# Evolution of thyroid cancer mortality in adults in Brazil

*Evolução da mortalidade por câncer de tireoide em adultos no Brasil*

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## RESUMO

**Objetivo:** Avaliar a tendência da mortalidade por câncer de tireoide no Brasil entre 1980 e 2010. **Materiais e métodos:** Estudo ecológico, de séries temporais. As taxas de mortalidade por câncer de tireoide ajustadas por idade segundo sexo foram calculadas entre 1980 e 2010. Os dados foram analisados por três estratégias distintas: regressão polinomial, *joinpoint analysis* e médias móveis. **Resultados:** Mais de 70% das mortes ocorrem nos idosos, independente do sexo. Entre adultos jovens, a mortalidade é baixa, sem diferença entre homens e mulheres. Entre adultos maduros e idosos a mortalidade é crescente e com aumento expressivo para mulheres. Há uma tendência de mortalidade decrescente no sexo feminino para adultos e global; e no sexo masculino para 40-59 anos e global, ambos excluindo os idosos, com significância estatística. **Conclusão:** O conhecimento sobre a tendência permite estabelecer prioridades e alocar recursos de forma direcionada para a modificação positiva desse cenário na população brasileira. Arq Bras Endocrinol Metab. 2013;57(7):538-44

**Descritores**
Câncer de tireoide; mortalidade; série histórica; epidemiologia

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## ABSTRACT

**Objective:** To assess the trend of thyroid cancer mortality in Brazil between 1980 and 2010. **Materials and methods:** An ecological study of time series. Mortality rates for thyroid cancer adjusted by age according to gender were calculated between 1980 and 2010. Data were analyzed by three distinct strategies: polynomial regression, joinpoint analysis, and moving averages. **Results:** Over 70% of deaths occur in the elderly, regardless of sex. Among young adults, the mortality rate is low, with no difference between men and women. Among mature adults and elderly, mortality is increasing, and significantly, for women. There is a trend of decreasing mortality in all female adults and overall population, and in males and 40-59 years and overall population, both excluding the elderly, with statistical significance. **Conclusion:** Knowledge about trends allows setting priorities and allocating resources toward positive changes in this scenario in the Brazilian population. Arq Bras Endocrinol Metab. 2013;57(7):538-44

**Keywords**
Thyroid cancer; mortality; historical series; epidemiology

## INTRODUCTION

Thyroid nodules are the most frequent clinical manifestation among thyroid diseases, and thyroid cancer is considered a rare tumor in most of the world (1). For unknown reasons, it is three times more common in women than in men (2).

Malignant tumors of the thyroid are divided according to the histological type and can be classified into differentiated (papillary and follicular), medullary, and undifferentiated or anaplastic (3). The differentiated carcinomas represent 90% of cases of thyroid malignancy. When diagnosed early, they are curable and can occur at any age, most often between 30 and 40 years old (4). Generally, the cases have good prognosis and long survival, similar to people who never had cancer in over 80% of cases (5,6).

The cases of thyroid cancer have increased steadily in the United States and other countries over the years, with three times the incidence of the 1970s (6). According to estimates from the National Cancer Institute, in Brazil in 2012, 10,590 new cases are expected, with an estimated risk of 11 cases per 100,000 women (7). The project GLOBOCAN estimated, for the year 2008 that 35,383 deaths would be related to this cause

for both sexes, with a mortality rate adjusted for age in females from 0.6/100,000 and 0.3/100,000 for males (8).

The incidence of thyroid cancer has increased significantly in recent decades, particularly among women, and this trend was observed worldwide (9). However, despite the progression of incidence over the years, the mortality rate has remained virtually unchanged (10).

Several epidemiological studies suggest this scenario as a result of improvements in the accuracy of diagnostic methods and increased sensitivity to find cases, with the widespread use of cervical ultrasound and fine needle aspiration cytology (9-12). Moreover, it is believed that the increase in incidence is not exclusively related to diagnostic methods, but due to risk factors (13,14).

The increasing incidence of thyroid cancer after high doses of ionizing radiation, either because of exposure to treatments, or as an environmental risk factor is the most well established factor for the development of thyroid cancer (15). However, exposure to low doses of radiation in routine diagnostic X-ray does not increase the risk of development of thyroid cancer (6,15), which suggests that radiation exposure is not the sole risk factor.

Other exposure factors, such as obesity (16), changing levels of iodine in the diet (17), history of benign thyroid disease such as goiter, benign nodules and adenomas (18), contraceptive use, hormone replacement therapy, and reproductive factors, may also be related with this type of neoplasm (19).

The increased frequency of thyroid cancer is a concern even with improved survival in some studies (1,2,4). It is important to know the histological subtypes related to this growth to identify possible causes, and implement preventive measures. It is also important to know the patterns of mortality as indicators of disease occurrence. Thus, this study aims to evaluate thyroid cancer mortality in Brazil in the period between 1980 and 2010 by different techniques: moving averages, polynomial regression, and joinpoint analysis.

## MATERIALS AND METHODS

We conducted a descriptive, retrospective, time series study, based on secondary data collected from the Data Department of the Brazilian Unified Health System (Datasus). Codes for thyroid cancer were included in the analysis: for CID to 10, between 1996 and 2010, code C73 (malignant neoplasm of the thyroid), and for ICD 9, between 1980 and 1995, code 193 (malignant neoplasms of the thyroid gland).

The specific mortality rates and age-adjusted per 100,000 men and women were calculated for each year between 1980 and 2010. Rates were calculated for specific age ranges, using 5-year intervals from age 20 in moving average analysis; and twenty years (Young Adultss: 20 to 39 years; Mature Adults: 40 to 59 years old and Adults: 60 or older) in the analysis of age, looking for an age effect on the rates. Mortality rates were adjusted based on the world standard population for overall comparisons, as proposed by Segi and cols. (20) and modified by Doll and cols. (21).

After obtaining standardized rates, with the goal of minimizing the difficulty in performing trend analysis mainly caused by the presence of cyclical fluctuations, we used filters that reduced the variability shown in the series by three different techniques: polynomial regression, joinpoint analysis, and moving averages.

### Moving average

Moving average is used to obtain the average value of the observed variable within a given period. Thus, for each amount included in calculating the average, the oldest value is deleted. In simple moving average (SMA), each data used in the averaging will have the same weight (22).

### Polynomial regression

Initially, we drew the scatter diagrams for mortality rates and years of study to visualize the kind of relationship between these variables.

Then, the we started modeling process, considering mortality rates as the dependent variable (Y) and the years of study as an independent variable (X). To study the trend, we chose to estimate regression models. To avoid collinearity between the terms of the regression equation, a centralized variable was used (23).

The first model to be tested was the simple linear regression ($Y = \beta_0 + \beta_1 X$), and then higher order models were tested: second degree or parabolic ($Y = \beta_0 + \beta_1 X + \beta_2 X_2$), and third degree ($Y = \beta_0 + \beta_1 X + \beta_2 X_2 + \beta_3 X_3$) (23).

The best model was considered the one with the highest coefficient of determination (R2). When two models were similar for the same location, in a statistical point of view, we opted for the simplest model, i.e., the lower order.

### Joinpoint analysis

To calculate the increase in annual mortality rate (APC), as well as variation of the past 5 to 10 years (AAPC), used the joinpoint analysis method (inflection point), which allows adjustment of data from a series to the fewest possible joinpoints (zero, or a straight line without inflection points), and which tests whether the inclusion of more joinpoints is statistically significant. The significance tests used are based on the method of Monte Carlo permutation and calculating the annual percent change ratio using the logarithm of the ratio. To describe the linear trend for the period, the estimated annual percent change and the 95% confidence interval (95% CI) were computed for each of their trends, composing a regression line according to the natural logarithm of the indices, using the calendar year as a regression variable (24).

As determined in Resolution 196/96, projects involving survey/research and bibliographic databases of public access and use (eg. Datasus) exclude the need for approval by an Ethics Committee in Research.

## RESULTS

Figure 1 shows the mortality rate in three age groups of men and women. Note that in the first age group, young adults (20-39 years), mortality is low and there is no difference between men and women. However, in both remaining age groups, mature adults (40-59 years) and older adults (60 years or more), an increasing mortality is significantly increased in females.

In an attempt to smooth curves, figure 2 shows mortality historical series drawn with its moving average for gender. It is observed that in the whole series, 21 years, mortality from thyroid cancer in females is higher.

The proportions of mortality rates for thyroid cancer by sex in different age groups are shown in figure 3. This shows that over 70% of deaths from this cancer occur in older adults (60 years or more) regardless of sex.

The findings of polynomial regression and joinpoint analysis are summarized in table 1. All equations synthesis of the variation in mortality rate of thyroid cancer, independent of age and sex, were first degree ones. In males and females, the highest coefficient of determination was found in the age group of 40-59 years (mature adults) to decreased mortality.

The joinpoint technique (Table 1) points out to a trend in decreasing mortality rate for females ages 20-39 years, 40-59 years and in overall population, and 40-59 years for males and overall population, with statistical significance. Note that the range of 40-59 years had the highest decreases in both sexes (AAPC of -2.6 and -1.9 for females in males).

## DISCUSSION

We observed, in this study, that thyroid cancer mortality was higher in the age groups above 40 years, and more common in women than in men. Still, it is observed that there is a declining trend in mortality for both sexes.

Many studies worldwide have examined thyroid cancer in its two main indicators: incidence and mortality.

Epidemiological studies show that the incidence of thyroid cancer has continuously grown in the United

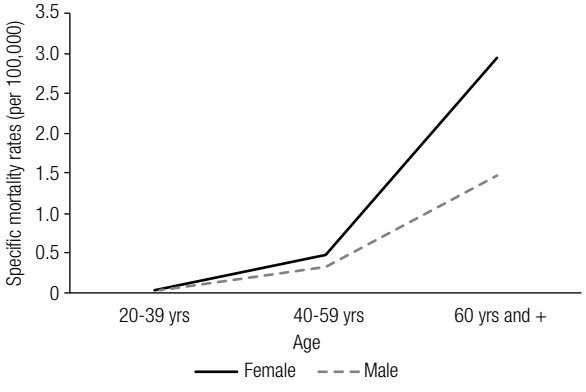


**Figure 1.** Average mortality for thyroid cancer in adults according to sex and age. Brazil, 1980-2010.

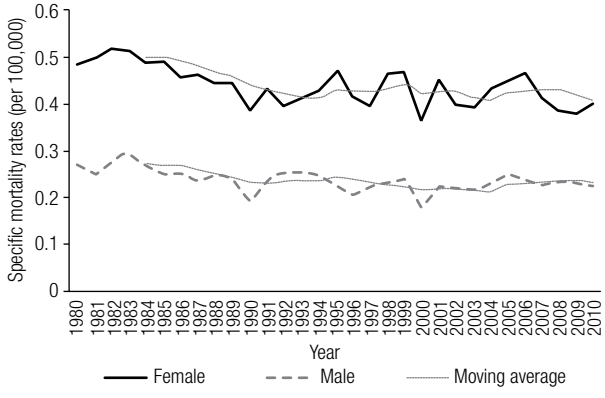


**Figure 2.** Time series of mortality and moving average for thyroid cancer in adults according to sex. Brazil, 1980-2010.

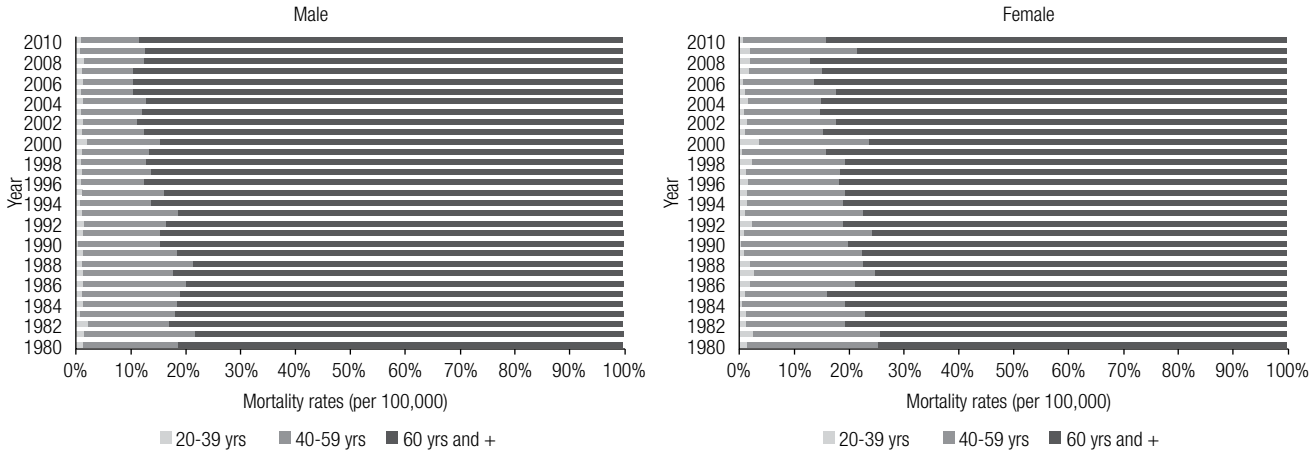


**Figure 3.** Evolution of mortality rates for thyroid cancer in adults according to age and sex. Brazil, 1980-2010

**Table 1.** Time trend of thyroid cancer mortality rates in adults according to sex and age. Brazil, 1980-2010

| | Age | Equation | $R^2$ | Trend | p value | AAPC* | 95% CI |
|---|---|---|---|---|---|---|---|
| Female | 20 – 39 years | y = -0.0050x + 0.0458 | 0.1110 | Decreasing | 0.054 | -1.3 | -2.8; -0.2 |
| | 40 – 59 years | y = -0.0131x + 0.6999 | 0.8287 | Decreasing | < 0.001 | -2.6 | -3.0; -2.2 |
| | 60 years + | y = -0.0010x + 2.9616 | 0.0012 | NS** | 0.856 | NS** | |
| | Global | y = -0.0030x + 0.4856 | 0.4185 | Decreasing | 0.001 | -0.7 | -1.0; -0.4 |
| Male | 20 – 39 years | y = -0.0001x + 0.0279 | 0.0027 | NS** | 0.769 | NS** | |
| | 40 – 59 years | y = -0.0062x + 0.4227 | 0.6182 | Decreasing | < 0.001 | -1.9 | -2.4; -1.3 |
| | 60 years + | y = -0.0006x + 1.4803 | 0.0011 | NS** | 0.859 | NS** | |
| | Global | y = -0.0014x + 0.2594 | 0.2726 | Decreasing | 0.003 | -0.6 | -0.9; -0.2 |

* AAPC: Annual Average Percent Change; ** NS: Non-significant.

States and other countries, such as Canada, and Australia, as well as in Europe, Asia and the Middle East, where thyroid cancer is the 2nd most common type of cancer among women in Kuwait. In the United States, differentiated thyroid cancer (DTC) is a tumor whose incidence has grown over the years between 1992 and 2002, and it is currently the eighth most common cancer among women. This increase reached levels of 6.3% per year between 1997 and 2003 [Surveillance, Epidemiology, and End Results Program (SEER) – available on the website of the American Cancer Society] (25-27).

National cancer registries [National Cancer Institute (INCA) – data from population-based registries] and Brazilian publications confirm the increased incidence of CDT, particularly among women, although, as recorded worldwide, CDT mortality is also decreasing in Brazil (28).

Mitchell and cols. (29) studied the trend for thyroid cancer in the United States, and noted that the incidence increased during the last 26 years, occurring predominantly in women and in the states of the northeast and southeast. It declined in the Midwest, showing regional differences. Similar results were observed in Spain (30), where it was also shown that the distribution of thyroid cancer across the country is uneven, with the highest densities in incidence in the Canary Islands, in the province of Lugo, east of La Coruña, and in the western parts of Asturias and Orense.

Netea-Maier and cols. (31) mention that the persistent increase in the incidence of thyroid cancer has been reported worldwide. When evaluating the trend for incidence and mortality in the Netherlands by means of the National Cancer Registry, the authors specifically observed an increase in the incidence of papillary cancer, as opposed to other subtypes, in which reductions were observed. Mortality, different from the present study, have diminished, in which it has been reported that the incidence especially follicular and anaplastic cancer has decreased.

In Taiwan, Lin and cols. (32) evaluated the trends in the clinical characteristics of patients with papillary carcinoma, and concluded that, after using the Cox model after 1993, patients underwent more aggressive surgical procedures, had tumors of smaller sizes, lower levels of thyroglobulin postoperatively, less advanced stages of the tumor at diagnosis, increased disease-free survival, and lower mortality rates. These findings identify changes in the profile of morbidity and mortality due to the early detection of cancer.

In Italy, Crocetti and cols. (33) analyzed the incidence and mortality of cancer of diverse topographies in Italian cancer registries, and thyroid cancer in men showed an increased incidence, but a reduced mortality, corroborating the situation in Brazil indicated by the present study.

In the study conducted with the cancer registries in Scotland, Reynolds and cols. (34) observed that thyroid cancer is three times more common among women and older adults. Moreover, there is an increased incidence in both sexes, being more evident among women. Furthermore, mortality has progressively reduced over the last 50 years, accompanied by an increased survival of incident cases. It was also shown that the decline in mortality over the increasing incidence reflects increased survival, thanks to the introduction and implementation of standardized protocols for early detection and treatment.

Corroborating these findings, the study by Davies and Welch (35) showed increased incidence of thyroid cancer in the United States for the year 2001. The same authors, assessing the trend in 30 years, between 1973 and 2002, quantified the growth in incidence from 3.6 to 8.7 per 100,000 inhabitants, associated especially with increased papillary type. The mortality rate, however, remained stable during the period (36).

Study in Luxembourg (37) noted that 310 new cancers were diagnosed between 1990 and 1999, with 304 differentiated carcinomas (80% papillary, 14.5% follicular, medullary and 3.5%) and 6 anaplastic/undifferentiated tumors. The male/female ratio was 1:3.2, and the mean age 48.3 years. The standardized incidence rate for the two 5-year periods of 1990-1994 and 1995-1999 increased from 7.4 per 100,000 to 10.1 per 100,000 in females, and from 2.3 to 3.6 per 100,000 per 100,000 in males. The incidence rates increased, especially for the papillary type, and appeared primarily due to an increase in carcinomas diagnosed due in some measure, to a change of histological criteria and more efficient diagnostic tools. This increase appears to be independent of the number of surgical treatments and immigration rates.

In Puerto Rico, between 1985 and 2004, the overall incidence rate of thyroid cancer increased from 3.0 to 7.0 per 100,000 inhabitants (a 2.3-fold increase), with an annual percentage change (APC) of 53% ($p < 0.05$) during the period from 1985 to 2004. Incidence rates were higher for women (from 4.7 in 1985 to 10.5 per 100,000 women in 2004) compared with those for men (from 1.1 in 1985 to 3.0 per 100,000 men in 2004). The trend in increase was primarily due to an increase in the incidence of papillary thyroid cancer, which rose from 2.4 to 6.0 per 100,000 inhabitants (a 2.5-fold increase), with an APC of 5.7% ($p < 0.05$). The mortality rate by thyroid cancer was very low (0.4 in 1985 and 0.3 per 100,000 in 2004), with an APC of -1.1%, which is not significant ($p > 0.05$). Therefore, the incidence of thyroid cancer in Puerto Rico increased significantly from 1985 to 2004, primarily due to an increase in papillary cancer. However, mortality remained low (38).

A study evaluating mortality in Belgrade, Serbia, found the opposite result. It was shown that the average percentage of deaths from thyroid cancer in all deaths was almost twice as high in females (0.11%) than in men (0.6%), and among deaths from all malignant cancers (women and men 0.54% and 0.27%, respectively). During this 20 year period, the average standardized mortality was 1.5 times higher in females (0.74 per 100,000) than in men (0.51 per 100,000). During the study period, the mortality rates increased for thyroid cancer (0.40%) and decreased in women (-0.42%) in men. In particular, in the age group of 60-69 years, in males, a significant trend towards decreased mortality of 3.5% / year was detected (39).

Finally, to assess the epidemiology of thyroid cancer in France, Colonna and cols. found that between 1980 and 2005, the incidence increased, but mortality decreased in men and women. Annual cases have increased fivefold, and projections for 2008 were 8,000 cases and 400 deaths. The main subtype was increased with papillary carcinoma, similar to other locations. Survival rates for 1 and 5 years were high (92 and 94%, and 87 and 93%, respectively, for men and women) (40).

According to INCA, it is clear that thyroid cancer in Brazil gains importance due to the epidemiological profile that this disease is showing, and with it, the issue has become increasingly present in political agendas

and techniques in all levels of government. Knowledge about the situation allows this disease to be prioritized and resources to be allocated toward positive changes in this scenario in the Brazilian population.

This study has limitations: first of all, secondary data does not allow to specify the type of carcinoma (differentiated, anaplastic, and medullary). Although differentiated carcinomas account for 90% of all thyroid malignancies (28), some differences concerning prognosis for each of them could describe a slightly differentiated trend.

A second point to address is the fact that mortality is higher in women than in men, which goes against the results of much of the literature that shows that perhaps the male sex is a factor for poor prognosis. Indeed, mortality is higher in the group of women, which corroborates findings reported nationally and internationally (25-40). This does not mean that thyroid cancer among men is presented as a problem of lower order. The big difference in incidence among both sexes possibly affects the mortality data. In this regard, further studies need to be developed in order to obtain accurate information about the incidence of thyroid cancer in both sexes, in order to analyze it not only for mortality data, but also for lethality and survival, in a way that prognosis for each sex can be directly evaluated.

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