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Community-based lung cancer screening by low-dose computed tomography in China: First round results and a meta-analysis

Yanju Li [a,1], Yihui Du [b,1], Yubei Huang [e,1], Yingru Zhao [a], Grigory Sidorenkov [b], Marleen Vonder [b], Xiaonan Cui [a], Shuxuan Fan [a], Monique D. Dorrius [b,c], Rozemarijn Vliegenthart [c], Harry J.M. Groen [d], Shiyuan Liu [f], Fengju Song [e], Kexin Chen [e,*], Geertruida H. de Bock [b,*], Zhaoxiang Ye [a,*]

[a] Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Centre for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Department of Radiology, Tianjin, People's Republic of China
[b] University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Radiology, Groningen, the Netherlands
[d] University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases, the Netherlands
[e] Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Molecular Epidemiology, Tianjin, Tianjin's Clinical Research Center for Cancer, Department of Cancer Epidemiology and Biostatistics, Tianjin, People's Republic of China
[f] Shanghai Changzheng Hospital, The Second Military Medical University Shanghai, Department of Radiology, Shanghai, People's Republic of China

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ABSTRACT

Objective: To evaluate the efficiency of low-dose computed tomography (LDCT) screening for lung cancer in China by analyzing the baseline results of a community-based screening study accompanied with a meta-analysis.
Methods: A first round of community-based lung cancer screening with LDCT was conducted in Tianjin, China, and a systematic literature search was performed to identify LDCT screening and registry-based clinical studies for lung cancer in China. Baseline results in the community-based screening study were described by participant risk level and the lung cancer detection rate was compared with the pooled rate among the screening studies. The percentage of patients per stage was compared between the community-based study and screening and clinical studies.
Results: In the community-based study, 5523 participants (43.6% men) underwent LDCT. The lung cancer detection rate was 0.5% (high-risk, 1.2%; low-risk, 0.4%), with stage I disease present in 70.0% (high-risk, 50.0%; low-risk, 83.3%), and the adenocarcinoma present in 84.4% (high-risk, 61.5%; low-risk, 100%). Among all screen-detected lung cancer, women accounted for 8.3% and 66.7% in the high- and low-risk group, respectively. In the screening studies from mainland China, the lung cancer detection rate 0.6% (95 %CI: 0.3%–0.9%) for high-risk populations. The proportions with carcinoma in situ and stage I disease in the screening and clinical studies were 76.4% (95 %CI: 66.3%–85.3%) and 15.2% (95 %CI: 11.8%–18.9%), respectively.
Conclusions: The stage shift of lung cancer due to screening suggests a potential effectiveness of LDCT screening in China. Nearly 70% of screen-detected lung cancers in low-risk populations are identified in women.

1. Introduction

Lung cancer is the most common cancer and the leading cause of cancer-related death, accounting for 20% of all diagnosed cancers and 27% of all cancer deaths in China [1]. The five-year survival rate of lung cancer is only 19.7% because diagnosis and treatment is often at an advanced stage [2,3]. The US National Lung Screening Trial (NLST), the Dutch-Belgian NELSON trial, the Multicentric Italian Lung Detection

* Corresponding authors at: Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Department of Radiology, Tianjin 300060, People's Republic of China (Z. Ye). University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, the Netherlands, Postal address: PO Box 30.001, FA 40, 9700 RB Groningen, the Netherlands. (G.H. de Bock).
E-mail addresses: chenkexin@tijmu.edu.cn (K. Chen), g.h.de.bock@umcg.nl (G.H. de Bock), zye@tmu.edu.cn (Z. Ye).
[1] Yanju Li,Yihui Du and Yubei Huang contributed equally.

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(MILD) trial, and the German Lung cancer Screening Intervention (LUSI) demonstrated that lung cancer screening by low-dose computed tomography (LDCT) is effective in reducing lung cancer mortality [4–7]. A recently published systematic review comprising lung cancer screening trials in Western countries indicated that lung cancer screening by LDCT for heavy smokers reduced the lung cancer mortality by 17% and the overall mortality by 4% [8].

In published trials, age and smoking have been used to determine eligibility for lung cancer screening. However, smoking is not the only risk factor for lung cancer in China, with nearly half of lung cancers are diagnosed in never-smokers [9]. It remains a challenge to define inclusion criteria for lung cancer screening in China [10], with high-risk populations previously defined by the presence of smoking and one or more of the following risk factors: passive smoking, cooking fume exposure, occupational carcinogen exposure, and family history of cancer. Liu et al. proposed expanding this to screen all individuals aged $\geq$ 40 years based on research in the Sichuan province [11]. A lung cancer screening study in a general Shanghai population had a detection rate of 1.23% in individuals aged $\geq$ 35 years [12]. In the last decade, there has been an increased trend for lung cancer to be found in the young, in females, and in non-smokers in China [13]. Given the geographic variation in lifestyle and air quality across the country [14], there is a need to evaluate lung cancer screening in a general population in northern China.

LDCT screening for lung cancer is known to be effective in reducing lung cancer mortality by detecting lung cancer early [5]. This not only shifts the tumor stage, but also changes the histological distribution, with adenocarcinoma and squamous cell carcinoma benefiting most from screening, while large/small cell carcinomas are insufficiently detected [7,15]. Given that histological type may be associated with specific risk factors, like smoking [16], it is important quantify the percentage stage shift and change in histological distribution due to screening in China.

The aim of this study was to evaluate the efficiency of LDCT screening for lung cancer in China. We analyzed the baseline results of a community-based screening study and compared the lung cancer detection rate in a general population with that in other screening studies in China comprising high-risk and general populations, and we quantified the effect of screening on stage shift and histological type distribution.

2. Methods

2.1. Design of the LDCT lung cancer screening study

The Netherlands and China Big 3 (NELCIN-B3) project (NO. 2016YFE0103000) was initiated with the aim to improve the early detection of lung cancer, chronic obstructive pulmonary disease and cardiovascular disease by chest CT screening. Details can be found in the previously published design papers [17,18]. For the current study, data from the first screening round in Tianjin were analyzed. Ethical approval was issued by the Committee on Ethics of Biomedicine Research of Second Military Medical University, Shanghai (No.2018SL028) in the lead institute. Written informed consent was obtained from all participants when they were enrolled.

2.2. Participants

From May 2017 to December 2019 participants were recruited by local media and inclusion criteria were checked by doctors in 5 community health service centers (located at Youyi Street, Yuexiu Street, Chentangzhuang Street, Xiawafang Street and Jianshan Street). Asymptomatic residents were included if they met the following inclusion criteria: age 40–74 years, resident in the Hexi district of Tianjin city for at least 3 years, and with no self-reported history of any malignant tumor. Participants who had a chest CT scan within the last 12 months were excluded. The included participants were stratified into high- and low-risk groups according to the risk assessment criteria in the latest NCCN Clinical Practice Guideline in Oncology for Lung Cancer Screening, Version 1.2021 [19]. High-risk was defined as individuals aged $\geq$ 50 years with a smoking history of $\geq$ 20 pack-years.

2.3. CT image acquisition and interpretation

Participants were invited to undergo an initial LDCT scan, and a 3- or 6-month follow up LDCT scan (Figure S1 describes the protocol further) during baseline screening at the Department of Radiology at Tianjin Medical University Cancer Institute and Hospital (TJMUCIH) between June 2017 and December 2020. All spiral CT images were obtained using the same CT scanner (Somaton Definition AS 64, Siemens Healthineers, Erlangen, Germany) with a low-dose setting (120kVp, reference tube current of 35mAs, effective dose $\leq$ 2 mSv) at end-inspiration and a scan range from the apex to the base of the lungs. Three reconstruction kernels were used: D45F and B80F at 1.0/0.7 mm thickness/increment (lung setting) and B30F at 2.0/1.0 mm thickness/increment (soft tissue setting). The CT images were read in the Carestream Picture Archiving and Communication Systems v. 11.0 by one of 4 specially trained resident radiologists and checked by one of 2 senior radiologists.

Any non-calcified solid, part-solid, or non-solid nodules with average diameters $\geq$ 4 mm (mean of the longest diameter of the nodule and its perpendicular diameter on the axial plane) identified on lung window setting were recorded. In case of multiple nodules, a maximum of the 5 largest nodules were recorded. The diameter, position, shape, margin, and attenuation were recorded for each nodule. For part-solid nodules, the diameter of the solid component was measured additionally.

2.4. Lung nodule evaluation and cancer diagnosis

The screen-detected nodules were evaluated according to the NCCN Clinical Practice Guideline in Oncology for Lung Cancer Screening, Version 2.2018 [20] and managed according to the protocol in Figure S1. Further work-up could include contrast-enhanced CT, positron emission tomography (PET)-CT, biopsy, and surgery. Lung cancer diagnosis was confirmed through surgical pathology or biopsy. Screen-detected lung cancer was defined as lung cancer diagnosed by further work-up initiated for a positive screening result [21]. For participants with a confirmed diagnosis, the histological type and tumor stage were collected [22,23].

2.5. Participant questionnaire data

A questionnaire interview was performed to obtain general characteristics and known risk factors for lung cancer, including exposure to smoking, cooking oil fumes, and occupational carcinogens. A current smoker was defined as an individual who smoked at least 1 cigarette a day for 6 months or more. A former smoker was defined as an individual who smoked at least 1 cigarette a day for 6 months or more and reported having quit at the time of the interview. A passive smoker was defined as a never smoker who inhaled smoke produced by others $\geq$ 1 day a week for $\geq$ 15 min indoors [24]. Exposure to cooking oil fumes was defined as any amount of reported cooking fume exposure. Occupational exposure to carcinogens included asbestos, cadmium, nickel, arsenic, radon, chloro-ethyl, and x-ray radiation.

2.6. Statistical analysis

Statistical analyses were performed with IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables are reported as frequency and percentage. Continuous variables are reported as means and standard deviation (SD). The community-based screening and *meta*-analysis results were compared for detection rate, stage, and histological type

distribution.

2.7. Meta-analysis of published studies

A systematic search was conducted in PubMed, Web of Science, and Embase. The databases were searched to February 2021, starting from 1996 for PubMed, 1945 for Web of Science, and 1947 for Embase. Both screening and clinical studies were included. The search strategy used was related to lung cancer, screening, cancer stage, histological type, and China. The detailed search strategy for each database is presented in the supplementary materials. Study selection was performed independently by 2 reviewers (DY, LY). For clinical studies (i.e., no screening), we included cancer registry-based studies. Hospital-based studies were excluded due to the possibility of selection bias. The screening studies were stratified according to the screened population (i.e., high-risk and general population). The study population was considered high-risk based on age criteria and a history of smoking, passive smoking, cooking fume exposure, family history of cancer, or other risk factors. If screening was conducted in a population only restricted by age, it was considered a general population.

For each included study, 2 reviewers (DY, LY) independently assessed quality using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data (Table S1) [25]. The lung cancer detection rate in the first round of screening studies was pooled separately for studies of high-risk and general populations. The proportion of patients at each stage and histological type were also pooled separately as follows: (1) for all identified screening studies, (2) for screening studies in high-risk populations, (3) for screening studies in general populations,

Table 1
Characteristics of participants and lung cancer detection in community-based screening by LDCT.

Characteristics	Overall No. (%)	LC, No. (detection rate %)	Men No. (%)	LC, No. (detection rate %)	Women No. (%)	LC, No. (detection rate %)
Age (years)						
40–49	551(10.0)	1(0.2)	174(7.2)	0(0)	377(12.1)	1(0.3)
50–59	1740 (31.5)	5(0.3)	595(24.7)	1(0.2)	1145 (36.7)	4(0.3)
60–69	2715 (49.2)	17(0.6)	1327 (55.2)	12(0.9)	1388 (44.5)	5(0.4)
70–74	517(9.4)	7(1.4)	310(12.9)	4(1.3)	207(6.6)	3(1.4)
Overall	5523 (100)	30(0.5)	2406 (100)	17(0.7)	3117 (100)	13(0.4)
Smoking status[a]						
Current smoker (pack-year)						
<10	216(3.9)	0(0)	167(6.9)	0(0)	49(1.6)	0(0)
≥10 to < 20	242(4.4)	1(0.4)	218(9.1)	1(0.5)	24(0.8)	0(0)
≥20 to < 30	236(4.3)	7(3.0)	213(8.9)	6(4.2)	23(0.7)	1(4.3)
≥30	504(9.1)	3(0.6)	490(20.4)	3(0.6)	14(0.4)	0(0)
Overall	1198 (21.7)	11(0.9)	1088 (45.2)	10(0.9)	110(3.5)	1(0.9)
Former smoker (cessation years)						
<10	271(4.9)	1(0.4)	255(10.6)	1(0.4)	16(0.5)	0(0)
≥10 to < 15	108(2.0)	0(0)	103(4.3)	0(0)	5(0.2)	0(0)
≥15	171(3.1)	3(1.8)	168(7.0)	3(1.8)	3(0.1)	0(0)
Overall	550(10.0)	4(0.7)	526(21.9)	4(0.8)	24(0.8)	0(0)
Never smoker	3767 (68.2)	15(0.4)	790(32.8)	3(0.4)	2977 (95.5)	12(0.4)
Passive smoker in never smokers[b]						
Yes	1185 (31.5)	5(0.4)	161(20.4)	1(0.6)	1024 (34.4)	4(0.4)
No	2580 (68.5)	10(0.4)	629(79.6)	2(0.3)	1951 (65.5)	8(0.4)
Exposure to cooking oil fumes[c]						
Yes	3380 (61.2)	15(0.4)	1432 (59.5)	9(0.6)	1948 (62.5)	6(0.3)
No	2136 (38.7)	15(0.7)	972(40.4)	8(0.8)	1164 (37.3)	7(0.6)
Occupational exposure to carcinogens[d]						
Yes	209(3.8)	1(0.5)	132(5.5)	0(0)	77(2.5)	1(1.3)
No	5310 (96.1)	29(0.5)	2272 (94.4)	17(0.7)	3038 (97.5)	12(0.4)
Family history of cancer [e]						
Lung cancer	766(13.9)	7(0.9)	320(13.3)	3(0.9)	446(14.3)	4(0.9)
Other malignant tumor	1366 (24.7)	5(0.4)	558(23.2)	3((0.5)	808(25.9)	2(0.2)
No	3376 (61.1)	18(0.5)	1523 (63.3)	11(0.7)	1853 (59.4)	7(0.4)
Education level [f]						
Uneducated	25(0.5)	0(0)	5(0.2)	0(0)	20(0.6)	0(0)
Primary school	148(2.7)	2(1.4)	42(1.7)	2(4.8)	106(3.4)	0(0)
Junior school	1833 (33.2)	7(0.4)	819(34.0)	6(0.7)	1014 (32.5)	1(0.1)
High/secondary /technical school	2109 (38.2)	14(0.7)	807(33.5)	7(0.9)	1302 (41.8)	7(0.5)
College/university and above	1403 (25.4)	7(0.5)	731(30.4)	2(0.3)	672(21.6)	5(0.7)

[a] Missing value in 8 cases. [b] Missing value in 2 cases. [c] Missing value in 7 cases. [d] Missing value in 4 cases. [e] Missing value in 15 cases. [f] Missing value in 5 cases.

and (4) for registry-based clinical studies. Summary measures are presented as proportions with 95% confidence intervals (CIs) and were pooled using a random effects model.

3. Results

3.1. Characteristics of included participants

A total of 7936 people from 5 community health centers were recruited and completed the questionnaires, of whom 2413 declined to participate in CT screening and 5523 (69.6%) agreed to lung cancer screening by LDCT. Among the participants, 969 (17.5%) were at high-risk for lung cancer. The mean age was 60.2 ± 7.4 years and 43.6% was men. The proportion of never-smokers was 68.2% (32.8% in males and 95.5% in females). Current smokers had been smoking for an average 25.9 ± 18.6 pack-years. Average smoking cessation time was 11.0 ± 9.5 years for former smokers. Among never smokers, 68.5% were also not passive smokers (79.6% in males and 65.5% in females). Finally, 38.7% of participants (40.4% in males and 37.3% in females) reported no exposure to cooking oil fume and 61.1% (63.3% in males and 59.4% in females) had no family history of cancer (Table 1).

3.2. Lung nodule detection

Of the 5523 participants, 1381 non-calcified nodules were detected in 936 (16.9%) participants (male 457, 19.0%; female 479,15.4%), with 253(27.0%) having more than 1 nodule. 240 (4.3%) participants needed 3- or 6-month follow up, 40 (0.7%) participants needed further work-up (37 with lung nodules, 3 with other suspected malignant tumors; Fig. 1). There were 1096 (79.4%) solid nodules, 73 (5.3%) part-solid nodules, and 212 (15.4%) non-solid nodules. The average nodule diameter ranged from 4 mm to 50 mm, and the mean diameter was 6.1 ± 4.0 mm. The nodule detection rates were 20.1% and 16.3% in the high-risk and low-risk groups, respectively.

3.3. Lung cancer detection

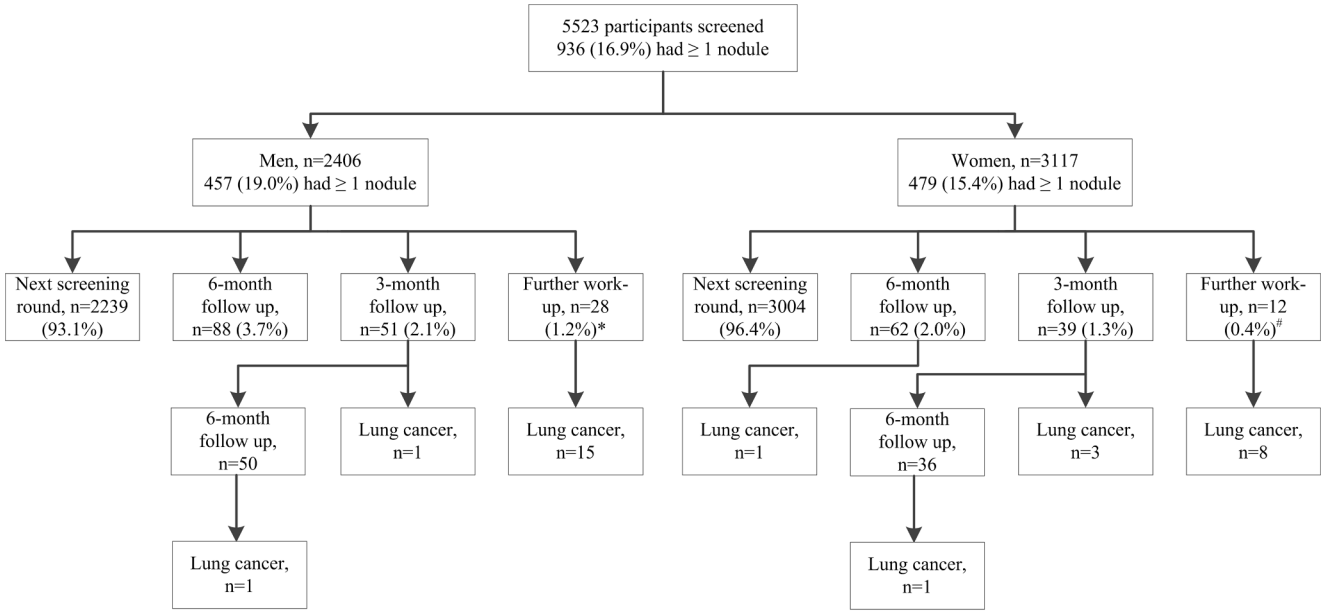
During the baseline screening and 3- or 6-month follow-up, LDCT detected 32 lung cancer nodules in 30 participants (Fig. 1). Among them, 27 were confirmed by surgery and 4 by biopsy (no serious surgical complications occurred), while 1 was diagnosed as suspicious lung cancer based on PET-CT results and tumor shrinkage after radiotherapy. The lung cancer detection rate was 0.5%, distributed as 0.7% (17/2406) in men and 0.4% (13/3117) in women, and generally increased with age, was higher in current and former smokers than in never smokers, and was higher in participants with a family history of lung cancer than those without (Table 1). Of those with lung cancer, 70.0% had stage I disease (58.8% in men and 84.6% in women) and 84.4% had adenocarcinoma (77.8% in men and 92.9% in women), with minimally invasive adenocarcinoma in 3, and invasive adenocarcinoma in 24 (Table 2). In never smokers with lung cancer, 86.7% were stage I lung cancer and 100% were adenocarcinoma (Table S2). The lung cancer detection rate was 1.2% in high-risk group and 0.4% in low-risk group. Most lung cancers in the high-risk group (69.2%) manifested as solid nodules, while most lung cancers in the low-risk group (73.7%) were part-solid and non-solid nodules. Participants with stage I lung cancer accounted for 50.0% of the high-risk group and 83.3% of the low-risk group. Those with adenocarcinoma accounted for 61.5% and 100% in the high-risk and low-risk groups, respectively (Table 3).

3.4. Characteristics of studies in the meta-analysis

The study selection (Figure S2) and characteristics of the included studies (Tables S3, S4 and S5) are presented in the supplementary material. The quality assessments of the included screening and clinical studies are presented in Table S6. Requirements were not satisfied for sample size in 6 studies, study description of subjects in 2 studies, and female coverage in 3 studies.

The literature search yielded 16 LDCT screening studies for lung cancer [12,26–40], and all were included in the *meta*-analysis. Of those, 14 were conducted in mainland China, 9 were conducted in a general population, and 7 were conducted in high-risk populations (definitions of high-risk varied; Table S3). Thirteen studies were cohort designs, with 9 being prospective and 4 being retrospective (Table S3). The number of included participants per study ranged from 1,023 to 22,260, and the proportion of men ranged from 46.3% to 94.7%.

The systematic search yielded 17 clinical studies of lung cancer using registry data [41–57]. All were included, with 11 conducted in mainland



*26 due to positive lung nodules, 2 due to incidental findings on other suspected malignant tumors.
#11 due to positive lung nodules, 1 due to incidental findings on other suspected malignant tumors.

Fig. 1. Lung cancer detection in the first round of screening.

Table 2
Clinical characteristics of participants with screen-detected lung cancer at baseline in community-based LDCT screening.

Characteristics of lung cancer	Overall		Men		Women	
	Number	Percentage (%)	Number	Percentage (%)	Number	Percentage (%)
Stage						
Stage I	21	70.0	10	58.8	11	84.6
Stage II	2	6.7	2	11.8	0	0
Stage III	5	16.7	5	29.4	0	0
Stage IV	2	6.7	0	0	2	15.4
Histological type						
Adenocarcinoma	27	84.4	14	77.8	13	92.9
Squamous cell carcinoma	3	9.4	3	16.7	0	0
Adenosquamous carcinoma	1	3.1	1	5.6	0	0
Unknown	1	3.1	0	0	1	7.1

Table 3
Baseline results of community-based LDCT screening stratified by participant risk status.*

Variables	High-risk		Low-risk	
	No.	Percentage (%)	No.	Percentage (%)
Participants[a]	969	17.5	4552	82.4
Age (mean ± sd)	62.6 ± 5.3		59.6 ± 7.6	
Female participants	37	3.8	3079	67.6
Nodule detection	195	20.1	740	16.3
LC detection	12	1.2	18	0.4
Female patients	1	8.3	12	66.7
LC component				
Solid	9	69.2	5	26.3
Part-solid	3	23.1	9	47.4
Non-solid	1	7.7	5	26.3
LC stage				
Stage I	6	50.0	15	83.3
Stage II	2	16.7	0	0
Stage III	4	33.3	1	5.6
Stage IV	0	0	2	11.1
LC histological type				
Adenocarcinoma	8	61.5	19	100
Squamous cell carcinoma	3	23.1	0	0
Adenosquamous carcinoma	1	7.7	0	0
Unknown[b]	1	7.7	0	0

[a] Questionnaire missed in 2 participants
[b] LC was diagnosed according to the PET-CT results and tumor shrinkage after radiotherapy.
* NCCN Clinical Practice Guideline in Oncology for Lung Cancer Screening, Version 1.2021.

China and 6 conducted in Taiwan. The number of included patients ranged from 99 to 124,148, and the proportion of men ranged from 0% to 76.5%.

3.5. Meta-analysis: Prevalence of lung cancer

In the 7 screening studies in high-risk populations, the pooled lung cancer detection rate was 0.6% (95 %CI: 0.3%–0.9%) (Table 4, Figure S3); in the 9 studies in general populations, the pooled detection rate was 0.9% (95 %CI: 0.6%–1.1%) (Table 4, Figure S4). After excluding 2 studies from the Taiwan region, the pooled detection rate was 0.7% (95 %CI: 0.5%–1.0%) in the general population (Table 4, Figure S5). No publication bias was observed for the studies in high-risk or general populations, as indicated by Egger's test (P = 0.893 and P = 0.196, respectively) and symmetrical funnel plots (Figure S6 and Figure S7, respectively).

3.6. Meta-analysis: Risk factors prevalence

It was not possible to quantify the prevalence of risk factors and participant age in the included papers due to differences in risk factors selection, reporting, and metrics. However, participants in studies comprising high-risk populations more often had at least one risk factor than those from studies comprising a general population (Table S5). Concerning participant age, no apparent differences were observed between the studies by the inclusion of high-risk and general populations (Table S3).

Table 4
Pooled detection rate of lung cancer by sex in high risk and general populations.

Study population	Number of studies	Proportion of men in the participants and 95 %CI	Lung cancer detection rate and 95 %CI	I^2
High risk population	7	65.9% (58.3–73.1%)	0.6% (0.3–0.9%)	92.6%
-Men	2	–	–	–
-Women	2	–	–	–
General population	9	60.1% (55.6–64.4%)	0.9% (0.6–1.1%)	87.5%
-Men	7	–	0.7% (0.5–1.0%)	83.3%
-Women	7	–	1.0% (0.6–1.4%)	84.1%
General population in mainland China	7	61.0% (55.8–66.1%)	0.7% (0.5–1.0%)	87.6%
-Men	6		0.7% (0.5–1.1%)	85.8%
-Women	6		0.8% (0.5–1.2%)	78.6%

-, not applicable.

3.7. Meta-analysis: Stage shift of lung cancer

Of the 16 screening studies, 13 reported the stage of screen-detected lung cancer in high-risk populations (n = 6) and general populations (n = 7). The proportion of men among all patients with lung cancer was similar in high-risk and general populations at 50.8% (95 %CI: 38.0%–63.4%) and 49.8% (95 %CI: 32.6%–67.0%), respectively. The pooled proportion of early stage (carcinoma in situ and stage I) lung cancer in all included studies was 76.4% (95 %CI: 66.3%–85.3%), and it was generally lower in high-risk (65.1%; 95 %CI: 42.7%–84.8%) than in general (83.7%; 95 %CI: 77.6%–89.1%) populations.

In the 5 registry-based clinical studies that reported lung cancer stage, men accounted for 68.8% (95 %CI: 60.8%–75.9%) of patients with lung cancer. The pooled proportion of early stage disease was 15.2% (95 %CI: 11.8%–18.9%) in all patients with lung cancer. Compared to clinical diagnosis, LDCT was 4–5 times more likely to detect early stage lung cancer in high-risk and general populations (Table 5).

3.8. Meta-analysis: Histological types of lung cancer

Of the 16 screening studies, 14 reported the histological type of

Table 5
Pooled stage and histology data for lung cancers in the screening and registry-based clinical studies.

Stage/Histology	Screening studies, percentage (95% CI)			Registry-based clinical studies, percentage (95% CI)
	Overall	High-risk population	General population	
Stage	13 studies	6 studies	7 studies	5 studies
Carcinoma in situ or stage I	76.4% (66.3–85.3%)	65.1% (42.7–84.8%)	83.7% (77.6–89.1%)	15.2% (11.8–18.9%)
Stage II	8.1 % (4.5–12.3%)	10.3 % (3.5–19.3%)	7.6% (3.9–12.1%)	6.2% (4.0–8.9%)
Stage III	13.0% (6.5–21.0%)	20.3% (6.3–38.7%)	7.6% (3.0–13.5%)	26.3% (18.1–35.5%)
Stage IV				51.3% (44.6–57.9%)
Histology	14 studies	5 studies	9 studies	12 studies
Adenocarcinoma	85.9% (75.1–94.3%)	72.5% (49.6–90.8%)	91.9% (81.1–98.8%)	54.5% (50.6–58.4%)
Squamous cell carcinoma	7.4% (2.1–14.8%)	15.0% (4.2–22.9%)	4.2% (0.0–12.4%)	29.0% (25.2–33.0%)
Small cell carcinoma	2.4% (0.4–5.4%)	7.2% (2.4–13.7%)	0.6% (0.0–2.5%)	8.4% (6.5–10.6%)
Other specified carcinoma				5.2% (2.0–9.7%)
Unclassified	0.2% (0.0–1.8%)	0.9% (0.0–6.0%)	0.0% (0.0–1.3%)	–

-, In the registry-based clinical studies, the unclassified histological type was not included in the calculation of proportion of each histological type

screen-detected lung cancer, with 5 in high-risk populations and 9 studies in general populations. In the high-risk and general populations, men accounted for 50.0% (95 %CI: 37.4%–62.6%) and 50.7% (95 %CI: 39.6%–61.8%), respectively. The pooled proportion of adenocarcinoma in those studies was 85.9% (95 %CI: 75.1%–94.3%), and it was generally lower in high-risk populations (72.5%; 95 %CI: 49.6%–90.8%) than in general populations (91.9%; 95 %CI: 81.1%–98.8%).

In the 12 registry-based clinical studies that reported lung cancer histology, men accounted for 63.3% (95 %CI: 59.9%–66.5%). Among all patients with lung cancer, the pooled proportion of adenocarcinoma was 54.5% (95 %CI: 50.6%–58.4%; Table 5), but this was higher in women than that in men (Table S7). Adenocarcinoma was 1.3- to 1.7-times more likely to be detected by LDCT screening in high-risk and general populations when compared to clinical diagnosis.

The distribution of lung cancer stage and histological type by community-based screening in Tianjin in the North of China were comparable to the results of pooled data from Chinese screening studies.

4. Discussion

In this study, we evaluated the efficiency of LDCT screening for lung cancer in China by analyzing the baseline results of a community-based screening study, comparing the lung cancer detection rate, stage, and type in a general population with that in high-risk populations, and by quantifying the effects of screening. We found that LDCT screening helped to detect early stage lung cancer in both high- and low-risk populations in China. Most screen-detected lung cancers in low-risk populations were present in women. Moreover, the lung cancer detection rate in the community-based general population was similar to those populations with diverse definitions of high-risk (0.5% vs 0.6%; 95 %CI: 0.3%–0.9%). Lung cancer was 4- to 5-times more likely to be detected at an early stage by LDCT screening than clinically. Compared to registry-based clinical studies, LDCT screening detected more adenocarcinoma (85.9% vs 54.5%).

LDCT screening is effective for early lung cancer detection in both high- and low-risk populations. Screen-detected lung cancer in the low-risk group was predominantly identified in women and was predominantly stage I and adenocarcinoma when compared with the high-risk group. This was consistent with another study in Asia [16], where the main criterion of high-risk was smoking history. However, most women in China (95.5% in this study) are never-smokers. In addition, given the potential harms including false positives and radiation harm due to screening, especially in a low-risk group, the entry criteria for lung cancer screening should be carefully investigated for Chinese women.

The present study did not use any specific risk factor(s) to select the screening population other than age, yet the lung cancer detection rate was similar to the pooled detection rate in high-risk populations. This might indicate, that beyond the already considered risk factors (e.g., smoking, family history of lung cancer, occupational exposure, passive smoking, and cooking oil fume) that are commonly included to define a high-risk population, other potential risk factors play an important role in the general population of Tianjin. Air pollution and education level may be such risk factors [58,59]. A previous study showed that men may have a higher incidence of lung cancer induced by particulate matter ($PM_{2.5}$) [58], and it is notable that the population attributable fraction of lung cancer due to air pollution in Tianjin is among the highest in China [14]. Low education is considered a relevant risk factor for lung cancer, but the underlying mechanism is not clear [59]. We included individuals aged between 40 and 74 years, although there is no consensus on the entry age of lung cancer screening in China. LDCT lung cancer screening studies have been performed in populations including younger individuals aged $\geq$ 45 years [31] or even $\geq$ 35 years [12]. However, more research is required to justify the screening in younger individuals.

Compared to other countries, the lung cancer detection rate in the present study was lower than that in I-ELCAP (1.3%), NLST (1.1%), NELSON (0.9%), ITALUNG (1.4%), LUSI (1.23%) and MILD (0.7%) [7,60–64]. This could be explained by the fact that all studies in Western countries targeted high-risk smokers, while this study had less strict inclusion criteria for both elements (e.g. the participants were not only included based on smoking but also based on exposure to cooking fumes, passive smoking, or family history of cancer). When the Tianjin population was stratified into high- and low-risk groups according to the latest NCCN Guidelines (Version 1.2021), the detection rate of lung cancer (1.2%) became similar to that in Western populations. Although the pooled lung cancer detection rates were also comparable between high-risk and general populations after removing the screening studies from Taiwan, the high heterogeneity across the included studies requires explanation. First, the definition of "high-risk" was diverse and risk level even varied in the general population studies (Table S5). Second, variation in the nodule management protocols between studies could account for the heterogeneity in lung cancer detection rate. The less stringent definition for positive nodules in the protocol applied for nodule management will have contributed to a higher rate of lung cancer detection (Table S3). For example, in the study of Fan et al., surgery was recommended for non-calcified nodules ($\geq$4 mm) with marked malignant features [12], which resulted in a high detection rate of 1.2% in the general population and in nearly half of the screen-detected lung cancers being adenocarcinoma in situ.

In the setting of lung cancer screening in China, early stage disease was present in 76.4%, representing an approximate 5-fold increase over the clinical setting. As reported, the 5-year survival was in the range of 68% to 92% for stage I lung cancer [65], which is much higher than at a late stage. This indicates that LDCT lung cancer screening could reduce cancer mortality and improve survival.

Compared with the clinical setting, LDCT screening also detected a higher proportion of lung adenocarcinomas. This likely reflects the relatively slow rate of adenocarcinoma growth [66,67], which results in a long preclinical window in which it can be detected by LDCT [68]. In

addition, the *meta*-analysis included registry-based studies with longer time spans. The gradual increase in rates of adenocarcinoma detection over recent decades might also have contributed to the apparent high detection rate, with screening studies conducted circa 2011–2017 and registry studies conducted circa 1984–2018 [69]. LDCT screening may therefore be more effective for the early detection of lung adenocarcinoma and less effective for the early detection of squamous, large, or small cell carcinomas.

The proportion of early stage lung cancer (76.4%) in screening studies in China was higher than in the NLST (59.9%), NELSON (58.6%), and ITALUNG (36%) studies [4,5,70]. This is mainly because of the higher percentage of lung adenocarcinoma (85.9%) in this study than in the NLST (52.5%), NELSON (60.6%), and ITALUNG (43%) studies [4,5,70]. Our *meta*-analysis included studies in both general risk and high-risk populations. Lung cancer in an Asian population not at high-risk were predominantly adenocarcinomas (96%) [16], and a higher proportion of stage I lung cancers were found among adenocarcinomas (46%) than among squamous cell carcinomas (35%) [71] due to slower growth.

The strength of the present study is that it is a community-based lung cancer screening restricted for age only, allowing it to provide a more comprehensive basis for identifying other risk factors for lung cancer screening in China. Furthermore, adding to the work of Cheng et al. who qualitatively summarized the prospective cohort studies and trials of lung cancer screening in China [72], we quantified the efficiency of lung cancer screening in China through a systematic research.

There are several limitations in this study. First, comparison of the lung cancer detection rate was only based on the first round of lung cancer screening, so the conclusion cannot be generalized to the detection rate at incident screening rounds. Data from annual screening rounds will follow in time. Second, the potential inter-reader agreement in nodule detection among the 4 resident radiologists and between the 2 senior radiologists was not evaluated, which might affect the nodule detection rate. Third, there was significant heterogeneity across the included screening studies due to variety in both the inclusion criteria and the nodule management protocols. These diverse criteria make it unfeasible to conduct subgroup analyses. Finally, 3 of the 5 registry-based clinical studies of lung cancer reporting cancer stage were from Taiwan. Given that the smoking rate is lower in Taiwan [73], the proportion of early stage lung cancer could be higher than in mainland China, which might result in a slight overestimation of stage shift due to screening.

In conclusion, lung cancer was 4- to 5-times more likely to be detected at an early stage by LDCT screening than by clinical diagnosis. The stage shift of lung cancer at detection due to LDCT screening in both high- and low-risk populations in China may lead to a subsequently improved lung cancer survival. Screen-detected lung cancer in the low-risk group was predominantly identified in women. LDCT screening detected more adenocarcinoma compared to not screening.

CRediT authorship contribution statement

Yanju Li: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Yihui Du:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Yubei Huang:** Methodology, Formal analysis, Investigation, Resources. **Yingru Zhao:** Methodology, Data curation, Funding acquisition. **Grigory Sidorenkov:** Conceptualization, Methodology. **Marleen Vonder:** Methodology, Investigation. **Xiaonan Cui:** Investigation, Data curation. **Shuxuan Fan:** Investigation, Data curation. **Monique D. Dorrius:** Formal analysis, Investigation. **Rozemarijn Vliegenthart:** Formal analysis, Investigation. **Harry J.M. Groen:** Formal analysis, Investigation. **Shiyuan Liu:** Funding acquisition. **Fengju Song:** Resources, Funding acquisition. **Kexin Chen:** Conceptualization, Resources, Supervision, Funding acquisition. **Geertruida H. Bock:** Conceptualization, Methodology, Supervision. **Zhaoxiang Ye:** Conceptualization, Methodology, Resources, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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