Modelling lung cancer mortality rates from smoking prevalence: Fill in the gap

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ABSTRACT

Background: The objective of this study is to estimate the gap between smoking prevalence and lung cancer mortality and provide predictions of lung cancer mortality based on previous smoking prevalence.
Materials and methods: We used data from the Spanish National Health Surveys (2003, 2006 and 2011) to obtain information about tobacco use and data from the Spanish National Statistics Institute to obtain cancer mortality rates from 1980 to 2013. We calculated the cross-correlation among the historical series of smoking prevalence and lung cancer mortality rate (LCMR) to estimate the most likely time gap between both series. We also predicted the magnitude and timing of the LCMR peak.
Results: All cross-correlations were statistically significant and positive (all above 0.8). For men, the most likely gap ranges from 20 to 34 years. The age-adjusted LCMR increased by 3.2 deaths per 100,000 people for every 1 unit increase in the smoking prevalence 29 years earlier. The highest rate for men was observed in 1995 (55.6 deaths). For women, the most likely gap ranges from 10 to 37 years. The age-adjusted LCMR increased by 0.28 deaths per 100,000 people for every 1 unit increase in the smoking prevalence 32 years earlier. The maximum rate is expected to occur in 2026 (10.3 deaths).
Conclusion: The time series of prevalence of tobacco smoking explains the mortality from lung cancer with a distance (or gap) of around 30 years. According to the lagged smoking prevalence, the lung cancer mortality among men is declining while in women continues to rise (maximum expected in 2026).

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1. Introduction

Tobacco smoking is the leading cause of preventable deaths in developed countries [1]. Particularly, tobacco use is responsible of 71% of lung cancer mortality [2]. Lung cancer is usually detected at advanced stages and, once detected, the survival expectance is poor. The gap between tobacco use and the development of lung cancer disease is of up to 3 or 4 decades [3]. Therefore, knowledge of tobacco use over time can help to predict morbidity and mortality of diseases related to tobacco smoking. The MPOWER strategy suggests the monitoring of smoking trends as an essential tool for tobacco control. Whilst historical series of smoking prevalence rates are available only for some developed countries [4], their reconstruction based on health surveys is reliable and valid [5–7]. On the other hand, mortality from lung cancer has been studied over the years, and thanks to the completeness and reliability of death registers it allows to monitor time trends in lung cancer mortality [8,9].

Few studies [7] have systematically evaluated the time gap between the two aforementioned series and how this gap can predict future mortality rates. Therefore, we propose to explore the cross-correlation between smoking prevalence and lung cancer mortality rates in order to better model the future lung cancer

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mortality rates, using data from a nationally representative survey and universal vital statistics in Spain.

2. Material and methods

2.1. Data

Smoking data were obtained from the three 2003, 2006 and 2011 waves of the Spanish National Health Survey. All surveys included information on smoking status, age at smoking initiation (for current and former smokers) and age at smoking cessation (for former smokers). We then reconstructed the smoking prevalence for each year from 1940 to 2011, stratified by age and sex, as detailed in previous studies [7,10].

Lung cancer mortality data from 1980 to 2013 were available from the National Statistics Institute (INE). Annual population data for the denominator were also available during the study period from the INE. This information was aggregated by sex and age groups. From these data we calculated from 1980 to 2013 the crude mortality rate, the standardized mortality rate (using the standard population of the World Health Organization [11]) and age-specific mortality rates for lung cancer; all the rates calculated in deaths per 100,000 people.

The objective of our statistical analysis was, first, to estimate the most likely gap between the smoking prevalence and the lung cancer mortality rates; and second, to use this most likely gap to predict future lung cancer mortality rates, assuming the same previous trend of smoking prevalence, and the year with the maximum mortality rate.

2.2. Estimating the most likely time gap between smoking prevalence and lung cancer mortality rates

We calculated the cross-correlation between the time series of smoking prevalence and lung cancer mortality rates and its corresponding 95% confidence interval (CI). The cross-correlation is a standard method of estimating the degree to which two series are correlated. The cross-correlation, similar to the Pearson correlation, measures the correlation between two time series after applying a lag (k) to one of them. For two time series x, y and a lag of k units of time, the cross-correlation is calculated as:

$$\frac{\sum(x_i)(y_{i-k})}{\sqrt{\sum(x_i - \bar{x})^2}\sqrt{\sum(y_{i-k} - \bar{y})^2}}$$

In our case, we applied a lag of k years (0–40) to the lung cancer mortality rate series. Thus, the lung cancer mortality rate in a given year (e.g.: 2010) was matched with the smoking prevalence k years before (e.g.: 1980 for a k = 30 year lag). Then, we calculated the correlation between the two series and estimated the most likely gap between the smoking prevalence series and the lung cancer mortality rate series by choosing the lag that maximizes this cross-correlation. Therefore, our parameter of interest in the modeling is k.

We calculated the gap for the crude, age-standardized and age-specific mortality rates because lifetime smoking (pack-years) and the different patterns of smoking vary by age and cohort and may affect the estimation of the gaps.
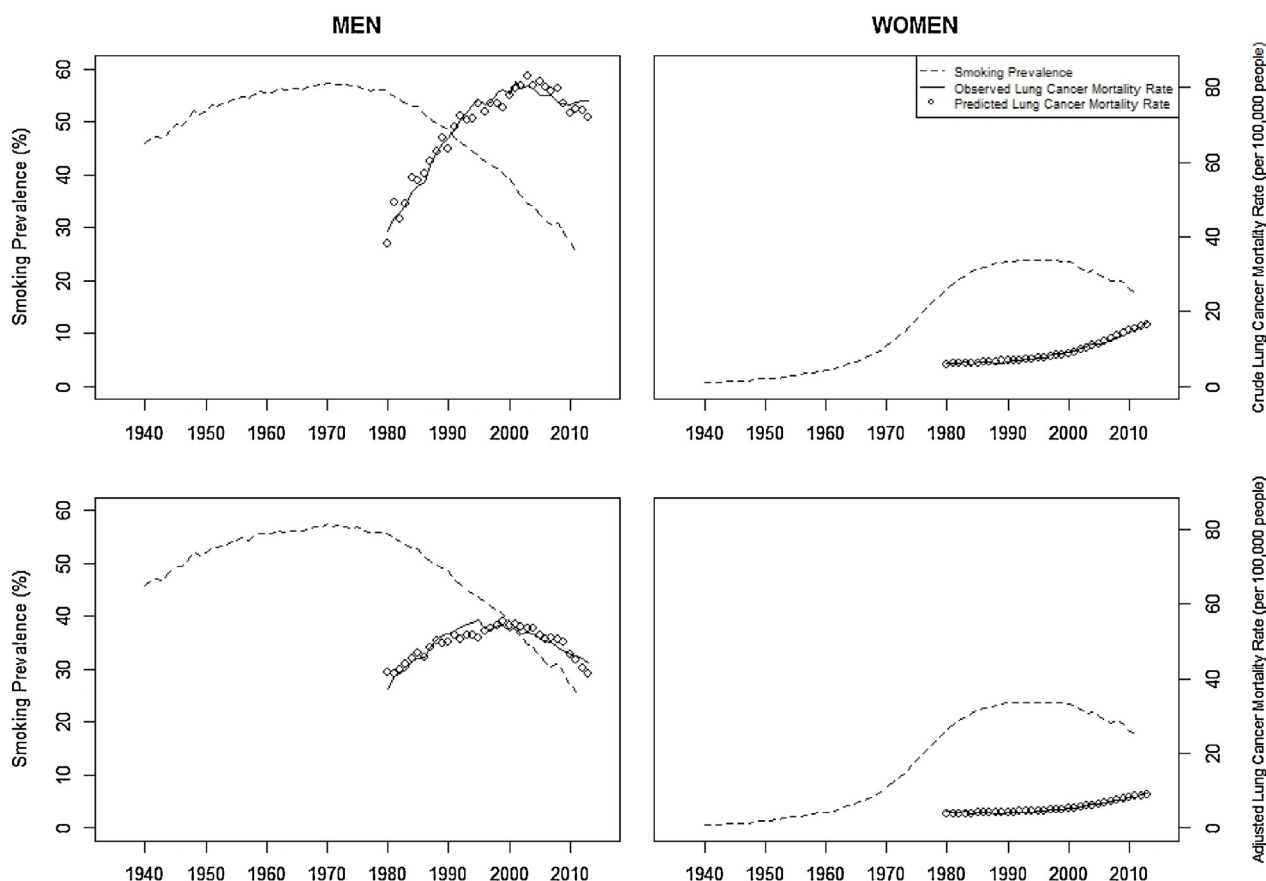

Fig. 1. Time series of smoking prevalence (1940–2011) and observed and predicted crude and adjusted lung cancer mortality rates (1980–2013) in Spain for men and women.

2.3. Predicting future lung cancer mortality rates based on current smoking prevalence

In order to predict future lung cancer mortality rates, we estimated a linear regression model where the independent variable was the smoking prevalence and the dependent variable was the lagged lung cancer mortality rate. A different model was estimated for each combination of rate (crude, standardized and age-specific) and prevalence (crude and age-specific), a total number of 12 models. The target model was $R_t = \alpha + \beta P_{(t-k)}$, where R_t is the lung cancer mortality rate (crude, standardized or age-specific) observed at time t, $P_{(t-k)}$ is the smoking prevalence k years before (crude, standardized or age-specific), α is an intercept

parameter, β is the increase in R_t per unit increase in $P_{(t-k)}$ and k is the most likely time gap (maximized cross-correlation among the series). Using these models we predicted lung cancer mortality rates (crude, standardized and age-specific) and their 95% prediction intervals (PI) by sex in 2020 and estimated the peak of lung cancer mortality rates only for women based on previous smoking prevalence, as the peak of lung cancer mortality rates was previously observed for men.

3. Results

Fig. 1 shows the time series of smoking prevalence and the crude and adjusted lung cancer mortality rates, for men and

Table 1
Cross-correlation and their 95% confidence interval (95%CI) between smoking prevalence and lung cancer mortality rate, gap (in years), linear model and prediction (95% PI) for the lung cancer mortality rate for the year 2020 and maximum prevalence observed for men and predicted for women (95% PI).

	Lung cancer mortality rates			
	Crude rate	Adjusted rate	Specific rate (40–64 years)	Specific rate (>=65 years)
Men				
Maximum rate observed (year)[a]	81.6 (2001)	55.6 (1995)	93.8 (1995)	390.3 (1994)
Smoking prevalence (overall)				
Cross-correlation	0.979 (0.958–0.989)	0.907 (0.820–0.953)	0.862 (0.740–0.929)	0.923 (0.850–0.961)
Gap[b]	33	29	27	31
Linear model	$R_t = -284.83 + 6.41P_{t-33}$	$R_t = -127.76 + 3.19P_{t-29}$	$R_t = -219.22 + 5.42P_{t-27}$	$R_t = -733.27 + 19.62P_{t-31}$
Predicted rate for the year 2020	39.1 (33.5–44.7)	22.0 (15.8–28.1)	25.0 (9.6–40.5)	230.7 (198.6–262.7)
Smoking prevalence (16–39 years)				
Cross-correlation	0.942 (0.886–0.971)	0.849 (0.717–0.922)	0.826 (0.677–0.910)	0.833 (0.688–0.914)
Gap[b]	28	23	20	26
Linear model	$R_t = -272.27 + 5.98P_{t-28}$	$R_t = -98.71 + 2.58P_{t-23}$	$R_t = -121.21 + 3.55P_{t-20}$	$R_t = -606.5 + 16.75P_{t-26}$
Predicted rate for the year 2020	38.3 (29.0–47.5)	25.9 (18.5–33.2)	41.4 (26.8–56.1)	236.0 (189.0–283.1)
Smoking prevalence (40–64 years)				
Cross-correlation	0.848 (0.715–0.922)	0.883 (0.776–0.940)	0.880 (0.771–0.939)	0.873 (0.758–0.935)
Gap[b]	34	30	27	33
Linear model	$R_t = 5.53 + 1.32P_{t-34}$	$R_t = -29.86 + 1.57P_{t-30}$	$R_t = -67.61 + 2.95P_{t-27}$	$R_t = 168.53 + 3.81P_{t-33}$
Predicted rate for the year 2020	64.7 (51.5–78.0)	39.7 (34.7–44.6)	56.0 (45.6–66.5)	361.0 (327.8–394.1)
Women				
Smoking prevalence (>15 years)				
Cross-correlation	0.996 (0.991–0.998)	0.990 (0.981–0.995)	0.992 (0.984–0.996)	0.968 (0.937–0.984)
Gap[b]	32	32	32	37
Linear model	$R_t = 5.34 + 0.58P_{t-32}$	$R_t = 3.56 + 0.28P_{t-32}$	$R_t = 4.86 + 0.83P_{t-32}$	$R_t = 28.05 + 1.42P_{t-38}$
Predicted rate for the year 2020	18.7 (18.0–19.4)	10.1 (9.6–10.6)	24.1 (22.7–25.5)	57.9 (54.3–61.5)
Maximum rate predicted (year)	19.1 (18.4–19.8) (2026)	10.3 (9.8–10.8) (2026)	24.6 (23.2–26.0) (2026)	62.0 (58.1–65.9) (2031)
Smoking prevalence (16–39 years)				
Cross-correlation	0.993 (0.985–0.996)	0.993 (0.985–0.996)	0.994 (0.989–0.997)	0.980 (0.960–0.990)
Gap[b]	30	31	30	37
Linear model	$R_t = 5.84 + 0.30P_{t-30}$	$R_t = 3.80 + 14.98P_{t-30}$	$R_t = 5.54 + 0.44P_{t-29}$	$R_t = 28.99 + 0.97P_{t-37}$
Predicted rate for the year 2020	18.2 (17.2–19.1)	10.2 (9.8–10.7)	23.3 (22.2–24.5)	62.2 (59.1–65.2)
Maximum rate predicted (year)	18.3 (17.4–19.2) (2022)	10.4 (9.9–10.8) (2023)	23.5 (22.4–24.7) (2022)	68.5 (65.1–71.9) (2029)
Smoking prevalence (40–64 years)				
Cross-correlation	0.998 (0.995–0.999)	0.989 (0.977–0.994)	0.990 (0.979–0.995)	0.959 (0.919–0.979)
Gap[b]	13	14	10	15
Linear model	$R_t = 4.61 + 0.64P_{t-13}$	$R_t = 3.17 + 0.34P_{t-14}$	$R_t = 3.79 + 0.75P_{t-10}$	$R_t = 26.54 + 1.24P_{t-15}$
Predicted rate for the year 2020	20.0 (19.5–20.6)	11.2 (10.6–11.8)	21.6 (20.1–23.2)	54.9 (50.9–58.8)

R_t: Lung cancer mortality rate, P_t: Smoking prevalence.
[a] The lung cancer mortality rates peak were previously observed for men.
[b] Years lagged with the maximum correlation among the series.

women. All the cross-correlations obtained among the two time series were statistically significant, above 0.8 in magnitude and were all positive (Table 1).

For men, the most likely gap ranges from 20 to 34 years (Table 1). The maximum cross-correlation between the smoking prevalence and the crude lung cancer mortality rate was obtained for a gap of 33 years ($r = 0.979$). The estimated linear model with this gap predicts an increase of 6.41 deaths per 100,000 inhabitants for every unit increase (i.e., 1%) in the smoking prevalence 33 years earlier. The corresponding predicted crude lung cancer mortality rate in 2020 is 39.1 per 100,000 people (95% PI: 33.5–44.7). The maximum cross-correlation for the adjusted mortality rate is 0.907, corresponding to a gap of 29 years, and the linear model predicts an increase of 3.19 deaths/100,000 and a predicted adjusted mortality rate in 2020 of 22.0/100,000 people (95% PI: 15.8–28.1). The highest rate for men was observed in 1995 (55.6 deaths per 100,000 people).

For women, the most likely gap ranges from 10 to 37 years (Table 1). The maximum cross-correlation between the smoking prevalence and crude mortality rates was obtained for a gap of 32 years ($r = 0.996$). A 1% increase in the smoking prevalence for women was estimated to be associated with an increase of 0.58 deaths/100,000 people 32 years later. This model predicted a crude mortality rate in 2020 of 18.7 deaths per 100,000 women (95% PI: 18.0–19.4). The maximum crude mortality rate is predicted to occur in 2026, when the rate is estimated to be 19.1 deaths per 100,000 women (95% PI: 18.4–19.8). Regarding the adjusted lung cancer mortality rate, the maximum cross-correlation with smoking prevalence in women was obtained for a gap of 32 years ($r = 0.990$). The resulting linear model estimated an increase of 0.28 deaths per 100,000 people per 1% increase in the smoking prevalence; this resulted in a predicted adjusted lung cancer mortality rate of 10.1 deaths/100,000 people in 2020 (95% PI 9.6–10.6). The maximum adjusted rate is predicted to occur in 2026, when the rate is estimated to be 10.3 deaths per 100,000 women (95% PI: 9.8–10.8).

When focusing in lung cancer mortality rates by sex and age-groups, we observed that for mortality rates in men from 40 to 64 years, the maximum cross-correlation with their corresponding smoking prevalence was obtained from for a gap of 27 years ($r = 0.880$). For mortality rates in men over 65 years the maximum cross-correlation was obtained from the overall smoking prevalence for a gap of 31 years ($r = 0.923$). For women from 40 to 64 years, the maximum cross-correlation was obtained from the smoking prevalence from 16 to 39 years for a gap of 30 years ($rn = 0.994$), and the maximum rate predicted was 23.5 for the year 2022. For women over 65 years, the maximum cross-correlation was also obtained from the smoking prevalence from 16 to 39 years for a gap of 37 years ($r = 0.980$), and the maximum mortality rate predicted was 68.5 in 2029. The smoking prevalence from 40 to 64 years has still not reached their maximum and therefore there is not estimation for the maximum rate, but it is the age group with the smallest gap between smoking prevalence and the mortality rates, from 10 to 15 years.

4. Discussion

In this study we have proposed a method (cross-correlations) to estimate the most likely gap between smoking prevalence and lung cancer mortality rates in the Spanish population, and subsequently used this method to predict lung cancer mortality rates in the near future based in recent previous time series of smoking prevalence. Furthermore, we have estimated the future peak (and starting point of the decline) in lung cancer mortality rates in women, where the peak has not occurred yet, and whose lung cancer mortality rates are predicted to continue increasing up until 2026. This is the first

description, to our knowledge, of the cross-correlation among the time series of smoking prevalence and lung cancer mortality rates in Spain.

Smoking is not the only factor affecting lung cancer mortality rates. Improvements in the treatment of lung cancer can lower the mortality rate in the future. At the same time, there may be an important role for competing causes of mortality in smokers, such as coronary heart disease. As coronary heart disease mortality decreases, the pool of smokers that end up dying from lung cancer may increase. Future studies should clarify this competing risk phenomenon and assess whether improvements in lung cancer care versus decreases in coronary heart disease mortality may affect each other substantially. In this sense, we have validated our model and recalculated it letting out the lung cancer mortality rate observed in 2011, 2012 and 2013. We did not find differences in the model and gap between series. Moreover, the predicted lung cancer mortality rates (without 2011–2013 data) and the observed data for 2011–2013 were similar, with minor differences. These could be partially explained by improvements in the treatment of other tobacco-related diseases.

The time series of prevalence of tobacco smoking seems to accurately explain the mortality from lung cancer with a time distance (or gap) of about 30 years, which is consistent with previous knowledge on the causal relationship between smoking and lung cancer [12,13] and coherent with the tobacco epidemic model that predicts a time lag of around 30 years between the peaks in the time series of smoking prevalence and the proportion of deaths attributed to smoking [14]. We found different linear coefficients in each model due to the different magnitudes of each rate (i.e., 65+ rates in men have a steeper slope than the age-standardized rate because the rate itself is much larger). However, the cross-correlation between time series was still very high and the most likely gaps were independent of the choice of each rate. As some studies hypothesize that tobacco is a stronger effect in women [15], other disagree [16]. Moreover, smoking cessation has also been described to be less sustained in women [17]. Prognosis after lung cancer diagnosis is usually better for women as the lethality from lung cancer is higher in men [18], and the tobacco smoking is lower in women [19].

The shortest gap between the two time series was obtained in women, for the smoking prevalence in the group from 40 to 64 years, where the most likely gap was estimated to range from 10 to 15 years, depending on the specific mortality rate age-group. This group of women was among the first smoking initiators in Spanish women by the time the prevalence started increasing in the late 1970s [20]. The histological type of lung cancer has been different in men and women, being more frequent the squamous cell and small cell carcinoma in men and the adenocarcinoma for women. The adenocarcinomas are related to the use of filter and low-tar cigarettes and by a different susceptibility to tobacco in women [21].

According to previous prevalence of tobacco smoking, our results predict an increase in lung cancer mortality rates for women in the next decade. Another study [22] conducted in Spain showed a significant increase of lung cancer mortality rates in women in the most recent years (the crude and adjusted mortality rates increased from 11.83 and 6.82 in 2006 to 17.34 and 9.34 in 2013, respectively). We have estimated that the crude and adjusted mortality rates for women will be 18.7 and 10.1, respectively, in 2020. If this is the case, the mortality rates among women will increase at a slower pace in the next years. This phenomenon may be due to the sharp increase in smoking prevalence 32 years ago: according to the Spanish National Health Surveys, the smoking prevalence increased by 7.7% between 1974 and 1981 (11.7% in 1974 to 19.4% in 1981, corresponding to a 32 year lag from 2006 and 2013, respectively) and "only" by 3.8% between 1981 and 1988 (19.4% in 1981 to 23.2% in 1988, that would correspond to a 32 year lag in 2020). Smoking prevalence then peaked in the mid-90s, which is now reflected in our estimated peak

of lung cancer mortality rates in women in 2026. On the other hand, our results show similar lung cancer mortality rates by sex compared to previous studies conducted in Spain with different methods (e.g.: Age-Period-Cohort model [24], JoinPoint Regression [22] or Poisson Regression [23]. The predicted rates using the Age-Period-Cohort Model [24] and Poisson Regression [23])were slightly higher for women compared to ours. The reason behind this could be that these other methods do not use historical smoking prevalence to predict future lung cancer rates. Our study is the first one, to our knowledge, that considers the previous smoking prevalence to make the prediction. This aspect allows for a potentially more reliable prediction of long-term lung cancer mortality rates that can help in implementing tobacco control policies for specific groups.

A strength of this study is that we used data from several sources, including a reconstruction of smoking prevalence with a validated method and with a large sample (over 60,000 individuals) [7], and a calculation of lung cancer mortality rates from vital statistics. The main limitation of the study is the reconstruction of the smoking prevalence retrospectively from recent surveys that could lead to an underestimation of the smoking prevalence, especially in a more distant past [7]. This limitation could also lead to an underestimation of the gap between time series. However, we believe that this bias could have a limited effect in our results given that we found a very high cross-correlation (close to 1). Future studies should be using other data sources to obtain a more valid estimate of smoking prevalence to address this potential limitation. Limitations of this study include its ecological nature, as we cannot determine an individual-level causal relationship between smoking and lung cancer (although previous studies have already demonstrated this). A second limitation is that the time span of this study is limited by the available 34 years of lung cancer mortality data and, while the time series of smoking prevalence is broader, it is reconstructed from a sample of face-to-face surveys. This may introduce some error and can bias our results, although this reconstruction has been validated before [7].

5. Conclusions

In conclusion, the time series of smoking prevalence can be used to estimate the lung cancer mortality rate with a gap of around 30 years in Spain. The gap should be empirically re-estimated for any population with its own data, as the tobacco epidemic varies in different contexts. In Spain, according to previous smoking prevalence, the lung cancer mortality among men is declining while in women continues to rise (maximum expected in 2026). Therefore, smoking cessation programs, particularly among women, should take into account our predictions in order to reduce the impact of the mortality for lung cancer in the next decades.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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