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Abstract

Screening for lung cancer (LC) by low-dose computed tomography (LDCT) has been demonstrated to reduce LC mortality in randomized clinical trials (RCTs), and its implementation is in preparation in many countries. However, definition of the target population, which was based on various combinations of age ranges and definitions of heavy smoking in the RCTs, is subject to ongoing debate. Using epidemiological data from Germany, we aimed to estimate prevalence of preclinical LC and positive predictive value (PPV) of LDCT in potential target populations defined by age and smoking history. Populations aged 50 to 69, 55 to 69, 50 to 74 and 55 to 79 years were considered in this analysis. Sex-specific prevalence of preclinical LC was estimated using LC incidence data within those age ranges and annual transition rates from preclinical to clinical LC obtained by meta-analysis. Prevalence of preclinical LC among heavy smokers (defined by various pack-year thresholds) within those age ranges was estimated by combining LC prevalence in the general population with proportions of heavy smokers and relative risks for LC among them derived from epidemiological studies. PPVs were calculated by combining these prevalences with sensitivity and specificity estimates of LDCT. Estimated prevalence of LC was 0.3% to 0.5% (men) and 0.2% to 0.3% (women) in the general population and 0.8% to 1.7% in target populations of heavy smokers. Estimates of PPV of LDCT were <20% for all definitions of target populations of heavy smokers. Refined preselection of target populations would be highly desirable to increase PPV and efficiency of LDCT screening and to reduce numbers of false-positive LDCT findings.

KEYWORDS
lung cancer, pack-years, preclinical cancer, predictive value, screening

1 | INTRODUCTION

Lung cancer (LC) is one of the most common cancers worldwide and causes more deaths than any other type of cancer in both men and

women.[1] The use of tobacco products is the main cause of LC, meaning that LC is very preventable,[2-4] and incidence closely mirrors the history of the smoking epidemic in various countries.[5] However, even with complete eradication of tobacco use, the effect of past smoking will remain relevant for many coming decades. For instance, risk for LC was demonstrated to remain >3-fold higher than that of never smokers even after 25 years since quitting,[6] which underlines the importance of efforts to limit the burden of LC deaths by early detection in a curable stage. Screening high-risk individuals for LC has gained momentum after the National Lung Cancer Screening Trial (NLST) demonstrated a 20% reduction in mortality with low-dose computed tomography (LDCT) as compared to X-ray screening.[7] The largest European Screening Trial (NELSON) has also recently demonstrated results in favor of LDCT screening of high-risk individuals,[8] and preparations for the implementation of LDCT-based screening are underway in many countries, including Germany.

Efficiency of screening strongly depends on the sensitivity and specificity of the screening test and the prevalence of the disease in the target population. There is consensus that preselection of high-risk people with increased prevalence of preclinical LC is crucial to make LDCT screening efficient. Given the predominant role of smoking and age for LC risk, randomized trials have used various definitions of heavy smoking, typically defined by a minimum number of pack-years, such as 20 or 30 pack-years (along with excluding former smokers who quit more than 10 or 15 years ago), and various age ranges for selecting high-risk target populations for LDCT screening.[7,9] However, data are scarce on how different selection criteria would translate into positive predictive values (PPVs) and negative predictive values (NPVs) of LDCT, which are crucial metrics regarding efficiency of screening and potential harms due to false-positive results.

Using epidemiological data from Germany, we aimed to estimate prevalences of preclinical LC among potential target populations at high risk for LC screening, defined by various age ranges and various definitions of heavy smoking, and to use these prevalences to estimate expected PPVs and NPVs for LDCT in LC screening. In our analyses, LDCT positivity was defined as any suspicious LDCT result requiring follow-up examination.

2 | MATERIALS AND METHODS

2.1 | Prevalence of preclinical LC in the general population within the potential target age ranges

As a first step, we derived prevalence of preclinical LC in the general population within the potential target age ranges. LC incidence (INC) at a certain age can be expressed as a product of the prevalence of preclinical LC (PREVLC) and the annual transition rate from preclinical to clinically detected LC at that age (TRANS): INC = PREVLC × TRANS. Prevalence of preclinical LC, therefore, can be calculated as the ratio of incidence and annual transition rate, PREVLC = INC / TRANS.

Age- and sex-specific LC incidences per 100 000 individuals together with LC case numbers in 5-year age groups for men and

What's new?

Lung cancer screening using low-dose computed tomography (LDCT) is nearing implementation in various countries. However, defining the target population, particularly which individuals will benefit most from LDCT screening, remains a critical issue. Here, using data from Germany, the authors investigated different combinations of age range and smoking history and examined how well these combinations estimated preclinical lung cancer prevalence. Analyses show that expected positive predictive values of lung cancer screening by LDCT were below 20 percent for heavy smokers, within all age ranges investigated. The findings highlight the need for improved target population preselection for lung cancer screening by LDCT.

women in Germany in 2016 were drawn from the German Center for Cancer Registry Data.[10] The following potential target populations for screening were considered based on age ranges included in various LDCT trials[11]: 50 to 69, 50 to 74, 55 to 69 and 55 to 74 years.

The annual transition rate between preclinical and clinical LC was calculated as a reciprocal value of the mean sojourn time (MST) of LC in the preclinical stage. Bivariate random-effects meta-analysis[12] was used to pool previously reported MST estimates[13] from six CT-based LC early detection trials enrolling men and women of at least 40 years.[14-19] Meta-analysis was performed using the R package *mada*.[20] A summary estimate of 2.34 years (95% CI, 1.66-3.31) was obtained (Supplementary Figure 1), which translates to an annual transition rate of 42.7% (=1/2.34; 95% CI, 30.2-60.2). MST was considered constant across all age groups and both genders in this analysis. Other potential annual transition rates of 30%, 40%, 50%, and 60% were considered in sensitivity analyses.

2.2 | Prevalence of preclinical LC among heavy smokers

Proportions of men and women in Germany with at least 20, 30 and 40 pack-years smoking history were calculated using data from the European Commission's Eurobarometer Survey on smoking conducted in 2017.[21] At least 1 pack-year smoking history was required for the individuals to be classified as ever smokers. Individuals who quit within 1 year of data collection were considered to be current smokers. Among former smokers, only those with the corresponding pack-year smoking history who quit within 10 years were considered as heavy smokers. Such or similar selection criteria have been applied for ex-smokers in various LC screening trials.[11] Individuals with insufficient information to derive pack-years or time of cessation (<8% of data among self-reported current and former smokers) were classified based on self-reported smoking status and these individuals were allocated to the respective

pack-year categories according to the proportions observed among current and former smokers with non-missing information. Population weights provided with the survey data were used for all calculations.

Prevalence of preclinical LC among heavy smokers was estimated from the prevalence of preclinical LC in the general population (PREVLC$_{general\ population}$), the proportion of heavy smokers in the general population (PROP$_{heavy\ smokers}$, derived from the Eurobarometer Survey) and the relative risk (RR) of LC of heavy smokers compared to those not meeting the heavy smoking definition as follows (derivation of the equation can be found in Supplementary Methods):

$$PREVLC_{heavy\ smokers} = \frac{RR*PREVLC_{general\ population}}{RR*PROP_{heavy\ smokers} + (1 - PROP_{heavy\ smokers})}.$$

RRs for LC among individuals with at least 20, 30 and 40 pack-years compared to the complementary groups not meeting these heavy smoking definitions were estimated by combining RR estimates for specific pack-year categories compared to nonsmokers, which were extracted from a pooled analysis of nine case-control studies comprising 13 169 LC cases and 16 010 sex- and age-matched controls,[22] with data on the distribution of those categories in the German population, which were extracted from the Eurobarometer Survey.

2.3 | Sensitivity and specificity of LDCT for LC detection

Estimates of diagnostic performance of LDCT for LC detection are available from randomized clinical trials (RCTs)[7,23] as well as modeling studies. In our main analysis, sensitivity and specificity of LDCT for LC detection were assumed to be 85% and 94%, respectively, in analogy with a previous modeling study.[13] These estimates are consistent with recent data of a German LDCT trial (LUSI), which suggested sensitivity of LDCT screening to be between 83% and 91% in Germany depending on the mode of calculation.[23] Other potential sensitivity

and specificity estimates between 80% and 98% for LDCT screening were considered in sensitivity analyses.

2.4 | PPVs and NPVs

Using standard formulas,[24] we calculated expected sex-specific PPVs and NPVs for LC screening with LDCT among individuals with at least 20, 30 and 40 pack-year smoking history among those aged 50-69, 55-69, 55-69 and 55-79 years based on sensitivities and specificities of LDCT and prevalences of preclinical LC derived as outlined earlier.

3 | RESULTS

3.1 | Prevalence of preclinical LC in the general population

LC prevalence estimates calculated using LC incidence data and assuming an annual transition rate between preclinical and clinical LC of 42.7% are shown in Table 1. Estimates of LC prevalence among men varied between 0.33% among 50- to 69-year-olds and 0.49% among 55- to 74-year-olds. Among women, prevalence estimates were between 0.21% and 0.28% among 50 to 69 and 55 to 74-year-olds, respectively. Other potential annual transition rates between preclinical and clinical LC (ie, 30%, 40%, 50% and 60% that translate to MSTs of 3.33, 2.5, 2.0 and 1.65 years, respectively) resulted in prevalence estimates between 0.15% and 0.69%. For instance, the estimated LC prevalence for men aged 50 to 69 years was 0.47% for a transition rate of 30% and 0.24% for a transition rate of 60%. The corresponding prevalence estimates for women were 0.30% and 0.15%, respectively.

Age-specific prevalence estimates by 5-year age groups are shown in Supplementary Table 1. Prevalence was estimated to be higher for men than for women of all age groups.

TABLE 1 Estimated sex-specific prevalence of preclinical lung cancer in Germany in 2016

Target population age	Incidence per 100 000	Prevalence (%) based on annual transition rate[a] of				
		42.7%[b]	30%[c]	40%[c]	50%[c]	60%[c]
Men						
50 to 69	141.4	0.33	0.47	0.35	0.28	0.24
50 to 74	165.9	0.39	0.55	0.41	0.33	0.28
55 to 69	182.4	0.43	0.61	0.46	0.36	0.30
55 to 74	208.4	0.49	0.69	0.52	0.42	0.35
Women						
50 to 69	90.2	0.21	0.30	0.23	0.18	0.15
50 to 74	99.6	0.23	0.33	0.25	0.20	0.17
55 to 69	112.9	0.26	0.38	0.28	0.23	0.19
55 to 74	120.9	0.28	0.40	0.30	0.24	0.20

[a]Annual transition rate between preclinical and clinically manifested lung cancer used to calculate prevalence estimates.
[b]Main analysis.
[c]Sensitivity analyses.

TABLE 2 Sex-specific proportion of individuals classified by smoking status in Germany in 2017

Target population age	Nonsmoker (%)	Ever smoker (current + former) (%)			
		Total	≥20 PY[a]	≥30 PY[a]	≥40 PY[a]
Men					
50 to 69	43.3	56.7	30.7	21.9	17.7
50 to 74	45.2	54.8	28.2	20.4	16.4
55 to 69	44.4	55.6	28.5	22.4	19.7
55 to 74	46.7	53.3	25.6	20.4	17.6
Women					
50 to 69	59.3	40.7	15.5	11.3	7.5
50 to 74	60.2	39.8	13.8	10.0	6.4
55 to 69	59.7	40.3	14.5	13.4	8.5
55 to 74	60.8	39.2	12.6	11.3	6.9

Note: Estimates derived from the Eurobarometer Survey.[21]
[a]Proportion of individuals with corresponding pack-year smoking history (excluding former smokers who quit >10 years ago).

TABLE 3 PPVs and NPVs of lung cancer screening with computed tomography in Germany after preselection of target population by pack-years

Preselection by	Men			Women		
	Prevalence of LC in preselected population (95% CI[a]) (%)	PPV[b] (95% CI) (%)	NPV[b,c] (%)	Prevalence of LC in preselected population (95% CI[a]) (%)	PPV[b] (95% CI) (%)	NPV[b,c] (%)
Screening population of 50- to 69-year-olds						
≥20 PY	0.88 (0.63-1.25)	11.2 (8.2-15.2)	99.9	0.82 (0.58-1.16)	10.5 (7.7-14.3)	99.9
≥30 PY	0.98 (0.69-1.38)	12.3 (9.0-16.6)	99.8	0.93 (0.66-1.31)	11.7 (8.6-15.9)	99.9
≥40 PY	1.04 (0.74-1.48)	13.0 (9.6-17.5)	99.8	0.99 (0.70-1.40)	12.4 (9.1-16.8)	99.8
Screening population of 50- to 74-year-olds						
≥20 PY	1.11 (0.79-1.57)	13.7 (10.1-18.4)	99.8	0.97 (0.69-1.37)	12.2 (8.9-16.4)	99.8
≥30 PY	1.22 (0.86-1.72)	14.8 (11.0-19.9)	99.8	1.09 (0.77-1.54)	13.5 (9.9-18.1)	99.8
≥40 PY	1.30 (0.92-1.84)	15.7 (11.6-20.9)	99.8	1.17 (0.83-1.65)	14.4 (10.6-19.2)	99.8
Screening population of 55- to 69-year-olds						
≥20 PY	1.20 (0.85-1.70)	14.7 (10.9-19.7)	99.8	1.11 (0.78-1.56)	13.7 (10.1-18.4)	99.8
≥30 PY	1.30 (0.92-1.84)	15.7 (11.6-21.0)	99.8	1.10 (0.78-1.55)	13.6 (10.0-18.2)	99.8
≥40 PY	1.36 (0.96-1.92)	16.3 (12.1-21.7)	99.8	1.15 (0.82-1.63)	14.2 (10.5-19.0)	99.8
Screening population of 55- to 74-year-olds						
≥20 PY	1.50 (1.06-2.12)	17.7 (13.2-23.5)	99.8	1.27 (0.90-1.80)	15.4 (11.4-20.6)	99.8
≥30 PY	1.60 (1.13-2.26)	18.7 (14.0-24.7)	99.7	1.27 (0.90-1.79)	15.4 (11.4-20.6)	99.8
≥40 PY	1.67 (1.19-2.37)	19.4 (14.5-25.6)	99.7	1.35 (0.96-1.91)	16.2 (12.0-21.6)	99.8

Abbreviations: CI, confidence intervals; LC, lung cancer; NPV, negative predictive value; PPV, positive predictive value.
[a]CIs were calculated using CIs for the estimated preclinical lung cancer among the general population, that is, considering the annual transition rate between preclinical and clinical lung cancer of 30.2% and 60.2%.
[b]PPVs and NPVs of low-dose computed tomography screening with sensitivity of 85% and specificity of 94%.
[c]CIs for all NPVs were very close to the displayed values (eg, CI, [99.8-99.9] for the observed value of 99.8) and therefore not displayed in the table.

3.2 | Prevalence of heavy smoking

Proportions of individuals in Germany classified by smoking status are shown in Table 2. Among the four potential target populations for screening differing in age structure, 43% to 47% of men and 59% to 61% of women were nonsmokers. Proportions of men and women with at least 20 pack-year smoking history were 26% to 31% and 13% to 16%, respectively. When considering a higher smoking exposure, 20% to 22% (men) and 10% to 13% (women) had at least 30 pack-year smoking history and 16% to 20% (men) and 6% to 9% (women) had 40 pack-year smoking history.

3.3 | LC risk among heavy smokers

The association of heavy smoking with LC risk, that is, RR for LC among heavy smokers as compared to the complementary groups of individuals not classified as heavy smokers, is shown in Supplementary Table 2. RR estimates for different age ranges and pack-year cutoffs ranged from 4.38 to 10.66 among men and from 6.34 to 9.05 among women.

3.4 | Prevalence of preclinical LC among heavy smokers and PPV of LC screening

Prevalence of preclinical LC among heavy smokers together with PPV and NPV of LC screening with LDCT after preselection of the target population by various pack-year definitions is shown in Table 3. Preselection on high-risk individuals with at least 20, 30 or 40 pack-years for LC screening is expected to result in LC prevalences between 0.88% (20 pack-years, 50 to 69-year-olds) and 1.67% (40 pack-years,

55 to 74-year-olds) among men and between 0.82% and 1.35%, respectively, among women. Expected LC prevalence among heavy smokers did not exceed 1.7% in any of the analyzed populations. Assuming a sensitivity of 85% and a specificity of 94%, screening with LDCT among individuals with at least 20 pack-year smoking history is expected to result in PPVs of 11.2% (men) and 10.5% (women) in the age range of 50 to 69 years. Higher PPVs are expected for higher ages, such as 55 to 74 years (PPV = 17.7% (men) and PPV = 15.4% (women)). Among all analyzed populations, expected PPVs range between 10.5% and 19.4%, with higher PPVs among older populations and with higher pack-year smoking history.

PPVs of the screening with LDCT with sensitivities and specificities between 80% and 98% are demonstrated in Table 4. PPVs in population with LC prevalence of 0.9% were between 3.5% and 4.3% when specificity of LDCT was 80%, between 6.8% and 8.2% for specificity of 90% and between 26.6% and 30.8% for specificity of 98%. Corresponding PPVs in population with 1.5% LC prevalence were 5.7% to 6.9%, 10.9% to 13.0% and 37.9% to 42.7% for specificities of 80%, 90% and 98%, respectively.

TABLE 4 PPVs of low-dose computed tomography screening corresponding to sensitivities and specificities between 80% and 98%

Specificity level (%) of LDCT	Positive predictive value, PPV (%) corresponding to sensitivity of LDCT of									
	80%	82%	84%	86%	88%	90%	92%	94%	96%	98%
Prevalence of lung cancer = 0.9%, that is, equivalent to estimated lung cancer prevalence among 50- to 69-year-old men with at least 20 pack-year smoking history										
98	26.6	27.1	27.6	28.1	28.6	29.0	29.5	29.9	30.4	30.8
96	15.4	15.7	16.0	16.3	16.7	17.0	17.3	17.6	17.9	18.2
94	10.8	11.0	11.3	11.5	11.8	12.0	12.2	12.5	12.7	12.9
92	8.3	8.5	8.7	8.9	9.1	9.3	9.5	9.6	9.8	10.0
90	6.8	6.9	7.1	7.2	7.4	7.6	7.7	7.9	8.0	8.2
88	5.7	5.8	6.0	6.1	6.2	6.4	6.5	6.6	6.8	6.9
86	4.9	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.9	6.0
84	4.3	4.4	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3
82	3.9	4.0	4.1	4.2	4.3	4.3	4.4	4.5	4.6	4.7
80	3.5	3.6	3.7	3.8	3.8	3.9	4.0	4.1	4.2	4.3
Prevalence of lung cancer = 1.5%, that is, equivalent to estimated lung cancer prevalence among 55- to 74-year-old men with at least 20 pack-year smoking history										
98	37.9	38.4	39.0	39.6	40.1	40.7	41.2	41.7	42.2	42.7
96	23.3	23.8	24.2	24.7	25.1	25.5	25.9	26.4	26.8	27.2
94	16.9	17.2	17.6	17.9	18.3	18.6	18.9	19.3	19.6	19.9
92	13.2	13.5	13.8	14.1	14.3	14.6	14.9	15.2	15.5	15.7
90	10.9	11.1	11.3	11.6	11.8	12.1	12.3	12.5	12.8	13.0
88	9.2	9.4	9.6	9.8	10.0	10.3	10.5	10.7	10.9	11.1
86	8.0	8.2	8.4	8.6	8.7	8.9	9.1	9.3	9.5	9.6
84	7.1	7.2	7.4	7.6	7.7	7.9	8.1	8.2	8.4	8.5
82	6.3	6.5	6.6	6.8	6.9	7.1	7.2	7.4	7.5	7.7
80	5.7	5.9	6.0	6.1	6.3	6.4	6.5	6.7	6.8	6.9

Abbreviation: LDCT, low-dose computed tomography.

4 | DISCUSSION

Prevalence of preclinical LC is low even among heavy smokers. We estimated in our study that in potential target populations for screening between 50 and 74 years in Germany, prevalence of LC in men would be 0.9% to 1.5% for those with at least 20 pack-year smoking history and 1.0% to 1.7% for those with at least 40 pack-year smoking history. The corresponding LC prevalences among women with the same smoking history would be 0.8% to 1.3% and 1.0% to 1.4%, respectively. Screening those with at least 20 or more pack-year smoking history as done in the LDCT screening trials would result in PPVs below 20% among potential target populations for screening in Germany, that is, more than 80% of positive LDCT results would be expected to be false positive for any combination of age range and definition of heavy smokers.

Our results are in agreement with and expand previous findings from large RCTs each of which had applied one specific combination of age range and heavy smoking definition as selection criterion. Prevalences of LC between 0.6% (NLST[7]) and 1.2% (LUSI[23]) have been found among study participants in the various trials. In the NLST, an even higher false positivity rate (96.4%, which corresponds to a PPV of 3.6%) was reported, using a definition of LDCT positivity that yielded higher sensitivity (94%) but substantially lower specificity (74%) than those assumed in our main analysis (85% and 94%, respectively).[7] As demonstrated in our sensitivity analyses, PPVs below 4% would also be expected in Germany with such low specificity, even in case of close to perfect sensitivity. In the NELSON trial, an apparently much higher PPV (43.5%) was reported.[8] However, this estimate referred to classification of LDCT findings after follow-up of initial suspicious ("indeterminate") LDCT results by follow-up CT scans after several weeks or months. Recalculation of PPV for all initially positive or indeterminate LDCT findings (among which the indeterminate findings accounted for a majority of 82%), that is, for all findings requiring further follow-up (as done in our analysis) would yield a PPV estimate of 8.0%, which is even lower than the estimates of 10% to 20% derived in our main analyses. Again, this somewhat lower PPV can be explained by the lower LDCT specificity as the one assumed in our main analysis. Taken together, these results imply that our already very low PPV estimates for any combination of age range and heavy smoking definition may rather be too optimistic than too pessimistic, which underlines the importance of better preselection of target populations for screening.

Smoking history undoubtedly is the most relevant factor to identify high-risk individuals for screening as tobacco smoking contributes to the development of up to 90% of LC.[4,25] Nevertheless, only a small proportion of smokers, even with a long smoking history, will develop LC.[26] Despite that, screening for LC was recommended right after the demonstrated successful mortality reduction by NLST trial[7] among those with at least 30 pack-year smoking history in the United States. European countries will follow shortly, after having awaited findings from the NELSON trial where reduction in LC mortality was confirmed very recently.[8]

Despite the evidence in mortality reduction among the heavy smokers, the question on how to best identify the target population for screening remains open. Multiple studies showed that only approximately 20% to 30% of LC patients would have been eligible for screening with NLST criteria, meaning that 70% to 80% of LC would be missed by screening.[27-36] LC screening recommendations in the United States are now in the process to be changed to screen a larger proportion of the population that might reduce the number of potentially missed LC. The new suggested recommendation lowered the bar for both age (starting at 50 instead of 55 years) and the smoking history (at least 20 instead of 30 required pack-year history).[37] The 20 pack-year eligibility criterion was also used in the majority of the LC screening trials in Europe.[38-41] In the German LUSI trial, the same way as in the NELSON trial, heavy smoking was defined as continued smoking of ≥15 or ≥10 cigarettes per day for at least 25 or 30 years (which translates to at least 18.75 and 15 pack-years), respectively. With lowering the threshold of smoking exposure for qualifying as heavy smoker, a larger proportion of the population including a larger proportion of LC cases becomes eligible for screening (Supplementary Table 3). At the same time, however, as demonstrated in our analyses (see Table 3), this will further reduce prevalence of LC and PPV in the population eligible for LC screening.

Given the limitations of preselecting people for LC screening based on smoking history and age alone, and given the tradeoff between reducing the proportion of missed LC cases and further lowering the PPV of LDCT scans by relaxing smoking history based screening eligibility criteria, alternative approaches have been proposed based on more comprehensive individual risk stratification. LC risk models incorporating information on smoking history together with sociodemographic factors, personal and family history of cancer, history of other lung diseases such as emphysema and chronic obstructive pulmonary disease (COPD) and many more have demonstrated enhanced LC risk prediction compared to risk prediction based on smoking history alone.[42-44] LC prevalence was slightly higher but still rather low (1.7%) in the baseline findings of the UK screening trial that included individuals identified to be at larger risk for LC by the Liverpool Lung Project risk model.[45] Nevertheless, risk-based LC screening models, possibly along with environmental and occupational exposure risk assessment, have potential to improve the preselection of high-risk individuals for screening. The same applies for novel biomarkers that might be combined with risk factor information for enhanced risk stratification. Search for such enhanced risk stratification should therefore be intensified in order to make LDCT based screening more efficient and to reduce the numbers of false positive results, their adverse psychological consequences for screenees as well as potential harms and complications, use of healthcare system resources and costs of follow-up examinations. From a practical perspective, ideal candidates for biomarkers might be markers that can be determined in biospecimen that are routinely collected in medical practice, such as blood samples. For example, recent research has demonstrated that the combination of epigenetic signatures of smoking history in peripheral blood with self-reported smoking history may enhance prediction of LC risk compared to self-reported smoking history alone.[46] Other biomarker candidates for enhanced preselection of LDCT-based screening might be novel breath sample-based signatures[47] if promising results from preliminary studies can be confirmed by thorough validation. In addition, liquid biopsies performed in combination with positive LDCT results may also help to reduce the frequency of false-positive screening results.

Our study has several limitations that need to be addressed. Firstly, LC prevalence was estimated based on mean length of the preclinical disease phase (MST). MST estimates between 3 months[48] and a few years[13,49] have been reported from chest X-ray and CT-based studies, with shorter MST estimates from the chest X-ray-based studies. Given that LDCT is more accurate and therefore superior to chest X-ray for LC screening,[50] we focused on data from the CT-based studies only. We used MST estimates calculated by Chien et al[13] as these were not available from the original studies. Because MST was calculated using the same approach in all studies, differences between estimates should not be affected by the underlying calculations but rather reflect differences in individual study designs and patients characteristics.

Secondly, we used the same estimate of MST across both genders and all ages as available subgroup-specific data are still sparse. Slightly higher annual transition rates between preclinical and clinical LC have been reported for women than for the men.[51] In addition, more pronounced differences in MST could be expected for histological subtypes of LC than for age or sex. For instance, more aggressive small cell LC may have shorter MST than slow-growing cancers.[48] More studies would be needed in this area to obtain detailed estimates of MST for LC development in various populations.

Thirdly, our calculations were restricted to epidemiological data from Germany. Nevertheless, similarly low PPVs would also be expected in countries with different smoking prevalences and LC incidence rates.

Finally, diagnostic performance parameters of LDCT were based on data from the literature. To be consistent, we used the same assumption for LDCT performance (ie, sensitivity = 85%, specificity = 94%) as was used for estimation of MST for LC in the study reporting MST for preclinical LC.[13] Specificity of LDCT turned out to be even lower, however, in trials published since then which may explain the even lower PPVs observed in these trials. A higher sensitivity of LDCT-based classification generally comes with a reduction in both specificity and PPV and vice versa. Higher PPVs at no loss or even increase in sensitivity could only be achieved by developing either better screening exams or better preselection criteria for high-risk individuals for LC screening.

In summary, the prevalence of asymptomatic screening-detectable LC among heavy smokers is low despite heavy smoking being a very strong risk factor for LC. Preselection of screenees by age and heavy smoking alone is expected to result in PPVs <20%, regardless of the specific definition of age range and heavy smoking. Further research should aim for better preselection of the target populations for LDCT screening, for example, by more refined risk scores or inclusion of informative biomarkers, in order to focus LDCT-based screening on populations with higher LC prevalence. More refined preselection of screenees should aim at achieving both more complete identification of people with preclinical LC, as well as reduction of unnecessary screenings of people without LC in order to increase the PPV of LDCT-based screening and thereby reduce the number of false-positive test results and their adverse consequences.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. U.S. Department of Health and Human Services. *The Health Consequences of Smoking: A Report of the Surgeon General*. Atlanta, Georgia: U.S. Public Health Service; 2004.
3. U.S. Department Of Health Human Services. *How Tobacco Smoke Causes Disease: the Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, Georgia: U.S. Public Health Service; 2010.
4. Mons U, Gredner T, Behrens G, Stock C, Brenner H. Cancers due to smoking and high alcohol consumption estimation of the attributable cancer burden in Germany. *Dtsch Arztebl Int*. 2018;115:571-577.
5. Brenner H, Krilaviciute A. Commonly applied selection criteria for lung cancer screening may have strongly varying diagnostic performance in different countries. *Cancers (Basel)*. 2020;12:3012.
6. Tindle HA, Stevenson Duncan M, Greevy RA, et al. Lifetime smoking history and risk of lung cancer: results from the Framingham heart study. *J Natl Cancer Inst*. 2018;110:1201-1207.
7. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med*. 2011;365:395-409.
8. de Koning HJ, van der Aalst CM, de Jong PA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med*. 2020;382:503-513.
9. Field JK, van Klaveren R, Pedersen JH, et al. European randomized lung cancer screening trials: post NLST. *J Surg Oncol*. 2013;108:280-286.
10. German Centre for Cancer Registry Data, Robert Koch Institute: Database Query with estimates for cancer incidence, prevalence and survival in Germany, based on data of the population based cancer registries https://doi.org/10.18444/5.03.01.0005.0014.0001 2019.
11. Pinsky PF. Lung cancer screening with low-dose CT: a world-wide view. *Transl Lung Cancer Res*. 2018;7:234-242.
12. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58:982-990.
13. Chien CR, Chen TH. Mean sojourn time and effectiveness of mortality reduction for lung cancer screening with computed tomography. *Int J Cancer*. 2008;122:2594-2599.
14. Sone S, Li F, Yang ZG, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. *Brit J Cancer*. 2001;84:25-32.

15. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet*. 2003;362:593-597.

16. Diederich S, Thomas M, Semik M, et al. Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. *Eur Radiol*. 2004; 14:691-702.

17. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the lung screening study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer*. 2005;47:9-15.

18. Novello S, Fava C, Borasio P, et al. Three-year findings of an early lung cancer detection feasibility study with low-dose spiral computed tomography in heavy smokers. *Ann Oncol*. 2005;16:1662-1666.

19. Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, Miettinen OS. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med*. 2006;355:1763-1771.

20. Doebler P. R package 'mada', vol. 2020, 2015.

21. European Commission and European Parliament, Brussels (2017): Eurobarometer 87.1, TNS opinion, Brussels [producer]. GESIS Data Archive, Cologne. ZA6861 Data file Version 1.2.0, doi:https://doi.org/10.4232/1.12922.

22. Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer—relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer*. 2012;131: 1210-1219.

23. Becker N, Motsch E, Trotter A, et al. Lung cancer mortality reduction by LDCT screening: results from the randomized German LUSI trial. *Int J Cancer*. 2020;146:1503-1513.

24. Fletcher RH, Fletcher SW, Fletcher GS. *Clinical Epidemiology: the Essentials*. 5th ed. Philadelphia, the US: Lippincott Williams & Wilkins; 2013.

25. Centers for Disease Control and Prevention. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, Georgia: Centers for Disease Control and Prevention; 2010.

26. Crispo A, Brennan P, Jockel KH, et al. The cumulative risk of lung cancer among current, ex- and never-smokers in European men. *Brit J Cancer*. 2004;91:1280-1286.

27. Kumar V, Becker K, Zheng HX, Huang Y, Xu Y. The performance of NLST screening criteria in Asian lung cancer patients. *BMC Cancer*. 2015;15:916.

28. Laisaar T, Sarana B, Benno I, Laisaar KT. Surgically treated lung cancer patients: do they all smoke and would they all have been detected with lung cancer screening? *ERJ Open Res*. 2018;4:00001-2018.

29. Lee YJ, Choi SM, Lee J, et al. Utility of the National Lung Screening Trial Criteria for estimation of lung cancer in the Korean population. *Cancer Res Treat*. 2018;50:950-955.

30. Li CC, Matthews AK, Dong XQ. Examination of chronic smoking behavior and eligibility for low-dose computed tomography for lung cancer screening among older Chinese male smokers. *J Gerontol Series Biol Sci Med Sci*. 2017;72:S22-S25.

31. Nemesure B, Plank A, Reagan L, Albano D, Reiter M, Bilfinger TV. Evaluating efficacy of current lung cancer screening guidelines. *J Med Screen*. 2017;24:208-213.

32. Wang Y, Midthun DE, Wampfler JA, et al. Trends in the proportion of patients with lung cancer meeting screening criteria. *J Am Med Assoc*. 2015;313:853-855.

33. Wu GX, Goldstein L, Kim JY, Raz DJ. Proportion of non-small-cell lung cancer patients that would have been eligible for lung cancer screening. *Clin Lung Cancer*. 2016;17:E131-E139.

34. Yang P, Wang Y, Wampfler JA, et al. Trends in subpopulations at high risk for lung cancer. *J Thorac Oncol*. 2016;11:194-202.

35. Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? *J Med Screen*. 2012; 19:154-156.

36. Gracie K, Kennedy M, Ellames D, et al. What proportion of patients with lung cancer would have been eligible for CT screening according to various proposed inclusion criteria? *Thorax*. 2016;71:A76-A77.

37. U.S. Preventive Services Task Force. Draft Recommendation Statement. Lung Cancer: Screening, 2020.

38. Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. *Eur J Cancer Prev*. 2012;21:308-315.

39. Infante M, Cavuto S, Lutman FR, et al. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. *Am J Respir Crit Care Med*. 2015;191:1166-1175.

40. Paci E, Puliti D, Pegna AL, et al. Mortality, survival and incidence rates in the ITALUNG randomised lung cancer screening trial. *Thorax*. 2017;72:825-831.

41. Wille MM, Dirksen A, Ashraf H, et al. Results of the randomized Danish lung cancer screening trial with focus on high-risk profiling. *Am J Respir Crit Care Med*. 2016;193:542-551.

42. Raji OY, Duffy SW, Agbaje OF, et al. Predictive accuracy of the liverpool lung project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. *Ann Intern Med*. 2012;157:242-250.

43. Weber M, Yap S, Goldsbury D, et al. Identifying high risk individuals for targeted lung cancer screening: independent validation of the PLCOm2012 risk prediction tool. *Int J Cancer*. 2017;141:242-253.

44. Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: prostate, lung, colorectal and ovarian cancer screening trial models and validation. *J Natl Cancer Inst*. 2011;103:1058-1068.

45. Field JK, Duffy SW, Baldwin DR, et al. UK lung cancer RCT pilot screening trial: baseline findings from the screening arm provide evidence for the potential implementation of lung cancer screening. *Thorax*. 2016;71:161-170.

46. Zhang Y, Elgizouli M, Schottker B, Holleczek B, Nieters A, Brenner H. Smoking-associated DNA methylation markers predict lung cancer incidence. *Clin Epigenetics*. 2016;8:127.

47. Nardi-Agmon I, Peled N. Exhaled breath analysis for the early detection of lung cancer: recent developments and future prospects. *Lung Cancer Targets Ther*. 2017;8:31-38.

48. Chien CR, Lai MS, Chen TH. Estimation of mean sojourn time for lung cancer by chest X-ray screening with a Bayesian approach. *Lung Cancer*. 2008;62:215-220.

49. Wu D, Erwin D, Rosner GL. Sojourn time and lead time projection in lung cancer screening. *Lung Cancer*. 2011;72:322-326.

50. van Beek EJ, Mirsadraee S, Murchison JT. Lung cancer screening: computed tomography or chest radiographs? *World J Radiol*. 2015;7:189-193.

51. Wang D, Levitt B, Riley T, Wu W. Estimation of sojourn time and transition probability of lung cancer for smokers using the PLCO data. *J Biometr Biostat*. 2017;8:360.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.