*Revista Brasileira de Pesquisa em Ciências da Saúde*

ISSN: 2446-5577

*Original article*

# Non-Hodgkin lymphoma mortality trend in an area of glyphosate exposure: comparison between Chapecó-SC and the national picture

*Tendência de mortalidade por linfoma não Hodgkin em uma área de exposição ao glifosato: comparativo entre Chapecó-SC e o cenário nacional*

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Received: June 24, 2020; Accepted: November 4, 2020; Published: May 2021.

**Abstract**

**Introduction**: Cancer is currently the second leading cause of death worldwide and one of the major public health problems. Non-Hodgkin Lymphoma (NHL) is among the cancers that most affect rural workers, which could be associated with a few factors related to the development of the disease, including contact with pesticides and herbicides. **Methods**: This is an ecological study of the temporal series of mortality of people over 20 years old. It has been analyzed the number of deaths reported by the mortality system for the municipality of Chapecó and for Brazil, taking in account the period between 1980 and 2014. That information has been taken from DATASUS. There have been used the Codes 200 and 202 of ICD-9 in the period 1980-1995, and C82-C85 of ICD-10 for 1996-2014. Data analyses have been done by using Microsoft Office Excel and Stata. **Results**: Annual mortality rates by NHL for individuals aged 20 and over, in Brazil, during 1980 and 2014, ranged from 1.69 to 3.06 per 100,000 inhabitants, while in Chapecó rates ranged from zero to 9.67 per 100,000 inhabitants in the same period. **Conclusion**: The trend of increased incidence of death in non-Hodgkin's lymphoma is observed in both Chapecó and Brazil, but Chapecó rates are much higher than in Brazil, indicating that in this region there are a few factors that may influence the development of the disease.

**Keywords**: non-Hodgkin lymphoma; mortality; epidemiology.

**Resumo**

**Introdução**: O câncer é atualmente a segunda causa de morte mundial, sendo um dos grandes problemas de saúde pública. O linfoma não Hodgkin (LNH) está entre os tipos de câncer que mais afetam trabalhadores rurais, tendo diversos fatores relacionados ao desenvolvimento da doença, dentre eles o contato com pesticidas e herbicidas. **Métodos:** Um estudo ecológico do tipo série temporal de mortalidade, sendo a população de estudo os óbitos de pessoas maiores de 20 anos notificados pelo sistema de mortalidade para o município de Chapecó e para o Brasil, entre os anos de 1980 a 2014. As informações foram retiradas do DATASUS. Foram utilizados os códigos 200 e 202 do CID-9 no período de 1980-1995, e C82 a C85 do CID-10 para 1996-2014. As análises de dados foram feitas nos programas Microsoft Office Excel e Stata. **Resultados**: As taxas anuais de mortalidade por LNH para indivíduos de 20 anos ou mais no Brasil durante 1980 e 2014 variaram de 1,69 a 3,06 por 100.000 habitantes, enquanto em Chapecó as taxas variaram de zero a 9,67 por 100.000 habitantes no mesmo período. **Conclusão**: A tendência de aumento na incidência de óbito em Linfoma não Hodgkin é observada tanto em Chapecó quanto no Brasil, porém as taxas de Chapecó são bem maiores que a brasileira, indicando que nesta região há um conjunto de fatores que pode favorecer o agravo.

**Palavras-chave**: linfoma não Hodgkin; mortalidade; epidemiologia.

## Introduction

Cancer is currently the second leading cause of death in the world becoming a major public health problem in both developed and developing countries. Approximately 30% of the world's occurrence of cancer could be prevented, such as work-related cancers[1].

The National Cancer Institute estimates 6,580 new cases of non-Hodgkin lymphoma (NHL) in men and 5,450 in women by 2020 indicating differences in incidence according to gender, estimated at a risk of 6.31 new cases per 100,000 men and 5.07 per 100,000 women[2]. Even with a slight difference in incidence, according to a survey conducted in the Mortality System, non-Hodgkin lymphoma appears as the second cause of death from hematological neoplasia in both sexes[3].

Non-Hodgkin lymphoma is among the three most frequent types of cancer related to rural workers due to exposure to pesticides used by farmers[1]. Findings from a major international study titled Agricultural Health Study (AHS) suggest that various types of cancer, including non-Hodgkin lymphoma, may be linked to a variety of pesticides[4]. In a systematic review[5], 23 of the 27 studies on lymphoma associated non-Hodgkin type (NHL) in farmers. Most of them were adult men, who worked as farmers, pesticide applicators. Studies have shown an increased risk, and many have shown associations with dose-response. Agricultural health studies also include epidemiological evidence of increased risk of NHL due to exposure to pesticides and solvents with increasing exposure.

In Chapecó agriculture is based on the production of soybeans, wheat, corn, beans and triticale[6]. In the Chapecó region, the pesticides most used in corn farming are herbicides such as glyphosate, especially in transgenic corn. Glyphosate and fungicides are used in soybean plantations.

There is still little knowledge about the incidence of cancer due to occupational exposure in Brazil and much still needs to be studied[1]. In view of this, the aim of this study was to perform a temporal trend analysis of mortality due to non-Hodgkin lymphoma in Chapecó-SC compared to the national scenario.

## Materials and Methods

### *Type of study*

This is an ecological study of the time series type of mortality.

### *Study site*

The study covered, in addition to national data, data from the municipality of Chapecó located in western Santa Catarina, 670 km from Florianópolis, southern region of the country. Chapecó has an estimated population of 209,553 for the year 2016. According to the United Nations Development Program (UNDP), the Human Development Index in 2010 was 0.790, ranking the municipality 67$^{th}$ in Brazil[7].

### *Study population*

The study population consisted of the set of deaths reported in the Mortality System (SIM). Because Chapecó is a regional reference in oncology, deaths were considered only in residents in the municipality.

### *Data collect*

The data are secondary and were collected on the website of the Department of Informatics of the Unified Health System (DATASUS). All deaths of individuals of both genders, aged 20 or older, between 1980 and 2016 were analyzed. We chose to work with the age group from 20 years of age due to being the productive or retired age group of the population.

The evaluated data were categorized according to the work of Boccolini and collaborators[3] in which the International Classification of Diseases (ICD) 9 and 10 were considered, because of the period analyzed. In this study, the NHL received codes 200 and 202 according to ICD-9 (from 1980 to 1995) and codes C82 to C85 according to ICD-10 (from 1996). The specific rates were calculated from 20 years of age for the age groups, using intervals of 20 years old (20 to 39, 40 to 59, 60 to 79 and 80 or older).

### *Data analysis*

Initially, a descriptive analysis was performed observing mortality due to NHL in the study period according to age group. Mortality rates were standardized by the direct method, considering the Brazilian population of 2010, to allow the comparison of trends.

The temporal trend analysis was

performed using the Prais-Winsten procedure for generalized linear regression. The use of generalized regression model was necessary since simple linear regressions should not be used in time series due to serial autocorrelations, which often occur in population data analyses[8]. From this analysis it was possible to evaluate whether the trends of mortality due to non-Hodgkin lymphoma pointed to a decrease or increase or remained stable in the period studied. The choice of the method is due to the quantification of trends and consequently their[8].

Data processing and analysis were carried out in the *Microsoft Office Excel* version 2016 and Stata version 12.0 (Stata-Corp LP, College Station, TX).

***Ethical considerations***

As this is a study that used aggregated secondary databases and free access *Online*, without the possibility of identifying individuals, according to Resolution 466/12, the present study did not require an assessment of risks to humans.

**Results**

In the period analyzed there were 89,418 deaths due to non-Hodgkin lymphoma in individuals aged 20 years or older in Brazil and 87 in Chapecó, with a national average rate of 2.35 deaths due to NHL per 100,000 inhabitants; and 3.21 deaths due to NHL per 100,000 inhabitants in the municipality of Chapecó. When analyzing the standardized mean rate for the municipality of Chapecó, an increase was observed for 4.09 deaths per NHL per 100,000 inhabitants.

The annual gross mortality rates due to NHL for individuals aged 20 or older in Brazil during 1980 and 2016 ranged from 1.69 to 3.06 per 100,000 inhabitants, while in Chapecó the rates ranged from zero to 9.67 per 100,000 inhabitants in the same period. Standardized mortality rates in the municipality of Chapecó ranged from zero to 11.26 per 100,000 inhabitants. Table 1 shows the national and local coefficients of mortality due to NHL per 100,000 inhabitants (crude and standardized).

**Table 1**. Mortality rates due to non-Hodgkin lymphoma per 100,000 inhabitants in Brazil and Chapecó-SC, gross and standardized rates, 1980-2016.

| Year | Brazil | Chapecó Gross Rate | Chapecó Standardized Rate* |
|---|---|---|---|
| 1980 | 1,76 | 2,52 | 1,89 |
| 1981 | 1,69 | 2,39 | 1,80 |
| 1982 | 1,74 | - | - |
| 1983 | 1,81 | 4,25 | 4,45 |
| 1984 | 1,75 | - | - |
| 1985 | 1,76 | - | - |
| 1986 | 1,83 | 1,83 | 2,43 |
| 1987 | 1,75 | - | - |
| 1988 | 1,85 | - | - |
| 1989 | 1,78 | 1,61 | 1,23 |
| 1990 | 1,95 | - | - |
| 1991 | 1,97 | - | - |
| 1992 | 1,97 | 6,04 | 7,95 |
| 1993 | 2,21 | 1,56 | 2,58 |
| 1994 | 2,24 | - | - |
| 1995 | 2,37 | - | - |
| 1996 | 1,94 | 1,33 | 2,11 |
| 1997 | 2,42 | 5,12 | 5,72 |
| 1998 | 2,52 | 2,48 | 3,95 |
| 1999 | 2,57 | 3,62 | 4,43 |
| 2000 | 2,52 | 3,41 | 5,82 |

| | | | |
|---|---|---|---|
| 2001 | 2,62 | 1,10 | 1,66 |
| 2002 | 2,59 | 2,16 | 2,13 |
| 2003 | 2,75 | 2,11 | 3,83 |
| 2004 | 2,80 | 2,07 | 3,12 |
| 2005 | 2,66 | 2,96 | 3,43 |
| 2006 | 2,93 | 4,82 | 8,65 |
| 2007 | 2,80 | 4,33 | 4,83 |
| 2008 | 2,76 | 1,76 | 1,95 |
| 2009 | 2,83 | 2,44 | 4,51 |
| 2010 | 2,79 | - | - |
| 2011 | 2,89 | 6,27 | 7,58 |
| 2012 | 3,06 | 2,32 | 2,76 |
| 2013 | 2,84 | 2,93 | 3,40 |
| 2014 | 2,37 | 2,13 | 2,89 |
| 2015 | 2,90 | 9,67 | 11,26 |
| 2016 | 2,98 | 3,39 | 4,02 |

*Rate standardized by the Brazilian population of 2010 - direct method

Table 2 shows the absolute and proportional distribution of deaths due to non-Hodgkin lymphoma, according to the age groups used.

**Table 2**. Number and proportion of deaths from non-Hodgkin lymphoma for Brazil and Chapecó, according to age groups, 1980-2016

| Age (in years) | Chapecó | | Brazil | |
|---|---|---|---|---|
| | n | % | n | % |
| 20-39 | 11 | 12,64 | 12.580 | 14,07 |
| 40-59 | 26 | 29,89 | 25.635 | 28,67 |
| 60-79 | 35 | 40,23 | 40.088 | 44,83 |
| 80 or older | 15 | 17,24 | 11.115 | 12,43 |
| **Total** | **87** | **100,00** | **89.418** | **100,00** |

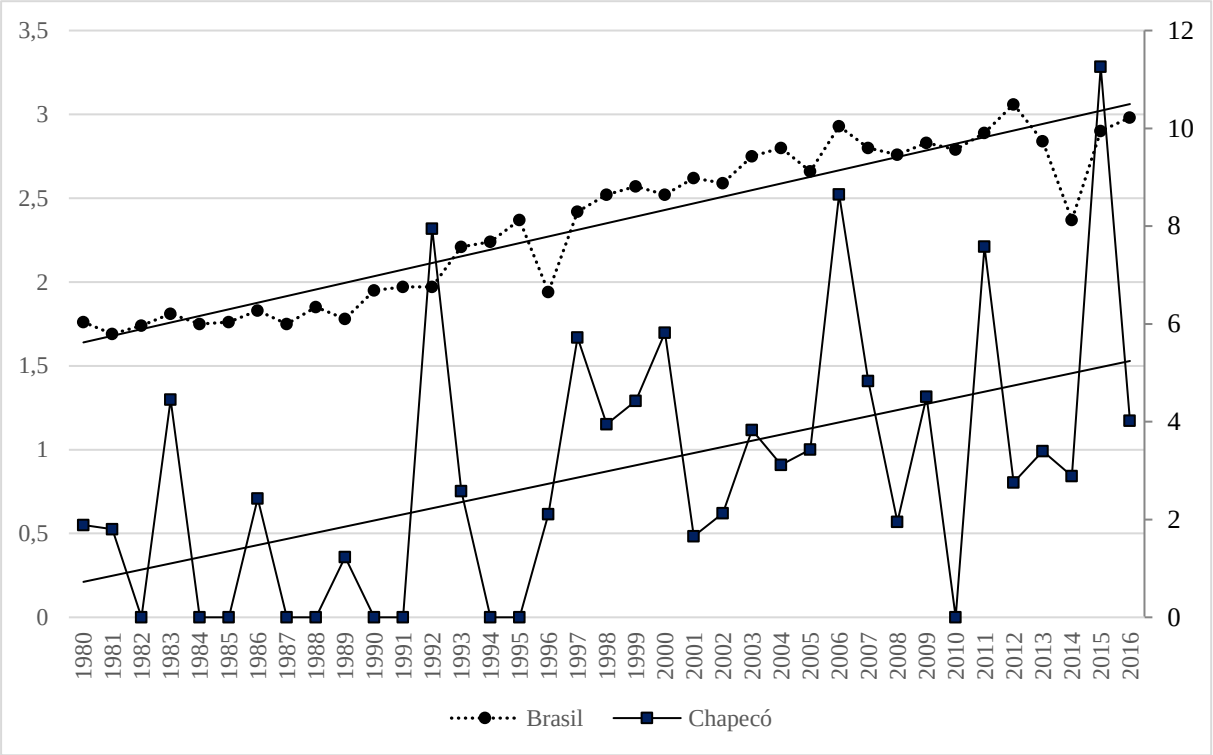
The generalized linear regression, by the Prais-Winsten method, showed a tendency to increase mortality rates due to NHL in both Brazil and Chapecó ($p<0.001$ for both time trends), and the trend of increase in Chapecó was higher than in Brazil (2.98 and 2.36, respectively). Table 3 shows the temporal trend for mortality due to non-Hodgkin lymphoma for Brazil and Chapecó.

**Table 3**. Temporal trend of mortality due to non-Hodgkin lymphoma for Brazil and Chapecó/SC, 1980-2016

| | | CI 95% | | | |
|---|---|---|---|---|---|
| **Local** | **Tendency** | **Inferior** | **Superior** | **p** | **Interpretation** |
| Chapecó | 2,98 | 2,06 | 3,90 | <0,001 | Increase |
| Brazil | 2,36 | 1,78 | 2,93 | <0,001 | Increase |

Figure 1 shows the graph of the distribution of the coefficients of Brazil and Chapecó (standardized), with the respective trend lines.

**Figure 1**. Mortality rates due to non-Hodgkin lymphoma in Brazil and Chapecó in the period 1980-2016 and respective trend lines.




## Discussion

Both Brazil and the municipality of Chapecó showed a tendency to increase mortality from non-Hodgkin lymphoma, with Chapecó demonstrating a greater upward trend than Brazil. The municipality of Chapecó had higher rates than Brazilian rates after the 1990s, reaching almost four times the rate in Brazil in 2015.

One limitation of the study was the use of public secondary data, which does not allow a causal association with the occupation of individuals because they did not have access to individual data. Another limitation was the impossibility of calculating the annual increment since some years did not have a record of death due to NHL in Chapecó.

Despite having years of zero death due to NHL, due to the low population and the event being rare, Chapecó demonstrates a tendency to increase in death rates higher than Brazil, with a statistically significant difference. Of the 10 years without registration of deaths due to NHL in the municipality of Chapecó, nine refer to years prior to 1996, the year in which ICD-9 was replaced by ICD-10. The update of the International Classification of Diseases in its tenth review may have resulted in a greater sensitivity in the record of death due to NHL.

Considering the proportional distribution of deaths stratified by age group, Brazil and Chapecó presented similar percentages, with higher proportions in the age group from 60 to 79 years old. A study on the trend of mortality from non-Hodgkin lymphoma in Brazil[3] already demonstrated an increase in the standardized mortality rate in age groups over 39, and this increase was more evident in individuals over 60 or older.

Since 1990, although mortality from general cancer has stable or, in some developed countries, decline, some types of cancer such as non-Hodgkin lymphoma have not yet presented such a trend[3]. In Chapecó it is observed that from the 1990s there is substantial growth, even compared to the national picture. This data may indicate that in Chapecó there is some factor that may influence the increase in mortality from LHN more markedly than in Brazil.

Glyphosate is the active agent of the main herbicides marketed in Brazil and used on a large

scale in agricultural sectors for weed control, especially in corn and soybean plantations[9].

Findings from a major international study titled Agricultural Health Study (AHS) suggest that several types of cancer, including non-Hodgkin lymphoma, may be linked to a variety of pesticides. Studies show three-fold increased risk of non-Hodgkin lymphoma associated with substantial exposure to pesticides and herbicides[4], and an association of prolonged contact with glyphosate with NHL was also found[10].

The agro-industry is the predominant economic sector in Chapecó, agriculture based on the production of soybeans, wheat, corn, beans and triticale. This form exposure to pesticides in this region can be significant, which indicates a special look at this risk factor and the need for future studies that analyze the occupational exposure of this population.

The trend of increased incidence of death in non-Hodgkin lymphoma is observed in both Chapecó and Brazil, but Chapecó's rates are much higher than the Brazilian one, indicating that in this region there are a set of factors that may favor the occurrence of the disease, and analytical studies are needed to evidence which these associations would be.

**Conflict of interest:** The authors stated that there was no conflict of interest.

**Financing:** None.

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