Addressing lung cancer screening eligibility in Spain using 2013 and 2021 US Preventive Service Task Force criteria: cross-sectional study

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More than 30% of lung cancer cases in Spain could not have been detected through screening for not meeting the inclusion criteria. The degree of fulfilment at a national level should be assessed to establish criteria tailored to each country's context. https://bit.ly/491Zx8j

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Abstract

Objectives The aim of the study was to ascertain the percentage of Spanish lung cancer cases that would fulfil the lung cancer screening inclusion criteria recommended by the United States Preventive Service Task Force (USPSTF) in 2013 and 2021.

Methods A cross-sectional study was carried out. All lung cancer cases registered in the Thoracic Tumor Registry with data on date of birth, date of diagnosis, smoking habit, number of pack-years and time elapsed since smoking cessation were included.

Results The study included 15 006 patients diagnosed with lung cancer in Spain between 2016 and 2022. Eligibility to participate in screening increased from 53.7% to 63.5% (an increase of 9.8%) according to the 2013 and 2021 recommendations, respectively. The percentage of eligible men rose by 9.2 percentage points with the 2021 *versus* 2013 recommendations, whereas this rise was 11.5 percentage points in women. Under the 2021 recommendations, 36.6% of women and 5.3% of men would not have fulfilled the screening inclusion criteria due to being never-smokers; 14.9% of women and 11.0% of men would not have fulfilled the age criterion; and 27.0% of ex-smokers among women compared to 35.6% among men would not have been eligible due to >15 years having elapsed since smoking cessation.

Conclusions In Spain, over one-third of lung cancer cases could not be detected through screening, by virtue of not meeting the most recent inclusion criteria stated by the USPSTF. The degree of fulfilment in a potential nationwide screening programme should be analysed, with the aim of establishing inclusion criteria in line with each country's context.

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, causing 18% of all cancer-related deaths [1]. With the aim of reducing lung cancer mortality, the implementation of a screening programme was proposed, and many studies were carried out to analyse the effectiveness of screening using low-dose computed tomography (LDCT). The first large-scale clinical trial to evaluate the effectiveness of lung cancer screening with LDCT was the National Lung Screening Trial (NLST) undertaken in the USA [2]. This study reported a 20% reduction in lung cancer mortality with the use of LDCT, as compared with use of chest x-rays, after three screening rounds. In light of this, the United States Preventive Services Task Force (USPSTF) recommended implementation of screening in the USA [3]. In Europe, other studies have been conducted, with the Dutch–Belgian Randomised Lung Cancer Screening Trial (NELSON) being the most important of these on the basis of its sample size [4]. Different European countries have initiated or planned pilot programmes, but only Croatia has recently implemented a population-based lung cancer screening programme [5]. The reluctance displayed by European countries when it comes to implementing lung cancer screening is mainly due to the uncertainties that surround the screening, as recently described in a Report of the European Network for Health Technology Assessment (EUnetHTA) [6].

In the USA, lung cancer screening inclusion criteria are provided by the USPSTF recommendations, and these recommendations have also been adopted by other countries. These criteria rely on the age of inclusion and intensity of tobacco use, and also take into account years since smoking cessation. The first screening recommendations drawn up by the USPSTF were published in 2013 [3], but different studies have indicated that these criteria excluded a large proportion of individuals at risk of developing lung cancer [7–9]. To make these criteria less restrictive, they were updated in 2021, changing the lower age limit (from 55 to 50 years) and tobacco use (from 30 to 20 pack-years), without amending the 15-year abstinence period in ex-smokers [10].

In Spain, lung cancer is the second most common cancer, only behind colorectal cancer. It is estimated that in 2023, 31 282 new cases of lung cancer will be diagnosed, 28.8% in women and 71.2% in men [11]. For the moment, no lung cancer screening programme has been implemented in Spain, although in 2022 the CASSANDRA Project for lung cancer screening was launched, establishing inclusion criteria similar to those recommended by the USPSTF. The Spanish Ministry of Health has recently published a new report including an analysis questioning the risk–benefit ratio of this screening and raising doubts about its cost effectiveness [12].

The aim of the present study was to ascertain the proportion of subjects diagnosed with lung cancer in Spain who would fulfil the lung cancer screening inclusion criteria recommended by the USPSTF, both initially in 2013 and as reformulated in 2021, and who could thus be detected in a hypothetical lung cancer screening programme. Having such information would make it possible to envisage the possible benefit of the hypothetical implementation of a screening programme and to ascertain which characteristics would imply a greater shortfall of detected cases, in every instance suitably adapted to the Spanish context and with potentially extrapolable results.

Lessons for clinicians

- The first guidelines of the United States Preventive Services Task Force (USPSTF) for the inclusion of participants in lung cancer screening were issued in 2013. In 2021, these criteria were expanded with the aim of increasing the volume of lung cancer cases detected. However, studies conducted in other countries such as the United States found that the expansion of the criteria does not improve the participation of some groups of population, such as women, in this screening.
- With the updated recommendations issued in 2021, a 9.8% increase was observed in the number of eligible Spanish lung cancer patients. Under the 2021 recommendations, 36.5% of lung cancer cases would not be eligible for participation (30% among men and 52.5% among women). Expansion of the inclusion criteria does not seem to improve screening eligibility or prevent inequalities in access to screening. The degree of fulfilment in a potential nationwide screening programme should be analysed, with the aim of establishing inclusion criteria in line with each country's context.

Methods

Study design

We designed a cross-sectional study using the Thoracic Tumors Registry (TTR) (Registro de Tumores Torácicos) as data source. The TTR is a monographic lung cancer registry created in 2015 by the Spanish Lung Cancer Group (Grupo Español de Cáncer de Pulmón). The characteristics of the subjects included were recently described [13]. The first case of lung cancer was registered in 2016, and by 15 March 2022 a total of 22 807 patients had been included. For inclusion purposes, patients are required to have been diagnosed with lung cancer by means of a pathology test, without sex or age restrictions. A total of 81 Spanish hospitals provided the registry with lung cancer cases. In 2016, the TTR was registered at ClinicalTrials.gov (NCT02942458), and the study protocol was approved by the institutional committee of the Puerta de Hierro University Teaching Hospital (Majadahonda, Madrid) (no. PI 148/15). The TTR's representativeness of lung cancer cases in Spain has been shown by a recent study [14], meaning that data supplied by the TTR allow for lung cancer cases in Spain to be characterised and monitored.

This study included all patients in the TTR having correctly registered data on date of birth, date of diagnosis, smoking habit, number of pack-years and time elapsed since smoking cessation. Patients diagnosed with mesothelioma, thymic tumour and carcinoid tumor were excluded.

Data collection

The following variables were recorded for each subject: sex (male/female); date of birth; race/ethnicity; date of diagnosis; smoking habit (smokers/ex-smokers/never-smokers); tobacco use (in packs-years); date of commencement of smoking; date of smoking cessation; stage at diagnosis and histological type (adenocarcinoma, squamous cell carcinoma, small-cell carcinoma, other (adenoid squamous cell carcinoma, large-cell carcinoma, sarcomatoid carcinoma, NOS (not otherwise specified)/undifferentiated, large-cell neuroendocrine carcinoma and thymoma)).

Date of birth and date of diagnosis were used to calculate age at diagnosis in years. In the case of ex-smokers, we calculated the number of years elapsed between cessation of smoking habit and diagnosis of lung cancer. In the case of smokers, date of commencement of smoking habit and registered date of diagnosis were used to calculate duration of smoking habit until diagnosis of the disease (in years).

Statistical analysis

The characteristics of study subjects diagnosed with lung cancer were described, using the median and interquartile range in the case of quantitative variables, and absolute and relative frequencies in the case of categorical variables.

To analyse the number of subjects who would be eligible for lung cancer screening, we created two dichotomous variables according to fulfilment of the 2013 and 2021 USPSTF inclusion criteria (yes/no), and then calculated the prevalence of fulfilment and non-fulfilment for both guidelines, along with their 95% confidence intervals (95% CIs). We specified the number and proportion of subjects who failed to meet each criterion for each of the recommendations (2013 and 2021). The following additional analyses were performed: a criteria-fulfilment subanalysis by sex; and a criteria-fulfilment subanalysis by stage at diagnosis (excluding stage 0 and the stage classified as "other" in the subanalysis).

All statistical analyses were performed using the Stata v.17.0 computer software program.

Results

At the date of study, the TTR contained 22 807 cases of lung cancer diagnosed in Spain from 2016 to 2022. For analysis purposes, 7801 records were excluded; the reasons for exclusion are described in figure 1. Ultimately, this study included 15 006 patients diagnosed with lung cancer in Spain from 2016 to 2022.

The main characteristics of the subjects included are shown in table 1: 71.3% were men; adenocarcinoma was the most frequent histological type (53.9%); the great majority were smokers or ex-smokers (47.7% and 38.0%, respectively); and median age at diagnosis was 66 years.

Table 2 shows the percentage of subjects diagnosed with lung cancer who would be eligible to participate in screening, according to the 2013 and 2021 recommendations. There was an increase from 53.7% to 63.5% (9.8 percentage points) in fulfilment of the lung cancer screening inclusion criteria according to the 2013 and 2021 recommendations, respectively.

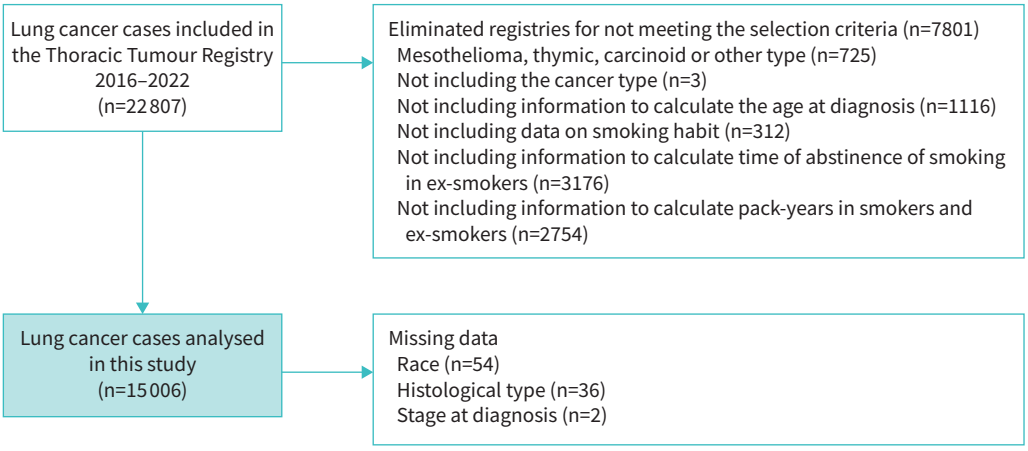

FIGURE 1 Flowchart of the included lung cancer cases.

According to the recommendations, 14.3% and 34.1% of cases of lung cancer would not fulfil the criteria for smoking habit and time elapsed since smoking cessation, respectively. In the case of the age and tobacco use criteria, *i.e.*, those that changed in the interim between the 2013 and 2021 recommendations, the percentage of eligible subjects increased by 8 percentage points in each case.

TABLE 1 Main characteristics of included subjects

Sex	
Male	10 698 (71.3)
Female	4308 (28.7)
Race	
Caucasian	14 722 (98.1)
Latin	176 (1.2)
Asian	26 (0.2)
African	6 (0.4)
Other	22 (0.2)
Histological type of lung cancer	
Adenocarcinoma	8087 (53.9)
Squamous cell carcinoma	3560 (23.7)
Small-cell carcinoma	2219 (14.8)
Other	1104 (7.6)
Stage at diagnosis	
0	5 (0.03)
I	1227 (8.2)
II	1014 (6.8)
III	3493 (23.3)
IV	6995 (46.6)
Limited small-cell carcinoma	746 (5.0)
Extended small-cell carcinoma	1426 (9.5)
Other	98 (0.7)
Age at diagnosis years	
Median (minimum–maximum)	66 (18–93)
Tobacco use	
Smoker	7164 (47.7)
Ex-smoker	5696 (38.0)
Never-smoker	2146 (14.3)
Packs-years (smokers and ex-smokers)	
Median (IQR)	50 (35–70)
Years elapsed from cessation to diagnosis (ex-smokers)	
Median (IQR)	9 (3–18)

Data are presented as n (%) unless indicated otherwise. Missing data: race (n=54); histological type (n=36); stage at diagnosis (n=2).

TABLE 2 Subjects eligible and ineligible to participate in lung cancer screening by reference to the criteria recommended by the US Preventive Service Task Force in 2013 and 2021

	2013 criteria		2021 criteria	
	n	% (95% CI)	n	% (95% CI)
Subjects who would fulfil the inclusion criteria	8053	53.7 (52.9–54.5)	9532	63.5 (62.7–64.3)
Subjects who would not fulfil the inclusion criteria	6953	46.3 (45.5–47.1)	5474	36.5 (35.7–37.3)
Age				
Fulfil (55–80 years old in 2013; 50–80 years old in 2021)	12 018	80.1	13 191	87.9
Do not fulfil – younger (<55 years old in 2013; <50 years old in 2021)	2131	14.2	958	6.4
Do not fulfil – older (>80 years old)	857	5.7	857	5.7
Smoking habit				
Fulfil (smoker or ex-smoker)	12 860	85.7	12 860	85.7
Do not fulfil (never-smoker)	2146	14.3	2146	14.3
Tobacco use in smokers and ex-smokers				
Fulfil (⩾30 PY in 2013; ⩾20 PY in 2021)	10 937	85.1	12 054	93.7
Do not fulfil (<30 PY in 2013; <20 PY in 2021)	1923	14.9	806	6.3
Time since smoking cessation in ex-smokers				
Fulfil (<15 years)	3752	65.9	3752	65.9
Do not fulfil (⩾15 years)	1944	34.1	1944	34.1

PY: pack-years.

A subanalysis was performed by sex. Figure 2 shows that, whereas the percentage of men diagnosed with lung cancer who were eligible to participate in screening increased by 9.2 percentage points under the 2021 as compared with the 2013 recommendations, this increase was 11.5 percentage points in the case of women after expansion of the USPSTF criteria.

Table 3 shows the percentage of lung cancer cases that would have met the screening inclusion criteria by sex for the 2013 and 2021 guidelines. In men and women alike, there was an increase in the percentage of eligible subjects under the two amended criteria, namely, age and tobacco use. With respect to age, it was

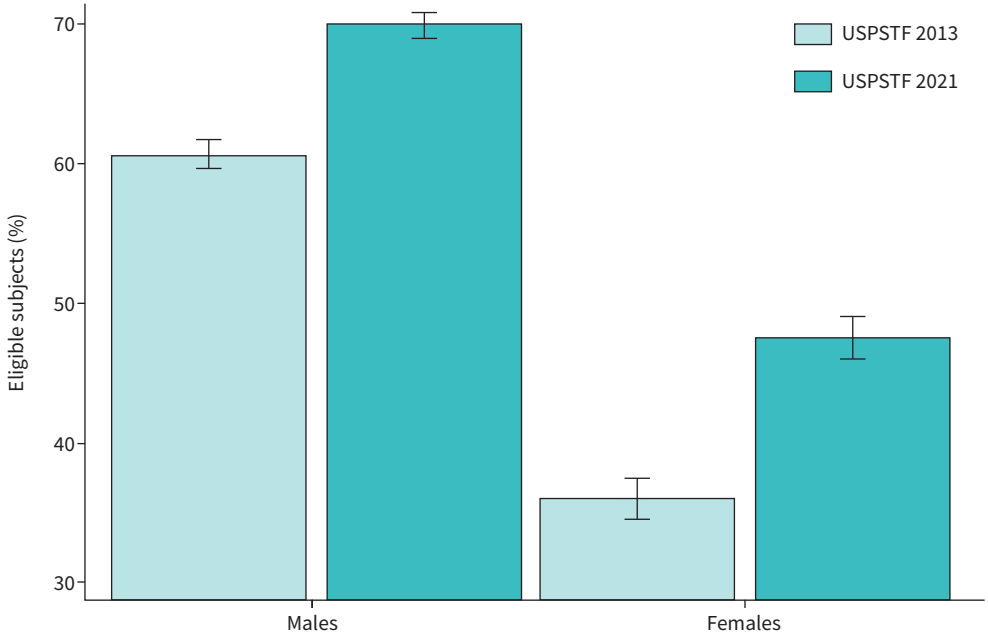

FIGURE 2 Percentages and 95% confidence intervals of subjects eligible to participate in lung cancer screening according to the inclusion criteria recommended by the US Preventive Service Task Force (USPSTF) in 2013 and 2021, by sex.

observed that, under the 2021 criteria: 14.9% of women diagnosed with lung cancer would not fulfil the age criterion for participating in screening *versus* 11% of men; and 9.4% of women could not participate in screening for being of an age younger than that set by the USPSTF. Furthermore, 12.3% of women diagnosed with lung cancer would not be eligible for screening, since they would not meet the minimum number of packs per year stipulated by the USPSTF, *versus* 4.6% of men.

As regards the unmodified criteria, taking both recommendations into account, 36.6% of women diagnosed with lung cancer would not have fulfilled the screening inclusion criteria due to being never-smokers, in comparison with 5.3% of men. In contrast, however, 35.6% of male ex-smokers with lung cancer would have been excluded from screening, on the basis of >15 years having elapsed since smoking cessation, *versus* 27.0% of women ex-smokers.

Supplementary table S1 shows the number and percentage of subjects who did not meet each of the four criteria, as well as those who did not meet any combination of these criteria. This information is provided for the total sample and according to sex. Thus, according to the 2021 criteria, 28% of the women were ineligible because they did not meet only one criteria (as they were never-smokers) and 8% of women were ineligible because they did not meet two criteria at the same time (as they were never-smokers and did not meet the age criteria).

Additionally, fulfilment of screening criteria by stage at diagnosis was analysed and no relevant differences were found in the percentage of eligible and ineligible subjects by stage at diagnosis (table 4).

Discussion

The results of this study suggest that, though the change in the inclusion criteria means an increase in the number of eligible subjects for lung cancer screening, women would continue to be inadequately covered. To our knowledge, this is the first study to analyse the impact of the most widely used inclusion criteria in the event of a hypothetical lung cancer screening programme being implemented in a European context.

Our results show that there would be an increase of 10 percentage points in the number of persons diagnosed with lung cancer who would be eligible in Spain, and this is consistent with previous studies [8, 9, 15, 16]. However, important disparities have been observed in the inclusion of participants by reference to different variables, such as race, sex and socioeconomic level [8, 9]. Despite the expansion of criteria, it has neither

TABLE 3 Subjects eligible and ineligible to participate in lung cancer screening according to the criteria recommended by the US Preventive Service Task Force in 2013 and 2021, by sex

	2013 criteria		2021 criteria	
	Men	Women	Men	Women
	n % (95% CI)	n % (95% CI)	n % (95% CI)	n % (95% CI)
Subjects who would fulfil the inclusion criteria	6501 60.8 (59.8–61.7)	1552 36.0 (34.6–37.5)	7487 70.0 (69.1–70.8)	2045 47.5 (46.0–49.0)
Subjects who would not fulfil the inclusion criteria	4197 39.2 (38.3–40.1)	2756 64.0 (62.5–65.4)	3211 30.0 (29.2–30.9)	2263 52.5 (51.0–54.0)
Age, n (%)				
Fulfil (55–80 years old in 2013; 50–80 years old in 2021)	8770 (82.0)	3248 (75.4)	9524 (89.0)	3667 (85.1)
Do not fulfil – younger (<55 years old in 2013; <50 years old in 2021)	1307 (12.2)	824 (19.1)	553 (5.2)	405 (9.4)
Do not fulfil – older (>80 years old)	621 (5.8)	236 (5.5)	621 (5.8)	236 (5.5)
Smoking habit, n (%)				
Fulfil (smoker or ex-smoker)	10 128 (94.7)	2732 (63.4)	10 128 (94.7)	2732 (63.4)
Do not fulfil (never-smoker)	570 (5.3)	1576 (36.6)	570 (5.3)	1576 (36.6)
Tobacco use in smokers and ex-smokers, n (%)				
Fulfil (⩾30 PY in 2013; ⩾20 PY in 2021)	8933 (88.2)	2004 (73.3)	9659 (95.4)	2395 (87.7)
Do not fulfil (<30 PY in 2013; <20 PY in 2021)	1195 (11.8)	728 (26.7)	469 (4.6)	337 (12.3)
Time since smoking cessation in ex-smokers, n (%)				
Fulfil (<15 years)	3037 (64.4)	715 (73.0)	3037 (64.4)	715 (73.0)
Do not fulfil (⩾15 years)	1679 (35.6)	265 (27.0)	1679 (35.6)	265 (27.0)

PY: pack-years.

TABLE 4 Subjects eligible and ineligible to participate in lung cancer screening according to the inclusion criteria recommended by the US Preventive Service Task Force in 2021, by stage at diagnosis

	2021 criteria		
	Do not fulfil	Fulfil	Total
Stage at diagnosis[#]			
I	474 (38.6)	753 (61.4)	1227 (100)
II	368 (36.3)	646 (63.7)	1104 (100)
III	1124 (32.2)	2369 (67.8)	3493 (100)
IV	3059 (43.7)	3936 (56.3)	6995 (100)
SCLC limited	129 (17.3)	617 (82.7)	746 (100)
SCLC extended	281 (19.7)	1145 (80.3)	1426 (100)

Data are presented as n (%). SCLC: small cell lung cancer. [#]: subjects with stage 0 (n=5) and stage classified as other (n=98) were excluded from the analysis.

been shown nor is it to be expected that the observed disparities in eligibility would diminish [15]. Hence, the expansion of criteria would not seemingly suffice to increase the population impact of screening or prevent disparities in terms of eligibility. Additionally, these changes in criteria make for a considerable increase in healthcare costs and resources (rate of lung cancers detected per subject screened is reduced), even though it has not been determined whether expansion of criteria has an impact on the inclusion of high-risk persons. If this is not so, the inclusion of subjects at lower risk of developing lung cancer could entail an increase in the number of false positives and a decrease in the risk/benefit ratio [17].

Our results show that with the expansion of criteria there is a greater overall benefit for women than for men. Even so, 52.5% of women diagnosed with lung cancer in Spain would still fail to meet the criteria. This lower degree of eligibility in the case of women is principally accounted for by differences between men and women in age at diagnosis and intensity of tobacco use. Lung cancer tends to be diagnosed in women at an earlier age than in men [13]: in fact, our results show that ∼10% of all cases diagnosed in women in Spain would not meet the age criterion due to being younger, as opposed to 5% in the case of men. It should be mentioned that in Spain, mortality from lung cancer is on the rise. In 2021, lung cancer mortality rates in women increased by 6.9 percentage points, while in men this increase was 0.9 percentage points compared to data for 2020 [18]. A projection for 2025 [19] concludes that the incidence of lung cancer will increase considerably in practically all age groups in the case of women, while for men the increase is smaller in magnitude and occurs in subjects aged 70 and over. Hence, in the future, even more cases of lung cancer will not be diagnosed early through screening owing to the increasing number of cases among women.

The results of our study show that a high percentage of lung cancer cases occurred in never-smokers, especially in women. Some studies highlight a growing trend in the incidence of lung cancer among never-smokers in recent decades [20–22]. Moreover, the sociodemographic and clinical characteristics of lung cancer in never-smokers are known to be different from those of lung cancer in smokers and ex-smokers [23, 24]. Some authors have even contended that these are different clinical entities, with differences in the epidemiology and biological and molecular factors [25].

Previous studies observed that around 40% of lung cancers in ex-smokers occur >15 years after smoking cessation [26]. Despite previous evidence, the USPSTF maintains that, to participate in screening, an ex-smoker must have quit smoking no more than 15 years previously. The results of our study are in line with previous results and show that around one-third of ex-smokers, regardless of sex, had developed lung cancer >15 years after smoking cessation.

Although the performance of screening cannot be solely reduced to its inclusion and exclusion criteria, we believe that their adequacy should be considered locally and nationally. Establishing inclusion criteria for participation in any type of screening programme is a key element, as it not only impacts the cost but also the risk–benefit relationship. Even though a screening programme cannot cover the entire population, a significant percentage of lung cancer cases would not be detected in Spain by using the most recently recommended inclusion criteria. Furthermore, the burden of lung cancer is likely to increase in never- or former smokers as the prevalence of smoking decreases. Lung cancer is a significant public health problem that is likely to continue to grow, and the scientific community agrees that early diagnosis is probably the solution to reducing its burden. However, we should not forget that screening should comply with a wide

range of quality criteria, which are not always met in the case of lung cancer [27]. There are still many uncertainties regarding the implementation of the lung cancer screening programme, such as low participation in screening [28], false positives or overdiagnosis [6, 27, 29–31], that should be addressed, some of them at a national level as differences may arise between regions.

This study has limitations. Firstly, a considerable number of lung cancer cases had to be excluded from this study for not including the necessary data in the registry entry (n=7801 (34.2%)). Secondly, this study has a cross-sectional design, and it is likely that the number of eligible subjects increases with time, particularly in women, due to the delayed impact of the tobacco epidemic in Spain. Thirdly, the criteria set in the USA reflect the characteristics of the smoking epidemic and tobacco use in that country, and there is no reason why these should necessarily reflect what happens in Spain, where the tobacco epidemic is behind that of the United States. A further limitation would be the lack of information on non-cancer subjects, as this study analyses the data of a monographic cancer registry. Therefore, the specificity of the screening was not assessed. Lastly, there is a possible overrepresentation of metastatic stages in the TTR. That said, however, no differences were found when the fulfilment subanalysis was performed by stage at diagnosis, and the percentage of stage IV cases (46.6%) compares well with Surveillance, Epidemiology and End Results Programme (SEER) data (48.8%) [32]. We feel that all cases should be included in this analysis, regardless of stage, since they reflect lung cancer cases that will appear in the population.

The main advantage of this study is the use of the TTR as a data source, since this monographic registry has previously been shown to be representative of lung cancer cases diagnosed in Spain, both by sex and by age [14]. Another additional advantage is that the registry covers a short time period (only 5 years), so that the cases included are comparable to current lung cancer incidence, something that would not occur in a series of cases recruited over a long period of time. Population-based cancer registries do not usually include tobacco consumption characteristics and could not be used for this purpose.

To conclude, the inclusion criteria currently used in lung cancer screening exclude an important percentage of the population at risk of developing this type of cancer. If screening were to be implemented in Spain using the USPSTF recommendations, at least 36% of lung cancers would not be detected by such screening. Furthermore, this percentage would rise by just over half in the case of women. These results highlight the fact that expansion of the criteria does not address the problem, and that it is necessary to have scientific evidence, focusing especially on subjects underrepresented in clinical trials, such as women and never-smokers. A possible solution lies in the use of tools that would enable individual risk of lung cancer to be calculated, which have been shown to be more sensitive than the current criteria. In the case of lung cancer, the Proposal for a Council Recommendation (CR) on Strengthening Prevention through Early Detection 2022/0290 envisages staggered implementation to ensure both the quality and analysis of results [33]. Lastly, the degree of fulfilment with the inclusion criteria in a potential nationwide screening programme should be analysed, with the aim of establishing inclusion criteria in line with each country's context.

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Author contributions: A. Ruano-Ravina and M. Provencio had the original idea and designed the methodology. C. Candal-Pedreira prepared the database, performed the data analysis and wrote the first draft of the manuscript. All authors have read and provided intellectual input to the manuscript. All authors have approved the final version of the manuscript and take public responsibility of its content.

The Thoracic Tumor Registry is registered at www.ClinicalTrials.gov with identifier number NCT02942458.

Data sharing statement: The data that support the findings of this study are available from the corresponding author, ARR, upon reasonable request.

Transparency declaration: The corresponding author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflict of interest: A. Ruano-Ravina is an associate editor of this journal. The remaining authors declare no conflicts of interest regarding the publication of this article.

Ethics statement: The study protocol was approved by the institutional committee of the Puerta de Hierro University Teaching Hospital (Majadahonda, Madrid) (number PI 148/15).

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