Low-dose chest computed tomographic screening and invasive diagnosis of pulmonary nodules for lung cancer in never-smokers

Yeon Wook Kim [1,2], Hye-Rin Kang[1], Byoung Soo Kwon[1,2], Sung Yoon Lim[1,2], Yeon Joo Lee[1,2], Jong Sun Park[1,2], Young-Jae Cho[1,2], Ho Il Yoon[1,2], Kyung Won Lee[3], Jae Ho Lee[1,2] and Choon-Taek Lee [1,2]

Affiliations: [1]Division of Pulmonary and Critical Care Medicine, Dept of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea. [2]Division of Pulmonary and Critical Care Medicine, Dept of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea. [3]Dept of Radiology, Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

Correspondence: Choon-Taek Lee, Dept of Internal Medicine, Seoul National University Bundang Hospital, 173–82 Gumi-Ro, Bundang-gu, Seongnam 13620, Republic of Korea. E-mail: ctlee@snu.ac.kr

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ABSTRACT

Background: Although lung cancer screening using low-dose computed tomography (LDCT) is now widely used in clinical practice, the characteristics and outcomes of diagnostic procedures related to screen-detected nodules in never-smokers remain unclear. We aimed to determine the incidence of nodules considered for invasive biopsy and evaluate the final diagnoses and procedure-related complications in never-smokers in comparison to ever-smokers who underwent LDCT screening.

Methods: We evaluated 37 436 asymptomatic adults (17 968 never-smokers and 19 468 ever-smokers) who underwent LDCT screening for lung cancer between January 2009 and December 2018 at a tertiary centre in South Korea. The rates of invasive diagnostic procedures for detected nodules and related complications, and the diagnostic outcomes were determined in the never-smoker and ever-smoker groups.

Results: Among the never-smokers, 2908 (16.2%) out of 17 968 had positive nodules. Overall, 139 (0.77%) out of 17 968 never-smokers and 194 (1.00%) out of 19 468 ever-smokers underwent invasive biopsy (p=0.022). Lung cancer was diagnosed in 84 (0.47%) out of 17 968 never-smokers and 123 (0.63%) out of 19 468 ever-smokers (p=0.032). The proportions of participants diagnosed with benign disease after invasive biopsy (false-positive) were 50 (0.28%) out of 17 968 and 69 (0.35%) out of 19 468 in the never-smoker and ever-smoker groups, respectively (p=0.191). Multivariate analyses revealed no significant associations of smoking with the risk of a false-positive diagnosis (OR 0.98, 95% CI 0.62–1.57) and complications (OR 1.33, 95% CI 0.65–3.73) after biopsy. Of the 84 never-smokers with lung cancer, 82 (97.6%) had adenocarcinoma, and 75 (89.3%) were in stage I with a favourable prognosis.

Conclusions: LDCT screening in never-smokers resulted in a notable detection rate of lung nodules, which warranted invasive biopsy. The lung cancer detection rate was lower in never-smokers than in ever-smokers. However, no significant differences in the false-positive and complication rates were observed between the two groups. Accordingly, a more specifically tailored management strategy is needed for screen-detected nodules in Asian never-smokers.

Introduction

Lung cancer remains the leading cause of cancer-related deaths in both males and females globally [1]. Because of the latency of symptom presentation, subsequent delay in diagnosis of the disease is common, leading to poor survival outcomes [2]. Therefore, many studies have been focused on developing effective screening methods for early detection. Recently, two large randomised trials, the National Lung Screening Trial (NLST) and the Dutch–Belgian randomised low-dose computed tomography (LDCT) screening (NELSON) trial, proved the benefits of lung cancer screening with LDCT, showing significant reduction in lung cancer mortality in heavy smokers [3, 4]. Based on the promising results of the NLST, the US Preventive Services Task Force (USPSTF) recommends lung cancer screening in individuals aged 55–80 years who are either current smokers or have quit smoking within the past 15 years, with a smoking history of ⩾ 30 pack-years [5].

With the NLST and NELSON trials, lung cancer screening with LDCT in heavy smokers seems established. However, the results of several large cohort studies suggested that LDCT screening might be beneficial to many individuals who do not meet the current LDCT screening criteria recommended by the USPSTF [6, 7]. In this respect, the potential effects of LDCT screening in never-smokers are important, but little known. The incidence of lung cancer in never-smokers has been increasing steadily, especially in Asian regions [8]. Large cohort studies suggest that although the age-adjusted incidence rates of lung cancer per 100 000 person-years among never-smokers remain 12–30 times lower than those of current smokers, the absolute rates are as high as 4.8–20.8 per 100 000 person-years [9]. In addition, epidemiological studies have identified significant sex and geographical variations. In Eastern Asia, never-smokers comprise ∼22% of all lung cancer patients (61% of female cases and 11% of male cases), whereas only ∼5% of all lung cancer patients in Europe are never-smokers (21% of female cases and 2% of male cases) [10]. In South Korea, the numbers of newly diagnosed lung cancers and related deaths have increased steadily since the 1990s, despite a notable decrease in the cigarette smoking rate [11]. Particularly among females, the incidence of lung cancer increased by more than two-fold from 2000 to 2014, and >85% of female lung cancer patients are never-smokers [12]. These data indicate that currently, the incidence and mortality of lung cancer are less influenced by smoking. Furthermore, studies have demonstrated that lung cancer in never-smokers differs in clinical and molecular characteristics from that in ever-smokers, indicating a distinct disease entity [10, 13]. Previously, our group reported the results of LDCT screening in never-smokers, including an overall lung cancer detection rate of 0.45% (0.86% in ever-smokers), with a female predominance [14].

Another important issue related to lung cancer screening involves the potential harms and overdiagnosis and/or false-positive findings. Lung nodules are commonly detected during LDCT screening, and are likely to be subjected to invasive diagnostic procedures (*e.g.* surgical, percutaneous and bronchoscopic biopsies) [15]. The decision on whether to biopsy or resect a pulmonary nodule remains difficult and is mainly determined by clinical judgment [16]. In this regard, previous studies identified a considerable proportion of patients with benign nodules who underwent unnecessary invasive diagnostic procedures [3, 17]. However, there are limited data on the incidence and results of invasive diagnostic procedures for screen-detected nodules in never-smokers, especially in Asian countries with prevalent ground-glass opacity nodules (GGNs) which make decisions for invasive diagnosis more difficult [18]. Information on the performance of invasive procedures in this group would be important considering the high prevalence of lung cancer among never-smokers in Asia, with a higher proportion of curable cases detected by screening [10, 14].

Therefore, we conducted a retrospective hospital-based cohort study of asymptomatic participants who voluntarily underwent lung cancer screening *via* LDCT. We evaluated the incidence and results of invasive diagnostic procedures for nodules detected during LDCT screening in South Korea. The aim of this study was to determine the incidence of nodules considered for invasive biopsy and evaluate the final diagnoses and the complications related to invasive procedures in never-smokers compared to ever-smokers in a real-world lung cancer screening setting.

Materials and methods

Study design and participants

We designed a single-centre, retrospective cohort study of adults aged ⩾18 years who voluntarily underwent LDCT screening for lung cancer, regardless of their smoking history, between January 2009 and December 2018 at the Health Promotion Centre of Seoul National University Bundang Hospital, a

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tertiary centre in South Korea. All participants were asymptomatic at the time of the first visit and underwent LDCT screening as part of a health check-up. Among those who received LDCT screening, questionnaires were used to evaluate their smoking status (never-, ex- or current smoker), amount of smoking in pack-years, and the duration of smoking cessation among ex-smokers. Never-smokers were defined as adults who had never smoked or had smoked <100 cigarettes in their lifetime [19]. Participants with a previous history of lung cancer at the time of baseline screening, and those with unknown history on smoking status were excluded. Individuals with data on smoking status but without the amount of smoking were included. This study was approved by the institutional review board of Seoul National University Bundang Hospital (B-1907–550–007). The institutional review board waived the need for written informed consent from the participants.

Procedures

Unenhanced LDCT scans were performed using Brilliance iCT 256 scanner (Phillips Medical Systems, Best, the Netherlands) at a peak tube voltage of 100 kV and a reference tube current of 20–50 mA. All LDCT images were reconstructed with 3-mm or thinner slices in the axial plane and a 3-mm slice in the coronal plane and were initially stored in a dedicated electronic picture archiving and communication system. All images were interpreted by board-certified experienced chest radiologists. A positive nodule detected by LDCT was defined as any noncalcified nodule with a longest diameter of $\geqslant$4 mm. Patients with positive nodules were referred to the pulmonary division and received further follow-up and diagnostic evaluations according to the National Comprehensive Cancer Network guidelines and the Lung-RADS recommendation (edition 1.0) [20, 21].

For this study, all participants were categorised into two groups based on the smoking history data retrieved from the medical records: never-smokers and ever-smokers. Since there were missing data on the amount of smoking in a considerable proportion of ever-smokers, we were unable to further stratify this group by smoking amount. A pulmonary physician (YWK) and a radiologist (KWL) reviewed all the images that yielded readings of positive pulmonary nodules. All participants with positive nodules were further classified using the Lung-RADS criteria. Since the Lung-RADS was first released in 2014, images taken before 2014 were re-evaluated retrospectively for this study [21]. In cases with multiple nodules, a single dominant nodule was selected for the analyses. The location, size and type of each nodule and the medical records of participants with positive nodules were reviewed. For images with inconsistent findings, a consensus decision was reached following a discussion.

Decisions regarding follow-up and invasive procedures for pathologic evaluations were made by the attending specialist in the pulmonary division. According to the guidelines, the decision to perform invasive biopsy mainly depended on the radiologic findings of the detected nodule and was not additionally weighted by the smoking history or other demographic factors [20, 21]. The pathologic diagnosis of a nodule was performed using video-assisted thoracoscopic surgery (VATS), percutaneous needle biopsy or bronchoscopic biopsy. As a biopsy was considered based on a suspicion of malignancy, no routine attempts were made to collect respiratory specimens for microbiological examination. A bronchoscopy was performed to collect respiratory specimen for cytology testing and the evaluation of other infectious conditions when appropriate. Medical records documenting a change in the nodule size, the diagnostic procedures and any associated complications were obtained for participants who underwent such procedures. For biopsied nodules which exhibited growth, the volume doubling time was calculated using the modified Schwartz formula [22]. A procedure-associated complication was defined as any complication that occurred within 72 h of the invasive diagnostic procedure. The follow-up data were reviewed for up to 1 month after the procedure to evaluate the delayed complications. Participants who presented with suspicious nodules, but did not undergo pathologic diagnosis were included in the analyses of positive nodules, but not in the analyses of nodules that received invasive diagnosis. The pathologic reports and the final diagnoses of evaluated nodules, as well as the staging reports and records of initial treatment and outcomes for diagnosed lung cancer were obtained. Lung cancer staging was based on the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer stage classification of nonsmall cell lung cancer [23].

Outcomes

The main outcomes of this study were the rates of invasive diagnostic procedures for detected nodules and the related complications, rate of lung cancer detection and the incidence and rate of false-positive results, which were defined as a pathologic diagnosis of nonmalignancy of the biopsied nodule. These outcomes were compared between never-smokers and ever-smokers. Moreover, the characteristics of the nodules selected for invasive biopsy and the staging, treatment and mortality of diagnosed lung cancer in both groups were also evaluated.

Statistical analysis

Characteristics of participants are presented as mean±SD for continuous variables and as frequencies (%) for categorical variables. To compare the baseline characteristics and the diagnostic processes and results between the two groups, t-tests were used to analyse continuous variables and Pearson Chi-squared tests were used to analyse categorical variables. Univariate and multivariate analyses of the main outcomes were performed using logistic regression models adjusted for demographic factors (smoking status, age, sex). Estimation and comparison of incidence and survival was done with Kaplan–Meier analyses with log-rank tests. Cox proportional hazard models were used for the multivariate analyses. The odds ratios, hazard ratios (HRs) and 95% confidence intervals were calculated, and p-values <0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA) and STATA, version 14.2 (StataCorp., College Station, TX, USA).

Results

Characteristic of participants

The flowchart of the study is shown in figure 1. During the study period, 41 138 participants received LDCT screening. After exclusion of 3702 participants with unknown smoking history or with previously diagnosed lung cancer, 37 436 participants were eligible for analysis. Among them, 17 968 were never-smokers and 19 468 were ever-smokers. The baseline characteristics of all participants are described in table 1. Regardless of smoking status, almost one-third of participants were aged <45 years at the time of baseline computed tomographic screening. Male participants accounted for 63.6% of the total population and were dominant in ever-smokers (93.4%), whereas 68.6% of never-smokers were female. During the study period, 6066 (16.2%) out of 37 436 participants (2908 never-smokers and 3158 ever-smokers) had positive nodules of ⩾4 mm which were detected by LDCT. At baseline LDCT screening, 32 558 (87.0%) out of 37 436 had results of Lung-RADS category 1 or S, and 3871 (10.3%), 522 (1.4%), 324 (0.9%) and 161 (0.4%) out of 37 436 had results of category 2, 3, 4A, 4B or 4X lung nodules, respectively. The Lung-RADS category distributions did not differ significantly between groups. In

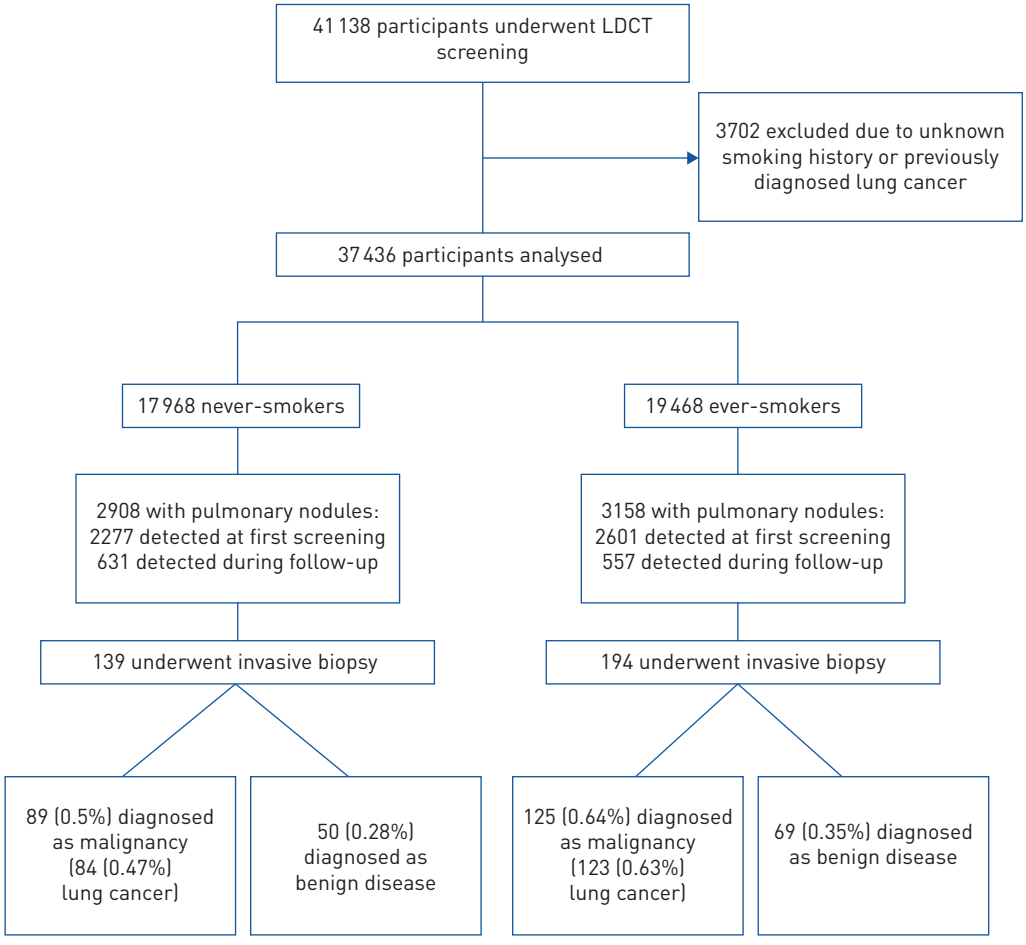

FIGURE 1 Flow diagram of the study population. LDCT: low-dose computed tomography

TABLE 1 Characteristics of participants who underwent low-dose computed tomography (LDCT) screening

	Total	Never-smoker	Ever-smoker	p-value
Subjects	37436	17968	19468	
Age at baseline screening years	49.5±11.2	50.5±11.6	48.6±10.8	<0.001
<45	12850 (34.3)	5556 (30.9)	7294 (37.5)	<0.001
45–49	6439 (17.2)	3002 (16.7)	3437 (17.7)	
50–54	6441 (17.2)	3117 (17.3)	3324 (17.1)	
55–59	4805 (12.8)	2395 (13.3)	2410 (12.4)	
60–64	2975 (7.9)	1625 (9.0)	1350 (6.9)	
65–69	2101 (5.6)	1176 (6.5)	925 (4.8)	
70–74	1248 (3.3)	748 (4.2)	500 (2.6)	
⩾75	577 (1.5)	349 (1.9)	228 (1.2)	
Male	23827 (63.6)	5644 (31.4)	18183 (93.4)	<0.001
BMI kg·m^{-2}	24.0±3.2	23.3±3.2	24.7±3.1	<0.001
Total follow-up months	34.8±35.5	34.0±34.4	35.6±36.4	<0.001
Lung-RADS category at baseline LDCT screening				0.281
1 or S	32558 (87.0)	15691 (87.3)	16867 (86.6)	
2	3871 (10.3)	1792 (10.0)	2079 (10.7)	
3	522 (1.4)	253 (1.4)	269 (1.4)	
4A	324 (0.9)	155 (0.9)	169 (0.9)	
4B or 4X	161 (0.4)	77 (0.4)	84 (0.4)	
Subjects with positive lung nodule	6066 (16.2)	2908 (16.2)	3158 (16.2)	0.922
Nodule detected at baseline screening	4878 (13.0)	2277 (12.7)	2601 (13.4)	0.048
Nodule detected during follow-up	1188 (3.2)	631 (3.5)	557 (2.9)	<0.001
Received invasive biopsy	333 (0.89)	139 (0.77)	194 (1.00)	0.022
Diagnosed as lung cancer	207 (0.56)	84 (0.47)	123 (0.63)	0.032
Diagnosed as metastatic carcinoma or lymphoma	7 (0.02)	5 (0.03)	2 (0.01)	0.215
Diagnosed as benign (false-positive)	119 (0.32)	50 (0.28)	69 (0.35)	0.191

Data are presented as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; Lung-RADS: Lung Imaging Reporting and Data System.

addition, 139 (0.77%) out of 17968 never-smokers and 194 (1.00%) out of 19468 ever-smokers underwent invasive biopsy for pathologic diagnosis (p=0.022). Lung cancer was diagnosed in 84 (0.47%) of the 17968 never-smokers and 123 (0.63%) of the ever-smokers (p=0.032) who underwent lung cancer screening. The proportion of participants diagnosed with benign disease after invasive biopsy (false-positive) did not differ significantly between groups (0.28% in never-smokers *versus* 0.35% in ever-smokers, p=0.191) (table 1).

Characteristics and clinical course of participants with positive nodules

The characteristics of participants with positive screening results for lung nodules are described in table 2. Positive nodules were slightly less frequently detected in never-smokers at the baseline LDCT screening, compared to ever-smokers (2277 (78.3%) out of 2908 *versus* 2601 (82.4%) out of 3158; p<0.001). Never-smokers had a significantly higher proportion of cases with GGNs (part-solid nodules and pure GGNs; 1490 (51.2%) out of 2908), whereas most nodules detected in ever-smokers were solid (1895 (60.0%) out of 3158). Among those with positive nodules, 333 (5.5%) out of 6066 underwent invasive biopsy, and the proportion of invasive biopsy in never-smokers (4.8%) was slightly less than that in ever-smokers (6.1%) (p=0.020).

The clinical features and diagnostic processes of the 333 participants who underwent invasive procedures for pathologic diagnosis of nodules are shown in table 3. The predominant nodule type considered for biopsy was GGN (58.3%) in never-smokers, whereas solid nodules (56.2%) were the predominant type considered for biopsy in ever-smokers. The frequency of invasive biopsy at first detection of relevant nodule, and the nodule size when considered for biopsy were significantly higher in ever-smokers. However, the age at diagnosis, time from baseline screening to invasive biopsy, lung cancer detection rate and false-positive malignancy rate did not differ significantly between the two groups.

Detailed information on the invasive diagnostic process and related complications is presented in table 4. Compared to ever-smokers, a higher proportion of never-smokers with nodules underwent VATS (64.0% *versus* 52.6%, p=0.037) for pathologic diagnosis. In both groups, the most common complication related to invasive biopsy was pneumothorax. The proportion of participants who underwent re-biopsy and the complication rates related to any invasive diagnostic procedure did not differ significantly between groups.

TABLE 2 Characteristics of participants with positive nodules detected by low-dose computed tomography screening

	Total	Never-smoker	Ever-smoker	p-value
Subjects	6066	2908	3158	
Age at baseline screening years	52.5±11.6	53.7±11.8	51.4±11.3	<0.001
<45	1524 (25.1)	620 (21.3)	904 (28.6)	<0.001
45–49	961 (15.8)	439 (15.1)	522 (16.5)	
50–54	1050 (17.3)	509 (17.5)	541 (17.1)	
55–59	917 (15.1)	460 (15.8)	457 (14.5)	
60–64	614 (10.1)	327 (11.2)	287 (9.1)	
65–69	488 (8.0)	246 (8.5)	242 (7.7)	
70–74	329 (5.4)	190 (6.5)	139 (4.4)	
⩾75	183 (3.0)	117 (4.0)	66 (2.1)	
Male	3759 (62.0)	852 (29.3)	2907 (92.1)	<0.001
BMI kg·m^{-2}	23.9±3.2	23.3±3.2	24.6±3.1	<0.001
Nodule detected at baseline screening	4878 (80.4)	2277 (78.3)	2601 (82.4)	<0.001
Nodule detected during follow-up	1188(19.6)	631 (21.7)	557 (17.6)	<0.001
Lung-RADS category at first detection of nodule				0.784
2	4801 (79.1)	2298 (79.0)	2503 (79.3)	
3	654 (10.8)	322 (11.1)	332 (10.5)	
4A	401 (6.6)	193 (6.6)	208 (6.6)	
4B or 4X[#]	210 (3.5)	95 (3.3)	115 (3.6)	
Location of dominant nodule				0.017
Right upper lobe	1509 (24.9)	773 (26.6)	736 (23.3)	
Right middle lobe	797 (13.1)	364 (12.5)	433 (13.7)	
Right lower lobe	1352 (22.3)	642 (22.1)	710 (22.5)	
Left upper lobe	1207 (19.9)	570 (19.6)	637 (20.2)	
Left lower lobe	1186 (19.6)	556 (19.1)	630 (19.9)	
Trachea or main bronchus	15 (0.2)	3 (0.1)	12 (0.4)	
Subjects with multiple nodules	1736 (28.6)	835 (28.7)	901 (28.5)	0.875
Nodule type				<0.001
Solid	3296 (54.3)	1401 (48.2)	1895 (60.0)	
Part-solid	694 (11.4)	318 (10.9)	376 (11.9)	
Pure GGN	2023 (33.3)	1172 (40.3)	851 (26.9)	
Cavitary	53 (0.9)	17 (0.6)	36 (1.1)	
Size of nodule at first detection mm	7.0±5.2	7.1±4.6	6.9±5.6	0.241
Diagnostic evaluation for detected nodule				
Invasive biopsy	333 (5.5)	139 (4.8)	194 (6.1)	0.020
Bronchoscopy without biopsy	65 (1.1)	35 (1.2)	30 (0.9)	0.338
FDG-PET	190 (3.1)	69 (2.4)	121 (3.8)	0.001
Pathologic diagnosis				
Lung cancer	207 (3.4)	84 (2.9)	123 (3.9)	0.031
Metastatic carcinoma or lymphoma	7 (0.1)	5 (0.2)	2 (0.1)	0.213
Benign disease (false-positive)	119 (2.0)	50 (1.7)	69 (2.2)	0.192

Data are presented as n, mean±SD or n (%), unless otherwise stated. BMI: body mass index; Lung-RADS: Lung Imaging Reporting and Data System; GGN: ground-glass nodule; FDG-PET: fluorodeoxyglucose positron emission tomography. [#]: 91 (43.3%) out of 210 participants who had category 4B or 4X nodules at first detection eventually did not undergo any invasive biopsy.

Among never-smokers who underwent invasive biopsy, those in whom a relevant nodule was detected at baseline had a higher rate of lung cancer diagnosis and a lower rate of false-positive diagnosis than those in whom the nodule was detected during follow-up (supplementary table S1).

Final diagnoses and clinical outcomes

Of the 333 participants who underwent invasive biopsy, 207 were diagnosed with lung cancer (table 5). Adenocarcinoma (82 (97.6%) out of 84) was the major histological type diagnosed in never-smokers. Compared to ever-smokers, never-smokers had a significantly higher detection rate of lung cancer at stage I (89.3% *versus* 68.3%), a higher rate of surgical resection as initial treatment (92.9% *versus* 82.1%) and a lower rate of lung cancer-related mortality (2.4% *versus* 12.2%). Table 6 shows the final diagnoses of 119 participants with false-positive results following invasive diagnosis. A significant proportion of biopsied nodules were finally diagnosed as tuberculosis or non-tuberculosis mycobacterial (NTM) disease.

TABLE 3 Characteristics of participants who underwent invasive procedures for diagnosis of detected pulmonary nodules

	Total	Never-smoker	Ever-smoker	p-value
Subjects	333	139	194	
Age at diagnosis years	61.4±11.2	60.4±11.9	62.0±10.6	0.195
Time of nodule detection				0.068
At baseline screening LDCT	231 (69.4)	104 (74.8)	127 (65.5)	
During follow-up screening	102 (30.6)	35 (25.2)	67 (34.5)	
Nodule type				0.003
Solid	160 (48.0)	51 (36.7)	109 (56.2)	
Part-solid	95 (28.5)	47 (33.8)	48 (24.7)	
Pure GGN	60 (18.0)	34 (24.5)	26 (13.4)	
Cavitary	18 (5.4)	7 (5.0)	11 (5.7)	
Time of planning invasive diagnosis				0.030
At first detection of relevant nodule	179 (53.8)	65 (46.8)	114 (58.8)	
During follow-up	154 (46.2)	74 (53.2)	80 (41.2)	
Number of LDCT screenings before biopsy	2.2±1.4	2.1±1.3	2.2±1.5	0.513
Time from baseline LDCT screening to biopsy months	30.4±33.8	29.4±34.7	31.1±33.2	0.654
Nodule size at biopsy mm	19.6±12.4	17.5±8.3	21.2±14.7	0.007
Volume-doubling time of the biopsied nodules exhibiting growth[#] days	711.4±702.4	608.5±587.4	784.3±771.3	0.267
Diagnosed as lung cancer	207 (62.2)	84 (60.4)	123 (63.4)	0.582
Diagnosed as metastatic carcinoma or lymphoma	7 (2.1)	5 (3.6)	2 (1.0)	0.107
False-positive for malignancy	119 (35.7)	50 (36.0)	69 (35.6)	0.939

Data are presented as n, mean±SD or n (%), unless otherwise stated. LDCT: low-dose chest computed tomography; GGN: ground-glass nodule. [#]: analysis based on nodules that showed growth increase of ⩾ 2 mm in maximal diameter.

However, the distributions of the final diagnoses did not differ significantly according to smoking status. Overall, bronchoscopy was performed in 84 (70.6%) out of 119 participants who received a false-positive diagnosis. 32 patients were diagnosed with mycobacterial disease, and the diagnostic yield of bronchoscopy for mycobacteria detection was 43.8% (14 out of 32). Supplementary table S2 presents the results of

TABLE 4 Diagnostic procedures and related complications in those who received invasive biopsy

	Total	Never-smoker	Ever-smoker	p-value
Subjects	333	139	194	
Type of biopsy				
VATS	191 (57.4)	89 (64.0)	102 (52.6)	0.037
Range of resection, n/N (% of VATS cases)				0.938
Lobectomy	95/191 (49.7)	44/89 (49.4)	51/102 (50.0)	
Segmentectomy or wedge resection	96/191 (50.3)	45/89 (50.6)	51/102 (50.0)	
Percutaneous needle biopsy	101 (30.3)	38 (27.3)	63 (32.5)	0.316
Bronchoscopic biopsy[#]	41 (12.3)	12 (8.6)	29 (14.9)	0.084
Received re-biopsy for insufficient diagnosis	10 (3.0)	5 (3.6)	5 (2.6)	0.591
Any complications related to invasive diagnostic procedure	55 (16.5)	20 (14.4)	35 (18.0)	0.376
Complications related to non-surgical biopsy				0.687
Pneumothorax	18 (5.4)	6 (4.3)	12 (6.2)	
Bleeding	6 (1.8)	2 (1.4)	4 (2.1)	
Complications related to surgical procedures				0.357
Pneumothorax requiring pleurodesis	16 (4.8)	6 (4.3)	10 (5.2)	
Post-operative pneumonia	7 (2.1)	2 (1.4)	5 (2.6)	
Bleeding requiring surgery	2 (0.6)	0 (0)	2 (1.0)	
Chylothorax	4 (1.2)	3 (2.2)	1 (0.5)	
Wound problem	1 (0.3)	1 (0.7)	0 (0)	
Bronchial stenosis	1 (0.3)	0 (0)	1 (0.5)	
Persistent pleural effusion	1 (0.3)	1 (0.7)	0 (0)	
Acute coronary syndrome or stroke	2 (0.6)	0 (0)	2 (1.0)	

Data are presented as n or n (%), unless otherwise stated. VATS: video-assisted thoracic surgery. [#]: including endobronchial ultrasound (EBUS) and radial EBUS-guided biopsy.

TABLE 5 Characteristics of diagnosed lung cancers according to smoking status

	Total	Never-smoker	Ever-smoker	p-value
Subjects	207	84	123	
Cancer histology				0.001
Adenocarcinoma	176 (85.0)	82 (97.6)	94 (76.4)	
Adenosquamous carcinoma	2 (1.0)	0 (0)	2 (1.6)	
Squamous cell carcinoma	16 (7.7)	1 (1.2)	15 (12.2)	
Other nonsmall cell carcinoma	9 (4.3)	1 (1.2)	8 (6.5)	
Small cell carcinoma	4 (1.9)	0 (0)	4 (3.3)	
Lung cancer staging				0.018
IA	142 (68.6)	66 (78.6)	76 (61.8)	
IB	17 (8.2)	9 (10.7)	8 (6.5)	
II	11 (5.3)	3 (3.6)	8 (6.5)	
III	14 (6.8)	3 (3.6)	11 (8.9)	
IV	19 (9.2)	3 (3.6)	16 (13.0)	
NA for TNM staging[#]	4 (1.9)	0 (0)	4 (3.3)	
Initial treatment				0.014
Surgery	179 (86.5)	78 (92.9)	101 (82.1)	
CCRT	9 (4.3)	1 (1.2)	8 (6.5)	
Chemotherapy	17 (8.2)	3 (3.6)	14 (11.4)	
Supportive care only	2 (1.0)	2 (2.4)	0 (0)	
Lung cancer-related death	17 (8.2)	2 (2.4)	15 (12.2)	0.012

Data are presented as n or n (%), unless otherwise stated. NA: not applicable; TNM: tumour, node, metastasis; CCRT: concurrent chemoradiation therapy. [#]: cases of small cell carcinoma.

subgroup analysis of the main outcomes of patients in both groups after further stratification by age and sex. Notably, the differences in the rates of invasive biopsy and lung cancer diagnosis between never- and ever-smokers remained significant only among participants who were aged ⩾55 years at baseline.

Table 7 presents the results of univariate and multivariate regression analyses of the potential demographic factors associated with the incidence of clinical outcomes in all participants. Although smoking was not significantly associated with nodule detection in the univariate analysis (OR 1.002, 95% CI 0.95–1.06), multivariate analyses revealed that smoking was significantly associated with a higher probability of positive nodule detection (OR 1.11, 95% CI 1.03–1.19), invasive biopsy (OR 1.36, 95% CI 1.00–1.83) and lung cancer diagnosis (OR 1.73, 95% CI 1.16–2.58).

Figure 2 presents the overall incidence rates of invasive biopsy, any procedure-related complications, lung cancer diagnosis and lung cancer-related mortality over time in never- and ever-smokers. Notably, there was a trend towards a higher incidence of invasive biopsy and lung cancer diagnosis over time in ever-smokers. Overall, no significant differences were observed in the incidence of complications related to

TABLE 6 Final diagnosis of benign nodules confirmed by invasive biopsy according to smoking status

	Total	Never-smoker	Ever-smoker	p-value
Subjects	119	50	69	
Final diagnosis confirmed by biopsy				0.252
Tuberculosis	27 (22.7)	12 (24.0)	15 (21.7)	
NTM disease	12 (10.1)	5 (10.0)	7 (10.1)	
Other infectious condition[#]	6 (5.0)	1 (2.0)	5 (7.2)	
Sarcoidosis	5 (4.2)	3 (6.0)	2 (2.9)	
Noninfectious inflammatory nodule[¶]	52 (43.7)	26 (52.0)	26 (37.7)	
Hamartoma	6 (5.0)	1 (2.0)	5 (7.2)	
Other benign nodule	11 (9.2)	2 (4.0)	9 (13.0)	
Surgical resection of benign disease	37 (31.1)	15 (30.0)	22 (31.9)	0.827

Data are presented as n or n (%), unless otherwise stated. NTM: nontuberculosis mycobacteria. [#]: includes fungal infection and abscess; [¶]: includes chronic inflammatory nodule, vasculitis, organising pneumonia and eosinophilic pneumonia.

TABLE 7 Univariate and multivariate regression analyses of characteristics to predict clinical outcomes according to smoking status

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Positive nodule detection				
Sex (female)	1.09 (1.03–1.15)	0.003	1.06 (0.98–1.15)	0.129
Age at baseline screening	1.03 (1.03–1.03)	<0.001	1.03 (1.03–1.03)	<0.001
Smoking status (ever-smoker)	1.002 (0.95–1.06)	0.922	1.11 (1.03–1.19)	0.009
Invasive biopsy				
Sex (female)	0.83 (0.66–1.04)	0.108	0.82 (0.59–1.12)	0.208
Age at baseline screening	1.08 (1.07–1.09)	<0.001	1.08 (1.07–1.09)	<0.001
Smoking status (ever-smoker)	1.29 (1.04–1.61)	0.022	1.36 (1.00–1.83)	0.048
Lung cancer diagnosis				
Sex (female)	0.91 (0.69–1.22)	0.538	1.05 (0.70–1.59)	0.806
Age at baseline screening	1.09 (1.08–1.10)	<0.001	1.09 (1.08–1.11)	<0.001
Smoking status (ever-smoker)	1.35 (1.02–1.79)	0.033	1.73 (1.16–2.58)	0.007
Diagnosed benign after biopsy (false-positive)				
Sex (female)	0.64 (0.43–0.97)	0.033	0.53 (0.32–0.89)	0.018
Age at baseline screening	1.05 (1.04–1.07)	<0.001	1.06 (1.04–1.07)	<0.001
Smoking status (ever-smoker)	1.27 (0.89–1.84)	0.192	0.98 (0.62–1.57)	0.941
Procedure-related complication				
Sex (female)	0.54 (0.29–1.01)	0.053	0.51 (0.22–1.13)	0.098
Age at baseline screening	1.10 (1.07–1.13)	<0.001	1.10 (1.08–1.13)	<0.001
Smoking status (ever-smoker)	1.62 (0.93–2.80)	0.087	1.33 (0.65–3.73)	0.432

invasive procedures between groups. Multivariable Cox proportional hazard analyses adjusted for age and sex revealed that ever-smokers had a higher risk of undergoing invasive biopsy (HR 1.38, 95% CI 1.02–1.87) and receiving lung cancer diagnosis (HR 1.79, 95% CI 1.20–2.67), but did not have a significantly elevated risk of procedure-related complications (HR 1.37, 95% CI 0.67–2.81). The survival estimates revealed that patients with screen-detected lung cancer in the never-smoker group had a better survival outcome than their counterparts in the ever-smoker group.

Discussion

This study mainly aimed to evaluate and compare the incidence and results of invasive biopsies performed for LDCT screen-detected nodules in never-smokers and ever-smokers. Notably, a significant proportion (0.77%) of never-smokers screened with LDCT underwent invasive procedures for the pathologic diagnosis of the detected nodules, and this frequency was slightly lower than that observed among ever-smokers (1.00%). Moreover, there were no significant differences between the groups in terms of the false-positive rates for malignancy, complication rates related to invasive diagnostic procedures and the final pathological diagnosis of benign nodules. Among patients with screen-detected lung cancer, never-smokers more frequently presented with adenocarcinoma and stage I disease, leading to a higher surgical resection rate and better survival outcomes compared to ever-smokers. This is the first study to identify the diagnostic procedure rates in never-smokers screened with LDCT with relevant information on the complications related to biopsies and final diagnoses, including false-positive results in comparison to ever-smokers. Outcomes of this study were determined using data from a real-world setting involving lung cancer screening in an Asian country.

Although the existing evidence from large randomised trials in support of LDCT screening is limited to heavy smokers, a large survey analysis revealed that a large proportion of never-smokers wish to undergo lung cancer screening [24]. In Eastern Asia, where the incidence of lung cancer and related mortality are relatively high among never-smokers and continue to increase, LDCT screening is fairly widely applied to both never- and ever-smokers [25–27]. Although the causes of this geographic variation are not completely understood, possible explanations include differences in susceptibilities to environmental risk factors such as particulate matter, occupational chemicals, indoor air pollution and radon. Hormonal and genetic factors may also play an important role in lung cancer aetiology in never-smokers [10, 28].

The results from our study, performed in South Korea, shows that a substantial proportion (16.2%) of never-smokers who underwent LDCT screening had positive nodules. Although affected by the screening selection criteria used to define positive findings, and the geographic location of the screening programme,

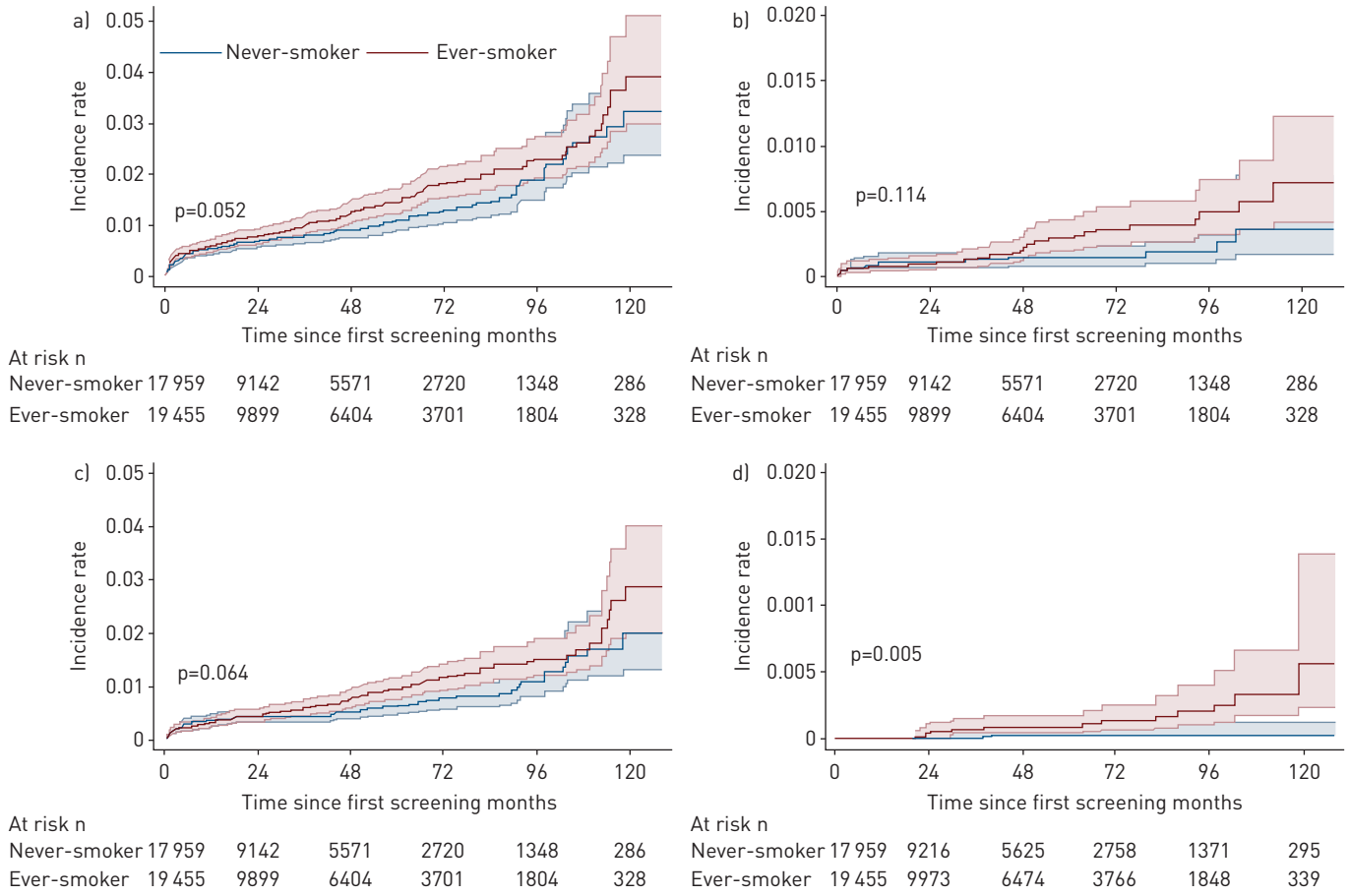

FIGURE 2 Cumulative incidence of a) invasive biopsy, b) procedure-related complications, c) lung cancer diagnosis and d) lung cancer-related mortality in never-smokers and ever-smokers.

the overall incidence rates of positive screening tests reported was 39.1% in the NLST [3], 6.0% in the NELSON trial [29] and 11.8% in the Danish Lung Cancer Screening Trial [30]. The considerable incidence of nodule detection among never-smokers in our study is probably due to the high prevalence of GGNs observed in Asian populations [31]. Although the incidence rates of invasive biopsy (0.77%) and lung cancer diagnosis (0.47%) were slightly lower among never-smokers relative to ever-smokers, these rates remained notable. The overall incidence of lung cancer and predominance of adenocarcinoma among never-smokers were consistent with the findings of prior studies reporting the incidence and characteristics of lung cancer in screened general populations in Asia [26, 27, 32]. This concurrence supports the validity of our findings.

Other important findings from our study include the high proportion of screen-detected early-stage adenocarcinomas that were suitable for curative treatment, and the notable incidence of screen-detected lung cancer among never-smokers who received screening at relatively younger ages than those reported in previous studies. As most lung cancers in never-smokers are diagnosed at advanced stages [33], our results also reveal the potential benefits of LDCT screening for early detection and treatment in this group. Our results indicate that nodules detected in never-smokers should not be underestimated and emphasise the need for careful follow-up and relevant decision-making process regarding the need for invasive diagnosis. Our observations regarding the incidence of screen-detected lung cancer in younger participants also emphasise the need for age-targeted screening strategies in Asian populations.

Previous studies on lung cancer screening revealed that the wide introduction of LDCT screening has led to an appreciable increase in the frequency of invasive procedures and the number of procedure-related complications [3, 15, 34]. One serious area of concern related to the harms in lung cancer screening involves the complications resulting from biopsies of screen-detected nodules. In our study, 14.4% of never-smokers who underwent invasive biopsy developed procedure-related complications, and this rate was not significantly different than the rate in ever-smokers (18.0%). No procedure-related deaths were reported, although two life-threatening vascular events occurred in ever-smokers. Although limited data

are available regarding major complications (including death) that result from biopsy of screen-detected nodules, we observed a relatively low frequency of major complications in our study, especially among never-smokers [3, 34, 35]. This may be attributable to the relatively less invasive nature of the diagnostic procedures used in our study, compared to those in previous studies. A significant proportion (35.9%) of never-smokers who underwent biopsy received non-surgical initial diagnostic procedures. All surgical procedures were attempted using VATS, with a significant proportion (50.6%) of limited resection. Therefore, our results reflect the safety of the diagnostic procedures applied to the screen-detected nodules in asymptomatic subjects in our study population. Nevertheless, given the notable incidence of procedure-related complications in never-smokers relative to ever-smokers, a deliberate strategy is needed to avoid unnecessary invasive procedures, especially surgical procedures, in screened never-smokers.

Another harm associated with LDCT screening is the performance of unnecessary but inevitable invasive biopsies in patients with benign nodules. In our study, 36.0% of never-smokers who underwent biopsies were diagnosed as benign disease. The false-positive rate was similar to that observed among ever-smokers (35.6%), but was higher compared to previous studies which reported false-positive rates between 8.9% and 27.4% [36–38]. The high false-positive rate in our study might be due to the high incidence of mycobacterial disease in Asia [39, 40]. This conjecture is supported by the fact that a significant proportion of the final diagnoses involved tuberculosis or NTM, which can present as nodules that are difficult to distinguish from malignancy by imaging. Given the increasing trend in the incidence of lung cancer and the high frequency of this malignancy among never-smokers in Asia [1, 41], our results support the need for an independent strategy for lung cancer screening and management of detected nodules, especially for never-smokers [39]. To reduce invasive procedures in those with benign nodules, meticulous follow-ups and consideration of possible benign disease would be warranted even in cases with Lung-RADS category 4 nodules. Regarding diagnostic evaluations, less-invasive attempts to rule out prevalent benign diseases prior to surgery planning would help reduce the performance of unnecessary surgical procedures and related complications.

Our study has limitations. First, this was a retrospective cohort study from a single centre, and the strategies for LDCT screening and follow-ups were not strictly controlled. Second, this study was not designed to evaluate the effectiveness of lung cancer screening over nonscreening in never-smokers, and therefore our results do not directly support the general need for LDCT screening in this population. The number of cases of confirmed lung cancer was relatively small due to the low incidence in the study population. A large trial with a control group of unscreened never-smokers and related cost–benefit analysis would be needed to provide evidence for these issues. Third, data on exposures to possible risk factors for lung cancer such as second-hand smoke or air pollution were not available, which might be an important factor when evaluating lung cancer screening in never-smokers [42]. For ever-smokers, information on the amount of smoking and duration of smoking cessation was not available for a sufficient number of participants, making further subgroup analyses impossible. Fourth, this study featured a hospital-based design, and therefore the population may not fully represent the general population. To minimise selection bias, we included only asymptomatic adults who visited the centre for health check-ups and did not set specific conditions under which lung cancer screening would be recommended for never-smokers. The concordance of our results regarding the overall incidence and distribution of pathologic subtypes of lung cancer with the results of previous Asian population-based studies supports the validity of our results.

The main strength of our study is the large sample size of a hospital cohort. Our study represents an asymptomatic Asian population undergoing LDCT screening at a tertiary medical centre in a real-world setting. Moreover, comprehensive data on the results of LDCT screening and diagnostic evaluations were collected. Above all, our data provide unique results which can aid further discussions on the outcomes of LDCT screening among Asian never-smokers. This will be an important issue related to lung cancer screening to be addressed in the future.

In conclusion, LDCT screening in never-smokers resulted in a significant detection rate of lung nodules which led to invasive diagnostic procedures. Although the lung cancer detection rate was lower among never-smokers, the procedure-related complication rates and false-positive rates were comparable to those of ever-smokers. Our results indicate the need for a specifically tailored strategy for the management of screen-detected nodules in Asian never-smokers.

Author contributions: Y.W. Kim and C-T. Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. Y.W. Kim and C-T. Lee contributed to concept and design of this study. Y.W. Kim, H-R. Kang and C-T. Lee contributed to data collection, data analysis, data interpretation, manuscript preparation, revision and final approval of the manuscript. B.S. Kwon, S.Y. Lim, Y.J. Lee, J.S. Park, Y-J. Cho, H.I. Yoon, K.W. Lee and J.H. Lee contributed to the data collection, data analysis, revision, and final approval of the manuscript.

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