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Cost-utility analysis of a potential lung cancer screening program for a high-risk population in Germany: A modelling approach

Florian Hofer[a,*], Hans-Ulrich Kauczor[b], Tom Stargardt[a]

[a] Hamburg Center for Health Economics (HCHE), University of Hamburg, Esplanade 36, 20354 Hamburg, Germany
[b] Department of Diagnostic and Interventional Radiology, University Hospital Heidelberg, Germany

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ABSTRACT

Background: Lung cancer is the leading cause of cancer death in Germany. Although several randomized trials in Europe have evaluated the effectiveness of lung cancer screening programs, evidence on the cost-effectiveness of lung cancer screening is scarce.
Objective: To evaluate the cost-effectiveness of a population-based lung cancer screening program from the perspective of a German payer.
Methods: We conducted a cost-effectiveness analysis from the public payer perspective for a high-risk population defined as heavy former and current smokers (≥20 cigarettes per day) between 55 and 75 years of age. The underlying model consisted of two Markov models. We differentiated between a population-based annual screening program and standard clinical care. Depending on stage at diagnosis, simulated patients were assigned to one of five treatment paths according to the German clinical guideline for the diagnosis and treatment of lung cancer. Costs, life years saved, and quality adjusted life years (QALYs) were used as outcomes. Values for input parameters were taken from the literature. The model was run for 60 cycles with a cycle length of three months. Deterministic and probabilistic sensitivity analyses were conducted.
Results: In the base case, annual lung cancer screening led to an increase in incremental costs (€ 1,153 per person) compared to standard clinical care. However, the screening approach was associated with an incremental gain in life years (0.06 per person) and QALYs (0.04 per person). Thus, the incremental cost-effectiveness ratio (ICER) was € 19,302 per life year saved and € 30,291 per QALY. A probabilistic sensitivity analysis with 10,000 draws resulted in average ICERs of € 22,118 per life year and € 34,841 per QALY.
Conclusion: We provide evidence that lung cancer screening for a high-risk population may be more effective, but also more costly, than standard clinical care from the perspective of a German payer.

1. Introduction

Lung cancer remains the leading cause of cancer-related death and the most common form of cancer worldwide [1,2]. Its incidence is highest in elderly current or former smokers [3,4]. Five-year survival is substantially increased if lung cancer is diagnosed at an early stage [5], for example through population-based screening.

The National Lung Screening Trial (NLST) in the United States reported a relative reduction in lung cancer mortality of 20% in association with an annual population-based screening program using low-dose computed tomography (LDCT) [6]. LDCT is the method of choice due to its lower radiation dose compared to standard computed tomography (CT) and its ability to detect smaller nodules compared to x-ray scans [7]. Following approaches similar to the NLST, randomized trials have been conducted in several European countries, including Germany [8–14]. Their findings suggest that annual screening using low-dose CT is effective for early diagnosis of lung cancer [10,15,16]. Moreover, evidence from the International Early Lung Cancer Action Project (I-ELCAP) – a pooled analysis of several international observational studies – suggests that lung-cancer screening may achieve a stage shift and reduce mortality [17,18].

Several studies on the cost-effectiveness of lung cancer screening have been conducted to date, albeit primarily in the US and Canada, where the cost of care differs substantially from that in Europe [19–23]. For example, ten Haaf et al. report treatment costs for the initial care phase for stage III lung cancer patients ranging from approximately CAN$ 30,000 to CAN$ 50,000 [24], while corresponding costs for Germany are estimated to be € 20,000 (~CAN$ 30,000) [25].

* Corresponding author.
E-mail address: florian.hofer@uni-hamburg.de (F. Hofer).

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Similarly, costs for CT chest examinations are reported to be two to three times higher in the US (~US$ 200 – US$ 300) than in Germany (~US$ 75) [19,22,26]. Evidence from Germany is limited to a study by Treskova et al. which focuses primarily on comparing the NLST and NELSON trial screening protocols. Using microsimulation, treatment costs based on UK cost data, and a high adherence rate compared to other cancer screening programs, the authors calculate incremental cost-effectiveness ratios (ICERs) between € 16,754 and € 23,847 per life year gained, depending on the screening protocol [27].

German statutory health insurers currently reimburse several cancer screening programs (e.g. for breast cancer, prostate cancer, and skin cancer) but do not include lung cancer screening in their reimbursement scheme. This study therefore aims to evaluate the potential cost-effectiveness of a population-based lung cancer screening program using LDCT from a payer perspective.

2. Methods

The key advantage of lung cancer screening programs is that they make it possible to diagnose patients at an early stage of disease [6]. Capturing this in a model requires simulating the period of disease progression before diagnosis (i.e. the natural history of disease) and, separately, the treatment of lung cancer and aftercare [28]. To do so, we combined two Markov models covering both periods. Costs, life years gained, and quality-adjusted life years (QALYs) were chosen as outcomes. We ran the model for an annual LDCT-based lung cancer screening program and for diagnosis through standard clinical care (i.e. when the patient becomes symptomatic).

We considered individuals aged between 55 and 75 to be eligible for the screening program. This age range is similar to that recommended in US lung cancer screening guidelines and also reflects the data used to parametrize our model. This yielded a simulated cohort of 1,600,270 people, which according to a combination of data from the Federal Statistical Office and the nationwide Epidemiological Survey on Addiction equals the number of heavy current and former smokers (≥20 cigarettes per day) aged 55 to 75 within the German system of statutory health insurance (approximately 89% of the German population) [29,30]. However, the underlying data contained no information about the duration of heavy smoking habits and may – although based on best empirical evidence – be an overestimation of the number of people eligible. Prior to the first cycle, we estimated the starting distribution of the population according to data from the first screening round of the German LUSI trial [15].

We chose a cycle length of three months and ran the model for 60 cycles (i.e. 15 years). Half-cycle correction was applied [31]. Costs and quality-adjusted life years were discounted by 3% per year. Model calculations were conducted using the “heemod” package for R statistics [32]. The calibration of model parameters was performed with Microsoft Excel [33].

2.1. Model structure

We used a cohort-based Markov model because lung cancer is a non-communicable disease and there was no need to account for interaction between individuals [34]. The structure of the model was informed by recent studies evaluating the cost-effectiveness of different cancer interventions and on feedback from radiologists and experts in modelling [23,28,35]. As noted above, our model consisted of two separate components to distinguish between (a) the natural history of disease and (b) treatment paths and aftercare depending on patients’ lung cancer stage at diagnosis (see Fig. 1).

The natural history component of our model consisted of seven states, representing lung cancer stages I to IV, a state of no apparent lung cancer, and a state for death. Lung cancer stages IIIa and IIIb were modelled separately because of different treatment regimens [36]. The lung cancer stages in the natural history model thus represent the hypothetical stages into which the lung cancer would be classified if it were diagnosed within the current cycle. Individuals who developed lung cancers may (a) progress to any higher stage, (b) remain in their current stage, (c) get diagnosed or (d) die within the current cycle. Transition probabilities between lung cancer states and incidence rates were estimated using Bayesian calibration methods and German incidence data from the German Centre for Cancer Registry Data [37–39]. We set up a Metropolis Hastings algorithm with 50,000 runs and a “burn in” of 10,000 runs [33,40].

After diagnosis, the simulated patients entered the second component of our model, in which we estimated treatment and aftercare. This included five states for treatment (i.e., surgery alone; a combination of surgery and chemotherapy; a combination of surgery, chemotherapy and radiotherapy; a combination of chemotherapy and radiotherapy; and palliative care), four states for aftercare (which differ in the risk of death, local recurrence or distant metastases), and a state for death. The patients were assigned to treatment paths based on lung cancer stage at diagnosis. Treatment paths were designed in accordance with German clinical practice guidelines [36]. Estimates of treatment allocation were based on the Italian ITALUNG trial and expert opinion as data from the German LUSI trial were not available [11]. For example, we assumed that 90% of stage I patients were treated with surgical resection alone, 5% with a combination of surgical resection and chemotherapy, and 5% with a combination of surgical resection, chemotherapy and radiotherapy (see Table 1 for further details).

After entering the aftercare states, patients were at risk of local recurrence or distant metastases [41]. In these cases, we assumed patients were treated by a combination of chemo- and radiotherapy or received palliative care. In any of the states, all individuals were at risk of all-cause mortality.

The probability of being diagnosed and thus entering the second component of our model differed between individuals who (a) took part in the annual LDCT-based lung cancer screening program or (b) were diagnosed through standard clinical care (i.e., when they became symptomatic). Individuals in the cohort receiving standard clinical care could only be diagnosed when they developed symptoms such as cough, hemoptysis or fatigue that had been identified through a physician visit related to the symptoms. Since the model ran in three-month periods, one quarter of the participants in the screening cohort could also be diagnosed through annual CT screening in each period if they were adherent. Annual screening was assumed to follow the same screening protocol as that in the German LUSI trial, which focused on nodule size and volume doubling time (VDT) [13]. For a simplified presentation of the screening algorithm applied in the LUSI trial, see Fig. 2.

2.2. Model parameters

2.2.1. Screening effectiveness and early recall rates

Screening effectiveness was estimated using reported screening sensitivity per lung cancer stage and tumor type from ten Haaf et al., weighted by the reported distribution of tumor types in the NELSON trial [10,42]. We accounted for adherence, which was assumed to be equal to the average adherence of established cancer screening programs in Germany (such as those for breast cancer, skin cancer and prostate cancer) [43]. Early recall rates (as defined in Section 2.2.3) were taken from the German LUSI trial. The authors reported an early recall rate without subsequent lung cancer diagnosis of approximately 21% for the initial screening round and a reduction to approximately 4.5% for all consecutive screening rounds [15]. All estimations for screening effectiveness and early recall rates are given in Table 1.

2.2.2. Mortality

We assumed that all-cause mortality would not differ between the two cohorts. Mortality rates for individuals without apparent lung cancer were derived from mortality tables for the general population in Germany [44] and were allowed to vary across time [45]. Because only

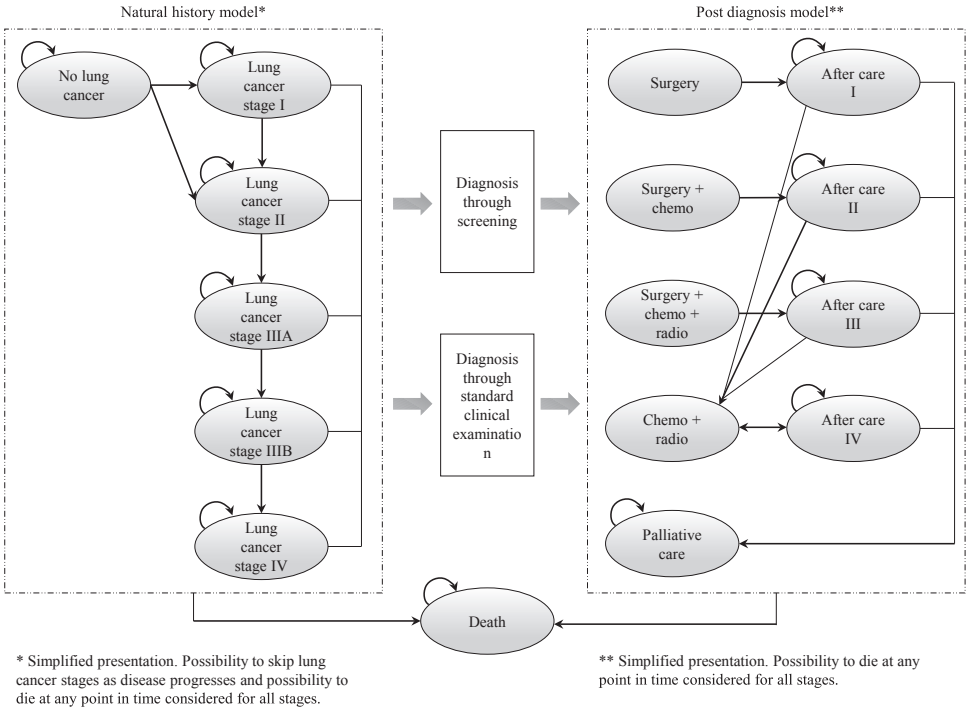

Fig. 1. Markov models for natural history and post-diagnosis.

former and current heavy smokers were eligible for the screening program, mortality rates were adjusted using a time-dependent hazard ratio [46].

For lung cancer states in the natural history component of our model, we used mortality rates calibrated by the Metropolis Hastings algorithm using priors informed by results of a systematic review [47]. Results from another systematic review were used to estimate mortality rates for the treatment and aftercare component of our model [5].

2.2.3. Measurement of costs for diagnostic procedures

In the cohort receiving standard clinical care, diagnosis consisted of several procedures recommended in German clinical practice guidelines [36]. There were fewer diagnostic procedures in this cohort because individuals receiving standard clinical care must first develop symptoms and subsequently actively consult a physician about these. The costs of diagnosis in this cohort totaled approximately € 356 and comprised (a) an examination of past medical history (€ 28.22), (b) a chest x-ray (€ 8.87) and lump sum payment for the radiologist (€ 5.58), (c) sonography (€ 16.38), (d) a contrast-enhanced CT scan (€ 92.67), (e) an MRI scan for further staging (€ 126.59) in 80% of patients, and (f) bronchoscopy in an outpatient setting (€ 103.11). Prices were taken from the German outpatient reimbursement catalogue [26].

To estimate costs in the screening program, we assumed that each participant would receive a consultation with a radiologist and a non-enhanced low-dose CT scan (€ 68.88). For costing, we again used data from the German outpatient reimbursement catalogue. In addition, we added a lump sum of € 30 per case to represent the additional costs typically incurred in structured screening programs, such as those for documentation. Similar lump sums have been applied in established screening programs in Germany in the past (e.g. in mammography screening) [26]. In cases where the first scan showed abnormities, the participant was either placed on early recall (3–6 months after the initial CT scan) or referred immediately to a pulmonologist. Participants placed on early recall underwent an additional CT scan and a second consultation with a radiologist (€ 98.88). If the second CT scan confirmed a positive result, the patient was referred to a pulmonologist (€ 28.22) (see Fig. 2). The same costs applied to patients who had been referred to a pulmonologist immediately. For more detailed information on the proportion of early recalls and immediate referrals see Table 1. Independent of whether the participant had been referred to a pulmonologist immediately or after a second CT scan, 80% of patients were assumed to undergo an MRI scan for further staging and a bronchoscopy in an outpatient setting. The same costs were assumed for patients who had been recalled immediately but were not subsequently diagnosed with lung cancer – the only difference being that we assumed, based on the results of the German LUSI trial (see Table 1), that only a small proportion of these patients received unnecessary bronchoscopies (0.49% of participants for the first screening round and 0.18% for all consecutive screening rounds) [15].

Costs for diagnosis in the screening setting thus totaled (a) € 198 for each screening participant who had been assigned to early recall and received a negative result after a second CT, (b) € 430 for participants who had been assigned to early recall and received a positive result after a second CT, and (c) € 331 for participants who were referred immediately to a pulmonologist.

2.2.4. Measurement of costs for treatment and aftercare

There was no difference in the costs of treatment and aftercare for participants in the screening program or patients receiving standard clinical care. Inpatient costs for the five treatment paths were estimated according to Schwarzkopf et al. (inflated to reflect 2016 prices), who reported costs for lung cancer treatment using administrative data from a major German statutory health insurer [25]. Because Schwarzkopf et al. used a different subdivision of treatments, we consulted the authors to validate our estimations based on their study. For palliative care, we assumed that 50% of patients underwent chemotherapy and 50% received best supportive care. Note that costs for palliative care as stated in Table 1 occurred every cycle. Costs for aftercare were assumed to be € 100 per cycle. This assumption was based on the costs of procedures reported in the German clinical practice guideline for lung cancer diagnosis and treatment [36].

2.2.5. Quality of life

Methods for assessing quality of life in lung cancer patients vary widely, differ in quality, and lead to a wide range of reported values [48,49]. We applied pooled quality of life scores taken from a meta-

Table 1
Input Parameters.

Parameter	Base-case value	Distribution	Reference
Costs (in €)			
CT (thorax)	68.88	Gamma	[26]
lump sum for CT screening	30	Gamma	Assumption based on [26]
contrast agents CT (thorax)	23.79	Gamma	[26]
Lump sum consultation radiologist	5.58	Gamma	[26]
Lump sum medical history (pulmonologist)	28.22	Gamma	[26]
X-ray (thorax)	8.87	Gamma	[26]
Sonography	16.38	Gamma	[26]
MRT	126.59	Gamma	[26]
Bronchoscopy	103.11	Gamma	[26]
Surgery	14,400	Gamma	[25]
Surgery + chemotherapy	20,450	Gamma	[25]
Surgery + chemotherapy + radiotherapy	26,000	Gamma	[25]
Chemotherapy + radiotherapy	21,300	Gamma	[25]
Palliative care (per cycle)	6,300	Gamma	[25]
After care (per cycle)	100	Gamma	Assumption
Utilities			
Natural history model			
All states	0.891	Beta	[51]
Post diagnosis model			
Disutility for unnecessary bronchoscopy	−0.03	Beta	[23,53]
Surgery	0.825	Beta	[48]
Surgery + chemotherapy	0.825	Beta	[48]
Surgery + chemotherapy + radiotherapy	0.772	Beta	[48]
Chemotherapy + radiotherapy	0.573	Beta	[48]
Palliative care	0.573	Beta	[48]
After Care I	0.825	Beta	[48]
After Care II	0.825	Beta	[48]
After Care III	0.772	Beta	[48]
After Care IV	0.573	Beta	[48]
Transition probabilities			
Natural history model			
No apparent lung cancer to lung cancer stage I	0.0050	Dirichlet (based on beta distribution)	Model calibration, [38,39]
No apparent lung cancer to lung cancer stage II	0.1×10^{-7}	Dirichlet (based on beta distribution)	Model calibration, [38,39]
No apparent lung cancer to death	time dependent	Dirichlet (based on beta distribution)	[44]
Lung cancer stage I to stage II	0.3558	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage I to stage IIIA	0.0328	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage I to stage IIIB	0.1×10^{-7}	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage I to stage IV	0.0869	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage I to diagnosis	0.0246	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage I to death	0.1544	Dirichlet (based on beta distribution)	Model calibration, [38,47]
Lung cancer stage II to stage IIIA	0.2480	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage II to stage IIIB	0.0060	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage II to stage IV	0.1290	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage II to diagnosis	0.0270	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage II to death	0.1231	Dirichlet (based on beta distribution)	Model calibration, [38,47]
Lung cancer stage IIIA to stage IIIB	0.2246	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage IIIA to stage IV	0.1455	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage IIIA to diagnosis	0.0811	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage IIIA to death	0.1527	Dirichlet (based on beta distribution)	Model calibration, [38,47]
Lung cancer stage IIIB to stage IV	0.0336	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage IIIB to diagnosis	0.5177	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage IIIB to death	0.1853	Dirichlet (based on beta distribution)	Model calibration, [38,47]
Lung cancer stage IV to diagnosis	0.6584	Dirichlet (based on beta distribution)	Model calibration, [38,39]
Lung cancer stage IV to death	0.2978	Dirichlet (based on beta distribution)	Model calibration, [38,47]
Post diagnosis model			
Surgery to death	0.0407	Dirichlet (based on beta distribution)	[5]
Surgery + chemotherapy to death	0.0438	Dirichlet (based on beta distribution)	[5]
Surgery + chemotherapy + radiotherapy to death	0.0765	Dirichlet (based on beta distribution)	[5]
Chemotherapy + radiotherapy to death	0.1052	Dirichlet (based on beta distribution)	[5]
Palliative care to death	0.1416	Dirichlet (based on beta distribution)	[5]
After Care I to death	0.0407	Dirichlet (based on beta distribution)	[5]
After Care II to death	0.0438	Dirichlet (based on beta distribution)	[5]
After Care III to death	0.0765	Dirichlet (based on beta distribution)	[5]
After Care IV to death	0.1052	Dirichlet (based on beta distribution)	[5]
After Care I to chemotherapy + radiotherapy	0.0053	Dirichlet (based on beta distribution)	[41]
After Care II to chemotherapy + radiotherapy	0.0064	Dirichlet (based on beta distribution)	[41]
After Care III to chemotherapy + radiotherapy	0.0081	Dirichlet (based on beta distribution)	[41]
After Care IV to chemotherapy + radiotherapy	0.0081	Dirichlet (based on beta distribution)	[41]
After Care I to palliative care	0.0081	Dirichlet (based on beta distribution)	[41]
After Care II to palliative care	0.252	Dirichlet (based on beta distribution)	[41]
After Care III to palliative care	0.0448	Dirichlet (based on beta distribution)	[41]
After Care IV to palliative care	0.0448	Dirichlet (based on beta distribution)	[41]
Distribution of treatments per lung cancer stage			

(*continued on next page*)

Table 1 (*continued*)

Parameter	Base-case value	Distribution	Reference
Stage I			
Surgery alone	0.9	Dirichlet (based on beta distribution)	Assumption based on [11]
Surgery + Chemo.	0.05	Dirichlet (based on beta distribution)	Assumption based on [11]
Surgery + Chemo. + Radio.	0.05	Dirichlet (based on beta distribution)	Assumption based on [11]
Stage II			
Surgery + Chemo.	0.8	Dirichlet (based on beta distribution)	Assumption based on [11]
Surgery + Chemo. + Radio.	0.2	Dirichlet (based on beta distribution)	Assumption based on [11]
Stage IIIA			
Surgery + Chemo. + Radio.	0.2	Dirichlet (based on beta distribution)	Assumption based on [11]
Chemo. + Radio.	0.8	Dirichlet (based on beta distribution)	Assumption based on [11]
Stage IIIB			
Chemo. + Radio.	0.5	Dirichlet (based on beta distribution)	Assumption based on [11]
Palliative Care	0.5	Dirichlet (based on beta distribution)	Assumption based on [11]
Stage IV			
Palliative Care	1		Assumption based on [11]
Screening Parameters (%)			
Adherence	0.5400	Beta	[43]
Sensitivity Stage I	0.4339	Beta	[42]
Sensitivity Stage II	0.4692	Beta	[42]
Sensitivity Stage IIIA	0.6910	Beta	[42]
Sensitivity Stage IIIB	0.7709	Beta	[42]
Sensitivity Stage IV	0.9781	Beta	[42]
Early recall rates/ immediate referrals first round	0.2135	Beta	[15]
Proportion early recalls	0.8825	Beta	[15]
Proportion immediate referrals	0.1175	Beta	[15]
Proportion without subsequent diagnosis	0.9599	Beta	[15]
Early recall rate/ immediate referrals subsequent rounds	0.0453	Beta	[15]
Proportion early recalls	0.6601	Beta	[15]
Proportion immediate referrals	0.3399	Beta	[15]
Proportion without subsequent diagnosis	0.9037	Beta	[15]
Unnecessary bronchoscopies first round	0.0049	Beta	[15]
Unnecessary bronchoscopies subsequent rounds	0.0018	Beta	[15]

analysis by Sturza [48]. These had been used in the same manner in previous cost-effectiveness analyses of lung cancer prevention initiatives [22,28]. Following that approach, quality of life scores for late-stage lung cancer patients in our model were comparable to those reported for German patients [50]. For people without a lung cancer diagnosis, we used baseline quality of life scores for people aged between 55 and 75 years in Germany [51]. We did not adjust quality of life scores for screened individuals who had been assigned to early recall in our base case scenario because indeterminate results did not impact the quality of life reported by the NLST [52]. However, impairment of quality of life for patients undergoing unnecessary bronchoscopies was taken into account following the approach of Mahadevia et al. and a systematic review by Earle et al. [23,53].

2.3. Sensitivity analysis

We conducted seven deterministic one-way sensitivity analyses to examine model sensitivity to different parameters. To do so, rates of newly developed cancers (equal to the underlying population risk), adherence, early recall rates, and costs for screening were varied by +/- 50%. Furthermore, we simulated a variation in the intervention by assuming biennial or semi-annual screening intervals and altered the time horizon (to 10 and 20 years respectively) and discount rate. In addition, a Monte Carlo simulation with 10,000 repetitions was

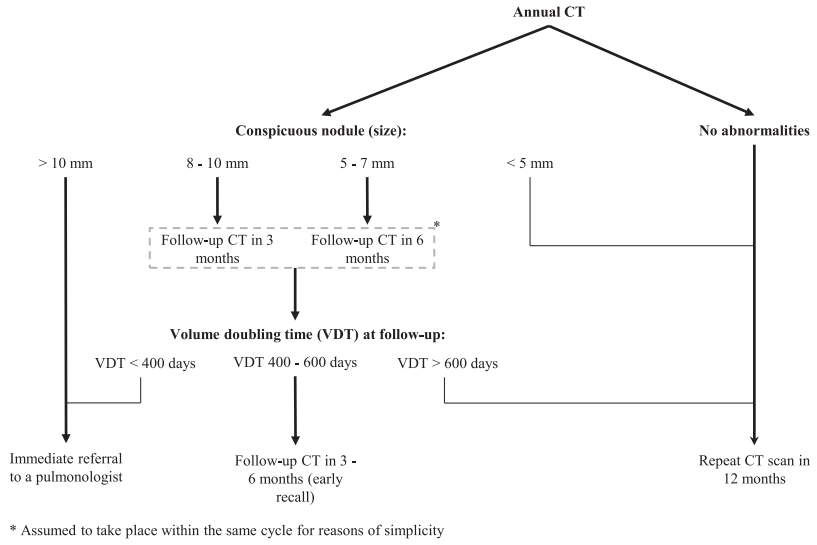

Fig. 2. Screening algorithm.

Table 2
Resource consumption.

Procedure	Frequency (over 15 years)	
	standard care cohort	screening cohort
CT screening sessions	–	9,398,585
early recalls	–	*547,834*
true positives	–	*76,588*
Surgery	11,570	36,365
Surgery + chemotherapy	10,850	26,658
Surgery + chemotherapy + radiotherapy	13,606	24,228
Chemotherapy + radiotherapy	16,880	15,763
Palliative care (number of patients)	106,286	98,442

performed to account for heterogeneity. Input parameters were randomly drawn from beta, gamma or Dirichlet distributions (see Table 1) [54,55].

3. Results

Following the intention-to-treat approach, our model suggested a surplus of 0.06 life years (0.04 QALYs) per person in the screening cohort compared to those receiving standard clinical care. The average costs per person amounted to € 2,787 in the standard clinical care cohort and € 3,940 in the screening cohort. The difference was attributable mainly to screening costs associated with the high number of CT scans in the screening cohort (9,398,585 over 15 years, see Table 2). Based on the assumption of an eligible population of 1,600,270 people in Germany, our simulation resulted in an incremental gain of 95,581 life years (60,906 QALYs) and an incremental budget impact of € 1.84 billion for the screening program over 15 years. The higher costs of screening were due to the screening itself (about 71% of the difference) but also to treatment (27%) and aftercare (2%) for substantially higher numbers of diagnoses at an early stage. Compared to standard clinical care, the ICERs for an annual screening program were € 19,302 per life year saved and € 30,291 per QALY gained.

Fig. 3 shows model sensitivity for the abovementioned parameters. Overall, model results were robust with no variation exceeding ~€ 31,000 per life year gained or ~€ 48,000 per QALY gained. The highest sensitivity was observed for the rate of newly developed cancers, especially in cases where this rate was lower than calibrated by the Metropolis Hastings algorithm. Screening intervals (i.e. biennial or semi-annual) and the cost of screening also had a relatively large influence on the ICERs, especially in the cost-utility analysis. In contrast, variations in early recall rates changed the ICERs to a smaller degree. If a longer time horizon (i.e., 20 years) would be chosen the ICERs would decrease to € 16,260 per life year and € 27,176 per QALY respectively.

After 10,000 repetitions, the Monte Carlo simulation revealed average ICERs of € 22,118 per life year and € 34,841 per quality adjusted life year, both of which are above our base case ICERs (Fig. 4).

4. Discussion

We provide evidence on the cost-effectiveness and cost-utility of a population-based lung cancer screening program for a high-risk population comprising current and former heavy smokers. To our knowledge, we are the first to do so using cost data from a German payer and treatment algorithms based on a German lung cancer screening trial. According to our base case, the program leads to higher costs but also to a gain in life years and QALYs. Although there is no official cost-effectiveness threshold in Germany for accepting or rejecting health interventions, the program would be regarded as cost-effective according to the threshold used by the World Health Organization (WHO) (~€ 48,000 per QALY) [56]. Sensitivity analysis suggests that our results are robust.

Compared to the ICERs for established cancer screening programs in Germany, the ICERs in our base case analysis appear to be at a level that would be acceptable to German health insurers. A cost-utility analysis for colorectal cancer screening, for example, reported an ICER of € 12,200 per QALY [57], and a cost-effectiveness analysis for cervical cancer screening reported an ICER of € 28,400 per life year gained [58]. Changing our interval for screenings suggested that a biennial screening approach would be less cost-effective than an annual approach (€ 24,594 per life year gained and € 38,694 per QALY gained), while a semi-annual screening interval led to lower ICERs (€ 16,711 per life year gained and € 26,076 per QALY gained). This is in concordance with the findings of a recently published Canadian study [24]. However, another Canadian study, which incorporated quality of life, found biennial screening intervals to be superior to annual screening intervals [59].

Several previous cost-effectiveness studies have yielded similar results for high-risk populations, albeit in Canada and the US. A recently published German microsimulation reported ICERs between € 16,754 and € 23,847 per additional life year depending on the screening protocol [27]. They did not report ICERs after quality adjustment of life years. Aside from their different modelling approach, the difference between our ICERs and those reported by Treskova et al. is attributable mainly to distinct assumptions regarding adherence rates, time horizon of lung cancer screening and estimated costs. For example, Treskova et al. included costs for positron emission tomography (PET), which is not generally reimbursed by German statutory health insurers in an outpatient setting. Nevertheless, some lung cancer patients may have access to PET. If we were to assume that 10% of lung cancer patients in our model undergo PET scans, our ICERs would increase by approximately € 600. Further differences are due to the estimation of costs for lung cancer treatment. Whereas Treskova et al. based their cost estimation on UK cost data, we chose to use claims data from a German statutory health insurer as reported and validated by Schwarzkopf et al. Furthermore, Treskova et al. assumed in their base case that a lung cancer screening sessions would cost €150, while we assumed a cost of € 99. A recently published cost-effectiveness study from Switzerland reported ICERs between € 24,972 and € 48,369 per life year gained and between € 35,674 and € 69,099 per QALY gained, depending on the evaluated screening scenario [60]. While Switzerland is comparable to Germany in terms of health care delivery, it is less so in terms of reimbursement rates and hence health care costs.

US and Canadian studies that included results from the NLST found LDCT screening to be cost-effective, with ICERs of US$ 34,000 per life year gained [24], US$ 58,000 per life year gained [19], US$ 28,300 per QALY [22] and US$ 81,000 per QALY [19]. In contrast, older studies that did not consider results from the NLST were inconclusive, reporting ICERs of US$ 19,000 per life year gained [21] and US$ 144,000 to 207,000 per QALY [20]. One explanation for our lower ICERs is the substantially lower cost of health care in Germany, which leads to lower costs for early recalls, treatment and lung cancer screening sessions.

In our model, lung cancer screening led to a 2.25% reduction in all-cause mortality after 5 years. After 15 years, this number fell to 0.83%. The largest international trial, the NLST, reported a 20% reduction of lung cancer specific mortality and a 6.7% reduction of all-cause mortality [6]. Incorporating the adherence rate of the NLST (90%) for the screening cohort into our model (adherence in base case: 54%) would result in a 3.54% reduction of 5-year (all-cause) mortality. These findings are in line with Treskova et al. and Tomonaga et al., who found lung cancer specific mortality reduction in German and Swiss screening settings to be substantially lower than that of the NLST [27,60].

Early recall rates and false positive results are a major concern in cancer screening programs [61]. The LUSI trial reported lower early recall rates (approximately 21% for the initial screening round and approximately 4.5% for subsequent rounds) than the NLST, which is probably due to a more rigorous screening protocol [6,15]. The NELSON trial and the DLCST, which used screening protocols similar to

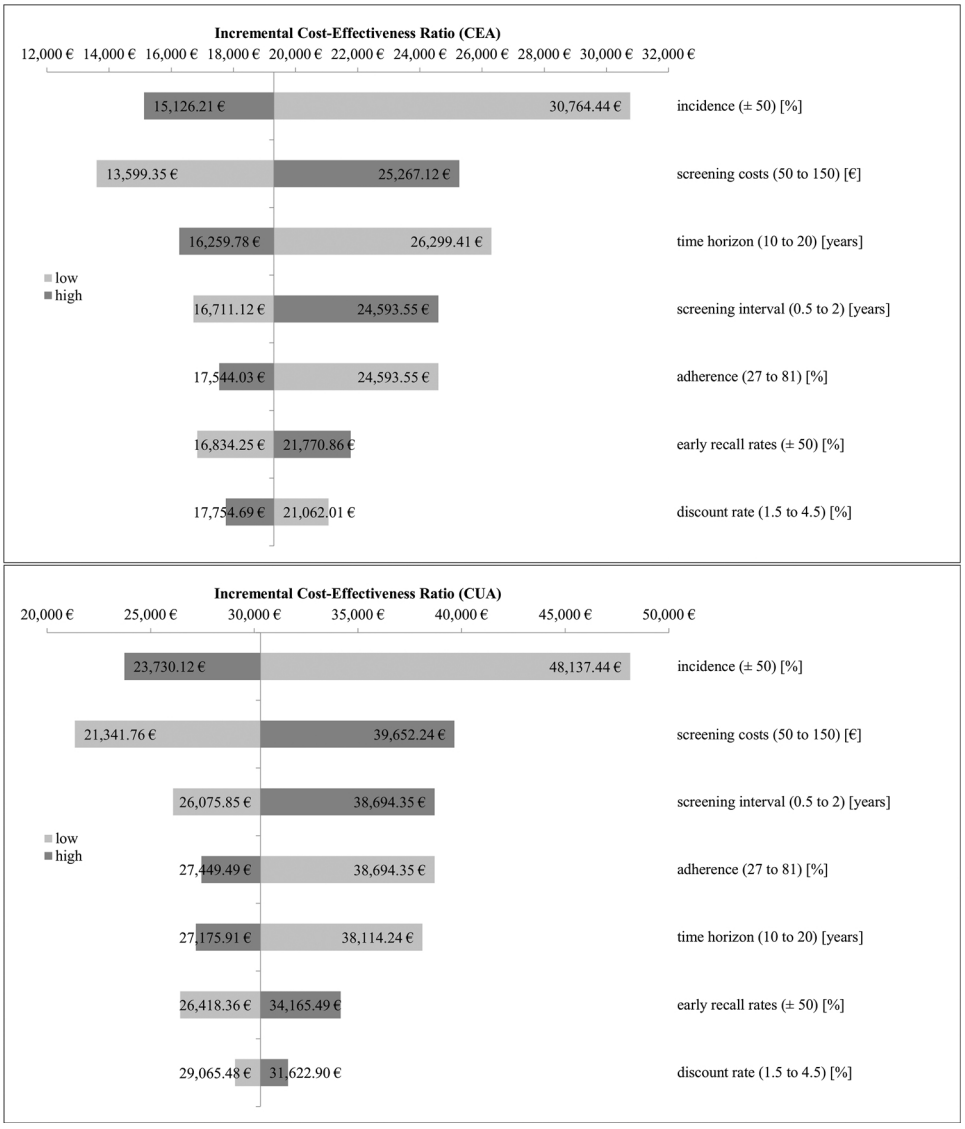

Fig. 3. Tornado diagrams.

those in the LUSI trial, reported even lower early recall rates [16,62]. As a result, our estimation of early recall rates can be regarded as conservative. In our model, the screening program led to 547,834 early recalls. Applying the early recall rates seen in the NLST (23%), the NELSON trial (approximately 19% for initial screening round and approximately 1% for subsequent rounds) and the DLCST (approximately 8% for initial screening round and approximately 2% for subsequent rounds) would result in 2,069,394, 254,901 and 212,817 early recalls in our simulation, respectively. The corresponding ICERs per QALY would be € 52,065, € 26,106 and € 25,556.

Within the CUA component of our study, the influence of early recalls was captured in two dimensions: (a) additional costs due to repeated CT examinations and (b) dis-utilities due to mental stress associated with retrospectively unnecessary biopsies [23,53]. Based on the findings of the NLST, we assumed that there were no dis-utilities for patients with indeterminate screening results [52]. If we allowed for dis-utilities caused by indeterminate results of 0.015 or 0.03, however, the corresponding ICERs per QALY gained would increase to € 30,381 and € 32,185 compared to standard clinical care.

There are also practical issues in implementing a population-based lung cancer screening program. First, it is questionable how quickly population-based CT screening could become accessible in Germany, especially in rural areas. This is important, as there is evidence that screening uptake is correlated with physician density and distance between screening participants and providers [63]. Before implementing such a program, it would thus be necessary to ensure that the infrastructure in place could guarantee sufficient access or could be improved to do so at a reasonable cost. Second, the fact that this program would serve only a high-risk population of smokers with self-inflicted health risks might pose a political hurdle. German statutory health insurers are not allowed to distinguish between high-risk and low-risk individuals when calculating premiums. Because resources for health care are finite, providing additional services for people with self-inflicted health risks – even if doing so is cost-effective – might prove controversial among the general public [64].

Our model has several important limitations. First, we did not include the effect of cumulative radiation exposure on screening participants [65]. Attending annual LDCT screenings over 15 years with an assumed average radiation dosage of 1.5 mSv would result in an additional cumulative radiation exposure of 22.5 mSv per patient [66]. However, due to additional radiation exposure caused by subsequent examination of potential cases of lung cancer, the cumulative radiation dosage may be substantially higher in total [67]. Nevertheless, recent studies suggest that the potential benefits of lung cancer screening in preventing death are higher than the potential harm of increased radiation exposure [68,69]. Second, due to a lack of data we were neither

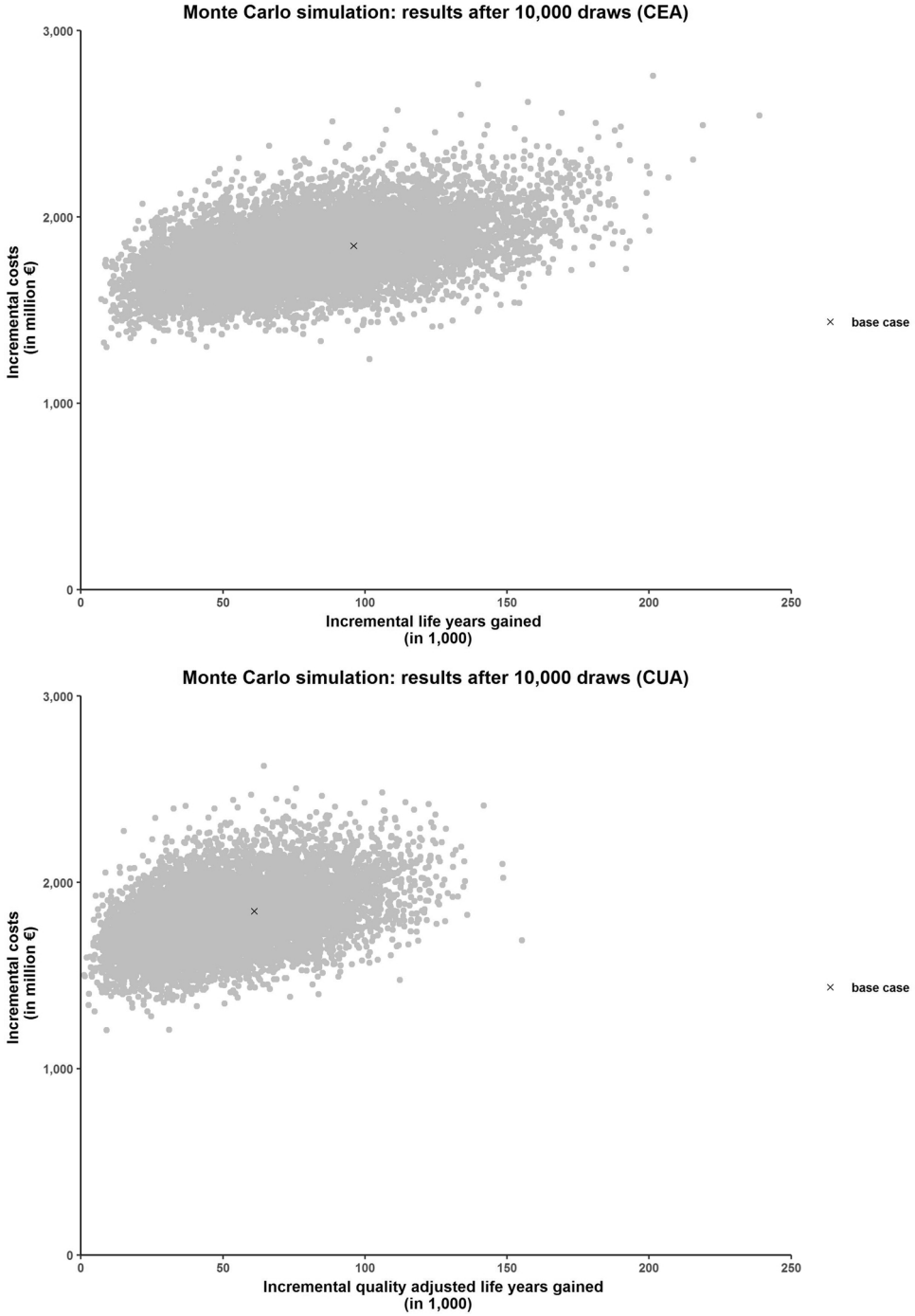

Fig. 4. Probabilistic sensitivity analyses.

able to determine the actual duration of heavy smoking behavior, nor the time passed since individuals changed their (heavy) smoking habits. This may affect the number of people eligible for screening and thus total budget impact / total life years saved. Furthermore, our base case results regarding resource consumption (e.g. number of early recalls, number of screening sessions) have to be interpreted with caution, as they are highly dependent on the underlying properties of our cohort [24,27]. However, to most extend changes of the underlying properties of our cohort and its influence on the ICERs were most likely captured within our sensitivity analyses. Third, health behavior may be affected by introducing a lung cancer screening program. For example, the NELSON trial found that individuals with negative screening results were more adherent, thus leading to selection issues. Moreover, current smokers were more likely to participate in subsequent screening rounds, indicating that lung cancer screening programs might be perceived as a "health reassurance" for high-risk individuals [62]. In contrast, a study investigating the effect of telling people their lung age before a smoking cessation intervention found that a substantial portion of individuals with a favorable lung age quit smoking after the intervention. The authors assumed that smokers might recognize that it is not too late to stop smoking [70].

Fourth, due to our cohort-based modelling approach, we were not able to reliably estimate the number of potentially overdiagnosed individuals, which is a major concerns regarding (lung) cancer screenings [61]. Treskova et al. estimated that overdiagnoses may account for between 9 and 22 percent of total lung cancer diagnoses, depending on

the modelled screening scenario [27]. Fifth, diagnosis and treatment for small cell lung cancer (SCLC) was not modelled separately. These were, however, implicitly included because incidence was reported within European and US RCTs and in the cost data by Schwarzkopf et al. [6,8,11,15,16,25,62,71]. However, because SCLC is associated with high treatment costs even after early diagnosis, our model may underestimate the cost of treatment. Given a prevalence of SCLC within the European RCTs of 5% and 14% [15,16], the impact of not having modelled diagnosis and treatment of SCLC on our results is likely to be low. Sixth, the prevalence of so called "grey screenings" is unknown. Some insured individuals may have access to full dose CT scans beyond a screening program for various reasons [72]. If the proportion of these individuals were high, it would mean that our model would overestimate the incremental effect of a structured LDCT-screening program in terms of life years / QALYs gained and costs. Seventh, using payer data from 2015 may have led us to underestimate the cost of chemotherapy because new agents have entered the market since then. For example, the number of personalized therapies, which are associated with substantially higher costs for payers, is increasing. Incorporating a 50% increase in expenses for all treatment paths associated with chemotherapeutic agents results in ICERs of € 20,334 per life year gained and € 31,911 per QALY gained, respectively. Eighth, as our cohort is 64 years old on average, we did not consider indirect costs due to sick pay. Given the cohort model approach it is not possible to reliably estimate the proportion of lung cancer patients that are still part of the workforce at the moment of their diagnosis. Finally, we implicitly assumed that individuals in the screening cohort did not change their radiologist. As mentioned by Becker et al., the reported drop in early recall rates may be lower if the choice of radiologist is at the patient's discretion [15]. However, as shown by our one-way sensitivity analyses, the effect of a smaller drop in early recall rates is small as it does not affect screening sensitivity.

5. Conclusion

We provide evidence that a population-based lung cancer screening program in Germany for heavy smokers using low-dose computed tomography is more effective, but also more costly, than standard clinical care. Compared to established screening programs and the WHO threshold for cost-effectiveness analyses, the intervention would be cost-effective. The budget impact of the intervention, however, would be high, totaling € 1.84 billion over 15 years. Moreover, the cost-effectiveness of the intervention is due to heavy smokers having a much higher likelihood of developing lung-cancer – a behavioral aspect of the intervention that might represent a political challenge to its implementation. Future research may benefit from using patient-level data from ongoing RCTs to analyze the cost-effectiveness of the screening program for different subgroups of patients.

Author contributions

FH contributed to the study design, statistical analysis, interpretation of results, synthesis and drafting of the manuscript. TS contributed to the study design and statistical analysis. All authors contributed to the interpretation of results and the critical revision of the manuscript. All authors take responsibility for the accuracy and integrity of the data analysis.

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Conflict of interests

All authors declare that they have no conflicts of interest.

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