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Cost-effectiveness of low-dose CT screening for non-smokers with a first-degree relative history of lung cancer

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Abstract

Background Lung cancer is the leading cause of cancer-related deaths worldwide, with non-smokers in China accounting for over 40% of cases. Despite the proven efficacy of low-dose computed tomography (LDCT) in early detection and reduction of lung cancer mortality, the current paradigm of lung cancer screening, heavily focused on smoking status and age, may inadequately address the unique risk factors associated with non-smokers, particularly those with a family history of the disease. This study evaluates the cost-effectiveness of LDCT screening for non-smokers with a first-degree relative (FDR) history of lung cancer, a group at particularly high-risk.

Methods We developed a state-transition Markov model to evaluate the incremental cost-effectiveness ratios (ICERs) of 16 screening strategies for a hypothetical cohort of 100,000 non-smoking individuals aged 50 with a FDR history of lung cancer, considering various starting ages (50, 55, 60, 65 years) and intervals (one-off, annual, biennial, triennial). The willingness-to-pay (WTP) threshold was set at three times China's 2022 per-capita GDP. Sensitivity analyses, scenario analyses and subgroup analysis by sex, were conducted.

Results Compared to no screening, all strategies except one-off screening at age 50, were cost-effective for both sexes. Biennial LDCT starting at age 55 was found to be most effective, with an ICER of CNY 68,932/QALY for males, and CNY 80,056/QALY for females. This cost-effectiveness probability for this strategy was approximately 90% for both sexes. Sensitivity analyses indicated that annual screening at age 55 was optimal without discounting. For males, biennial at age 60 was optimal if the FDR-related odds ratio for lung cancer incidence was below 1.492. Triennial screening at age 55 was optimal for females at full adherence. Ignoring disutility from false-positive results, annual at age 55 was optimal for both sexes.

Conclusions LDCT screening for non-smokers with a FDR history of lung cancer is cost-effective, especially biennial screening at 55. These findings support the development of more inclusive screening guidelines, which could enhance early detection and reduce mortality rates.

Keywords Lung Cancer, LDCT screening, Non-smokers, Cost-effectiveness, Modelling study

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Introduction

Lung cancer continues to be a leading cause of the global cancer burden, with an alarming 12.4% of all new cancer cases and 18.7% of cancer-related deaths attributed to it in 2022 [1]. In China, the situation is particularly dire, where lung cancer claims the primary cause of cancer mortality, with an estimated 733,291 deaths in 2022, accounting for 40.3% of the global total [2]. The burden of lung cancer in China is projected to increase mainly due to an aging population and population growth [3]. There is an urgent need for collective action to reduce this burden.

Lung cancer screening based on low-dose CT (LDCT) has demonstrated significant efficacy in early detection and in reducing the mortality rate [4, 5]. However, existing lung cancer screening guidelines focus solely on age and smoking history, potentially excluding at-risk non-smokers and overlooking a significant number of lung cancer cases [6–8]. It has been estimated that lung cancer in non-smokers is the seventh leading cause of cancer-related deaths worldwide, with a rising trend [9, 10], particularly in Asian countries like China, where over 40% of lung cancer cases occur in non-smokers [11]. The current smoking-focused screening strategy may not adequately address the distinct risk profiles and demographic characteristics of non-smokers. Consequently, there is a compelling need to develop a targeted LDCT screening strategy specifically for non-smokers.

The long-term cost-effectiveness of LDCT screening must be carefully evaluated in the development of a screening strategy. While the benefits of LDCT screening in reducing lung cancer mortality, the harms of false positives, overdiagnosis, and radiation-induced cancer incidence cannot be ignored [12]. A targeted approach for high-risk populations can more effectively balance these risks with the benefits, thereby enhancing cost-effectiveness [13, 14]. For non-smokers, a first-degree relative (FDR) history of lung cancer is a significant risk factor, highlighting the importance of screening strategies that consider genetic and environmental influences [15, 16]. Nevertheless, the cost-effectiveness of LDCT screening for non-smokers with a FDR history of lung cancer remains largely unexplored.

In response to this gap, we conducted this study to evaluate the cost-effectiveness of LDCT screening for non-smokers with a FDR history of lung cancer in China. Our analysis aimed to determine the optimal starting age and screening intervals for this specific high-risk group, thereby informing a more strategic and cost-effective approach to early lung cancer detection.

Methods

We conducted a model-based economic evaluation to assess the cost-effectiveness of LDCT screening for non-smokers with a FDR history of lung cancer in China, from a health-care system perspective. The FDR was defined as one's parents, siblings or offsprings. The non-smokers were defined as those who have never smoked. The model was constructed using TreeAge Pro 2022 software and the analysis adhered to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [17].

Markov model

A state-transition Markov model was developed to simulate lung cancer progression and evaluate the costs and quality-adjusted life years (QALYs) outcomes in a lifetime horizon (until death or 78 years old, the expected life years). The model initialized with a hypothetical cohort of 100,000 individuals aged 50 years old. It was assumed that this cohort was initially lung cancer-free but had a FDR history of lung cancer at the baseline.

The Markov model encapsulated both the natural history and the post-diagnosis progression of lung cancer, with a detailed description available in prior literatures [18–20]. In summary, the natural history consisted of six states: healthy, lung cancer stages I through IV, and death. We assumed that individuals in the healthy state would develop to lung cancer stage I at the age- and sex-specific incidence rates. Once lung cancer is developed, patients may experience progression to more advanced stages, be diagnosed through LDCT screening or standard clinical care upon symptom onset, maintain their current stage, or die. The post-diagnosis component of the model comprised five states: post-treatment lung cancer stages I through IV, and death. It was presumed that patients underwent immediate treatment upon diagnosis. Additionally, we have incorporated age- and sex-specific natural background death rates and acknowledged that individuals with lung cancer face stage-specific mortality from this disease in addition to a natural background death rate. A model cycle-length of 1-year, with half-cycle correction was assumed. Details of the Markov model was depicted in Fig. S1.

Screening strategies

We evaluated 16 LDCT screening strategies, defined by varying starting ages (50, 55, 60, or 65 years) and screening intervals (one-off, annual, biennial, or triennial). No screening approach served as the reference strategy. One-off screening was assumed to occur at each starting age. The age limits were set at 50 and 74 years, respectively, conform with Chinese screening guideline for heavy smokers, balancing life expectancy with the feasibility of screening implementation [8].

Model input parameters

The key model input parameters were shown as Table 1, aligning the gender distribution with China's demographic profiles as of 2022 [21].

Lung cancer incidence rate

The lung cancer incidence rates among non-smokers with a FDR history of the disease (I_{FDR}), stratified by age and sex, were estimated as $I_{FDR} = I_N \times OR_{FDR}$, where I_N was the general non-smoking population's incidence rates, and OR_{FDR} was FDR-related odds ratio (OR).

Estimation of I_N

I_N was modeled as $I_N = I_G/(RR_{s\_to\_NS} \times \mathrm{P} + 1 - \mathrm{P})$, where I_G being the overall Chinese incidence rate, from the Global Burden of Diseases (GBD) 2018 [22] (Table S1). The variable $RR_{s\_to\_NS}$ denoted the smoker-to-non-smoker relative risk, with values of 2.41 (range, 2.18–2.65) for males and 2.42 (range, 2.11–2.77) for females [23]. The smoker proportion, P, was determined from National Tobacco Use Surveillance Data between 2019 and 2020 [24] (Table S2).

Estimation of OR_{FDR}

The association between a FDR history of lung cancer and lung cancer risk among non-smoking Chinese individuals varied significantly among studies. To achieve a precise assessment, we reviewed all related published studies and conducted a meta-analysis for eligible studies. We named the resulting estimate as OR_{FDR}.

The databases were searched from the inception of each database until June 2024 in Pubmed, Web of Science, China National Knowledge Infrastructure (CNKI) and Wanfang Data. We used the following keywords and Mesh terms in the search strategy: ('family history' OR 'familial aggregation') AND ('lung cancer' OR 'lung carcinoma' OR 'lung neoplasm' OR 'lung adenocarcinoma' OR 'NSCLC' OR 'Lung Neo-plasms' (MeSH) OR 'Small Cell Lung Carcinoma' (MeSH) OR 'Carcinoma, Non-Small-Cell Lung' (MeSH)) AND ('China' or 'Chinese') AND ('non-smoker' OR 'non-smoking' OR 'never smoking' OR 'never smoker' OR 'who do not smoke'). For CNKI and Wanfang Data, these terms were translated into Chinese. The inclusion criteria focused on case-control or cohort studies examining the association between a FDR history of lung cancer and lung cancer risk in non-smokers, providing raw data such as odds ratios, hazard ratios, risk ratios, relative ratios, standardized incidence ratios, and their 95% confidence intervals (CIs), or sufficient data to calculate a crude odds ratio. Adjusted estimates were given precedence when both adjusted and unadjusted estimates were available. The exclusion criteria were conference proceedings, abstracts/summaries, case reports/series, reviews and repeated publications. The pooled summary estimates and 95% CIs of OR_{FDR} were analyzed in Stata Statistical software. Heterogeneity across studies was assessed using the I^2 statistic. A random-effects model was applied for studies with moderate heterogeneity ($I^2 > 50\%$); otherwise, a fixed-effects model was utilized. The data extracted from eligible studies were shown in Table S3, with the meta-analysis results featured in Fig. S2-S3. The pooled point estimates and 95% CIs served as base-case values and sensitivity analysis ranges for subsequent cost-effectiveness analysis. The final estimates were 1.88 (range, 1.01–3.49) for males and 2.27 (range, 1.77–2.91) for females.

Natural background death rate

The age- and sex-specific natural background death rates for non-smokers with a FDR history of lung cancer (D_{FDR}) were assumed to mirror those of the general non-smoking population, estimated as $D_{FDR} = D_G - D_s$, with GBD 2018 data for all-cause mortality D_G (Table S4), and smoking-attributed mortality D_s (Table S5) [22].

Transition probabilities, stage-specific mortality and performance of LDCT

Transition probabilities and stage-specific mortality rates for lung cancer were derived from peer-reviewed studies [25, 26], and the sensitivity and specificity of LDCT screening were informed by a Chinese randomized controlled trial [27]. Overdiagnosis rates were sourced from the US National Lung Screening Trial [28], and the additional radiation-induced cancer risk per LDCT screening was calculated based on an Italian LDCT screening trial [29].

Adherence, and diagnose rate through standard clinical care

The adherence rate to LDCT screening was set at 54.6%, reflecting data from Chinese National Lung Cancer Screening cohort [30], which included 92,909 individuals with a FDR history of lung cancer. The likelihood of diagnosis through standard clinical care was extracted from the existing literature [18].

Cost and utility

Direct medical costs, including diagnosis, treatment, maintenance, and background medical treatment costs, were collected. Diagnosis-related costs included LDCT test and lung biopsy, as reported by the Cancer Screening Program in Urban China (CanSPUC). Stage-specific lung cancer treatment costs were derived from Chinese medical insurance bureaus, with maintenance costs estimated at 10% of the total treatment cost [27]. We postulated that individuals with undiagnosed lung cancer in the natural

Table 1 Key input parameters of Markov model for lung cancer screening

Parameters	Base case (range)	Distribution	Reference
Smoker-to-non-smoker relative risk of lung cancer ($RR_{s\_to\_NS}$)			[23]
Male	2.41(2.18–2.65)	Triangular(2.18, 2.41, 2.65)	
Female	2.42(2.11–2.77)	Triangular(2.11, 2.42, 2.77)	
FDR-related odds ratio of lung cancer incidence (OR_{FDR})			Meta-analysis
Male	1.88(1.01–3.49)	Triangular(1.01, 1.88, 3.49)	
Female	2.27(1.77–2.91)	Triangular(1.77, 2.27, 2.91)	
Transition Probabilities			[25]
Lung cancer stage I to stage II	0.3682 (± 50%)	Beta(9.33, 16.01)	
Lung cancer stage I to stage III	0.0328(± 50%)	Beta(14.83, 437.29)	
Lung cancer stage I to stage IV	0.0745(± 50%)	Beta(14.15, 175.75)	
Lung cancer stage II to stage III	0.2260(± 50%)	Beta(11.67, 39.96)	
Lung cancer stage II to stage IV	0.1510(± 50%)	Beta(12.89, 72.50)	
Lung cancer stage III to stage IV	0.1455(± 50%)	Beta(12.98, 76.26)	
Mortality			
Lung cancer stage I to LC death	0.1739(± 50%)	Beta(12.52, 59.48)	[25]
Lung cancer stage II to LC death	0.2942(± 50%)	Beta(10.55, 25.31)	
Lung cancer stage III to LC death	0.4626(± 50%)	Beta(7.79, 9.06)	
Lung cancer stage IV to LC death	0.5880(± 50%)	Beta(5.74, 4.02)	
After care I to death	0.089(± 50%)	Beta(13.91, 142.23)	[26]
After care II to death	0.153(± 50%)	Beta(12.86, 71.32)	
After care III to death	0.288(± 50%)	Beta(10.65, 26.34)	
After care IV to death	0.353(± 50%)	Beta(9.59, 17.60)	
Performance of LDCT			
Sensitivity of LDCT	0.981(0.884–0.999)	Triangular (0.884, 0.981, 0.999)	[28]
Specificity of LDCT	0.782(0.768–0.796)	Beta(2,643.78, 737.01)	
Overdiagnosis rate when screening	0.031(± 50%)	Beta(14.86, 464.46)	
The additional risk of LC per screening (1/100,000)			[29]
Male, aged 50–54	2.1(± 50%)	Triangular(1.05, 2.1, 3.15)	
Male, aged 55–59	1.9(± 50%)	Triangular(0.95, 1.9, 2.85)	
Male, aged 60–64	1.7(± 50%)	Triangular(0.85, 1.7, 2.55)	
Male, aged $\geq$ 65	1.4(± 50%)	Triangular(0.7, 1.4, 2.1)	
Female, aged 50–54	5.5(± 50%)	Triangular(2.75, 5.5, 8.25)	
Female, aged 55–59	5.1(± 50%)	Triangular(2.55, 5.1, 7.65)	
Female, aged 60–64	4.5(± 50%)	Triangular(2.25, 4.5, 6.75)	
Female, aged $\geq$ 65	3.8(± 50%)	Triangular(1.9, 3.8, 5.7)	
Adherence to LDCT screening	54.6% (75% and 100% were assumed in scenario analysis)		
Diagnose rate through standard clinical care			[18]
Lung cancer stage I	2.46%(± 50%)	Beta(14.96, 593.32)	
Lung cancer stage II	2.7%(± 50%)	Beta(14.91, 537.48)	
Lung cancer stage III	51.8%(± 50%)	Beta(6.89, 6.41)	
Lung cancer stage IV	65.8%(± 50%)	Beta(4.60, 2.39)	
Cost (CNY)			
LDCT test cost	239.97(± 50%)	Gamma(15.37, 0.06)	[19]
Biopsy diagnosis cost	1,202.9(± 50%)	Gamma(15.37, 0.01)	
Treatment cost			[25]
Stage I	51,554.43(± 50%)	Gamma(15.37, 0.000298)	
Stage II	80,568.43(± 50%)	Gamma(15.37, 0.000191)	
Stage III	87,601.46(± 50%)	Gamma(15.37, 0.000175)	
Stage IV	112,562.91(± 50%)	Gamma(15.37,0.000136)	
Background medical treatment costs	5348.1(± 50%)	Gamma(15.37, 0.003)	[31]
Utility			

Table 1 (continued)

Parameters	Base case (range)	Distribution	Reference
Utility for general individuals, by sex and age			[32]
Male, aged 40–50	0.99(0.987–0.994)	Beta(4,355.01, 43.99)	
Male, aged 51–60	0.984(0.980–0.988)	Beta(3,872.04, 62.96)	
Male, aged 61–70	0.976(0.971–0.980)	Beta(3,514.87, 86.43)	
Male, aged $\geq$ 71	0.947(0.936–0.958)	Beta(1,514.71, 84.77)	
Female, aged 40–50	0.988(0.986–0.991)	Beta(11,257.88, 136.74)	
Female, aged 51–60	0.982(0.979–0.986)	Beta(7,713.61, 141.39)	
Female, aged 61–70	0.964(0.958–0.971)	Beta(3,480.26, 129.97)	
Female, aged $\geq$ 71	0.936(0.926–0.946)	Beta(2,153.09, 147.22)	
Utility of lung cancer by stage			[33], [34], [35]
Lung cancer stage I	0.85(0.78–0.89)	Beta(136.78, 24.14)	
Lung cancer stage II	0.75(0.68–0.80)	Beta(149.31, 49.77)	
Lung cancer stage III	0.69(0.56–0.79)	Beta(42.18, 18.95)	
Lung cancer stage IV	0.69(0.38–0.70)	Beta(21.46, 9.64)	
Disutility associated with a false-positive result	0.063(± 50%) for 3 months	Beta(14.33, 213.21)	[36]
Discount rate	5% (0-8%)	-	[38]

history model would seek background medical treatment for lung disease symptoms, with costs estimated from the national per capita health expenditure figures for 2022 as documented in the China Health Statistics Yearbook [31]. All costs in this study were adjusted to 2022 Chinese yuan (CNY) using the medical consumer price index.

Health outcome was measured in terms of QALYs, with utility scores for healthy individuals derived from a survey of 10,056 Chinese adults [32] and lung cancer utility scores sourced from a meta-analysis [33] and epidemiological studies [34, 35]. A disutility of 0.063 (range, 0-0.08) [36], associated with false-positive LDCT results and lasting three months, was accounted for. Both cost estimates and QALYs were discounted at a rate of 5% (range, 0-8%) [38].

For parameters with an unknown uncertainty range, the plausibility range was assumed to be 50% of the base value. The selection of the distribution for each parameter was informed by the characteristics of the parameters and the underlying data.

Model validation

Three steps were conducted to validate the model, including face validation, internal validation, and external validation.

In face validation, the structure of this model had been well used, and found to be reliable, sensible and can be explained intuitively.

In internal validation, two team members independently examined the model programming and calculation results, and gave a unanimous judgement.

In external validation, two references were used to assess whether the model's predictions match the observed results. First, the observed lung cancer incidence rate across the entire Chinese population served as a reference point, given the scarcity of data specific to non-smokers. We assumed a hypothetical cohort of individuals aged 50, entering the model without any screening interventions, and compared our projected sex-specific lung cancer incidence rates with those estimated in the GBD studies from 2019 to 2021 for the 50–54 age group. Our model indicated an increase in incidence rates with age, aligning well with the GBD estimates, as depicted in Fig. S4. Second, the model's projections on the distribution of lung cancer diagnoses by stage were compared against data from a comprehensive multi-center retrospective epidemiological survey conducted between 2005 and 2014 [37]. Fig. S5 illustrated a strong correlation between the simulated and reported data, validating the model's external predictive accuracy.

Data analysis

The model projected the expected costs and QALYs for each strategy, ranking them by QALYs gained. The incremental cost-effectiveness ratios (ICERs) were calculated for different screening strategies against no screening, and the strategy preceding it on the cost-effectiveness efficiency frontier. We identified the cost-effectiveness frontier to obtain the most cost-effective strategy. In alignment with the World Health Organization's guidance, we applied a willingness-to-pay (WTP) threshold of three times the per-capita gross domestic product (GDP) of China in 2022 (per-capita GDP, CNY 85,698) per QALY gained.

Univariate sensitivity analysis was performed for the key parameters within their respective ranges to identify the main sensitive parameters. Probability sensitivity analyses based on 10,000 simulations were further conducted to determine the probability of each strategy being cost-effective compared with all other strategies.

Screening adherence rate was reported to have a substantial influence on the ICERs [19, 38, 39]. Potential harms associated with LDCT screening, including disutility associated with false-positive results, radiation-induced lung cancer risk, and overdiagnosis rate, were challenging to quantify and lack precise evidence in China. We hence created scenario analyses as followings: (1) improving screening adherence rate to 75% and 100%; (2) disregarding false-positive disutility; (3) excluding radiation-induced lung cancer risk; (4) ruling out overdiagnosis; (5) disregarding all above potential harms.

Subgroup analyses were performed to account for sex-specific differences in incidence rates and demographics. For robust results, we modeled a 100,000-person cohort, including both genders at age 50, and analyzed them separately.

Results

Base-case analysis

Compared to no screening, all 16 screening strategies increased QALYs and costs, by 13 to 2,016 QALYs and CNY 13,133,000 to 293,562,000 for 100,000 individuals over a lifetime horizon; and one-off screening at age 50 (50_one-off) was not cost-effective at the given WTP threshold. The cost-effectiveness efficiency frontier included six screening strategies. Screening at age 50, regardless of intervals, did not find a place on the efficiency frontier. Annual screening starting at 55 (55_annual) maximized QALY gains but was dominated by biennial screening starting at 55 (55_biennial), which was preceding it on the efficiency frontier, with an ICER of CNY 483,260 per QALY gained. Furthermore, the 55_biennial strategy was more cost-effective than the subsequent strategy, 60_biennial strategy, with an ICER of CNY 124,230 per QALY gained. Consequently, the 55_biennial strategy emerged as the optimal approach. (Table 2; Fig. 1).

Subgroup analysis showed similar patterns for both sexes, with 55_biennial being more cost-effective in males (Table S6-S7 & Fig. S6).

Sensitivity analysis

Univariate sensitivity analyses revealed that the results remained largely unchanged across parameter ranges (Fig. S7-S9 in the Supplement). ICER thresholds under extreme parameter values were detailed in Table S8-S13 in the Supplement. The OR_{FDR}, and discount rate had a significant impact on the ICERs. Subgroup analysis demonstrated a consistency in the results. The 55_annual strategy was optimal without discounting, for both sexes. In addition, for males, the 60_biennial strategy was optimal if OR_{FDR} was lower than 1.492, while 55_annual strategy would be optimal if it was 3.49. For females, the 55_biennial strategy maintained its optimal status across the full spectrum of OR_{FDR}.

Probabilistic sensitivity analysis indicated a 91.1% probability of 55_biennial being optimal at the WTP threshold. Below CNY 92,500 to 125,000 WTP, 60_biennial

Table 2 Base-case cost-effectiveness results compared among different strategies in 100,000 individuals over the lifetime

Strategy	Cost (CNY, thousand)	QALYs	Incremental Cost (CNY, thousand)		Incremental QALYs		ICER (CNY/QALY)	
			Vs No screening	Vs the strategy preceding it on the efficiency frontier	Vs No screening	Vs the strategy preceding it on the efficiency frontier	Vs No screening	Vs the strategy preceding it on the efficiency frontier
No screening	47,172	1,346,222	-	-	-	-	-	-
50_one-off	74,180	1,346,235	27,008	27,008	13	13	Dominated	Dominated
55_one-off	69,844	1,346,406	22,672	22,672	184	184	123,770	123,770
60_one-off	64,801	1,346,505	17,629	17,629	283	283	62,381	62,381
65_one-off[a]	60,305	1,346,508	13,133	13,133	286	286	45,934	45,934
65_triennial[a]	76,034	1,346,826	28,862	15,729	604	318	47,850	49,576
65_biennial	90,284	1,346,988	43,112	14,250	766	162	56,322	87,816
65_annual	133,424	1,347,261	86,252	57,390	1,039	435	83,024	131,721
60_triennial[a]	107,935	1,347,344	60,763	31,901	1,122	518	54,183	61,554
50_triennial	191,588	1,347,608	144,416	83,653	1,386	264	104,251	Dominated
55_triennial	139,067	1,347,617	91,895	31,132	1,395	273	65,904	114,062
60_biennial[a]	135,850	1,347,652	88,678	27,915	1,430	308	62,046	90,692
60_annual	206,314	1,347,891	159,142	70,464	1,669	239	95,397	Dominated
50_annual	429,412	1,347,963	382,240	293,562	1,741	311	219,584	Dominated
55_biennial[a]	175,816	1,347,973	128,644	39,966	1,751	321	73,471	124,230
50_biennial	252,412	1,347,976	205,240	76,596	1,754	3	117,031	Dominated
55_annual[a]	303,528	1,348,238	256,356	127,712	2,016	265	127,210	Dominated

a: These strategies comprised the cost-effectiveness efficiency frontier

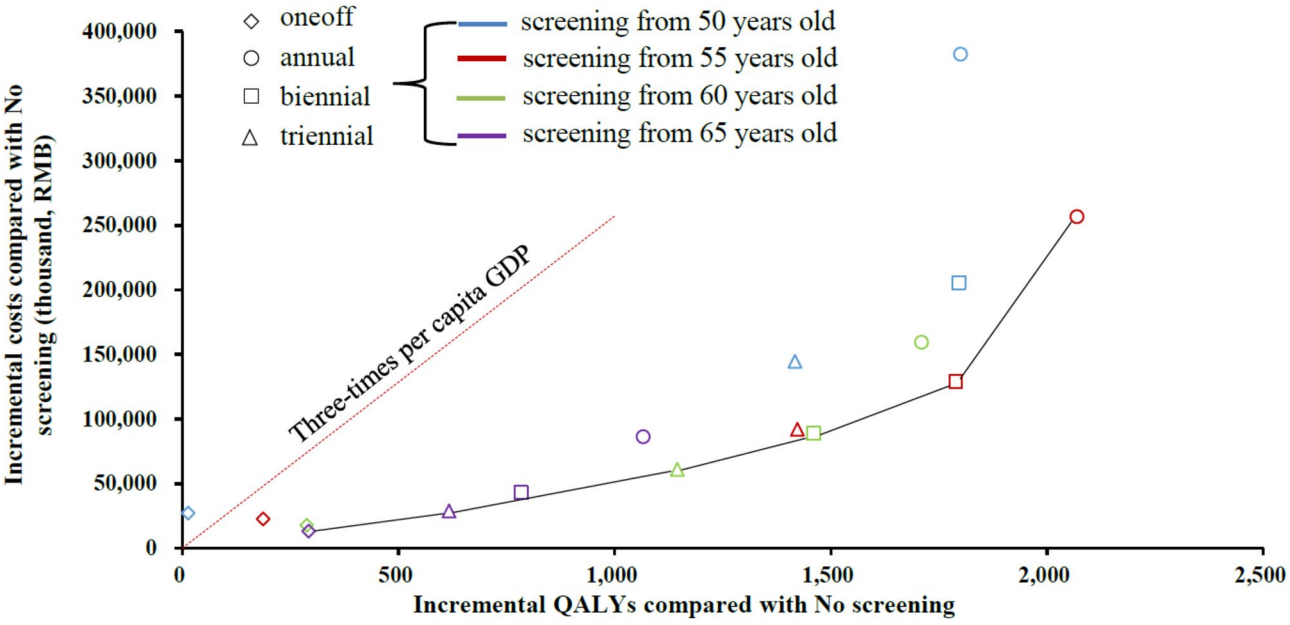

Fig. 1 Cost-effectiveness frontiers for all 16 screening strategies. Incremental QALYs and incremental costs of intervention strategies are obtained for 100,000 individuals

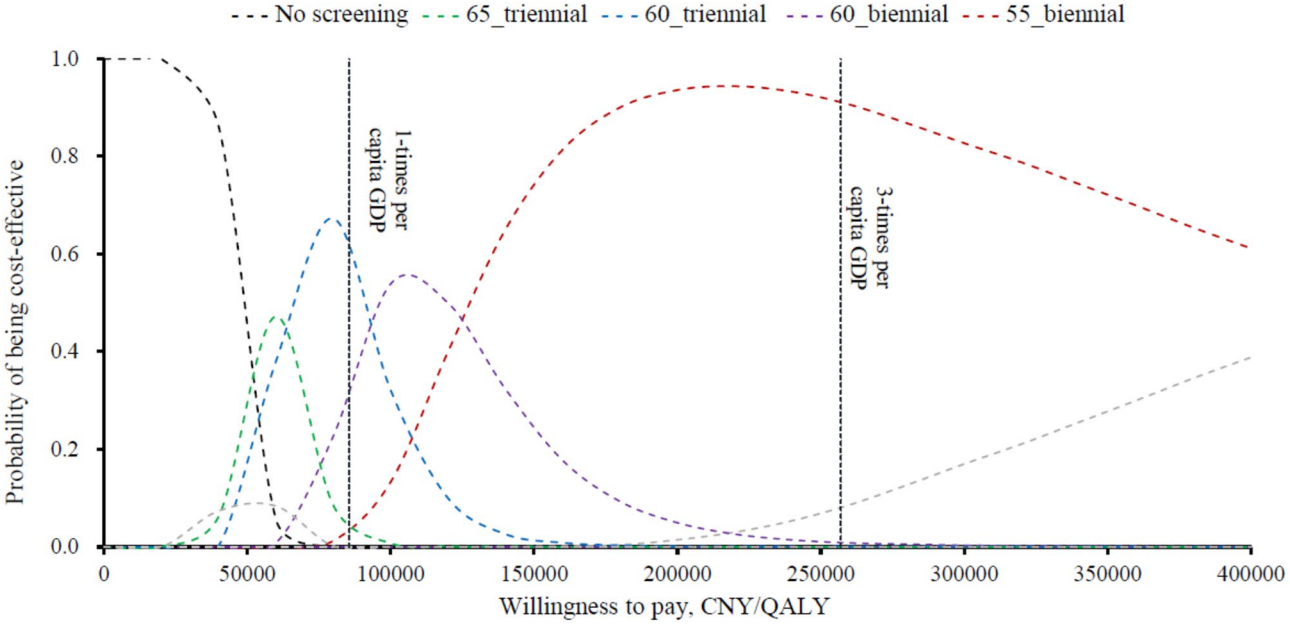

Fig. 2 Cost-effectiveness acceptability curves for all strategies. Intervention strategies that never have the highest probability of being cost-effective within the willingness-to-pay threshold of three-times per-capita GDP are represented in grey. QALY, quality-adjusted life years

was optimal, followed by 60_triennial at lower thresholds (Fig. 2). Subgroup analysis showed 55_annual was optimal for males when the WTP was above CNY 380,000 (Fig. S10).

Impact of improving screening adherence rate

The impact of improving screening adherence rate on ICERs were shown as Fig. S11 and Fig. 3. The results revealed that, at the given WTP threshold, except for 50_one-off and 50_annual, all screening strategies were cost-effective compared to no screening, under the assumption of 75% or 100% adherence. Higher adherence levels resulted in more QALYs gained. Probabilistic sensitivity analysis revealed that, at a 75% adherence rate, the 55_biennial strategy was most optimal at the given WTP threshold,, followed by the 55_triennial strategy; at a 100% adherence rate, the 55_ triennial strategy was most optimal, followed by the 55_biennial strategy.

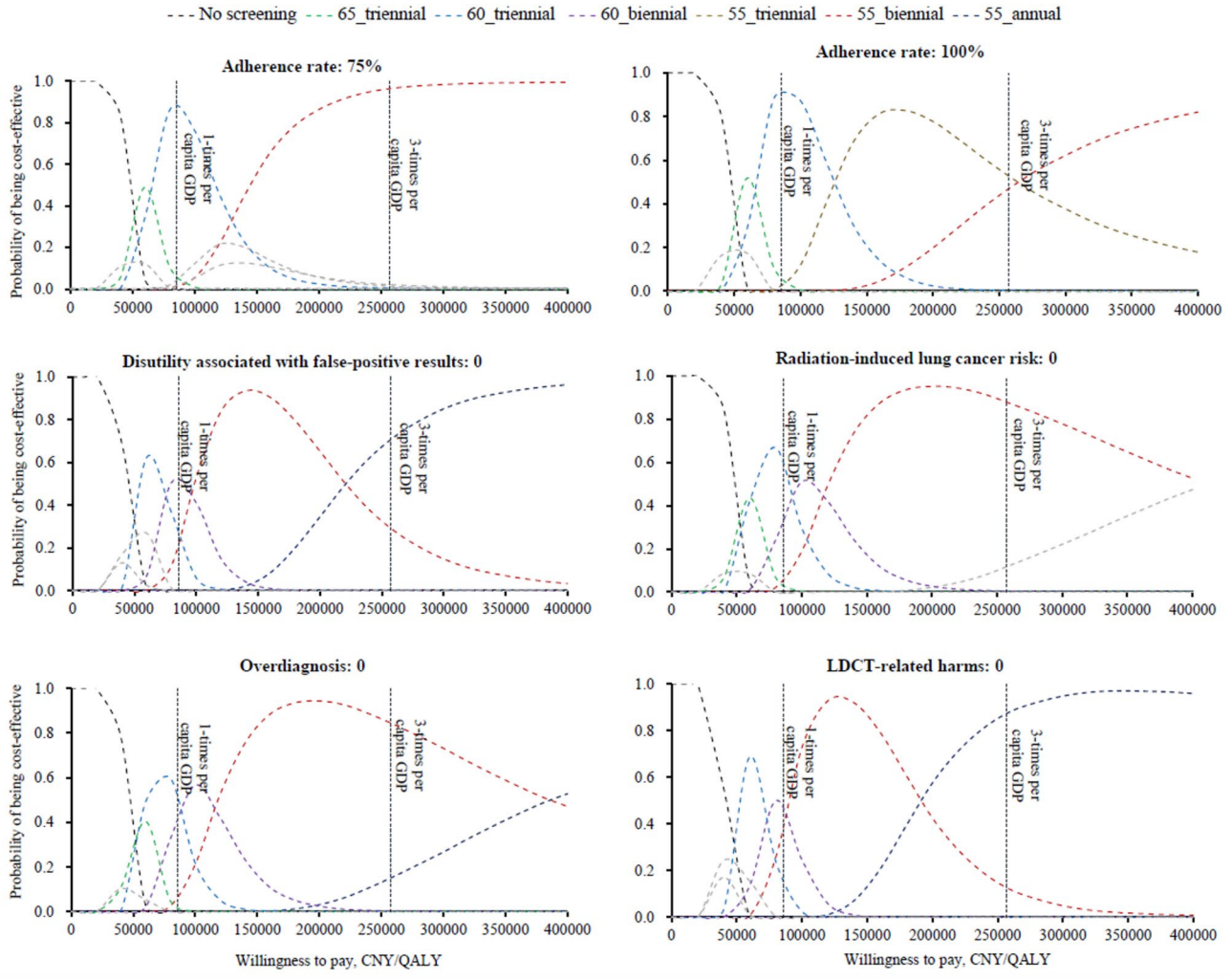

Fig. 3 Cost-effectiveness acceptability curves for all strategies at higher screening adherence rate or when disregarding potential LDCT-harms. Intervention strategies that never have the highest probability of being cost-effective within the willingness-to-pay threshold of three-times per-capita GDP are represented in grey. QALY, quality-adjusted life years

Subgroup analysis indicated that the 55_biennial strategy was most optimal for both males and females at a 75% adherence rate. However, at full adherence, the 55_triennial strategy emerged as the optimal strategy for females. (Fig. S12-S13).

Impact of disregarding potential harms from LDCT screening

The impact of disregarding potential harms on ICERs were shown as Fig. S14 and Fig. 3. The data demonstrated that more QALYs would be gained if we ignored the harms associated with LDCT screening. Notably, disregarding false-positive disutility, the 50_annual strategy maximized QALY gains, followed by the 55_annual strategy, which was identified as the most cost-effective strategy at the given WTP threshold. Conversely, when not accounting for the risk of radiation-induced lung cancer or overdiagnosis, the 55_biennial strategy, was deemed as the optimal approach under the same WTP threshold (Fig. 3).

Subgroup analysis, as detailed in Fig. S15-S16, revealed consistent patterns across different sex groups.

Discussion

Despite smoking being the primary lung cancer cause, diagnoses are rising among non-smokers in China and other Asian regions [9–11]. The present study targeted non-smokers with a FDR history of lung cancer, who were more likely to benefit from LDCT screening. The study indicated that, at a WTP threshold of three-times the 2022 per-capita GDP, LDCT screening is a cost-effective approach for non-smokers with a FDR history of lung cancer. However, this did not extend to the practice of one-off screening at the age of 50, due to the lower risk profile of this age group. The timing of starting screening

is crucial, and biennial screening at age 55 was the most cost-effective strategy for both sexes.

Compared to the recommendations for smokers, the optimal screening starting age and screening intervals were later and longer for non-smokers with an FDR history of lung cancer [6–8]. For example, the latest Chinese guideline, issued in 2021, advocated for annual LDCT screening for those who smoked at least 30 pack-years from the age of 50 [8]. Our findings affirm that heavy smokers face a significantly higher risk of developing lung cancer when compared to non-smokers who have a family history of the disease among their FDRs [8, 15]. This highlights the critical need for targeted screening initiatives that take into account the distinct risk profiles of non-smoking populations, ensuring that preventative measures are tailored to those who may be at elevated risk due to their genetic predisposition.

The familial risk of lung cancer, quantified by FDR-related OR, was a key sensitivity parameter. This OR had been reported to vary with country, sex, and smoking status [40]. Our analysis, therefore, targeted Chinese non-smokers, stratified by sex. Existing literature had demonstrated that the OR was predominantly influenced by the number of affected FDRs [41, 42]. For example, a case-control study in Anhui Province, China, reported an OR of 1.48 for individuals with one affected FDR, rising to 2.96 for those with two affected FDRs [42]. However, due to the limited data, our model did not initially account for this variation. Nevertheless, our sensitivity analysis provided valuable insights, revealing that for males, starting screening at 60 might be optimal with lower OR as 1.492, while higher OR favored annual screening from age 55. These findings show that personalizing screening based on family risk could be beneficial. More research is needed to clarify how many family members with lung cancer affects an individual's risk, helping to improve LDCT screening recommendations.

The WTP threshold is pivotal in determining the most cost-effective strategy. Our research indicated that a WTP threshold between CNY 92,500 to 125,000, corresponding to 1.08 to 1.46 times the 2022 per-capita GDP, made biennial screening starting at age 60 the most optimal approach. Further lowering the WTP threshold suggested that triennial screening, beginning at either 60 or 65, could be more suitable. These findings underscore the importance of aligning screening strategies with local economic contexts, as resource availability and societal values significantly influence cost-effectiveness thresholds. Thus, policy makers should weigh the cost and efficacy of screening strategies against the local economic context to select the most fitting approach.

Consistent with previous studies [19, 38, 39], our studies confirmed that higher adherence rates to LDCT screening were associated with greater gains in QALYs. With perfect adherence, triennial screening starting at 55 would be optimal, yielding a lower cost and a higher number of QALYs compared to biennial screening at the same age, which was the optimal strategy at a 75% adherence rate. This highlights the importance of raising public awareness of cancer screening. Potential harms of LDCT screening, such as false-positive results, radiation-induced cancer risk, and overdiagnosis, significantly influence its cost-effectiveness. Notably, when the disutility linked to false-positive results is excluded from the analysis, more frequent screening strategies tend to exhibit greater cost-effectiveness. Previous evidence has revealed that patients with indeterminate lung nodules experience anxiety specific to lung cancer [43] and distress while waiting for CT scan outcomes [44]. To mitigate these effects, screening programs should prioritize rapid reporting of results and provide educational resources to manage patient anxiety. Additionally, future research could quantify the long-term psychological burden of false positives in non-smokers, further informing screening guidelines.

Our subgroup analysis, aligning with a cohort study within the framework of CanSPUC, has identified that being male was a persistent risk factor for lung cancer among non-smokers [45]. While our results indicate that biennial screening starting at age 55 remains cost-effective for both sexes, the slightly lower QALY gains for females (1,719 QALYs vs. 1,747 QALYs for males in a 100,000-person cohort) reflect differences in baseline incidence rates. However, the incremental ICERs for both sexes remain well below the WTP threshold of three times the per-capita GDP (CNY 257,094/QALY). Given the minimal disparity in cost-effectiveness outcomes, we recommend maintaining a unified screening strategy for simplicity and equity in public health implementation. Future studies could explore personalized screening intervals based on sex-specific risk profiles if more granular data become available.

No existing studies have comprehensively evaluated the cost-effectiveness of LDCT for non-smokers in the context of lung cancer screening. A previous Chinese study did establish a risk-adapted starting age for LDCT screening [15]. This was done by taking into account a comprehensive set of risk factors, using a 10-year cumulative risk of lung cancer for heavy smokers as the threshold. The study identified that non-smokers with a FDR history of lung cancer should start annual screening at 53 for men and 55 for women. However, this study didn't consider the frequency of screening, long-term benefits, or potential risks, nor did it assess cost-effectiveness. A separate study conducted in Japan and the United States attempted to assess the cost-effectiveness of LDCT screening for non-smokers, but was constrained to a comparison of three screening strategies—LDCT, chest

X-ray, and no screening—thus failing to establish the optimal starting age or the ideal screening frequency [46].

Our findings provide actionable insights for public health policymakers aiming to expand lung cancer screening programs to high-risk non-smokers. First, integrating FDR history of lung cancer into national screening guidelines is critical to systematically identify high-risk non-smokers. Second, healthcare systems should focus on training providers in risk communication and shared decision-making, particularly for managing anxiety associated with indeterminate or positive screening results. Furthermore, improving screening adherence through public awareness campaigns and streamlined diagnostic pathways is critical to maximizing health benefits. Health systems should prioritize strategies that enhance participant engagement and minimize barriers to participation.

This study has several limitations. First, we had to estimate non-smoker lung cancer rates from overall rates, smoking proportions, and smoking-related risks, due to lack of direct data. Despite this systematic approach, this estimation might not fully capture non-smoker-specific nuances. Second, in our pursuit to craft universally applicable and easily executable guidance, we treated our modeled cohort as a single entity. This simplification led to a model that, while useful, oversimplified the complex realities of lung cancer progression in non-smokers. Notably, our analysis did not include lung cancer histology, a factor that could significantly alter parameters such as transition probabilities, stage-specific mortality rates, and the efficacy of LDCT screening. A 16-year evaluation of prospective cohort study conducted in China found, although significant differences in histology types were found between individuals who smoked and individuals who never smoked, the variation was slight with adenocarcinoma being the most prevalent in both groups, at 83.0% and 78.8%, respectively [47]. Consequently, without specific data on how histology affects these parameters, we relied on broader sources like the CanSPUC program and Chinese cohorts, which include both high-risk smokers and non-smokers. These limitations might lead to a slight overestimation of the benefits of LDCT screening for certain subgroups (e.g., non-adenocarcinoma cases). To address these gaps, future research should include longitudinal studies monitoring histology-specific outcomes in non-smokers and trials evaluating LDCT performance across diverse populations. Third, we used a health-care system perspective and did not include broader economic impacts such as productivity loss or the quality of life of caregivers. Lastly, the study did not account for the increased risk of secondary cancers potentially linked to radiation exposure during screening [48], nor did it address the implications of incidental findings that may arise from such screenings.

Conclusions

In conclusion, our study marks the first in-depth cost-effectiveness evaluation of LDCT screening for non-smokers with a FDR history of lung cancer. It concludes that biennial screening starting at age 55 is the most cost-effective strategy under a WTP threshold of three times the 2022 per capita GDP, for both sexes. The analysis identifies familial risk, WTP threshold, adherence rates and disutility associated with false-positive results as critical in shaping the optimal screening approach. By promoting the inclusion of high-risk non-smokers in screening programs, our research supports a more inclusive strategy for lung cancer prevention and control.

Abbreviations

CanSPUC	Cancer screening program started in urban China
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CNY	Chinese yuan
FDR	First-degree relative
GBD	Global Burden of Diseases
GDP	Gross domestic product
ICER	Incremental cost-effectiveness ratio
LDCT	Low-dose computed tomography
OR	Odds Ratio
QALY	Quality-adjusted life year
WTP	Willingness-to-pay

Supplementary Information

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Supplementary Material 1

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Author contributions

YL: Conceptualization, Methodology, Formal Analysis, Writing Original Draft; XLG, HFX, XYW, HWL, HW: Methodology, Data Curation, Validation, Review & Editing; RHK, QC, RRQ, MFZ, CC, LYZ, SZL: Validation, Review & Editing; YLQ: Project Administration, Review & Editing, Supervision; SKZ: Review & Editing, Supervision, Project Administration, Funding Acquisition; The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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