Gastric Cancer (GC) mortality rates in Spain decreased significantly for both sexes in Spain. In the under-35 age group, rates were stable after an initial significant decline. In the 35-64 age group, the decline was more pronounced in men than in women. In the 65+ age group, rates fell significantly for both sexes, but more so for women than for men. The net drift and local drift also showed significant decreases for all age groups from 24 years onwards.

GC mortality rates increased with age and decreased with calendar time and successive birth cohorts, regardless of sex. The ratio of age-specific rates between men and women increased with age, and birth cohort relative risk estimates followed a steady downward trend until the mid-1970s, after which the decline stabilized. The period relative risk decreased for both sexes, with a more pronounced decrease in men.
Age, period and cohort effects on gastric cancer mortality in Spain, 1980-2021

Lucía Cayuela¹, Álvaro Giráldez-Gallego²,³, Marta Garzón-Benavides²,³, José Manuel Sousa-Martín²,³, Aurelio Cayuela⁴


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Correspondence: Aurelio Cayuela. Unit of Public Health, Prevention and Health Promotion. South Seville Health Management Area. Hospital Universitario de Valme. Ctra. de Cádiz, km. 548,9. 41014 Seville, Spain

e-mail: aurelio.cayuela@gmail.com

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Data availability statement: the data that support the findings of this study are openly available from the Spanish National Statistics Institute (INE) database: https://www.ine.es/dyngs/INEbase/listaoperaciones.htm
Lay summary
This study aimed to examine how different factors such as age, period, and cohort (A-P-C) affect mortality from gastric cancer (GC) in Spain over a 41-year period from 1980 to 2021. The study analyzed aggregated data obtained from the National Institute of Statistics, and used statistical methods such as joinpoint regression software and National Cancer Institute A-P-C tools to estimate mortality rates and trends by sex and age group. The study found that overall GC mortality rates decreased significantly for both sexes in Spain during the study period. However, there were some variations in the trends by age group and sex. In the under-35 age group, rates were stable after an initial significant decline. In the 35-64 age group, the decline was more pronounced in men than in women. In the 65+ age group, rates fell significantly for both sexes, but more so for women than for men.

The study also found that GC mortality rates increased with age, and decreased with calendar time and successive birth cohorts, regardless of sex. The ratio of age-specific rates between men and women increased with age, and birth cohort relative risk estimates followed a steady downward trend until the mid-1970s, after which the decline stabilized. The relative risk decreased for both sexes, with a more pronounced decrease in men.

Overall, the study provides important insights into the trends and factors that affect mortality from GC in Spain. The findings suggest that efforts to reduce GC mortality should focus on early detection and prevention strategies, particularly for those at higher risk due to age and sex.

ABSTRACT
Background: this study aimed to evaluate the effects of age, time period and cohort (A-P-C) on gastric cancer (GC) mortality in Spain from 1980 to 2021.

Methods: an ecological trend study was performed (with aggregated data obtained from the Spanish National Statistics Institute (INE). Joinpoint regression software was used to estimate rates by sex and age group (< 35, 35-64, > 64 years) and mortality trends. The National Cancer Institute A-P-C tools were used to assess the effects of age, time of death
and birth cohort.

**Results:** GC mortality rates in Spain decreased significantly in both sexes. In the under-35 age group, rates were stable after an initial significant decline. In the 35-64 age group, the decline was more pronounced in males than in females. In the 65+ age group, rates fell significantly for both sexes, but more so for females than for males. The net drift and local drift also showed significant decreases across all age groups from 24 years onwards. GC mortality rates increased with age and decreased with calendar time and successive birth cohorts, regardless of sex. The ratio of age-specific rates between males and females increased with age, and birth cohort relative risk estimates followed a steady downward trend until the mid-1970s, after which the decline stabilized. The relative risk decreased for both sexes, with a more pronounced decrease in males.

**Conclusion:** GC mortality rates in Spain have been decreasing over time and across successive birth cohorts, with a stabilizing trend observed for those under 35 years of age.

**Keywords:** Gastric cancer. Mortality. Trends. Age-period-cohort analysis. Joinpoint analysis.

**INTRODUCTION**

Globally, the incidence and mortality rates of gastric cancer (GC) have been declining, although the decline has not been consistent in all regions (1,2). A recent study found that GC mortality rates have been decreasing since 1990 in all countries examined, including the European Union (EU 27), across all age groups and genders (3). However, the rates have stabilized in some areas, particularly among younger age groups, such as French and US women aged 35 to 64 years and Canadian males in the same age group (3,4). Moreover, rates have even increased in other areas (5).

By 2020, GC ranked fifth in diagnoses (after breast, lung, colorectal, and prostate) with almost 1.1 million new cases and fourth in deaths (after lung, colorectal, and liver) with 768,793 cases (6).

In Spain, GC mortality rates increased moderately in the 1950s and early 1960s, but have fallen sharply since then until 2008, particularly among females and in some of the inland and northern regions of mainland Spain (7-9). A recent study analyzed trends in GC mortality in Spain from 1980 to 2015, among other countries, but did not stratify by age or examine
possible trends (5). However, as age-standardized mortality rates (ASMRs) is essentially a weighted summary measure, it tends to reflect trends in older age groups rather than age differences between generations.

Age-period-cohort models separate temporal variation into three components: age, period, and birth cohort, all of which can significantly impact the mortality of GC. Age is a crucial factor as the probability of developing GC increases with age. Meanwhile, period and cohort effects reflect the short- and long-term impacts of various environmental, societal and lifestyle factors. This can help better understand the main drivers of trends by gender, as well as predict scenarios and assess the impact of prevention and intervention strategies (7,10). Therefore, this study aimed to update and assess the impact of A-P-C effects on GC mortality in Spain from 1980 to 2021.

METHODS

The Spanish National Statistics Institute provided data on population (estimated on 1 July each year) and mortality for the period 1980-2021, disaggregated by age, sex and calendar period. Cases were identified using the ninth and tenth revisions of the International Classification of Diseases (codes 151 and C16 for CG).

For the joinpoint regression analysis, the data was organized into 18 age groups spanning five-year intervals, ranging from < 5 years to 85+ years. These age groups were further stratified based on both gender and year, facilitating a thorough examination of trends within various demographic categories.

To apply the A-P-C model, the dataset was structured into eight five-year periods, spanning from 1982-1986 to 2017-2021. Additionally, the data was divided into 13 five-year age groups, ranging from 20-24 to 80-84 years old. This configuration resulted in a total of 20 birth cohorts, labeled according to the central year of birth, ranging from 1902 to 1997. For each age group and five-year period, the matrix of age-specific death rates was computed, forming a crucial component of the A-P-C model analysis.

Statistical analyses

ASMRs were estimated by gender and age group (< 35, 35-64, > 64 years) using the direct method and the revised European Standard Population (11). The joinpoint regression
program version 4.9.1.0 was used to estimate rates and mortality trends (12). Using the default settings of the software (13), the turning points in the trend and the annual percentage change (APC) were estimated for each of the identified periods. The average annual percentage change (AAPC) between 1980 and 2021 was also estimated. This is a geometric weighted average of the different APCs. The weights correspond to the length of each period within a given period. To check whether the trends are parallel for both genders, the “pairwise comparison” option of the software was used (14). All calculated rates are expressed per 100,000 persons. Furthermore, the male-to-female ratio was estimated.

The effects of age, time of death and birth cohort were assessed using the National Cancer Institute A-P-C tools (available from https://analysistools.nci.nih.gov/apc/). The following estimable functions were analyzed (15): longitudinal age-specific rates, period and cohort rate ratios, and local drifts with net drift. The longitudinal age curve gives the fitted longitudinal age-specific rates in reference cohorts adjusted for period deviations, while the period (or cohort) relative risk (RR) is the period (or cohort) RR adjusted for age and non-linear cohort (or period) effects in a period (or cohort) relative to the reference. The net drift is the overall log-linear trend by calendar period and birth cohort and gives the overall annual percentage change, whereas the local drifts are the log-linear trend by calendar period and birth cohort for each age group and give the annual percentage change for each age group. All A-P-C analyses used the central age, calendar period and birth cohort group as the reference group. Wald’s Chi-squared tests were used to test the significance of estimable functions. Statistical significance was established at $p < 0.05$.

RESULTS

In Spain, 259,442 people died of GC during the study period, with more affected males (156,596) than females (102,846). Figure 1 shows ASMRs and trends for GC in Spain from 1980 to 2021, by gender. The ASMRs decreased significantly in both sexes during this period, from 48.7 per 100,000 in 1980 to 13.4 in 2021 for males and from 25.5 in 1980 to 6.3 in 2021 for females. Although the joinpoint analysis rejected parallelism, the significant decline observed was similar for both sexes, with an average annual percentage change (AAPC) of -3.3 % in females and -3.1 % in males. The joinpoint analysis also identified several inflection
points in the downward trend for both sexes, with four for females and three for males. These turning points defined distinct periods of significant decline, with the declines in males gradually accelerating over time and the intensity of the decline in females varying.

Figure 2 displays ASMRs by age group (< 35, 35-64, and ≥ 65 years) and gender. Joinpoint analysis did not reject parallelism in the < 35 age group for both sexes, where a significant decrease was observed during the study period (AAPC: -2.4 %, p < 0.05). However, the rates were stable for both sexes from 2008 to 2021 after an initial period of significant decrease (1980-2008; AAPC: -4.1 %, p < 0.05). The joinpoint analysis rejected parallelism in the 35-64 age group. A significant decrease was observed for both sexes throughout the study, with a more pronounced decline in males (APC: -3.3 %) than in females (APC: -2.4 %). After an initial period of decline, the rate of decline accelerated for males (1994-2021; APC: -3.4 %) and slowed for females (2005-2021; APC: -1.6 %). In the 65+ age group, the joinpoint analysis also rejected parallelism. The rates decreased significantly for both sexes during the study period, with a more significant decrease for females than for males (AAPC: -3.4 % and -3.0 %, respectively, p < 0.05). The joinpoint analysis identified two turning points defining three periods (1980-1987, 1987-2002, and 2002-2021) of significant decline (AAPC: -2.8, -4.1 %, and -3.1 %, respectively, p < 0.05) for females. After an initial period of significant decline for males (1980-2012; AAPC: -2.9 %, p < 0.05), the downward trend strengthened (2012-2021, AAPC: -3.6 %, p < 0.05). The male/female ratio remained around 1.2 for those under 35, 2.4 for those aged 35-64, and 2.1 for those aged 65+ years of age, respectively.

Figure 3A shows the net and local drifts for GC mortality in Spain between 1982 and 2021, indicating the annual percentage change in the expected age adjusted rates and age-specific rates, respectively. Males had a higher overall net drift of -3.2 % per year (95 % CI: -3.4 % to -3.0 %), compared to females, with a net drift of -2.6 % per year (95 % CI: -2.7 % to -2.4 %). A significant decrease in local drifts was observed for all age groups over 24 years for both sexes. Nonetheless, some gender-specific differences were identified. Females had a gradual decline in local drifts with age, starting from 45 years onwards, whereas males showed the most substantial reductions in the 30-49 age groups.

Figure 3B illustrates the longitudinal age curves, estimated cohort RR trend, and estimated period RR trend for GC mortality rates in Spain by sex. Both sexes had comparable longitudinal trends, although males had higher rates. With increasing age, mortality
increased gradually, peaking in the same birth cohort for both sexes. However, the ratio of age-specific rates between males and females increased with age, ranging from 1.3 for 20-24-year-olds to 2.7 for 65-69-year-olds, and then fell to 2.1 for 80-84-year-olds. In both sexes, the relative risk estimates in birth cohorts steadily decreased from the beginning of the last century until the mid-1970s, after which the decline stabilized. From 1982-1986 to 2017-2021, the period RR decreased for both sexes, although the decline was more prominent among males. All estimated functions, including cohort and period RRs, net and local drifts, were statistically significant ($p < 0.01$) for both sexes.

**DISCUSSION**

Our findings revealed that GC mortality rates increased with age, decreased in successive birth cohorts, and showed a period effect of steadily decreasing risk. In addition, similar to the stabilizing decline in risk observed for cohorts born since the 1970s, stabilizing rates were also observed for those younger than 35 years. *Helicobacter pylori* (*H. pylori*) plays a crucial role in the development of GC (16). However, infection alone is not sufficient to cause the disease. How *H. pylori* infection interacts with other risk factors is not well understood, suggesting that there may be other factors that contribute to the development of GC (17).

Our data shows that there has been a reduction in GC mortality in both sexes, but the rates are still higher in males with a male-female ratio of around 2.1. In almost all countries, there are differences in GC incidence between sexes, with males having rates 1.5 to 3 times higher than females (2). Furthermore, countries with larger differences in *H. pylori* infection rates between males and females, such as the US and the EU, also have larger differences in GC mortality rates (18).

**Age-effect**

The incidence of GC increases progressively with age (19), and our study showed that GC mortality rates increased with age in both sexes. This aligns with previous findings from other studies (16). Older age reflects cell DNA damage accumulating over time, which can result from biological processes or exposure to risk factors.
Rates below the age of 35 years followed parallel trends by sex, suggesting that the possible determinants of GC mortality have had an equal impact on both sexes. Furthermore, the stable trend in the under 35s is similar to that observed in other countries (4,20). For example, in the United States (1992-2019), A-P-C modelling showed stable incidence and incidence-based mortality rates in people younger than 50 years, but a significant downward trend in people older than 50 years (21). In addition, rates of non-cardia stomach cancer are decreasing in older adults but increasing in those younger than 50 years. The main causes of this type of cancer are *H. pylori* infection and autoimmune gastritis. Researchers have suggested that increased use of antibiotics in recent years may be linked to increased incidence of autoimmune gastritis, which may have contributed to the increased incidence of non-cardia GC (22).

**Period effect**

Our results showed, in both sexes, a similar period effect of steadily decreasing the risk of GC death. Supporting similar findings from previous studies that showed a similar trend in both high- and low-risk areas and both sexes (9). This downward trend in GC has generally been attributed to changes in some risk factors associated with its etiology, such as improved food preservation, specifically refrigeration (23), changes in the population’s diet (24), as well as a decrease in the prevalence of *H. pylori* infection (25). However, as with other cancers, the etiology of GC is not fully understood, as other risk factors have been identified in the literature, such as socioeconomic status (26), contaminants in drinking water (27), occupational exposures (28) and cigarette smoking (29).

**Cohort effects**

For birth cohorts, a progressive reduction in mortality risk has been observed for both sexes since the 20th century, and a stabilization has been observed since the 1970s for younger generations in Spain. This trend is consistent with that observed in other countries (7,21,30). In most countries, the incidence rates of GC have uniformly decreased in successive male and female birth cohorts across most age groups. However, in several countries, the rates have stabilized or increased among more recently born cohorts in either males or females. For instance, in Brazil, Israel, the Philippines and the United Kingdom, the rates peaked in
the 1910-1920 birth cohorts, which coincided with the period of the First World War for both sexes (2). Concurrent studies on *H. pylori* and CG have shown that generally, both the GC mortality rate and the prevalence of *H. pylori* increase with age, decrease over time and decline in later birth cohorts (31).

Our study has strengths and weaknesses. One of the strengths of this study is that the entire Spanish population has been followed for 42 years. Therefore, it is a dynamic cohort, with entries and exits throughout the study period. Covers generations born roughly between 1902 and 1997, making it a reliable time series. However, the study is limited in several ways. First, we used mortality data due to the limited availability of incidence data. These were the only available data that met the continuity and completeness criteria (32).

Furthermore, although the limitations of epidemiological evidence based on mortality studies have been highlighted, they remain a fundamental element in understanding the disease and its determinants. Due to the relatively poor survival of GC patients and the proven accuracy of death certificates by GC in Spain (34), we consider mortality data as a proxy for GC incidence (33). Despite diagnostic and therapeutic advances, GC remains highly lethal. According to the CONCORD-3 study, there has been a slight increase in the five-year age-standardized net survival rate (%) from diagnosis (from 25.7 in the 2000-2004 period to 27.6 in the period 2010-2014) in recent decades. These figures show a continuous improvement in GC survival in Spain, although they are still lower than in other European countries such as France and Italy (34).

Another limitation of the study is the inability to analyses time trends by location. GC can be classified as either cardia or non-cardia cancer (showing differences in risk factors) (16), but a significant proportion of the cases in the study were labelled as “location unspecified”, which precludes an analysis of trends by location.

Segmented models like the ones used here can suffer from overfitting. However, we used the National Cancer Institute (NCI) joinpoint software, which employs conservative model selection algorithms. Additionally, frequentist permutation model selection, the most conservative option, was used to reduce the risk of overfitting (13).

While our A-P-C models provided useful insights, they have limitations that must be acknowledged when interpreting the results (15,31). For example, younger age groups with few cases may produce unreliable projections due to randomness in conventional A-P-C
parameter estimation. To address this issue, the age groups were narrowed to 25-29 years and 80-84 years. Finally, to prevent drawing inaccurate conclusions from group-level data, which is known as the ecological fallacy, we can only propose potential explanations for the observed trends (35).

In conclusion, the study found that the rates of GC mortality have been decreasing in Spain over time and across successive birth cohorts. However, there has been a stabilization in rates for those under 35 years old. These findings emphasize the importance of monitoring GC mortality rates and developing effective preventative measures.

REFERENCES


Fig. 1. Age standardized mortality rates (all ages) and trends estimated by joinpoint analysis for gastric cancer in Spain over the period 1980-2021 by gender. *Indicates that the annual percent change (APC) is significantly different from zero at the alpha = 0.05 level. Final selected model: men – 2 joinpoints, women – 3 joinpoints. Rejected parallelism.
Fig. 2. Age standardized mortality rates and trends estimated by joinpoint analysis for gastric cancer in Spain over the period 1980-2021 by gender and age group (< 35, 35-64 and 65+ years).
Fig. 3. A. Net drift (annual percentage change in expected overall age-adjusted rates) and local drift (expected age-specific rates over time) for gastric cancer mortality in Spain (1982-2021). B. Results of age, period, and cohort modelling for men and women. Gastric cancer mortality by sex, Spain, 1982-2021.