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Health and economic impact at a population level of both primary and secondary preventive lung cancer interventions: A model-based cost-effectiveness analysis

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ABSTRACT

Objectives: Robust economic evaluations are needed to identify efficient strategies for lung cancer prevention that combine brief and intensive smoking cessation intervention programmes with screening using low-dose computed tomography (LDCT) at different ages, frequencies, and coverages. We aimed to assess the cost-effectiveness of smoking cessation approaches combined with lung cancer screening in the European context at a population level from a societal perspective.

Materials and Methods: A microsimulation model that describes the natural history of lung cancer and incorporates several prevention strategies was developed. Discounted lifetime QALYs and costs at a rate of 3% were used to calculate incremental cost-effectiveness ratios, defined as additional costs in 2017 Euros per QALY gained.

Results: Smoking cessation interventions reduce the incidence of lung cancer by 8%-46% and are consistently more effective and cost-effective when starting at younger ages. Screening reduces lung cancer mortality by 1%-24% and is generally less effective and more costly than smoking cessation interventions. The most cost-effective strategy would be to implement intensive smoking cessation interventions at ages 35, 40 and 45, combined with screening every three years between the ages of 55 and 65.

Conclusions: Combining smoking cessation interventions with LDCT screening is a very attractive prevention strategy that substantially diminishes the burden of lung cancer. These combined prevention strategies, especially when providing several intensive interventions for smoking cessation at early ages, are more cost-effective than both approaches separately and allow for a more intensified LDCT without losing efficiency.

1. Introduction

Despite some global decline, lung cancer continues to present a huge challenge for health policies with over 470 thousand cases reported annually in Europe. This figure represents approximately 12% of all cancers, 65% of which are diagnosed in men[1]. Since the 1930s, lung cancer has gradually increased, mostly caused by changes in the prevalence of tobacco consumption, and has emerged as one of the most important cancers worldwide[2].

The current burden of lung cancer is determined by the tobacco

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consumption that the population had about 30 years ago[3]. Thus, the way to reduce the impact of lung cancer on the population must be approached from two fronts. On the one hand, to reduce the future incidence of the disease through cessation strategies and, on the other hand, to avoid mortality of those who already have a high risk of cancer [4]. This latter group would be made up of subjects who have maintained very high tobacco consumption and have reached the age at which lung cancer is most frequent, even those who have quit smoking in the last 10–15 years. Primary prevention would have little or no benefit in these people and early detection would be the only alternative to reduce mortality. Early detection with annual low-dose computed tomography (LDCT) has been shown to significantly reduce lung cancer mortality in high-risk patients[5]. However, the optimal timing of lung cancer screening intervals is still an ongoing debate[6]. In 2017, a task force of the European Society of Thoracic Surgeons (ESTS) strongly recommended the implementation of screening programmes in European countries and issued ten general recommendations concerning screening with computed tomography[7]. All studies on lung cancer prevention have focused either on smoking cessation or on early detection. Only some authors include smoking cessation in the context of early detection for ethical reasons without considering what the utility would be in reducing the incidence of lung cancer in patients of advanced age. Furthermore, smoking cessation in patients undergoing LDCT screening remains unclear and no studies compared drug-based treatment to smoking cessation counselling[8].

Health policy decision-makers are increasingly aware of the importance of taking efficiency criteria into account. Budgetary constraints in the different health systems mean that not all available interventions can be included in healthcare plans. In this context, it is becoming common in public health systems to use outcomes from economic evaluations, such as cost-effectiveness analyses, to inform about decisions on the allocation of healthcare resources[9]. The dual aim of any healthcare prevention strategy is to improve population health, while at the same time staying within the bounds of economic constraints. Health economic evaluations are key to enabling health benefits to be maximized with an efficient use of resources.

This study presents a cost-effectiveness analysis of single and combined primary and secondary preventive strategies for lung cancer at different times throughout life. The aim of the study was to identify which single or combined preventive choices are more cost-effective to reduce the burden of lung cancer in Spain. Since not all smokers would reach the same risk of lung cancer, we have prioritized individuals with a high risk of dying from lung cancer in the short term and individuals with a potential high risk of developing lung cancer in the medium term. In addition, since the prevalence of smoking in Spain is very different in men than in women, and consequently the incidence of and mortality from lung cancer are also very different, we decided to consider only men in this analysis.

2. Material and methods

2.1. Model

A Markov-based microsimulation model was developed for describing the longitudinal progression of the natural history of lung cancer. Six mutually exclusive health states were considered: one healthy state in terms of lung cancer (*Healthy*); three lung cancer states: local (*LC I-II*), regional (*LC IIIa*) and distant (*LC IIIb-IV*), corresponding to stages I and II, stage IIIa, and stages IIIb and IV, respectively; death caused by lung cancer (*LC death*); and death by other causes (*Other death*) [**Supplementary appendix Figure S1a**]. This aggregation of the states in local, regional, and distant is a simplification of reality that favours obtaining some parameters, but which could have an uncertain impact on the results. Since the risk of lung cancer depends on the smoking habit (i.e. the Markov property is not fulfilled because future health states not only depend on the current health state), some parts of the model were microsimulated by adding certain functionalities to the Markov model (*Smoking*, *Quitting* and *Survival*) [**Supplementary appendix Figure S1b**]. The model follows a single theoretical cohort of 100,000 men aged 35 in 1-month increments until they reach the age of 80 or die. Forty simulations of the cohort for each strategy (see the Prevention strategies section) were performed to reflect a certain degree of variability in the parameters. Transition probabilities between the different health states are age-dependent and were divided into nine transition matrices corresponding to each age group in five-year intervals ([35–40), …, [75–80)). Initial probabilities were extracted from published scientific literature and clinical trials, and subsequently calibrated to reproduce the male lung cancer burden in Spain. The model was coded in R using the Rcpp package[10] and C++[11]. For details on the modelling of the effect of smoking, the effect of quitting and the effect of diagnosis see the Supplementary appendix.

2.2. Prevention strategies

Three different intervention strategies were modelled. Two of them are focused on reducing smoking prevalence in the population with *brief and intensive smoking cessation interventions*, thereby reducing future lung cancer incidence and, consequently, mortality, while a third is an organized screening intervention strategy aimed at detecting lung cancer at earlier stages in a bid to reduce mortality. The brief intervention strategy for quitting smoking is based on the 5 A's method developed by the Agency for Health Care Policy and Research in the United States [12]. In it, healthcare providers ask every patient about their tobacco use, advise smokers to quit, assess smokers' willingness to make a quit attempt, assist smokers in their quit attempt and arrange follow-up contacts[13]. The intensive intervention for quitting smoking is a behavioural and drug-based treatment including follow-up contacts over a 12-month period. Smoking cessation interventions were evaluated assuming different periodicities (once, twice, and thrice in a lifetime) and starting age (35 or 55 years). Finally, the screening intervention was based on LDCT using different frequencies. The optimal frequency of screening is still controversial. Guidelines for screening have generally suggested annual, biennial or three consecutive annual scans[14], and actually health benefits and reduction in costs are unclear for less frequent intervals. In order to observe the health and economic impact of the screening frequency and the effect of smoking cessation interventions on the reduction of lung cancer burden, several screening periodicities at different ages were evaluated. Specifically, these were once in a lifetime (at age 55), twice in a lifetime (at ages 55 and 56 or 55 and 60) and thrice in a lifetime (at ages 55, 56, 57 or 55, 60 and 65), and every 1, 2, 3 and 4 years starting at age 55 (corresponding to twenty times, ten times, seven times and five times in a lifetime, respectively). We considered that interventions will be offered free of charge at the time of the routine visit to the physician. For this reason, we assumed that all patients would accept the interventions.

The strategies evaluated in this project comprised combinations of these three interventions according to two risk groups based on the NLST trial[15]. The "highly at risk" group was defined as the population aged between 55 and 74 with a smoking history of $\geq$ 30 pack years. The "potentially at high risk" group was defined as the population aged <55 (in the model a starting age of 35 was assumed) who, by the time they are 55, will have a smoking history of $\geq$ 30 pack years if they do not change their smoking consumption[16].

2.3. Input data, model parameters and assumptions

The initial transition probabilities before calibration mimicking the baseline natural history of lung cancer and calibration targets were based on published data. The initial transitions between alive health states were extracted from Hinde et al.[17]. The initial transitions to the *LC death* state were based on the age-specific five-year relative survival rate calculated by EUROCARE, transformed into monthly intervals[18].

We did not implicitly include recurrence after treatment in the model. However, mortality is captured in the 5-year relative survival rate used to calculate probability of death from lung cancer given that most disease recurrences will be before 5 years after treatment and most of the patients will die in this period[19]. The initial transitions to the *Other death* state were based on the age-specific risk of death calculated by the Spanish National Institute of Statistics (INE), transformed into monthly intervals[20]. The probability of survival following diagnosis by screening for each cancer stage was adapted from the American Cancer Society data[21]. These data were weighted by the distribution of both tumour type and cancer stage based on screening[22,23].

The data on cancer incidence and mortality used for calibration were provided by the International Agency for Research on Cancer (IARC) via the CANCER*Mondial* database[24]. Specifically, the incidence data were drawn from Globocan[25], while the mortality data were extracted from the WHO Cancer Mortality Database[26]. For more details on model calibration, see Supplementary appendix. We defined the term coverage as the percentage of the eligible population at risk that have access to the program. In Spain, an average of 75% of the male population aged 35–74 years old (66% at 35–54 and 89% at 55–74) is attended to by the Primary Health Care of the Spanish NHS and therefore, it is possible to identify their risk[27]. Around 25% of them are high-risk smokers (68% of smokers at age 35–54 and 25% of the current and former smokers at age 55–74), which gives us the eligible population, high-risk individuals residing in the territory who will have access to the interventions[28]. Specifically, the baseline coverage for smoking cessation interventions and screening was set at 18.69%[27,29]. The effectiveness of smoking cessation interventions and the sensitivity of LDCT screening was extracted from published literature[22,30–32].

The costs incurred for smoking cessation and screening programmes were obtained using various sources[30,33]. The cost incurred for post-diagnosis treatment was estimated with administrative data for patients with lung cancer in Catalonia (Spain) from a hospital perspective[34]. The aggregate cost for all stages was calculated as the mean over the first three years following diagnosis or up to death. This cost included (a) diagnosis (diagnostic tests, ambulatory and emergency visits, inpatient nights), (b) surgery (operating room and inpatient nights), (c) chemotherapy (day hospital and cytotoxic drugs), (d) radiotherapy (number of fractions), (e) other inpatient care (not related to diagnosis, surgery, chemotherapy or radiotherapy treatments for lung cancer, e.g., hospital admissions related to COPD or other comorbidities and palliative care), and (f) continuing care including recurrence (ambulatory and emergency visits, tests, scans, biopsies, etc., made in the continuing phase) [34]. Some recurrence costs were included in the post-diagnosis treatment if they occur within three years following diagnosis. In some studies, direct costs of lung cancer are estimated at approximately a quarter of the total cost, so healthcare costs were increased fourfold in order to add indirect costs and simulate cost-effectiveness from a societal perspective[35,36]. Health state utilities were extracted from published literature[37,38].

Relevant input data including costs and utilities, and selected model parameters and intervention assumptions, are shown in Supplementary appendix Table S1. Influential data were varied in deterministic one- and two-way sensitivity analyses and probabilistic sensitivity analyses.

2.4. Model outcomes and cost-effectiveness analysis

Lifetime health outcomes predicted by the model for each strategy were expressed as quality-adjusted life years (QALYs), calculated by adding the time spent in each state multiplied by the respective utility. Costs are presented in euros (€) indexed at year 2017. Both health and economic outcomes were discounted at an annual rate of 3%[39]. Next, the incremental cost-effectiveness ratio (ICER) was calculated as the difference in cost between two strategies, divided by the difference in health effect (QALYs). It is represented as the incremental cost of a strategy associated with one additional QALY compared with another strategy. Deterministic and probabilistic sensitivity analyses were performed to identify which input data, model parameters and assumptions were critical in driving a decision.

The willingness-to-pay threshold is defined as between €22,000 and €25,000 per QALY [40]. This threshold is similar to that reported in other European countries[41].

3. Results

3.1. Smoking cessation interventions alone

Any of the smoking cessation interventions alone was systematically more effective when the age at which the intervention started was younger [Table 1 and Supplementary appendix Table S3]. The percentage reduction in lung cancer incidence and mortality was similar and varied from 1.6% to 5.4% at age 55 depending on the intervention (brief or intensive) and frequency, and from 3.5% to 11.9% at age 35. The brief intervention was more effective and saved money compared with no intervention, irrespective of age and frequency. The intensive intervention was also always more effective than no intervention and was cost-saving when started at age 35 and cost-effective at very low cost per QALY when started at age 55 compared with no intervention. The incremental cost-effectiveness analysis including only smoking cessation interventions indicated that having three rounds at ages 35, 40 and 45 was cost-saving when using brief intervention and cost €7244 per QALY when using intensive intervention compared with the next most costly strategy after eliminating strategies that were dominated (more costly and less effective, or less cost-effective—higher ICERs—than more effective options) [Fig. 1]. The percentage reduction in lung cancer incidence and mortality was practically equal, reaching 7.6% for the brief intervention and around 12% for the intensive intervention.

3.2. Screening alone

Screening alone was more effective and more costly than no intervention, irrespective of age and frequency, and generally less effective and more costly than smoking cessation interventions [Table 1 and Supplementary appendix Table S4]. Screening reduced lung cancer mortality by between 1% and 7% in the base case analysis depending on frequency. The incremental cost-effectiveness analysis that included screening-only strategies showed that screening once at age 55 would come in below the threshold at a cost of €17,352 per QALY compared with no intervention [Fig. 2]. Repeated LDCT screenings for more than 10 years or over age 65 were dominated by screenings at younger ages or exceeded by far the cost-effectiveness threshold, not being cost-effective. Therefore, along with the large number of strategies included in the analysis, screening strategies were restricted to the age group 55–65 (data not shown).

3.3. Combining smoking cessation and screening interventions

Strategies combining smoking cessation interventions and screening achieved the greatest reduction in incidence and mortality, especially when the intervention involved three rounds of intensive intervention at ages 35, 40 and 45 [Table 1 and Supplementary appendix Table S7]. The percentage reduction in incidence was around 12% and lung cancer mortality varied between 12% and 18% depending on screening frequency. The effect of smoking cessation interventions within the combined strategies was critical because when more rounds of these interventions were included, the screening frequency (shorter intervals) was higher at nearly the same cost [Supplementary appendix]. If only one round of intensive intervention is implemented at age 35, the most cost-effective strategy is for this to be combined with screening every 1 year from ages 55–65 at a cost of €23,687 per QALY compared with the next most costly strategy [Table 1 and Supplementary appendix, Table S5 and **Figure S4**]. If two rounds of intensive intervention are

Table 1
Percentage reduction in lung cancer incidence and mortality, costs, QALYs and incremental cost-effectiveness ratios for non-dominated strategies according to different analysis.

	% ASIR reduction[1]	% ASMR reduction[2]	Cost (€)	QALYs	ICER (€/QALY)
No intervention	–	–	1359	23.31187	–
Smoking cessation intervention alone					
3x BSCI @35, 40, 45	7.6%	7.6%	1273	23.33337	**cost-saving**
3x ISCI @35, 40, 45	11.8%	11.9%	1339	23.34246	**€7,244**
Screening alone					
1x SCR @55	0%	0.9%	1457	23.31751	**€17,352**
3x SCR @55, 60, 65	0%	2.4%	1591	23.32099	€25,441
2y-SCR @55–65	0%	4.1%	1765	23.32543	€29,910
1y-SCR @55–65	0%	7.4%	2156	23.33473	€34,877
Combined once in a lifetime brief smoking cessation intervention at age 35 plus screening[1]					
1x BSCI @35+ 1xSCR @55	3.6%	4.3%	1415	23.32550	**€4,079**
1x BSCI @35+ 2xSCR @55, 56	3.6%	4.9%	1506	23.32963	**€22,171**
1x BSCI @35+ 3xSCR @55, 60, 65	3.5%	5.6%	1545	23.33061	€39,638
1x BSCI @35+ 1y-SCR @55–65	3.7%	10.6%	2087	23.34255	€45,432
Combined once in a lifetime intensive smoking cessation intervention at age 35 plus screening[1]					
1x ISCI @35+ 1xSCR @55	6.6%	7.4%	1445	23.33545	**€3,653**
1x ISCI @35+ 3y-SCR @55–65	6.9%	9.3%	1571	23.33936	€32,249
1x ISCI @35+ 1y-SCR @55–65	6.9%	13.4%	2090	23.35273	€38,774
Combined twice in a lifetime brief smoking cessation intervention at age 35 & 40 plus screening[1]					
2x BSCI @35, 40+ 1xSCR @55	5.6%	6.2%	1390	23.33013	**€1,675**
2x BSCI @35, 40+ 2xSCR @55, 60	5.7%	5.1%	1458	23.33352	**€20,259**
2x BSCI @35, 40+ 2xSCR @55, 56	6.1%	7.1%	1472	23.33405	€25,585
2x BSCI @35, 40+ 3xSCR @55, 56, 57	5.8%	7.3%	1555	23.33688	€29,459
2x BSCI @35, 40+ 1y-SCR @55–65	6.0%	12.5%	2036	23.34664	€49,242
Combined twice in a lifetime intensive smoking cessation intervention at age 35 & 40 plus screening[1]					
2x ISCI @35, 40+ 1xSCR @55	10.0%	7.4%	1434	23.33966	**€2,703**
2x ISCI @35, 40+ 2xSCR @55, 60	9.9%	8.4%	1504	23.34328	**€19,192**
2x ISCI @35, 40+ 4y-SCR @55–65	9.9%	8.8%	1561	23.34622	**€19,567**
2x ISCI @35, 40+ 2y-SCR @55–65	10.2%	10.3%	1701	23.34738	€120,757
2x ISCI @35, 40+ 1y-SCR @55–65	9.9%	13.4%	2064	23.35020	€128,704
Combined thrice in a lifetime brief smoking cessation intervention at age 35, 40 & 45 plus screening[1]					
3x BSCI @35, 40, 45+ 1xSCR @55	7.3%	8.0%	1366	23.33397	**€304**
3x BSCI @35, 40, 45+ 2xSCR @55, 60	7.8%	9.1%	1432	23.33812	**€15,971**
3x BSCI @35, 40, 45+ 4y-SCR @55–65	7.6%	9.7%	1492	23.34003	€31,436
3x BSCI @35, 40, 45+ 1y-SCR @55–65	7.6%	13.9%	1998	23.35052	€48,191
Combined thrice in a lifetime intensive smoking cessation intervention at age 35, 40 & 45 plus screening[1]					
3x ISCI @35, 40, 45+ 1xSCR @55	11.5%	11.9%	1430	23.34431	**€2,173**
3x ISCI @35, 40, 45+ 2xSCR @55, 60	11.9%	13.1%	1491	23.34894	**€13,195**
3x ISCI @35, 40, 45+ 3y-SCR @55–65	11.7%	13.6%	1550	23.35219	**€18,215**
3x ISCI @35, 40, 45+ 1y-SCR @55–65	11.9%	17.9%	2028	23.36250	€46,378
All strategies					
3x BSCI @35&40&45	7.6%	7.6%	1273	23.33337	**cost-saving**
3x ISCI @35&40&45	11.8%	11.9%	1339	23.34246	**€7,244**
3x ISCI @35&40&45+ 3y-xSCR-HR @55–65	11.7%	13.6%	1550	23.35219	**€21,703**
3x ISCI @35&40&45+ 1y-xSCR-HR @55–65	11.9%	17.9%	2028	23.36250	€46,376

[1] Percentage of age standardized incidence rate (ASIR) reduction compared to no intervention; [2]Percentage of age-standardized mortality rate (ASMR) reduction compared to no intervention; [3]Once in a lifetime (1x), twice in a lifetime (2x), thrice in a lifetime (3x), every year (1y), every 2 years (2y), every 3 years (3y), every 4 years (4y)

implemented at ages 35 and 40, the most cost-effective strategy is for this to be combined with screening every 4 years from ages 55–65 at a cost of €24,171 per QALY compared with the next most costly strategy [Table 1, Supplementary appendix, Table S6 and **Figure S5**]. The most cost-effective strategy below the threshold was to perform three rounds of intensive intervention at ages 35, 40 and 45 combined with screening every three years between ages 55 and 65 at a cost of €21,703 per QALY compared with the next most costly strategy, and €4,732 per QALY compared with no intervention [Table 1, Fig. 3 and Supplementary appendix Table S7 and **Figure S6**]. Increasing the frequency of screening to every two years or decreasing the interval would be a dominated strategy. This would be the same as increasing the frequency of screening to once a year which would have an ICER of €46,376 per QALY, being cost-effective when compared with the next most costly strategy, or €13,213 per QALY with no intervention. Additional baseline analyses are included in the Supplementary appendix.

3.4. Sensitivity analysis

The deterministic and probabilistic sensitivity analyses shown in both the main manuscript and the supplemental appendix correspond to the most cost-effective strategy (3xISCI @35, 40 and 45+ 3y-SCR @55–65) compared to no intervention. The effect on cost-effectiveness of some parameters and assumptions is presented in Fig. 4. Intervention coverage varied between 5% and 91%, where the latter figure corresponds to the maximum percentage of the smoking population aged 35–74 that could attend primary healthcare in Spain. Both smoking cessation and screening coverage have a high impact on the ICERs, but the effect is inverted (Supplementary appendix, **Figure S7**). The cost-effectiveness of the intervention became more substantial as the coverage of smoking cessation strategies was increased and less substantial as screening coverage was increased. Smoking cessation interventions have more QALYs per unit of cost than screening when

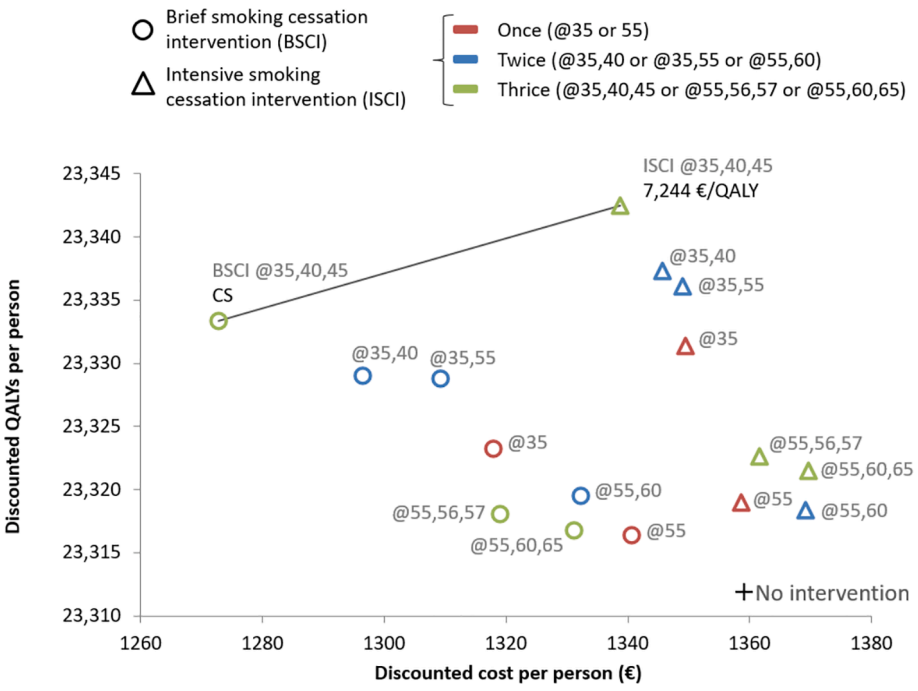

Fig. 1. Cost-effectiveness efficiency frontier for smoking cessation intervention-alone strategies by frequency and age. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy.

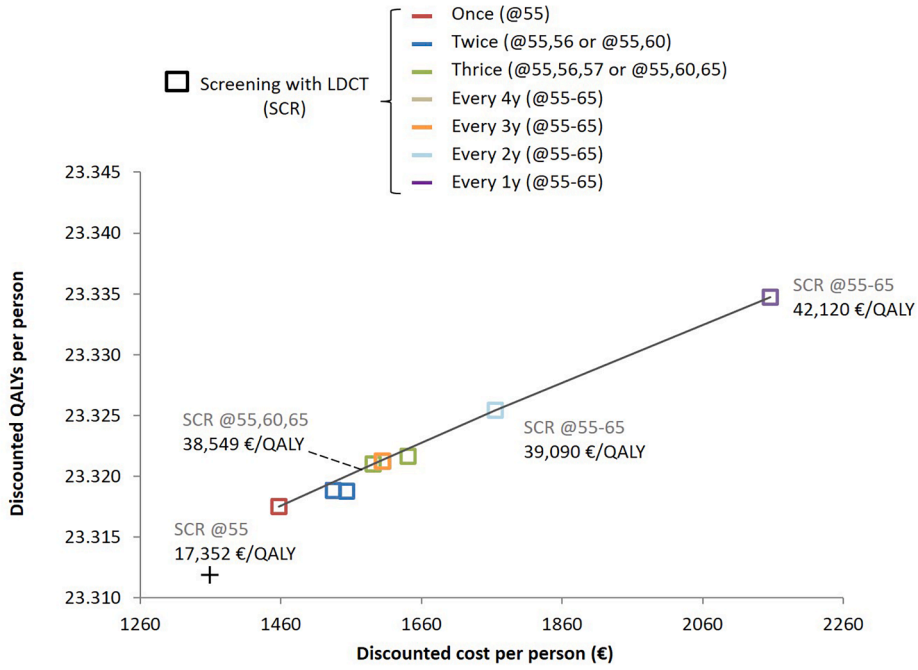

Fig. 2. Cost-effectiveness efficiency frontier for screening-only strategies by frequency and age. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy.

coverage improves, indicating that an increase in screening coverage among a population with lower risk is not efficient. The influence of the probability of survival was marginal when varied between half and double. The uncertainty of the cost of screening was higher than that of the cost of smoking cessation strategies, and a 75% decrease in the costs of both interventions would lead to cost-savings. A 75% increase in the effectiveness of the intensive smoking cessation intervention has a great impact on ICER, approaching €20,000 per QALY gained. However, the same increase in screening sensitivity is minimal. In all cases, the cost per QALY would not exceed the willingness-to-pay threshold (€22,000-€25,000 per QALY), except for the interaction between the effectiveness of the intensive intervention and the sensitivity of the screening. A 75% decrease in both effectiveness of the intensive intervention and sensitivity of screening would make the strategy no longer cost-effective compared to no intervention. Additional deterministic and probabilistic sensitivity analyses are included in the results section of the

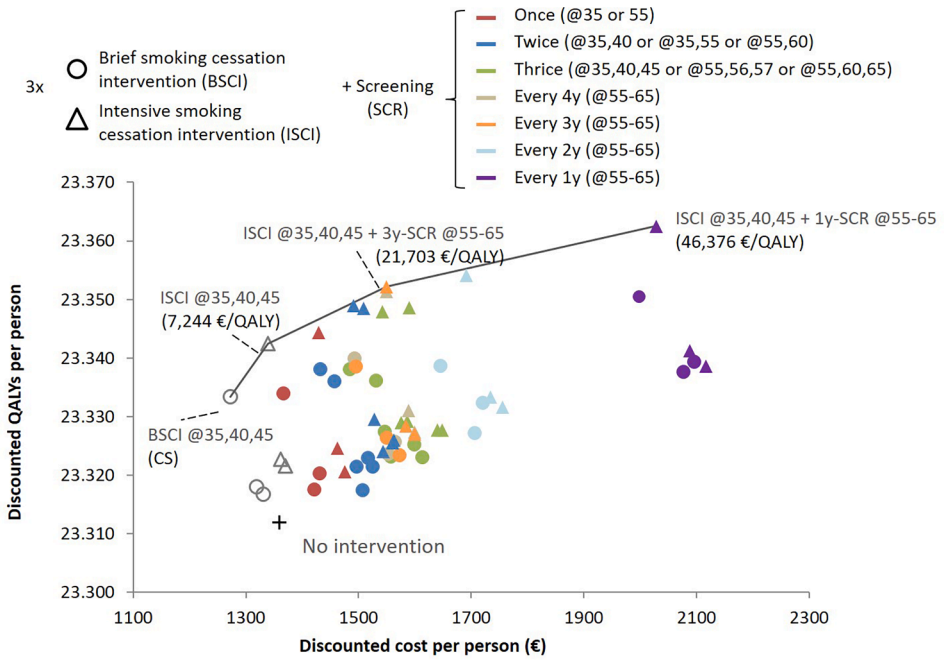

Fig. 3. Cost-effectiveness efficiency frontier for combined smoking cessation intervention applied three times plus screening by frequency and age. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy.

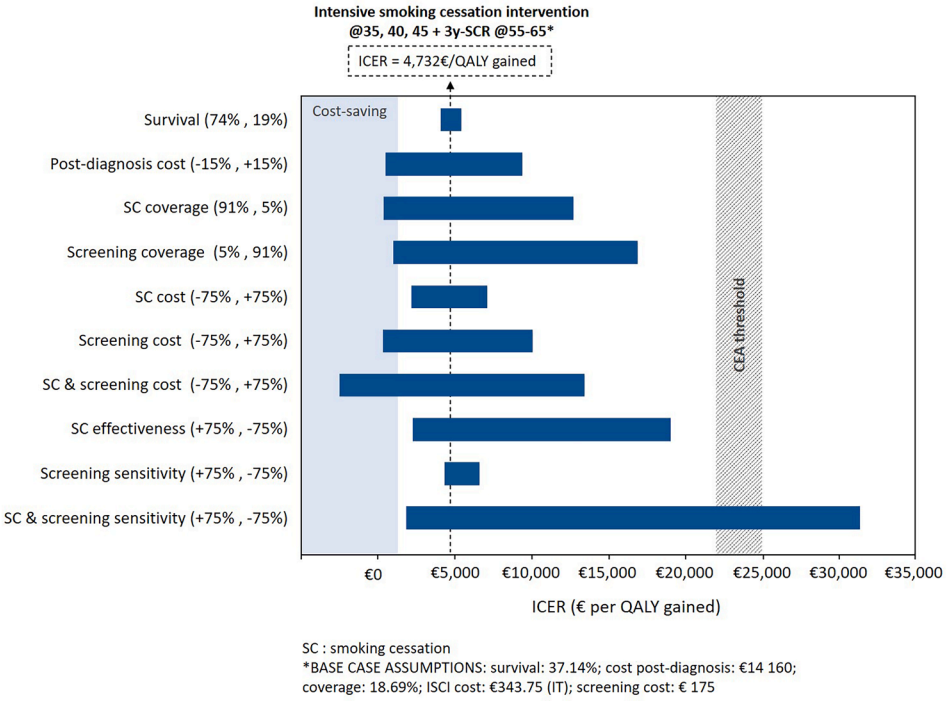

Fig. 4. One- and two-way sensitivity analysis for the intensive cessation smoking intervention strategy at ages 35, 40, 45 plus screening every 3 years from ages 55–65 compared to no intervention.

Supplementary appendix.

4. Discussion

Our results show that an intensive intervention for smoking cessation at ages 35, 40 and 45 combined with screening using LDCT every three years at ages between 55 and 65 years is a cost-effective strategy with an increase of €21,703 per QALY compared with intensive smoking cessation intervention alone, and €4732 per QALY compared with no intervention. In Europe, it is estimated that 477,534 new cases of lung cancer were diagnosed in 2018, more than 391,000 of which were caused by smoking, and up to 184,000 of which, and a similar number of deaths, might have been avoided with the implementation of this strategy. According to the country scenario, a long series of efficient strategies can

be adapted to reduce lung cancer incidence and mortality. A simple 5 A's smoking cessation strategy administered three times among the potentially high-risk population would save money or have a low overall cost depending on the coverage. This strategy might avoid between 8% and 31% of cases and deaths, covering at least 19% of smokers and ex-smokers under age 55 with a smoking history of $\geq$ 30 pack-years. A similar approach using intensive smoking cessation methods would result in an additional reduction of 4%-16%. Although quitting smoking at any age can lower the risk of lung cancer, the risk is still higher than that for people who never smoked. Therefore, some people such as heavy smokers could benefit from screening. Including screening with LDCT would not have a significant impact on incidence but could add between 2% and 24% to the reduction in lung cancer mortality depending on the combination of smoking cessation interventions used, their frequency and coverage. Therefore, early smoking cessation interventions and screening of heavy and older smokers should be considered as complementary strategies and not as two mutually exclusive prevention alternatives.

To our knowledge, there is no European study available on the cost-effectiveness of lung cancer prevention strategies combining smoking cessation interventions and LDCT screening. Four cost-effectiveness analyses for lung cancer prevention have been performed in Europe; however, none of them combined smoking cessation interventions and secondary prevention with LDCT[17,42–44]. Regarding the economic evaluations for lung cancer screening performed in non-European countries, the comparison of the cost-effectiveness models may be hampered by methodological heterogeneity. However, all of them assessed the implementation of LDCT compared with no screening and only three studies included smoking cessation activities with a single course of nicotine replacement or varenicline. All three studies concluded that lung cancer screening with LDCT appears to be cost-effective and that a supplementary smoking cessation programme can improve outcomes[45–47]. To our knowledge, no articles have been published including both brief and intensive smoking cessation intervention programmes separately or in combination with screening using LDCT and evaluating a wide range of combinations depending on age, frequency, and coverage.

There are several inherent limitations to simulation models that have often been mentioned, such as the uncertainty of the input parameters or certain methodological assumptions[48]. Attempts have been made to address these issues using the best available data in the literature with consensus decisions based on an expert lung cancer panel, calibrating the model to reproduce the real scenario as accurately as possible, and performing sensitivity analyses. The lack of crucial information on certain aspects of the natural history of lung cancer is also an important limitation. Furthermore, our model did not consider the potential for overdiagnosis or lead-time bias. Overdiagnosis may lead to unnecessary treatment of asymptomatic patients, and thereby increase costs with few health benefits. An adjusted model for overdiagnosis would improve cost-effectiveness of LDCT screening. Lead-time bias may extend the time between diagnosis and death but not the survival, and thereby potentially decrease costs with some additional health benefits. An adjusted model for lead-time bias would worsen the cost-effectiveness of LDCT screening. It is uncertain how these two outcomes offset each other. In our model, the impact on cost-effectiveness of the two biases would be lessened because we considered an average cost of treatment for all stages, and therefore, only changes would occur in the QALYs. The study focused on the risk of lung cancer, disregarding all multiple benefits of smoking cessation interventions and LDCT screening in reducing or detecting tumours of other locations or pulmonary or cardiovascular disease. Both smoking cessation interventions and screening would have been more cost-effective if we had accounted for the QALYs gained through preventing these illnesses. Even with these limitations, simulation models are a useful resource and are commonly used to address important health policy issues that cannot be explored through experimental studies[9]. These results can help healthcare decision-makers to make the most efficient choices concerning this critical disease, together with their associated costs. As smoking prevalence and its attributable disease burden change over time, and new information becomes available, it will be important to reassess the model. The adequacy of the screening interval and the age range according to nodule specifications, as well as the calibration and evaluation of the optimal strategies in women will also be of crucial importance in next steps.

Despite global efforts to control tobacco consumption in many countries with the adoption of the WHO Framework Convention on Tobacco Control (WHO FCTC) (first ratified by 40 states in 2005, and then by 53 states and the European Union in 2013), there is still a great deal of work to be done in this field. Smoking remains the scourge of worldwide cancer statistics and several other diseases. The use of price and tax measures, and state intervention in the tobacco market via a variety of actions, are necessary but not sufficient. The provision of smoking cessation interventions is still scarce in Spain. Although brief smoking cessation intervention is increasing, the 5 A's steps are not fully implemented and information about tobacco consumption is not systematically recorded. Regarding intensive smoking cessation intervention, the available programmes are voluntarily implemented and are not usually included in the public service portfolio[49]. The implementation of smoking cessation programmes using any of the described approaches, whether alone or in combination with screening using LDCT, can substantially reduce lung cancer mortality. Our model predicts that for every 140 smokers or former smokers screened every three years, lung cancer mortality can be reduced by one. This number shrinks to one in 26 on adding smoking cessation interventions via intensive intervention at early ages, assuming coverage of smokers and former smokers currently attending the public health system only. If the entire smoking population were included, one lung cancer death could be avoided by intervening on 7 smokers or former smokers with the combined strategy.

More precise screening eligibility criteria may help to further improve the effectiveness and cost-effectiveness of these strategies in the near future. However, the need to drastically reduce lung cancer morbidity and mortality is already urgent and implementing those intervention strategies already available that have been shown to be effective and efficient in Europe is of the highest importance to achieve more sustainable health systems

5. Conclusion

As indicated by the WHO, 90% of lung cancers could be avoided by eliminating tobacco use[50]. However, screening with LDCT is the only approach to avoid mortality of those who already have a high risk of cancer. A long-term organized approach combining primary prevention with smoking cessation interventions and secondary prevention with LDCT screening would result in a large decrease in the burden of lung cancer in the near future. These combined prevention strategies, especially when providing several intensive interventions for smoking cessation at early ages, are more cost-effective than both approaches separately and allow for a more intensified LDCT screening without losing efficiency. Spain is currently in the IV phase of the epidemic curve and shows similar behaviour to the rest of the countries of southern Europe[45]. The similarity in the regions anticipates that these results will also be of more general interest. It is of vital importance to allocate resources efficiently at a time of health and economic crisis like now, where health policymakers must decide in circumstances of large uncertainty and face difficult trade-offs given the health, economic and social challenges that arise.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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