

University of Groningen



Cost-effectiveness of lung cancer screening by low-dose CT in China

Du, Yihui; Li, Yanju; Sidorenkov, Grigory; Vliegenthart, Rozemarijn; Heuvelmans, Marjolein A.; Dorrius, Monique D.; Groen, Harry J.M.; Liu, Shiyuan; Fan, Li; Ye, Zhaoxiang

Published in: Journal of the National Cancer Center

DOI: 10.1016/j.jncc.2021.11.002

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version Publisher's PDF, also known as Version of record

Publication date: 2022

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA): Du, Y., Li, Y., Sidorenkov, G., Vliegenthart, R., Heuvelmans, M. A., Dorrius, M. D., Groen, H. J. M., Liu, S., Fan, L., Ye, Z., Greuter, M. J. W., & de Bock, G. H. (2022). Cost-effectiveness of lung cancer screening by low-dose CT in China: a micro-simulation study. Journal of the National Cancer Center, 2(1), 18-24. https://doi.org/10.1016/j.jncc.2021.11.002

Copyright Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverneamendment.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Contents lists available at ScienceDirect

Journal of the National Cancer Center



journal homepage: www.elsevier.com/locate/jncc

Cost-effectiveness of lung cancer screening by low-dose CT in China: a micro-simulation study



Yihui Du^{1,†}, Yanju Li^{2,†}, Grigory Sidorenkov¹, Rozemarijn Vliegenthart³, Marjolein A. Heuvelmans¹, Monique D. Dorrius^{1,3}, Harry J.M. Groen⁴, Shiyuan Liu⁵, Li Fan⁵, Zhaoxiang Ye^{2,*}, Marcel J.W. Greuter³, Geertruida H. de Bock^{1,*}

¹ Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

² Department of Radiology, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Centre for

Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

³ Department of Radiology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

⁴ Department of Pulmonary Diseases, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

⁵ Department of Radiology, Shanghai Changzheng Hospital, the Second Military Medical University, Shanghai, China

ARTICLE INFO

Keywords: Cost-effectiveness Low-dose computed tomography Lung neoplasm Mass screening Microsimulation model General population

ABSTRACT

Background: The effectiveness of lung cancer screening with low-dose computed tomography (LDCT) has been established. The current study evaluates the cost-effectiveness of lung cancer screening with LDCT in a general population in China.

Methods: A previously validated micro-simulation model was used to simulate a cohort of men and women on a lifetime horizon in the presence and absence of LDCT screening. The modeling data were collected from numerous national and international sources. Simulated screening scenarios included different combinations of screening intervals and start and stop ages. Additional costs (valued in Chinese Yuan, CNY; 1 USD = 6.8976 CNY, 1 EUR = 7.8755 CNY in 2020), life-years gained (LYG) and mortality reduction due to screening were also determined. The costs and life-years were discounted by 3%. All results were scaled to 1,000 individuals. The average cost-effectiveness ratio (ACER) was calculated. A willingness-to-pay threshold of CNY 217.3k / LYG was considered. A healthcare system perspective was adopted.

Results: Compared to no screening, lung cancer screening by LDCT in a general Chinese population yielded 21.0 – 36.7 LYG in men and 9.2 - 16.6 LYG in women across the scenarios. For men, biennial LDCT screening yielded an ACER of CNY 171.4k – 306.3k / LYG relative to no screening. Biennial screening performed between 55 and 75 years of age was optimal at the defined threshold; it resulted in CNY 174.6k / LYG and a lung cancer mortality reduction of 9.1%, and this scenario had a 75% probability of being cost-effective. For women, the ACER ranged from CNY 364.2k to 1193.3k / LYG.

Conclusions: In China, lung cancer screening with LDCT in the general population including never smokers could be cost-effective for men with 75% probability, but not for women. The optimal strategy for men would be performing biennial screening between 55 and 75 years of age.

1. Introduction

Lung cancer is the most common cause of cancer death in both men and women in China.¹ It accounts for \sim 30% of all cancer-related deaths in men and 23% in women.¹ The age-standardized 5-year relative survival of patients with lung cancer is as low as 20%.² The main reason for this poor survival is that 47% of lung cancers are diagnosed at an advanced stage (stages IIIB- IV).³ Smoking is considered the primary risk factor for lung cancer. In the Americas, 88% of lung cancer deaths in men and 79% in women are attributable to smoking.⁴ In Europe, these numbers are 92% and 62%, respectively.⁴ However, in China, only 45% of lung cancer deaths in men and 6% in women are attributable to smoking.⁵ Because nearly half of lung cancers are diagnosed in neversmokers, smoking is not the only major risk factor of lung cancer in

* Corresponding authors.

https://doi.org/10.1016/j.jncc.2021.11.002

2667-0054/© 2021 Chinese National Cancer Center. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

E-mail addresses: zye@tmu.edu.cn (Z. Ye), g.h.de.bock@umcg.nl (G.H. de Bock).

[†] These authors contributed equally to this work.

Received 29 June 2021; Received in revised form 29 October 2021; Accepted 2 November 2021



Fig. 1. Flowchart of the micro-simulation model for lung cancer screening

China³; also factors such as passive smoking, air pollution, and low fruit intake are thought to play a major role in $China^{5,6}$.

Screening for lung cancer with low-dose computed tomography (LDCT) has been demonstrated to be effective in heavy smokers in Western countries⁷. In a Western setting, lung cancer screening by LDCT in a high-risk group has shown a reduction in lung cancer mortality by 17%.8 The high-risk group in Western countries is defined based on the age and smoking behavior of the individuals. The National Lung Screening Trial (NLST) applied inclusion criteria of smokers aged between 55 and 74 years with \geq 30 pack-years of smoking, which only covers 26.7% of the lung cancers diagnosed in the US population aged >40 years.⁹ If we would apply the NLST criteria to the Chinese population, more patients would not benefit from screening because nearly half of lung cancers are diagnosed in never-smokers in China and this population is not eligible for screening. A lung cancer screening study in Shanghai showed that the NLST criteria would miss 88% of the lung cancer cases detected in the participants with at least one risk factor of lung cancer.¹⁰ There is no clear evidence regarding which risk factors should be used to define a high-risk population for lung cancer screening in a Chinese population.¹¹ Several lung cancer screening studies are ongoing and the inclusion criteria are not restricted to smoking alone.¹²⁻¹⁴ From the perspective of identifying most lung cancers, Liu et al. proposed to implement lung cancer screening by LDCT in the whole Chinese population aged \geq 40 years.¹⁵

The cost-effectiveness of lung cancer screening by LDCT has been analyzed in several countries and the results varied.^{16–18} These studies were conducted in smokers and the costs related to screening and lung cancer diagnosis and treatment were country-specific, which makes it complicated to transfer these results on cost-effectiveness studies to the Chinese context. Therefore, we aim to evaluate the cost-effectiveness of lung cancer screening by LDCT in a general population in China. We present the following article in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Reporting Checklist.

2. Methods

2.1. Model overview

A Simulation Model on Radiation Risk and Cancer Screening (SiM-RiSc) was used, which was previously validated and described in detail.¹⁶ Fig. 1 depicts the flowchart of the model. This model simulates individual life histories from birth to death as well as the development of lung cancer. When screening is modeled, small lung cancers can be detected according to a size-dependent sensitivity of LDCT screening. The participants with detected lung cancer will have a longer survival due to the earlier detection and a higher survival probability compared to no screening.

Several components, included in the model, were extensively described in previous literature.¹⁶ Briefly, in the life history component, a natural death age was simulated based on an age-specific life expectancy separately for both men and women. In the tumor development component, tumor onset in a proportion of the individuals was simulated based on a sex- and age-specific tumor incidence distribution. Subsequently, the tumor was believed to grow exponentially¹⁹. Tumor volume doubling time (VDT) and the size of symptomatic tumors were randomly sampled for each individual from log-normal distributions. After detecting in a screening or no screening setting, the number of survival years was calculated in the tumor survival component based on tumor size, lymph node, and metastasis (TNM-stage). The resulting death age because of the tumor was compared with the natural death age, and the lower one of the two ages was taken as the final death age. In the screening component, the sensitivity and specificity of the screening LDCT technique and the screening interval were included. In addition, in the tumor induction component, the number of radiation-induced tumors due to screening was calculated.

2.2. Simulated population and screening strategies

Two cohorts of the Chinese general population including 100,000 men and 100,000 women, were simulated. Based on the inclusion criteria of the NLST trial and the Chinese context, the Chinese guidelines for lung cancer screening recommend commencing screenings at age 50 and stopping at age 74 years.²⁰ In addition, to explore the cost-effectiveness of younger screening start ages, the start ages of 40 and 45 years old were also included. Therefore, in this study 16 screening startages (40, 45, 50, and 55 years), screening stop age (70 and 75 years), and screening intervals (annual and biennial) by comparing to no screening. Ethical approval was waived for this simulation study.

2.3. Parameters of the model

The following three components were adjusted in this study in order to simulate the Chinese population. The life expectancy of the Chinese population was extracted from the WHO global health observatory data repository, where sex-specific all-cause mortality for the most recent

Table 1

Input parameters of the SiMRiSc model for evaluating the cost-effectiveness of lung cancer screening by LDCT in the Chinese population.

Input parameter	Value		Reference		
Life expectancy at hirth [years]	Men Womer		²¹ , Supplementary Fig. 1		
Life expectancy at birth [years]	75.0	77.9			
Lung cancer incidence	Men	Women			
Cumulative risk until 74 years	7.0%	3.1%			
Cumulative lifetime risk	21.0%	9.0%			
Mean age at diagnosis of lung cancer [years]	66.3	66.0			
Incidence peaking age [years]	80.0	80.0			
SD of the incidence distribution [years]	14.0	15.0			
Lung cancer growth			41,42		
VDT, log-transformed geometric mean	4.59 ± 0.21				
SD of log-transformed VDT	0.74				
Symptomatic tumor component			42,43		
diameter, log-transformed geometric mean	3.04 ± 0.014				
SD of log-transformed diameter	0.61				
T	Supplementary Table 1, Supplementary Ta	16			
Lung cancer survival	Supplementary Fig. 4				
LDCT sensitivity and specificity					
	0%; diameter $< 3 \text{ mm}$		44		
LDCT sensitivity	(0.5*diameter-1.5)*100%; 3 mm ≤ diamete				
-	100%; diameter $\geq 5 \text{ mm}$				
LDCT specificity	94.36 % (95% CI: 93.88-94.81%)		24		
Lung cancer induction	Men	Women			
Equivalent lung organ dose per LDCT scan [mSv]	2.3	2.7	45		
Estimate for calculating ERR of lung cancer per Sv	0.32 (95% CI: 0.15- 0.70)	1.40 (95% CI:			
exposure		0.94-2.10)			
Cost (Chinese Yuan)					
LDCT examination	550		28		
Diagnosis per patient	1793		Estimated from a tertiary hospital		
Treatment per patient	66,020 (95% CI: 62,664–69,376)	3			

Abbreviations: ERR, excess relative risk; LDCT, low-dose computed tomography; mSv, milli-Sievert; SD, standard deviation; SiMRiSc, simulation model on radiation risk and cancer screening; VDT, volume doubling time.

year (2016) is provided (Supplementary Fig. 1).²¹ The lung cancer incidence in the Chinese general population, which was assumed as a normal distribution based on age, was estimated for men and women based on a 2015 report of the cancer statistics in China (Supplementary Fig. 2 and Supplementary Fig. 3).^{22,23} The specificity of lung cancer screening by LDCT was extracted from a study of LDCT screening for lung cancer in the Chinese population.²⁴ The input parameters of other components including VDT of lung cancer, the size distribution of symptomatic lung cancer, lung cancer survival (Supplementary Table 1 and Supplementary Table 2; Supplementary Fig. 4), sensitivity of LDCT screening, and tumor induction are described in the supplement to the current study and in a previous publication,¹⁶ and are also summarized in Table 1. The attendance rate was set at 100%. To evaluate the cost-effectiveness of lung cancer screening with the currently reported attendance rates, an attendance of 33.9% in men and 50.9% in women was additionally applied.25

A healthcare system perspective was adopted.²⁶ Costs related to the LDCT examination and diagnosis and treatment of lung cancer were considered based on the Chinese context and valued in the Chinese Yuan (CNY) currency. To make an international comparison, the annual average exchange rate of USD/CNY and EUR/CNY in 2020 was provided as follows, 1 USD = 6.8976 CNY, 1 EUR = 7.8755 CNY.²⁷ The cost of LDCT screening was estimated between CNY 400 and 700 per scan.²⁸ A median value of CNY 550 was applied for the LDCT cost in the model. The cost of diagnostic techniques for lung cancer was obtained from the Tianjin Cancer Hospital (Supplementary Table 3). With the proportion of utilization of each diagnostic technique reported from a multicenter survey in China,³ the weighted average diagnostic cost was estimated at CNY 1,793 per patient. The treatment cost for lung cancer was extracted from a multicenter study in China. The reported treatment regimens included surgery, chemotherapy only, radiotherapy only, targeted therapy, surgery and chemotherapy, chemotherapy and radiotherapy, and surgery and chemotherapy and radiotherapy³; the average treatment cost was CNY 66,020 per patient.³ Discounting of 3% for costs and lifeyears was applied.²⁹ Values of all input parameters are summarized in Table 1.

2.4. Validation of the model

The model was validated by comparing the modeling outcomes with the observed data from a lung cancer screening study in China.²⁴ The number of screen-detected lung cancers and interval lung cancers in the first and subsequent rounds were validated by comparison with the observed data in the Sichuan population.²⁴ The size distribution of screen-detected lung cancers was validated by comparison with observed data in the Shanghai general population.³⁰ A ratio of expected/modeled (E) and observed (O) numbers with 95% confidence interval (CI) was calculated.

2.5. Outcomes and cost-effectiveness

The numbers were calculated for life years, lung cancer deaths, interval lung cancers, cancer stage, false positives, and radiation-induced lung cancers on a lifetime horizon, and cost in the presence and absence of screening. All results were scaled to 1,000 individuals. The average cost-effectiveness ratio (ACER) was defined as the ratio of the difference in costs and the difference in life years of the screening intervention compared to no screening. The willingness-to-pay threshold was approximately three times the gross domestic product (GDP) per capita in China in 2020 (US\$ 10500.4).³¹ An ACER of < CNY 217.3k per lifeyears gained (LYG) (US\$ 31.5k /LYG) was, therefore, an indication that lung cancer screening is cost-effective relative to no screening. A scenario was considered efficient if it was not dominated by another scenario or a linear combination of other scenarios. The efficient scenarios constituted the efficient frontier. For the efficient scenarios, the incremental cost-effectiveness ratios (ICER) were determined by dividing the incremental costs by the incremental health effects.

Table 2

Outcomes of the scenarios of lung cancer screening by LDCT per 1000 men and per 1000 women.

Scenario*	Number of discounted io* LYG [#]		Number of averted death		Number of false positives		Discounted additional cost (million CNY) [#]		LC mortality reduction		ACER (kCNY)	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
A-40-70	28.0	10.6	5.0	0.8	1531	1590	12.3	12.6	10.0%	3.2%	440.6	1,193.3
A-40-75	31.0	12.2	6.5	1.6	1691	1781	13.1	13.5	13.0%	6.1%	422.2	1,105.9
A-45-70	31.0	12.9	5.1	1.2	1260	1316	10.8	11.1	10.0%	4.5%	350.0	861.7
A-45-75	34.5	14.8	6.6	1.9	1419	1508	11.7	12.1	13.0%	7.4%	340.1	821.9
A-50-70	32.7	14.3	5.0	1.5	992	1046	9.2	9.4	9.8%	5.6%	280.0	659.9
A-50-75	36.7	16.3	6.5	2.1	1151	1237	10.2	10.6	12.8%	8.2%	277.3	649.2
A-55-70	30.6	14.2	4.5	1.5	731	779	7.3	7.5	9.0%	6.0%	237.2	530.8
A-55-75	35.3	16.6	6.0	2.2	890	971	8.5	8.9	12.0%	8.6%	239.7	536.5
B-40-70	21.0	9.2	3.9	1.1	788	818	6.4	6.5	7.8%	4.1%	306.3	714.1
B-40-75	22.7	10.0	4.8	1.5	852	895	6.8	6.9	9.6%	5.7%	297.7	686.2
B-45-70	22.9	10.1	3.8	1.1	634	661	5.6	5.7	7.5%	4.3%	243.4	566.0
B-45-75	25.9	11.6	5.1	1.8	729	775	6.1	6.3	10.1%	6.8%	237.4	541.9
B-50-70	24.6	11.7	3.9	1.4	518	547	4.9	5.0	7.7%	5.2%	198.6 ^{\$}	425.2
B-50-75	26.9	12.9	4.8	1.8	582	623	5.3	5.5	9.5%	6.9%	198.0 ^{\$}	422.4
B-55-70	22.1	10.6	3.3	1.2	369	392	3.8	3.9	6.5%	4.6%	171.4 ^{\$}	364.2
B-55-75	26.1	12.8	4.6	1.8	465	507	4.5	4.7	9.1%	7.0%	174.6 ^{\$}	368.3

Abbreviations: ACER, average cost-effectiveness ratio; CNY, Chinese Yuan; kCNY, thousand Chinese Yuan; LC, lung cancer; LDCT, low dose computed tomography; LYG, life years gained.

* Screening interval (A-annual, B-biennial) – screening start age – screening stop age.

[#] Costs and LYG were discounted by 3% annually.

 $\$ Cost-effective scenarios at a cost-effectiveness threshold of CNY 217.3k / LYG.

2.6. Sensitivity analysis

One-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed for the optimal scenario. In one-way sensitivity analysis, the impact of costs and attendance rate on the costeffectiveness of LDCT screening were evaluated. A lower cost of the LDCT examination (CNY 400) and a higher cost of LDCT examination (CNY 700) were applied in the sensitivity analysis. The costs of lung cancer diagnosis and treatment showed variation by 20% compared to the base value. Since immunotherapy for advanced lung cancer has gradually been approved and applied in China, the treatment cost of stage IV lung cancers was increased by 50% in order to evaluate the effect on cost-effectiveness. Imperfect attendance was evaluated by assuming a 50% attendance rate. The PSA was performed using 100 Monte Carlo simulations to test the robustness of the model.

3. Results

3.1. Model validation results

The number of simulated screen-detected lung cancers was 5.9 per 1000 screens in the first screening round and ranged from 2.7 to 3.1 per 1000 screens in the four subsequent screening rounds. The number of simulated interval lung cancers was 0.21 / 1000 screens in the first screening round and 0.26 / 1000 screens in the 4 subsequent screening rounds. The simulated size distribution of screen-detected lung cancers in the first screening round was 55.8% for diameter ≤ 10 mm, 29.2% for diameter between 10 and 20 mm, and 15.0% for diameter > 20 mm. The modeled numbers were within the 95% CIs of the observed numbers in an LDCT screening program in the Chinese population and the E/O ratios were close to 1.0 and non-significant (Supplementary Table 4). The modeled size distributions were also within the 95% CI of the observed sizes, except for a slight overestimation of the largest tumors; again the E/O ratios were not significant (Supplementary Table 5).

3.2. Cost-effectiveness results

Table 2 displays the outcomes of all modeled screening scenarios per 1,000 screened participants with a 100% attendance rate. Compared

to no screening, lung cancer screening by LDCT yielded 21.0 - 36.7 discounted LYG in men and 9.2 - 16.6 discounted LYG in women across the different scenarios. The number of averted deaths ranged from 3.3 to 6.6 in men and from 0.8 to 2.2 in women. Among all the screen-detected lung cancers, stage I disease accounted for 55.0%-59.6% in men and 56.9%-61.6% in women (Supplementary Table 6 and Supplementary Table 7). For men, the ACER relative to no screening was CNY 237.2k –440.6k in the annual screening scenarios and CNY 171.4k – 306.3k in the biennial screening scenarios. For women, these values were CNY 530.8k - 1193.3k in the annual screening scenarios and CNY 364.2k - 714.1k in the biennial screening scenarios.

When applying the cost-effectiveness threshold of CNY 217.3k / LYG, two biennial screening scenarios for men, B-55-70 and B-55-75 were cost-effective compared to no screening and also efficient. The ACER was CNY 171.4k and 174.6k, respectively. The ICER of scenario B-55-75 was 192.6k, the largest below the willingness to pay threshold; therefore it was considered optimal for men. For women, lung cancer screening was not cost-effective in all evaluated scenarios (Fig. 2).

The cost-effectiveness of the evaluated scenarios with a reported attendance rate of 33.9% in men and 50.9% in women is presented in Supplementary Table 8. Two annual (A-55-70 and A-55-75) and four biennial screening scenarios (B-50-70, B-50-75, B-55-70, and B-55-75) in men were cost-effective and the ACER ranged from CNY 165.8k to 202.9k. None of the scenarios for women were cost-effective.

3.3. Sensitivity analyses

The ACER was most sensitive to the cost of the LDCT examination in the one-way sensitivity analysis. When the cost of the LDCT examination decreased from CNY 550 to 400, the ACER decreased from CNY 174.6k to 137.3k. If the cost of the LDCT examination increased to a price as high as CNY 700, scenario B-55-75 in men still would be cost-effective when applying the threshold of CNY 217.3k. Moreover, when the treatment cost for stage IV lung cancer rose by 50% from CNY 66,020 to 99,030, the ACER decreased from CNY 174.6k to 168.2k. (Fig. 3)

The results of the PSA show that there was a probability of 75% that the ACER of B-55-75 is below the cost-effectiveness threshold (Supplementary Fig. 5).



Fig. 2. The cost-effectiveness in cost per life-years gained (LYG) of all evaluated scenarios for men and women. The dashed line is the cost-effectiveness threshold of CNY 217.3k / LYG. The scenarios are labeled screening interval (A, Annual; B, Biennial) - screening start age - screening stop age. The scenarios above the dashed line are cost-effective. The solid grey line is the efficient frontier for men (blue) and women (purple) and the scenarios are labeled with the incremental cost-effectiveness ratio (ICER).



Fig. 3. Tornado diagram of the one-way sensitivity analysis on the average cost-effectiveness ratio of scenario B-55-75 in men. The vertical line indicates the base value for the average cost-effectiveness ratio of B-55-75. The blue bars indicate results when decreasing the base-case value of the input parameter, red bars indicate results when increasing the base-case value of the input parameter. CNY, Chinese Yuan; LDCT, low-dose computed tomography; LYG, life-years gained.

4. Discussion

This modeling study explored the cost-effectiveness of national lung cancer screening with LDCT in the general Chinese population, including never smokers, between 40 and 75 years old. The results showed that biennial screening for lung cancer with LDCT in men had a 75% probability of being cost-effective, and the optimal strategy was biennial screening from age 55 to 75, yielding an ACER of 174.6k. Lung cancer screening in women was not cost-effective in any of the evaluated scenarios in the current study. The cost-effectiveness was most sensitive to the cost of the LDCT examination.

In the present study, the strategy of annual screening from age 55 to 75 years in men had an ACER of CNY 239.7k, which is equivalent to USD 34.8k or EUR 30.4k if applying the average currency exchange rate from China foreign exchange trade system 2020 (6.8976 CNY/USD, 7.8755 CNY/EUR).27 The ACER of the NLST strategy (annual screening in heavy smokers aged 55-74 years) in the US population was USD 36.4k per LYG with the 3% discounting rate for cost and life years.³² Although our results with Chinese data are similar to those obtained in US heavy smokers, our study simulated screening in a general population. In addition, the LDCT examination in the US was much more expensive than in our study (US\$271 vs US\$ 80).32 The cost-effectiveness analysis of annual screening in heavy smokers aged between 55 and 75 years in Taiwan indicated that the ACER was USD 19.7k per quality-adjusted LYG with the 3% discounting rate for cost and life years,³³ which is much lower than our study mainly due to the much higher risk population included for screening in the previous study in Taiwan. In our study, none of the evaluated annual screening strategies in men were cost-effective because their ACERs exceeded the threshold of 3-fold GDP per capita in China. However, two biennial screening strategies in men were potentially cost-effective and efficient with ACERs slightly below the threshold. Given that over 70% of Chinese men aged \geq 45 years are current or former smokers,³⁴ the optimal strategy for males would be biennial screening between 55 and 75 years of age.

None of the evaluated screening strategies in the general female population were cost-effective due to the much lower lung cancer incidence in women than in men. Therefore, screening for lung cancer should not be recommended for general women in China. The lung cancer incidence has increased from 17.6 per 100 000 women in 2005 to 25.8 in 2014 but remained stable for men in Shanghai, China.³⁵ Although the rising incidence among women might in part be due to the introduction of LDCT screening, the role of air pollution and genetic susceptibility of relatively young women requires further research.³⁶ Therefore, the identification of the risk factors in Chinese women and selection of high-risk women for lung cancer screening should contribute to a cost-effective screening strategy.

When applying the reported current attendance rate, more screening scenarios in men became cost-effective compared to a 100% attendance. However, the number of LYG for those scenarios was much decreased. A high participation rate is critical for a successful lung cancer screening program and should therefore be achieved to fully realize the benefits of lung cancer screening.³⁷

The sensitivity analysis showed that the ACER was most sensitive to the cost of the LDCT examination. This is reasonable because LDCT cost contributes most to the total costs of the screening program.³² Even if the cost of the LDCT examination increases to a price as high as CNY 700, the scenario of biennial screening in men aged 55-75 years will still be cost-effective. Besides, if immunotherapy is applied nationally in China, the increased treatment cost for advanced lung cancers in the non-screening setting overwhelmed that in screening setting due to the much higher proportion of advanced lung cancer among patients with lung cancer detected outside the scope of a screening more cost-effective in men. The PSA evaluated the robustness of being cost-effective at 75%, which would be of use for decision-makers.

To our knowledge, this study is the first to evaluate the costeffectiveness of lung cancer screening in a general population in China. Compared to prior publications in other countries, the main strength is that the cost-effectiveness was evaluated in a general population, including never smokers. The findings could be of interest for policy-makers for decision-making about the implementation of lung cancer screening in China.

There are some limitations to this study. First, for the validation of the model, the observed lung cancer detection rate for each screening round was obtained from a screening study in a high-risk group of smokers, due to a lack of observed data for multiple screening rounds in the general population.²⁴ However, the reported first-round detection rate in that study was similar to the data obtained from a meta-analysis for the first-round lung cancer detection rate in a general population [0.6% vs. 0.7% (95% CI: 0.5%-1.0%)].38. In addition, the modeled numbers of screen-detected and interval lung cancers were well within the 95% CI of the observed data, although generally lower than the observed point estimates. Second, the costs of diagnostic techniques for lung cancer were obtained from one tertiary hospital in China, and the diagnostic costs might be not generally applicable across the country. In the sensitivity analysis, the effect of varying the diagnostic cost was evaluated. Third, the lung cancer survival data were obtained from a report of the International Association for the Study of Lung Cancer (IASLC), due to the lack of data from the Chinese population. However, the 5year survival of stage-specific lung cancer in China was comparable with that in the IASLC report.^{2,39,40} Fourth, the distribution of histological types of lung cancer in the population was not incorporated in the model. However, we estimate that such stratification would have a limited effect on the overall cost-effectiveness estimation for the evaluated population.

5. Conclusions

Overall, screening for lung cancer with LDCT in the Chinese general population including never smokers is could be cost-effective for men, but cost-prohibitive for women. Biennial LDCT screening from age 55 to 75 years in Chinese men was found to be the potentially optimal screening regime with regards to costs and effectiveness.

Declarations of competing interest

The authors declare that they have no conflict of interests.

Acknowledgment

Yihui Du is grateful for the PhD financial support from China Scholarship Council (CSC file No. 201708340072). This funding source had no role in the design, data collection, management, analysis, interpretation, preparation, review, approval of the manuscript, and decision to submit the manuscript for publication.

Author contributions

Y.D., Y.L., G.S., Z.Y., H.G. and G.B. conceived and designed this study. Y.L., G.S., R.V., H.G., S.L., L.F., Z.Y., M.G. and G.B. performed the administrative support. All of the authors performed the collection and assembly of data, data analysis and interpretation, manuscript writing and final approval.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2021.11.002.

References

- Cao M, Li H, Sun D, et al. Cancer burden of major cancers in China: A need for sustainable actions. *Cancer Commun (Lond)*. 2020;40(5):205–210. doi:10.1002/cac2.12025.
- Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003– 15: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Heal*. 2018;6(5):e555–e567. doi:10.1016/s2214-109x(18)30127-x.
- Shi JF, Wang L, Wu N, et al. Clinical characteristics and medical service utilization of lung cancer in China, 2005-2014: Overall design and results from a multicenter retrospective epidemiologic survey. *Lung Cancer*. 2019;128:91–100. doi:10.1016/j.lungcan.2018.11.031.
- World Health Organization. Mortality attributable to tobacco. WHO global report. Geneva: World Health Organization; 2012.
- Xia C, Zheng R, Zeng H, et al. Provincial-level cancer burden attributable to active and second-hand smoking in China. *Tob Control.*, 2019;28(6):669–675. doi:10.1136/tobaccocontrol-2018-054583.
- Chen W, Xia C, Zheng R, et al. Disparities by province, age, and sex in sitespecific cancer burden attributable to 23 potentially modifiable risk factors in China: a comparative risk assessment. *Lancet Glob Heal*. 2019;7(2):e257–e269. doi:10.1016/s2214-109x(18)30488-1.
- Duffy SW, Field JK. Mortality Reduction with Low-Dose CT Screening for Lung Cancer. N Engl J Med. 2020;382(6):572–573. doi:10.1056/NEJMe1916361.
- Sadate A, Occean B V, Beregi JP, et al. Systematic review and meta-analysis on the impact of lung cancer screening by low-dose computed tomography. *Eur J Cancer*. 2020;134:107–114. doi:10.1016/j.ejca.2020.04.035.
- Pinsky PF, Berg CD. Applying the National Lung Screening Trial eligibility criteria to the US population: what percent of the population and of incident lung cancers would be covered? J Med Screen. 2012;19(3):154–156. doi:10.1258/jms.2012.012010.
- Yang W, Qian F, Teng J, et al. Community-based lung cancer screening with lowdose CT in China: Results of the baseline screening. *Lung Cancer*. 2018;117:20–26. doi:10.1016/j.lungcan.2018.01.003.
- Oudkerk M, Liu S, Heuvelmans MA, et al. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol.* 2021;18(3):135–151. doi:10.1038/s41571-020-00432-6.
- Cheng YI, Davies MPA, Liu D, et al. Implementation planning for lung cancer screening in China. Precis Clin Med. 2019;2(1):13–44. doi:10.1093/pcmedi/pbz002.
- Du Y, Sidorenkov G, de Bock GH, et al. Methods of computed tomography screening and management of lung cancer in Tianjin: design of a population-based cohort study. *Cancer Biol Med.* 2019;16:181–188. doi:10.20892/j.issn.2095-3941.2018.0237.
- Du Y, Li Q, Sidorenkov G, et al. Computed Tomography Screening for Early Lung Cancer, COPD and Cardiovascular Disease in Shanghai: Rationale and Design of a Population-based Comparative Study. Acad Radiol. 2021;28(1):36–45. doi:10.1016/j.acra.2020.01.020.
- Liu D, Huang Y, Zhou Q, et al. Pulmonary nodules/lung cancer comprehensive management mode: Design and application. *Chinese J Lung Cancer*. 2020;23(5):299–305. doi:10.3779/j.issn.1009-3419.2020.103.06.
- Du Y, Sidorenkov G, Heuvelmans MA, et al. Cost-effectiveness of lung cancer screening with low-dose computed tomography in heavy smokers: a microsimulation modelling study. *Eur J Cancer*. 2020;135:121–129. doi:10.1016/j.ejca.2020.05.004.
- Veronesi G, Navone N, Novellis P, et al. Favorable incremental cost-effectiveness ratio for lung cancer screening in Italy. *Lung Cancer*. 2020;143:73–79. doi:10.1016/j.lungcan.2020.03.015.
- Wade S, Weber M, Caruana M, et al. Estimating the Cost-Effectiveness of Lung Cancer Screening with Low-Dose Computed Tomography for High-Risk Smokers in Australia. *J Thorac Oncol.* 2018;13(8):1094–1105. doi:10.1016/j.jtho.2018.04.006.
- Heuvelmans MA, Vliegenthart R, de Koning HJ, et al. Quantification of growth patterns of screen-detected lung cancers: The NELSON study. *Lung Cancer*. 2017;108:48– 54. doi:10.1016/j.lungcan.2017.02.021.
- Zhou Q, Fan Y, Wang Y, et al. China national lung cancer screening guideline with lowdose computed tomography (2018 version). *Chinese J Lung Cancer*. 2018;21(2):67–75. doi:10.3779/j.issn.1009-3419.2018.02.01.
- GHO | By category | Life tables by country China. https://apps. who.int/gho/data/view.main.60340. Accessed December 29, 2020.
- Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–132. doi:10.3322/caac.21338.

- 23. National Data. https://data.stats.gov.cn/english/. Accessed December 29, 2020.
- 24. Qiao L, Zhou P, Li B, et al. Performance of low-dose computed tomography on lung cancer screening in high-risk populations: The experience over five screening rounds in Sichuan, China. *Cancer Epidemiol.* 2020;69:101801. doi:10.1016/j.canep.2020.101801.
- Guo LW, Chen Q, Shen YC, et al. Evaluation of a low-dose computed tomography lung cancer screening program in Henan, China. JAMA Netw Open. 2020;3(11):e2019039. doi:10.1001/jamanetworkopen.2020.19039.
- 26. Peking University, China Pharmaceutical University, Fudan University et al. China Guidelines for Pharmacoeconomic Evaluations. 2019.
- CNY Central Parity Rate CFETS. http://www.chinamoney.com.cn/english/bmkcpr/. Accessed January 19, 2021.
- Financing Lung Cancer Screening in China | Milken Institute. https://milkeninstitute.org/reports/financing-lung-cancer-screening-china. Accessed December 29, 2020.
- Attema AE, Brouwer WBF, Claxton K. Discounting in economic evaluations. *Pharma-coeconomics*. 2018;36(7):745–758. doi:10.1007/s40273-018-0672-z.
- Fan L, Wang Y, Zhou Y, et al. Lung cancer screening with low-dose CT: baseline screening results in Shanghai. Acad Radiol. 2019;26(10):1283–1291. doi:10.1016/j.acra.2018.12.002.
- GDP per capita (current US\$) | Data. https://data.worldbank.org/indicator/NY.GDP. PCAP.CD. Accessed December 29, 2020.
- Criss SD, Cao P, Bastani M, et al. Cost-effectiveness analysis of lung cancer screening in the United States: a comparative modeling study. *Ann Intern Med.* 2019;171(11):796– 804. doi:10.7326/m19-0322.
- Yang SC, Lai WW, Lin CC, et al. Cost-effectiveness of implementing computed tomography screening for lung cancer in Taiwan. *Lung Cancer*. 2017;108:183–191. doi:10.1016/j.lungcan.2017.04.001.
- Prevention CCDC and. The 2015 China Adult Tobacco Survey. 2015. http://www.chinacdc.cn/zxdt/201512/t20151228_123960.htm.
- Liang F, Wu C, Gu H, et al. Lung cancer incidence in females rises significantly in urban sprawl of Shanghai after introduction of LDCT screening. *Lung Cancer*. 2019;132:114– 118. doi:10.1016/J.LUNGCAN.2019.04.020.
- Zhang Y, Chen H. Lung cancer screening: who pays? who receives?—the Chinese perspective. *Transl Lung Cancer Res.* 2021;10(5):2389–2394. doi:10.21037/tlcr.2020.03.16.
- Baldwin DR, Brain K, Quaife S. Participation in lung cancer screening. Transl Lung Cancer Res. 2021;10(2):1091. doi:10.21037/TLCR-20-917.
- Li Y, Du Y, Huang Y, et al. Community-based lung cancer screening by low-dose computed tomography in China: first-round results and a meta-analysis. *Eur J Radiol.* 2021;144:109988. doi:10.1016/J.EJRAD.2021.109988.
- Health Commission of PRC NChinese guidelines for diagnosis and treatment of primary lung cancer 2018 (English version). *Chinese J Cancer Res.* 2019;31(1):1–28. doi:10.21147/j.issn.1000-9604.2019.01.01.
- Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (Eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11(1):39–51. doi:10.1016/j.jtho.2015.09.009.
- Henschke CI, Yankelevitz DF, Yip R, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology*. 2012;263(2):578–583. doi:10.1148/radiol.12102489.
- Du Y, Sidorenkov G, Heuvelmans MA, et al. Supplementary data for a modelbased health economic evaluation on lung cancer screening with low-dose computed tomography in a high-risk population. *Data Brief.* 2020;31:105999. doi:10.1016/j.dib.2020.105999.
- Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC lung cancer staging project: proposals for the revisions of the T Descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. J Thorac Oncol. 2015;10(7):990–1003. doi:10.1097/jto.00000000000559.
- Xie X, Zhao Y, Snijder RA, et al. Sensitivity and accuracy of volumetry of pulmonary nodules on low-dose 16- and 64-row multi-detector CT: an anthropomorphic phantom study. *Eur Radiol.* 2013;23(1):139–147. doi:10.1007/s00330-012-2570-7.
- Rampinelli C, De Marco P, Origgi D, et al. Exposure to low dose computed tomography for lung cancer screening and risk of cancer: Secondary analysis of trial data and riskbenefit analysis. *BMJ*. 2017;356. doi:10.1136/bmj.j347.