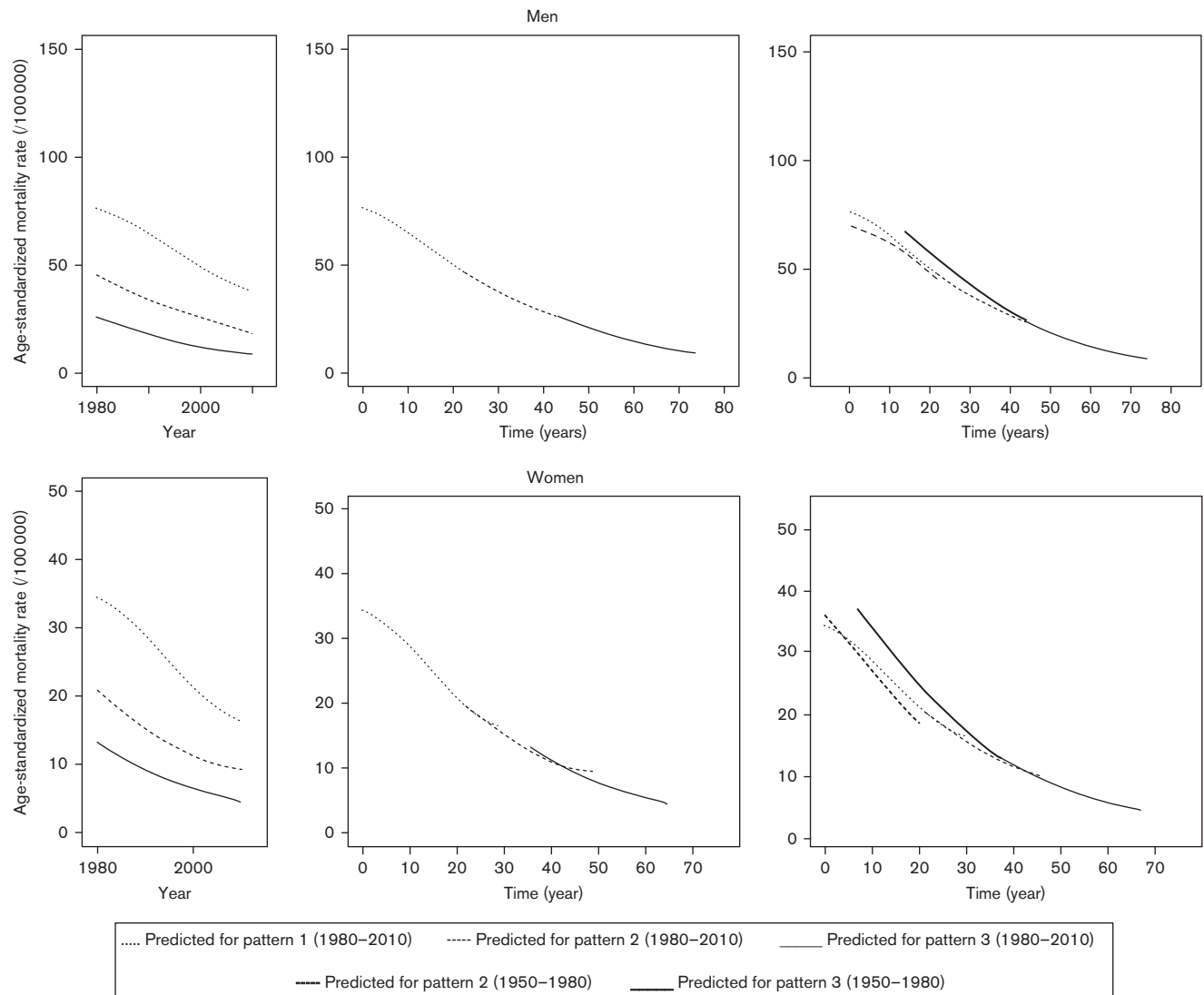
Pattern 1 presented the highest mortality rates, with a median decrease in rates of  $-2.32\%/year$  in men and  $-2.79\%/year$  in women (Fig. 3). Pattern 3 showed the lowest mortality rates, with a median decrease of  $-3.62\%/year$  in men and  $-3.41\%/year$  in women. Pattern 2 had intermediate values, with a median decrease of  $-2.70\%/year$  in men and  $-3.09\%/year$  in women. Despite the decrease to more than half of the initial rate in all patterns, the variation was significantly different across patterns during 1980–1995 (Fig. 3) both in men (pattern 1 vs. pattern 2 vs. pattern 3: median,  $-1.88\%/year$  vs.  $-2.44\%/year$  vs.  $-3.73\%/year$ ;  $P < 0.001$ ) and in women (pattern 1 vs. pattern 2 vs. pattern 3: median,  $-2.08\%/year$  vs.  $-2.98\%/year$  vs.  $-3.36\%/year$ ;  $P = 0.001$ ). During 1996–2010, the differences in the variation across patterns were less pronounced in men (pattern 1 vs. pattern 2 vs. pattern 3: median,  $-2.90\%/year$  vs.  $-2.76\%/year$  vs.  $-3.56\%/year$ ;  $P = 0.049$ ) and in women (pattern 1 vs. pattern 2 vs. pattern 3: median,  $-2.97\%/year$  vs.  $-2.78\%/year$  vs.  $-3.49\%/year$ ;  $P = 0.096$ ) (Fig. 3).

The mortality rates observed in each pattern were inversely related to the median gross national income *per capita* for the countries included in each pattern, both in 1980 (pattern 1 vs. pattern 2 vs. pattern 3: men, US\$ 1420 vs. US\$ 3290 vs. US\$ 11 320,  $P < 0.001$ ; women, US\$ 1980 vs. US\$ 3080 vs. US\$ 11 320,  $P = 0.001$ ) and in 2010 (pattern 1 vs. pattern 2 vs. pattern 3: men, US\$ 7500 vs. US\$ 12 655 vs. US\$ 45 780,  $P < 0.001$ ; women, US\$ 5990 vs. US\$ 12 055 vs. US\$ 42 970,  $P < 0.001$ ) (Fig. 3).

Most countries included in pattern 1 were from Latin America and Eastern Europe (Fig. 4), whereas those from Northern America, Western Europe and Oceania were predominantly in pattern 3. Pattern 2 included mainly countries from Latin America and Eastern and Southern Europe.

Assuming that the patterns characterized by the highest rates precede temporally those with lower mortality, the overlap of model predictions supports a lag between patterns 1 and 2 of 23 years for men and 21 years for women, and a 20-year and 16-year lag between patterns 2 and 3, respectively (Fig. 2).

The predictions for 1950–1980 for patterns 2 and 3 were in accordance with those estimated for 1980–2010 in the patterns that preceded them temporally (Fig. 2). The estimated rates for the years before 1980 in countries included in pattern 2 and the predictions for 1980–2010 in pattern 1 presented similar RSEs in men (89.2 vs. 85.7%) and women (83.7 vs. 83.8%). Similarly, the estimated rates for the years before 1980 in countries included in pattern 3 and the predictions for 1980–2010

**Fig. 2**

Trends in age-standardized (direct method, World standard population) stomach cancer mortality rates for ages 35–74 years for each pattern identified, temporal relation between the patterns identified and validation of the proposed temporal relation between patterns, in men and women.

in patterns 2 and 1 presented similar RSEs in men (72.4 vs. 78.1%) and women (65.4 vs. 71.4%).

## Discussion

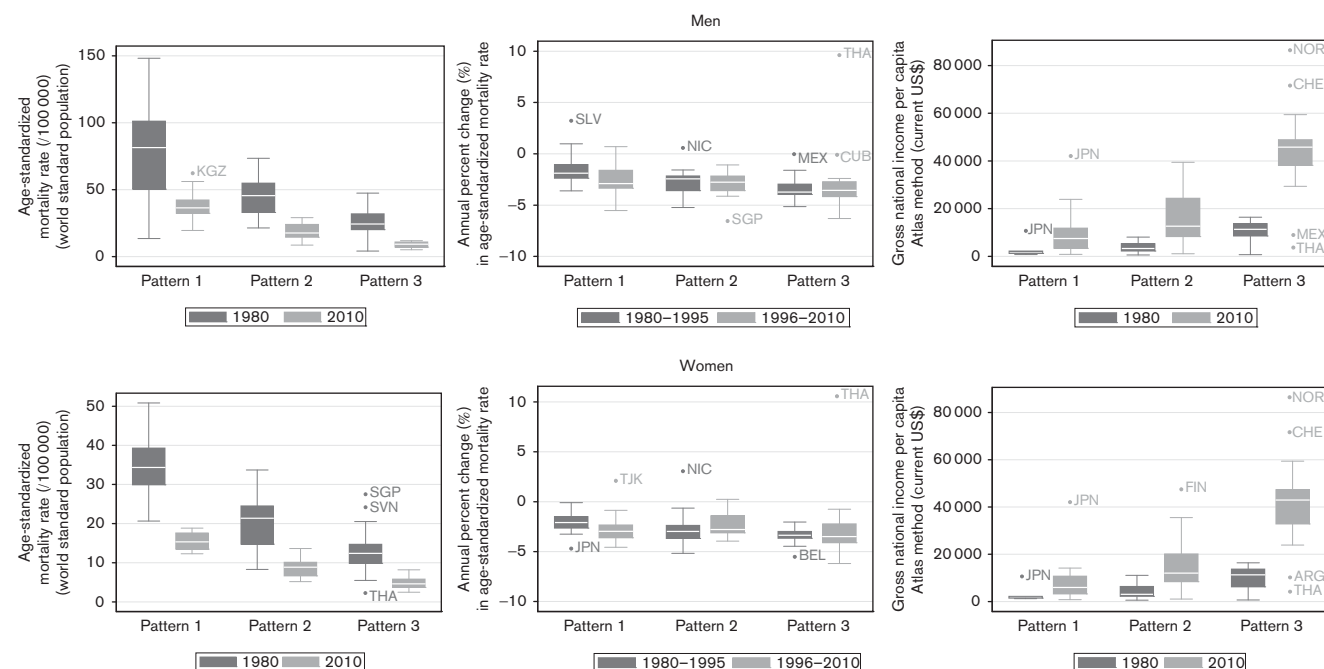
Three patterns of stomach cancer mortality worldwide were identified for men and women, corresponding to a similar model of variation between 1980 and 2010. Assuming that the patterns characterized by the highest rates precede temporally those with lower mortality, a temporal sequence of ~70 years is proposed for the downward trend from the highest to the lowest rates observed in these countries, with a lag of ~20 years between subsequent patterns. As noted previously within Europe (Levi *et al.*, 2004), however, in relative terms, the

decrease was larger, although not in absolute value, in countries in pattern 3 (with generally lower rates) than in pattern 1.

This study differs from previous investigations on gastric cancer mortality by using a-posteriori approach to identify similar patterns of variation across settings.

When compared with studies that grouped countries according to geographical criteria (Levi *et al.*, 2004; Bertuccio *et al.*, 2009; Ferlay *et al.*, 2010), our approach yielded a distinct grouping (Fig. 4). On the one hand, Western and Northern Europe have been treated as homogeneous regions for gastric cancer mortality; in our study, although these countries shared the same overall

Fig. 3



Estimated age-standardized (World standard population) stomach cancer mortality rates for ages 35–74 years in 1980 and 2010, annual per cent change in the estimated age-standardized (World standard population) stomach cancer mortality rates for ages 35–74 years during 1980–1995 and 1996–2010 and gross national income *per capita* (Atlas method, current US\$), for each pattern identified in men and in women. ARG, Argentina; BEL, Belgium; CHE, Switzerland; CUB, Cuba; FIN, Finland; JPN, Japan; KGZ, Kyrgyzstan; MEX, Mexico; NIC, Nicaragua; NOR, Norway; SGP, Singapore; SLV, El Salvador; SVN, Slovenia; THA, Thailand; TJK, Tajikistan. Gross national income per capita, Atlas method (current US\$), for 1980 and 2010, retrieved from The World Bank (2012).

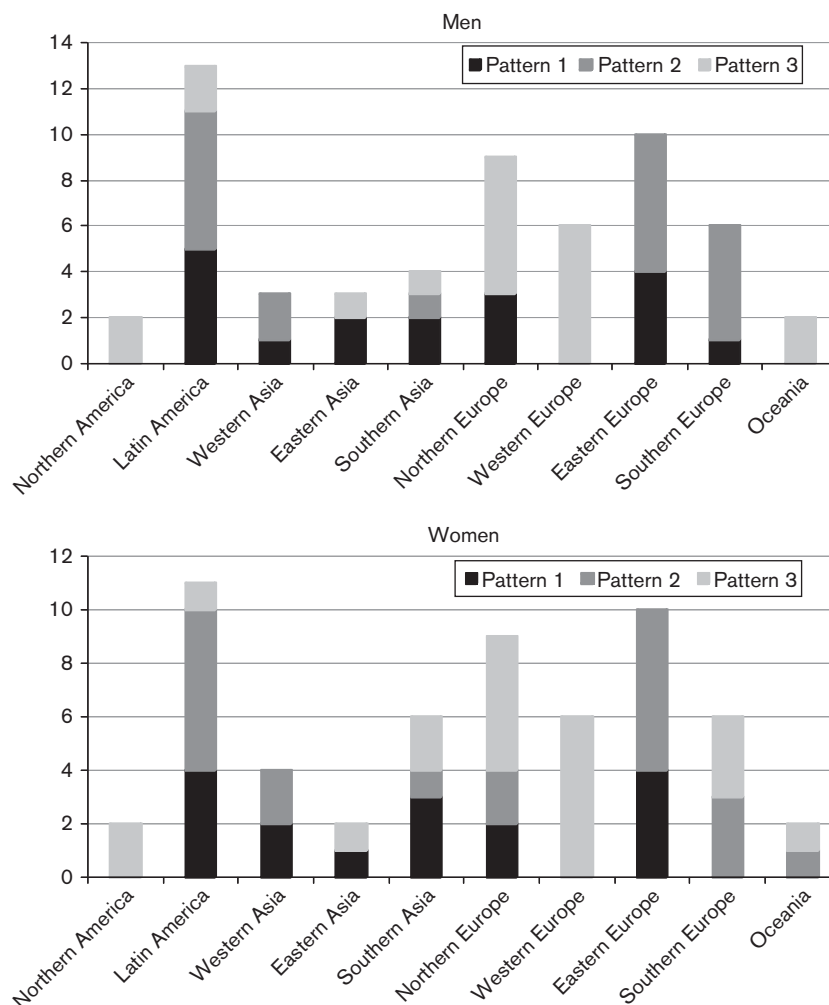
variation, most of them in pattern 3, these regions also include countries with rates compatible with earlier patterns. Major differences were observed in the Central Eastern European settings, usually referred to as a group presenting the highest stomach cancer mortality rates in Europe; our analysis shows that Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia are no longer in the first stage of gastric cancer mortality trends, in contrast with most of the others still in pattern 1 (e.g. Belarus, Russian Federation). Also, more than half of the Latin American countries, usually presented jointly as a group with some of the highest stomach cancer mortalities of the world, are not in the first stage of the downward trend according to our analysis, and some of them may be placed in pattern 3 (Cuba and Mexico in men and Argentina in women). On the other hand, Thailand is in pattern 3, unlike most other Asian countries (pattern 1), probably reflecting the fact that some South-Eastern Asian countries present low gastric cancer rates despite the high prevalence of *Helicobacter pylori* infection. This is an odd pattern, corresponding to the so-called ‘Asian enigma’ (Miwa *et al.*, 2002), that our model was not able to isolate from the more general patterns that include a large number of countries.

In a recent study by Bray *et al.* (2012), the grouping of the countries to obtain the trends in stomach cancer

incidence between 1988 and 2002 was based on their socioeconomic level. Population-based registries were grouped by the Human Development Index (HDI) region into medium, high and very high, yielding a distinct group from ours. On the one hand, a few countries from medium HDI areas, such as Hong Kong special administrative region and Thailand, were included in our pattern 3, presenting the lowest mortality rates. On the other hand, most of those included in high HDI areas were in fact in pattern 1, namely, Colombia, Costa Rica, Ecuador, Estonia and Latvia. Japan, which was included in very high HDI areas, was the country with the highest mortality rates included in pattern 1. In our study, the median HDI for 2011 was higher for countries in pattern 3 and lower for countries in pattern 1 (pattern 1 vs. pattern 2 vs. pattern 3: men, 0.750 vs. 0.803 vs. 0.900,  $P < 0.001$ ; women, 0.736 vs. 0.796 vs. 0.895,  $P < 0.001$ ). This is in accordance with the hypothesis of the decrease in gastric cancer rates being primarily attributed to an increase in the socioeconomic status at the country level.

This study is based on mortality data routinely submitted to the WHO by each member state, but data quality may vary across countries (Mathers *et al.*, 2005). By the end of 2003, only 64 of the 115 countries with available data had a complete series, and huge differences were observed in the coverage of registration, with only 23 countries

Fig. 4



Countries included in each pattern, by geographic regions.

classified as having high-quality data. However, this is not expected to have substantially influenced our results as death certification from gastric cancer is sufficiently reliable and valid to allow inference on trends in most countries worldwide, particularly below the age of 75, and no relevant changes in coding and classification of gastric cancer have been introduced over the last decades across subsequent Revisions of the ICD. Furthermore, no significant differences were observed across the patterns in the proportion of countries with different data quality classifications (data not shown). However, the unavailability of mortality data from African countries, specifically of long time series allowing for proper modelling, restricts the global validity of our findings, taking into account that some of these countries present unexpectedly low rates of gastric cancer, given the high prevalence of *H. pylori* infection observed, which corresponds to a well-known pattern that was poorly represented in our dataset (Holcombe, 1992; Lunet and Barros, 2003).

For China, the mortality rates reported to the WHO do not refer to national data but to sample registration systems, which have been proven to be a cost-effective approach to obtain representative information (Mathers *et al.*, 2005; Setel *et al.*, 2005). However, within-country variation in the trends of gastric cancer mortality has been reported in several settings (Tovar-Guzman *et al.*, 2001; Lunet *et al.*, 2004; Lau *et al.*, 2006; Inghelmann *et al.*, 2007; Garcia-Esquinas *et al.*, 2009), and the pattern assigned to these countries on the basis of non-national data may not necessarily correspond to the national pattern.

Mortality data used in this study include all malignant neoplasms of the stomach; however, some studies have shown that trends are unequal across distinct histological and topographical types. Although the frequency of tumours classified as diffuse seems to have remained stable or even increased over time, the variation in the

rate of tumours of the intestinal histological type, which account for most of the gastric adenocarcinomas, explains the overall decrease that has been observed consistently (Kaneko and Yoshimura, 2001; Bashash *et al.*, 2008; Wu *et al.*, 2009). Similarly, although tumours in the cardia region have been increasing, depicting a pattern of change that resembles more closely that observed for oesophageal adenocarcinoma, the decrease has been more pronounced for tumours located in the lower thirds of the stomach (fundus, corpus, antrum, pylorus), which are also the most frequent (Botterweck *et al.*, 2000; Liu *et al.*, 2004; Dassen *et al.*, 2010).

The variations in the levels of economical development across these countries and, more specifically, tobacco consumption and infection with *H. pylori*, are likely to explain the patterns observed, and also represent an opportunity for intervention. The fact that the patterns are essentially the same for both sexes, despite the magnitude of the mortality rates being approximately twice as high among men, reflects a similar variation in the exposure to the main risk factors throughout the last decades. The impact of the current sex-specific trends in the exposure to tobacco (Strong *et al.*, 2008) will probably be reflected in the patterns observed in the next decades.

National age-standardized trends in gastric cancer mortality reflect decreases both in the period and in the cohort of birth effects. Both of these are still observed in most countries, except in the ones with very low rates, where the cohort effect tended to level off over recent years, and hence in younger generations (Malvezzi *et al.*, 2010). A cohort effect may also explain the higher proportional decrease in pattern 3 than in pattern 1, as the high-prevalence *H. pylori* generations are being progressively replaced in these countries.

The improvement in gastric cancer diagnosis that followed the development of endoscopic technology (Dan *et al.*, 2006), as well as advancements in treatment (Wong and Jackson, 2011), such as surgical techniques and the use of multiple chemotherapy regimens, together with enhanced surveillance programs (Lee *et al.*, 2012), may also account for the decreasing trends. However, their impact is likely to be limited as gastric cancer survival is globally low and only moderate improvements have been achieved in the last decades (Ozols *et al.*, 2007; Verdecchia *et al.*, 2009; Matsuda *et al.*, 2011). Early detection of stomach cancer has improved in several settings, but screening programmes have been implemented only in Korea and Japan (No authors listed, 2007; Hamashima *et al.*, 2008), and this is unlikely to be a major determinant of the patterns observed in other areas of the world.

In conclusion, we identified a useful summary model for the variation in stomach cancer mortality with three different stages that develop sequentially through a period of ~70 years. It may contribute toward more

accurate predictions of the future trend in countries where rates remain high despite the decreasing trend.

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## Conflicts of interest

There are no conflicts of interest.

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