Trends in lung cancer mortality in Brazil from the 1980s into the early 21st century: age-period-cohort analysis

Tendência de mortalidade por câncer de pulmão no Brasil de 1980 ao século 21: uma análise idade-período-coorte

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Abstract

The aim of this study was to describe the pattern of trends in lung cancer mortality in Brazil and identify the effects of the factors age, period and cohort (APC) on mortality rates. A time series study was conducted using secondary population-based data. Lung cancer mortality rates by sex were calculated for the period 1980 to 2007. APC models were adjusted to identify the influence of age, period and cohort effects on rates. Lung cancer mortality rates are significantly higher among men. Specific rates for men over the age of 64 and for women of all ages are increasing. There was a greater increase of adjusted rates among women. With respect to the age effect, mortality risk increases with age starting with the earliest age groups. With regard to the cohort effect, there is a lesser risk of mortality among men born after 1950 and an increasing risk across all cohorts among women. The results regarding younger generations indicate that present trends are likely to continue. The cohort effect among women suggests an increasing trend in mortality rates, whereas a decrease in rates among men under the age of 65 suggests that this trend will continue. These trends reflect tobacco control measures adopted since 1986.

Lung Neoplasms; Logistic Models; Mortality

Introduction

Lung cancer is the most common type of neoplasm worldwide in terms of mortality and incidence [1,2]. The Brazilian National Cancer Institute (Instituto Nacional de Câncer – INCA) estimated that 27,630 new cases of lung cancer occurred in Brazil in 2010, making lung cancer the second and fourth most common type of cancer among men and women respectively (not including non-melanoma skin cancers) [3].

Studies of trends in lung cancer mortality in Brazil have revealed that the age-adjusted mortality rate among men increased from 10.6 to 13.1 deaths/100,000 between 1979 and 2004. During the same period, the increase was from 3.0 to 5.4 deaths/100,000 among women. Considering the relative variation, the increase in the age-adjusted mortality rate among women (80%) was much greater than among men (23.6%). Age-specific mortality rates are higher among men of all ages and increase with age in both sexes. A decline was detected in the age-specific mortality rate among men aged between 30 and 69 years, whereas an increasing trend was reported among men over the age of 69 and women over the age of 29 [4,5,6,7].

In the United States, age-adjusted lung cancer mortality rates have declined among males and increased among females since 1995. This trend reflects historical differences in per capita cigarette consumption between genders: peak

consumption in women followed some twenty years later than in men [8,9]. In Canada, a decline in mortality rates has been observed among men since the 1980s. In contrast, cigarette consumption has increased among women since 1982, with a significant annual upward trend of 1.1% between 1998 and 2007. Tobacco use among men in this country began to decline in the 1960s and among women in the 1980s [10]. In Argentina, age-adjusted rates have decreased moderately over the last three decades [11]. Given that lung cancer is mostly tobacco-related, these trends essentially reflect smoking habits of subsequent generations of men and women in various American countries [12]. In the United Kingdom, age-specific lung cancer mortality rates among men of all ages have been in decline since the 1980s. Among women, rates rose across all age groups over most of this period up to the late 1980s. Rates in women over the age of 75 continued to rise during the 1990s and into the 21st century. This trend reflects past smoking behavior in the United Kingdom: although men started to smoke earlier and more heavily than women, smoking cessation in males has resulted in a fall in lung cancer mortality rates [13].

The study of mortality by time trend analysis can be a useful instrument for lung cancer assessment. It provides a source of information to support policy decision-making, as well as serving as a tool to aid in the assessment of the impact of preventive measures already under implementation [14].

Time trends may reflect differences in population structure (such as age), access to health services and the quality of care. Mortality rates are also influenced by disease risk and protective factors, which may change over time and affect different population groups [14].

This study aims to describe the pattern of trends in lung cancer mortality rates in Brazil and identify the influence of age, period and cohort effects on these rates among men and women. For this purpose, an age-period-cohort (APC) model, which quantifies the effect of these three dimensions within a time trend analysis, was used.

Methods

Data source

Two data sources were used for the purposes of this study: the Mortality Information System and information on the resident population obtained from the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE), both available at http://www.datasus.gov.br.

In this article, the term "lung cancer" is used to represent malignant neoplasm of the bronchi and lungs. The classification codes used under the International Classification of Diseases (ICD) was revised between 1980 and 2007. The classification codes for this neoplasm from the ICD-9, used until 1996, were 162.2 to 162.5, 162.8 and 162.9. In the ICD-10 the classification code for this neoplasm changed to C34.

For each year, tables with number of deaths per population by sex and age group were generated using TabWin, a tabulation software available at http://www.datasus.gov.br.

Data analysis

Crude, specific and age-adjusted mortality rates per 100,000 men and women were calculated for each year between 1980 and 2007. Specific rates were calculated for age groups using five-year intervals starting at the age of 35. Mortality rates were adjusted based on the world standard population for global comparisons as proposed by Segi et al. [15] and modified by Doll et al. [16]. To build the APC regression models, number of deaths and population at risk were grouped into five-year intervals according to age at death (from age 35 to 39 years through to age 80 years and over) and year of death (from 1980 to 1984 through to 2000 to 2004). Since there was no available data to complete the 2005-2009 interval, the last year included in the APC model was 2004.

To compare crude mortality rates, it is necessary to consider the extent to which differences are influenced by age structure (age). When age-specific mortality rates are studied over a given time period, they reflect a mixture of effects related to the year of death (period) and birth (cohort). APC models were developed in order to quantify the contribution of these phenomena and distinguish the influence of these three variables on time trends within the rates.

It is important to understand the concept of age, period and cohort effects in order to identify the demographic components of mortality changes over time. Age is the most important source of variation because the risk of death increases with the biological aging process and the age pattern of mortality displays quite regular changes over time [17].

The period effect assumes that a series of environmental factors, such as wars, economic crises, famine and pandemics influence the whole population exposed to these events. Period effects can also arise from public health endeavors and technological advances deployed in the

health field, leading to lower mortality rates at all ages. In addition to these factors, changes in the ICD can also affect mortality rates [17].

Cohort effects can occur when individuals born in the same period have similar characteristics, which can influence their morbidity and mortality risk. Early-life exposures have an important effect on susceptibility to certain diseases and mortality in adult life. This is therefore a relevant factor to be taken into account when analyzing chronic diseases and cancers where one of the main causes of the disease is long-term exposure to carcinogenic agents [17].

In this study, in order to provide an overview of the magnitude of lung cancer mortality rates and their time trends, APC models were adjusted using the Epi 1.1.12 library [18] of the statistical package R, version 2.9 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

The APC model is a descriptive tool that uses a tabulated data base in which deaths and at-risk populations are recorded by age group over a given time period. The effects of age, period and cohort are modeled as categorical variables, generating a large number of parameters to be estimated. To limit the parameters to a reasonable number and obtain appropriate curves for the estimated effects, ages are grouped into five-year intervals. Since cancer is a rare disease, the use of intervals helps to improve data stability [19].

The model for tabulated data can be written in the form of a log-linear regression as:

$$\log(r_{ijk}) = \log\left(\frac{d_{ijk}}{n_{ijk}}\right) = \tau + \alpha_i + \beta_j + \gamma_k,$$

where r_{ijk} denotes the mortality rate expected in the age **i**, period **j** and cohort **k** cell; d_{ijk} denotes the expected number of deaths which is assumed to be a Poisson distribution; n_{ijk} denotes the population at risk of death (the $\log(n_{ijk})$ corresponds to the *offset* term, or the log-linear adjustment term for contingency tables); τ represents the intercept or mean adjusted rate; α_i represents the i^{th} row age effect for $i = 1,...,\alpha$ age groups; β_j represents the j^{th} column period effect for $j = 1,...,p$ periods; and γ_k represents the k^{th} diagonal cohort effect for $k = 1,...,(\alpha+p-1)$ cohorts [17].

The main difficulty with adjusting a model involving these three factors is the linear relationship between age, period and cohort. Any model that includes these three variables on a linear scale will be constrained because the birth cohort corresponds to the difference between year of death and age at death, leading to a condition known as the "non-identifiability problem" [17].

There is no consensus as to the best methodology for solving this problem [19,20]. One possibility is to employ a reduced model, using only the age and period factors,

$$\log(r_{ij}) = \log\left(\frac{d_{ij}}{n_{ij}}\right) = \tau + \alpha_i + \beta_j \text{ [17].}$$

Given that the cohort effect can be interpreted as a special case of the interaction between two categorical variables, the equation above satisfies the assumption that there is no interaction [21]. Any violation of that assumption can be detected from graphs presenting the age-specific mortality rate by period. Lack of parallelism between the curves suggests the presence of the cohort effect [22]. This study used weighted parameterization, as proposed by Holford [20], as an alternative solution to the "non-identifiability problem".

Given that lung cancer is a chronic, non-communicable disease, rate is assumed in this model to be constant within each of the given age and period categories. Individuals are also assumed to be independent cases and, consequently, contributions to different cells in the data base are also independent. Accordingly, the APC models for rates can be adjusted using Poisson Regression for event counts. This methodology permits the use of an *offset* term $log(n_{ijk})$, which compensates for population fluctuations in order to adjust the mean rate [19].

The age-specific log-rates are parameters in the model and can be used directly with their estimated standard errors to form confidence intervals for the log-rates [19]. The computer program Epi 1.1.12 [18] provided interval estimates of the parameters that were calculated based on the equation *95%CI = point estimate±1.96*standard error*.

Age-period-cohort, age-cohort, cohort, age-period, age and period models were developed separately for men and women and in sequence.

The adjusted effects were evaluated by the likelihood ratio test, which compares the nested models' goodness-of-fit by evaluating the deviance and degrees of freedom [14]. In addition, the Akaike Information Criterion (AIC) was used to compare the non-nested models.

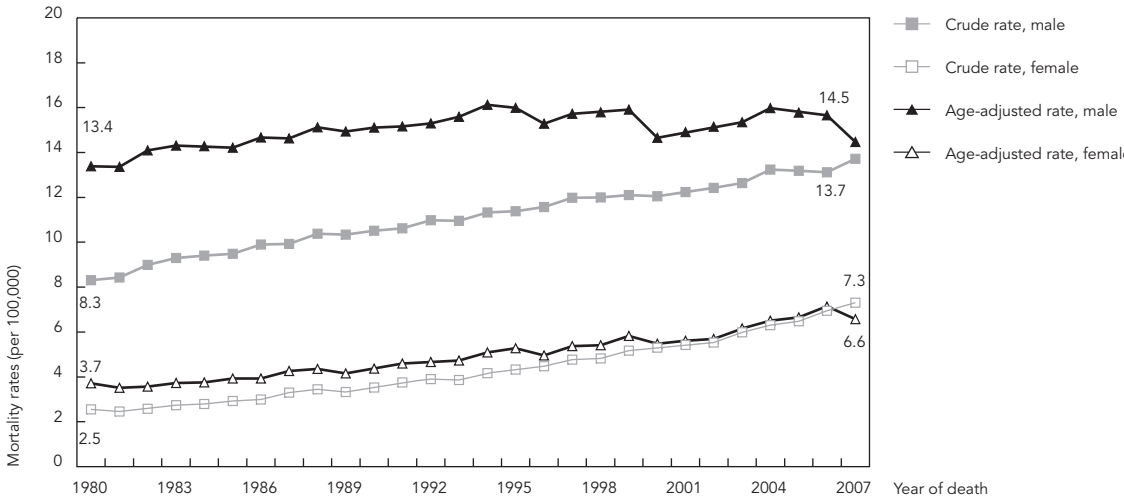
Results

In 2007, crude lung cancer mortality rates were 13.7 and 7.3 deaths/100,000 among men and women, respectively.

In absolute terms, mortality rates (both crude and age-adjusted) among men and women were observed to differ in magnitude in all periods (Figure 1). Lung cancer mortality among men was higher than among women. For the period 1980 to 2007, the sex ratio (men/women) of the

Figure 1

Crude and age-adjusted lung cancer mortality rates, by sex. Brazil, 1980-2007.



age-adjusted lung cancer mortality rates decreased from 3.6:1 to 2.2:1. Over the same period, considering the relative variation, the increase in age-adjusted rates was greater among females (78.4%) than among males (8.2%).

The age-specific lung cancer mortality rates for age groups up to 35 years were less than 1 death/100,000 and were therefore not included in the analysis.

Lung cancer specific mortality rates increase with age, regardless of birth cohort, and rates are much higher among men than among women (Figure 2).

The period effect observed is different for men and women. In Figure 3, age-specific mortality rates among men can be seen to decline slightly up to 64 years of age, while among women a steady increase is observed after 40 years of age. With regard to men, it can be seen that the assumption that there is no interaction between age and period is not confirmed. Among men, the curves for older age groups are overlaid, indicating that the use of reduced models is inappropriate.

Analysis of the cohort dimensions revealed a considerable increase in mortality rates among women as compared to men across all cohorts (Figure 4). Among men, the increase was observed only in age groups over 64 years of age.

For both sexes, the model that considers only age is the single-factor model that produces the best fit or lowest AIC ($AIC_{age:female}$ = 2,716; $AIC_{age:male}$ = 2,186), in comparison to the models comprised of period ($AIC_{period:female}$ = 79,520; $AIC_{period:male}$ = 262,100) and cohort ($AIC_{cohort:female}$ = 2,976; $AIC_{cohort:male}$ = 12,330).

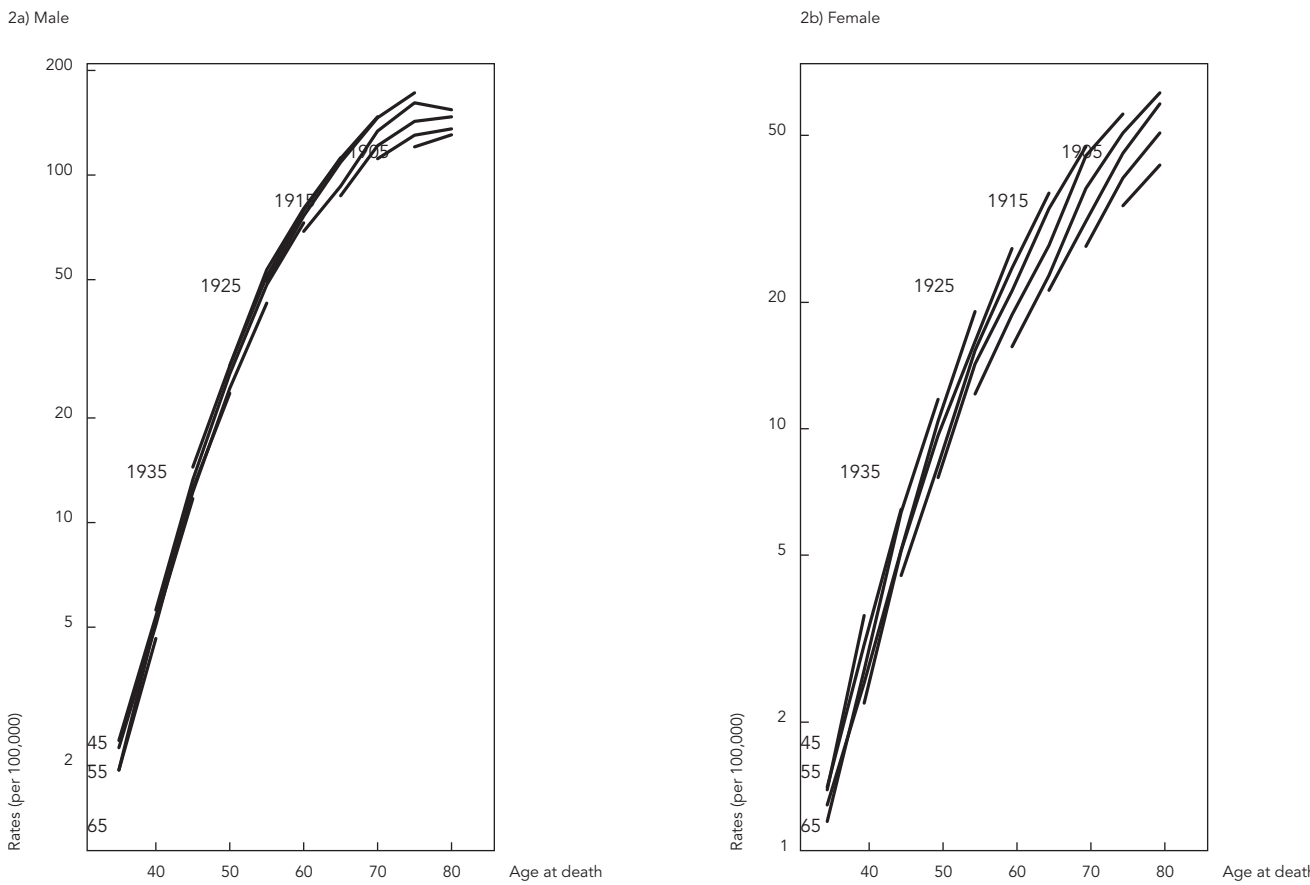
With respect to the two-factor models, the age-cohort model produced the best fit for both sexes ($AIC_{age\text{-}cohort:female}$ = 567; $AIC_{age\text{-}cohort:male}$ = 670), but among men it yielded more gain in goodness of fit than the age-period model, as can be seen from the difference between the respective AICs ($AIC_{age\text{-}period:female}$ = 590; $AIC_{age\text{-}period:male}$ = 1,870).

As the cohort effect corresponds to the interaction between period and age, it would not be appropriate to present models that include the cohort effect but exclude the other two factors. For both sexes, the full model offers greatest explanatory power regarding time trends in lung-cancer mortality in Brazil for the period 1980 to 2004 ($AIC_{age\text{-}period\text{-}cohort\text{-}female}$ = 565; $AIC_{age\text{-}period\text{-}cohort\text{-}male}$ = 660).

It should be noted that among women the age-period model yields quite satisfactory results. The difference between the residual deviance in this model and the full model is small when the same situation is compared for men

Figure 2

Specific lung cancer mortality rates by age at death and birth cohort, males and females. Brazil, 1980-2004.



($\Delta Deviance_{female}$ = -33; $\Delta Deviance_{male}$ = -1,219). However, a detailed analysis of the relative risks associated with all cohorts shows statistical significance and therefore the results from the full model for both sexes are presented.

Figure 5 integrates the plots of the point estimates for the effects on lung cancer mortality of the three factors studied for the period 1980 to 2004. The age effect can be interpreted in terms of rates per 100,000 population and is adjusted for the period and cohort effects. This estimate shows a rising trend in the occurrence of the disease among both sexes, with a smaller rise among women than among men. This difference is statistically significant for all ages.

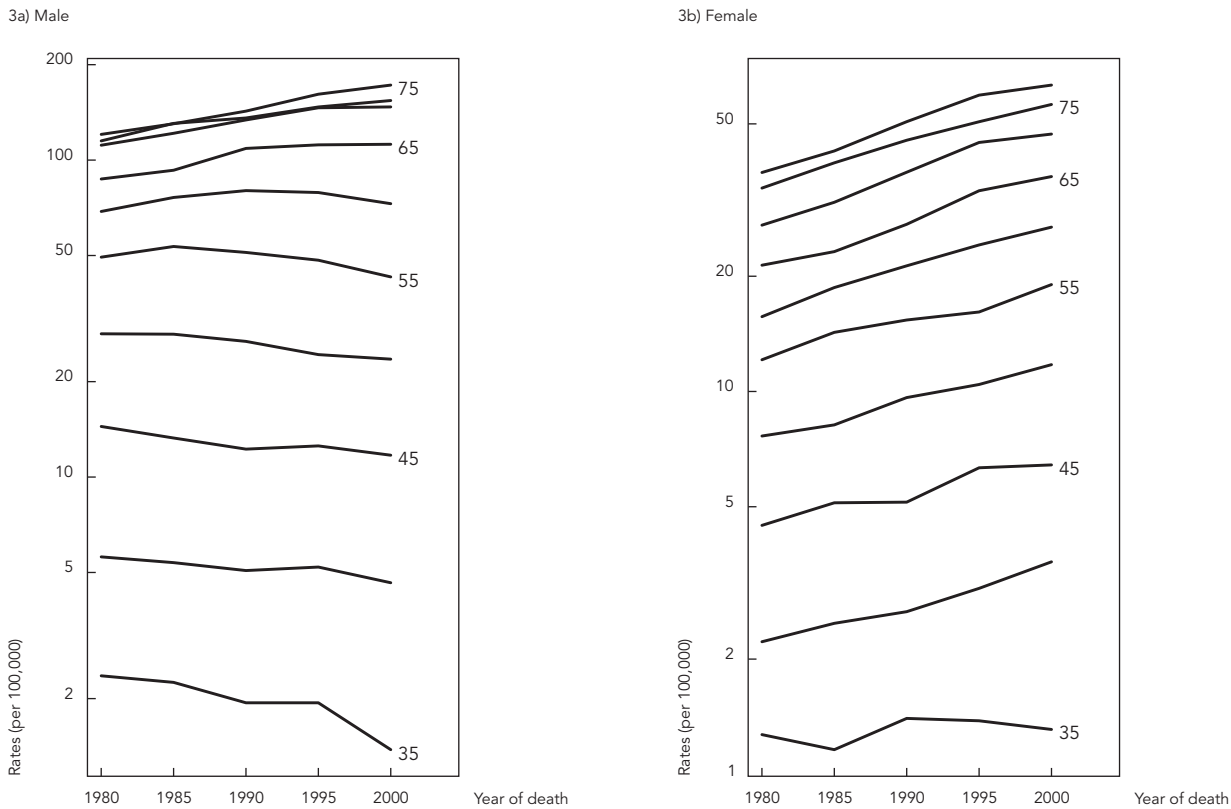
The cohort effect curves (on the log-relative risk scale) are different for men and women. Among men, a slight increase in risk of lung cancer mortality is observed for successive generations born in the period 1923 to 1942. The greatest relative risk is attributed to the generations born between 1928 and 1933 (RR = 1.15; 95%CI: 1.14-1.16). The cohort effect is statistically significant for all categories, except for those born between 1945 and 1949 (RR = 0.99; 95%CI: 0.97-1.02).

The cohort effect is statistically significant for all categories among women, with increases from RR = 0.54; (95%CI: 0.51-0.57) in 1895 to RR = 2.57; (95%CI: 2.34-2.82) in 1967. The cohort effect continues to increase among women.

The period effect, adjusted for age and cohort effects, is approximately one for both sexes, indicating that it has little influence on time trends in lung-cancer mortality. However, this effect should be taken into consideration because the cohort effect also represents an interaction between age and period.

Figure 3

Specific lung cancer mortality rates by year of death and age at death, males and females. Brazil, 1980-2004.



Discussion

The analysis of time trends in mortality has a long history in public health and is important because it can predict future trends [20]. Mortality rate is commonly used in evaluating cancer time trends [14].

The results of this study indicate that lung cancer mortality rates were significantly higher among men than among women for the period 1980 to 2007. Age-specific rates decreased among men up to 64 years of age, but increased among men aged 65 years and over and among women across all age groups. Age-adjusted rates increased among both sexes, with a greater increase among women. Data from surveys of Brazilian children show that, although tobacco use is declining, girls in some cities smoke more than boys [23].

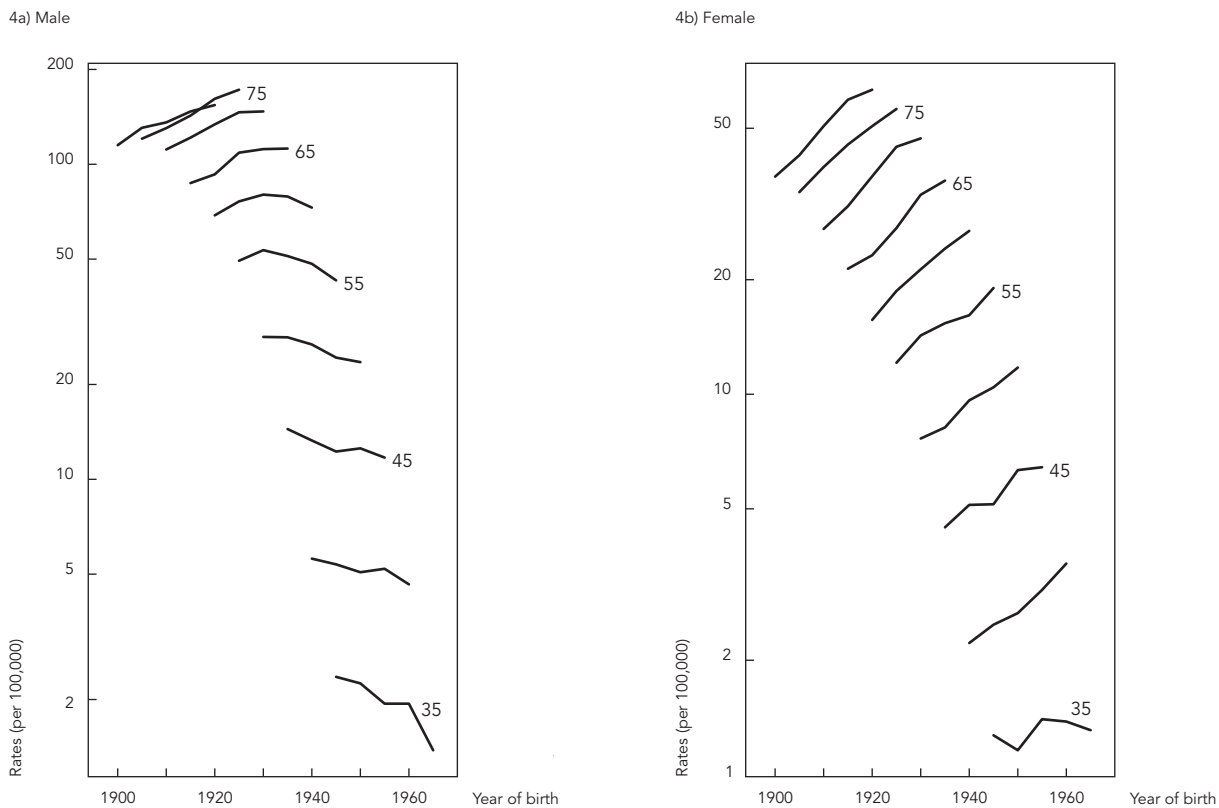
The epidemiologic model to assess tobacco use establishes that current tobacco-related mortality is influenced by the prevalence of smokers in the past [12,24].

Tobacco use in Brazil increased during the 1950s and 1960s, peaking in 1970. Since most people begin to smoke in their teens and lung cancer has a long latency period, the declining age-specific mortality rate among young men is believed to be a result of a history of national level interventions to reduce the prevalence of tobacco use in the country [25,26].

National studies indicate that smoking prevalence has diminished among both sexes, but that this trend is stronger among men. Data on smoking prevalence in Brazil, first obtained in 1989, showed that 43.3% of men and 27% of women aged 18 years or over smoked [27]. In 2003, another national survey showed that that 27.1% of adult males and 18.4% of adult females smoked [27]. A more recent study carried out in 2008 indicates that 18.9% of men and 11.5% of women aged 15 years or over smoked on a daily basis [28].

Figure 4

Specific lung cancer mortality rates by birth cohort and age at death, males and females. Brazil, 1980-2004.



The increasing trend in age-adjusted lung cancer mortality rates among women observed by this study is similar to findings of other studies carried out in Brazil and worldwide [4,6,7,8,13,17,29]; probably reflecting the fact that peak prevalence of smoking among women occurred some years after than in men [12,27].

The findings of this study are similar to those regarding the age effect on lung cancer mortality rates discovered by Yang [17]. Mortality risk increases rapidly with age.

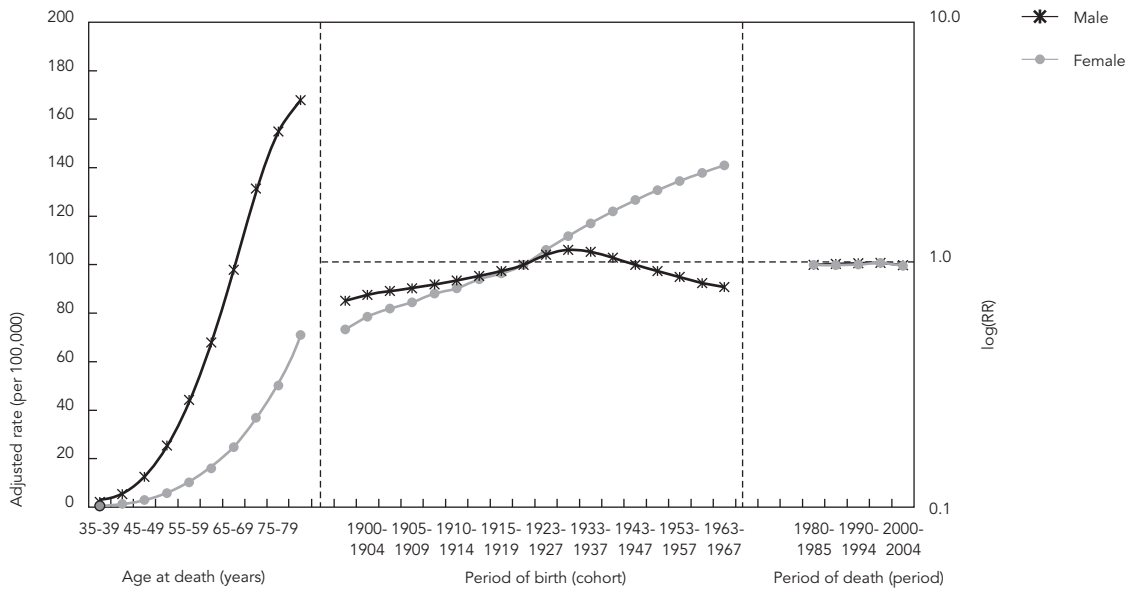
Period effects generally result from changes in factors that have a simultaneous influence on mortality rates for all individuals. With respect to lung cancer, the period effect recorded by this study is small in comparison to the age and cohort effects [17].

The presence of period and cohort effects has been reported in some articles on trends in lung cancer mortality rates. However, inconsistencies in the pattern of results do not allow us to draw conclusive inferences about the role of such effects. For example, a monotonic increase was found among Belgian women, while in the United States the same effect produced an inverted U curve [30]. In England and Wales, period effects were not observed when cohort effects were considered in APC models of lung cancer mortality [31]. The latter finding is similar to those described in this paper. Trends in mortality rates can also be influenced by changes in diagnostic and treatment protocols over time. However, in relation to lung cancer, the advances in these parameters during the study period presented a limited influence on mortality rates.

Studies of trends in lung cancer mortality indicate significant effects related to the birth cohort [14,17,29]. Cohort-associated risk generally relates to patterns of tobacco use from one generation to the next [24,29,32]. The results of this study are in agreement with such findings. The increase in mortality among women born after 1925

Figure 5

Results of the fitted APC-model. Brazil, 1980-2004.



occurred in parallel with increasing tobacco use in women from these generations.

With regard to the cohort effect, the results of this study indicate that this effect among men born after 1950 is due primarily to the influence of lung cancer among young adults, reflecting patterns of tobacco use in this group. These findings are similar to those reported by other authors [17,29,33].

The results of the cohort effect among women suggest that smoking behavior began to change after World War II, period in which women acquired habits commonly associated with men.

The analyses of APC models refer essentially to two time parameters (age and period) and the difference between these parameters in the model. The solution adopted here to solve the "non-identifiability problem" tends to give greater weight to the cohort effect than to the period effect. Preponderance is relatively satisfactory, given that more recent generations have a better knowledge of the etiological factors that contribute to lung cancer so allowing for changes in trends. The solution is appropriate for the case of lung cancer because there were no significant advances in diagnostic techniques, screening programs or treatment during the period studied that could have led to a substantial change in mortality rates [29,32]. On the other hand, effects associated with cohorts reflect processes of exposure to risk factors across the life-course [17].

The results of this study suggest that the most influential factors for both sexes are age and birth cohort. In addition, based on the descriptive analysis, this is not a model artifact.

Limitations

Few studies exist that use APC models to analyze lung cancer mortality. Yang [17] describes this model as limited and still under development, with varying results depending on the assumptions made when building the model. Methodological discussions on model specifications and "non-identifiability problems" are contained in papers published over the last five years [17,19,20].

Using Poisson distribution in the regression models imposes the condition that the mean and the variance of the distribution of the phenomenon under study must be equal. This condition is often not met, as in this study, where the mean is smaller than the variance, resulting in a phenomenon known as over-dispersion. The negative binomial regression model is a flexible alternative to the Poisson regression because it incorporates

a new parameter that provides a control for overdispersion of the response variable. This model was adjusted, but the results were no different from those observed in the Poisson model.

Smoking prevalence is an important factor influencing lung cancer mortality rates. A limitation of this study is that this characteristic was not included in the model due to the lack of availability of annual data in Brazil. Given the consistent reduction in smoking prevalence in recent years, it is possible that a reduction in lung cancer mortality rates would be observed (even among women) if this information were included in the APC model.

Conclusions

In summary, the data regarding most recent generations indicates that present trends in age-adjusted lung cancer mortality rates should continue for some years to come. The cohort effect observed among women born after 1925 suggests an increase in mortality associated with greater smoking prevalence among women in these cohorts. In contrast, reductions in tobacco use and mortality among younger men suggest that the trend that began with the population born after 1950 will continue as tobacco use diminishes in this group. These trends should be seen as a result of tobacco control measures and actions developed by governmental and non-governmental organizations and civil society over the last 19 years in Brazil [27,28]. One of the current challenges facing the Brazilian National Tobacco Control Program is to understand smokers' characteristics in order to develop even more effective strategies to halt tobacco use.

Resumo

Os objetivos deste artigo foram descrever os padrões da tendência de mortalidade por câncer de pulmão no Brasil e identificar os efeitos dos fatores idade, período e coorte (APC) sobre as taxas. Foi realizado um estudo de série temporal utilizando dados secundários de base populacional. Taxas de mortalidade foram calculadas, por sexo, de 1980 a 2007. Modelos APC foram ajustados para identificar como idade, período e coorte influenciam as taxas. As taxas de mortalidade são mais elevadas entre os homens. As taxas específicas estão aumentando para homens maiores de 64 anos e mulheres de todas as idades. As taxas ajustadas cresceram mais entre as mulheres. O efeito idade revela um aumento do risco desde as idades mais precoces. O efeito coorte indica um menor risco para os homens nascidos desde 1950, e risco crescente para mulheres de todas as coortes. Os resultados para gerações jovens indicam que as tendências atuais devem continuar. O efeito coorte entre mulheres sugere um aumento do risco. Estas tendências refletem as medidas de controle do tabaco adotadas desde 1986.

Neoplasias Pulmonares; Modelos Logísticos; Mortalidade

Contributors

M. C. Souza was responsible for the conceptualization of the study, data analysis and coordinated the drafting of this manuscript. A. G. G. Vasconcelos contributed to the interpretation of findings and drafting of this manuscript. O. G. Cruz participated in data analysis, interpretation of findings and drafting of this manuscript.

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