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Early View

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Title Page

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

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Take home message

LDCT screening in never-smokers resulted in a significant detection rate of lung nodules considered for invasive biopsy, with notable rates of diagnosis of benign disease and complications.

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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, 2,908/17,968 (16.2%) had positive nodules. Overall, 139/17,968 (0.77%) never-smokers and 194/19,468 (1.00%) ever-smokers underwent invasive biopsy (p=0.022). Lung cancer was diagnosed in 84/17,968 (0.47%) of never-smokers and 123/19,468 (0.63%) of ever-smokers (p=0.032). The proportions of participants diagnosed with benign disease after invasive biopsy (false-positive) were 50/17,968 (0.28%) and 69/19,468 (0.35%) in the never-smoker and ever-smoker groups (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, 82/84 (97.6%) had adenocarcinoma, and 75/84 (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.

Abstract Word Count: 288

Keywords: lung cancer screening, low-dose computed tomography, never-smoker, invasive biopsy, adenocarcinoma

Introduction

Lung cancer remains the leading cause of cancer-related deaths in both men and women 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 researches have been focused on developing effective screening methods for early detection. Recently, two large randomized trials, the National Lung Screening Trial (NLST) and the Dutch-Belgian randomized 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 had quit smoking within the past 15 years, with a smoking history of 30 pack-years or more [5].

With 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 [9]. Epidemiological studies also have identified significant gender and geographic variations. In Eastern Asia, never-smokers comprise approximately 22% of all lung cancer patients (61% of female cases and 11% of male cases), whereas only approximately 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 women, the incidence of lung cancer increased by more than 2-fold from 2000 to 2014, and more than 85% of female lung cancer patients are never-smokers [12]. These data indicate that currently, the incidence and mortality of lung cancer would be less influenced by smoking. Studies have also demonstrated that lung cancer in never-smokers differ 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 that 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 ≥18 years of age 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 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 fewer than 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 (IRB no: 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 100kV 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 (PACS) system. All images were interpreted by board-certified experienced chest radiologists. A positive nodule detected by LDCT was

defined as any non-calcified nodule with a longest diameter of at least 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 (NCCN) 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 which 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 at 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 hours 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 NSCLC, eighth edition [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 non-malignancy 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 means and standard deviations for continuous variables and as frequencies (%) for categorical variables. To compare the baseline

characteristics and the diagnostic processes and results between the two groups, Student's t-test was used to analyse continuous variables and the Pearson chi-square test was 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 (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs) were calculated, and p-values <0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, N.Y., 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 3,702 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 under 45 years of age at the time of baseline CT 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, 6,066/37,436 (16.2%) participants (2,908 never-smokers and 3,158 ever-smokers) had positive nodules of ≥4 mm which were detected by LDCT. At baseline LDCT screening, 32,558/37,436 (87.0%) had results of Lung-RADS category 1 or S, and 3,871/37,436 (10.3%), 522/37,436 (1.4%), 324/37,436 (0.9%), 161/37,436 (0.4%) of category 2, 3, 4A, 4B or 4X lung nodules, respectively. The Lung-RADS category distributions did not differ significantly between groups. In addition, 139/17,968 (0.77%) never-smokers and 194/19,468 (1.00%) ever-smokers underwent invasive biopsy for pathologic diagnosis (p=0.022). Lung cancer was diagnosed in 84/17,968 (0.47%) of the never-smokers and 123/19,468 (0.63%) of the ever-smokers (p=0.032) who underwent lung cancer screening. Proportion of participants diagnosed with benign disease after invasive biopsy (false-positive) did not differ significantly between groups (0.28% in never-smokers vs. 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 (2,277/2,908, 78.3% vs. 2,601/3,158, 82.4%; p<0.001). Never-smokers had a significantly higher proportion of cases with GGNs (part-solid nodules and pure GGNs; 1,490/2,908, 51.2%), whereas most nodules detected in ever-smokers were solid (1,895/3,158, 60.0%). Among those with positive nodules, 333/6,066 (5.5%) 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% vs. 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. 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 1).

Final diagnoses and clinical outcomes

Of the 333 participants who underwent invasive biopsy, 207 were diagnosed with lung cancer (Table 5). Adenocarcinoma (82/84, 97.6%) 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% vs. 68.3%), a higher rate of surgical resection as initial treatment (92.9% vs. 82.1%), and a lower rate of lung cancer-related mortality (2.4% vs. 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. However, the distributions of the final diagnoses did not differ significantly according to smoking status. Overall, bronchoscopy was performed in 84/119 (70.6%) of participants who received a false-positive diagnosis. Thirty-two patients were diagnosed with mycobacterial disease, and the diagnostic yield of bronchoscopy for mycobacteria detection was 43.8% (14/32). Supplementary Table 2 presents the results of 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 (A) invasive biopsy, (B) any procedure-related complications, (C) lung cancer diagnosis and (D) 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 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 program, 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 likely 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. Our results therefore 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 non-screening 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 to 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 that would undergo 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.

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None.

Author's contributions

YWK and CTL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. YWK and CTL contributed to concept and design of this study. YWK, HRK, CTL contributed to data collection, data analysis, data interpretation, manuscript preparation, revision, and final approval of the manuscript. BSK, SYL, YJL, JSP, YJC, HIY, KWL, and JHL contributed to the data collection, data analysis, revision, and final approval of the manuscript.

Declaration of interests

The authors declare no conflict of interest.

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Table 1. Characteristics of participants who underwent LDCT screening

	Total (n = 37,436)	Never-smoker (n=17,968)	Ever-smoker (n=19,468)	p value
Age at baseline screening, n (%)				<0.001
< 45 yr	12,850 (34.3)	5,556 (30.9)	7,294 (37.5)	
45 – 49 yr	6,439 (17.2)	3,002 (16.7)	3,437 (17.7)	
50 – 54 yr	6,441 (17.2)	3,117 (17.3)	3,324 (17.1)	
55 – 59 yr	4,805 (12.8)	2,395 (13.3)	2,410 (12.4)	
60 – 64 yr	2,975 (7.9)	1,625 (9.0)	1,350 (6.9)	
65 – 69 yr	2,101 (5.6)	1,176 (6.5)	925 (4.8)	
70 – 74 yr	1248 (3.3)	748 (4.2)	500 (2.6)	
≥ 75 yr	577 (1.5)	349 (1.9)	228 (1.2)	
Mean ± SD	49.5 ± 11.2	50.5 ± 11.6	48.6 ± 10.8	<0.001
Sex, male, n (%)	23,827 (63.6)	5,644 (31.4)	18,183 (93.4)	<0.001
BMI, mean ± SD	24.0 ± 3.2	23.3 ± 3.2	24.7 ± 3.1	<0.001
Total months of follow up, mean ± SD	34.8 ± 35.5	34.0 ± 34.4	35.6 ± 36.4	<0.001
Lung-RADS category at baseline LDCT screening, n (%)				0.281
1 or S	32,558 (87.0)	15,691 (87.3)	16,867 (86.6)	
2	3,871 (10.3)	1,792 (10.0)	2,079 (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, n (%)	6,066 (16.2)	2,908 (16.2)	3,158 (16.2)	0.922
Nodule detected at baseline screening, n (%)	4,878 (13.0)	2,277 (12.7)	2,601 (13.4)	0.048
Nodule detected during follow up, n (%)	1,188 (3.2)	631 (3.5)	557 (2.9)	<0.001
Received invasive biopsy, n (%)	333 (0.89)	139 (0.77)	194 (1.00)	0.022
Diagnosed as lung cancer, n (%)	207 (0.56)	84 (0.47)	123 (0.63)	0.032
Diagnosed as metastatic carcinoma or lymphoma, n (%)	7 (0.02)	5 (0.03)	2 (0.01)	0.215
Diagnosed as benign (false-positive), n (%)	119 (0.32)	50 (0.28)	69 (0.35)	0.191

LDCT=low-dose chest computed tomography, SD=standard deviation, BMI=body mass index, Lung-RADS=Lung Imaging Reporting and Data System

Table 2. Characteristics of participants with positive nodules detected by LDCT screening

	Total (n=6,066)	Never-smoker (n=2,908)	Ever-smoker (n=3,158)	p value
Age at baseline screening				<0.001
< 45 yr	1,524 (25.1)	620 (21.3)	904 (28.6)	
45 – 49 yr	961 (15.8)	439 (15.1)	522 (16.5)	
50 – 54 yr	1,050 (17.3)	509 (17.5)	541 (17.1)	
55 – 59 yr	917 (15.1)	460 (15.8)	457 (14.5)	
60 – 64 yr	614 (10.1)	327 (11.2)	287 (9.1)	
65 – 69 yr	488 (8.0)	246 (8.5)	242 (7.7)	
70 – 74 yr	329 (5.4)	190 (6.5)	139 (4.4)	
≥ 75 yr	183 (3.0)	117 (4.0)	66 (2.1)	
Mean ± SD	52.5 ± 11.6	53.7 ± 11.8	51.4 ± 11.3	<0.001
Sex, male, n (%)	3,759 (62.0)	852 (29.3)	2,907 (92.1)	<0.001
BMI, mean ± SD	23.9 ± 3.2	23.3 ± 3.2	24.6 ± 3.1	<0.001
Nodule detected at baseline screening, n (%)	4,878 (80.4)	2,277 (78.3)	2,601 (82.4)	<0.001
Nodule detected during follow up, n (%)	1,188(19.6)	631 (21.7)	557 (17.6)	<0.001
Lung-RADS category at first detection of nodule, n (%)				0.784
2	4,801 (79.1)	2,298 (79.0)	2,503 (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, n (%)				0.017
Right upper lobe	1,509 (24.9)	773 (26.6)	736 (23.3)	
Right middle lobe	797 (13.1)	364 (12.5)	433 (13.7)	
Right lower lobe	1,352 (22.3)	642 (22.1)	710 (22.5)	
Left upper lobe	1,207 (19.9)	570 (19.6)	637 (20.2)	
Left lower lobe	1,186 (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, n (%)	1,736 (28.6)	835 (28.7)	901 (28.5)	0.875

Nodule type, n (%)				<0.001
Solid	3,296 (54.3)	1,401 (48.2)	1,895 (60.0)	
Part-solid	694 (11.4)	318 (10.9)	376 (11.9)	
Pure GGN	2,023 (33.3)	1,172 (40.3)	851 (26.9)	
Cavitary	53 (0.9)	17 (0.6)	36 (1.1)	
Size of nodule at first detection, mm, mean ± SD	7.0 ± 5.2	7.1 ± 4.6	6.9 ± 5.6	0.241
Diagnostic evaluation for detected nodule, n (%)				
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, n (%)	207 (3.4)	84 (2.9)	123 (3.9)	0.031
Metastatic carcinoma or lymphoma, n (%)	7 (0.1)	5 (0.2)	2 (0.1)	0.213
Benign disease (false-positive), n (%)	119 (2.0)	50 (1.7)	69 (2.2)	0.192

LDCT=low-dose chest computed tomography, SD=standard deviation, BMI=body mass index, Lung-RADS=Lung Imaging Reporting and Data System, GGN=ground glass nodule, FDG-PET=fluorodeoxyglucose positron emission tomography

*91 of 210 (43.3%) participants who had category 4B or 4X nodules at first detection eventually did not undergo any invasive biopsy.

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

	Total (n=333)	Never-smoker (n=139)	Ever-smoker (n=194)	p value
Age at diagnosis, mean ± SD	61.4 ± 11.2	60.4 ± 11.9	62.0 ± 10.6	0.195
Time of nodule detection, n (%)				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, n (%)				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, n (%)				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 screening before biopsy, mean ± SD	2.2 ± 1.4	2.1 ± 1.3	2.2 ± 1.5	0.513
Time from baseline LDCT screening to biopsy, months, mean ± SD	30.4 ± 33.8	29.4 ± 34.7	31.1 ± 33.2	0.654
Nodule size at biopsy, mm, mean ± SD	19.6 ± 12.4	17.5 ± 8.3	21.2 ± 14.7	0.007
Volume doubling time of the biopsied nodules exhibiting growth, days, mean ± SD*	711.4 ± 702.4	608.5 ± 587.4	784.3 ± 771.3	0.267
Diagnosed as lung cancer, n (%)	207 (62.2)	84 (60.4)	123 (63.4)	0.582
Diagnosed as metastatic carcinoma or lymphoma, n (%)	7 (2.1)	5 (3.6)	2 (1.0)	0.107
False-positive for malignancy, n (%)	119 (35.7)	50 (36.0)	69 (35.6)	0.939

SD=standard deviation, LDCT=low-dose chest computed tomography, GGN=ground glass nodule
*Analysis based on nodules that showed growth increase of 2 mm or more in maximal diameter.

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

	Total (n=333)	Never-smoker (n=139)	Ever-smoker (n=194)	p value
Type of biopsy, n (%)				
Video-assisted thoracic surgery (VATS)	191 (57.4)	89 (64.0)	102 (52.6)	0.037
Range of resection, 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, n (%)	10 (3.0)	5 (3.6)	5 (2.6)	0.591
Any complications related to invasive diagnostic procedure, n (%)	55 (16.5)	20 (14.4)	35 (18.0)	0.376
Complications related to non-surgical biopsy, n (%)				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, n (%)				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)	

*Including EBUS (endobronchial ultrasound) and radial-EBUS guided biopsy

Table 5. Characteristics of diagnosed lung cancers according to smoking status

	Total (n=207)	Never-smoker (n=84)	Ever-smoker (n=123)	p value
Cancer histology, n (%)				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 non-small 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, n (%)				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, n (%)				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, n (%)	17 (8.2)	2 (2.4)	15 (12.2)	0.012

NA=not applicable, CCRT=concurrent chemoradiation therapy

*Cases of small-cell carcinoma

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

	Total (n=119)	Never-smoker (n=50)	Ever-smoker (n=69)	p value
Final diagnosis confirmed by biopsy, n (%)				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)	
Non-infectious 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, n (%)	37 (31.1)	15 (30.0)	22 (31.9)	0.827

NTM: non-tuberculosis 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

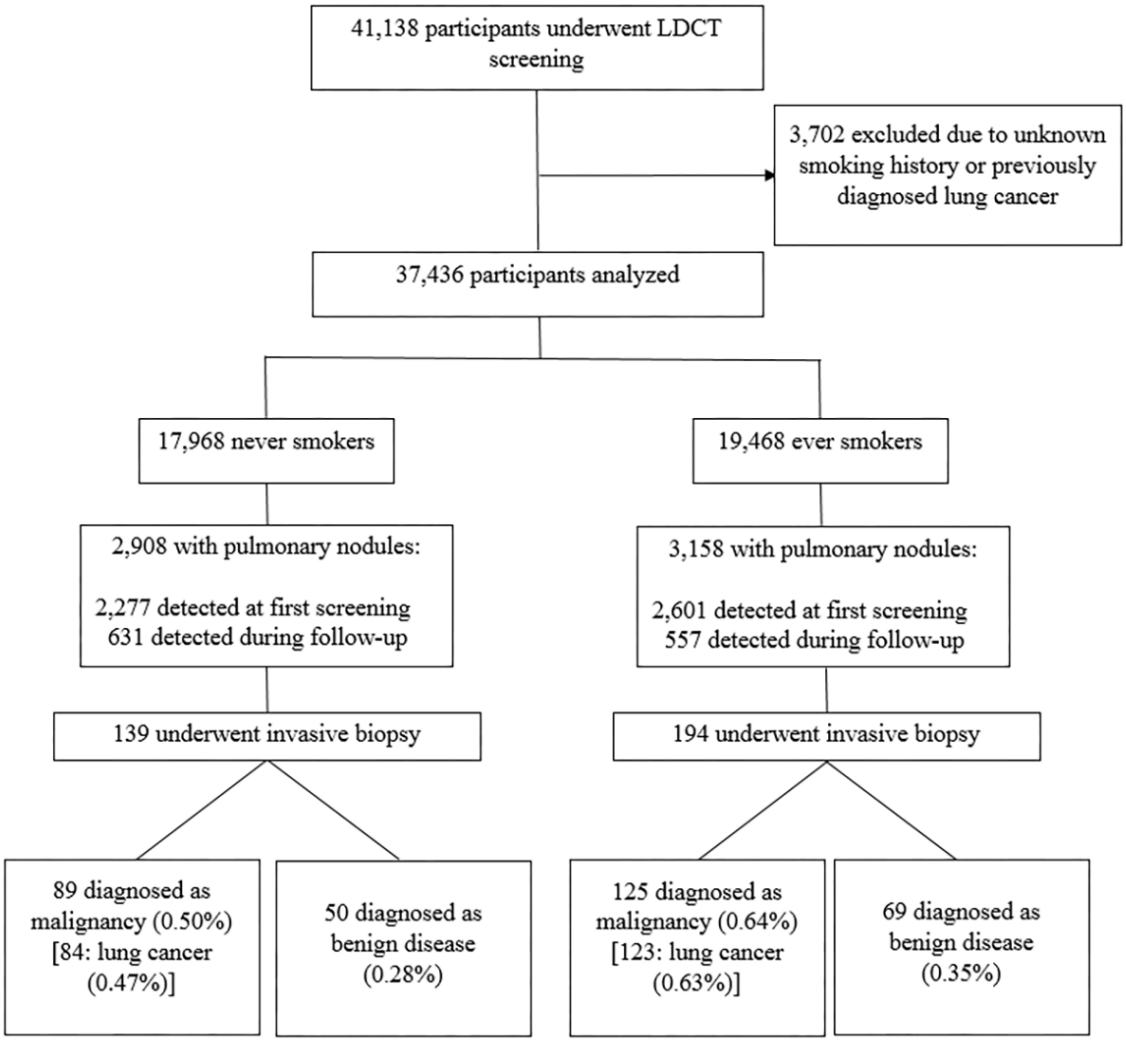
Clinical outcome	Variable	Univariate		Multivariate	
		OR (95% CI)	p value	OR (95% CI)	p value
Positive nodule detection	Sex (female)	1.09 (1.03 – 1.15)	0.003	1.06 (0.98 – 1.15)	0.129
	Age at baseline screening	1.03 (1.03 – 1.03)	<0.001	1.03 (1.03 – 1.03)	<0.001
	Smoking status (ever-smoker)	1.002 (0.95 – 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

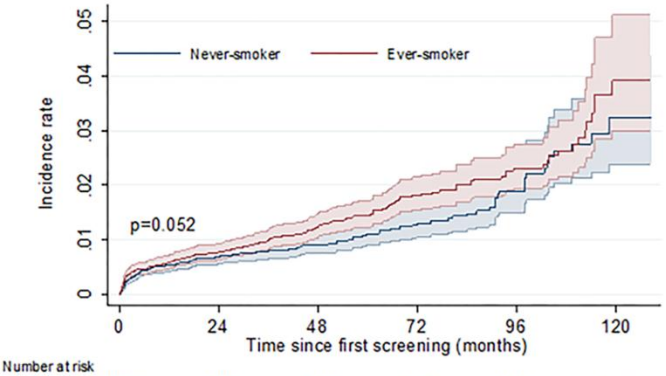
OR=odds ratio, CI=confidence interval

Figure legends

Figure 1. Flow diagram of the study population

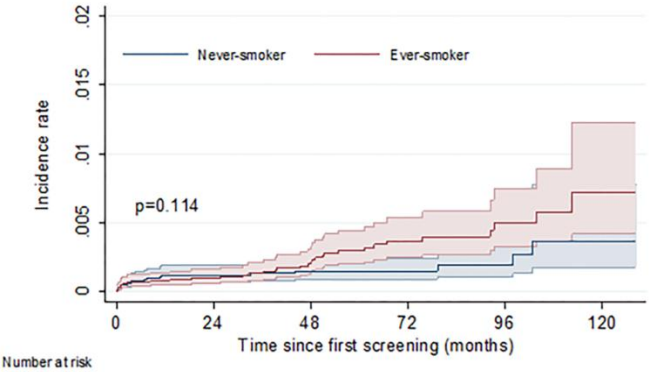
Figure 2. Cumulative incidence of (A) invasive biopsy, (B) procedure-related complications, (C) lung cancer diagnosis, and (D) lung cancer-related mortality in never-smokers and ever-smokers


41,138 participants underwent LDCT screening
3,702 excluded due to unknown smoking history or previously diagnosed lung cancer
37,436 participants analyzed
17,968 never smokers
19,468 ever smokers
2,908 with pulmonary nodules:
2,277 detected at first screening
631 detected during follow-up
3,158 with pulmonary nodules:
2,601 detected at first screening
557 detected during follow-up
139 underwent invasive biopsy
194 underwent invasive biopsy
89 diagnosed as malignancy (0.50%) [84: lung cancer (0.47%)]
50 diagnosed as benign disease (0.28%)
125 diagnosed as malignancy (0.64%) [123: lung cancer (0.63%)]
69 diagnosed as benign disease (0.35%)



Number at risk

Never-smoker	17959	9142	5571	2720	1348	286
Ever-smoker	19455	9899	6404	3701	1804	328



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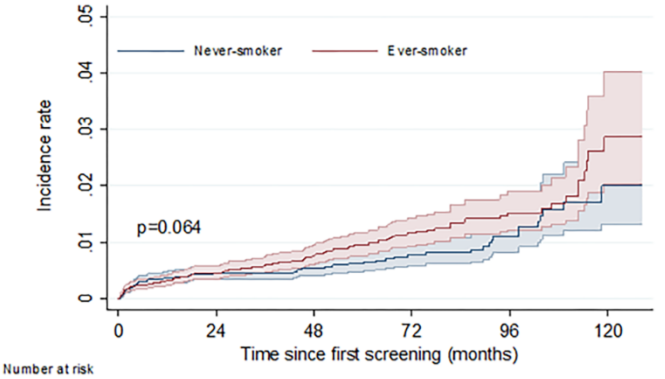

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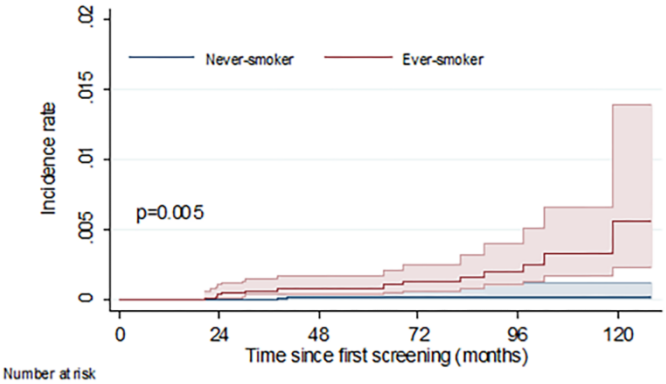

Number at risk

Never-smoker	17959	9216	5625	2758	1371	295
Ever-smoker	19455	9973	6474	3766	1848	339

Supplementary Table 1. Characteristics and outcomes of biopsied nodules of never-smokers detected at baseline and during follow-up

	Total (n=139)	Detected at baseline (n=104)	Detected during follow-up (n=35)	p-value
Age at diagnosis, mean ± SD	60.4 ± 11.9	60.1 ± 11.7	61.3 ± 12.6	0.608
Nodule type, n (%)				0.009
Solid	51 (36.7)	30 (28.8)	21 (60.0)	
Part-solid	47 (33.8)	41 (39.4)	6 (17.1)	
Pure GGN	34 (24.5)	27 (26.0)	7 (20.0)	
Cavitary	7 (5.0)	6 (5.8)	1 (2.9)	
Time of planning invasive diagnosis, n (%)				0.070
At first detection of relevant nodule	65 (46.8)	44 (42.3)	21 (60.0)	
During follow-up	74 (53.2)	60 (57.7)	14 (40.0)	
Time from detection to biopsy, months, mean ± SD	19.8 ± 30.0	19.7 ± 30.0	20.2 ± 30.4	0.922
Nodule size at detection, mm, mean ± SD	15.4 ± 8.2	16.2 ± 8.3	12.7 ± 7.7	0.029
Nodule size at biopsy, mm, mean ± SD	17.5 ± 8.3	18.1 ± 8.2	15.7 ± 8.3	0.146
Type of biopsy, n (%)				
Video-assisted thoracic surgery (VATS)	89 (64.0)	71 (68.3)	18 (51.4)	0.073
Percutaneous needle biopsy	38 (27.3)	25 (24.0)	13 (37.1)	0.132
Bronchoscopic biopsy*	12 (8.6)	8 (7.7)	4 (11.4)	0.496
Diagnosed as lung cancer, n (%)	84 (60.4)	74 (71.2)	10 (28.6)	<0.001
Diagnosed as benign (false-positive), n (%)	50 (36.0)	30 (28.8)	20 (57.1)	0.003

SD=standard deviation, GGN=ground glass nodule

*Including EBUS (endobronchial ultrasound) and radial-EBUS guided biopsy

Supplementary Table 2. Subgroup analyses of main outcomes stratified by age and sex

Subgroups	Total	Never-smoker	Ever-smoker	p value
Age <55 (N=25,730)	25,730	11,675	14,055	
Received invasive biopsy, n/N (%)	117 (0.5)	50 (0.4)	67 (0.5)	0.565
Diagnosed as lung cancer, n/N (%)	65 (0.3)	29 (0.2)	36 (0.3)	0.902
Diagnosed as benign (false-positive), n/N (%)	52 (0.2)	21 (0.2)	31 (0.2)	0.469
Any procedure-related complication, n/N (%)	13 (0.1)	4 (0.0)	9 (0.1)	0.290
Age ≥55 (N=11,706)	11,706	6,293	5,413	
Received invasive biopsy, n/N (%)	216 (1.8)	89 (1.4)	127 (2.3)	<0.001
Diagnosed as lung cancer, n/N (%)	142 (1.2)	55 (0.9)	87 (1.6)	<0.001
Diagnosed as benign (false-positive), n/N (%)	67 (0.6)	29 (0.5)	38 (0.7)	0.085
Any procedure-related complication, n/N (%)	42 (0.4)	16 (0.3)	26 (0.5)	0.041
Sex: male (N=23,827)	23,827	5,644	18,183	
Received invasive biopsy, n/N (%)	226 (0.9)	42 (0.7)	184 (1.0)	0.070
Diagnosed as lung cancer, n/N (%)	136 (0.6)	20 (0.4)	116 (0.6)	0.013
Diagnosed as benign (false-positive), n/N (%)	87 (0.4)	21 (0.4)	66 (0.4)	0.921
Any procedure-related complication, n/N (%)	42 (0.2)	7 (0.1)	35 (0.2)	0.284
Sex: female (N=13,609)	13,609	12,324	1,285	
Received invasive biopsy, n/N (%)	107 (0.8)	97 (0.8)	10 (0.8)	0.973
Diagnosed as lung cancer, n/N (%)	71 (0.5)	64 (0.5)	7 (0.5)	0.904
Diagnosed as benign (false-positive), n/N (%)	32 (0.2)	29 (0.2)	3 (0.2)	0.990
Any procedure-related complication, n/N (%)	13 (0.1)	13 (0.1)	0 (0)	0.244