



## Original research article

## The remarkable geographical pattern of gastric cancer mortality in Ecuador



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## ABSTRACT

**Aim:** This study was aimed to describe the gastric cancer mortality trend, and to analyze the spatial distribution of gastric cancer mortality in Ecuador, between 2004 and 2015.

**Methods:** Data were collected from the National Institute of Statistics and Census (INEC) database. Crude gastric cancer mortality rates, standardized mortality ratios (SMRs) and indirect standardized mortality rates (ISMRS) were calculated per 100,000 persons. For time trend analysis, joinpoint regression was used. The annual percentage rate change (APC) and the average annual percent change (AAPC) was computed for each province. Spatial age-adjusted analysis was used to detect high risk clusters of gastric cancer mortality, from 2010 to 2015, using Kulldorff spatial scan statistics.

**Results:** In Ecuador, between 2004 and 2015, gastric cancer caused a total of 19,115 deaths: 10,679 in men and 8436 in women. When crude rates were analyzed, a significant decline was detected (AAPC:  $-1.8\%$ ;  $p < 0.001$ ). ISMR also decreased, but this change was not statistically significant (APC:  $-0.53\%$ ;  $p = 0.36$ ). From 2004 to 2007 and from 2008 to 2011 the province with the highest ISMR was Carchi; and, from 2012 to 2015, was Cotopaxi. The most likely high occurrence cluster included Bolívar, Los Ríos, Chimborazo, Tungurahua, and Cotopaxi provinces, with a relative risk of 1.34 ( $p < 0.001$ ).

**Conclusion:** There is a substantial geographic variation in gastric cancer mortality rates among Ecuadorian provinces. The spatial analysis indicates the presence of high occurrence clusters throughout the Andes Mountains.

## 1. Introduction

Although gastric cancer incidence rates have been declining in most parts of the world in recent decades, it is still the fifth most common type of cancer and the third leading cause of cancer death, for both sexes, worldwide. In 2012, it was estimated that 95,000 new gastric cancer cases (7% of total cancer incidence) and 723,000 deaths occurred (9% of total cancer mortality) [1]. In Ecuador, on the other hand, in 2015, gastric cancer was the leading cause of cancer death and the tenth cause of general mortality, for both sexes, causing a total of 1503 deaths—2.32% of total mortality [2].

From the epidemiological point of view, gastric cancer is characterized by its wide geographical distribution variability around the world [3]. For instance, high incidence rates of this disease are found in East Asia, Central, and Eastern Europe, and low incidence rates are described in Africa and North America. In Latin America and the Caribbean Region, the incidence rates for gastric cancer are of similar magnitude to those in Europe, but these are much higher than those in North America [1]. Additionally, high variability in gastric cancer

distribution has also been reported inside smaller areas, as countries or provinces [4–7]. This marked geographic variation suggests that environmental exposures might play an important role in the carcinogenesis of this tumor [7].

Various tools have been used to explore spatial and temporal trends, in order to explain some of this heterogeneity. One of these tools is the time trend analysis, a method used to monitor the growing burden of cancer; the temporal analysis of mortality from gastric cancer allows evaluating the effectiveness of intervention programs and the impact of public policies on cancer control [8]. Spatial and geographic epidemiology techniques are other useful tools; they are widely used to identify distribution patterns, and to show the risk factors of a territorial (and thus of an environmental) nature, that influence geographical patterns [6]. Additionally, substantial advances in geographical information systems (GISs) now provide researchers and public health practitioners with an excellent tool to explore and show geographic data [9].

Despite the importance of exploring patterns of distribution, that allow the determination of risk factors of environmental origin, no

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studies have been published until now showing the trend and geographic distribution of gastric cancer within Ecuador.

This paper is aimed at: a) describing the gastric cancer mortality trend by provinces; b) analyzing the spatial distribution of gastric cancer mortality, between 2004 and 2015; c) and investigating the presence of high occurrence clusters, between 2010 and 2015, in Ecuador.

## 2. Methods

### 2.1. Data sources

Data were collected from the National Institute of Statistics and Census (INEC) database, in its “Statistical Reports” section of: live birth, death, and fetal death [2].

Death registries include the “basic cause” of death, coded according to the International Classification of Diseases (ICD). For the codification of deaths, from 2004 to 2015, ICD-10 codes were used. Death registries were selected for cases where basic cause of death matched the ICD-10 code C-16, for stomach cancer. Population data were collected from 2001 and 2010 censuses. Data for Santa Elena and Santo Domingo de los Tsachilas provinces were not reported before 2010, as they were provincialized only in 2007. Data on these populations were not available until the 2010 Census.

### 2.2. Statistical analysis

Data on both the numbers of the population and the numbers of cancer-related deaths were classified by province, and crude gastric cancer mortality rates were calculated per 100,000 persons. The gastric cancer mortality rates were standardized by age through the indirect method. For this, the age-specific population and cases in Ecuador in 2014–2015 were used as the reference population. To calculate expected deaths, the population in each 5-year age group of each of the 24 Ecuadorian provinces was multiplied by the age-specific gastric cancer mortality rates of the reference population. Standardized mortality ratios (SMRs) were calculated, adding the total number of expected deaths of all age-groups in each province, and dividing the observed deaths by this sum. In addition, indirect age-standardized mortality rates (ISMRs) were calculated by multiplying the SMR of each province by the crude rate of the reference population.

For the time trend analysis, we used joinpoint regression analysis to identify the years when there were significant changes in ISMRs and crude rates. Joinpoint regression analysis fits a series of joined straight lines to the ISMRs, on a logarithmic scale [10]. Straight line segments are joined at “joinpoints”, where mortality trend changes with statistical significance [11]. The slope of each line segment, of the best-fitting model, was expressed as the annual percentage rate change (APC) and average annual percent change (AAPC). Significance tests were performed using the Monte Carlo permutation technique. The Joinpoint Regression Program version 4.4.0.0, from the Surveillance Research Program of the US National Cancer Institute, was used for the statistical analysis [10].

For ISMRs and SMRs geographical distribution description, the data has been grouped into three time periods: 2004–2007, 2008–2011, and 2012–2015. The person-years for each four-year period were obtained by multiplying populations by four.

Spatial age-adjusted analysis was used to detect high risk clusters of gastric cancer mortality, from 2010 to 2015, using Kulldorff spatial scan statistics, which was implemented in version 9.3 of the SaTScan software. For this analysis, 24 Ecuadorian provinces were selected as geographical units. Data from 2004 to 2009 were excluded due to changes in the administrative structure of the country, as explained earlier.

Identification of spatial high rate clusters was done under the Poisson probability model assumption, using a maximum spatial cluster

size of 25% for the total study population at risk. In this model, the null hypothesis is that the risk is constant over space and time, while the alternative hypothesis is that the risk inside and outside of the scanning window is different. For each scanning window the number of cases inside and outside was noted, and the likelihood ratio and the relative risk were calculated to test the hypothesis. The scanning window with the maximum likelihood, and with more than its expected number of cases, was denoted as the most likely high occurrence cluster. The other windows with statistically significant likelihood value detected are defined as secondary clusters, and are ranked according to their likelihood ratio test statistics [12–14]. The p-value for the detected clusters was evaluated using 9999 Monte Carlo simulation.

The GIS layer was obtained from the INEC geoportal [2]. All the geographical and cartographic outputs have been presented in ArcGIS version 10.0. Maps are presented for four year periods, shading each province according to the SMRs intervals.

The null hypothesis of uniform time trend and spatial distribution of gastric cancer mortality was rejected if the p-value was < 0.05.

## 3. Results

Within the period 2004–2015, gastric cancer caused a total of 19,115 deaths in Ecuador: 10,679 in men, 8436 in women. This corresponds to an average crude mortality rate of 10.9 deaths per 100,000 persons in both sexes: 12 deaths per 100,000 men and 9.4 deaths per 100,000 women. The ISMRs and SMRs for each province are shown in Table 1. The ISMR ranged among the provinces from 2.63 to 16.6 cases per 100,000 persons in the 2004–2007 period, 2.28–16.6 cases per 100,000 persons in the 2008–2011 period, and 2.51–14.8 cases per 100,000 persons in the 2012–2015 period.

Between 2004 and 2015, crude gastric cancer mortality rates decreased from 11.45 to 9.31 per 100,000 population; while ISMR decreased from 9.24 to 9.23 per 100,000 population in the same period. Fig. 1 presents the temporal trend of ISMR and crude rates.

In the 2004–2015 period the crude rates showed a statistically significant decrease (AAPC: –1.8%;  $p < 0.001$ ). Two periods were showed in joinpoint regression analysis: an initial period of statistically significant decrease during 2004 to 2012 (APC: –1.12%;  $p = 0.04$ ), followed by a decrease, which was not statistically significant during 2012 to 2015 (APC: –4.52%;  $p = 0.07$ ). Overall, the ISMR of the entire country between 2004 and 2015 decreased, but this change was not statistically significant (APC: –0.53%;  $p = 0.36$ ).

The ISMR trends by provinces showed a statistically significant decrease in Azuay (APC: –2.84%;  $p = 0.003$ ), Pichincha (APC: –1.86%;  $p = 0.03$ ), and Tungurahua (APC: –3.36%;  $p = 0.002$ ), in the 2004–2015 period, and in Pastaza (APC: –6.37%;  $p = 0.04$ ) in the 2006–2015 period. However, in Zamora Chinchipe a significant increase was detected (APC: 9.85%;  $p = 0.002$ ) in the 2004–2015 period (See Table 1).

In Fig. 2, the indirect age-standardized mortality rates for each province are shown. From 2004 to 2007, the province with the highest ISMR was Carchi, followed by Cotopaxi; from 2008 to 2011, Carchi had the highest ISMR, followed by Chimborazo; and, from 2012 to 2015, Cotopaxi had the highest ISMR, followed by Santo Domingo de los Tsachilas. In contrast, Napo and Orellana presented the lowest mortality rates.

The spatial analysis identified three statistically significant clusters for high occurrence of gastric cancer deaths, from 2010 to 2015. The most likely cluster included the following provinces: Bolivar, Los Ríos, Chimborazo, Tungurahua, and Cotopaxi (See Fig. 3). The overall relative risk (RR) within the cluster was 1.34, with an observed number of 2066 cases compared to 1631 expected cases ( $p < 0.001$ ).

A statistically significant secondary cluster for high occurrence was also detected in El Oro, Loja, Azuay, Zamora Chinchipe, and Cañar, with a calculated RR of 1.20 for 1729 observed cases and 1481 expected cases ( $p < 0.001$ ). Finally, the second secondary cluster included

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