Brain cancer mortality in an agricultural region of Rio de Janeiro, Brazil: a population-based age-period-cohort study, 1996-2010

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Abstract

Background: The brain cancer etiology is poorly understood, although several studies indicate that residents of agricultural regions have an increased risk of mortality, the hypothesis being the intense exposure to pesticides. Both the trend and the age-period-cohort effect of brain cancer mortality in Rio de Janeiro, Brazil, were estimated.

Methods: This is a descriptive epidemiologic study of mortality from brain cancer in 20-year-old or older residents of an agricultural region (Serrana) and a non-agricultural region (Metropolitan), between 1996 and 2010. The trend analysis was estimated through Joinpoint regression and the individual effects of age-period-cohort were performed using log-linear Poisson regression.

Results: The estimated annual percentage change in brain cancer mortality in the Serrana region was 3.8% (CI95% 0.8 and 5.6), in contrast, the Metropolitan region was virtually stable: -0.2 (CI95% -1.2 and 0.7). The age-period-cohort analysis showed an age effect in both regions. In the Serrana region a relevant cohort effect was observed: individuals who were born from 1955/59 to 1985/89 have showed increasing relative risk. On the other hand, an increased RR not was observed in the Metropolitan region.

Conclusion: This study showed an increasing trend in time series of brain cancer mortality among adults living in an agricultural area in the state of Rio de Janeiro. The cohort effect seems to be a consequence of changes in the environmental exposure. These findings reinforce the hypothesis that residents of agricultural regions have increased brain cancer mortality.

Keywords: brain cancer; age-period-cohort; agriculture; trend; pesticide
Background

Malignant brain neoplasms are intracranial tumors that are more frequent in adult males. About 70% of these tumors originate in glial cells (gliomas) and present high lethality, once only 3% of cases with this histological type of cancer survive for more than five years after diagnosis [1, 2, 3]. The brain cancer etiology is not well known, although genetic and environmental factors are related to its development [4, 5, 6].

Individuals with agricultural occupations, as well as non-farmers living in rural communities, have higher mortality rates for some specific cancers, among which brain cancer. The main hypothesis reported in the literature for this excessive mortality is the exposure to pesticides [7, 8, 9, 10, 11]. Besides that, several pesticides are believed to be carcinogens or possible carcinogens in humans [12, 13].

The Serrana region is the main agricultural area in the state of Rio de Janeiro, especially in the production of fruits, vegetables and flowers. The Serrana region showed the largest per capita consumption of pesticide and fertilizer and the largest population contingent engaged in agricultural activities. In contrast, the Metropolitan region has the lowest per capita consumption of pesticide and fertilizer and the smallest population contingent engaged in agricultural activities. Such environmental difference served as motivation for this ecological investigation [14, 15].

Due to the inexistence of local population-based cancer registry, this brain tumor mortality study is a first approach to explore the magnitude of this health problem. In this sense, the evaluation of the effects of age, birth period and cohort on brain cancer mortality may contribute to the identification at an ecological level of etiologic factors related to their development [16]. This technique assumes, a priori, that the effects of age can represent biological changes that occur during aging; the period when death occurred may also reflect important changes on mortality behavior; while the cohort effect may suggest changes in the pattern of environmental exposure [17, 18].

The aim of this study was to analyze trends and assess the effects of age, birth period and cohort in the brain cancer mortality rates in the Serrana region of the state of Rio de Janeiro, and compare them with the rates in the Metropolitan region of the same state.

Methods

Study design and population.

This is an ecological study on the distribution of deaths from brain cancer, classified as C71 (malignant neoplasm of brain) in ICD-10 (WHO, 1996) [19], in people over 19 years of age living in the Serrana region and in the Metropolitan region of the state of Rio de Janeiro, between 1996 and 2010. Mortality data were obtained from the database of the Mortality Information System (SIM) [20]. The data on population contingents during the same period were obtained from DATASUS electronically, which came from the Brazilian Institute of Geography and Statistics [21].

Study Area
In this study, the Serrana region is composed of the municipalities of Bom Jardim, Duas Barras, Nova Friburgo, Petrópolis, São José do Vale do Rio Preto, Sumidouro and Teresópolis, with a population estimated at a little over seven hundred and ten thousand inhabitants in 2010. Nova Friburgo, Petrópolis and Teresópolis concentrate circa 90% of this contingent [21]. The Serrana region is the main agricultural area of the state and, according to the 2006 agricultural census, 5.34% of its workers were engaged in agricultural activities [22].

The Metropolitan region of the state of Rio de Janeiro is formed by the municipalities of Belford Roxo, Duque de Caxias, Guapimirim, Itaboraí, Itaguaí Japeri, Mage, Marica, Mosque, Nilópolis, Niterói, Nova Iguaçu, Paracambi, Queimados, Rio de Janeiro (capital city), São Gonçalo, São João de Meriti, Seropédica and Tanguá. It concentrated, in 2010, an estimated population of over eleven million six hundred thousand inhabitants, of which 54% lived in the capital city [21]. According to the 2006 agricultural census, 0.01% of its workers were engaged in agricultural activities [22].

**Study variables**

Brain cancer mortality rates of each age group were calculated per one hundred thousand inhabitants and adjusted by the world population [23]. To analyze the age, period and cohort (APC) effects, we took into consideration the following variables: age (in five-year intervals), the number of deaths (grouped into five-year periods), the population at risk in the middle of each interval of five years (person-time) and the period of study grouped in five years.

**Statistical analysis**

We performed a descriptive analysis of mortality rates (mean and standard deviation), as well as the global and specific adjusted rate ratio by age groups.

The trend analysis was performed using log-linear Poisson regression, with the objective of verifying significant changes in the behavior of the rates over the years. An Estimated Annual Percentage Change (EAPC) was calculated for each change over the periods. Periods with p<0.05 were considered statistically significant. The choice of the model was by the permutation method, which took into account the value of p<0.05 (24). These analyses were done by the software application Joinpoint version 3.4 (Statistical Research and Applications Branch, National Cancer Institute, USA).

To analyze the effects of age, period and cohort, and assess the Relative Risk (RR), the models were adjusted by log-linear Poisson regression, assuming the following: Poisson distribution for the number of deaths observed during the study period, constant mortality rates and events, independent from each other. The logarithm (log) of mortality rates is an additive function of the parameters as described by [25, 26].

$$\log (D_{ij} / P_{ij}) = \mu + (A)\alpha_i + (P)\beta_j + (P-A)\gamma_k$$

Where: $D_{ij}$ = number of deaths in the i-th age group in the j-th period; $P_{ij}$ = population in the i-th age group and j-th period; $A$ = age, $P$ = period; $\mu$ = intercept adjusted mean, $\alpha_i =$
effect of the i-th age group; $\beta_j =$ effect of the j-th period; $\gamma_k =$ effect of the k-th cohort. The model that best fit the data was selected by the deviance function, assessed by comparing the effects of each parameter in relation to the full model (age, period and cohort). The models with $p < 0.05$ were considered statistically significant.

To overcome the uncertainty associated with nonidentifiability, the parameterization proposed by Holford, (1991) [27] was chosen. For the analysis, we used the statistics package R version 2.15.1, Epi version 1.1.9 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

**Results**

Between 1996 and 2010, there were 412 deaths caused by brain cancer in individuals over 19 years of age in the Serrana region, corresponding to an average rate of 4.20 deaths per 100,000 inhabitants (standard deviation=0.85). In the Metropolitan area there were 5,322 deaths from the same type of cancer, and the average rate was of 3.39 deaths per 100,000 inhabitants (standard deviation = 0.23). The average age was 64 and 65 years in the Serrana and Metropolitan regions, respectively. Comparing the two regions, we notice that the ratio of adjusted mortality rates in the Serrana region was higher in all age groups, the average increase being 40% higher.

Figure 1 shows the variation in adjusted mortality rates in the two regions studied from 1996 to 2010. There were two distinct periods concerning the behavior of the rates. In the Serrana region it was observed that between 1996 and 1999 the EAPC was -9.6% (95% CI: -30.4 - 17.5); between 1999 and 2010 the EAPC was 4.2% (95% CI: 0.4 - 8.1). In contrast, in the Metropolitan region it was observed that between 1996 and 1998 the EAPC was 18.4% (95% CI: -8.8 - 53.6); and between 1998 and 2010 the EAPC was -0.5% (95% CI: -1.8 - 0.9).

Figure 1. Trends in mortality from brain cancer adjusted by world population in the Serrana region and Metropolitan area between 1996 and 2010. Axis X shows the mortality rates per one hundred thousand inhabitants, and axis Y shows the calendar year.

According to the results shown in Table 1, the risk of death from brain cancer increases with age in both regions, with the greatest increases in the Serrana region. The oldest age group (75 to 79 years of age) showed a RR of 33.63 (95% CI: 15.24 – 74.22) in the Serrana region and 23.78 (95% CI: 22.55 – 25.07) in the Metropolitan region, taking as reference the age group from 20 to 24 years of age.

Figure 2. Estimates on the age-period-cohort effects on brain cancer mortality in residents of the Serrana region of the state of Rio de Janeiro, 20 to 79 years of age, from 1996 to 2010. Estimates are based by assuming reference groups for age (20-24 years of age) and period (1996-2000), and age median (1945-1949) for birth cohort. Estimates on the age-period-cohort effects on brain cancer mortality in residents of the Metropolitan area of Rio de Janeiro, 20 to 79 years of age, from 1996 to 2010.
Estimates are based by assuming reference periods for age (20-24 years of age) and period (1996-2000), and age median (1940-1944) for birth cohort.

**Figure 3. Comparison Age-period-cohort of specific-age mortality rate.**

The median birth cohort was the 1945/49 five-year period for the Serrana region, with positive and statistically significant RR from 1955/59, reaching 4.17 (95% CI: 1.79 – 9.74) for the youngest, born between 1985/89. In the Metropolitan region, the median occurred between 1940/44 and RR varied between 0.89 (95% CI: 0.83 - 0.89) and 1.03 (95% CI: 1.04 - 1.07). Finally, the presence of an occurrence-period effect was not observed in either regions (Table 1).

Figure 2 illustrates the effect of individual curves of age, period and cohort, revealing differences between the curves of the birth cohort effect in the Serrana and Metropolitan regions of the state of Rio de Janeiro. Figure 3 shows the comparison Age-period-cohort of specific-age mortality rate.

Lastly, Table 2 summarizes the parameters fit (goodness of fit) between the models, and the complete one reflects the best fit of the individual effects of age, period and cohort in comparison with those of two factors.

**Discussion**

In this study, different trend patterns between the regions studied were observed. The study revealed that the Serrana region showed higher mortality rates and an increasing trend over the analyzed period (1996-2010). In contrast, there was an inverse trend with a decline in mortality rates in the Metropolitan region.

In the world, there is a variation in mortality trends for these tumors. In Brazil, a study by Monteiro and Koifman, (2003) [28] in the state of Rio de Janeiro observed an increase in brain cancer mortality in individuals over 65 years of age in the period between 1980 and 1998. In the USA, Legler and collaborators (1999) [29] analyzed brain cancer mortality rates between 1975 and 1999. These authors observed stability in the distribution of mortality, except in the age group between 64 and 74 years of age, which showed an EAPC increase of 5.5% between 1979 and 1995. In Italy, in the Umbria region, Stracchi et al (2008) [30] observed a growing tendency for brain cancer mortality of 2.33% (IC 95% 1.42 – 3.23) in males and 1.78% (IC 95% 0.62-2.95) in females.

One explanation for the increased brain cancer incidence and, possibly, brain cancer mortality observed in recent decades can be attributed to better diagnosis due to the advent of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), as well as aging of the population, once age represents an important risk factor for these types of tumors [32, 33, 34]. However, it is discussed in the literature that these technologies do not fully explain the increase in incidence and mortality; such increase would have a significant contribution from environmental risk factors [35].
The differences in the magnitude of brain cancer mortality rates observed in this study may not be explained by the greater availability of access to MRI and CT, because the magnitude of adjusted mortality rates in the Serrana region is higher than the estimated rates in Rio de Janeiro. In other words, it was expected that the most developed region (Rio de Janeiro) presented greater rates of mortality. Thus, the main explanation for this difference is the pattern of exposure to distinct environmental carcinogens between these regions.

In this study, we observed the statistically significant effect of age on the distribution of brain cancer mortality rates in both regions. Indeed, age is an important risk factor in the development of several types of tumors. The number of cell divisions increases due to human aging and, during this process, errors in DNA replication are critical for the formation of mutations, and when they occur in DNA repair mechanisms, they are crucial to the development of tumors [36]. On the other hand, the flaws in DNA replication can be induced by several environmental agents [12].

The most recent birth cohorts in the Serrana region had higher Relative Risk rates. This effect may reflect changes in exposures to environmental agents that occurred after 1950 and that have been present since then. It is believed that environmental factors are decisive in the development of brain cancer, because many substances are identified in the literature as inducers or promoters of carcinogenesis, including several pesticides [37, 38, 39, 40].

The hypothesis for this difference in Relative Risk rates between the birth cohorts of these regions is due to the differentiated pattern of environmental exposures – the greater relative risk in cohorts of population born in the 1980s may reflect exposures that occurred in childhood, because these individuals were 30 years old or younger when they died. The literature reports that exposure to pesticides during intrauterine life and childhood are risk factors for developing brain cancer [41, 42]. Studies indicate that humans may be exposed to pesticides from several sources, such as food, agricultural and residential areas [43]. Another important aspect is the exposure “window”, which would mean a specific development period of a child that is crucial to determine the biological effects associated with pesticides, and that may significantly contribute to the developing of cancer in adult life, although the relation of causality remains debatable [44].

Over the past 30 years, the Serrana region has gone through the process of agricultural modernization [45]. Currently, this region is the main agricultural area, producing mainly vegetables, fruits and flowers, and shows the largest contingents of workers engaged in agricultural activities in the state [46, 22, 15]. The use of pesticides to grow fruits, vegetables and flowers is intense, according to the Brazilian Institute of Geography and Statistics data; the sales volume of pesticides in the Serrana region in 1996 represented circa 50% of the total sales volume in the entire state [14].

The main pesticides used in horticulture, fruits and flowers cultivation belong to the class of organophosphate and carbamate [47]. Over the last years, the carcinogenesis
mechanism associated with the induction and promotion of tumors by chemicals has been quite researched. Organophosphate and carbamate pesticides have two possible mechanisms of carcinogenesis, one is based on genotoxicity (ability to react with DNA) and the other by means of epigenetic mechanisms (DNA damage) [48]. In vitro evidence verified that phenophos, parathion, terbuphos, diazinon, malathion and phorate induce DNA mutations and methylation, observing that the herbicide paraquat promotes changes in the histones acetylation in cell cultures [49, 50, 51].

The Serrana region demands investigation, because other studies have observed that farmers and residents have high estimates of risk of death from certain cancers, with highlight to those located in the brain [52, 53]. In this scenario, it is possible to think that exposure to these substances may have an important role for the development of brain cancer, as shown here by the mortality rate.

These results are to be analyzed with caution, once ecological studies have limitations that are inherent to its design [54]. A common limitation of studies that use data based on death certificates is the accuracy of mortality statistics. In Rio de Janeiro, Monteiro, Koifman and Koifman, (1997) [55] observed an accuracy of 90.1% in the reporting of death from brain cancer. In the Serrana region, the data about deaths from brain cancer showed a positive predictive value of 90% [56]. It was also observed that the proportion ratio of the reported deaths in chapter 18 (Sign Symptoms and Abnormal Findings in Physical Examination and Laboratorial Works) was 4.95% in the period, and values lower than 6% indicate a good quality of the record [57]. Another study limitation is inherent to uncertainties attributed to the nonidentifiability [58, 18] of the models because the three components age-period-cohort are linear and it is impossible to estimate all three effects on the regression models simultaneously; this way, the use of a solution proposed by Holfrold (1991) was chosen.

The originality of this study is evidenced by detecting differences in the epidemiological pattern of these neoplasms analyzed according to factors internationally accepted to study the distribution of diseases, such as the distribution of mortality by age groups (age effect), calendar year of occurrence of death (period effect) and the birth year of the deceased (cohort effect) [59]. This approach enabled generating hypotheses about the contribution of different environmental factors that can possibly explain regional disparities in the distribution of mortality from brain cancers.

This study contributes to the understanding of ecological risk factors for death from brain cancer. The age-period-cohort model showed to be efficient to indicate important differences in the pattern of mortality that suggests different exposures between the regions. Furthermore, a significant cohort effect which suggests that residing in an agricultural area during early life increases the risk of mortality was identified, corroborating the hypothesis that environmental exposures are determinants in mortality from brain cancer. Other studies in this population are to be prioritized in order to determine possible individual factors associated with the development of cancer.

Conclusion
This study showed an increasing trend in time series of brain cancer mortality among adults living in an agricultural area in the state of Rio de Janeiro. The exploratory analysis of these data revealed the presence of significant effect of birth cohorts on the distribution of mortality from 1950 on, reaching a RR four times higher among those born between 1980 and 1989.
References


20. **Mortality Information System (DATASUS).** Available at: http://tabnet.datasus.gov.br/tabdata/sim/dados/cid10_indice.htm


# Tables

Table 1. Estimates of Relative Risk (RR) and confidence interval with 95% reliability of age, birth cohort and period, in the Metropolitan and the Serrana regions.

<table>
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<th>Metropolitan region</th>
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<tr>
<td>25 to 29</td>
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Table 2. Goodness of fit of age-period-cohort models

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Figure 1.
Figure 2

Serrana region

Metropolitan region
Figure 3

Serrana region

Metropolitan region

Age at diagnosis

Date of diagnosis

Date of birth

Age at diagnosis

Date of diagnosis

Date of birth