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Cost-effectiveness of risk model-based lung cancer screening in smokers and nonsmokers in China

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Abstract

Background China bears the largest global burden of lung cancer, with a striking 40% of cases occurring in individuals who have never smoked. While the mortality-reducing benefits of low-dose computed tomography (LDCT) for lung cancer screening are established, the quest for an optimal screening strategy continues, considering the potential adverse effects of LDCT. The Chinese NCC-LCm2021 model was developed based on a nationwide population to identify at-risk individuals among smokers and nonsmokers. However, the cost-effectiveness of this model has yet to be determined.

Methods The cost-effectiveness analysis simulates a Chinese birth cohort using a calibrated Markov model based on individual data from a prospective cohort of the Guangzhou Lung Cancer Screening Program. Health utility was extracted from the literature. Cost parameters were obtained from the price of basic medical services in public medical institutions. Our analysis evaluated 236 distinct screening strategies, varying by screening initiation age, risk thresholds, and smoking status. The primary outcomes were quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs).

Results For smokers, four strategies on the efficiency frontier yielded incremental QALYs ranging from 0.011 to 0.039 compared to no screening, with ICERs ranging from $21,874 to $55,038 when compared to the previous efficient strategies. The optimal strategy was annual screening of smokers aged 45 years and older with a 3-year risk of lung cancer incidence of 0.55%, offering the largest gain in QALYs at a willingness-to-pay (WTP) threshold of $38,224 (three times GDP per capita). This optimal strategy dominated the 2023 Chinese guideline-recommended strategy. For nonsmokers, the strategies on the efficiency frontier yielded incremental QALYs ranging from 0.006 to 0.041 compared to no screening, with ICERs ranging from $26,517 to $37,994 when compared to the previous efficient strategies. Correspondingly, the optimal strategy is annual screening of nonsmokers aged 45 years and older with a 3-year risk of lung cancer incidence of 0.20%.

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Conclusions This economic evaluation found that lung cancer screening strategies based on the Chinese NCC-LC_{m2021} model were cost-effective for both smokers and non-smokers in China. Furthermore, tailoring risk thresholds to smokers and nonsmokers can enhance the cost-effectiveness of lung cancer screening.

Keywords Lung cancer, Screening, Cost-effectiveness, Risk prediction model

Background

China has an important cancer prevalence with lung cancer being the leading cause of cancer-related death [1]. Low-dose computed tomography (LDCT) screening has shown to reduce lung cancer mortality [2]. However, it has significant side effects that includes overdiagnosis, false positives, and increased cancer incidence due to radiation exposure [3]. To balance the trade-off between benefits and harms, the US Preventive Services Task Force (USPSTF) recommends annual screening for lung cancer with LDCT in high-risk patients aged 50 to 80 years with a 20 pack-year smoking history and currently smoke or have quit within the past 15 years by proving its cost-effectiveness [4, 5]. The 2023 Chinese guidelines for low-dose CT screening for lung cancer recommend annual screening for people aged 50 years and older with a smoking history of at least 20 pack-years [6]. Nonsmokers are excluded from LDCT screening based on previous studies showing that the unnecessary costs and harms outweigh the health benefits of screening in nonsmokers in the USA [7]. However, as the incidence of lung cancer among non-smokers has been sharply increasing in China and Asia over the past few decades, screening high-risk non-smokers is crucial to controlling the burden of lung cancer among Asians [8].

Therefore, developing validated criteria to accurately identify high-risk individuals for lung cancer, regardless of smoking status, is critically important in China. Numerous studies have shown that risk prediction models exhibit potential advantages in optimizing lung cancer screening criteria [9–12]. The combination of all the significant risk factors into one algorithm results in a personalized risk score that reflects the individual risk of lung cancer incidence or mortality by using various risk prediction models. Scholars have developed various risk prediction models tailored to diverse populations both domestically and internationally. The classic traditional model, such as, the Bach model and the PLCOm2012 model in the USA [13], the LLP risk model in the UK [14], and the PanCan model in the Canada [15], have demonstrated fine predictive performance. Based on these models, researchers explored the optimal risk thresholds for screening eligibility by cost-effectiveness analysis from the healthcare perspectives of the USA, UK, and Canada, respectively [16–18]. Similarly, Chinese researchers conducted a cost-effectiveness analysis for lung cancer screening in smokers based on the Henan Risk prediction model from Chinese healthcare perspective and recommended risk threshold for high risk population for LDCT screening [19]. However, compared to various lung cancer risk prediction models developed from regional smoking population in China, including the Henan Risk prediction model, the NCC-LCm2021 model stands out for its establishment on 1.5 million nationwide Chinese population and rigorous external validation [19–26]. The model has demonstrated its excellent capacity to predict lung cancer risk effectively not only in smokers but also in non-smokers. In addition, the modeling study recommended thresholds for model application (model-recommended strategy): ≥ 0.47% for nonsmokers and ≥ 0.51% for smokers. These risk thresholds were determined on the basis of obtaining relevant mortality benefits, but no further cost-effectiveness studies were available [23].

While previous studies have examined LDCT lung cancer screening eligibility for smokers in China [27–31], optimal risk threshold remains undefined for non-smokers. To address this gap, we conducted a cost-effectiveness analysis using the largest Chinese population risk-based prediction model and individual data from a prospective cohort. Our aim was to optimize screening strategies for both smokers and non-smokers in China.

Methods

Cohort characteristics

This study was based on the Guangzhou Lung Cancer Screening Program, which targeted smokers and non-smokers who met the specified criteria. The program recruited 11,708 participants between December 2015 and July 2021. Eligible participants were Guangzhou residents aged 40–74, excluding those diagnosed with lung cancer within the past 5 years. The research team recruited participants through various methods, including distributing leaflets, conducting inquiries via telephone and television broadcasts, holding regular health forums on lung cancer screening, and collaborating with community-based organizations for outreach and referrals. Demographic data, smoking history, occupational exposure history, personal and family medical history, and current health status were collected via questionnaires. Details of this screening program have been published previously [32]. The study cohort included 5966 nonsmokers and 2541 smokers. For each risk threshold

defining the at-risk population, we calculated the corresponding cohort proportion. Additionally, we determined the lung cancer incidence rates (per 100,000 person-years) for different risk groups among the screened smokers and non-smokers, as detailed in Additional file 1: Tables S1 and S2, respectively.

Study design

Utilizing data from a representative cohort within the Guangzhou Lung Cancer Screening Program, we constructed a semi-Markov state-transition decision mode. The base scenario simulated smokers or never-smokers to assess the cost-effectiveness of a risk model-based screening strategy compared with no screening. The rationale for this study is described in Fig. 1. In the screening strategy, individuals aged 45 to 74 were subjected to a 3-year lung cancer risk stratification, categorizing them into low- and high-risk groups based on their predicted risk. This stratification employed various hypothetical minimum risk thresholds to identify the high-risk populations. Those in the high-risk group were screened annually using LDCT, with positive findings leading to clinical intervention. In contrast, the low-risk group was not recommended for further screening. This analysis was performed using TreeAge Pro Healthcare 2020 (Williamstown, MA) [33].

Risk prediction models

We assessed an individual's risk of developing lung cancer over a 3-year period using the China NCC-LCm2021 risk prediction model. For non-smokers, the model incorporates key risk factors such as age, sex, body mass index (BMI), family history of lung cancer among first-degree relatives, and a history of chronic respiratory diseases. For smokers, the model also considers smoking-related risk predictors, such as daily cigarettes smoked and years of smoking. In addition, we externally validated the Chinese NCC-LCm2021 model based on the Guangzhou Lung Cancer Screening Program cohort, which showed an area under the receiver operating characteristic curve (AUC) of 0.66, further confirming the usability of the model in the study cohort. Detailed validation methods could be found in Additional file 1: Method S1.

Risk model–based screening strategy

Based on population characteristics and model differences, we considered a range of clinically relevant 3-year risk thresholds for lung cancer incidence in two different populations within the screening cohort. For non-smokers, the risk threshold ranges from 0.2 to 0.7%, while for smokers, it extends from 0.2 to 1.7%. The overall risk was higher in the smoking population compared to the non-smoking population due to differences in model parameters and the fact that the smoking model increased smoking-related risk. In comparison to non-screening and full-screening approaches, programs that operate within these specified risk thresholds have consistently demonstrated a positive net benefit and reasonable calibration [23]. We also examined the potential advantages associated with varying screening start ages. For smokers and non-smokers, we considered ages 45, 50, 55, and 60 years. Eligibility for annual lung cancer screening was determined by meeting the age criteria and exceeding the 3-year risk thresholds for the respective strategy. Based on these risk thresholds and screening initiation ages, we identified 108 risk model-based screening strategies for non-smokers and 128 for smokers. The model-recommended strategy by previous research of screening

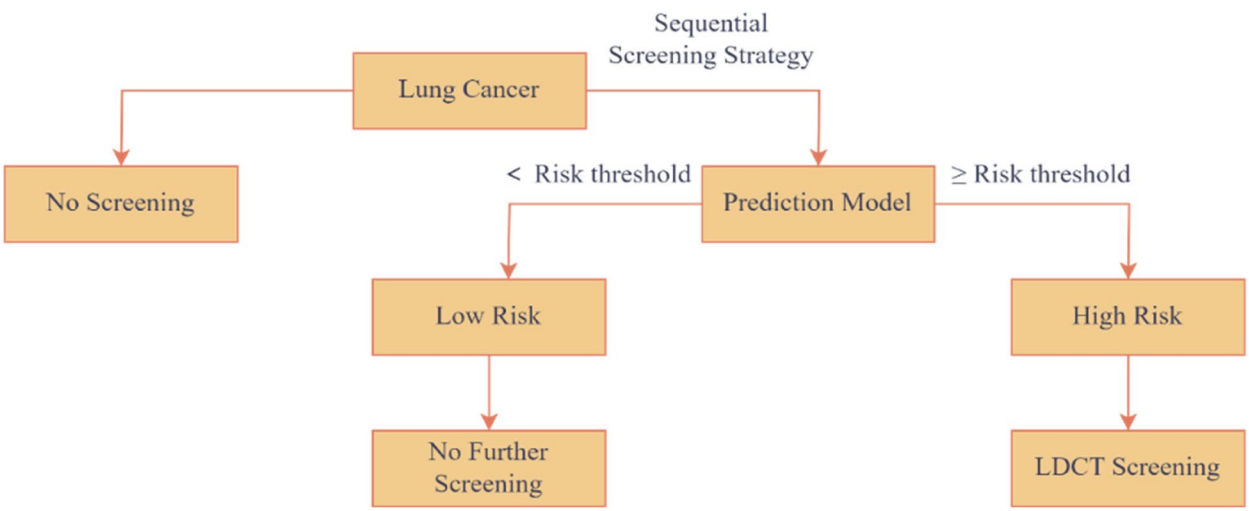

Fig. 1 The rationale of the study

nonsmokers over 50 years of age with a risk threshold of 0.47% and smokers with a threshold of 0.51% was included. We added the screening strategy recommended by the 2023 Chinese guideline for annual screening of smokers over the age of 50 to the screening as well. The characteristics of these strategies are outlined in Additional file 1: Table S5.

Markov model description

The Markov state-transition model delineates two distinct components: treatment pathways and the natural progression of lung cancer. It also integrates post-treatment outcomes based on cancer stage at diagnosis, facilitating a thorough assessment of screening strategies. The natural history component encompasses seven states: stages I to IV of lung cancer, a no-cancer state, and a death state. Notably, stage IIIa and IIIb lung cancers are analyzed separately due to their distinct treatment protocols. Diagnosis through presentation of clinical symptoms or screening is a key bridge between the natural history and post-diagnostic parts of the model. Upon diagnosis, the simulated patient advances to the model's second component, where treatment and postoperative care are assessed. Across all states, individuals face the risk of all-cause mortality. The Markov model is depicted in Fig. 2.

Markov model input parameters

Consistent with many Markov modeling studies, the input parameters for our analysis included transition probabilities, costs, and health utilities. We used published data from China for calibration the transition probabilities from the German dataset in the natural history module [33]. Detailed validation methods are in Additional file 1: Method S2 [34–46].

Clinical and epidemiological data

The detection rates of lung cancer by varying threshold strategies using LDCT were sourced from the Guangzhou Lung Cancer Screening Program [32]. The probability of transitioning from health to all-cause mortality was derived from the National Population Census [37, 45]. Post-diagnosis, lung cancer-specific mortality was closely tied to the clinical stage at the time of diagnosis. Post-diagnostic regression probabilities were refined using survival rates, categorized according to the tumor, node, and metastasis (TNM) staging system for different clinical stages. These rates were taken from the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Program and the national multicenter clinical epidemiological survey of lung cancer [39, 47]. The possibility of cancer expansion is detailed by stage, according to the literature [48]. Given that our

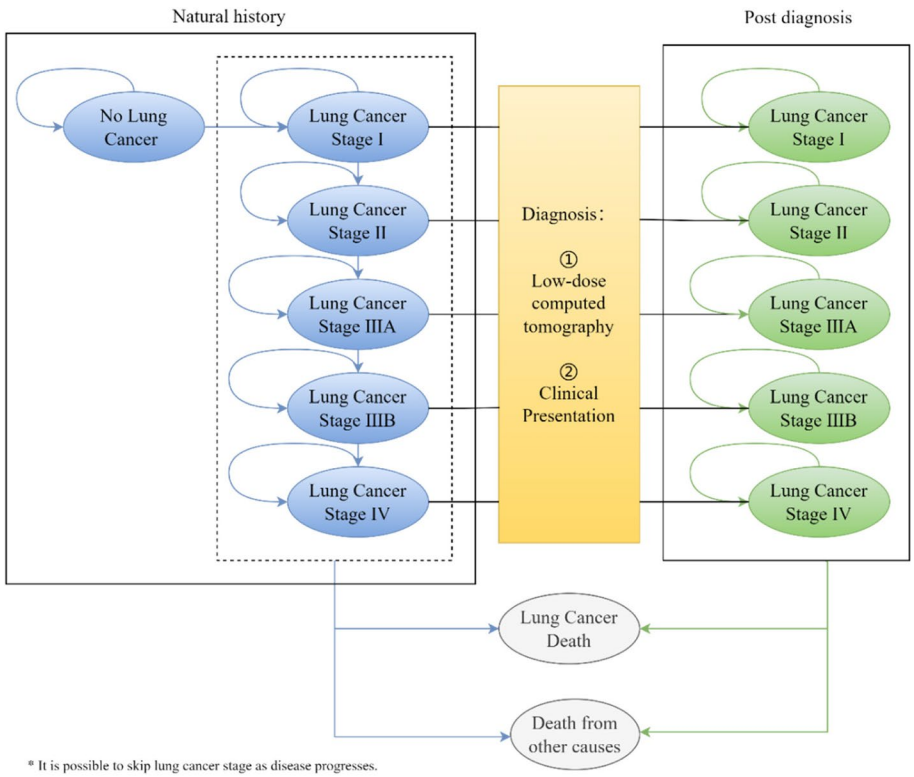

Fig. 2 Markov model for natural history and post-diagnosis

study recalibrated the Markov model's cycle length to 3 months, the transition probabilities reflect this interval. Finally, all rates were converted into probability for model consistency.

Screening parameters and effectiveness

Sensitivity and specificity values were extracted from a Sichuan, China-based study, which included five screening rounds and a cohort of 9522 participants [49]. The probability of a confirmed positive diagnosis for LDCT screening can be calculated using the sensitivity values, while the probability of a false positive diagnosis can be estimated based on the specificity values. This study assumes full attendance of all patients at screening sessions.

Cost input (screening, diagnosis, and treatment)

The analysis included costs associated with LDCT screening, diagnostic evaluations for positive results, and treatment expenses based on the stage of lung cancer at diagnosis. Costs for screening and diagnostic procedures were extracted from a published basic medical database [50]. The recall and referral rate from the Guangzhou Lung Cancer Screening Program were utilized to calculate the costs associated with both baseline and annual screenings. Additionally, treatment costs for distinct phases of lung cancer management and end-of-life care were obtained from peer-reviewed literature [27, 28]. All costs in this study are reported in 2023 US dollars. A 5% annual discount rate was used to calculate costs and QALYs.

Quality of life

The life years of simulated individuals were adjusted for quality of life using published health utility scores by clinical stage. Utility values for individuals without clinical lung cancer were extracted from studies evaluating the quality of life within the general Chinese population [51]. Given the scarce published data on the quality of life of lung cancer patients at different stages in mainland China, we used data from a published study conducted in Taiwan, China, while accounting for differences in population characteristics. The latter has also utilized the EQ-5D questionnaire to measure the quality of life of lung cancer patients at different stages [52].

Comprehensive details are provided in Table 1.

Analyses

The primary outcome measures were (1) the cost-effectiveness efficiency frontier, which connects strategies providing the maximum health benefits at each cost level, and (2) the incremental cost-effectiveness ratios (ICERs) for each screening strategy compared to the previous one on the efficiency frontier. We adopted the World Health Organization's suggested threshold, set at three times the per capita gross domestic product, equating to $38,224.

One-way sensitivity analyses were conducted by varying each parameter within the specified risk thresholds. A first-order Monte Carlo simulation involving 10,000 individuals was performed to compare the effectiveness of LDCT screening strategies with a no-screening approach.

To enhance the assessment of model uncertainty, a probabilistic sensitivity analysis (PSA) was conducted, employing 10,000 iterations of second-order Monte Carlo simulation. During this period, different values are randomly selected from their respective distributions. Most of the parameters involved in the model can be evaluated simultaneously to further assess uncertainty and thus more accurately reflect real-world events.

Several scenario analyses of screening strategies were conducted to further investigate the composition of the efficient frontiers in our study. A lung cancer screening adherence rate of 40% was obtained from a one-time LDCT screening in a population-based cohort conducted in 12 cities across 8 provinces in China [54]. A significant disutility of 0.063 was applied for a false-positive result [55]. The relative risks of the smoking cessation interventions considered were taken from previous literature [56].

Results

Base-case scenario

Our findings suggest that, for different initial screening ages, an early screening increases the cost of the screening investment but increases the QALY obtained. In addition, for the same screening age, the lower the modeled risk threshold for screening, the higher the cost of screening and health benefits.

Table 2 shows the costs and effectiveness of the 4 strategies in the smoking population (the strategies recommended by the modeling studies are listed for comparison). Compared with no screening, the incremental QALY and incremental cost for NCC-smoker-45–1.65% were 0.011 and $238.43, respectively, and the incremental QALY and incremental cost for NCC-smoker-45–0.25% were 0.039 and $1324.32, respectively. Compared to the previous efficient strategy, the ICER of NCC-smoker-45–1.65% is $21,874.31 and the ICER of NCC-smoker-45–0.25% is $55,038.46. Among these four strategies, NCC-smoker-45–0.55% is the best recommended strategy at the triple per capita GDP of China's willingness-to-pay (WTP) ($38,224) with the greatest gain in its QALYs. This optimized strategy results in a gain of 0.018 QALYs at similar cost compared to the strategy recommended in the China 2023 Guide.

Table 1 Input parameters of Markov model for lung cancer screening

Parameter	Baseline	Minimum	Maximum	Distribution	Reference
Data about transition probabilities					
Progression rate, per cycle					
No lung cancer to death	Time dependent	-	-	-	[45]
Stage I to stage II	0.3958	-	-	-	[33]
Stage I to stage IIIA	0.0728	-	-	-	[33]
Stage I to stage IIIB	0.00000001	-	-	-	[33]
Stage I to stage IV	0.2569	-	-	-	[33]
Stage I to diagnosis	0.1400	-	-	-	[33]
Stage I to death	0.0115	-	-	-	[33]
Stage II to stage IIIA	0.2480	-	-	-	[33]
Stage II to stage IIIB	0.0760	-	-	-	[33]
Stage II to stage IV	0.189	-	-	-	[33]
Stage II to diagnosis	0.077	-	-	-	[33]
Stage II to death	0.0268	-	-	-	[33]
Stage IIIA to stage IIIB	0.2746	-	-	-	[33]
Stage IIIA to stage IV	0.1555	-	-	-	[33]
Stage IIIA to diagnosis	0.2700	-	-	-	[33]
Stage IIIA to death	0.0641	-	-	-	[33]
Stage IIIB to stage IV	0.0536	-	-	-	[33]
Stage IIIB to diagnosis	0.5777	-	-	-	[33]
Stage IIIB to death	0.1300	-	-	-	[33]
Stage IV to diagnosis	0.7984	-	-	-	[33]
Stage IV to death	0.1800	-	-	-	[33]
Fatality rate after treatment, per cycle					
Stage I	0.0115	0.0092	0.0138	Beta	[39, 47]
Stage II	0.0268	0.02144	0.03216	Beta	[39, 47]
Stage IIIA	0.0641	0.05128	0.07692	Beta	[39, 47]
Stage IIIB	0.0641	0.05128	0.07692	Beta	[39, 47]
Stage IV	0.1004	0.08032	0.12048	Beta	[39, 47]
Screen parameters					
Sensitivity	0.8913	0.7696	0.9527	Beta	[49]
Specificity	0.9436	0.9388	0.9481	Beta	[49]
Baseline screening					
Early recall of smoking	0.1281	0.10248	0.15372	Beta	-
Immediate referrals of smoking	0.037	0.0296	0.0444	Beta	-
Early recall of non-smoking	0.1469	0.11752	0.17628	Beta	-
Immediate referrals of non-smoking	0.0111	0.00888	0.01332	Beta	-
Annual screening					
Early recall of smoking	0.0262	0.02096	0.03144	Beta	-
Immediate referrals of smoking	0.0157	0.01256	0.01884	Beta	-
Early recall of non-smoking	0.0465	0.0372	0.0558	Beta	-
Immediate referrals of non-smoking	0.0236	0.01888	0.02832	Beta	-
Utilities					
No lung cancer	0.933	0.929	0.951	Beta	[51]
Stage I	0.840	0.672	1.008	Beta	[52]
Stage II	0.790	0.632	0.948	Beta	[52]
Stage III	0.790	0.632	0.948	Beta	[52]
Stage IV	0.770	0.616	0.924	Beta	[52]

Table 3 shows the costs and effectiveness of four strategies in the nonsmoking population (strategies recommended by modeling studies are listed for comparison). The incremental QALY and incremental cost of NCC-non-smoker 45–0.60% compared with no screening were 0.006 and $157.25, respectively. The incremental QALY and incremental cost for NCC-non-smoker 45–0.20% were 0.041 and $1224.61, respectively. Compared with the previous high-efficiency strategy, the ICER for NCC-non-smoker 45–0.60% was $26,517.71, and the ICER for NCC-non-smoker 45–0.20% was $37,994.95. Among these 4 strategies, NCC-non-smoker 45–0.20% was the best recommended strategy. The results of the efficient frontier curve strategies are illustrated in Figs. 3 and 4. Regardless of smoking status, the strategies recommended by the modeling study did not reach the efficient frontier, i.e., they were dominated by the frontier strategies.

Sensitivity analyses

The sensitivity analysis targeted the optimal strategies: initiating screening at age 45 with a 0.20% 3-year risk

Table 1 (continued)

Parameter	Baseline	Minimum	Maximum	Distribution	Reference
Cost (USD)					
LDCT screening	54.32	43.456	65.184	Gamma	[50]
Biopsy and diagnosis	194	155.2	232.8	Gamma	[27, 28]
Prediagnosis	336.27	269.016	403.524	Gamma	[27, 28]
Terminal stage	4108.07	3286.456	4929.684	Gamma	[53]
Treatment costs per cycle					
Clinical stage I	2089.67	1650.839	1320.671	Gamma	[27, 28]
Clinical stage II	3265.7	2579.903	2063.922	Gamma	[27, 28]
Clinical stage III	3550.77	2805.108	2244.087	Gamma	[27, 28]
Clinical stage IV	4562.54	3604.407	2883.525	Gamma	[27, 28]

Table 2 Baseline results of screening strategies for the smoking population

Strategy	Cost (USD)	QALYs	Incremental cost (USD)	Incremental QALYs	ICER compared to no screening	ICER compared to previous efficient scenarios
No Screening	1820.19	13.39261	NA	NA	NA	NA
NCC-smoker-45-1.65%	2058.62	13.40351	238.43	0.01090	21,874.31	21,874.31
NCC-smoker-45-0.55%	2856.96	13.42542	1036.77	0.03281	31,599.21	36,437.24
NCC-smoker-45-0.30%	3101.58	13.43091	1281.39	0.03830	33,456.66	44,557.38
NCC-smoker-45-0.25%	3144.51	13.43169	1324.32	0.03908	33,887.41	55,038.46
(NCC model recommended strategy)	2550.16	13.41304	729.97	0.02043	35,730.30	abs.dominated
2023 Guidelines recommended strategy	2858.09	13.40719	1037.90	0.01458	71,186.56	abs.dominated

Table 3 Baseline results of screening strategies for the non-smoking population

Strategy	Cost (USD)	QALYs	Incremental cost (USD)	Incremental QALYs	ICER compared to no screening	ICER compared to previous efficient scenarios
No Screening	3452.54	12.90104	NA	NA	NA	NA
NCC-non-smoker-45-0.60%	3609.79	12.90697	157.25	0.00593	26,517.71	26,517.71
NCC-non-smoker-45-0.40%	3925.10	12.91841	472.56	0.01737	27,189.87	27,562.06
NCC-non-smoker-45-0.22%	4601.92	12.94029	1149.38	0.03925	29,283.57	30,933.27
NCC-non-smoker-45-0.20%	4677.15	12.94227	1224.61	0.04123	29,701.92	37,994.95
NCC-non-smoker-50-0.47% (NCC model recommended strategy)	3657.66	12.90706	205.12	0.00602	34,073.09	abs.dominated

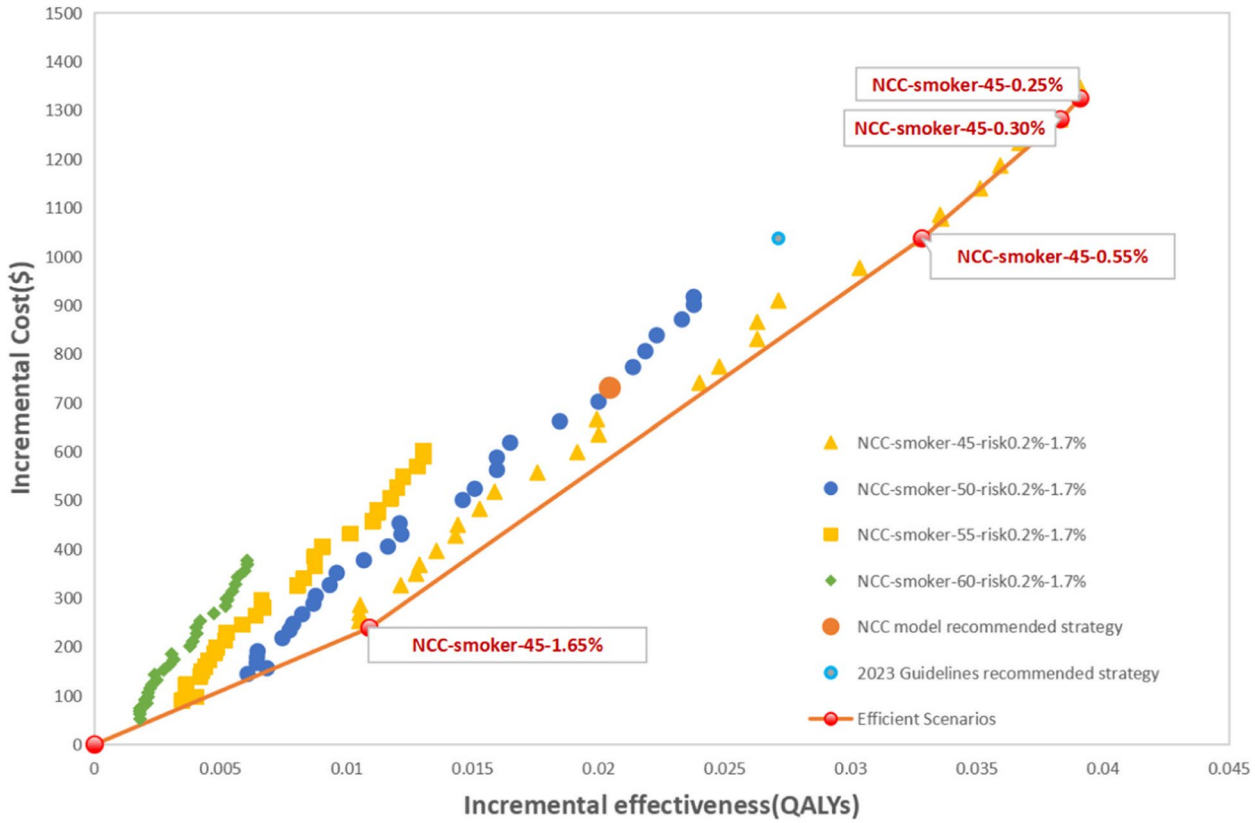

Fig. 3 Effective frontier curves for smoker model screening strategies

threshold for non-smokers and at age 45 with a 0.55% 3-year risk threshold for smokers. The tornado diagram (Additional file 1: Fig. S4 and S5) highlighted parameters that significantly influenced the ICER based on one-way sensitivity analysis outcomes.

For the smoker-optimized strategy, key determinants of the ICER included screening costs, the utility of clinical stage I, treatment costs for stage I and the screening sensitivity. In contrast, the cost of terminal-stage treatment exerted a minimal effect on the ICER. Importantly, for the strategy initiating screening at age 45 with a 0.55% 3-year threshold for smokers, the ICER remained below $38,224 across various parameter adjustments.

In the optimal strategy for non-smokers, the ICER was most sensitive to the utility of clinical stage I, screening costs, and treatment costs for stage I. Additionally, the fatality rate for clinical stage I and the costs of biological diagnosis also played significant roles.

Probabilistic sensitivity analyses

The results of the cost-effectiveness acceptability curves (Figs. 5 and 6) show that when the WTP is less than one time China's per capita GDP ($12,741), none of the screening strategies based on risk prediction models are cost-effective. When the WTP was about two times China's per capita GDP ($25,482), it was still more cost-effective not to screen for nonsmokers, and it was cost-effective to have a screening strategy for smokers (NCC-smoker-45-risk1.65%). When the WTP was approximately three times China's GDP per capita ($38,224), screening strategies on both the smoker and nonsmoker efficiency frontiers were cost-effective. The optimal strategy for smokers (NCC-smoker-45-risk0.55%) has a 97.1% probability of being cost-effective. The optimal strategy for nonsmokers (NCC-nonsmoker-45-risk0.20%) has a probability of being cost-effective of more than 80%. Although parameter variations have some impact on the results, the main conclusions we present remain robust to some extent.

Scenario analysis

The results of our scenario analysis suggest that when false positives are considered, the optimal screening strategy for smokers is NCC-smokers-45–1.65%, while the optimal screening strategy for nonsmokers becomes NCC-nonsmokers-45–0.22%. When considering lower adherence rates, the optimal screening strategy for smokers becomes NCC-smoker-45–1.65%, and for

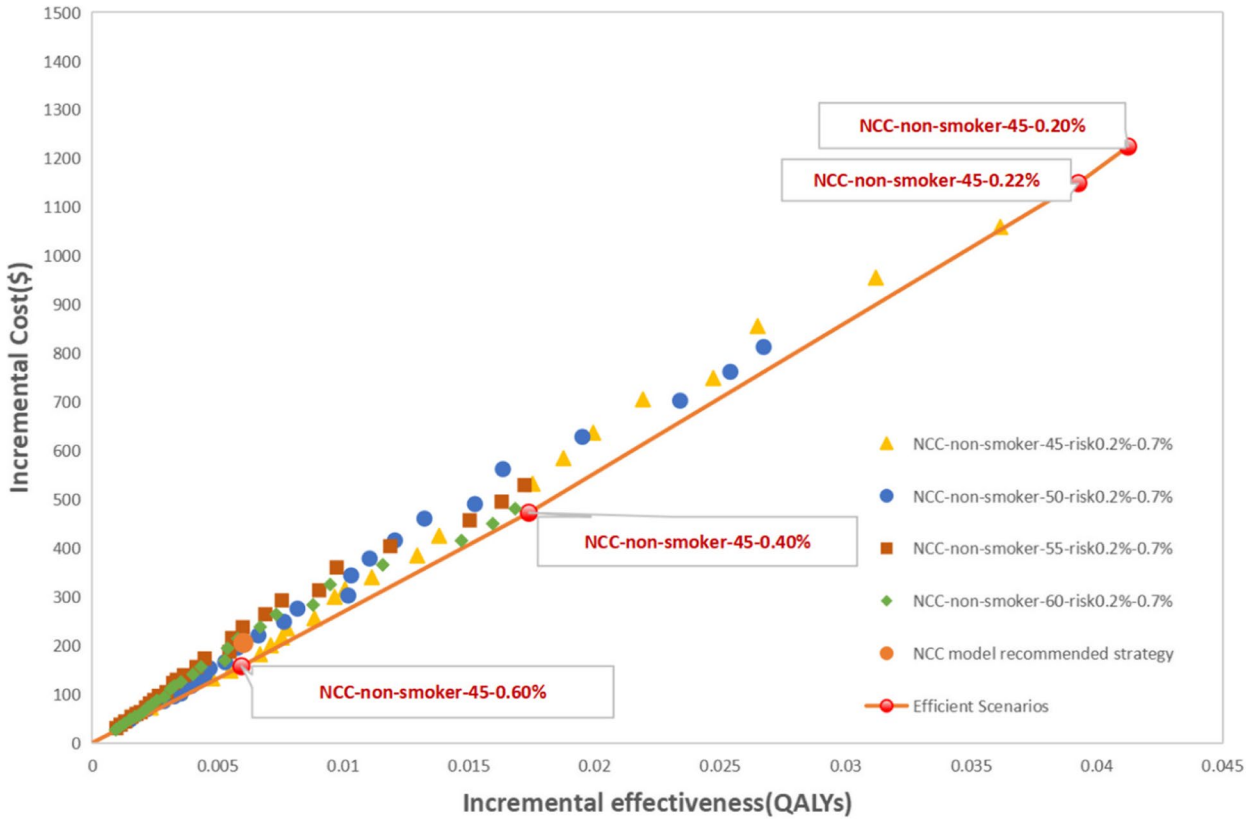

Fig. 4 Effective frontier curves for non-smoker model screening strategies. * ICER, incremental cost-effectiveness ratio; China NCCm2021, China National Cancer Center Lung Cancer 2021 risk prediction model; QALY, quality-adjusted life-year; All outcomes are discounted at a 5% annual rate. * The screening strategies are labeled as follows: for risk model-based strategies, the risk prediction model specified population-age start-3-year risk threshold for lung cancer incidence

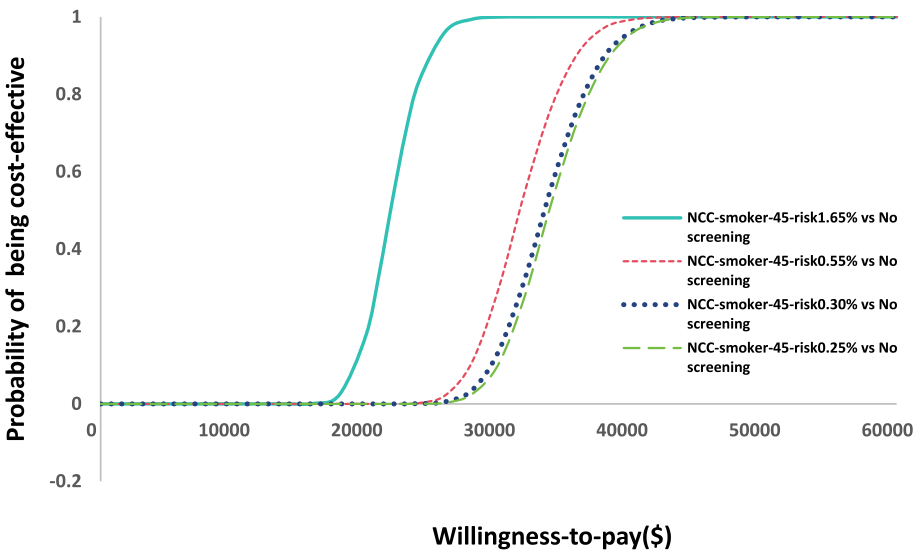

Fig. 5 Cost-effectiveness acceptability curves of strategies on the efficiency frontier for the smoking model

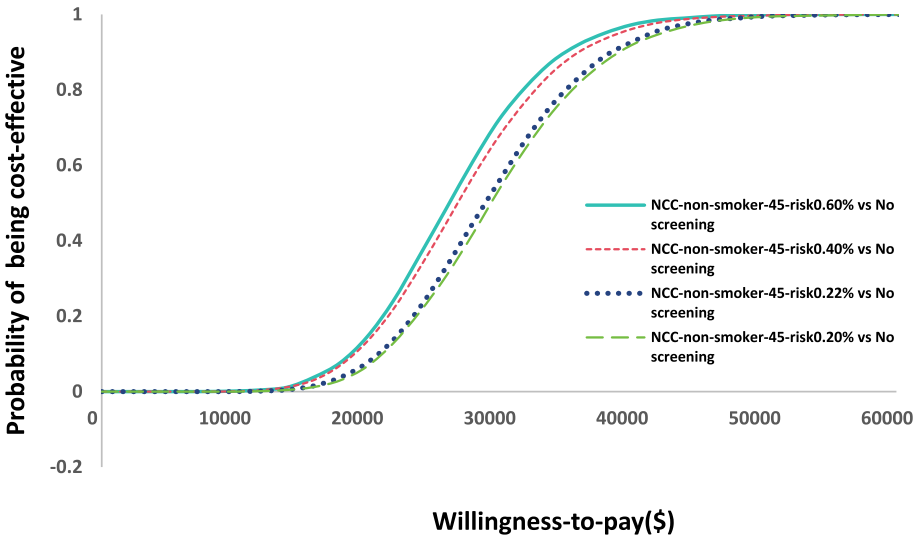

Fig. 6 Cost-effectiveness acceptability curves of strategies on the efficiency frontier for the non-smoking model

non-smokers, it becomes NCC-non-smoker-45–0.60%. In both scenarios, the combination of strategies on the efficiency frontier remains consistent with the base-case analysis, and risk-prediction model-based strategies continue to dominate for both smokers and non-smokers. However, when these two factors are taken into account, the ICER for screening strategies increases. This suggests that the potential benefits of screening may be somewhat diminished if real challenges such as false positives and low adherence are not addressed. Screening strategies when combined with smoking cessation interventions had higher incremental QALYs and lower ICERs than screening that did not take smoking cessation into account. Therefore, it is recommended that adherence incentives and smoking cessation practices be incorporated into lung cancer screening to maximize the cost-effectiveness of risk-based screening. The efficiency frontier screening strategies for each scenario are detailed in Additional file 1: Tables S10–S14.

Discussion

In this study, we assessed the cost-effectiveness of lung cancer screening strategies using validated risk prediction models to select participants. We evaluated 236 strategies across both non-smokers and smokers, focusing on various risk thresholds and screening initiation ages. We found that risk model-based screening strategies reduced screening costs and produced more QALYs than the recommendations for smokers in the 2023 Chinese guideline. Our base-case analysis identified four strategies on the cost-effectiveness frontier for annual screening of both smokers and non-smokers. Among smokers, the four screening strategies on the efficiency frontier provided incremental health benefits ranging from 0.011 to 0.039 QALYs compared to no screening. In nonsmokers, these benefits ranged from 0.006 to 0.041 QALYs, with the exact gains influenced by the specific combination of individual screening strategies. Although the absolute QALY gains were modest, ICER analyses showed that all screening strategies were cost-effective within acceptable thresholds. This indicates that even small individual health benefits from screening can yield significant public health value when scaled up, due to cumulative effects. Notably, initiating screening at age 45 with a 3-year risk threshold of 0.55% for smokers and at age 45 with a 0.20% threshold for non-smokers proved to be the optimal strategy and was dominant to both the current guideline-recommended strategy and the model-recommended strategy. In addition, the results of our probabilistic sensitivity analyses suggest that a screening strategy raising the risk threshold for smokers to 1.65% remains cost-effective when WTP decreases to two times GDP. However, when WTP declines to one times GDP, no screening becomes the dominant strategy. This provides a reference for setting screening thresholds in regions with limited economic resources.

To our knowledge, this study is the first to evaluate the cost-effectiveness of risk model-based lung cancer screening for non-smokers and smokers based on the nationwide prediction model of the Chinese NCC-LCm2021 model in China comprehensively. The strategies are in line with the current epidemic trend in China, where nonsmokers make up a large proportion of lung cancer patients [8]. More importantly, including non-smokers in the screening cohort broadened the scope of our investigation to encompass populations beyond the

scope of exclusively smoker-centered studies. This may provide valuable insights into the development of screening strategies in other Asian countries with a high prevalence of lung cancer that is not associated with smoking. To provide a practical foundation for decision-making, our scenario analysis systematically examined multiple critical scenarios, including low screening adherence, the negative utility associated with false-positive screening results, and potential smoking cessation interventions.

As the first lung cancer risk prediction model established and validated based on a nationwide cohort in China, the NCC-LCm2021 model sets the recommended screening threshold for nonsmokers at 0.47%, based on mortality benefit [23]. From a cost-effectiveness perspective, our study optimally adjusted the risk threshold for nonsmokers to 0.20%, and the results showed that the adjusted strategy not only added 0.035 incremental QALYs but also had a lower ICER. This demonstrates that the clinical benefits in QALYs gain of this adjustment from 0.47% to 0.20% outweigh the harms in cost and disutility of potential overdiagnosis.

As the first study in China to examine the cost-effectiveness of risk model-based lung cancer screening strategy, Liu et al. applied the Henan risk model to assess the absolute risk of developing lung cancer over a 5-year period among Chinese heavy smokers aged 50 years and older [19]. Their study recommended annual screening for individuals with a risk threshold of 1.70% or higher, biennial screening for those with a risk between 1.03 and 1.69%, and triennial screening for those with a risk below 1.03%. Although their study followed the guideline recommendation to start screening at the age of 50 years, the latest data from the National Cancer Center of China showed that the incidence and mortality of lung cancer increased rapidly from the age of 45 years [1]. Therefore, as suggested in our findings, starting screening at age 45 may be more consistent with this trend. Additionally, they recommend triennial lung cancer screening for those with lower predicted risk levels, but dynamic surveillance may be less effective with this screening frequency compared to annual screening.

Toumazis et al. demonstrated in a cost-effectiveness analysis that PLCOm2012-based lung cancer screening strategies outperformed USPSTF recommendations, with a 6-year risk threshold of 1.2% for heavy smokers being the optimal strategy [10]. While this study offers a valuable methodological framework, we have made improvements in adapting it to the Chinese population, and our optimal strategy achieved a 0.016 minor incremental QALY than theirs for heavy smokers. The localized adaptations we implemented provide a replicable methodology for assessing the cost-effectiveness of lung cancer screening programs in developing countries, especially for those with large proportion of lung cancer incidence in nonsmokers.

This study has several limitations. First, our screening cohort and some parameters were derived from the Guangzhou Lung Cancer Screening Program. However, given the differences in epidemiological data across various regions in China, the generalizability of our findings should be interpreted with caution. Second, the lack of socioeconomic subgroup analyses (e.g., urban-rural differences) limits the equity of screening assessments for populations in different social contexts. Future work could reduce disparities associated with region and socioeconomic status by considering these analyses to inform targeted healthcare allocation. Third, our model validation using the Guangzhou cohort aligns with documented limitations of lung cancer risk prediction models in Asian populations, demonstrating moderate discriminatory accuracy [57]. These necessitate multicenter data integration and incorporation of novel predictors (e.g., genomic biomarkers) to optimize model performance. Fourth, the potential radiation exposure associated with lung cancer screening was not addressed in our analysis. However, relevant evidence confirms that the benefits of LDCT screening in lung cancer far outweigh the radiation risks, which only manifest after 10–20 years and have a low mortality rate [58].

Conclusions

We conducted a cost-effectiveness analysis of screening based on risk prediction models to optimize risk thresholds for screening strategies for both smokers and nonsmokers, refine the evidence to support public policy on LDCT screening eligibility, and reduce the unnecessary overuse of limited healthcare resources in China.

Abbreviations

LDCT	Low-dose computed tomography
QALYs	Quality-adjusted life-years
ICERs	Incremental cost-effectiveness ratios
WTP	Willingness-to-pay
BMI	Body mass index
AUC	Area under the receiver
TNM	Tumor, node, and metastasis
IASLC	International Association for the Study of Lung Cancer
PSA	Probabilistic sensitivity analysis
USPSTF	U.S. Preventive Services Task Force

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04065-3.

Additional file 1: Table S1. Screen proportion and incident density by the risk groups of non-smokers. Table S2. Screen proportion and incident density by the risk groups of smoker. Method S1. External validation of the Chinese NCC-LCm2021 model. Table S3. Baseline characteristics of the cohort. Table S4. Parameters of the multivariate Cox regression model for never and ever smokers in the training cohort. Table S5. Characteristics

of the LDCT lung cancer screening strategies evaluated by the Markov model. Method S2. Validation for the natural history model of lung cancer. Table S6. Validity indicators and sources. Table S7. Validity indicator: incidence and mortality of lung cancer. Table S8. Incidence and morality of natural history model (3 months). Table S9. Transition probabilities in natural history model. Table S10. Results of false-positive scenario analysis of screening strategies for smokers. Table S11. Results of false-positive scenario analysis of screening strategies for non-smokers. Table S12. Results of adherence scenario analysis of screening strategies for smokers. Table S13. Results of adherence scenario analysis of screening strategies for non-smokers. Table S14. Results of smoking cessation scenario analysis of screening strategies for smokers. Fig. S1. Area under the Subject Work Characterization Curve. Fig. S2. Proportion for clinical stages. Fig. S3. Comparison between GBD observed value and simulation value in life expectancy. Fig. S4. Smoking model optimal strategy (45-0.55%) one-way sensitivity analysis tornado charts. Fig. S5. Non-smoking model optimal strategy (45-0.20%) one-way sensitivity analysis tornado charts.

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Authors' contributions
Conceptualization and design, TTZ, YW, XEY, and XCC; collection of data, YW, XEY, and LYZ; data analysis and interpretation, YW, XCC, XEY, and LYZ; administrative support, JJ, JXH, and WHL; manuscript writing, YW; language editing and proofreading, NB, LB, and AF; responsible for the overall content, TTZ; and all authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the First Affiliated Hospital of Guangzhou Medical University and approved by Guangzhou Municipal Health Commission and the Institutional Review Board (No. YKLS2015-25) and all participants provided written informed consent for participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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