Cost-Effectiveness of Lung Cancer Screening Using Low-Dose Computed Tomography Based on Start Age and Interval in China: Modeling Study

Zixuan Zhao¹*, PhD; Lingbin Du²*, MPH, PhD; Yuanyuan Li³, MD, PhD; Le Wang², PhD; Youqing Wang², MD; Yi Yang¹, PhD; Hengjin Dong¹, PhD

¹Department of Science and Education of the Fourth Affiliated Hospital, Center for Health Policy Studies, School of Public Health, Zhejiang University School of Medicine, Hangzhou, China
²Department of Cancer Prevention, Cancer Hospital of the University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China
³Department for Science and Education, Hangzhou Ninth People’s Hospital, Hangzhou, China
* these authors contributed equally

Corresponding Author:
Hengjin Dong, PhD
Department of Science and Education of the Fourth Affiliated Hospital, Center for Health Policy Studies
School of Public Health
Zhejiang University School of Medicine
No. 866 Yuhangtang Road, Xihu District
Hangzhou, 310058
China
Phone: 86 13221076129
Email: donghj@zju.edu.cn

Related Article:
This is a corrected version. See correction statement in: https://publichealth.jmir.org/2022/10/e43025

Abstract

Background: Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death in China. The effectiveness of screening for lung cancer has been reported to reduce lung cancer–specific and overall mortality, although the cost-effectiveness, optimal start age, and screening interval remain unclear.

Objective: This study aimed to assess the cost-effectiveness of lung cancer screening among heavy smokers in China by incorporating start age and screening interval.

Methods: A Markov state-transition model was used to assess the cost-effectiveness of a lung cancer screening program in China. The evaluated screening strategies were based on a screening start age of 50-74 years and a screening interval of once or annually. Transition probabilities were obtained from the literature and validated, while cost parameters were derived from databases of local medical insurance bureaus. A societal perspective was adopted. The outputs of the model included costs, quality-adjusted life years (QALYs), and lung cancer–specific mortality, with future costs and outcomes discounted by 5%. A currency exchange rate of 1 CNY=0.1557 USD is applicable. The incremental cost-effectiveness ratio (ICER) was calculated for different screening strategies relative to nonscreening.

Results: The proposed model suggested that screening led to a gain of 0.001-0.042 QALYs per person as compared with the findings in the nonscreening cohort. Meanwhile, one-time and annual screenings were associated with reductions in lung cancer–related mortality of 0.004%-1.171% and 6.189%-15.819%, respectively. The ICER ranged from 119,974.08 to 614,167.75 CNY per QALY gained relative to nonscreening. Using the World Health Organization threshold of 212,676 CNY per QALY gained, annual screening from a start age of 55 years and one-time screening from the age of 65 years can be considered as cost-effective in China. Deterministic and probabilistic sensitivity analyses were conducted.

Conclusions: This economic evaluation revealed that a population-based lung cancer screening program in China for heavy smokers using low-dose computed tomography was cost-effective for annual screening of smokers aged 55-74 years and one-time screening of those aged 65-74 years. Moreover, annual lung cancer screening should be promoted in China to realize the benefits of a guideline-recommended screening program.
Introduction

Lung cancer is a leading cause of death in China and globally. The incidence of lung cancer has recently increased dramatically, both in urban and rural areas, and it is currently the most common form of cancer in China. According to the National Central Cancer Registry of China, in 2015, the incidence of lung cancer was 57.26 cases/100,000 persons and the associated mortality rate was 45.87 deaths/100,000 persons, accounting for 20% and 27% of the values for all cancers, respectively [1]. At present, about 70%-75% of lung cancer patients are diagnosed in the middle or advanced stage of the disease [2]. Although there has been remarkable progress in treatment, the 5-year survival rate of patients with advanced lung cancer (stage IV) remains poor, at only 4.2% [3]. A previous study reported that surgical resection in the early stage of lung cancer (stage I) could significantly improve the 10-year survival rate to 92% [4]. Moreover, the disease burden of lung cancer in China is expected to substantially increase labor costs and medical expenditure in the near future. Therefore, promoting prevention, early diagnosis, and timely treatment can improve the prognosis and reduce the disease burden of lung cancer in China.

The effectiveness of low-dose computed tomography (LDCT) for the screening of lung cancer has been confirmed by the National Lung Screening Trial conducted at 33 medical centers in the United States [5]; the UK Lung Cancer RCT Pilot Screening Trial [6], a randomized controlled trial of LDCT screening for lung cancer versus usual care; and the Detection of Lung Cancer Through Low-dose CT Screening Trial conducted by the Dutch Cancer Society [7]. Several other studies have been conducted to explore the cost-effectiveness of lung cancer screening, although most were conducted in the United States and Europe. These studies reported notable differences in disease burden and treatment costs as compared with the findings in China. For example, the incremental cost-effectiveness ratio (ICER) has been reported to be €19,302 (US $22,542) per life year gained and €30,291 (US $35,377) per quality-adjusted life year (QALY) gained in Germany [8], while the ICER has been reported to be US $52,000 per life year gained and US $81,000 per QALY gained in the United States [9]. However, there has been only 1 similar study conducted in China, but this was limited to early versus nonearly lung cancer, which could have underestimated screening effectiveness [10]. In addition, risk factors and the epidemiology of lung cancer differ among countries. Therefore, the aim of this study was to evaluate the cost-effectiveness of LDCT for the screening of lung cancer in China from a societal perspective.

Methods

Study Design

This study was conducted in 2 steps. In the first step, a Markov state-transition model with a lifetime horizon was used to mimic the natural progression of lung cancer and assess the potential impact of LDCT screening compared with a lack of screening in a Chinese cohort aged 50 to 74 years. In the second step, the Markov state-transition model combined with real-world data was used to estimate the ICER of each specific screening strategy as compared with nonscreening. A discount rate of 5% was applied to the costs of both strategies. Important assumptions in this study are summarized inTextbox 1.

Textbox 1. Summary of key assumptions.

| Description of assumptions |
|-----------------------------|
| A simulated cohort of heavy smokers at a start age of 50-74 years was assumed to be followed up until the age of 79 years (mean life expectancy in China) or death. |
| A heavy smoker in this study was defined as a current smoker who smokes at least 20 pack-years. |
| Individuals in the screened cohort were assumed to undergo screening by low-dose computed tomography once or annually, and those with positive screening results were assumed to have undergone diagnostic biopsies. |
| While in the maintenance cancerous stages, the maintenance cost by stage was assumed to be 10% of the treatment cost. |
| All costs were expressed in CNY (2021; 1 CNY=0.1557 USD). |
| Future costs and effectiveness were discounted by 5%. |
| Adherence to screening and follow-up was assumed to be 100%. |

Study Population

The model simulated a cohort of 100,000 heavy smokers in China aged 50 to 74 years until the age of 79 years or death. A heavy smoker was defined as a current smoker who smokes at least 20 pack-years according to the China National Lung Cancer Screening Guidelines with LDCT (2018 version) [11] and the Cost-effectiveness Evaluation of the 2021 US Preventive Services Task Force Recommendation for Lung Cancer Screening [12].
Markov Model and Transition Probabilities

Lung cancer is assumed to progress sequentially from less advanced to more advanced preclinical stages, as depicted in Figure 1. The following 5 stages are distinguished based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition: carcinoma in situ (CIS), stage I, stage II, stage III, and stage IV [13]. In this study, stages IA, IB, IIIA, and IIIB were not considered because data were not available for clinical practice in population-based cancer registries in China [14]. The probability of deterioration from a healthy state to all-cause death was retrieved from the 2010 Population Census of the People’s Republic of China [15]. The probability of lung cancer-specific death was retrieved from the published literature [16]. Parameters of disease progression from a healthy state to lung cancer were based on the incidence of lung cancer among smokers in China [17]. The incidence of smokers was modeled as a multiplicative function of smoking rate, age, and sex-specific parameters. The incidence of lung cancer in the general population by sex and age (I_G) served as the baseline incidence. Specifically, the incidence of lung cancer for smokers (I_S) was modeled as I_S = OR * I_G / (1 + (OR – 1)) * R_S, and the incidence of lung cancer for nonsmokers (I_N) was modeled as I = I_S * R + I_N * (1 – R), where OR is the odds ratio for the incidence of lung cancer in smokers, which was extracted from a previous publication [16], R is the proportion of smokers by sex and age reported in the Global Adult Tobacco Survey [18], and I is the incidence of lung cancer in the general population of China. Finally, the incidence of lung cancer (I_20) among smokers in China was modeled as I_20 = I_N * RR, where the relative risk (RR) of lung cancer (>20 pack-years) attributable to smoking was derived from the published literature [19].

Figure 1. Schematic diagram of natural history for lung cancer screening. CIS: carcinoma in situ.

Individuals in the nonscreened cohort were diagnosed based on symptoms. The probability of progression to a more advanced stage of lung cancer or a clinical diagnosis, as described by Ten Haaf et al [20] and a hospital-based multi-center retrospective clinical epidemiological survey in China [21], is detailed in Table 1 [15-19,21-26]. Overall, 19.0% of lung cancer cases were clinically detected in stage I, 16.5% in stage II, 34.7% in stage III, and 29.9% in stage IV.

It was assumed that patients in the screened cohort underwent screening by LDCT at least once or annually and those with positive results underwent additional testing, including biopsy. The positive result rate and proportion of lung cancer by stage were derived from the Wenling lung cancer screening program, which was initiated in 2018 to conduct annual LDCT screening of local high-risk populations over a 3-year period. Of 10,175 asymptomatic individuals who were screened in 2018, 65 (0.64%) were diagnosed with lung cancer (Table 1). Annual screening was conducted in accordance with the protocol of the Cancer Screening Program in Urban China to determine the morphology and size of nodules [22]. The specificity and sensitivity of LDCT for screening of lung cancer were derived from the results of the Multicenter Italian Lung Detection trial [23]. The probability of progression to a more advanced stage or a maintenance state is detailed by stage in Table 1, as described in previous studies [16,22,24]. The proposed model was validated by comparing key outcomes to external empirical data that were not used for model development (Multimedia Appendix 1).
Table 1. Input parameters of the Markov model for lung cancer screening.

| Variable                                                                 | Base case value          | Distribution | Source |
|--------------------------------------------------------------------------|--------------------------|--------------|--------|
| **Lung cancer incidence in the general population (per 100,000 persons) by age in years** |                          |              |        |
| 50-54                                                                    | 81.0559                  | N/A          | Beta   |
| 55-59                                                                    | 162.0833                 | N/A          | Beta   |
| 60-64                                                                    | 256.0943                 | N/A          | Beta   |
| 65-69                                                                    | 373.6808                 | N/A          | Beta   |
| 70-74                                                                    | 498.0681                 | N/A          | Beta   |
| **Smoking rate in the general population**                               |                          |              |        |
| 50-64                                                                    | 0.60                     | N/A          | Beta   |
| 65-74                                                                    | 0.45                     | N/A          | Beta   |
| RR<sup>b</sup> (>20 pack-years)                                         | N/A                      | N/A          | Beta   |
| **Proportion of lung cancer by stage (nonscreened cohort)**              |                          |              |        |
| CIS<sup>c</sup>                                                          | N/A                      | N/A          | Beta   |
| I                                                                        | N/A                      | N/A          | Beta   |
| II                                                                       | N/A                      | N/A          | Beta   |
| III                                                                      | N/A                      | N/A          | Beta   |
| IV                                                                       | N/A                      | N/A          | Beta   |
| **Proportion of lung cancer by stage (LDCT<sup>d</sup> screened cohort)** |                          |              |        |
| CIS                                                                      | N/A                      | N/A          | Beta   |
| I                                                                        | N/A                      | N/A          | Beta   |
| II                                                                       | N/A                      | N/A          | Beta   |
| III                                                                      | N/A                      | N/A          | Beta   |
| IV                                                                       | N/A                      | N/A          | Beta   |
| Sensitivity of LDCT (%)                                                  | N/A                      | N/A          | Beta   |
| Specificity of LDCT (%)                                                  | N/A                      | N/A          | Beta   |
| **Mortality of all-cause death (%) by age group**                        |                          |              |        |
| 50-54                                                                    | N/A                      | N/A          | Beta   |
| 55-59                                                                    | N/A                      | N/A          | Beta   |
| 60-64                                                                    | N/A                      | N/A          | Beta   |
| 65-69                                                                    | N/A                      | N/A          | Beta   |
| 70-74                                                                    | N/A                      | N/A          | Beta   |
| **Lung cancer mortality rate in the general population (per 100,000 persons) by age group** |                        |              |        |
| 50-54                                                                    | N/A                      | N/A          | Beta   |
| 55-59                                                                    | N/A                      | N/A          | Beta   |
| 60-64                                                                    | N/A                      | N/A          | Beta   |
| 65-69                                                                    | N/A                      | N/A          | Beta   |
| 70-74                                                                    | N/A                      | N/A          | Beta   |
| **Transition probabilities (1 year)**                                    |                          |              |        |
| Lung cancer stage CIS to I                                              | N/A                      | N/A          | Beta   |
| Variable                                  | Base case value | Distribution | Source |
|------------------------------------------|-----------------|--------------|--------|
|                                          | Male            | Female       | Overall |        |
| Lung cancer stage I to II                | N/A             | N/A          | 0.3682  | Beta   |
| Lung cancer stage I to III               | N/A             | N/A          | 0.0328  | Beta   |
| Lung cancer stage I to IV                | N/A             | N/A          | 0.0745  | Beta   |
| Lung cancer stage II to III              | N/A             | N/A          | 0.2260  | Beta   |
| Lung cancer stage II to IV               | N/A             | N/A          | 0.1510  | Beta   |
| Lung cancer stage III to IV              | N/A             | N/A          | 0.1455  | Beta   |
| Lung cancer stage CIS to death           | N/A             | N/A          | 0.00    | Beta   |
| Lung cancer stage I to death             | N/A             | N/A          | 0.04    | Beta   |
| Lung cancer stage II to death            | N/A             | N/A          | 0.07    | Beta   |
| Lung cancer stage III to death           | N/A             | N/A          | 0.13    | Beta   |
| Lung cancer stage IV to death            | N/A             | N/A          | 0.18    | Beta   |

**Utility by stage**

| CIS | I | II | III | IV |
|-----|---|----|-----|----|
| N/A | N/A | N/A | 0.87 | N/A |
| N/A | N/A | N/A | 0.84 | N/A |
| N/A | N/A | N/A | 0.84 | N/A |
| N/A | N/A | N/A | 0.87 | N/A |
| N/A | N/A | N/A | 0.75 | N/A |

**Cost (CNY)**

| Cost (CNY)                  | Survey data |
|-----------------------------|-------------|
| Direct screening cost       | N/A         | 245.86 Gamma N/A |
| Indirect screening cost     | N/A         | 23.07 Gamma N/A |
| Prediagnosis cost           | N/A         | 628.36 Gamma N/A |
| Biopsy diagnosis cost       | N/A         | 1232.44 Gamma N/A |

**Treatment cost by stage**

| Stage | Cost (CNY)                  |
|-------|-----------------------------|
| CIS   | N/A                         |
| I     | N/A                         |
| II    | N/A                         |
| III   | N/A                         |
| IV    | N/A                         |

a N/A: not applicable.
b RR: relative risk.
c CIS: carcinoma in situ.
d LDCT: low-dose computed tomography.
e A currency exchange rate of 1 CNY=0.1557 USD is applicable.

**Cost Data**

The total cost of the screening program included direct expenses (ie, public advertising, management of screening invitations, salaries of staff members, and depreciation of screening equipment) and indirect expenses (ie, transportation and wages for missed work). In addition, the cost of diagnostic biopsies for participants with positive results after initial LDCT was considered. Screening-related costs were retrieved from data provided by the Wenling lung cancer screening program. Costs of treatment of lung cancer by stage were derived from a database of local medical insurance bureaus, which included 4947 patients and 107,248 relevant records. The cost of maintenance by stage accounted for 10% of the total treatment cost. All costs in this study are expressed in Chinese yuan (CNY) at a discount of 5% of rates in 2018. A currency exchange rate of 1 CNY=0.1557 USD is applicable.

**Quality of Life**

The putative benefit of cancer screening for early diagnosis was assumed to be a difference in life expectancy and QALY after treatment. As the severity and responsiveness to treatment vary according to stage, the specified utility score for each stage was used for calculation [25,27]. The utility score was 0.84 for lung
cancer stage I/II, 0.87 for CIS and stage III, and 0.75 for stage IV (Table 1).

**Evaluation Strategies**
As the scheduled screening program included several key characteristics, different combinations of screening intervals and start ages, as well as a nonscreening cohort, were evaluated (Table 2). In order to achieve more realistic economic evaluation outcomes, one-time screening was applied in this study because no periodic screening program has been implemented nationwide in China and most of the study participants were screened for lung cancer only once. Therefore, the rationale of one-time screening was based on limited financial support for lung cancer screening programs in China. Moreover, strategies with annual screening from different start ages were simulated to determine whether efforts are needed to promote periodic screening programs in China in order to realize relative benefits based on current guidelines.

**Table 2. Evaluation strategies.**

| Scenario | Screening tool | Screening interval | Start age (years) |
|----------|----------------|--------------------|-------------------|
| LDCT#1   | LDCT           | Annual             | 50, 55, 60, 65, and 70 |
| LDCT#2   | LDCT           | One time           | 50, 55, 60, 65, and 70 |
| Nonscreening | N/A            | N/A                | 50, 55, 60, 65, and 70 |

*a*LDCT: low-dose computed tomography.  
*b*N/A: not applicable.

**Outcomes and Cost-Effectiveness**
The main outcomes of the cost-effectiveness analysis for each strategy were QALYs and total costs. The ICER was calculated by dividing the incremental costs by the incremental QALYs gained for each screening strategy as compared to nonscreening. In China, there is no regulated or published cost-effectiveness threshold. Hence, the threshold recommended by the World Health Organization (WHO) is commonly used. Given that 3 times the gross domestic product per capita was used as a reference point, a tentative threshold value of 212,676 CNY was adopted in this study.

**Sensitivity Analysis**
The Markov state-transition model was developed using TreeAge Pro 2021 software (TreeAge Software, Inc). The parameters of direct screening cost, maintenance cost, discount rate, consumer price index (CPI) rate, incidence rate of heavy smokers, and specificity and sensitivity of LDCT uncertainty were investigated by 1-way deterministic sensitivity analyses. The costs of direct screening, as well as maintenance costs, CPI rate, and incidence rate of heavy smokers, were set to vary by 30% as compared to base values. The discount rate was set to range from 0% to 8%, and the sensitivity and specificity of LDCT were set to range from 0.63 to 0.97, respectively. Input parameters were randomly drawn from beta or gamma distributions (Table 1).

**Results**
The results of the model suggested that the QALYs of the screening cohort increased by 0.001 to 0.042 as compared to that of the nonscreening cohort. The reduction in lung cancer–associated mortality ranged from 0.004% to 1.171% for one-time screening and from 6.189% to 15.819% for annual screening (Table 3). The average costs per person in the nonscreening cohort, one-time screening cohort, and annual screening cohort were 24,896.93, 25,521.61, and 34,105.70 CNY, respectively, at a start age of 50 years, which seemed to be the most noncost-effective among the 5 age groups. Conversely, the most cost-effective start age was 70 years, with ICERs in the one-time screening and annual screening cohorts of 180,280.19 and 119,974.08 CNY per QALY gained. As compared to the nonscreening cohort, the ICER of the screening cohort, regardless of the screening interval, ranged from 119,974.08 to 614,167.75 CNY per QALY gained. Using the WHO threshold of 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.

The sensitivity of the model for the above-mentioned parameters is shown in Figure 2. Generally, the model results were robust with no variation exceeding 212,676 CNY per QALY gained, annual screening at a start age of 55-74 years was determined to be the most cost-effective in China. For one-time screening, the cost-effective start age was 65-74 years.
Table 3. Base case results with different screening settings (per 100,000 persons).

| Start age and strategy<sup>a</sup> | Cost (CNY,<sup>b</sup> millions) | QALYs<sup>c</sup> (10,000 years) | Lung cancer mortality reduction vs nonscreening (%) | ICER<sup>d</sup> Scr vs Non_scr | ICER Scr_annu vs Scr_once |
|-------------------------------|----------------------------------|---------------------------------|-------------------------------------------------|------------------------|----------------------------|
| **50 years**                  |                                  |                                 |                                                 |                        |                           |
| Non_scr                       | 2489.69                          | 135.92                          | N/A<sup>e</sup>                                 | N/A                    | N/A                       |
| Scr_once                      | 2552.16                          | 135.93                          | 0.0041                                          | 614,167.75             | N/A                       |
| Scr_annu                      | 3410.57                          | 136.30                          | 6.1886                                          | 245,746.19             | 235,467.06                |
| **55 years**                  |                                  |                                 |                                                 |                        |                           |
| Non_scr                       | 2380.25                          | 121.21                          | N/A                                             | N/A                    | N/A                       |
| Scr_once                      | 2448.97                          | 121.23                          | 0.0145                                          | 365,289.96             | N/A                       |
| Scr_annu                      | 3176.64                          | 121.62                          | 6.7044                                          | 192,119.62             | 183,886.78                |
| **60 years**                  |                                  |                                 |                                                 |                        |                           |
| Non_scr                       | 2154.69                          | 104.08                          | N/A                                             | N/A                    | N/A                       |
| Scr_once                      | 2230.61                          | 104.11                          | 0.0467                                          | 263,083.31             | N/A                       |
| Scr_annu                      | 2808.69                          | 104.50                          | 7.7816                                          | 154,401.89             | 146,456.38                |
| **65 years**                  |                                  |                                 |                                                 |                        |                           |
| Non_scr                       | 1773.45                          | 84.40                           | N/A                                             | N/A                    | N/A                       |
| Scr_once                      | 1860.84                          | 84.45                           | 0.1997                                          | 192,574.66             | N/A                       |
| Scr_annu                      | 2260.66                          | 84.77                           | 10.0628                                         | 131,284.57             | 122,745.38                |
| **70 years**                  |                                  |                                 |                                                 |                        |                           |
| Non_scr                       | 1184.22                          | 61.56                           | N/A                                             | N/A                    | N/A                       |
| Scr_once                      | 1279.79                          | 61.61                           | 1.1705                                          | 180,280.19             | N/A                       |
| Scr_annu                      | 1476.25                          | 61.80                           | 15.8193                                         | 119,974.08             | 103,182.45                |

<sup>a</sup>Non_scr: nonscreening; Scr_once: one-time screening; Scr_annu: annual screening.

<sup>b</sup>A currency exchange rate of 1 CNY=0.1557 USD is applicable.

<sup>c</sup>QALY: quality-adjusted life year.

<sup>d</sup>ICER: incremental cost-effectiveness ratio.

<sup>e</sup>N/A: not applicable.
Figure 2. Tornado diagrams. The tornado diagrams illustrate the change in the incremental cost-effectiveness ratio (ICER). The blue column shows the impact of decreasing the input parameters on the results. Similarly, the red column shows the impact of increasing the input parameters on the results. CPI: consumer price index; EV: expected value; LDCT: low-dose computed tomography.
Discussion

Principal Findings

This is the first cost-effectiveness analysis of a lung cancer screening program with different start ages and screening intervals using real-world data in China. In summary, using a lifetime societal perspective for one-time or annual LDCT for screening of heavy smokers, the annual screening strategy with a start age of 55-74 years showed strong dominance as compared with the nonscreening strategy. These results were sensitive to the rate of newly developed lung cancer and the specificity of LDCT. As compared with the nonscreening strategy, the one-time screening strategy was cost-effective for patients aged 65-74 years, using a cost-effectiveness threshold of 212,676 CNY per QALY gained. This finding is consistent with that in the UK Lung Screen trial, which demonstrated a long-term benefit from a single screen and provided potentially important data for inclusion in future modeling studies to optimize the screening interval [26]. All simulated results of probabilistic sensitivity analysis were robust when the main input parameters were varied.

Although the analytical approach was somewhat similar to that in a previous study by Yuan et al [28], the strategies were enriched by adding screening intervals and thus arrived at different conclusions. First, Yuan et al predicted that the ICERs of all screening strategies with a start age of 40-74 years were 3-fold lower than the gross domestic product per capita. However, this result is consistent with only part of the strategies in this study. Second, Yuan et al predicted a minimum ICER at a start age of 65 years, whereas the results of this study demonstrated a decreasing trend in ICER per QALY gained from a start age of 50-74 years, regardless of the screening interval. These differences may have resulted from a combination of several factors. For example, Yuan et al used a discount rate of 3%, while a rate of 5% was adopted in this study in accordance with the China Guidelines for Pharmacoeconomic Evaluations [29], and staging was simplified in the Markov model by ignoring the CIS stage. For comparison between annual screening and nonscreening, the ICER of 119,974 to 245,746 CNY in this study is comparable to previous estimates of US $24,934, US $49,200-96,700, and US $33,825 per QALY gained reported by studies conducted in New Zealand, the United States, and Canada, respectively [30-32].

Regarding the implications of policies related to lung cancer screening, the China National Lung Cancer Screening Guidelines with LDCT (2018 version) [11] were partially confirmed by the recommendations for lung cancer screening and early diagnosis and treatment guidelines in China [33] from a health economic perspective. Though the updated recommendations for lung cancer screening and early diagnosis and treatment guidelines raised the minimum cumulative smoking exposure from 20 to 30 pack-years relative to the 2018 version, the results were robust according to deterministic 1-way sensitivity analysis. In addition to the low utilization of lung cancer screening programs in China, there is a need to improve the accessibility and affordability of population-based screening programs to better capture the full extent of benefits associated with lung cancer screening. Annual lung cancer screening for heavy smokers at a start age of 55-74 years is considered cost-effective in China. Although screening from the age of 70 years had the lowest ICER per QALY gained as compared to nonscreening, it is unreasonable to simply use a start age of 70 years. An older start age is associated with fewer QALYs obtained.

Limitations

There were several limitations to this study that should be addressed. First, like most mathematical models, the model used in this study to estimate the incidence of lung cancer in heavy smokers was a simplification of the biological complexity of lung carcinogenesis and neglected the influence of various factors related to the development of lung cancer.
endogenous and exogenous risk factors, such as family history and residential/occupational exposure to radon, which may have led to underestimation of the incidence of lung cancer in the targeted population. Further, as heavy smokers are more likely to die from other diseases (eg, cardiovascular diseases and other cancers), its application to estimate the general probability of all-cause death in this population might have slightly underestimated the mortality rate in this work. Nevertheless, the use of this nomothetic approach has aided the development of prevention and control strategies against lung cancer in the United States [34]. Second, the cumulative burden of radiation from annual screening with LDCT was not considered. Albert et al reported that annual LDCT would result in additional radiation exposure of 1.5 mSv per year [35]. Still, recent studies have reported that the potential benefit of lung cancer screening to prevent death was greater than the potential harm of increased radiation exposure [36,37]. Third, smoking cessation events and other health-related behavioral changes due to screening participation were not incorporated in the model due to the lack of relevant data. Further research may benefit from the incorporation of patient-level data extracted from on-going randomized controlled trials with microsimulation models for cost-effectiveness analysis of lung cancer screening.

Conclusion
This economic evaluation revealed that a population-based lung cancer screening program in China for heavy smokers using LDCT could result in more QALYs, although with greater expense than nonscreening. Using the WHO threshold for cost-effectiveness analysis, the annual screening strategy from 55 to 74 years and one-time screening strategy from 65 to 74 years can be considered cost-effective. Moreover, annual screening was the most promising; thus, annual screening should be promoted in China to realize actual benefits.

Authors’ Contributions
Conceptualization: HD and ZZ; methodology: ZZ and LD; software: YL and LW; investigation: YW and YY; data curation: HD; writing-original draft preparation: ZZ; writing-review and editing: ZZ and LD; supervision: HD; funding acquisition: LD. All authors have read and agree to the published version of the manuscript.

Conflicts of Interest
None declared.

Multimedia Appendix 1
Validation of the natural history model of lung cancer.
[DOCX File, 366 KB-Multimedia Appendix 1]

References
1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66(2):115-132 [FREE Full text] [doi: 10.3322/caac.21338] [Medline: 26808342]
2. China Lung Cancer Prevention and Treatment Alliance. Chinese expert consensus on early diagnosis of primary bronchial lung cancer. Chinese Journal of Tuberculosis and Respiratory Diseases 2014;37(3):172-176. [doi: 10.3760/cma.j.issn.1001-0939.2014.03.005]
3. Miller KD, Nogueira L, Mariotto AB, Rowland JH, Yabroff KR, Alfano CM, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66(2):115-132 [FREE Full text] [doi: 10.3322/caac.21338] [Medline: 26808342]
4. International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006 Oct 26;355(17):1763-1771. [doi: 10.1056/NEJMoa060476] [Medline: 17065637]
5. The Lancet Oncology 2014 Nov;15(12):1342-1350. [doi: 10.1016/S1470-2045(14)70387-0] [Medline: 25282284]
6. Smith JP, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006 Aug 04;365(5):395-409 [FREE Full text] [doi: 10.1056/NEJMoa060476] [Medline: 17065637]
7. The Lancet Oncology 2014 Nov;15(12):1342-1350. [doi: 10.1016/S1470-2045(14)70387-0] [Medline: 25282284]
8. Milanetti G, et al. Targeted therapy in NSCLC: a review of current and future treatment strategies. Lung Cancer 2018;124:189-198 [FREE Full text] [doi: 10.1016/j.lungcan.2018.07.036] [Medline: 29239964]
9. Milanetti G, et al. Targeted therapy in NSCLC: a review of current and future treatment strategies. Lung Cancer 2018;124:189-198 [FREE Full text] [doi: 10.1016/j.lungcan.2018.07.036] [Medline: 29239964]
10. China Lung Cancer Prevention and Treatment Alliance. Chinese expert consensus on early diagnosis of primary bronchial lung cancer. Chinese Journal of Tuberculosis and Respiratory Diseases 2014;37(3):172-176. [doi: 10.3760/cma.j.issn.1001-0939.2014.03.005]
11. China Lung Cancer Prevention and Treatment Alliance. Chinese expert consensus on early diagnosis of primary bronchial lung cancer. Chinese Journal of Tuberculosis and Respiratory Diseases 2014;37(3):172-176. [doi: 10.3760/cma.j.issn.1001-0939.2014.03.005]
10. Sun C, Zhang X, Guo S, Liu Y, Zhou L, Shi J, et al. Determining cost-effectiveness of lung cancer screening in urban Chinese populations using a state-transition Markov model. BMJ Open 2021 Jul 01;11(7):e046742 [FREE Full text] [doi: 10.1136/bmjopen-2020-046742] [Medline: 32410726]

11. Zhou Q, Fan Y, Wang Y, Qiao Y, Wang G, Huang Y, et al. [China National Lung Cancer Screening Guideline with low-dose computed tomography (2018 version)]. Zhongguo Fei Ai Za Zhi 2018 Feb 20;21(2):67-75 [FREE Full text] [doi: 10.3779/j.issn.1009-3419.2018.02.01] [Medline: 29526173]

12. Toumazis I, de Nijs K, Cao P, Bastani M, Munshi V, Ten Haaf K, et al. Cost-effectiveness evaluation of the 2021 US Preventive Services Task Force recommendation for lung cancer screening. JAMA Oncol 2021 Dec 01;7(12):1833-1842. [doi: 10.1001/jamaoncol.2021.4942] [Medline: 34673885]

13. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017 Mar;67(2):138-155. [FREE Full text] [doi: 10.3322/caac.21390] [Medline: 28140453]

14. Wei W, Zeng H, Zheng R, Zhang S, An L, Chen R, et al. Cancer registration in China and its role in cancer prevention and control. The Lancet Oncology 2020 Jul;21(7):e342-e349. [doi: 10.1016/S1470-2045(20)30073-5] [Medline: 32615118]

15. Population Census Office of the State Council of the People's Republic of China, Department of Population and Employment Statistics of the National Bureau of Statistics of the People's Republic of China. Tabulation on the 2010 Population Census of the People's Republic of China. Beijing: China: China Statistics Press; 2010:112-113.

16. Zhang M, Wu C, Gong Y, Peng P, Gu K, Shi L, et al. Survival analysis of patients with lung cancer in Shanghai. China Oncology 2017;27(5):326-333. [doi: 10.19401/j.cnki.1007-3639.2017.05.002]

17. He J. China Cancer Registry Annual Report 2018. Beijing, China: People's Medical Publishing House; 2019:214-215.

18. CDC China. Global Adult Tobacco Survey (GATS) China 2015 Report. Shanghai, China: CDC China; 2016:93-96.

19. Osaki Y, Okamoto M, Kaetsu A, Kishimoto T, Suyama A. Retrospective cohort study of smoking and lung cancer incidence in rural prefecture. Japan. Environ Health Prev Med 2007 Jul;12(4):178-182 [FREE Full text] [doi: 10.1007/BF02897988] [Medline: 21432062]

20. Ten Haaf K, van Rosmalen J, de Koning HJ. Lung cancer detectability by test, histology, stage, and gender: estimates from the NLST and the PLCO trials. Cancer Epidemiol Biomarkers Prev 2015 Jan;24(1):154-161 [FREE Full text] [doi: 10.1158/1055-9965.EPI-14-0745] [Medline: 25312998]

21. Shi J, Wang L, Wu N, Li J, Hui Z, Liu S, LuCCRES Group. 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 Feb;128:91-100. [doi: 10.1016/j.lungcan.2018.11.031] [Medline: 30642458]

22. Chen W, Li N, Cao MM, Ren JS, Shi JF, Chen HD, et al. Preliminary analysis of cancer screening program in urban China from 2013 to 2017. China Cancer 2020;29:1-6 [FREE Full text]

23. Sozzi G, Boeri M, Rossi M, Verri C, Suatoni P, Bravi F, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: A correlative MILD trial study. JCO 2014 Mar 10;32(8):768-773. [doi: 10.1200/jco.2013.50.4357]

24. Banerjee AK. Preinvasive lesions of the bronchus. J Thorac Oncol 2009 Apr;4(4):545-551 [FREE Full text] [doi: 10.1097/JTO.0b013e31819676bd] [Medline: 19279508]

25. Chen S. Study on economic burden and quality of life of lung cancer patients. Wanfang. 2016. URL: https://d.wanfangdata.com.cn/thesis/ChJuagaVZaXNOXZdXMjAyMjA1MjYSCUQwMTwMBoIbXp0dnh3NHI%253D [accessed 2022-06-25]

26. Field JK, Vulkan D, Davies MP, Baldwin DR, Brain KE, Devaraj A, et al. Lung cancer mortality reduction by LDCT screening: UKLS randomised trial results and international meta-analysis. Lancet Reg Health Eur 2021 Nov;10:100179. [Medline: 34806061]

27. Sturza J. A review and meta-analysis of utility values for lung cancer. Med Decis Making 2010;30(6):685-693. [doi: 10.1177/0272989X10369004] [Medline: 20448248]

28. Yuan J, Sun Y, Wang K, Wang Z, Li D, Fan M, et al. Cost-effectiveness of lung cancer screening with low-dose CT in heavy smokers in China. Cancer Prev Res (Phila) 2022 Jan;15(1):37-44. [doi: 10.1158/1940-6207.CAPR-21-0155] [Medline: 34580085]

29. Liu G, Hu S, Wu J, Wu J, Yang L, Li H. China guidelines for pharmacoeconomic evaluations. Beijing, China: China Market Press; 2020:16-17.

30. McLeod M, Sandiford P, Kvizhinadze G, Bartholomew K, Crengle S. Impact of low-dose CT screening for lung cancer on ethnic health inequities in New Zealand: a cost-effectiveness analysis. BMJ Open 2020 Sep 24;10(9):e037145 [FREE Full text] [doi: 10.1136/bmjopen-2020-037145] [Medline: 32973060]

31. Criss SD, Cao P, Bastani M, Ten Haaf K, Chen Y, Sheehan DF, et al. Cost-effectiveness analysis of lung cancer screening in the United States: A comparative modeling study. Ann Intern Med 2019 Dec 03;171(11):796-804. [doi: 10.7326/M19-0322] [Medline: 31683314]

32. Ten Haaf K, Tammeëmagi MC, Bondy SJ, van der Aalst CM, Gu S, McGregor SE, et al. Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: A microsimulation modeling
33. He J, Li N, Chen W, Wu N, Shen H, Jiang Y, et al. China lung cancer screening and early diagnosis and early treatment guidelines (2021, Beijing). Chinese Journal of Oncology 2021;43(3):243-268 [FREE Full text] [doi: 10.1001/jama.2021.1077] [Medline: 33687469]

35. Albert JM. Radiation risk from CT: Implications for cancer screening. American Journal of Roentgenology 2013 Jul;201(1):W81-W87. [doi: 10.2214/ajr.12.9226]

36. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012 Jun 13;307(22):2418-2429 [FREE Full text] [doi: 10.1001/jama.2012.5521] [Medline: 22610500]

37. McCunney RJ, Li J. Radiation risks in lung cancer screening programs: a comparison with nuclear industry workers and atomic bomb survivors. Chest 2014 Mar 01;145(3):618-624. [doi: 10.1378/chest.13-1420] [Medline: 24590022]

Abbreviations

CIS: carcinoma in situ  
CPI: consumer price index  
ICER: incremental cost-effectiveness ratio  
LDCT: low-dose computed tomography  
OR: odds ratio  
QALY: quality-adjusted life year  
RR: relative risk  
WHO: World Health Organization