INTRODUCTION

Worldwide, lung cancer is the most common cancer type, with an age-standardized incidence rate of 22.5 per 100,000 in 2018. Prevalence is significantly elevated in North America and Europe, being, in this last case, Hungary the country with the highest incidence rate for both males and females. In Spain, lung cancer incidence rates are 42.1 per 100,000 for males and 14.0 per 100,000 for females; lung cancer incidence has displayed a decreasing trend in males and in-hospital mortality, and to revise disease management and the direct medical costs of secondary care.

METHODS: A retrospective observational study was set to analyse anonymized primary and secondary care records of patients admitted with lung cancer in Spain between 2011 and 2016. Data were obtained from the Primary Care Dataset and the Centralised Hospital Discharge Database.

RESULTS: Admissions files from 12,119 primary care and 113,574 secondary care patients were analyzed. Only 21% of all patients were females, yet the number of female patients presented an increasing trend over the study period. Non-small-cell lung carcinoma represented 85.29% of all lung malignant neoplasms; metastatic or secondary malignant neoplasms were diagnosed in 76.66% of admissions. Other relevant comorbid conditions registered at the hospital level were hypertension, disorders of lipid metabolism, diabetes mellitus and a history of tobacco use. In-hospital mortality was 22% over the study period and was associated with respiratory failure. Mean hospitalization time was 9.57 days and most admissions were due to emergencies. The mean cost of secondary care per patient was €8475, increasing significantly over the study period. Cost per patient was higher in those diagnosed with a squamous cell carcinoma.

CONCLUSIONS: Preventive and early detection measures are recommended, continuing to focus on females. In parallel, a multidisciplinary approach could optimize patient journey considering the presence of disease comorbidities, although its role in lung cancer mortality should be further explored.

ABSTRACT

Objective: This study aimed to describe the current status of lung cancer in Spain, including patient characteristics, use of healthcare resources and in-hospital mortality.

Methods: A retrospective observational study was set to analyse anonymized primary and secondary care records of patients admitted with lung cancer in Spain between 2011 and 2016. Data were obtained from the Primary Care Dataset and the Centralised Hospital Discharge Database.

Results: Admissions files from 12,119 primary care and 113,574 secondary care patients were analyzed. Only 21% of all patients were females, yet the number of female patients presented an increasing trend over the study period. Non-small-cell lung carcinoma represented 85.29% of all lung malignant neoplasms; metastatic or secondary malignant neoplasms were diagnosed in 76.66% of admissions. Other relevant comorbid conditions registered at the hospital level were hypertension, disorders of lipid metabolism, diabetes mellitus and a history of tobacco use. In-hospital mortality was 22% over the study period and was associated with respiratory failure. Mean hospitalization time was 9.57 days and most admissions were due to emergencies. The mean cost of secondary care per patient was €8475, increasing significantly over the study period. Cost per patient was higher in those diagnosed with a squamous cell carcinoma.

Conclusions: Preventive and early detection measures are recommended, continuing to focus on females. In parallel, a multidisciplinary approach could optimize patient journey considering the presence of disease comorbidities, although its role in lung cancer mortality should be further explored.

INTRODUCTION

Worldwide, lung cancer is the most common cancer type, with an age-standardized incidence rate of 22.5 per 100,000 in 2018. Prevalence is significantly elevated in North America and Europe, being, in this last case, Hungary the country with the highest incidence rate for both males and females. In Spain, lung cancer incidence rates are 42.1 per 100,000 for males and 14.0 per 100,000 for females; lung cancer incidence has displayed a decreasing trend in males over the past decade, yet it remains as one of the principal causes of disability and mortality.

The lung cancer age-standardized mortality rate worldwide was 18.6 per 100,000 in 2018, similar to that in Spain, where the 5-year relative survival rate was only 13.5% between 2010 and 2014. Nevertheless, a decrease in mortality has been observed, presumably promoted by the decreasing smoking prevalence, reversing the increasing trend followed until the mid-nineties; still, for females, lung cancer mortality maintained the growing trend at least until 2012. The differential incidence and mortality rates observed for females have been primarily related to variations in smoking habits, with studies indicating a higher smoking prevalence among Spanish teenage girls, when compared to boys, up to 2002. Tobacco smoke remains the principal factor in lung carcinogenesis, followed by indoor radon, a natural radioactive gas found in indoor environments. In addition, polymorphism in several chromosome regions (i.e. the cholinergic nicotine receptor genes) has been associated to lung cancer susceptibility, while less evidence has been found in association with the diet and alcohol consumption. A clear understanding of the effect that these factors may have will be of utmost importance for the implementation of preventive policies.

On the other hand, the development of more efficient diagnostic and treatment models contributes to control cancer incidence and mortality. It has been challenging to advance in this direction due to the complexity of lung carcinoma at the molecular and histological level. In general terms, two main groups have been described based on tumour histology and prognosis: small-cell carcinoma (SCLC) and non-small-cell carcinoma (NSCLC) that represent about 85% and 15% of all lung cancers, respectively. In turn, NSCLCs are classified into adenocarcinoma (ADC), squamous cell carcinoma (SCC) and large-cell carcinoma (LCC). Additionally, distinct genetic variants have an influence in...
disease prognosis, including mutations in the epidermal growth factor receptor (EGFR) gene, the Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) or the B-Raf Proto-Oncogene, Serine/Threonine Kinase (BRAF)\textsuperscript{13}.

These elements, together with other patient characteristics and risk factors are relevant for the revision of preventive and treatment protocols, including the implementation of lung cancer screening programs via low-dose computed tomography (CT), which could provide significant benefits when applied to high-risk populations\textsuperscript{14}. International consent in the generalized use of such screenings has not been reached; however, European experts recommend their application, following a risk stratification approach to be based on an accurate description of the population at risk\textsuperscript{15}. In addition, the access to real-world evidence that reflects current practice from complementary observational prospective and retrospective studies is considered crucial to revise preventive and treatment protocols, and to develop adequate resource allocation strategies\textsuperscript{16,17}.

Thus, the aim of this study was to describe the characteristics of patients with lung cancer in Spain and any factors that may play a role in lung cancer mortality, identify any temporal tendencies and analyze patients’ use of medical resources and direct medical costs of secondary care.

### Methods

#### Study setting and design

Healthcare records of patients admitted with lung cancer in primary and specialized healthcare centres in Spain were analyzed in a retrospective multicentre observational study. Data were obtained from the Primary Care Dataset and the Centralised Hospital Discharge Database via the Spanish Ministry of Health, two databases that compile data from private and public healthcare centres representative of all Spanish regions\textsuperscript{18}. Data is codified at the centre or hospital level by specialised doctors by using the Spanish ICD codification guides made available to health professionals, and centres are responsible for data codification, evaluation and confidentiality. Each database is validated internally and subjected to periodic audits. In this process, errors and unreliable data are eliminated. Data inclusion was established to comprise most recently available data at the moment of the analysis, starting 1 January 2011 to 31 December 2016.

| Setting and coding system | Years | Codes | Description |
|---------------------------|-------|-------|-------------|
| Diagnoses and tumour location |       |       |             |
| Primary care (ICPC-2)      | 2011–2015 | R84  | Malignant neoplasm of bronchus/lung |
| Secondary care (ICD-9-CM; ICD-O-3) | 2011–2015 | 162.2–162.9; 209.21 | Malignant neoplasm of bronchus and lung |
| Secondary care (ICD-10-CM; ICD-O-3) | 2016 | C34.0–C34.92 | Malignant neoplasm of bronchus and lung |
| Tumour type |       |       |             |
| Secondary care (ICD-O-3)   | 2011–2015 | 8012; 8041–8043; 8070–8076; 8140–8141 | Large cell carcinoma; Small cell carcinoma; Squamous cell carcinoma; Adenocarcinoma |

### Data extraction

Records of admissions in which lung cancer was registered as the admission motive were petitioned and identified by means of the International Classification of Primary Care second edition (ICPC-2) and the 9th and 10th revisions of the International Statistical Classification of Diseases and Related Health Problems, clinical modification (ICD-9-CM and ICD-10-CM) codes. The corresponding ICD-9-CM and ICD-10-CM were used to identify lung cancer diagnoses and tumour location, and, when available, the International Classification of diseases for Oncology, third edition (ICD-O-3) was used to categorize tumour morphology (Table 1).

The Spanish Ministry of Health was in charge of data extraction, with any parameters identifying the medical history and health centres previously re-coded to avoid any access to identifying information in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. In such cases, the Spanish legislation does not require patient consent and ethics committee approval according to the Law 14/2007, 3 July, on biomedical research, Spain\textsuperscript{19}. Patients were not directly involved in the research or the study design.

### Study variables

Both databases register information about the patient and admission details. Primary care data includes patients’ sex, age, income level and employment status, centre location, date of admission and admission motive. The secondary care database registers patients’ sex and age, hospital location, date of admission, type of admission, date of discharge, type of discharge (including death), service to discharged the patient, length of stay, readmission rate, admission motive, secondary diagnoses registered during the admission, tumour morphology (codified with the International Classification of diseases for Oncology (ICD-O-3) codes), medical procedures performed and cost of the admission.

### Data analysis

Admission motive data was used to identify patients with lung cancer. Primary care records were analyzed to determine patient characteristics and socioeconomic profile; all secondary care admission records were used to evaluate patient journey upon hospitalization: nature of the
admission, services to discharge the patient, days of stay and medical procedures. The analysis of patient characteristics via single-patient data was based on the first admission registered per patient due to lung cancer.

Direct medical costs of secondary care were estimated by using the admission cost determined in the database, based on the standardized average expenses of admissions and medical procedures determined by the Spanish Ministry of Health. This calculation included all expenses related treatment (examination, medication and surgery), nutrition, costs associated to personnel, medical equipment and resources.

To describe the patient population patients were grouped according to tumour histology. A descriptive univariate analysis was done. Frequencies and percentages are presented for dichotomous variables and mean and standard deviation or error were calculated for parametric quantitative variables. Odd ratios (OR) with 95% confidence interval (CI) were used to assess the association of secondary conditions with in-hospital mortality, with the group of patients non-deceased during the hospitalization as the reference group. Two-tailed T-student or one-way analysis of variance were used according to data distribution and two-sample Z tests were used to test for differences in sample proportions, with a \( p < .05 \) considered statistically significant in all cases.

Statistical analyses were performed using StataSE 12 for Windows\(^{11}\) and Microsoft Excel Professional Plus 2010.\(^{11}\)

### Results

Data obtained from primary care registries corresponded to 26,188 admissions from 12,119 patients with a diagnosis of lung or bronchial cancer between 2011 and 2016. Separately, the database for hospitalization and specialized care included 173,592 entries with lung or bronchial cancer as the admission motive that corresponded to 113,574 patients (Table 2). Males represented the majority of patients, and were significantly older than female patients in both settings (\( p < .001 \)).

Over 73% of the records included a histological description of the tumour. Only 14.71% of the specified diagnoses were of SCLC while 85.29% corresponded to NSCLC (Figure 1(A)). Overall, adenocarcinoma was the predominant tumour typology, with no differences observed between males and females. Additionally, tumour location was specified in 57.51% of secondary care files. Data suggested a predominance of patients with the tumour located in the upper lobe of the bronchus or lung (Figure 1(B)).

The temporal analysis revealed a minor increase in the number of patients diagnosed in primary care centres during the study period, from the 1549 patients attended in 2011 to the 2087 patients attended in 2016. The percentage of males attended in these centres steadily decreased, while the percentage of females increased (\( p < .001, 2011 \) vs. \( 2016 \)) (Figure 2(A)). On the contrary, the number of patients attended in secondary care remained stable over the study period; however, a slight decreasing trend was observed among males, compensated by an increase in the percentage of female patients (Figure 2(B)).

The principal diagnosis upon hospitalization (admission motive) was in all cases a lung carcinoma, and secondary diagnoses were utilised to perform an analysis of relevant comorbid conditions at the hospital level. Metastatic or secondary malignant neoplasms were registered in 76.66% of patients with a lung carcinoma (Table 3). The second most repeated comorbidity was hypertension, found in 33.57% of patients. A history of tobacco use appeared in 25.29% of

### Table 2. Patient descriptive parameters and tumour classification according to ICD-9-CM and ICD-10-CM.

| Setting                  | N     | % of patients | Age (SD) |
|--------------------------|-------|---------------|----------|
| Primary care centres     | 12,119| –             | 68.04 (12.34) |
| Males                    | 9380  | 77.23         | 68.97 (11.52) |
| Females                  | 2739  | 22.77         | 64.89 (14.35) |
| Secondary care centres   | 113,574| –             | 67.44 (11.25) |
| Males                    | 90,389| 79.59         | 68.16 (10.71) |
| Females                  | 23,181| 20.41         | 64.63 (12.77) |

### Figure 1. Percentage of patients per tumour typology (A) and location (B).
patients. Respiratory symptoms were common among these patients, as respiratory failure and bronchitis, likely to be symptoms of the disease. Chronic obstructive pulmonary disease (COPD) was registered in 12.19% of all patients. Other registered comorbidities were disorders of lipid metabolism and diabetes mellitus, diagnosed in 23.02% and 21.39% of patients respectively.

In-hospital mortality was 22% during the study period. Overall, 82.00% of patients deceased were males, averaging 69.06 (SD = 10.88) years. Females represented only 22.66% of deceased patients, and had a mean of 65.69 (SD = 13.27) years. Mortality was significantly higher in patients diagnosed with an SCLC, reaching 29.62% (p < .001).

Metastatic and secondary malignant neoplasms were more commonly diagnosed in this group and the overall number of malignant neoplasms was superior to the number of patients deceased, indicating the presence of multiple tumours per patient. Respiratory failure was associated with death in this population. Overall, the number of patients deceased during hospitalization remained stable over the study period.

The vast majority of hospitalization records included in the analysis (98.81%) corresponded to inpatient care, with a predominance of non-scheduled admissions that summed 64.58% vs. 35.42% of scheduled admissions. Only 16% of those were due to readmissions, understood as a second admission within a 30-day period following discharge.

Patients were hospitalized 9.57 days on average, 10.63 days when admissions were due to emergencies and 7.63 days in scheduled admissions. Internal medicine was the service to discharge 25.44% of the patients, 23.78% were attended by oncology services, 21.24% by pneumology and pulmonology services, 18.81% by thoracic surgery services and 4.85% by palliative care services. Altogether, imaging techniques were frequently used to diagnose these patients, as well as biopsies of distinct organs (Table 4). Chemotherapy was administered in 18.21% of all admissions, and lung resection performed in 12.08%.

Socioeconomic data gathered in primary care centres indicated that 70.90% of the patients had an annual rent under the €18,000; 11.81% of the patients were not active or unemployed while 74.14% were pensioners. Finally, a direct cost was associated to each admission in accordance with the nature of the hospitalization process and medical procedures utilized. The database registered a direct medical cost of lung cancer that reached the €962.6 million solely considering secondary care.

The mean cost per patient was €8475, increasing significantly over the study period, from €8364 per patient the year 2011 to €9164 per patient the year 2016 (p < .001). Interestingly, within the group of patients with an unspecified tumour type, SCC was responsible for the highest costs per patient, €9101 on average (p < .001), whereas, when the total costs incurred by these patients was considered,
adenocarcinomas were the NSCLC responsible for the largest portion of medical costs \( p < .001 \) (Figure 3).

**Discussion**

Lung cancer epidemiology has been extensively investigated in Spain, with special emphasis in the trends followed during the eighties and nineties when the first measures to control tobacco consumption in public buildings were implemented. A clear association was observed between these measures and lung cancer incidence, reversing the increasing incidence trend observed until 1994 among males aged 65–74\(^7\). A more restrictive legislation was approved the year 2005 and updated in 2011 including the prohibition of smoking in bars and restaurants\(^{20,21}\). This study aimed to analyze tendencies in lung cancer occurrence after 2011, to determine the characteristics of the population at risk and to provide complementary epidemiologic data to on-going observational studies.

The number of new lung cancer cases slightly increased in primary care while it remained stable in secondary care between 2011 and 2016. The portion of females increased in both cases. In addition, females diagnosed with a lung carcinoma were significantly younger than males. Previous data gathered between 1996 and 2002 indicates the higher smoking prevalence in Spanish girls aged 15–17 years old, accompanied with heavier smoking habits\(^{22}\); however, it is not clear whether enough time has elapsed to extract definitive conclusions. Likewise, the expected differential incidence of SCLC and NSCLC in males and females was not observed herein\(^9\). The differential trends in incidence in males and females have been previously observed, however, geographic and socioeconomic differences play an important role\(^{23,24}\).

The proportion of SCLC and NSCLC, 15\% vs. 85\% was consistent with previous descriptions, as it was the greater prevalence of adenocarcinoma\(^{25}\).

Hospitalization records showed the importance of internal medicine services in the treatment of lung cancer, together with oncology and pulmonology services, supporting the need of establishing protocols that facilitate multidisciplinary care of the disease, called to improve patients’ prognosis\(^{26}\). Consequently, the great number of emergency admissions found in this patient population could be reduced.

Regarding patient survival, the database does not permit an analysis of lung cancer mortality due to the lack of data on deaths occurred outside of healthcare centres. In-hospital mortality was 22\% over the study period, reaching 29.62\% in patients with SCLC, and remained stable between 2011 and 2016. Data gathered in Spain between 1975 and 1989 showed relative increments in mortality, especially among males, that contrasted with the decreasing trends measured in countries as England and Switzerland\(^{27}\). In general terms, global data indicate a decrease in lung cancer mortality over the past years, resulting from the decreasing mortality among males\(^{28}\).

The segregate analysis of patients that died during the hospitalization provided interesting data. Previous studies associated the presence of comorbid conditions in lung cancer directly to survival\(^{29}\). Herein, several differences appeared between the patients that died and the total patient population. The presence of metastatic and secondary malignant neoplasms appeared determinant in this pool of patients. On the other hand, the registration of other comorbidities as tobacco smoking appeared low at the hospital level. Preliminary results obtained from an observational cohort

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### Table 4. Medical procedures registered in patients with lung cancer.

| Medical procedures               | % of admissions |
|----------------------------------|-----------------|
| Imaging                          |                 |
| Thorax tomography                | 38.95           |
| Abdomen tomography               | 18.51           |
| Thorax radiography               | 21.69           |
| Biopsy                           | 39.77           |
| Lung and bronchus                | 12.52           |
| Lymph nodes                      | 3.98            |
| Chemotherapy                     | 18.21           |
| Radiotherapy                     | 3.15            |
| Surgery                          |                 |
| Lung resection or excision       | 12.08           |
| Respiratory therapy              | 22.96           |
| Oxygen enrichment                | 10.61           |
| Mechanical ventilation           | 1.62            |
| Medication via nebulizer         | 4.28            |

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**Figure 3.** Annual direct medical cost estimated for the group of patients with a specified tumour.
study taking place in Spain, indicated that up to 86% of patients hospitalized due to lung malignant neoplasms could be current or ex-smokers, which could indicate an incomplete registry of such factors in Spanish hospitals. Alcohol consumption has been previously appointed as a factor in lung cancer carcinogenesis, however, evidence in never smokers is contradictory. Similarly, the diagnosis of diabetes has been previously associated to a worsened prognosis in lung cancer patients, an affect that was not observed in this database. Nonetheless, it must be taken into account that data registered upon admission may be incomplete.

In terms of medical costs, evaluations made in the United States measured a mean direct medical cost per NSCLC treatment of around €14,000 per patient, with strong variations depending on cancer stage. Similarly, calculations in Australia show mean annual costs of cancer care of around €2800 per patient that increase to €31,000 the last year of life. Data obtained in different countries by distinct methods are hardly comparable, although in all cases delayed diagnoses suppose an important increase in costs. The present study shows a small increasing trend in the cost per patient over time that could be compensated by the implementation of prevention and early screening measures.

It is plausible that a number of limitations may have influenced the results of this study. The database providing secondary care data is codified with ICD-9 and ICD-10 codes, thus, data reliability is subjected to the accuracy of codification achieved at the hospital level. In addition, the shift from ICD-9 to ICD-10 between the years 2015 and 2016 should be taken into account to interpret quantitative data. The analysis of secondary conditions was limited to those registered disease comorbidity. Finally, the analysis of direct medical costs was restricted to secondary care settings and pharmaceutical were not quantifiable via this database. Further research should consider all medical costs to increase comparability.

Conclusions
Overall lung cancer incidence appeared stable in secondary care centres, yet, given the relative increase of female patients, preventive or early detection measures are recommended to reverse this trend, which is likely to have an influence in disease costs. In addition, a multidisciplinary approach is called to optimise patient journey. The potential roles of disease comorbidities in lung cancer prognosis should be further explored.

Notes
i. StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA.
ii. Microsoft Corporation, Redmond, WA, USA.
[6] Clíries R, Esteban L, Borràs J, et al. Time trends of cancer incidence and mortality in Catalonia during 1993-2007. Clin Transl Oncol. 2014;16(1):18–28.

[7] Linares I, Molina-Portillo E, Expósito J, et al. Trends in lung cancer incidence by histologic subtype in the south of Spain, 1985-2012: a population-based study. Clin Transl Oncol. 2016;18(5):489–496.

[8] Remon J, Molina-Montes E, Majem M, et al. Lung cancer in women: an overview with special focus on Spanish women. Clin Transl Oncol. 2014;16(6):517–528.

[9] Hecht SS. Lung carcinogenesis by tobacco smoke. Int J Cancer. 2012;131(12):2724–2732.

[10] World Health Organization. Radon and health [Internet]. [cited 2019 Dec]. Available from https://www.who.int/news-room/factsheets/detail/radon-and-health.

[11] Malhotra J, Malvezzi M, Negri E, et al. Risk factors for lung cancer worldwide. Eur Respir J. 2016;48(3):889–902.

[12] Rodríguez-Canales J, Parra-Cuentas E, Wistuba II. Diagnosis and molecular classification of lung cancer. Cancer Treat Res. 2016;170:25–46.

[13] Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008;359(13):1367–1380.

[14] Shen H. Low-dose CT for lung cancer screening: opportunities and challenges. Front Med. 2018;12(1):116–121.

[15] Oudkerk M, Devaraj A, Vliegenthart R, et al. European position statement on lung cancer screening. Lancet Oncol. 2017;18(12):e754–e66.

[16] Katkade VB, Sanders KN, Zou KH. Real world data: an opportunity to supplement existing evidence for the use of long-established medicines in health care decision making. J Multidiscip Healthc. 2018;11:295–304.

[17] Justo N, Espinoza MA, Ratto B, et al. Real-world evidence in healthcare decision making: global trends and case studies From Latin America. Value Health. 2019;22(6):739–749.

[18] Law 14/2007, 3rd July, on biomedical research (BOE, 4 July 2007). Rev Derecho Genoma Hum. 2007;26(2):283–325.

[19] Ministerio de Sanidad, Consumo y Bienestar Social. Sanidad en datos [Health figures] [Internet]. [cited 2019 Dec]. https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm [Spanish].

[20] Law 28/2005, 26th December, regarding health measures against tobacco addiction and regulating sales, supplies, consumption and advertising of tobacco products. Boletín Oficial Del Estado (Boe). 2005;309:42241–42250.

[21] Law 42/2010, 30th December, modifying law 28/2005, 26th December, regarding health measures against tobacco addiction and regulating sales, supplies, consumption and advertising of tobacco products. Boletín Oficial Del Estado (Boe). 2010;318:109188–109194.

[22] Mendoza R, López Pérez P, Sagrera MR. Gender differences in the evolution of adolescent’s tobacco consumption in Spain (1986-2002). Adiciones. 2007;19(3):273–287.

[23] Houston KA, Mitchell KA, King J, et al. Histologic lung cancer incidence rates and trends vary by race/ethnicity and residential county. J Thorac Oncol. 2018;13(4):497–509.

[24] Zhang Y, Ren JS, Huang HY, et al. International trends in lung cancer incidence from 1973 to 2007. Cancer Med. 2018;7(4):1479–1489.

[25] Molina JR, Yang P, Cassivi SD, et al. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584–594.

[26] Bilfinger TV, Albano D, Perwaiz M, et al. Survival outcomes among lung cancer patients treated using a multidisciplinary team approach. Clin Lung Cancer. 2018;19(4):346–351.

[27] Bonfill X, Moreno C, Prada G, et al. Lung cancer mortality among males of Catalonia and Spain compared with other European countries between 1975-1977 and 1987-1989. Int J Cancer. 1996;65(6):751–754.

[28] López-Campos JL, Ruiz-Ramos M, Fernandez E, et al. Recent lung cancer mortality trends in Europe: effect of national smoke-free legislation strengthening. Eur J Cancer Prev. 2018;27(4):296–302.

[29] Parés-Badell O, Banqué M, Macià F, et al. Impact of comorbidity on survival by tumour location: breast, colorectal and lung cancer (2000-2014). Cancer Epidemiol. 2017;49:66–74.

[30] Provencio M, Carcereny E, Rodriguez-Abreu D, et al. Lung cancer in Spain: information from the Thoracic Tumors Registry (TTR study). Transl Lung Cancer Res. 2019;8(4):461–475.

[31] Akhtar N, Bansal JG. Risk factors of lung cancer in nonsmoker. Curr Probl Cancer. 2017;41(5):328–339.

[32] García-Lavandeira JA, Ruano-Ravina A, Barros-Dios JM. Alcohol consumption and lung cancer risk in never smokers. Gac Sanit. 2016;30(4):311–317.

[33] Zhu L, Cao H, Zhang T, et al. The effect of diabetes mellitus on lung cancer prognosis. Br J Cancer. 2016;115(1):475.

[34] Luo J, Hendryx M, Qi L, et al. Pre-existing diabetes and lung cancer prognosis: a PRISMA-compliant meta-analysis of cohort studies. Medicine (Baltimore). 2016;95(17):e3528.

[35] Guillén TR, DaCosta Byfield S, Hogarth DK, et al. A retrospective analysis of delays in the diagnosis of lung cancer and associated costs. CEOR. 2017;9:261–269.

[36] Goldsberry DE, Yap S, Weber MF, et al. Health services costs for cancer care in Australia: estimates from the 45 and Up Study. PLoS One. 2018;13(7):e0201552.