EClinicalMedicine 42 (2021) 101176

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

# A modeling analysis to compare eligibility strategies for lung cancer screening in Brazil

Adalberto Miranda-Filho[a,*], Hadrien Charvat[a], Freddie Bray[a], Arn Migowski[b,c], Li C. Cheung[d], Salvatore Vaccarella[a], Mattias Johansson[a], Andre L. Carvalho[a], Hilary A. Robbins[a,*]

[a] International Agency for Research on Cancer, 150 Cours Albert Thomas, Lyon 69372 CEDEX 08, France
[b] Cancer Early Detection Division, Brazilian National Cancer Institute (INCA), Brazil
[c] National Institute of Cardiology (INC), Rio de Janeiro, Brazil
[d] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS, Bethesda, MD, USA

ARTICLE INFO

*Article History:*
Received 27 July 2021
Revised 10 October 2021
Accepted 12 October 2021
Available online xxx

*Keywords:*
Lung cancer screening
Tobacco smoking
Early cancer detection
Brazil

ABSTRACT

*Background:* Country-specific evidence is needed to guide decisions regarding whether and how to implement lung cancer screening in different settings. For this study, we estimated the potential numbers of individuals screened and lung cancer deaths prevented in Brazil after applying different strategies to define screening eligibility.

*Methods:* We applied the Lung Cancer Death Risk Assessment Tool (LCDRAT) to survey data on current and former smokers (ever-smokers) in 15 Brazilian state capital cities that comprise 18% of the Brazilian population. We evaluated three strategies to define eligibility for screening: (1) pack-years and cessation time (≥30 pack-years and <15 years since cessation); (2) the LCDRAT risk model with a fixed risk threshold; and (3) LCDRAT with age-specific risk thresholds.

*Findings:* Among 2.3 million Brazilian ever-smokers aged 55–79 years, 21,459 (95%CI 20,532–22,387) lung cancer deaths were predicted over 5 years without screening. Applying the fixed risk-based eligibility definition would prevent more lung cancer deaths than the pack-years definition [2,939 (95%CI 2751–3127) vs. 2,500 (95%CI 2318–2681) lung cancer deaths], and with higher screening efficiency [NNS=177 (95%CI 170–183) vs. 205 (95%CI 194–216)], but would tend to screen older individuals [mean age 67.8 (95%CI 67.5–68.2) vs. 63.4 (95%CI 63.0–63.9) years]. Applying age-specific risk thresholds would allow younger ever-smokers to be screened, although these individuals would be at lower risk. The age-specific thresholds strategy would avert three-fifths (60.1%) of preventable lung cancer deaths [*N* = 2629 (95%CI 2448–2810)] by screening 21.9% of ever-smokers.

*Interpretation:* The definition of eligibility impacts the efficiency of lung cancer screening and the mean age of the eligible population. As implementation of lung screening proceeds in different countries, our analytical framework can be used to guide similar analyses in other contexts. Due to limitations of our models, more research would be needed.



## 1. Introduction

Low-dose CT (LDCT) screening can prevent lung cancer deaths in high-risk populations. Two large randomized controlled trials - the US National Lung Screening Trial (NLST) and the Netherlands–Leuvens Longkanker Screenings Onderzoek (NELSON) - have shown a statistically significant lung cancer mortality reduction with LDCT screening among current and former smokers [1]. The NLST reported a 20% lung cancer mortality reduction with three annual LDCT screens compared to chest radiography [2] and NELSON showed a 24% reduction among men (primary analysis) and 33% among women with 4 screens over 5.5 years [3].

The US Preventive Services Task Force (USPSTF) first recommended screening in 2013 for ever-smokers aged 55–80 years with a history of 30 or more pack-years and less than 15 years since cessation [4]. Based on the most recent findings from clinical trials, several countries are now considering implementing population-based lung cancer screening programs [5,6]. In Brazil, a preliminary trial found that lung cancer screening was feasible among ever-smokers with 30 pack-years and yielded a similar lung cancer detection rate to the NLST, with the majority of patients diagnosed at stages 1A-1B [7]. Another study in Brazil offered lung cancer screening to current and

* Corresponding authors.
*E-mail addresses:* mirandaa@iarc.fr (A. Miranda-Filho), robbinsh@iarc.fr (H.A. Robbins).

https://doi.org/10.1016/j.eclinm.2021.101176

**Research in context**

*Evidence before this study*

Evidence is needed to guide decisions regarding how to define lung cancer screening eligibility and evaluate its potential impact in preventing lung cancer deaths. We performed a PubMed search without any date restrictions including the terms “lung cancer screening”, and “Brazil” and confirmed there is a lack of studies exploring the potential impact of different strategies to define eligibility for lung screening in Brazil.

*Added value of this study*

We estimated the potential benefits of lung cancer screening under different eligibility strategies in 15 state capital cities in Brazil. A pack-years eligibility strategy identifies 57.1% of preventable lung-cancer deaths as screening-eligible by screening 21.8% of all ever-smokers. A risk-model based strategy with a fixed threshold potentially identifies 67.1% of preventable lung-cancer deaths as screening-eligible by screening 22.1% of all ever-smokers. The risk-based strategy requires fewer participants screened to prevent one lung cancer death, but screens older individuals on average (mean age 67.8 vs. 63.4 years). Applying age-specific risk thresholds could reduce the mean age of the screened population.

*Implications of all the available evidence*

In this study, we developed an approach to estimate the potential benefits of large-scale lung cancer screening in Brazil. Our analytical framework can be used to guide further studies that provide country-specific evidence for the choice of eligibility strategies. In a short-term period, the full implementation of a lung cancer screening program in fifteen capital cities could prevent over 2,500 lung cancer deaths in Brazil by screening approximately 500,000 current and former smokers. Different strategies for eligibility substantially impact the efficiency of screening and the mean age of the population screened.

former smokers older than 45 years, regardless of tobacco exposure. In a secondary analysis, lung cancer detection was much higher among individuals identified as high-risk by the PLCOm2012 risk prediction model (5.7% vs. 0.2%) [8].

These findings stress the importance of identifying an appropriate target population for lung cancer screening, taking into consideration the epidemiological context of the local setting. Multiple studies have shown that risk prediction models may more efficiently select ever-smokers for screening compared with pack-years guidelines [9,10]. In this approach, predicted lung cancer risk is calculated using individual characteristics (e.g., age, smoking intensity and smoking duration) and then compared with a risk threshold to define who is eligible [11].

In many countries, evidence is needed regarding how to best define the target population for screening. The impact and efficiency of lung cancer screening is driven by eligibility criteria and the starting and stopping ages for screening. In each country, the population of current and former smokers has a unique demographic structure with respect to age and smoking prevalence, and therefore national modeling studies are required to understand the potential effects of different eligibility strategies and to choose the best target population. In this study we estimated the number of individuals screened and preventable lung cancer deaths for different eligibility strategies in Brazil. We focus on ever-smokers aged 55–79 years residing in 15 major cities across three regions that comprise 18% of the total Brazilian population.

## 2. Methods

### 2.1. General approach

Our general approach and analytical framework for comparing different eligibility strategies for lung cancer screening is shown in Supplementary Figure 1, which illustrates the overall steps of our analysis but not the detailed aspects of its implementation. The approach includes the following overarching steps: (a) use of national survey data to estimate the population of current and former smokers specific to age, smoking intensity, and quit-years; (b) application of potential eligibility strategies to classify individuals in the survey data as eligible or ineligible for screening; (c) estimation of the number of lung cancer cases and deaths over a specified time period; and (d) application of screening effectiveness estimates in the screening-eligible population to estimate the impact of screening on lung cancer cases and deaths. We did not estimate other impacts of screening, such as the number of nodule surveillance scans needed, or invasive procedures for benign nodules. The magnitude of these harms depends on the nodule management protocol employed [12].

### 2.2. Data source and population

To estimate the population of current and former smokers, we analyzed data from the 2006–2017 Brazilian Surveillance System of Risk and Protective Factors for Chronic Diseases (Vigitel) Survey. The survey selected households using probabilistic random sampling, targeting adults aged 18 years and older living in selected state capital cities [13]. We obtained non-identifiable individual-level data for 15 capital cities between 2006 and 2017 [14]. Some variables were not available for the years 2012–2017 and were imputed using data from 2006 to 2011 (see *Supplementary material*). The estimated total population by age and sex for mid-year 2014 was obtained from the Brazilian Institute of Geography and Statistics. We implemented a method combining bootstrap estimation with multiple imputation [15] to address missing data (see *Supplementary material*). We analyzed individuals aged 55 to 79, using an upper age threshold of 79 rather than 80 because population estimates were available only in 5-year age groups. Our study used publicly available secondary sources of data and no ethical committee approval was required.

### 2.3. Prediction of lung cancer deaths

We used a simplified version of the Lung Cancer Death Risk Assessment Tool (LCDRAT) [16] to predict lung cancer deaths in the Brazilian population. LCDRAT was developed using data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial [17] and has been validated externally in four US cohorts [11], although not specifically in the Brazilian setting due to lack of available cohort data. The model calculates five-year risk of lung cancer death in the absence of screening. The simplified version includes age, sex, smoking intensity, smoking duration, and time since smoking cessation [11]. LCDRAT accounts for competing causes of death using a separate component to predict mortality from causes other than lung cancer. To assess whether the LCDRAT projections are reasonable, we compared the number of lung cancer deaths predicted by LCDRAT to the number recorded by the national mortality system in Brazil [18].

### 2.4. Modeling the effect of screening eligibility strategies

We estimated the effect of different strategies to define screening eligibility among 55–79 year-olds in the Brazilian population described above. The first strategy follows the USPSTF 2013 categorical criteria, specifically at least 30 pack-years smoked and no more than 15 quit-years. For the second strategy, we applied eligibility

based on lung cancer death risk by the LCDRAT model of at least 1.2% over 5 years. This cut-point was previously chosen to select a similar number of individuals as USPSTF criteria in the US [16]. The third strategy consisted of choosing age-specific risk-thresholds that would select a similar number of ever-smokers in each age category as the pack-years strategy. The age-specific thresholds strategy was intended to reduce the mean age of the population selected using a fixed 1.2% risk threshold, while potentially maintaining the efficiency of risk-based eligibility.

We estimated the potential benefits of lung cancer screening by assuming that three rounds of annual LDCT screening would reduce lung cancer mortality by 20% as in the NLST [2]. The NLST lung cancer mortality ratio of 0.80 was previously shown to be consistent across categories of baseline risk, while the absolute number of lung cancers deaths prevented varies [19]. For each eligibility strategy, we estimated the number of individuals eligible for screening, the number of expected lung cancer deaths in the absence of screening, the number of lung cancer deaths prevented, and the number needed to screen (NNS) to prevent one lung cancer death [20].

The USPSTF recently updated its recommendation for lung cancer screening eligibility, lowering the age threshold from 55 to 50 and the pack-year threshold from 30 to 20 pack-years [21]. Such criteria substantially broaden the eligible population for screening and may not be well-suited to all settings, including settings that are newly implementing lung cancer screening and thus may require more restrictive initial criteria. Therefore, in this study focused on Brazil, we separately present results for the age group 50–54 years, but otherwise focus on results calculated among 55–79 year-olds.

Statistical analyses were performed using R software (further detail and code is provided in supplementary material).

### 2.5. Role of funding source

The funding source had no involvement in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

## 3. Results

Table 1 describes the current or former smoking Brazilian population aged 55–79 in the 15 state capital cities by sex, age, and geographical region. Of the population aged 55–79 in 2014, current smokers represented 11.8% (95%CI 11.2–12.3%) and former smokers represented 30.3% (95%CI 29.6–30.9%), for a total of 2.3 million ever-smokers. In brief, the LCDRAT risk model showed an overprediction of 17% more deaths compared with the national mortality system across a similar period (details and age-stratified results in the *Supplementary*).

The pack-years eligibility strategy selected similar proportions of individuals for screening across groups defined by age and region in both current and former smokers, although more male current smokers were selected than females (56.1% vs. 39.9%, respectively) (Table 2). Applying eligibility based on the LCDRAT risk model with a fixed 1.2% risk threshold, the proportion of individuals eligible increased strongly with age, ranging from 19.4% (55–59 years-old) to 100% (75–79 years-old) among current smokers and from less than 1% to 36.6% in former smokers. The populations selected by these two strategies are visually compared in *Supplementary Fig. 1*.

A comparison of the overall predicted benefits of screening using the pack-years, risk-based fixed-threshold, and age-specific thresholds strategies is shown in Table 3. For comparison, we estimated that if all ever-smokers were screened, 4378 deaths could be prevented over 5 years (among a total of 21,459 deaths) but with a high NNS of 538 (95%CI 517–599, Table 3). The pack-years strategy potentially identifies 57.1% ($N$ = 2500) of preventable lung cancer deaths by screening 21.8% of ever-smokers. The risk-based fixed-threshold strategy potentially identifies 67.1% ($N$ = 2939) of preventable lung cancer deaths by screening 22.1% of ever-smokers. The fixed-threshold strategy therefore requires fewer participants screened to prevent one lung cancer death, with the NNS=177 (95%CI 170–183) versus NNS=205 (95%CI 194–216). Applying age-specific thresholds chosen to select a similar number of individuals in each age category as the pack-years strategy, we estimated that over 5 years, LDCT screening could identify approximately 2629 (60.1%) preventable lung cancer deaths by screening 21.9% of current and former smokers. Supplementary Table 2 shows results obtained for the pack-years and fixed-threshold strategies when using eligibility criteria similar to the USPSTF 2021 recommendation, i.e., age 50–79 with at least 20 pack-years and no more than 15 quit-years.

Table 4 shows estimated outcomes by age group for different eligibility strategies, including the 50–54 year-old age group. As expected, the age-specific thresholds increased strongly with age, ranging from a 5-year lung cancer death risk of 0.36% for 50–54 year-olds to 3.46% among 75–79 year-olds. In general, the age-specific thresholds allowed more lung cancer deaths to be prevented in each age group than the pack-years strategy, thus yielding a lower NNS. Compared with the fixed-threshold strategy, age-specific thresholds prevented more deaths in younger age groups, but fewer deaths in older age groups.

Using the age-specific threshold strategy, the proportion of eligible smokers was similar across age groups, ranging between 19.6% and 23.1% (to match pack-year-based eligibility) (Table 4). In contrast,

**Table 1**
Estimated number and percentage of current and former smokers aged 55–79 years in fifteen state capital cities in Brazil, 2014.

| | Current smokers | | Former smokers | |
|---|---|---|---|---|
| | Percentage (95%CI) | Population (95%CI) | Percentage (95%CI) | Population (95%CI) |
| *Sex* | | | | |
| Female | 10.1 (9.4–10.7) | 333,966 (313,568–354,364) | 22.9 (22.1–23.6) | 759,432 (733,451–785,412) |
| Male | 14.4 (13.4–15.4) | 326,206 (302,834–349,579) | 41.2 (39.9–42.6) | 934,094 (903,271–964,917) |
| *Age* | | | | |
| 55–59 | 16.0 (14.8–17.3) | 265,599 (245,267–285,932) | 30.1 (28.7–31.6) | 499,234 (474,808–523,660) |
| 60–64 | 11.4 (10.4–12.3) | 177,705 (162,404–193,007) | 32.1 (30.6–33.5) | 501,678 (478,776–524,580) |
| 65–69 | 11.5 (10.2–12.9) | 114,801 (101,551–128,051) | 29.7 (28.2–31.3) | 295,796 (280,171–311,421) |
| 70–74 | 8.9 (7.6–10.1) | 69,847 (60,144–79,550) | 28.1 (26.4–29.8) | 221,454 (208,003–234,905) |
| 75–79 | 5.5 (4.5–6.6) | 32,220 (26,044–38,396) | 30.1 (28.1–32.2) | 175,363 (163,333–187,392) |
| *Region* | | | | |
| Northeast | 8.1 (7.7–8.6) | 118,469 (111,845–125,093) | 30.2 (29.4–30.9) | 440,877 (429,863–451,891) |
| South | 13.2 (12.5–14.0) | 83,198 (78,408–87,988) | 29.5 (28.5–30.4) | 185,336 (179,173–191,499) |
| Southeast | 13.1 (12.3–14.0) | 458,505 (428,466–488,544) | 30.5 (29.4–31.6) | 1,067,313 (1,028,093–1,106,533) |

The state capital cities analyzed include: Aracaju, Fortaleza, Joao Pessoa, Maceió, Natal, Recife, Teresina, Salvador, Belo Horizonte, Vitoria, Rio de Janeiro, São Paulo, Curitiba, Florianópolis and Porto Alegre.

**Table 2**
Estimated number and percentage of current and former smokers aged 55–79 years eligible for low-dose CT lung cancer screening under different eligibility strategies in fifteen state capital cities in Brazil.

| | Current smokers | | Former smokers | |
|---|---|---|---|---|
| | Percentage (95%CI) | Population and 95%CI | Percentage and 95%CI | Population and 95%CI |
| **Pack-year strategy** | | | | |
| *Sex* | | | | |
| Female | 39.9 (36.5–43.2) | 133,120 (119,437–146,804) | 10.3 (8.5–12.2) | 78,464 (64,374–92,554) |
| Male | 56.1 (52.1–60.1) | 182,941 (163,864–202,017) | 12.6 (10.4–14.8) | 117,722 (96,527–138,918) |
| *Age* | | | | |
| 55–59 | 46.9 (42.5–51.3) | 124,468 (108,379–140,557) | 10.1 (7.3–12.8) | 50,180 (36,121–64,238) |
| 60–64 | 45.0 (40.3–49.7) | 80,003 (69,365–90,640) | 12.1 (9.3–14.9) | 60,700 (46,362–75,039) |
| 65–69 | 50.8 (44.2–57.4) | 58,275 (47,981–68,568) | 12.2 (9.5–14.9) | 36,078 (27,964–44,191) |
| 70–74 | 49.3 (41.8–56.9) | 34,442 (27,601–41,283) | 12.4 (9.1–15.7) | 27,476 (19,964–34,987) |
| 75–79 | 58.6 (48.5–68.7) | 18,873 (13,821–23,925) | 12.4 (8.4–16.5) | 21,753 (14,506–28,999) |
| *Region* | | | | |
| Northeast | 44.9 (41.8–48.0) | 53,184 (48,477–57,891) | 10.4 (9.2–11.7) | 45,949 (40,229–51,668) |
| South | 46.6 (43.4–49.8) | 38,771 (35,212–42,330) | 11.9 (10.3–13.6) | 22,119 (18,994–25,245) |
| Southeast | 48.9 (45.2–52.5) | 224,106 (201,343–246,869) | 12.0 (9.6–14.4) | 1281,18 (102,096–154,141) |
| **Risk-based strategy with fixed threshold** | | | | |
| *Sex* | | | | |
| Female | 45.7 (42.4–49.0) | 152,733 (138,541–166,924) | 7.8 (6.6–9.0) | 59,306 (50,006–68,605) |
| Male | 60.5 (56.4–64.5) | 197,183 (179,352–215,014) | 11.8 (10.0–13.6) | 110,004 (92,817–127,191) |
| *Age* | | | | |
| 55–59 | 19.4 (16.2–22.6) | 51,507 (42,347–60,667) | 0.7 (0.1–1.3) | 3,396 (361–6,432) |
| 60–64 | 48.0 (43.3–52.7) | 85,339 (74,370–96,309) | 3.9 (2.3–5.5) | 19,518 (11,629–27,408) |
| 65–69 | 96.8 (94.9–98.6) | 111,078 (97,974–124,181) | 11.2 (8.4–13.9) | 32,967 (24,593–41,342) |
| 70–74 | 99.9 (99.7–100) | 69,772 (60,115–79,428) | 22.3 (18.4–26.1) | 49,323 (40,292–58,353) |
| 75–79 | 100 (NA) | 32,220 (26,079–38,361) | 36.6 (30.6–42.5) | 64,105 (52,699–75,512) |
| *Region* | | | | |
| Northeast | 54.6 (51.5–57.6) | 64,620 (59,801–69,440) | 9.4 (8.1–10.6) | 41,241 (35,623–46,859) |
| South | 50.0 (46.8–53.2) | 41,607 (38,147–45,067) | 10.6 (9.3–12.0) | 19,684 (17,107–22,260) |
| Southeast | 53.2 (49.6–56.7) | 243,688 (221,578–265,798) | 10.2 (8.5–11.8) | 108,385 (90,123–126,648) |

The state capital cities analyzed include: Aracaju, Fortaleza, Joao Pessoa, Maceió, Natal, Recife, Teresina, Salvador, Belo Horizonte, Vitoria, Rio de Janeiro, São Paulo, Curitiba, Florianópolis and Porto Alegre.

the proportion of eligible smokers selected by the fixed-threshold strategy increased strongly with age, ranging from 0.30% in 50–54 year-olds to 46.4% in 75–79 year-olds. The percentage of preventable lung cancer deaths eligible for screening similarly increased from 1.9% to 84.6% across the age ranges. Thus, the age-specific threshold approach might prevent more lung cancer deaths than pack-years criteria (2,629 vs. 2,500, Table 3), but fewer than the fixed-threshold approach (2,939). However, the mean age of eligible individuals was much lower for the age-specific threshold approach (63.8 years) than the fixed threshold approach (67.8 years), indicating that the age-specific thresholds approach would likely save more life-years per prevented death.

## 4. Discussion

Here, we developed an approach to estimate the potential benefits (but not harms) of large-scale lung cancer screening considering 2.3 million current and former smokers living in 15 state capital cities in Brazil. While it is imperative that such strategies be evaluated via pilot projects taking into consideration age structure, life-expectancy, and smoking profiles prior to the rollout of programmes, our study nonetheless provides evidence to guide the choice between different strategies for defining the target population for screening. We found that applying risk-model-based eligibility with a fixed risk threshold among 55–79 year-olds in Brazil would prevent more lung cancer

**Table 3**
Estimated outcomes of lung cancer screening under different eligibility strategies for current and former smokers aged 55–79 in fifteen state capital cities in Brazil.

| Outcomes | Screening strategies | | | |
|---|---|---|---|---|
| | All ever-smokers | Pack-years[§] | Fixed risk threshold (1.2%)[†] | Age-specific risk thresholds[*] |
| Number of eligible individuals | 2,353,698 (2,309,301–2,398,095) | 512,247 (477,315–547,180) | 519,226 (490,411–548,040) | 515,089 (485,524–544,655) |
| Percentage of eligible individuals | 100 | 21.8 | 22.1 | 21.9 |
| Lung cancer deaths in the absence of screening | 21,459 (20,532–22,387) | 12,254 (11,364–13,144) | 14,408 (13,486–15,330) | 12,886 (11,998–13,775) |
| Number of preventable lung cancer deaths eligible | 4,378 (4,189–4,567) | 2,500 (2,318–2,681) | 2,939 (2,751–3,127) | 2,629 (2,448–2,810) |
| Percentage of preventable lung cancer deaths eligible | 100 | 57.1 | 67.1 | 60.1 |
| NNS to prevent 1 lung cancer death | 538 (517–559) | 205 (194–216) | 177 (170–183) | 196 (187–205) |
| Mean 5-year lung cancer death risk | 0.91 (0.88–0.95) | 2.39 (2.26–2.53) | 2.77 (2.68–2.87) | 2.5 (2.39–2.61) |
| Mean age among screening-eligible individuals | 63.6 (63.5–63.8) | 63.4 (63–63.9) | 67.8 (67.5–68.2) | 63.8 (63.4–64.2) |

[§] 55–79 years-old, at least 30 pack-years smoked, and less than 15 years since quitting.
[†] Eligibility by the Lung Cancer Death Risk Assessment Tool (LCDRAT) with a single threshold of 1.2% 5-year risk.
[*] Eligibility by the Lung Cancer Death Risk Assessment Tool (LCDRAT) with 5-year risk thresholds defined individually by age group to select the same number of individuals as the pack-years strategy (see Table 4).

**Table 4**
Estimated outcomes of lung cancer screening under different eligibility strategies for current and former smokers aged 55–79 in fifteen state capital cities in Brazil, stratified by age group.

| | Screening strategies | | | |
|---|---|---|---|---|
| | All ever-smokers | Pack-years[§] | Fixed risk threshold (1.2%)[†] | Age-specific risk thresholds |
| *Age 50–54 years (threshold=0.36%)* | | | | |
| Number of eligible individuals | 972,991 (938,923–1007,059) | 195,576 (173,355–217,797) | 3,313 (380–6,245) | 204,668 (183,002–226,335) |
| Percentage of eligible individuals | 100 | 20.1 | 0.3 | 21.0 |
| Lung cancer deaths in the absence of screening | 2,197 (2,055–2,339) | 1,139 (1,003–1,275) | 42 (5–80) | 1,214 (1,077–1,351) |
| Number of preventable lung cancer deaths eligible | 448 (419–477) | 2,32 (205–260) | 9 (1–16) | 248 (220–276) |
| Percentage of preventable lung cancer deaths eligible | 100 | 51.8 | 1.9 | 55.3 |
| NNS to prevent 1 lung cancer death | 2,171 (2,055–2,288) | 842 (799–885) | 385 (378–392) | 826 (793–860) |
| *Age 55–59 years (threshold=0.64%)* | | | | |
| Number of eligible individuals | 764,833 (738,486–791,181) | 174,648 (153,788–195,508) | 54,903 (45,284–64,523) | 175,787 (156,823–194,751) |
| Percentage of eligible individuals | 100 | 22.8 | 7.2 | 23.0 |
| Lung cancer deaths in the absence of screening | 3,149 (2,945–3,354) | 1,780 (1,576–1,983) | 846 (697–995) | 1,873 (1,670–2,075) |
| Number of preventable lung cancer deaths eligible | 642 (601–684) | 363 (322–405) | 173 (142–203) | 382 (341–423) |
| Percentage of preventable lung cancer deaths eligible | 100 | 56.5 | 26.9 | 59.5 |
| NNS to prevent 1 lung cancer death | 1,191 (1,126–1,255) | 481 (456–505) | 318 (308–328) | 460 (443–477) |
| *Age 60–64 years (threshold=0.99%)* | | | | |
| Number of eligible individuals | 679,383 (655,194–703,572) | 140,703 (123,591–157,815) | 104,858 (91,804–117,912) | 141,786 (126,508–157,065) |
| Percentage of eligible individuals | 100 | 20.7 | 15.4 | 20.9 |
| Lung cancer deaths in the absence of screening | 4,363 (4,063–4,663) | 2,433 (2,144–2,722) | 2,194 (1,908–2,481) | 2,595 (2,297–2,893) |
| Number of preventable lung cancer deaths eligible | 890 (829–951) | 496 (437–555) | 448 (389–506) | 529 (469–590) |
| Percentage of preventable lung cancer deaths eligible | 100 | 55.7 | 50.3 | 59.4 |
| NNS to prevent 1 lung cancer death | 763 (718–809) | 283 (263–303) | 234 (224–244) | 268 (256–280) |
| *Age 65–69 years (threshold=1.55%)* | | | | |
| Number of eligible individuals | 410,597 (393,173–428,022) | 94,353 (81,555–107,151) | 144,045 (128,963–159,126) | 94,795 (82,191–107,400) |
| Percentage of eligible individuals | 100 | 23.0 | 35.1 | 23.1 |
| Lung cancer deaths in the absence of screening | 4,665 (4,228–5,101) | 2,808 (2,369–3,248) | 3,620 (3,175–4,064) | 2,942 (2,502–3,382) |
| Number of preventable lung cancer deaths eligible | 952 (863–1041) | 573 (483–663) | 738 (648–829) | 600 (510–690) |
| Percentage of preventable lung cancer deaths eligible | 100 | 60.2 | 77.5 | 63.0 |
| NNS to prevent 1 lung cancer death | 432 (398–465) | 165 (154–176) | 195 (183–207) | 158 (149–166) |
| *Age 70–74 years (threshold=2.57%)* | | | | |
| Number of eligible individuals | 291,301 (276,618–305,984) | 61,918 (51,918–71,917) | 119,094 (106,358–131,831) | 62,130 (52,814–71,446) |
| Percentage of eligible individuals | 100 | 21.3 | 40.9 | 21.3 |
| Lung cancer deaths in the absence of screening | 4,880 (4,415–5,344) | 2,795 (2,341–3,250) | 4,020 (3,544–4,497) | 2,942 (2,490–3,395) |
| Number of preventable lung cancer deaths eligible | 995 (901–1090) | 570 (478–663) | 820 (723–917) | 600 (508–693) |
| Percentage of preventable lung cancer deaths eligible | 100 | 57.3 | 82.4 | 60.3 |
| NNS to prevent 1 lung cancer death | 293 (270–316) | 109 (101–116) | 145 (136–154) | 104 (98–109) |
| *Age 75–79 years (threshold=3.46%)* | | | | |
| Number of eligible individuals | 207,583 (195,026–220,139) | 40,626 (31,970–49,282) | 96,325 (83,783–108,868) | 40,590 (32,455–48,726) |
| Percentage of eligible individuals | 100 | 19.6 | 46.4 | 19.6 |
| Lung cancer deaths in the absence of screening | 4,403 (3,878–4,927) | 2,438 (1,917–2,959) | 3,728 (3,185–4,270) | 2,534 (2,016–3,053) |
| Number of preventable lung cancer deaths eligible | 898 (791–1005) | 497 (391–604) | 760 (650–871) | 517 (411–623) |
| Percentage of preventable lung cancer deaths eligible | 100 | 55.3 | 84.6 | 57.6 |
| NNS to prevent 1 lung cancer death | 231 (208–255) | 82 (75–89) | 127 (115–138) | 78 (73–84) |

*Eligibility by the Lung Cancer Death Risk Assessment Tool (LCDRAT) with 5-year risk thresholds defined individually by age group to select the same number of individuals as the pack-years strategy.
[§] at least 30 pack-years smoked, and less than 15 years since quitting.
[†] Eligibility by the Lung Cancer Death Risk Assessment Tool (LCDRAT) with a single threshold of 1.2% 5-year risk.

deaths than a pack-years strategy, and with higher screening efficiency (lower NNS), but would screen older individuals. A strategy using different risk thresholds for each age group could ensure a larger proportion of eligible individuals at younger ages while maintaining some advantages of risk-based eligibility, although some eligible individuals would have low likelihood of benefit. Over 5 years, the age-specific threshold strategy could prevent approximately 2,629 lung cancer deaths in Brazil by screening 515,089 individuals (21.9% of current and former smokers).

Our models suggested that implementation of lung cancer screening in Brazil could avoid more than half of the preventable lung cancer deaths by screening approximately 20% of all current and former smokers. These conclusions are based on strong assumptions, including a screening program similar to the US NLST, which consisted of 3 annual screens followed by approximately 4 years of no-screening follow-up [2]. We note that several clinical trials have found a larger mortality reduction than the NLST, including the NELSON [3], MILD [22], and LUSI [23]. Therefore, it is possible that our estimates of the potential benefits of lung cancer screening in Brazil are conservative, particularly in women who may have higher screening benefit [3], and they almost certainly underestimate the benefits of longer-term screening (beyond 3 years).

Our overall results showed that a USPSTF-like pack-years strategy and a risk-based strategy with a fixed threshold (1.2% lung cancer death risk by LCDRAT) would screen similarly-sized populations in the 15 Brazilian cities, with 21.8% and 22.1% of ever-smokers eligible for screening, respectively. The risk-based strategy would yield a higher proportion of preventable lung cancer deaths (67.1% vs. 57.1%); these results are similar to calculations based on the US population (e.g., 62% and 54%) [24]. However, the risk-based strategy with a fixed risk threshold selected an older population on average (mean age 67.8 years vs. 63.4 years). Thus, even though risk-based screening is more efficient in terms of lung cancer deaths prevented (NNS=177 vs. 205), screening of older individuals might reduce life-years gained per death prevented and therefore cost-effectiveness. Concerns have previously been raised about lung cancer screening among older people, as they are more likely to present with comorbidities and shorter life expectancy [25], increasing the risk of overdiagnosis and overtreatment due to the competitive risks of mortality.

The approach of identifying age-specific risk thresholds might provide appealing trade-offs; however, the thresholds for screening among younger people were very low, with a 5-year lung cancer death risk of 0.36% and 0.64% among 50–54 and 55–59 year-olds, respectively. Prior studies suggest that individuals with very low absolute risk may likely experience more harms from screening with small chance of benefit [19]. Conversely, the high thresholds for older individuals (e.g., 2.57% risk among 70–74 year-olds and 3.46% among 75–79 year-olds) could imply that eligible individuals in older age groups may have a high burden of comorbidities. In the future, prediction models that explicitly prioritize individuals with high life expectancy may provide solutions to these dilemmas [25]. Life expectancy in Brazil is unequal among geographical regions, as the South and Southwest regions had higher life expectancy (77.2 and 76.9 years, respectively) compared with the Northwest (72.6 years) in 2014 [26]. In the United States, the overall life expectancy was higher than in Brazil (78.9 years) [27]; therefore, we would expect that screening the same age range could result in fewer life-years gained in Brazil.

Our analysis included individuals aged 55–79, but our age-stratified results could be used to consider other stopping ages, such as 74 which has been employed in the UK [28]. Other starting ages could also be considered, such as 50 instead of 55, although we estimated that the efficiency of screening is low in this age group. One possible solution to increase screening efficiency and reduce harms for younger individuals without strong risk factors could be to offer longer (e.g., 2-year) screening intervals provided the baseline screen is negative, or to generally offer longer screening intervals based on individual risk [29]. The choice of one of the three strategies is also inherently affected by the possible harms, which we have not quantified here, but would be expected to vary across eligibility strategies. One important limitation of the age-specific thresholds approach is that an individual participant could cross into a new age group and then be below the threshold, after previously being eligible. In practice, it would be preferable that screening continue once initiated, unless stopped due to low life expectancy, patient preferences, or other clinical reasons.

The overall prevalence of tobacco smoking among the adult population in Brazil decreased from 34.8% in 1989 to 10.1% in 2017 [30,31] thanks to the implementation of the MPOWER policies package [32]. Despite this, lung cancer is the leading cause of cancer death in Brazil, responsible for 35,160 deaths in 2020 [33], which has created enthusiasm for implementation of lung cancer screening. However, pulmonary tuberculosis and other granulomatous diseases are highly prevalent in Brazil, raising concerns about false-positives and complexity in nodule management [7]. Further, even though the health system is largely public, access is limited in some regions, and there is a lack of availability of CT scanners for much of the population. One remaining question is whether a single approach to lung cancer screening eligibility could be applied uniformly throughout the country, since there is substantial heterogeneity in life expectancy, smoking prevalence, and available resources across different regions.

Although lung cancer screening has been considered cost-effective in Canada [34], the US [35], and the UK [36], it may still be impractical or inefficient in low and middle resource settings. When available resources are finite, cost-effectiveness considerations point to enhanced focus on tobacco control measures, such as increasing excise taxes and prices on tobacco products, offering support for cessation, and implementing health warning labels on tobacco packaging [30,37]. Thus, developing the capacity to screen all eligible individuals in a high-quality program in resource-limited settings would be challenging. The effectiveness, feasibility and cost-effectiveness of LDCT screening vary among LMICs, as different countries differ in lung cancer epidemiological patterns and the readiness of their healthcare systems. This results in a need for country-specific analyses, including an in-depth evaluation of the quality of delivered cancer care. Moreover, more detailed economic evaluations of lung cancer screening in LMICs are needed [38]. In Brazil, the feasibility of lung cancer screening would be supported by its universally accessible public health system and its globally recognized tobacco control program. There are outpatient smoking cessation services throughout the country, which could be excellent places to identify individuals as eligible for screening. However, thorough analyses of screening harms, cost-effectiveness, and budget impacts still need to be done.

Our study is based on high-quality data sources and validated models to estimate the impact of screening. However, it is subject to important limitations and assumptions. The most important limitation is that we did not estimate harms of lung screening, such as surveillance scans, false-positives, invasive procedures, and overdiagnosis, to compare alongside the potential benefits. We assumed the 20% reduction in lung cancer mortality observed in NLST applies to all potentially eligible current and former smokers in Brazil. We used algorithms that were developed and validated in US data to estimate lung cancer cases and deaths [16]. These models have not yet been validated in Brazil, though we were able to confirm that they predicted a realistic number of deaths (see *Supplementary*). The Vigitel survey does not include information on lung cancer risk factors such as lung disease and family history of cancer, which are included in the full versions of the LCDRAT model. Other data, particularly among former smokers, were also not collected in Vigitel survey and were treated by multiple imputation (see *Supplementary*). Our estimates are generally anchored to the year 2014, but outcomes will evolve over time with changes in population age structure and smoking epidemiology.

Another important limitation relates to the risk model used and its capacity to predict lung cancer deaths in Brazil. LCDRAT was not calibrated for the Brazilian population, which differs from the US population in ways that could affect the performance of the model. There is uncertainty drawing from the fact that the Brazilian mortality statistics include cancers in never-smokers, which the LCDRAT model does not predict, and we therefore had to attempt to quantify using data from a third source (see Supplementary) [39]. A potentially important overestimation of lung cancer deaths for the youngest age group (50–54) cannot be ruled out and further studies may be needed to recalibrate the LCDRAT for the Brazilian setting.

Regarding our assessment of calibration for LCDRAT, we note that mortality information may be subject to missing diagnosis information on death certificates. Although death certificates for other cancers were considered valid in Brazil [40], there is no information on the completeness and accuracy for lung cancer mortality data. Therefore, it is possible that the observed overestimation by LCDRAT actually results from under-ascertainment by the mortality system, which tends to occur more often among older individuals. Thus, it is currently not possible to definitively assess whether the apparent overestimation was caused by the LCDRAT algorithm calibration or by lack of accuracy of death certificates.

In summary, our study provides evidence regarding the potential to avert lung cancer deaths via low-dose CT screening in Brazil. Different strategies for eligibility substantially impact the efficiency of screening and the mean age of the population screened. Our results suggest that implementation of a lung cancer screening program in fifteen capital cities in Brazil could prevent over 2,500 lung cancer deaths by screening approximately 500,000 current and former smokers, although the possible harms of screening were not evaluated here. As the implementation of lung cancer screening proceeds in different countries around the world, our analytical framework can be used to guide further studies that provide country-specific evidence for the choice of eligibility strategies.

## Data sharing statement

*Data used in this study are fully available at* http://svs.aids.gov.br/bases_vigitel_viva/vigitel.php.

## Funding

H. Robbins and M. Johansson were supported by the INTEGRAL project (NCI U19 CA203654). H. Robbins was additionally supported by NCI R03 CA245979.

## Contributions

Conceptualization, funding acquisition, and supervision of the study: AMF, AC and HAR; Data acquisition: AMF, AC, AM; Accessed the raw data: AMF, AM; Methodology: AMF, HC, HAR; Formal analysis and investigation: AMF, HC, LC; Data interpretation: AMF, FB, SV, AC, HAR, LC, MJ, AM; Writing: AMF, HAR; Review and manuscript approval: All Authors.

## Declaration of Competing Interest

The authors declare no competing interests.

## Acknowledgments

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101176.

## References

[1] Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction — evidence, pitfalls and future perspectives. Nat Rev Clin Oncol 2020 [Internet]Oct 12 [cited 2020 Dec 28]; Available from: http://www.nature.com/articles/s41571-020-00432-6.
[2] The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365(5):395–409.
[3] de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020 [Internet]Jan 29 [cited 2020 Feb 3]; Available from: http://www.nejm.org/doi/10.1056/NEJMoa1911793.
[4] Moyer VA, et al. Screening for lung cancer: U.S. preventive services task force recommendation statement. Ann Intern Med 2014;160(5):330–8.
[5] Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. Can Med Assoc J 2016;188(6):425–32.
[6] Marshall HM, Finn N, Bowman RV, Passmore LH, McCaul EM, Yang IA, et al. Cost of screening for lung cancer in Australia. Intern Med J 2019;49(11):1392–9.
[7] dos SRS, JP F, Chate RC, Ghefter MC, Kay F, Trajano ALC, et al. Do current lung cancer screening guidelines apply for populations with high prevalence of granulomatous disease? Results from the first Brazilian lung cancer screening trial (BRELT1). Ann Thorac Surg 2016;101(2):481–8.
[8] Teles GB da S, Macedo ACS, Chate RC, Valente VAT, Funari MB de G, Szarf G. LDCT lung cancer screening in populations at different risk for lung cancer. BMJ Open Respir Res 2020;7(1):e000455.
[9] Duffy SW, Field JK. Mortality reduction with low-dose CT screening for lung cancer. N Engl J Med 2020;382(6):572–3.
[10] Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368(8):728–36.
[11] Katki HA, Kovalchik SA, Petito LC, Cheung LC, Jacobs E, Jemal A, et al. Implications of nine risk prediction models for selecting ever-smokers for computed tomography lung cancer screening. Ann Intern Med 2018;169(1):10–9.
[12] Robbins HA, Callister M, Sasieni P, Quaife SL, Cheung LC, Brennan P, et al. Benefits and harms in the national lung screening trial: expected outcomes with a modern management protocol. Lancet Respir Med 2019;7(8):655–6.
[13] Malta DC, da Silva MMA, de Moura L. Morais Neto OL de. A implantação do Sistema de Vigilância de Doenças Crônicas Não Transmissíveis no Brasil, 2003 a 2015: alcances e desafios. Rev Bras Epidemiol 2017;20(4):661–75.
[14] Vigilância de Fatores de Risco para doenças crônicas não transmissíveis. [Internet]. Available from: https://www.saude.gov.br/saude-de-a-z/vigitel
[15] Schomaker M, Heumann C. Bootstrap inference when using multiple imputation: bootstrap inference when using multiple imputation. Stat Med 2018;37(14):2252–66 Jun 30.
[16] Katki HA, Kovalchik SA, Berg CD, Cheung LC, Chaturvedi AK. Development and validation of risk models to select ever-smokers for CT lung cancer screening. JAMA 2016;315(21):2300. Jun 7.
[17] Tammemägi MC, Katki HA, Hocking WG, Church TR, Caporaso N, Kvale PA, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013;368(8):728–36 Feb 21.
[18] Mortality System Information (SIM). Atlas On-line de Mortalidade . Available from: https://mortalidade.inca.gov.br/MortalidadeWeb/pages/Modelo10/consultar.xhtml;jsessionid=D4773961813F46091E4863E06878431E#panelResultado. Accessed in 02/12/2019.
[19] Kovalchik SA, Tammemagi M, Berg CD, Caporaso NE, Riley TL, Korch M, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013;369(3):245–54.
[20] Lung cancer risk models for screening (R package: lcrisks) [Internet]. Available from: https://dceg.cancer.gov/tools/risk-assessment/lcrisks
[21] US Preventive Services Task Force. Lung cancer screening draft recommendation statement [Internet]. 2020 [cited 2020 Sep 22]. Available from: [Internet]. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/draft-recommendation/lung-cancer-screening-2020.
[22] Pastorino U, Silva M, Sestini S, Sabia F, Boeri M, Cantarutti A, et al. Prolonged lung cancer screening reduced 10-year mortality in the MILD trial: new confirmation of lung cancer screening efficacy. Ann Oncol 2019;30(7):1162–9.
[23] Becker N, Motsch E, Trotter A, Heussel CP, Dienemann H, Schnabel PA, et al. Lung cancer mortality reduction by LDCT screening—results from the randomized German LUSI trial. Int J Cancer 2020;146(6):1503–13.
[24] Larose TL, Meheus F, Brennan P, Johansson M, Robbins HA. Assessment of biomarker testing for lung cancer screening eligibility. JAMA Netw Open 2020;3(3):e200409.
[25] Cheung LC, Berg CD, Castle PE, Katki HA, Chaturvedi AK. Life-gained-based versus risk-based selection of smokers for lung cancer screening. Ann Intern Med 2019.
[26] IBGE, 2017. Esperança de vida ao nascer e Taxa de mortalidade infantil, por sexo. [Internet]. [cited 2021 Aug 7]. Available from: https://sidra.ibge.gov.br/tabela/7362.
[27] Arias E, Heron M, Xu J. United states life tables, 2014. U S Life Tables 2014 2017;66(4):1–64. Available: https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_04.pdf.
[28] NHS England - National Cancer Program. Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography. Available from: https://www.england.nhs.uk/wp-content/uploads/2019/02/targeted-lung-health-checks-standard-protocol-v1.pdf. Accessed 2021 Aug 8.
[29] Robbins HA, Berg CD, Cheung LC, Chaturvedi AK, Katki HA. Identification of candidates for longer lung cancer screening intervals following a negative low-dose computed tomography result. JNCI J Natl Cancer Inst 2019;111(9):996–9.
[30] Overview of tobacco use, tobacco control legislation, and taxation in Brazil. World bank group global tobacco control program. Available from: [Internet]. [cited 2020 Sep 10]. Available from: http://documents1.worldbank.org/curated/en/576421560802645093/pdf/Brazil-Overview-of-Tobacco-Use-Tobacco-Control-Legislation-and-Taxation.pdf.
[31] Levy D, de Almeida LM, Szklo A. The Brazil SimSmoke policy simulation model: the effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation. PLoS Med 2012;9(11):e1001336.
[32] Lee K, Chagas LC, Novotny TE. Brazil and the Framework convention on tobacco control: global health diplomacy as soft power. PLoS Med 2010;7(4):e1000232.
[33] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209–49.
[34] Goffin JR, Flanagan WM, Miller AB, Fitzgerald NR, Memon S, Wolfson MC, et al. Cost-effectiveness of lung cancer screening in Canada. JAMA Oncol 2015;1(6):807–13.
[35] Black WC, Gareen IF, Soneji SS, Sicks JD, Keeler EB, Aberle DR, et al. Cost-effectiveness of CT screening in the national lung screening trial. N Engl J Med 2014;371(19):1793–802 Nov 6.
[36] Hinde S, Crilly T, Balata H, Bartlett R, Crilly J, Barber P, et al. The cost-effectiveness of the Manchester 'lung health checks', a community-based lung cancer low-dose CT screening pilot. Lung Cancer 2018;126:119–24.
[37] WHO GAP Appendix 3:'Best Buys' and other recommended interventions for the prevention and control of noncommunicable diseases. [Internet]. [cited 2021 Jan 4]. Available from: https://www.who.int/ncds/management/WHO_Appendix_-BestBuys.pdf
[38] Edelman Saul E, Guerra RB, Edelman Saul M, Lopes da Silva L, Aleixo GFP, Matuda RMK, et al. The challenges of implementing low-dose computed tomography for lung cancer screening in low- and middle-income countries. Nat Cancer 2020;1(12):1140–52.
[39] Thun MJ, Henley SJ, Burns D, Jemal A, Shanks TG, Calle EE. Lung cancer death rates in lifelong nonsmokers. J Natl Cancer Inst 2006;98(10):691–9.
[40] Miranda Filho AL, Meyer A, Monteiro GTR. Validação da causa básica de óbito por neoplasias selecionadas na microrregião Serrana, Rio de Janeiro, Brasil. Cad Saúde Colet 2014;22(3):246–51.