Inequalities in esophageal cancer mortality in Brazil: Temporal trends and projections

Juliano dos Santos¹, Karina Cardoso Meira², Taynána César Simões³, Raphael Mendonça Guimarães⁴, Mauricio Wiering Pinto Telles⁵, Laiane Felix Borges², Auzenda Conceição Parreira de Assis², Maria das Vitorias Silva, Isabelle Ribeiro Barbosa⁶, Angela Carolina Brandão de Souza Giusti⁶, Camila Alves dos Santos⁶, Dyego Leandro Bezerra de Souza*¹

¹ National Cancer Institute, Cancer Hospital III, Rio de Janeiro, Brazil, ² Federal University of Rio Grande do Norte, Health School, Natal, Brazil, ³ Research Center Renê Rachou, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, ⁴ Joaquim Venâncio Polytechnic School, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, ⁵ Federal University of Rio Grande do Norte, Department of Collective Health, Graduate Program in Collective Health, Natal, Brazil, ⁶ Federal University of Rio Grande do Norte, Graduate program in Collective health, Natal, Brazil

* dysouz@yahoo.com.br

Abstract

The main objective of the study was to analyze the effect of age, period and birth cohort on esophageal cancer mortality in Brazil and its geographic regions, per sex. An ecological study is presented herein, which evaluated the deaths by esophageal cancer and the distribution, per geographic region. Poisson Regression was utilized to calculate the effects of age, period and birth cohort, and projections were made with the statistical software R, using the age-period-cohort model. Projection of data covered the period 2015–2029. Regarding the geographic regions of Brazil, a decrease was verified, throughout time, for the mortality rates of the South and Southeast regions, for men and women. For the North, Northeast and Midwest regions, an increase was evidenced in mortality rates, mainly for men, after the 2000’s. Regarding the projections, a progressive increase of mortality rates was verified for the Northeast and North regions. Divergences evidenced for observed and projected esophageal cancer mortality rates revealed inequalities among the geographic regions of Brazil.

Introduction

Esophageal cancer is the eighth most incident type of cancer in the world, and is the sixth cancer-related cause of death, presenting high lethality with global 5-year survival under 15%[1–3]. Disparities are highlighted in the distribution of this neoplasm around the world, as approximately 80% of cases and mortality occur in developing countries. In this context, the highest incidence and mortality rates are verified in Oriental Asia, Micronesia/Polynesia, and Oriental Africa, while intermediate rates are observed in South America and the Caribbean, and the lowest rates are found in North America, North Europe and Occidental Africa [1–2].

Squamous cell carcinoma (SCC) and adenocarcinoma (AC) are the two most incident histological types of esophageal cancer, which present different distributions throughout the
world, in by sex, being most incident in men [4–8]. SCC is most incident in poor countries, and 83.1% of cases occur in Centro-Oriental Asia (79.0%) and Latin America (4.1%). In contrast, 46% of AC cases occur in developed countries located in Occidental Europe, North America and Oceania [8].

This disparity in the distribution of SCC and AC cases can be explained by the fact that these pathologies present differentiated risk factors in the carcinogenesis process. In esophageal carcinoma, risk factors that have been widely studied, with strong evidence of association include tobacco consumption, excessive consumption of alcoholic beverages, low ingestion of fruit and vegetable, exposure to occupational agents such as benzene, silica, asbestos, gamma radiation, rubber or paint industry, and formaldehyde [9–10]. Azevedo and Silva et al. (2016) verified a population attributable risk (PAR) for esophageal cancer and the aforementioned factors over 72.8% for men and 60.2% for women [11], and in both sexes, the highest contribution was from tobacco and alcohol consumption.

For esophageal adenocarcinoma carcinogenesis, the risk factors with strong evidence of association are gastroesophageal reflux, obesity, consumption of tobacco and Barrett’s esophagus [9–10]. Olsen et al. (2011) found a 76% population attributable risk for the combination of tobacco consumption, gastroesophageal reflux, and obesity. The factors that contributed the most to PAR were gastroesophageal reflux and obesity [12].

Esophageal cancer incidence and mortality are strongly associated with low socioeconomic conditions of specific regions of the world [1–3,5]. In this sense, it is necessary to analyze the mortality rate evolution due to this disease considering territorial socioeconomic disparities, especially in countries scarred by inequalities in healthcare.

Brazil presents considerable social and healthcare inequalities across its geographic regions. This occurs because each geographic region has its own characteristics. The South region, for example, presents the best indices related to human development. The richest and most populated region is the Southeast, which stands out due to the amount of job opportunities. The Midwest region, in turn, has its economy focused on agriculture and stockbreeding, and presents the second lowest demographic density of the country, despite containing Brazil’s capital. The Northeast region is geographically constituted by a semi-arid climate, besides presenting the lowest human development indices. The North region also presents low human development indices, occupying the second place regarding the worst levels of the country. This region is also characterized by its low demographic density, due to the vast environmental reserve constituted by the Amazon Forest, which represents an important ecosystem in the world [13].

Considering this scenario and the impact of esophageal cancer on the disease burden of the country, analysis of age-period and birth cohort as well as mortality projections are very important measures for public health planning and evaluation of effectiveness and efficacy of prevention and control actions [14–15].

In the light of the above, the main objective of the study presented herein was to analyze the effect of age, period and birth cohort regarding esophageal cancer mortality in Brazil and its geographic regions, per sex, and in 5-year age groups (after 20 years of age). Projections were also made for the period 2015–2029.

**Methods**

**Study design and population**

An ecological study is presented herein, which evaluates the esophageal cancer mortality rates, per sex and age group. The classification of the disease was 150 (esophagus neoplasm) and C15 (malignant esophagus neoplasm, for the 9th and 10th International Classification of Diseases,
respectively), for the period 1980–2014, in age groups 0–4 and over 80 years old, for Brazil and its geographic regions, according to sex.

Mortality data were provided by the Mortality Information System (MIS), within the website of the Department of Statistics of the Brazilian Unified Health System (DATASUS) [16]. This portal provides the data in an aggregated way, whose collection and compilation is done by the Ministry of Health and made available with free access and without identification of the individuals involved. Access can be made through the website: http://ww2.datasus.gov.br/DATASUS/ following the sequence: "Health Statistics (TABNET)", "Vital Statistics", "Mortality—1979 to 1995, by ICD-9" for deaths that occurred from 1980 to 1995, while the menu "Mortality—1996 to 2015, by CID -10" was accessed to obtain the deaths that occurred from 1996 to 2014. Access to such data occurred without privileged access.

Population data were obtained from the Brazilian Institute of Geography and Statistics (IBGE) [13]. For this evaluation, the population censuses of years 1980, 1991, 2000 and 2010 were utilized, also from DATASUS [17]. Data extraction on deaths and population occurred during January 15–18, 2017, and was accomplished by two different investigators.

It is important to highlight that within the study period (1980–2014), Brazil has experienced important improvements in death certification, regarding better coverage of Mortality Information Systems (SIM) and reduction of the proportion of ill-defined death causes [18].

**Study variables**

Despite improvements in the quality of the information presented in the last decades, as shown in Table 1, there are still differences in the quality of death registries throughout the geographic regions of Brazil. A correction approach was necessary for underreporting and relocation of ill-defined death causes, based on the methodology of the World Health Organization (WHO) [19]. Deaths with incomplete diagnoses for general cancer and incomplete diagnosis for digestive tract cancer were redistributed, proportionally by year and age group [20], as described by Giusti et al. (2016) [21].

Esophageal cancer mortality rates were then calculated per 100,000 inhabitants, standardized by the world population as proposed by Segi (1960), for the age groups 0–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, 85–89 years, 90–94 years, and 95–99 years.

Table 1. Estimated annual percentage variation (EAPC) of esophageal cancer mortality rates, in Brazil. 1980–2014.

| Sex  | Region | EAPC | 95% CI |
|------|--------|------|--------|
| Male | North  | -2.19| -2.80  | -1.57  |
|      | Northeast| -4.81| -5.96  | -3.65  |
|      | South  | -2.96| -3.58  | -2.34  |
|      | Southeast| -1.40| -1.73  | -1.07  |
|      | Midwest| -4.57| -5.60  | -3.52  |
|      | Brazil | -3.06| -3.72  | -2.40  |
| Female| North  | -2.40| -3.08  | -1.72  |
|       | Northeast| -4.84| -5.97  | -3.7   |
|       | South  | -3.06| -3.69  | -2.43  |
|       | Southeast| -1.49| -1.83  | -1.14  |
|       | Midwest| -4.94| -5.98  | -3.88  |
|       | Brazil | -3.22| -3.89  | -2.55  |

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years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, 75–79 years, 80–84 years, and over 85 years old [22].

Analysis of the effect of age, period, and birth cohort utilized the age group from 20 years old to over 85 years old, as the younger age groups presented scarce data on deaths by the specific studied cancer, which hindered the estimation of APC models. In this way, five-year intervals were considered for the age, period, and birth cohort, yielding a total of 13 age groups, seven periods and 19 birth cohorts.

Statistical analysis
Calculation considered Poisson Regression to evaluate the effects of age-period-cohort. It was considered that temporal effects (age-period and birth cohort) acted in a multiplicative form on the rates [14–15]. Therefore, the logarithm of the expected rate value is a linear function of the effect of age, period and cohort:

$$\ln(E[r_{ij}]) = \ln\left(\frac{\theta_{ij}}{N_{ij}}\right) = \mu + \alpha_i + \beta_j + \gamma_k,$$

In this equation, $E[r_{ij}]$ represents the expected mortality rates for each age $i$ and period $j$, $\theta_{ij}$ is the amount of deaths for each age $i$ and period $j$, and $N_{ij}$ is the population at risk of dying, for each age $i$ and period $j$. Also, $\mu$ represents the median of the effect, while $\alpha_i$ is the effect of the age of group $i$, $\beta_j$ is the effect of period $j$, and $\gamma_k$ is the effect of cohort $k$ [14,15]. Estimation of APC parameters presents the main limitation of not estimating the complete model, known as non-identifiable problem. This issue occurs due to the exact linear relationship between temporal effects (age-period and birth cohort). There is no consensus in scientific literature on the best methodology to correct this issue, and the study presented herein opted to estimate the APC effect parameters by estimable functions, proposed by Holford [14] and applied by the Epi library, from library Epi 1.1.18a. of software R version 3.2.1 (R Foundation of Computational Statistics, Vienna, Austria http://www.r-project.org).

The estimable functions limited the analysis of the effects to their linear and curve combinations. Curves are estimable functions of the parameters and remain constant independently of the parametrization applied. The linear trend of effects is divided into two components: the first is the linear effect of age and the second is the drift, linear effect of period and cohort [14, 15]. The longitudinal trend of age is the sum of age and slope of the period ($\alpha_L + \beta_L$), where $\alpha_L$ and $\beta_L$ are the linear trends of age, and period, respectively. The term drift represents the linear trend of the logarithm of age specific rates and is equal to the sum of the slopes of period and cohort ($\beta_L + \gamma_L$), where $\beta_L$ and $\gamma_L$ are the linear trends for the period and cohort, respectively [14,15].

The fit of the model was evaluated by the deviance, defined as twice the logarithm of the verisimilitude function of the complete model in relation to the logarithm of the verisimilitude function for the estimated model. The contribution of the effects was evaluated by comparing the deviance of the model with the specific effect in relation to the complete model (age-period-cohort). The results with $p \leq 0.05$ were considered statistically significant.

The reference age group was 50–54 years of age, the reference period was 1995–1999 and the reference cohort utilized a median value, as central cohorts are more stable: 1940–1944 [14,15].

For each period, projections were made with the Nordpred [23] program within software R, using the age, period and cohort model. Data were separated in five-year blocks; however, for analysis of these data, a minimum limit of 10 cases was established for each block. Projections were separated in observed and predicted deaths, for each geographic region of Brazil and
D_{tot} = D_{risk} + D_{pop}

\Delta_{tot} represents the overall total change occurred, \Delta_{risk} constitutes the share of change associated with the risk of developing the disease, \Delta_{pop} is calculated on the basis of changes in size and structure of the population, Nooo is constituted by the number of observed deaths, while Nfff is the number of projected deaths and Noff, finally, is the number of expected deaths when there is an increase in mortality rates throughout the observed period.

Results

For the study period, a statistically significant reduction was verified in the annual percentage change estimated for mortality due to ill-defined death certificates and those presenting codes referring to incomplete diagnosis for general cancer (195,197 to 199, 238 to 239 in CID-9 and C-76 to C-80 e C-97 in CID-10) as well as incomplete diagnosis for esophageal cancer (159 in CID-9 and C-26 in CID-10), shown in Table 1.

It must be mentioned that the study presented herein followed a correction approach necessary for relocation of ill-defined death causes and incomplete cancer diagnoses for general cancer and esophageal cancer, according to the recommendations of the WHO [19], as previously described in the study variables topic.

In the period 1980–2014, 183,602 deaths were attributed to esophageal cancer in Brazil, representing a standardized mean mortality rate of 5.40 deaths per 100,000 inhabitants. After correction for ill-defined causes there was a 7.52% increase in the number of deaths (197,305) corresponding to a mortality rate of 5.77 deaths per 100,000 inhabitants. The correction due to incomplete diagnoses for general cancer and esophageal cancer represented a 12.12% increase in the number of deaths (23,914). The correction process increased the number of deaths by 20.53% (221,219), which yields a mean mortality rate of 6.40 deaths per 100,000 inhabitants. Mortality rates were higher for men, in Brazil and its five geographic regions. In this period, adjusted mortality rates for men were higher than for women.

Evolution of esophageal cancer mortality rates in the last 35 years in Brazil suggests stationarity in mortality rates for both sexes. The rates for the last period of the historical series (2010–2014) were lower than at the beginning of the series for both sexes (1980–1984).

Regarding geographic regions, a progressive reduction was evidenced in the mortality rates for the South and Southeast regions, for both sexes. The North, Northeast and Midwest regions experienced increasing mortality rates, more pronounced for men, especially after the 2000’s (Table 2).

In Brazil and its five geographic regions, and in both sexes, the exploratory analysis of esophageal cancer mortality rates revealed a progressive increase after the age group 60–64 years old. The highest rates were verified for the age group over 80 years old (Figs 1 and 2). This profile is maintained when the effect of age is adjusted by the effect of the period and birth cohort, when estimating the complete model.
Regarding mortality rates per age groups, according to the birth cohorts, there was a decreasing pattern in the evolution of mortality rates after the 1950’s, for men and women in Brazil, as well as for the South, Southeast and Midwest regions. For the North region, an increase was detected in mortality rates for men and women, in more advanced age groups, starting from the 1920 birth cohort. Regarding the Northeast region, a similar pattern was

| Sex | Region | Standardized Mortality Rate | Periods | 1980–1984 | 1985–1989 | 1990–1994 | 1995–1999 | 2000–2004 | 2005–2009 | 2010–2014 |
|-----|--------|-----------------------------|---------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Male | North  | ECWCR                       |         | 1.76      | 1.97      | 1.88      | 1.76      | 2.13      | 2.31      | 2.54      |
|      |        | ECCRDC                      |         | 2.24      | 2.50      | 2.39      | 2.16      | 2.54      | 2.56      | 2.72      |
|      |        | ECCRDC +GCI + DTC           |         | 2.40      | 2.72      | 2.66      | 2.41      | 2.87      | 2.89      | 3.02      |
|      | Northeast | ECWCR                  |         | 1.55      | 1.74      | 1.91      | 2.28      | 2.80      | 3.85      | 4.50      |
|      |        | ECCRDC                      |         | 2.36      | 2.54      | 2.61      | 2.85      | 3.36      | 4.09      | 4.71      |
|      |        | ECCRDC +GCI + DTC           |         | 2.59      | 2.78      | 2.90      | 3.15      | 3.81      | 4.63      | 5.38      |
|      | Midwest | ECWCR                      |         | 4.00      | 4.29      | 4.19      | 4.87      | 5.70      | 5.43      | 5.88      |
|      |        | ECCRDC                      |         | 4.67      | 4.92      | 4.60      | 5.28      | 5.98      | 5.60      | 6.01      |
|      |        | ECCRDC +GCI + DTC           |         | 5.27      | 5.56      | 5.27      | 5.95      | 6.81      | 6.28      | 6.62      |
|      | Southeast | ECWCR               |         | 8.47      | 8.30      | 7.87      | 8.08      | 7.76      | 7.27      | 7.15      |
|      |        | ECCRDC                      |         | 9.00      | 8.77      | 8.12      | 8.60      | 8.78      | 7.64      | 7.44      |
|      |        | ECCRDC +GCI + DTC           |         | 10.01     | 9.83      | 9.20      | 9.57      | 9.89      | 8.55      | 8.24      |
|      | South  | ECWCR                      |         | 13.39     | 13.24     | 12.97     | 12.78     | 12.64     | 10.92     | 10.42     |
|      |        | ECCRDC                      |         | 14.61     | 14.31     | 13.80     | 13.41     | 13.13     | 11.29     | 10.70     |
|      |        | ECCRDC +GCI + DTC           |         | 15.92     | 15.72     | 15.31     | 15.06     | 14.45     | 12.45     | 11.85     |
|      | Brazil | ECWCR                      |         | 6.73      | 6.71      | 6.00      | 6.21      | 6.77      | 6.61      | 6.63      |
|      |        | ECCRDC                      |         | 7.47      | 7.39      | 7.03      | 7.25      | 7.51      | 6.93      | 6.87      |
|      |        | ECCRDC +GCI + DTC           |         | 8.24      | 8.20      | 7.89      | 8.09      | 8.42      | 7.74      | 7.65      |
| Female | North | ECWCR                      |         | 0.48      | 0.49      | 0.52      | 0.54      | 0.58      | 0.63      | 0.74      |
|       |        | ECCRDC                      |         | 0.59      | 0.60      | 0.65      | 0.66      | 0.68      | 0.68      | 0.79      |
|       |        | ECCRDC +GCI + DTC           |         | 0.63      | 0.68      | 0.75      | 0.73      | 0.79      | 0.78      | 0.89      |
|       | Northeast | ECWCR              |         | 0.47      | 0.59      | 0.55      | 0.71      | 0.92      | 1.24      | 1.30      |
|       |        | ECCRDC                      |         | 0.69      | 0.84      | 0.75      | 0.91      | 1.10      | 1.31      | 1.49      |
|       |        | ECCRDC +GCI + DTC           |         | 0.77      | 0.93      | 0.85      | 1.02      | 1.26      | 1.53      | 1.69      |
|       | Midwest | ECWCR                      |         | 1.04      | 1.26      | 1.22      | 1.75      | 1.52      | 1.48      | 1.40      |
|       |        | ECCRDC                      |         | 1.18      | 1.41      | 1.32      | 1.87      | 1.58      | 1.51      | 1.42      |
|       |        | ECCRDC +GCI + DTC           |         | 1.25      | 1.56      | 1.63      | 2.17      | 1.85      | 1.74      | 1.84      |
|       | Southeast | ECWCR            |         | 2.21      | 2.10      | 1.81      | 1.80      | 1.61      | 1.48      | 1.38      |
|       |        | ECCRDC                      |         | 2.34      | 2.20      | 1.91      | 1.90      | 1.70      | 1.54      | 1.42      |
|       |        | ECCRDC +GCI + DTC           |         | 2.69      | 2.57      | 2.24      | 2.19      | 1.94      | 1.68      | 1.64      |
|       | South  | ECWCR                      |         | 3.88      | 3.64      | 3.43      | 3.36      | 3.17      | 2.68      | 2.46      |
|       |        | ECCRDC                      |         | 4.24      | 3.92      | 3.64      | 3.60      | 3.27      | 2.76      | 2.51      |
|       |        | ECCRDC +GCI + DTC           |         | 4.84      | 4.46      | 4.19      | 3.88      | 3.68      | 3.12      | 2.84      |
|       | Brazil | ECWCR                      |         | 1.86      | 1.81      | 1.64      | 1.41      | 1.30      | 1.57      | 1.50      |
|       |        | ECCRDC                      |         | 2.05      | 1.99      | 1.70      | 1.54      | 1.39      | 1.64      | 1.58      |
|       |        | ECCRDC +GCI + DTC           |         | 2.34      | 2.29      | 2.08      | 2.07      | 1.98      | 1.84      | 1.81      |

1Esophageal cancer without correction (ECWCR)
2Esophageal cancer correction for ill-defined causes (ECCRDC)
3Esophageal cancer correction for ill-defined causes and diagnoses incomplete general cancer and cancer of the digestive tract (ECCRDC +GCI + DTC)

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Regarding mortality rates per age groups, according to the birth cohorts, there was a decreasing pattern in the evolution of mortality rates after the 1950’s, for men and women in Brazil, as well as for the South, Southeast and Midwest regions. For the North region, an increase was detected in mortality rates for men and women, in more advanced age groups, starting from the 1920 birth cohort. Regarding the Northeast region, a similar pattern was

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identified, for both sexes, for individuals born after the 1910–1914 cohort, for individuals over 65–69 years of age. For the Midwest region, after the 1960’s and for age groups over 60 years, increasing mortality rates were also detected (S1 and S2 Appendices).

Concerning death risk for the analyzed periods, there was a protection effect for Brazil (with relative risk, RR, under 1) for the last periods of the series (2005–2009) and 2010–2014 in relation to the reference period (1995–1999) for men. For women, an increasing death risk was present for the last periods of the historical series. Analysis of death risk per geographic region points to disparities across Brazilian regions. For the North and Northeast regions, there was an increase in risk (RR > 1) in relation to the reference period in the two last periods analyzed (Fig 3). The Southeast, South, and Midwest regions showed decreasing death risk for this neoplasm, with a protection effect (RR < 1), especially in periods 2005–2009 and 2010–2014 for both sexes (Fig 4).
Similarly, there were disparities in death risks for the different Brazilian geographic regions. For Brazil and both sexes, as well as for the South and Southeast regions, there was a progressive reduction in death risk after 1940’s. For the Midwest region, there was an increase in death risk after the 1945–1949 cohort until 1950–1955, and then a progressive reduction was observed for the birth cohorts after. A similar profile was observed for the Midwest region, with an increase in death risk after the 1945–1949 cohort until 1950–1955, and then a progressive reduction was observed for the birth cohorts after this. The Northeast region, nevertheless, presented a progressive increase in death risk for men and women (RR>1) after the 1945–1949 cohort (Fig 1).

Table 3 shows the deviance changes in the sequential construction of APC models. Regarding the evolution of rates for men and women, in Brazil and its geographic regions, the best adjusted model according to the value of deviance and p-value at the level of 5%, was the APC

![Fig 2. Mortality rates for esophageal cancer in males, according to age, death period, and geographical region in Brazil.](https://doi.org/10.1371/journal.pone.0193135.g002)
Fig 3. Results of the age-period-cohort model, adjusted for esophageal cancer mortality in males, according to geographical region, in Brazil.

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Fig 4. Results of the age-period-cohort model, adjusted for esophageal cancer mortality in females, according to geographical region, in Brazil.

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Table 3. Deviance changes in the sequential construction of APC models.

|        | Female |        | Male |        |
|--------|--------|--------|------|--------|
| Models | DF     | Resid DV | Pr(>Chi) | DF     | Resid DV | Pr(>Chi) |
| Age    | 85     | 1,114.57 |      | 85     | 1,098.9 |        |
| Age-drift$^3$ | 84     | 741.15   | <0.0001 | 84     | 1,012.46 | <0.0001 |
| Age-Cohort | 80     | 685.32   | <0.0001 | 80     | 836.16   | <0.0001 |
| Age-Period-Cohort | 77     | 221.98   | <0.0001 | 77     | 731.86   | <0.0001 |
| Age-Period | 81     | 269.71   | <0.0001 | 81     | 889.7    | <0.0001 |
| Age-drift$^4$ | 84     | 741.15   | <0.0001 | 84     | 1,012.46 | <0.0001 |

Midwest

|        | Female |        | Male |        |
|--------|--------|--------|------|--------|
| Models | DF     | Resid DV | Pr(>Chi) | DF     | Resid DV | Pr(>Chi) |
| Age    | 85     | 133.524  |        | 85     | 234.04   |        |
| Age-drift | 84     | 131.143  | 0.123  | 84     | 189.87   | <0.0001 |
| Age-Cohort | 80     | 108.197  | 0.0001 | 80     | 149.45   | <0.0001 |
| Age-Period-Cohort | 77     | 96.675   | 0.009  | 77     | 136.23   | <0.0001 |
| Age-Period | 81     | 116.76   | 0.0004 | 81     | 174.94   | <0.0001 |
| Age-drift | 84     | 131.143  | 0.002  | 84     | 189.87   | 0.002   |

North

|        | Female |        | Male |        |
|--------|--------|--------|------|--------|
| Models | DF     | Resid DV | Pr(>Chi) | DF     | Resid DV | Pr(>Chi) |
| Age    | 85     | 126.41   |        | 85     | 136.86   |        |
| Age-drift | 84     | 120      | 0.0114 | 84     | 124.94   | 5E-04   |
| Age-Cohort | 80     | 111.75   | 0.0831 | 80     | 109.75   | 0.004   |
| Age-Period-Cohort | 77     | 110.04   | 0.6363 | 77     | 108.29   | 0.691   |
| Age-Period | 81     | 118.41   | 0.078  | 81     | 123.78   | 0.003   |
| Age-drift | 84     | 120      | 0.6631 | 84     | 124.94   | 0.764   |

Northeast

|        | Female |        | Male |        |
|--------|--------|--------|------|--------|
| Models | DF     | Resid DV | Pr(>Chi) | DF     | Resid DV | Pr(>Chi) |
| Age    | 85     | 827.08   |        | 85     | 1,667.97 |        |
| Age-drift | 84     | 192.82   | <0.0001 | 84     | 247.88   | <0.0001 |
| Age-Cohort | 80     | 157.45   | <0.0001 | 80     | 214.79   | <0.0001 |
| Age-Period-Cohort | 77     | 135.23   | <0.0001 | 77     | 151.34   | <0.0001 |
| Age-Period | 81     | 171.39   | <0.0001 | 81     | 182.38   | <0.0001 |
| Age-drift | 84     | 192.82   | <0.0001 | 84     | 247.88   | <0.0001 |

South

|        | Female |        | Male |        |
|--------|--------|--------|------|--------|
| Models | DF     | Resid DV | Pr(>Chi) | DF     | Resid DV | Pr(>Chi) |
| Age    | 85     | 610.52   |        | 85     | 987.83   |        |
| Age-drift | 84     | 142.65   | <0.0001 | 84     | 458.72   | <0.0001 |
| Age-Cohort | 80     | 120.64   | 0.0001 | 80     | 443.65   | 0.004   |
| Age-Period-Cohort | 77     | 111.62   | 0.0643 | 77     | 365.2    | <0.0001 |
| Age-Period | 81     | 132.12   | 0.0034 | 81     | 375.99   | 0.029   |
| Age-drift | 84     | 142.65   | 0.032  | 84     | 458.72   | <0.0001 |

Southeast

|        | Female |        | Male |        |
|--------|--------|--------|------|--------|
| Models | DF     | Resid DV | Pr(>Chi) | DF     | Resid DV | Pr(>Chi) |
| Age    | 85     | 927.12   |        | 85     | 1,135.61 |        |
| Age-drift | 84     | 162.93   | <0.0001 | 84     | 819.37   | <0.0001 |
| Age-Cohort | 80     | 162.6    | 0.9883 | 80     | 701.07   | <0.0001 |
| Age-Period-Cohort | 77     | 144.5    | 0.0117 | 77     | 523.39   | <0.0001 |
| Age-Period | 81     | 144.99   | 0.974  | 81     | 639.7    | <0.0001 |

(Continued)
model. The South region for women and North region for men were exceptions, as in these cases the most explicative model was age-cohort (AC)—and the North region for women—the best-adjusted model was age-drift.

Projections of standardized mortality rates for esophageal cancer show increases for men in the Northeast region, and for women in the North and Northeast regions. Projections for the Midwest, South and Southeast regions as well as the pooled analysis for Brazil indicated a reduction in mortality rates for both sexes. Projections per sex are presented in Tables 4 and 5, with the adjusted rates for the observed period and the number of cases per region.

An increase is expected in the number of deaths (10,737) for the male population in Brazil, when comparing the last observed period in relation to the last projected period, representing a 30% growth, of which 62% is due to population increase and -32% is due to reduction in risk. Regarding women, the expected increase in the number of deaths was 4,288, with 40% growth due to changes in population and -32% in reduction of risk and 72% to population increase.

The modifications in the number of deaths, separated by sex, and in function of the risk of developing esophageal cancer and changes in population structure, are represented in Fig 5, which compares the last observed period with the last projected period for Brazil and its geographic regions.

Discussion

Brazil is a country of continental dimensions, with pronounced socioeconomic disparities and healthcare inequalities, which could explain the differences in the demographic and epidemiologic transition processes experienced by its five geographic regions [25–26].

While the South and Southeast regions present the best socioeconomic indicators, the North and Northeast regions suffer with the worst indicators. This reality strongly affects the access to health services, even though Brazil counts with a public universal healthcare system [25–26].

Herein the highest mortality rates were verified for the South and Southeast regions, with values similar to the rates observed in countries of Oriental Asia and South of Africa [1–3]. The lowest mortality rates were verified for the North and Northeast regions of Brazil [1–3]. The Northeast region presented an intermediate level, with rates similar to those of Uruguay, Argentina and Chile [5]. The North region presented mortality rates equivalent to those of United Kingdom, Germany and Cuba [27].

The high mortality rates for esophageal cancer in the Brazilian regions with higher socioeconomic development can be explained by the heterogeneous demographic process of the country. According to Vasconcelos & Gomes (2012) [28], since the 20th century there have been drops in mortality, birth rates and fecundity in Brazil, which started the aging process of the population. These changes, however, did not occur concomitantly nor homogeneously.

Table 3. (Continued)

|       | Brazil       |       |       |
|-------|--------------|-------|-------|
|       | Female       | Male  |       |
|       | Age-drift    | 84    | 162.93| 0.0112|
|       |              | 84    | 819.37| <0.0001|

1 Degrees of freedom  
2 Residual Deviance  
3 Linear trend of the logarithm of age specific rates, and is equal to the sum of the slopes of period and cohort (β_L + γ_L), where β_L and γ_L are the linear trends for the period and cohort.  
4 Longitudinal trend of age is the sum of age and slope of the period (α_L + β_L), where α_L and β_L are the linear trends of age, and period, respectively.

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throughout the country. While the Southeast, South and Midwest regions present a more advanced process, the North and Northeast regions present younger age structure, as these regions still present high fecundity, birth and mortality rates.

| Table 4. Observed and predicted number of deaths in males by age and world age-standardized rates (ASW) in Brazil. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (years)                     | 2000–2004       | 2005–2009       | 2010–2014       | 2015–2019       | 2010–2024       | 2025–2029       |
| BRAZIL                          | Observed        | Predicted       | Observed        | Predicted       | Observed        | Predicted       |
| 0–49                            | 4,424           | 4,411           | 4,215           | 3,910           | 3,753           | 4,389           |
| 50–74                           | 18,647          | 21,141          | 24,038          | 27,241          | 24,908          | 31,555          |
| ≥ 75                            | 4,656           | 5,880           | 6,799           | 6,965           | 6,535           | 9,845           |
| ASW                             | 8.42            | 7.74            | 7.65            | 6.89            | 6.37            | 6.00            |
| 95% CI                          | 8.23–8.51       | 7.62–7.88       | 7.51–7.73       | 6.79–6.91       | 6.21–6.43       | 5.92–6.03       |
| Northeast                       | Age (years)     | Observed        | Predicted       | Observed        | Predicted       | Observed        |
| 0–49                            | 451             | 586             | 790             | 926             | 1,052           | 1,081           |
| 50–74                           | 2,115           | 2,943           | 4,075           | 5,401           | 6,745           | 8,017           |
| ≥ 75                            | 833             | 1,219           | 1,539           | 1,688           | 2,170           | 2,864           |
| ASW                             | 3.81            | 4.63            | 5.38            | 6.06            | 6.46            | 6.63            |
| 95% CI                          | 3.61–3.94       | 4.56–4.84       | 5.25–5.63       | 5.93–6.21       | 6.31–6.57       | 6.47–6.80       |
| North                           | Age (years)     | Observed        | Predicted       | Observed        | Predicted       | Observed        |
| 0–49                            | 77              | 92              | 95              | 117             | 134             | 150             |
| 50–74                           | 340             | 449             | 564             | 688             | 830             | 985             |
| ≥ 75                            | 122             | 148             | 196             | 204             | 257             | 324             |
| ASW                             | 2.87            | 3.01            | 3.02            | 3.01            | 2.98            | 2.92            |
| 95% CI                          | 2.61–3.13       | 2.79–3.29       | 2.87–3.34       | 2.81–3.23       | 2.79–3.15       | 2.74–3.09       |
| Midwest                         | Age (years)     | Observed        | Predicted       | Observed        | Predicted       | Observed        |
| 0–49                            | 252             | 233             | 256             | 261             | 324             | 347             |
| 50–74                           | 889             | 1,126           | 1,427           | 1,767           | 2,013           | 2,364           |
| ≥ 75                            | 246             | 294             | 361             | 405             | 534             | 699             |
| ASW                             | 6.81            | 6.28            | 6.62            | 6.29            | 6.09            | 6.00            |
| 95% CI                          | 6.55–6.98       | 6.15–6.57       | 6.36–6.87       | 6.01–6.57       | 5.82–6.31       | 5.76–6.20       |
| Southeast                       | Age (years)     | Observed        | Predicted       | Observed        | Predicted       | Observed        |
| 0–49                            | 2,558           | 2,434           | 2,080           | 1,818           | 1,775           | 1,758           |
| 50–74                           | 10,102          | 10,957          | 12,000          | 13,190          | 13,853          | 14,536          |
| ≥ 75                            | 2,178           | 2,710           | 3,020           | 3,047           | 3,384           | 4,106           |
| ASW                             | 9.89            | 8.55            | 8.24            | 7.03            | 6.31            | 5.84            |
| 95% CI                          | 9.59–9.97       | 8.42–8.73       | 7.95–8.46       | 6.92–7.15       | 6.22–6.36       | 5.76–5.95       |
| South                           | Age (years)     | Observed        | Predicted       | Observed        | Predicted       | Observed        |
| 0–49                            | 1,085           | 1,067           | 992             | 813             | 839             | 976             |
| 50–74                           | 5,204           | 5,666           | 5,971           | 6,590           | 6,853           | 7,176           |
| ≥ 75                            | 1,278           | 1,510           | 1,683           | 1,722           | 1,964           | 2,327           |
| ASW                             | 14.45           | 12.45           | 11.85           | 9.96            | 8.98            | 8.49            |
| 95% CI                          | 14.21–14.62     | 12.14–12.63     | 11.63–12.05     | 9.71–10.17      | 8.76–9.15       | 8.27–8.65       |

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In this context, it is important to highlight that the industrialization and urbanization process, along with changes in habits and lifestyle, has been more intense in the South and Southeast regions of Brazil. This way, the epidemiological transition was more pronounced, with a

| Table 5. Observed and predicted number of deaths in females by age and world age-standardized rates (ASW) in Brazil. |
|---------------------------------|
|                                | 2000–2004 | 2005–2009 | 2010–2014 | 2015–2019 | 2010–2024 | 2025–2029 |
| **BRAZIL**                      |
| Age (years)                     |           |           |           |           |           |           |
| 0–49                            | 753       | 772       | 819       | 815       | 914       | 1,092     |
| 50–74                           | 4,645     | 5,330     | 5,865     | 6,705     | 7,433     | 8,121     |
| ≥ 75                            | 2,578     | 3,217     | 3,941     | 4,195     | 4,783     | 5,700     |
| ASW                             | 1.98      | 1.84      | 1.81      | 1.65      | 1.55      | 1.49      |
| 95% CI                          | 1.81–2.03 | 1.78–1.95 | 1.75–1.93 | 1.54–1.74 | 1.46–1.61 | 1.41–1.56 |
| **Northeast**                   |
| Age (years)                     |           |           |           |           |           |           |
| 0–49                            | 132       | 154       | 218       | 213       | 265       | 308       |
| 50–74                           | 767       | 1,079     | 1,275     | 1,613     | 1,847     | 2,118     |
| ≥ 75                            | 492       | 762       | 1,132     | 1,301     | 1,595     | 1,920     |
| ASW                             | 1.26      | 1.53      | 1.69      | 1.74      | 1.73      | 1.73      |
| 95% CI                          | 1.15–1.35 | 1.44–1.61 | 1.58–1.74 | 1.67–1.79 | 1.67–1.79 | 1.66–1.79 |
| **North**                       |
| Age (years)                     |           |           |           |           |           |           |
| 0–49                            | 21        | 16        | 29        | 27        | 31        | 35        |
| 50–74                           | 79        | 121       | 145       | 192       | 246       | 296       |
| ≥ 75                            | 53        | 51        | 105       | 143       | 207       | 280       |
| ASW                             | 0.79      | 0.78      | 0.89      | 1.01      | 1.06      | 1.07      |
| 95% CI                          | 0.57–0.92 | 0.58–0.93 | 0.65–1.03 | 0.92–1.18 | 0.98–1.18 | 0.98–1.19 |
| **Midwest**                     |
| Age (years)                     |           |           |           |           |           |           |
| 0–49                            | 55        | 42        | 45        | 49        | 54        | 57        |
| 50–74                           | 220       | 319       | 384       | 494       | 574       | 669       |
| ≥ 75                            | 109       | 115       | 190       | 241       | 343       | 475       |
| ASW                             | 1.85      | 1.74      | 1.84      | 1.78      | 1.71      | 1.67      |
| 95% CI                          | 1.71–2.01 | 1.58–1.95 | 1.70–2.01 | 1.61–1.95 | 1.59–1.84 | 1.43–1.82 |
| **Southeast**                   |
| Age (years)                     |           |           |           |           |           |           |
| 0–49                            | 362       | 363       | 358       | 347       | 383       | 393       |
| 50–74                           | 2,147     | 2,333     | 2,546     | 2,924     | 3,284     | 3,682     |
| ≥ 75                            | 1,200     | 1,374     | 1,589     | 1,612     | 1,766     | 2,078     |
| ASW                             | 1.94      | 1.68      | 1.64      | 1.47      | 1.4       | 1.37      |
| 95% CI                          | 1.85–2.01 | 1.78–1.79 | 1.55–1.75 | 1.38–1.54 | 1.32–1.43 | 1.30–1.43 |
| **South**                       |
| Age (years)                     |           |           |           |           |           |           |
| 0–49                            | 188       | 197       | 169       | 146       | 119       | 109       |
| 50–74                           | 1,433     | 1,478     | 1,518     | 1,533     | 1,584     | 1,634     |
| ≥ 75                            | 725       | 914       | 924       | 950       | 1,026     | 1,223     |
| ASW                             | 3.68      | 3.12      | 2.84      | 2.25      | 1.95      | 1.78      |
| 95% CI                          | 3.54–3.81 | 3.06–3.32 | 2.65–3.01 | 2.16–2.37 | 1.87–2.05 | 1.71–1.84 |

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progressive increase in incidence and mortality rates of chronic non-transmissible diseases, among these, cancer. The North and Northeast regions also present epidemiological transition processes, but these are characterized by superposition rather than substitution, with high morbidity burden due to transmissible diseases and external causes [28–29]. The cancer transition defended by Bray et al (2012) [30] was observed herein, where locations with lower human development indices are more exposed to cancers associated with infections (cervical, liver, non-Hodgkin lymphoma, among others) while regions with higher human development indices are associated with lifestyle and habit-related cancers. Higher prevalence of tobacco smoking must also be mentioned, which was an important risk factor for esophageal cancer in the South and Southeast regions, when compared with the North and Northeast [31, 32].

The South region of Brazil, despite presenting the highest socioeconomic development and best healthcare indicators, is recognizably the Brazilian location with the highest incidence and mortality rates for esophageal cancer, and this situation has been maintained for decades. The

Fig 5. World age-standardized rates (ASW), changes in numbers of deaths (No) relative change due to risk (Risk) and changes in the structure of population (Pop), between 2010–2014 (observed) and 2025–2029 (predicted) of esophageal cancer mortality in Brazil.

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mortality pattern of the Midwest region has been the same for the last two analyzed periods, and presented higher rates in comparison with the 1980’s, which were similar to those of countries with intermediate mortality.

This reality is a reflex of the particularities of each region, with habits and lifestyle connected to local culture. In South Brazil, as well as in Argentina and Uruguay, yerba mate tea (chimarrão) is consumed at high temperatures, several times a day [33]. In this sense, it is important to remark that studies have demonstrated an association between the consumption of yerba mate tea and esophageal cancer, based on meta-analysis studies [34] and pooled analyses [35]. These studies evidenced a positive association with the high consumption of yerba mate tea, when compared with low consumption. These case-control studies evaluated by pooled analyses were adjusted by the consumption of tobacco and alcohol, as well as by sex, age group, education level, and housing location (urban/rural) [35].

The results observed for the Midwest region can be explained by the intense migration of southerners to this region in the 1970’s, due to the expansion of agriculture frontiers. Migrants maintained the same cultural habits of drinking yerba mate tea, and a study carried out by Silva et al (2013) [36] calculated the incidence rate of esophageal cancer in two capitals of the Midwest: Cuiabá (Mato Grosso state) and Brasília (Federal District), which were similar to the incidence rates observed for the South region.

The South and Southeast regions were the first Brazilian regions to count with sanitation and access to consumption goods, such as refrigerators. This could explain the reduction in mortality rates by gastric cancer presented in the last 30 years, and the increase in mortality rates of the North and Northeast regions, in the same period, especially after the 2000’s [21]. It is possible that decreasing mortality rates for gastric cancer are a consequence of decreasing prevalence of *Helicobacter pylori*; such a decrease can reduce gastric cancer incidence and mortality and simultaneously contribute to increase esophageal cancer. The stomach infected by this bacterium produces less acid and inhibits the synthesis of ghrelin, which induces satiety—ghrelin prevents obesity and promotes gastric emptying. All these associated elements decrease the possibility of gastroesophageal reflux, a known risk factor, especially for esophageal adenocarcinoma [37–39].

It was also observed, for both sexes and for all geographic regions, a progressive increase in mortality rates with the aging process, reaching an incidence peak in individuals in their 60’s. These results corroborate those found in Korea [40], Osaka-Japan [41], Linzhou-China [42], Australia [43], Spain [44], Germany [27], Cuba [27] and the United Kingdom [27]. This was expected, as there is strong effect of age on the evolution of incidence and mortality rates of chronic diseases, which are a consequence of exposure to risk factors throughout life [14–15].

The similarity between esophageal cancer incidence and mortality rates must be mentioned, due to poor prognosis, as frequently diagnosis is made at advanced stages of the disease. Dysphagia, the main symptom of the disease, only manifests when a considerable extension of the organ is compromised (generally the distal two-thirds of the esophagus) [45–46]. Associated with late diagnosis, prognosis for this neoplasm is still reserved, as no improvements in survival were observed with adjuvant chemotherapy [47]. However, recent clinical advances have evidenced therapeutic improvements regarding neoadjuvancy implemented with the association of chemoradiotherapy for resectable tumors [43, 48–49].

The differences observed in esophageal cancer mortality for men and women, across Brazilian geographic regions, agree with other studies [50, 40–44]. Men present higher incidence and mortality due to higher exposure to risk factors for this neoplasm [9–12], and because men utilize less health services, such as medical tests and appointments [50].

Regarding death risk in the 5-year periods analyzed and projections, the male sex and regions South, Southeast and Midwest presented decreases in the last two 5-year periods and
when comparing the last observed period with the last projected period. These results are similar to those observed in Chile [5], Costa Rica [5], Argentina [5], Japan [41], Germany [27] and Spain [44]. This result could be a reflex of the interaction between the effect of healthcare service access period and birth cohort, reducing risk factor prevalence for esophageal cancer in the population of those regions (especially regarding tobacco consumption) [5–14,19–21,25–27,41–44].

The period effect refers to alterations in incidence and mortality trends, related to the changes that occur in a specific period and influence simultaneously all age groups [14–15]. Therefore, possibly the increase in death risk presented by regions North and Northeast, which remained in the projections, can be a consequence of improvements in SIM and death registries. This could have reduced the proportion of ill-defined registered deaths due to better access to health services and cancer assistance, after implementation of the National Policy for Cancer Attention [51]. The possibility of diagnosing the disease was increased, even if in late stages.

The birth cohort effect is caused by factors that affect one generation, promoting changes with different magnitudes in successive age and period groups, and enables the analysis of long-term exposure effects to risk factors. Still, the effect of birth cohort reflects the interaction between the effect of age and period as a result of accumulated exposure throughout time [14–15].

In this study, the progressive reduction in esophageal cancer death risk for birth cohorts after the 1950’s is remarkable for Brazil, the South, Southeast and North regions, for both sexes, and after the 1960’s for the Midwest region. This decrease in death risk can be a consequence of the birth cohort effect promoted by the reduction of tobacco consumption prevalence in these populations [40–44]. This hypothesis is reinforced because there has been a decrease in death risk, in Brazil, for esophageal [21] and lung [52] cancers starting with the same cohorts. Brazil has presented an important reduction in tobacco consumption prevalence in the last two decades, related to prevention and control measures that include education, prevention, treatment and policy actions [31–32, 45].

In contrast, there was an increase in death risk in the 1940’s for both sexes in the Northeast region. It is possible that, in this region, the poorest of Brazil, this reality could be explained by the interaction between the period and birth cohort effects, due to higher possibilities of diagnosing cancer along with better access to health services. Increased exposure to risk factors, such as tobacco consumption, is not probable, as studies have demonstrated reductions in tobacco prevalence for this geographic region, between 1989 and 2013 [31–32, 45].

The impossibility of evaluating the dynamics of mortality rates according to histological type is a limitation of the study. Esophageal spinocellular carcinoma and adenocarcinoma present different risk and protection factors [9–12] and according to recent studies, present different behavior regarding incidence and mortality [8]. The Brazilian Mortality Information System does not provide information on the histological type, one of its fragilities in the evaluation of the profile of cancer mortality in the Brazilian population. However, a study carried out with incidence data from population-based cancer registries in Brazil has identified that more than 70% of incident cases refer to squamous cell carcinoma [5].

Another vulnerability related to the Mortality Information System refers to the intra-regional differences in death registry quality. Nevertheless, this study attenuated this limitation by correcting the ill-defined death registries and those with incomplete diagnoses, through proportional distribution [19–21]. Additionally, Brazil does not count with a historical series on the prevalence of risk and protection factors for non-transmissible chronic diseases, which could certainly help better comprehend the behavior of mortality rates in different birth cohorts.

It must also be highlighted that there are inherent fragilities of the APC method. However, this type of study is utilized since the 1980’s, although scientific literature does not reach a consensus on the best statistical method for the correction of unidentified problems [14].
Supporting information

S1 Appendix. Mortality rates for esophageal cancer by birth cohort and age in females, according geographical region, in Brazil.
(TIF)

S2 Appendix. Mortality rates for esophageal cancer by birth cohort and age in males, according to geographical region, in Brazil.
(TIF)

Author Contributions

Conceptualization: Juliano dos Santos, Karina Cardoso Meira, Raphael Mendonça Guimarães, Angela Carolina Brandão de Souza Giusti, Dyego Leandro Bezerra de Souza.

Data curation: Juliano dos Santos, Karina Cardoso Meira, Taynâna César Simões, Raphael Mendonça Guimarães, Mauricio Wiering Pinto Telles, Laiane Felix Borges, Auzenda Conceição Parreira de Assis, Maria das Vitorias Silva, Isabelle Ribeiro Barbosa, Angela Carolina Brandão de Souza Giusti, Camila Alves dos Santos, Dyego Leandro Bezerra de Souza.

Formal analysis: Juliano dos Santos, Karina Cardoso Meira, Raphael Mendonça Guimarães, Laiane Felix Borges, Auzenda Conceição Parreira de Assis, Maria das Vitorias Silva, Isabelle Ribeiro Barbosa, Angela Carolina Brandão de Souza Giusti, Camila Alves dos Santos, Dyego Leandro Bezerra de Souza.

Investigation: Karina Cardoso Meira, Taynâna César Simões, Mauricio Wiering Pinto Telles, Laiane Felix Borges, Auzenda Conceição Parreira de Assis, Maria das Vitorias Silva, Isabelle Ribeiro Barbosa, Angela Carolina Brandão de Souza Giusti, Camila Alves dos Santos, Dyego Leandro Bezerra de Souza.

Methodology: Juliano dos Santos, Karina Cardoso Meira, Taynâna César Simões, Raphael Mendonça Guimarães, Mauricio Wiering Pinto Telles, Laiane Felix Borges, Auzenda Conceição Parreira de Assis, Maria das Vitorias Silva, Isabelle Ribeiro Barbosa, Angela Carolina Brandão de Souza Giusti, Camila Alves dos Santos, Dyego Leandro Bezerra de Souza.

Project administration: Dyego Leandro Bezerra de Souza.

Supervision: Karina Cardoso Meira, Mauricio Wiering Pinto Telles, Dyego Leandro Bezerra de Souza.

Validation: Dyego Leandro Bezerra de Souza.

Visualization: Dyego Leandro Bezerra de Souza.

Writing – original draft: Juliano dos Santos, Karina Cardoso Meira, Taynâna César Simões, Raphael Mendonça Guimarães, Mauricio Wiering Pinto Telles, Auzenda Conceição Parreira de Assis, Camila Alves dos Santos, Dyego Leandro Bezerra de Souza.

Writing – review & editing: Juliano dos Santos, Karina Cardoso Meira, Camila Alves dos Santos, Dyego Leandro Bezerra de Souza.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0. Cancer incidence and mortality worldwide: IARC Cancer Base No. 11. International Agency for Research on Cancer 2014. Available from: http://globocan.iarc.fr.
2. Thuler FP, Forones NM, Ferrari AP. Advanced esophageal cancer: still a delayed diagnosis. Arq Gastroenterol. 2006; 43(3):206–11. PMID: 17160236

3. American Cancer Society. Global cancer facts & figures 2008 [Internet]. 2nd ed. Atalanta: American Cancer Society; 2011. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveillance/documents/document/acspc-027766.pdf.

4. Thrift AP, Whiteman DC. The incidence of esophageal adenocarcinoma continues to rise: analysis of period and birth cohort effects on recent trends. Annals of Oncology 23: 3155–3162, 2012. https://doi.org/10.1093/annonc/mds181 PMID: 22847812

5. Barrios E, Sierra MS, Musseti C, Forman D. The burden of oesophageal cancer in Central and South America. Cancer Epidemiology 44S (2016) S53–S61.

6. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 Through 2008. Ca Cancer J Clin, 2012; 62:118–128. https://doi.org/10.3322/caac.20141 PMID: 22281605

7. Stewart B., Wild C. (Eds.). Oesophageal cancer. In: World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer, 2014.

8. Arnold M, Soerjomataram I, Ferlay J, Forman D. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015; 64:381–387. https://doi.org/10.1136/gutjnl-2014-308124 PMID: 25320104

9. Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. Gut 2013; 62:1406–1414. https://doi.org/10.1136/gutjnl-2012-302412 PMID: 22917659

10. Holmes RS, Vaughan TL. Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol. 2007 Jan; 17(1):2–9. https://doi.org/10.1016/j.sradonc.2006.09.003 PMID: 17185192

11. Azevedo e Silva G, Moura L, Curado MP, Gomes FS, Otero U, Rezende LFM. The Fraction of Cancer Attributable to Ways of Life, Infections, Occupation, and Environmental Agents in Brazil in 2020.PLoS One. 2016; 11(2): e0148761. https://doi.org/10.1371/journal.pone.0148761 PMID: 26863517

12. Olsen CM, Pandeya N, Green AC, Webb PM, David C. Population Attributable Fractions of Adenocarcinoma of the Esophagus and Gastroesophageal Junction. Am J Epidemiol. 2011; 174(5):582–590. https://doi.org/10.1093/aje/kwr117 PMID: 21719746

13. Brazilian Institute of Geography and Statistics. Available from: http://www.ibge.gov.br/home/estatistica/populacao/estimativa2016/estimativa_dou.shtm.

14. Holford TR. Understanding the effects of age, period, and cohort on incidence and mortality rates. Ann Rev Public Health 1991; 12: 425–457 [https://doi.org/10.1146/annurev.pu.12.050191.002233 PMID: 2049144].

15. Robertson C, Gandini S, Boyle P. Age-period-cohort models: a comparative study of available methodologies. J Clin Epidemiol 1999; 52: 569–583 [https://doi.org/10.1016/S0895-4356(99)00233-5 PMID: 10498897].

16. Computer science department of SUS. SIM—Mortality Information System. Available from: <http://dataset.saudes.gov.br/sistemas-e-aplicativos/eventos-v/sim-sistema-de-informacoes-de-mortalidade>. Accessed in: january 16, 2016.

17. Computer science department of SUS (DATASUS). Resident population. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?ibge/cnv/popbr.def.

18. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos Não Transmissíveis e Promoção da Saúde. Saúde Brasil 2014: uma análise da situação de saúde e das causas externas / Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância de Doenças e Agravos Não Transmissíveis e Promoção da Saúde.–Brasília: Ministério da Saúde, 2015. 462 p.: il.

19. Mathers CD, Bernard C, Ibbug K, Inoue M, Fat DM, Shibuya K, Stein C, Torimjima N, Xu H. Global Burden of Disease in 2002: data sources, methods and results. Global Programme on Evidence for Health Policy Discussion Paper No. 54 World Health Organization December 2003 (revised February 2004).

20. Mello JMH.; Gotlieb SLD; Laurenti R. O sistema de informações sobre mortalidade: problemas e propostas para o seu enfrentamento I-mortes por causas naturais. Rev. bras. Epidemiol. 2002; 5(2):197–211.

21. Giusti ACB, Salvador PTCO, Santos J, Meira KC, Camacho AR, Guimarães RM, Souza DLB. Trends and predictions for gastric cancer mortality in Brazil. World J Gastroenterol 2016 July 28; 22(28): 6527–6538. https://doi.org/10.3748/wjg.v22.i28.6527 PMID: 27605887

22. Segi M. Cancer mortality for selected sites in 24 countries (1950–57). Department of Public Health, Tohoku University of Medicine, Sendai, Japan. 1960.

23. Nordpred Software Package. Available from: https://www.kreftregisteret.no/en/Research/Projects/Nordpred/Nordpred-software/.
24. Møller B1, Fekjaer H, Hakulinen T, Sigvaldason H, Storm HH, Talbäck M, Haldorsen T. Prediction of cancer incidence in the nordic countries: Empirical comparison of different approaches. Stat Med. 2003; 22:2751–2766. https://doi.org/10.1002/sim.1481 PMID: 12939784

25. Omran A. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Memoriial Fund Quarterly. 49 (Part 1), p. 509–538, 1971.

26. Malta DC, da Silva JB Jr. Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas Não Transmissíveis no Brasil após três anos de implantação, 2011–2013. Epidemiol. Serv. Saúde, Brasília, v. 23, n. 3, p.599–608, Set. 2014.

27. World Health Organization. WHO mortality data and statistics [Internet]. Geneva: WHO; 2013. Available from: http://www.who.int/whosis/mort/download/en/index.html.

28. Vasconcelos AMN, Gomes MMF. Transição demográfica: a experiência brasileira. Epidemiol. Serv. Saúde[Internet]. 2012. 21(4): 539–548. http://dx.doi.org/10.5123/S1679-49742012000400003.

29. Guimarães RM, Muzi CD, Teixeira MP, Pinheiro SS. A transição da mortalidade por cânceres no Brasil e a tomada de decisão estratégica nas políticas públicas de saúde da mulher. R. Pol. Públ., São Luís, v. 20, n 1, p. 33–50, jan./jun. 2016.

30. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet, [S. l.], v. 13, n. 8, p.1–11, aug. 2012.

31. Malta DC, Iser BPM, Sá NNB, Yokota RTC, Moura L, Claro RM, Luz MGC. Tendências temporais no consumo de tabaco nas capitais brasileiras, segundo dados do VIGITEL, 2006 a 2011. Cad. Saúde Pública, Rio de Janeiro, 29(4):812–822, abr, 2013.

32. Wünsch-Filho V, Mirra AP, López RVM, Antunes LF. Tabagismo e câncer no Brasil: evidências e perspectivas. Ver Bras Epidemiol 2010; 13(2): 175–87.

33. Barros SGS, Ghisolfi ES, Luz LP, Barlem GG, Vidal RM, Wolff FH et al. Mate (chimarrão) é consumido em alta temperatura por população sob risco para o carcinoma epimérito de esôfago. Arq. Gastroenterol. [Internet]. 2000 Jan [citado 2017 Feb 08]. 37(1):25–30. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-28032000000100006&lng=en, http://dx.doi.org/10.1590/S0004-28032000000100006. PMID: 10962624

34. Szymańska K, Matos E, Hung RJ, Wünsch-Filho V, Eluf-Neto J, Menezes A, Daudt AW, Brennan P, Boffetta P. Drinking of mate and the risk of cancers of the upper area aerodigestive tract in Latin America: case control study. Cancer Causes Control 2010; 21:1799–806. https://doi.org/10.1007/s10552-010-9606-6 PMID: 20623173

35. Lubin JH1, De Stefani E, Abnet CC, Acosta G, Boffetta P, Victora G, Graubard BI, Muñoz N, Deneo-Pellegrini H, Franceschi S, Castellsagué X, Ronco AL, Dawsey SM. Mate drinking and esophageal squamous cell carcinoma in South America: pooled results from two large multicenter case-control studies. Cancer Epidemiol Biomarkers Prev 2014; 23: 107–16. https://doi.org/10.1158/1055-9965.EPI-13-0796 PMID: 24130226

36. Silva DRM, Curado MP, de Oliveira JC. High incidence of esophageal cancer in central-western Brazil: a migrant effect? Eur J Cancer Prev; 22(3): 235–43, 2013 May. https://doi.org/10.1097/CEJ.0b013e3283592c9d PMID: 22990005

37. Islami F, Kamangar F. Helicobacter pylori and esophageal cancer risk: a meta-analysis. Cancer Prev Res 2008; 1(5):329–339.

38. Zhuo X, Zhang Y, Wang Y, Zhuo W, Zhu Y, Zhang X. Helicobacter pylori infection and oesophageal cancer risk: association studies via evidence-based meta-analysis. Clin Oncology 2008; 20:757–762.

39. Xie FJ, Zhang YP, Zheng QQ, Jind HC, Wang FL, Chen M, Shao L, Zou DH et al. Helicobacter pylori infection and esophageal cancer: an updated meta-analysis. World J Gastroenterol 2013; 19(36):6098–6107.

40. Lee JK, Shin A, Lee JK, Mo C. Decreases in Smoking-Related Cancer Mortality Rates Are Associated with Birth Cohort Effects in Korean Men. Int. J. Environ. Res. Public Health 2016, 13, 1208; https://doi.org/10.3390/ijerph13121208 PMID: 27929405

41. Ito Y, Iokan A, Nakayama T, Tsukuman H, Nakamura T. Comparison of Trends in Cancer Incidence and Mortality in Osaka, Japan, Using an Age-Period-Cohort Model. Asian Pacific J Cancer Prev, 12, 879–888.

42. Liu SZ, Zhang F, Quam PL, Lu JB, Liu ZC, Sum XB. Time Trends of Esophageal Cancer Mortality in Linzhou City During the Period 1988–2010 and a Bayesian Approach Projection for 2020. Asian Pacific Journal of Cancer Prevention, Vol 13, 2012.

43. Adair T, Hoy D, Detrick Z, Lopez AD. Trends in oral, pharyngeal and oesophageal cancer mortality in Australia: the comparative importance of tobacco, alcohol and other risk factors. Journal of Public Health 2011 vol. 35 no. 3.
44. Seoane-Mato D, Aragonés N, Ferreras E, García-Pérez J, Cervantes-Amant M, Fernandez Navarro PF, Barriuso RP, López-Abente G. Trends in oral cavity, pharyngeal, oesophageal and gastric cancer mortality rates in Spain, 1952–2006: an age-period-cohort analysis. BMC Cancer. 2014 Apr 11;14:254. https://doi.org/10.1186/1471-2407-14-254 PMID: 24725381

45. Thuler FP, Forones NM, Ferrari AP. Neoplasia avançada de esôfago–diagnóstico ainda muito tardio. Arq Gastroenterol v. 43–no.3–jul./set. 2006.

46. Liu B, Bo Y, Wang K, Liu Y, Tang X, Zhao Y, Zhao E, Yuan L. Concurrent neoadjuvant chemoradiotherapy could improve survival outcomes for patients with esophageal cancer: a meta-analysis based on random clinical trials. https://doi.org/10.18632/oncotarget.14669 PMID: 28099899

47. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. The Lancet Oncology. 2007; 8(6):545–553. https://doi.org/10.1016/S1470-2045(07)70172-9 PMID: 17540306

48. Shapiro J, Van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, van Laarhoven HW, Nieuwenhuijzen GA, Hospers GA, Bonenkamp JJ, Cuesta MA, Blaisse RJ, Busch OR, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. The Lancet Oncology. 2015;16(9):1090–1098. https://doi.org/10.1016/S1470-2045(15)00040-6 PMID: 26254683

49. Kranzfelder M, Schuster T, Geinitz H, Friess H and Buchler P. Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer. The British Journal of Surgery. 2011; 98(6):768–783.

50. Gomes R, Nascimento EF; Araújo FC. Why do men use health services less than women? Explanations by men with low versus higher education. Cad. Saúde Pública, Rio de Janeiro, 23(3):565–574, mar, 2007.

51. Brazil. Ministry of Health. Ordinance. No. 874 of May 16, 2013. Available from:http://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt0874_16_05_2013.html.

52. Souza MC, Vasconcelos AG, Cruz OG. Trends in lung cancer mortality in Brazil from the 1980s into the early 21st century: age-period-cohort analysis. CadSaude Publica. 2012 Jan;28(1):21–30.