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Lung cancer incidence trends in Uruguay 1990–2014: An age-period-cohort analysis

Rafael Alonso[a,b,*], Marion Piñeros[c], Mathieu Laversanne[c], Carina Musetti[a], Mariela Garau[a,b], Enrique Barrios[a,b], Freddie Bray[c]

[a] *National Cancer Registry, CHLCC, Uruguay*
[b] *Department of Quantitative Methods, Faculty of Medicine, Montevideo, Uruguay*
[c] *International Agency for Research on Cancer, Section of Cancer Surveillance, France*

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ABSTRACT

Background: Uruguay, a country with one of the highest lung cancer rates worldwide, initiated a series of comprehensive anti-smoking measures in 2005. We assess the tobacco control policies in the context of cohort-driven lung cancer incidence trends over a 25-year period, providing baseline predictions to 2035.
Methods: Using data from the National Cancer Registry of Uruguay, an age-period-cohort analysis of trends 1990–2014 was performed. The NORDPRED package was used to predict the annual number of new cases of lung cancer and incidence rates up to 2035.
Results: In men, age-standardised (world) rates declined from a peak of 165.6 in 1995 to 103.1 by 2014, translating to a 70% reduction in the risk of lung cancer in men born in 1970 relative to the early-1940s. In females, rates increased steadily from 18.3 in 1991 to 30.0 by 2014, with successive increases in risk among generations of women born 1940–1960. There is however evidence of a decline in observed rates in women born recently. Extrapolations of the trends indicate an 8% reduction in the mean number of new lung cancer cases in men by 2035, but a 69% increase in women.
Conclusion: Despite observed and predicted reductions in lung cancer incidence in Uruguayan men, rates among women are set to continue to increase, with a large rise in the annual number of female lung cancer diagnoses expected before 2035. There are signals of a diminishing risk among recent generations of women born after 1960. The current analysis provides important baseline information in assessing the future impact of the recent tobacco control initiatives in Uruguay.

1. Introduction

Worldwide, lung cancer is the most commonly diagnosed cancer. In 2012, 1.8 million new lung cancer cases were estimated to have occurred globally, accounting for almost 13% of all new cancer cases (excluding non-melanoma skin cancer) [1]. In South America, over 64,000 new cases are diagnosed each year, the second most common cancer among men (after prostate) and the fourth most common among women [2]. While lung cancer mortality rates have begun to stabilize or decrease among males in the region, they continue to increase in most countries among females, reflecting their more recent uptake of tobacco smoking [3].

Uruguay, a country with a high Human Development Index [4] has an estimated 3.4 million inhabitants and an area of approximately 176,000 square kilometers, making it one of the smaller nations in South America. It has however one of the highest lung cancer rates among men in the Americas [5,6], and the Uruguayan government has implemented an unprecedented series of stringent tobacco control measures upon ratifying the WHO Framework Convention on Tobacco Control (FCTC) in 2004, including Latin America's first ban on smoking in enclosed public places [7–10], the world's largest pictorial warnings (80% of the front and back of cigarette packs), the first ban on differentiated branding [11], alongside a series of tobacco excise tax hikes [12].

While lung cancer mortality trends have been reported via collaborative studies in the region [13], the existence of a high-quality and national population-based cancer registry (PBCR) in Uruguay provides a unique opportunity to assess incidence trends by sex over the last quarter century, including analyses by main histological subtype, as well as a quantification of the future lung cancer burden in the country. Using age-period-cohort approaches and national data on smoking prevalence, we aim to provide baseline evidence from which to assess

* Corresponding author at: Registro Nacional de Cancer – CHLCC, Brandzen 1961, Piso 12 CP 11200, Montevideo, Uruguay.
E-mail address: alonsor@urucan.org.uy (R. Alonso).

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the future impact of the tobacco control measures now in place in Uruguay.

2. Materials and methods

2.1. Data sources

New cases of lung cancer (comprising lung, bronchus and trachea, ICD-10 C33-34) were obtained by age, sex and calendar year of diagnosis from the population-based National Cancer Registry of Uruguay. Data were available for consecutive years 1991–2014 with the exception of 2001, when administrative changes in the registry affected the completeness of data. For 1990, the collected data did not cover the whole country, only the capital and surroundings. New cases for 1990 and 2001 were estimated by linear interpolation from adjacent years to complete the five 5-year periods used in the age-period-cohort analysis. Detailed morphological data were available based on ICD-O-2 (for 2004) and ICD-O-3 (from 2005 onwards) and analyzed in the following recommended [5,14] subgroups: (1) Carcinoma: (1.1) Squamous-cell carcinoma, (1.2) Adenocarcinoma, (1.3) Small cell carcinoma, (1.4) Large cell carcinoma, (1.5) Other specified carcinoma, (1.6) Unspecified carcinoma; (2) Sarcoma; (3) Other unspecified. Annual population denominators for the corresponding years (1991–2014), sex and age were obtained from the National Institute of Statistics (INE) based on censuses performed in 1985, 1996, 2004 and 2011; population projections were available for the years 2015–2034. Information on smoking prevalence was obtained from national surveys.

2.2. Methods

Analysis was restricted to ages 35–74, except for the future predictions which are based on all ages. Truncated (ages 35–74) age-standardized incidence rates were adjusted for age using the direct method and the world standard population [15]. Synthetic and overlapping 10-year cohorts were obtained on subtracting the midpoints of 5-year age groups from the corresponding midyears of 5-year calendar time. These trends are presented as rates versus period by age, and also rates versus birth cohort by age. Assuming constant incidence rates within 5-year age-groups and periods, an age-period-cohort (APC) model was fitted on assuming the number of cases followed a Poisson random variable with the logarithm of the person-years at risk specified as an offset:

$$log(\lambda(a,p)) = \alpha_a + \beta_p + \gamma_c$$

where λ refers to the rate, α, β, and γ are functions of age a, period p and birth cohort $c = p - a$. The relative simplicity of fitting APC models belies difficulties in providing an informed presentation based on a unique set of model parameters, given the irresolvable issue of non-identifiability [16,17]. In order to provide a unique, non-arbitrary solution, we present incidence rate ratios using the full APC model, constraining the linear component of the period effect to have zero slope, thus assuming that the linear changes in trends were cohort-related. While caution is needed in interpreting the results given this assumption, it is in line with the evidence that smoking histories and rates of tobacco uptake and cessation are influenced by societal and peer-related factors, placing successive generations of men and women at higher (or lower) risk of lung cancer. The significance of age and (non-linear) period and cohort effects were tested via an analysis of deviance of the full APC and submodels, as proposed by Clayton and Schifflers [18,19].

The predicted number of lung cancer cases in five-year periods 2015–2019 through to 2030–2034 was estimated by age and sex via the age-period-cohort prediction model NORDPRED, developed in **R** [20]. NORDPRED, a function that extrapolates the age-, period- and cohort-trends into the future has been shown empirically to perform well in predicting cancer incidence [21,21] via a power function that levels off growth and an attenuation (or accentuation) of recent trends by 25%, 50% and 75% in the second, third and fourth prediction periods, respectively. The changes in the number of new cases of lung cancer in Uruguay, as observed in 2010–2014 relative to those predicted in 2030–2034, are presented on partitioning those due to risk (changing lung cancer rates) and those based on population projections (ageing and growth in the Uruguayan population). In the text, we use the phrase "by 2035" as a synonym for the last prediction period (2030–34). All data management and analyses were performed in **R** (version 3.3.1) or Stata (version 13), and *lowess* Stata function was used for smoothing rates in Fig. 1 [22–24].

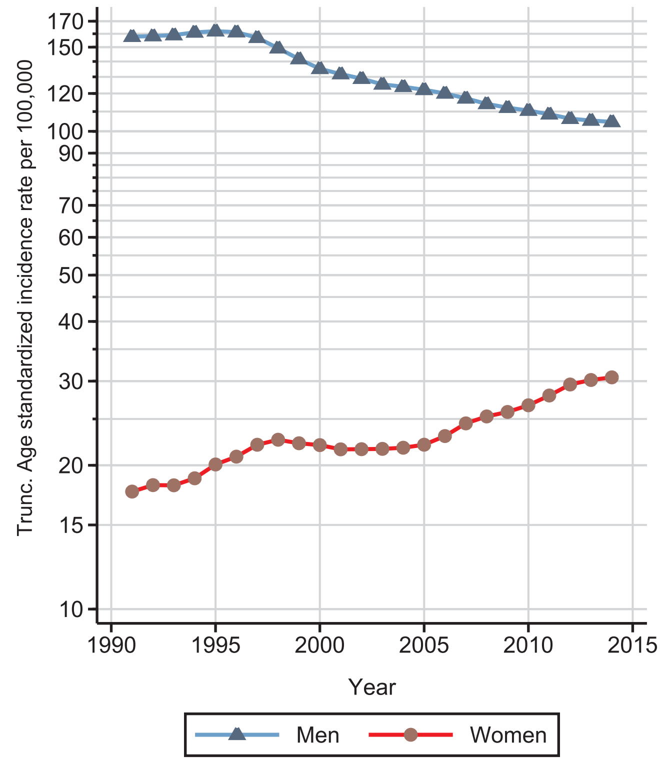

Fig. 1. Lung cancer age-adjusted (World standard) incidence rates over time, by sex, ages 35–74, Uruguay.

3. Results

A total of 26 741 new lung cancer cases (22 273 in males and 4 468 in females) were diagnosed at ages 35–74 years in Uruguay over the 25-year period 1990–2014, with 5 747 cases (5 079 in males and 666 in females) occurring in the first observed period (1990–1994) and 5 020 (3 819 in males, 1 201 in females) in the last (2010–2014) (Table 1).

3.1. Overall trends

Overall trends in lung cancer incidence showed a clear differential pattern between men and women. In males, the uniform decrease in age-adjusted rates after 1995 from 165.6 to 103.1 in 2014, contrasted with increasing rates in women, from 18.3 in 1991 to 30.0 by 2014. The male-female incidence ratio consequently changed from 8.1 in 1991 to 3.4 in 2014 (Fig. 1).

3.2. Observed and model-based trends by age, period and cohort

Fig. 2 illustrates the trends in rates versus birth cohort by age group. The quasi-parallelism of the incidence rates on the cohort scale indicates a greater influence of generation on changing risk of lung cancer