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Screening baseline characteristics of early lung cancer on low-dose computed tomography with computer-aided detection in a Chinese population

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ABSTRACT

Objectives: This study investigated appropriate baseline characteristics for screening a Chinese population at high risk of early lung cancer, assisted by low-dose computed tomography (LDCT) with computer-aided detection (CAD). Included is a discussion of the viability of using LDCT in the screening guideline and optimizing the guideline.

Methods: In 2014, 1016 individuals from Sichuan Province were enrolled who satisfied the criteria for high risk according to the 2013 National Comprehensive Cancer Network (NCCN) Guidelines for Non-Small Cell Lung Cancer. From 2014 to 2018, each subject was followed using LDCT with CAD, and pathologically confirmed lung cancers and baseline nodule characteristics (size and density) were recorded. Positive risk was considered a non-calcified solid or part-solid nodule on LDCT with diameter ≥5 mm and ground-glass nodule ≥8 mm, as newly recommended by the China National Lung Cancer Screening Guideline.

Results: From 2014–2018, 13 cases of lung cancer were detected; 5 of these were early stage (38.5%). According to the NCCN criteria, 54 women were included and one of these (1.8%) developed lung cancer. The prevalence of lung cancer was 0.7% at baseline. For the entire population (excluding subjects with a tumor mass at baseline, n = 4), the rate of positivity was 20.4% at baseline; applying the Chinese criteria, the false positive rate was 19.5% (197/1012).

Conclusions: Further studies are warranted to establish appropriate eligible criteria and management strategies for Chinese populations.

1. Introduction

Lung cancer is first among malignant tumors with regard to incidence and cancer-related mortality, worldwide and in China [1,2]. Year-by-year, the number of smokers and air pollution is increasing in China, and with it the incidence of lung cancer, with 733,300 newly diagnosed cases in 2015 [3]. Most patients are in an advanced stage at the time of diagnosis and are unable to accept surgery, which contributes to a high rate of mortality. Screening of high-risk populations is imperative for early detection, and thus there is a need for reliable and accurate screening guidelines.

The National Lung Screening Trial (NLST) has suggested that low-dose computed tomography (LDCT) is a useful method for early lung cancer screening. Compared with x-ray, LDCT was associated with a 20% decrease in lung cancer mortality [4]. In China, screening for lung cancer using LDCT has gradually become accepted, especially in Beijing, Tianjin, and Yunnan where the incidence of lung cancer is high. However, there are many differences in epidemiology and environmental exposure across China. Furthermore, it is not clear whether the LDCT screening criteria of American or European countries is appropriate for China.

At the time that our LDCT screening study began in 2014, we based our criteria for inclusion on the oncology clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) for high-risk populations (because the China National Lung Cancer Screening Guideline was not established at that time, and the first edition was published at 2015). These criteria focused on age and history (pack-years) of smoking. Specifically, the inclusion criteria for high-risk

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populations classified potential participants as either aged 55–74 years, ≥30 pack-year history of smoking tobacco, and quitting within 15 years; or aged ≥50 years, ≥20 pack-year history of smoking tobacco, and one additional risk factor other than second-hand smoke [5]. Yet, in foreign countries heavy smoking (especially ≥30 pack-year) is much more prevalent, compared with China [6,7]. In addition, adenocarcinoma appears to becoming more prevalent in non-smoking women (exposed to passive smoke), especially Asian women [6–10]. Yet, 2 Chinese studies found that non-smoking women with lung cancer did not meet the NLST criteria [6,7].

In 2018, the modified China National Lung Cancer Screening Guideline [11] was established, which was based on the results of the NLST and our own clinical practice. In this updated guideline, the inclusion criteria for a high-risk population consisted of ages 50–74 years, a ≥20 pack-year smoking history, and quitting within the past 5 years. Further characteristics that may be important were not included, such as second-hand smoke exposure. In addition, the size of a positive nodule was defined as ≥5 mm and ground-glass nodule ≥8 mm, while some studies determined thresholds of 4 or 6 mm [4,6,7,12].

Computer-aided detection (CAD) systems are useful for detecting small nodules, and are able to differentiate nodules from adjacent blood vessels. This could reduce the workload of radiologists and improve work efficiency [13–15]. Liang et al. [16] found that CAD systems could detect up to 70% of lung cancers that were not detected via computed tomography by a radiologist, and therefore CAD was useful as a second reader. Our previous study [17] investigated combining radiologists' readings of thin axial images with CAD, and the results suggested that the sensitivity of pulmonary nodule detection was 95.5%. In the present screening study, we also adopted this combined method.

Herein, the applicability of a screening guideline that utilizes LDCT with CAD for early detection of lung cancer in a high-risk population was investigated. Also discussed are modifications that are more appropriate for China, including the higher risk of second-hand smoke exposure in women, and positive nodule size.

2. Patients and methods

2.1. Study design

From 2014, individuals who were defined as being at high risk of lung cancer were enrolled for annual LDCT. During 4 years of follow-up, all lung cancers were recorded. The present study is a retrospective review of these cases to determine the baseline characteristics of those participants who developed lung cancer. Our Hospital's Drugs/Medical Apparatus & Ethics Committee approved the study protocol. Each participant provided written informed consent prior to data collection.

2.2. Study population

The subjects in this study were from a community nearby Chengdu in Sichuan Province, located in southwestern China (Fig. 1). Among the individuals who underwent the initial screening in 2014, 1023 satisfied the criteria for being at high risk of lung cancer, according to the NCCN (i.e., individuals at high risk of early lung cancer were defined as aged 50–74 years, a smoking history of ≥20 pack-years, and one additional risk factor other than second-hand smoke). Seven potential subjects were excluded because of incomplete data, and 4 patients were found with tumor mass and advanced stage at the baseline (initial screening); thus 1016 subjects were analyzed in the present study. From 2014 to 2018, the subjects of the study participated in follow-up examinations that included LDCT with CAD.

2.3. LDCT examination combined with CAD

CT scanning (PHILIPS Brilliance iCT) was acquired at the end of inspiration and from the thoracic inlet to the upper portion of the kidneys. The scanning parameters were as follows: 110 kV, 20 mA, and a pitch of 0.915. CT images were reconstructed as 0.625-mm thicknesses and displayed at a standard window setting (width 1600 HU; level –600 HU).

The original images were opened on a GE AW 4.4 workstation, and analyzed automatically by CAD software. The threshold of transverse diameter was set at 3 mm.

2.4. Imaging analyses

Four radiologists independently analyzed all the images (Luo HB, Qing HM, Wang XD, and Liu YY with 10, 8, 8, and 5 years' experience, respectively). They firstly verified all the detected pulmonary nodules via the CAD system, and then reviewed the thin-section CT images carefully in the CAD workstation concurrently to detect any further real pulmonary nodules. The result was a combination of these two. The CT dose was recorded, as well as the total number of nodules, location, margin (smooth, lobulated, speculated, or irregular), density (solid, partly-solid, pure ground-glass, calcium), and size. The demographic characteristics were collected at the same time, including gender, age, and body mass index.

2.5. Follow up

All subjects underwent LDCT annually. Furthermore, for subjects with solid or part-solid nodule ≥5 mm, ground-glass nodule ≥8 mm, or both, follow-up CT scans were performed at 1, 3, or 6 months, and annually thereafter for the 4 years. For subjects found to have lung cancer during the follow-ups, the histologic type and tumor stage were recorded. Early stage lung cancer was defined as stage 1.

2.6. Statistical analyses

All statistical analyses were performed with SPSS19.0 software (SPSS, Chicago, IL, USA). Descriptive data are presented as mean ± standard deviation for continuous data, and percentages for categorical data. To test for differences in means or percentages among different nodule size categories, we performed an analysis using the Mann-Whitney U test. A P-value < 0.05 was considered statistically significant.

3. Results

Initially, 1016 subjects were enrolled in the study (aged 61.4 ± 6.3 years). According to the high-risk inclusion criteria of the NCCN, there were only 54 women in the study population (5.3%). The mean CT dose was 1.18 ± 0.51 mSv. In the remaining 1012 subjects (excluding those with tumor mass at baseline, n = 4), only 141 (13.9%) participants had no nodule. The other 871 (86.1%) had at least one nodule (including calcified nodule), with the greatest number being 17 nodules in a single individual (Fig. 1).

Among 387 individuals with non-calcified nodules (solid and part-solid, or ground-glass), there were 181 and 164, respectively, with nodules sized ≥4–5 and ≥5–10 mm, and 26 and 16 subjects with nodules ≥10–15 and ≥15 mm (Table 1). Eleven subjects had not only solid but also part-solid non-calcified nodules ≥5 mm.

From 2014–2018, 13 cases of lung cancer were detected. At baseline, 7 patients were found with lung cancer, and the prevalence of lung cancer was 0.7% (Fig. 1). Excluding 4 subjects with tumor mass initially, 3 of 16 subjects with nodule(s) ≥15 mm were confirmed as having lung cancer at advanced stage, and these accepted surgery within one month after multidisciplinary discussion. The other 13 subjects continued to undergo the follow-up LDCT examinations, because their nodule size decreased or stabilized after anti-inflammatory therapy. The positive predictive value was 1.4% and the negative predictive value was 100% at baseline.

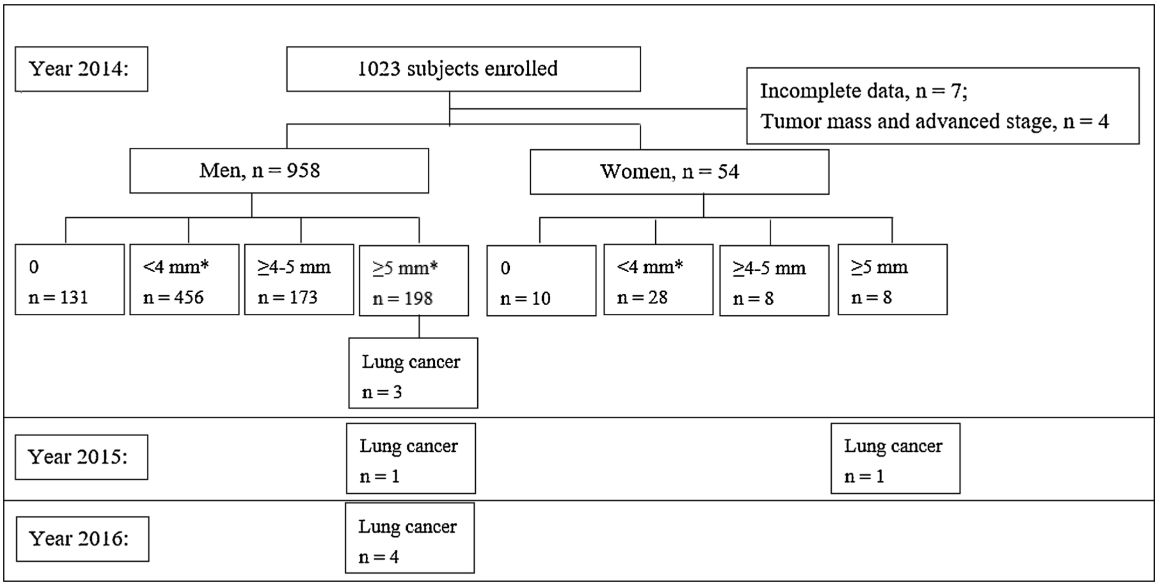

Fig. 1. Demographic and radiologic features of the participants.
* < 4 mm: non-calcified nodule size < 4 mm or calcified nodule; ≥ 5 mm: non-calcified nodule size ≥ 5 mm and ground-glass nodule ≥ 8 mm.

After the 4-year follow-up, 6 more subjects were found with lung cancer, and all originated from a positive nodule that was detected at baseline. At baseline, these 6 subjects had the following: 2 with ≥5–10 mm solid nodule; 2 with ≥10–15 mm solid nodule; 1 with ≥5–10 mm part-solid nodule; and 1 with gross-round nodule ≥8 mm (Tables 1 and 2). The one subject with ≥5–10 mm part-solid nodule was a woman. At the time of the 3-month follow-up, we had recommended that she should accept clinical intervention because of the increasing solid component. However, she refused and insisted on reexamination at 12 months, at which time the nodule had grown rapidly (≥15 mm). Regarding the man with the ground-glass nodule, the nodule size remained stable during the next 2 years, with an increased solid component at 24 months.

In this study, the thresholds for high risk of lung cancer at baseline were 5 mm for non- calcified nodules and 8 mm for ground-glass nodule. The positive rate was 20.4% (206/1012) (excluding subjects with a tumor mass at baseline, n = 4). If ≥4 mm was considered a positive criteria, then the positivity rate was higher, at 38.2% (387/1012).

The rate of 4-year cumulative lung cancer was 1.3% (13/1016). According to nodule size at baseline, the rates of 4-year cumulative lung cancer were 1.8, 11.5, and 18.8% at sizes ≥5–10, 10–15, and ≥15, respectively. In men and women, the rates of lung cancer were 1.2% and 1.8%. Appling the Chinese criteria for positivity yielded a false positive rate of 19.5% (197/1012). To lower the false positive rate, we combined nodule margin with nodule density and nodule size, and found that this would have excluded the true lung cancer subjects when reducing the false positive rate at the baseline (Table 3). Regarding the 13 patients who developed lung cancer, 38.5% (5/13) were early-stage cancer.

4. Discussion

This study investigated the appropriateness of specific characteristics for identifying individuals at high risk of lung cancer, for the purposes of early detection. A sizeable population of 1016 individuals from Sichuan province was enrolled in the year 2014 according to the NCCN characteristics, and baseline data was collected. Four patients were found with tumor mass and advanced stage cancer at the baseline screening. The remaining 1012 individuals were followed for 4 years. At baseline, another 3 individuals were found to have lung cancer, and the prevalence of lung cancer was 0.7% (7/1016). This is consistent with a few studies that reported rates of 0.7 to 1.0%, but lower than some studies that reported rates of 1.3 to 2.3% [6,12,18–22] (Table 4). By the last follow-up, 6 patients had developed lung cancer, and 5 (38.5%) were at early-stage on LDCT with CAD, which was lower than other similar studies [6,23,24], but higher than a Chinese study [25].

In the present study, a non-calcified nodule size ≥5 mm and ground-glass nodule ≥8 mm at baseline characterized 20.4% (206/1012) of our population. This is similar to the rate reported by the randomized Dutch-Belgian Lung Cancer Screening trial (NELSON;

Table 1
Detection rate of lung cancer in all subjects with non-calcified nodule ≥4 mm according to nodule density and size at baseline.

		≥4-5 mm	≥5-10 mm	≥10-15 mm	≥15 mm	*P*
Solid	Subjects, n	172	140	15	16	
	Lung cancer, n (%)	0	2 (1.4%)	2 (13.3%) [a,b]	3 (18.8%) [a,b]	< 0.001
Part-solid	Subjects, n	6	17	6	0	
	Lung cancer, n (%)	0	1 (5.9%)	0	0	0.694
Solid & part-solid	Subjects, n	3	7	4	0	
	Lung cancer, n (%)	0	0	0	0	
Ground-glass	Subjects, n	0	0	1	0	
	Lung cancer, n (%)	0	0	1 (100%)	0	
Total	Subjects, n	181	164	26	16	
	Lung cancer, n (%)	0	3 (1.8%)	3 (11.5%) [a,b]	3 (18.8%) [a,b]	< 0.001

[a] $P <$ 0.05 compared with ≥4-5 mm.
[b] $P <$ 0.05 compared with ≥5-10 mm.

Table 2
Summary of cases of confirmed lung cancer (n = 13).

	Age, y	Gender	Nodule, n	Density	Margin	Size, mm *	Stage	Histologic type
1	59	Male	6	Solid	Speculated	≥15	IIIA	ADC
2	67	Male	7	Solid	Lobulated	≥15	IIB	SCC
3	68	Male	3	Solid	Lobulated	≥15	IIB	ADC
4	62	Male	5	Solid	Irregular	≥10-15	IA	Mucous adenocarcinoma
5	61	Male	3	Solid	Smooth	≥10-15	IB	ADC
6	64	Male	2	Solid	Smooth	≥5-10	IB	Non small-cell carcinoma
7	71	Male	1	Solid	Smooth	≥5-10	IA	SCC
8	67	Female	1	Part-solid	Irregular	≥5-10	IB	SCC
9	64	Male	3	Ground-glass	Irregular	≥10-15	IIIA	ADC
10	73	Male	Mass	—	—	—	IIIB	ADC with pleural metastasis
11	51	Male	Mass	—	—	—	IIIB	ADC with lung metastasis
12	68	Male	Mass	—	—	—	IIIA	SCC
13	67	Male	Mass	—	—	—	IIIB	ADC with lung metastasis

ADC, adenocarcinoma; SCC, squamous-cell carcinoma.
* Size category at baseline.

Table 3
Detection rate of lung cancer in all subjects according to nodule density, size, and margin at baseline.

		≥5-10 mm	≥10-15 mm	≥15 mm
Solid	Case, n	75	10	15
	Lung cancer, n	0	1	3
Part-solid	Case, n	15	6	0
	Lung cancer, n	1	0	0
Ground-glass	Case, n	0	1	0
	Lung cancer, n	0	1	0

20.8%) and other studies [6,12,26], but higher than some studies [7,20,22]. However, 38.2% of our population had a nodule ≥4 mm, which differed from the 22.9% reported by another Chinese study, and 27.3% by the NLST trail [4,6].

We speculate that the above differences (higher positive rate but lower lung cancer prevalence) may be due to the larger populations of the other studies (e.g., 26715 in the NLST and 31567 in the I-ELCAP), and also the Chinese studies included non-smokers. This suggests that the positive criteria should be changed.

In the present study, 17.7% of the subjects had non-calcified nodules ≥4-5 mm at baseline, and no one in this subgroup developed lung cancer. This is similar to a study by Horeweg et al. [27], which found that the probability of lung cancer was low in participants with a nodule volume ≤100 mm^3 or a maximum transverse diameter < 5 mm, a probability that was comparable to that of participants without nodules.

In the subgroup of our population with a nodule ≥5 mm at baseline, in most (79.6%; 164/206) the nodule was ≥5–10 mm and 1.8% of these (with nodule size ≥5–10 mm) developed lung cancer. The percentage of participants who developed lung cancer was higher in the subgroup with a nodule ≥10 mm at baseline. The optimal nodule size threshold for best determining high risk of lung cancer has been debated for many years, and a higher threshold (i.e., ≥8 mm) to minimize false-positive results is usually recommended [28,29]. We consider that the threshold for node size should be increased, or the follow-up interval extended, for those with nodules ≥5–10 mm. This should minimize the false positive rate and soothe patients' anxiety. For patients with nodes ≥10 mm, or part-solid or ground-glass nodules, the question remains whether these nodules should be treated more aggressively, or the follow-up interval should be shorter. More prospective studies with a large population will be needed to answer these questions.

To investigate if the false positive rate could be lowered, we combined the nodule margin with nodule size. Although this method did reduce the false positive rate slightly, it also increased the false negative rate; that is, in the subgroup with ≥5–10 mm solid nodule(s) at baseline, 75 false positive subjects were excluded, but 2 lung cancer patients were also excluded. This suggested that for smaller nodules, the margin was less useful for indicating risk of malignancy. Some studies have suggested that volume is more accurate than size [30,31]. The role of volume should be studied more thoroughly, or perhaps a scoring system should be developed that combines size, margin, volume, and other radiologic features that would increase sensitivity and specificity.

When applying the NCCN high-risk criteria in the present study, only 54 women were enrolled, and the proportion of women was lower than in studies of other countries [4,12,18–20] (Table 4). Two Chinese studies also found that in China women with lung cancer rarely met the criteria of the NLST [6,7]. In our study, one of the women developed lung cancer with a part-solid nodule. The rate of lung cancer detection in the women was higher than that of the men, although not significantly. More and more studies (including from Asia) have shown that lung cancer in women is often unrelated to direct use of tobacco. This is also true in China, where the percentage of women who smoke is much less than in developed countries, but where exposure to secondhand smoke may be high [6–10]. Hu et al. [32] reported similar results in a retrospective study, in which 27 of 31 patients with resected nodule were women, but only one of them smoked. Another study from China suggested that more attention should be given to women older than 40 years who are passively exposed to tobacco smoke [23]. Yet, neither foreign screening criteria, nor the 2018 Chinese guideline utilizing LDCT for screening of early lung cancer, identified passive smoking by women as a high risk factor. We recommend that the criteria for identifying individuals at high risk of early lung cancer should be tailored for the Chinese population, especially with regard to non-smoking women.

The main strength of the present study was that the data were analyzed by specific categories, i.e., solid and part-solid nodule, and size of nodule. However, the sample was not large enough (e.g., for $\alpha = 0.05$, $\beta = 0.8$, and $P = 0.015$, the sample size would be ˜4500); the database we collected is incomplete. Further studies are warranted to assess the following aspects: the optimal threshold for nodule size; inclusion of other relevant radiological features; personalized follow-up interval and criteria (especially considering women who are passively exposed to smoke); and modifications of the guidelines toward better suitability for the Chinese population.

Author contribution

- Study conception and design: LY, RJ, ZP, XG.
- Acquisition of data: LH, QH, WX, HS, HC.
- Analysis of data: LY, LH, QH, WX.
- Interpretation of data: LY, RJ, ZP.

Table 4
Detailed summary of LDCT test baseline results from lung cancer screening trials.

	Screening	Participants for LDCT, n	M:F (F %)	Age, y	Smoking history	Nodule assessment (D/V)	Positive criteria	Positive, %	LC at BL, %
NLST (4)	Annual for 3 y	26715	15765:10950 (41%)	55-74	≥30 PY of cigarette smoking & who were either current smokers or had been smokers within the previous 15 y.	D	≥4 mm	27.3	1.1
NELSON (12)	BL, 1-, 3-, & 5.5-y	7557	6303:1254 (16.6%)	50-75	≥15 cigarettes per day for ≥25 y or ≥10 cigarettes per day for ≥30 y or had quit 10 y ago	V (or D for pleural-based nodules)	V ≥50 mm^3 or D ≥ 4.6 mm; or nonsolid nodule ≥8 mm; or VDT ≥ 400 d	20.8	0.9
UKLS (18)	Single	1994	1529:499 (25%)	50-75	As for formal individual risk stratification by LLPv2* (≥20 y)	V (or D if no segmentation software)	≥ 50 mm^3; pleural or juxtapleural nodules D ≥ 5 mm	26.9	2.1
MILD (19)	Annual or biennial	Annual 1190 Biennial 1186	814:376 (31.6%) 813:373 (31.5%)	≥49	≥20 PY current or former smokers (quit smoking within 10 y of recruitment), & no history of cancer within the previous 5 y	V	≥ 60 mm^3	Annual 14.9; Biennial 13.3	Annual 1.0; Biennial 0.5
DLCST (20)	Annual for 5 y	2052	1120:932 (45.4%)	50-70	≥20 PY or former smokers who quit after the age of 50 y & < 10 y ago	D	≥ 5 mm	8.72	0.8
DANTE (21)	Annual	1276	Male	60-74	≥20 PY active or quit < 10 y	D	≥10 mm or smaller (≥6 mm) but showing spiculated margins, or non-nodular lesions such as a hilar mass, focal ground-glass opacities	10.03	2.2
I-ELCAP (22)	Annual	31567	?	≥40	At risk for LC because of a history of cigarette smoking, occupational exposure (to asbestos, beryllium, uranium, or radon), or exposure to secondhand smoke without having smoked themselves	D	Solid or partly solid NPN ≥ 5 mm; NPN ≥ 8 mm	13.3	1.3
Shanghai (6)	Single	NLST eligible 256; Not NLST eligible 3256	NLST eligible 255:1 (0.4%); Not NLST eligible 1370:1886 (57.9%)	45–70	Showing at least one high-risk factor: ≥20 PY, & for former smokers, no more than 15 y since quitting; cancer history of any kind in close family members; cancer history of any kind for the participant; occupational exposure to carcinogenic agents; long history of passive smoking; &/or long-term exposure to cooking oil fumes	D	Longest D of ≥4 mm	Not NLST eligible 22.9	NLST eligible 2.3; Not NLST eligible 1.5
Taiwan (7)	Single	NLST eligible 148; Not NLST eligible 1615	NLST eligible 143:5 (3.4%); Not NLST eligible 886:729 (45.1%)	≥40	No other inclusion criterion	D	solid & part-solid ≥ 6 mm, & for ground-glass nodules ≥ 20 mm.	NLST eligible 2.7; Not NLST eligible 3.7	NLST eligible 0.7; Not NLST eligible 1.5
Beijing (23)	Single	NCCN (high risk group) 319	306:13 (4.1%)	55-74	≥30 PY history of smoking tobacco, & quitting within 15 y; or ≥20 PY history of smoking tobacco, & one additional risk factor other than second-hand smoke	D	≥5 mm & ground-glass nodule ≥8 mm	27	0.9
Sichuan (our study)	Annual	NCCN (high risk group) 1016	962:54 (5.3%)	≥50	≥30 PY history of smoking tobacco, & quitting within 15 y; or ≥20 PY history of smoking tobacco, & one additional risk factor other than second-hand smoke	D	solid & part-solid nodule ≥5 mm; or ground-glass nodule ≥8 mm	20.5	0.7

BL, baseline; D, diameter; LC, lung cancer; NPN, non-calcified pulmonary nodule; PY, pack years; V, volume.

- Manuscript writing: LY.
- Critical review of the article and final approval of the article: all authors.

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