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비흡연자의 조기 폐암 검진에서 저선량 흉부 전산화 단층촬영의 역할

Role of low-dose computerized tomography in lung cancer screening among never-smokers

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Abstract

Role of low-dose computerized tomography in lung cancer screening among never-smokers

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Introduction:

The incidence of lung cancer among never smokers has been increasing rapidly. The U. S. National Lung Screening Trial and the NELSON trial showed that screening using low-dose computerized tomography (LDCT) effectively reduced lung cancer mortality among heavy smokers. However, its effectiveness in never-smokers has not been well investigated. This study investigated the role of LDCT in lung cancer screening among never-smokers.

Methods:

The study was designed as a single-center, retrospective cohort study. We analyzed the data on patients who underwent LDCT screening between May 2003 and June 2016. Nodules detected by computerized tomography were classified according to the Lung Imaging Reporting and Data System criteria. The detection rate and lung cancer outcomes (type of cancer, staging of lung cancer, and mortality) according to smoking history were determined.

Results:

Of the 28,807 enrolled patients, 12,176 were never-smokers; of these patients, 7744 (63.6%) were women and 1218 (10.0%) were found to have lung nodules. Overall, lung cancer was diagnosed in 55 never-smokers (0.45%). In contrast, lung cancer was diagnosed in 143 (0.86%) of the 16,631 ever-smokers. Of the never-smokers with lung cancer, 51 (92.7%) presented with stage I disease, and all patients had adenocarcinomas.

Conclusions:

In the never-smoker population, LDCT screening helped to detect a significant number of lung cancers. Most of these lung cancers were detected at a very early stage. The positive results of the National lung screening trial in the United States and the NELSON trial may have established the value of LDCT screening for heavy smokers, but future research should consider the value of using LDCT screening in the never-smoker population.

keywords : low-dose chest computerized tomography; Never-smoker; lung cancer; adenocarcinoma

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Introduction

Lung cancer is the leading cause of death globally.[1] Lung cancer in never-smokers (LCINS) is becoming an increasingly prominent problem and is being referred to as a distinct disease entity.[2] The incidence of LCINS has increased, accounting for approximately 10% to 25% of all lung cancers.[1, 3-6] Park and Jang assumed an increase in LCINS in the Republic of Korea during the past decade on the basis of the fact that the crude lung cancer incidence among women has been increasing steadily (1.8-fold during 1999–2012).[7] Lung cancer-related death in never-smokers has been estimated as the seventh leading cause in cancer mortality.[8] LCINS has been reported in a younger population and more in women than has lung cancer in smokers.[4,5] Several factors, such as aging, cooking fumes, exposure to environmental carcinogens, exposure to secondhand smoke, and genetic susceptibility, have been suggested as causes of LCINS[5,9,10]; however, the definite cause still remains unknown. Although survival of LCINS has been shown to be slightly better than survival of lung cancer in ever-smokers, many patients with LCINS eventually die as a result of delayed detection.[5, 11-14]

Early detection is the only way to improve lung cancer outcomes. Over the past 40 years, many lung cancer screening trials with chest radiography or chest low-dose computerized tomography(LDCT) have been conducted in heavy smokers.[15] The Early Lung Cancer Action Project revealed that LDCT was more sensitive than chest radiography in lung cancer detection.[16] The National Lung Screening Trial (NLST), which was performed in the United States, proved that LDCT screening in heavy smokers decreased lung cancer

and all-cause mortality.[17] Recently, the NELSON trial from the Netherlands and Belgium revealed that LDCT screening among asymptomatic men and women who had smoked at least 15cigarettes daily for 25 years or 10 cigarettes daily for 30 years and were still smoking or stopped smoking less than 10 years ago reduced lung cancer death by 26% and 39%, respectively, at year 10.[18]

Few data on never-smokers have been published. Kondo et al. showed better lung cancer survival in an LDCT-screened group than in groups screened by chest radiography or in which screening was prompted by symptoms.[19] Recently, another retrospective cohort study of lung cancer screening in female never-smokers in the Republic of Korea[20] revealed a lung cancer rate of 0.5% in participants and recommended annual LDCT screening only when the initial tomography finding showed Lung Imaging Reporting and Data System (Lung-RADS) category 4 nodules.

In the Republic of Korea, national health insurance provides a cancer screening program to those older than 50 years; however, the program does not provide LDCT for lung cancer. Hence, many Korean hospitals operate their own health promotion centers that provide LDCT according to individual's need, regardless of the smoking history.

We conducted a retrospective study of the role of lung cancer screening in nonsmoker and smoker groups with use of these screening data. Our aim was to determine the role of LDCT in detecting LCINS versus in detecting lung cancer in smokers and to clarify the rate of lung cancer detection in never-

smokers in the real world.

Methods

Study design and participants.

This study was a single-center, retrospective cohort study of patients who underwent LDCT for lung cancer screening regardless of their smoking history at Seoul National University Bundang Hospital Health Promotion Center between March 2003 and June 2016. There were no specific exclusion criteria; however, participants with a history of lung cancer within 5 years or with unknown smoking history were excluded. In general, patients with lung nodules are referred to a pulmonologist according to the National Comprehensive Cancer Network (NCCN) guidelines[21] at that time or in accordance with the Lung-RADS recommendation[22] for further follow-up or diagnostic procedures.

Definitions and assessment

Participants were categorized into two groups (never-smokers and ever-smokers) on the basis of the smoking history obtained from their medical records. Never-smokers were defined as adults who had never smoked or had smoked less than 100 cigarettes in their lifetime.[23] Ever-smoker included current and ex-smokers. Among those who underwent LDCT, several questionnaires were used to evaluate their smoking status (never-smoker, ex-

smoker, or current smokers), duration of smoking cessation among ex-smokers, and smoking duration and amount of smoking (in pack-year) in the case of ex-smokers and current smokers. Those without data on smoking status were excluded from the study; however, individuals without data on amount of smoking were included.

LDCT was interpreted by one radiologist, and a physician (H-R. K.) reviewed the image again. We defined a positive nodule as any noncalcified nodule larger than 3mm in any diameter. One dominant nodule was selected if multiple nodules were found. Lung nodules were classified by the Lung-RADS criteria.[22] The size, location, attenuation, borderline, and type of nodules were reviewed. We reviewed the medical records of participants with positive nodules. LDCT follow-up and pathologic evaluations were decided by a clinician in the health promotion center and a chest specialist.

Lung cancer was diagnosed by pathological examination of a percutaneous needle biopsy specimen, bronchoscopy, and video-assisted thoracoscopic surgery. Clinical and radiological diagnosis of lung cancer was excluded from this study. Lung cancer was classified as prevalent (cancer diagnosed from the nodule at baseline) or interval (diagnosed from nodules found at follow-up LDCT, but not present at baseline LDCT) cancers according to the presence or absence of nodules at the first examination.

Tumor was staged according to the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer stage classification of NSCLC (eighth edition).[24]

The primary outcome of this study was the rate of detection of cancer in the never-smoker and ever-smoker groups, defined as the ratio of patients with cancer to all patients screened. Secondary outcomes were types of and staging of lung cancer, as well as mortality due to lung cancer, in both groups.

Statistical analysis

To compare the baseline characteristics between the never-smoker and ever-smoker groups, Student's *t* test, mean, and standard deviation were used to analyze continuous variables and the Pearson Chi-square test and Fisher's exact test were used to analyze categorical variables. The Pearson Chi-square test was used to compare the diagnosis of disease between the never-smoker and ever-smoker groups. Estimation of survival was done by using Kaplan-Meier estimates with log-rank tests. The hazard ratio (HR) of cancer development with adjustment for variables was estimated by Cox proportional hazard regression analysis. All *p* values less than 0.05 were considered statistically significant. All the statistical analyses were performed with STATA software (version 13.1, Stata Corp., College Station, TX).

This study was approved and consent was waived by the institutional review board at Seoul National University Bundang Hospital (B-1608/357-112).

Results

Participation

During the study period, 30,225 patients had underwent LDCT and 1418 patients with unknown smoking history or previous lung cancer history were excluded. Ultimately, 28,807 participants were included in this analysis. Included were 12,176 never-smokers (42.2% of the study population) and 16,631 ever-smokers (57.8% of the study population). Of the 20,315 men and 8492 women, 4432 (21.8%) and 7744 (91.2%), respectively, were never-smokers.

Lung nodules were found in 1218 participants in the never-smoker group (10.0%) and 2318 in the ever-smoker group (13.9%). Tuberculosis was highly prevalent in the Republic of Korea up to the 1990s. Some middle-aged to elderly Korean people have healed or inactive tuberculosis-related nodules.

The probability of lung nodule occurrence was significantly higher in the ever-smoker group than in the never-smoker group (p <0.001) (Figure 1).

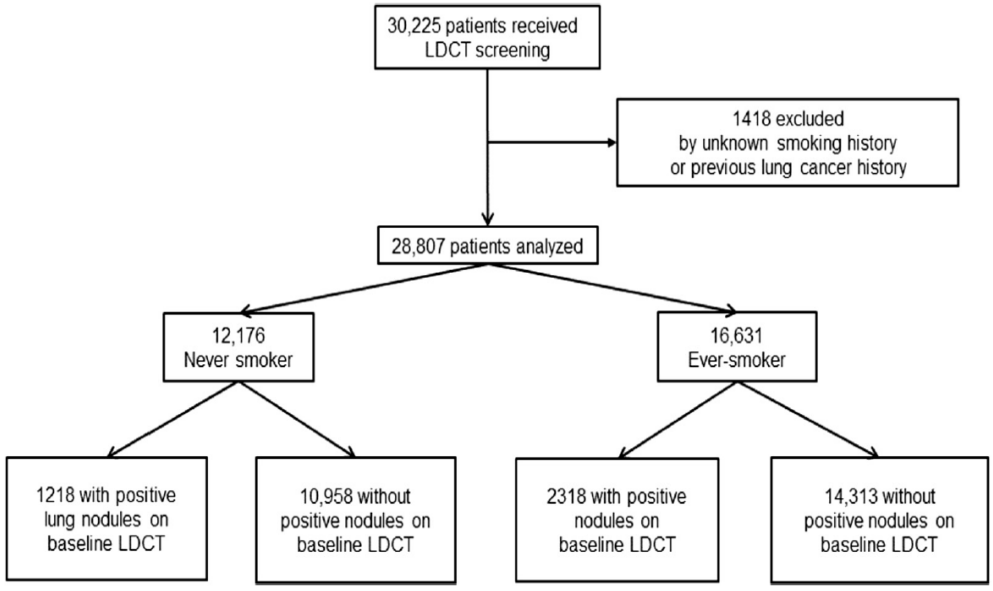

Figure 1. Flowchart of the patient selection process. LDCT, low-dose chest computed tomography.

The Baseline characteristics of all participants were described in Table 1. Female participants accounted for 29.5% of the overall study population and were dominant in the never-smoker group (63.6%) versus in the ever-smoker group (4.5%). Overall, the mean age of the participants was 52.1 years whereas the mean age of the never-smokers and ever-smokers were 53.2 and 51.3 years, respectively ($p < 0.0001$). Of the ever-smokers, 7761(46.7%) were current smokers and 8870 (53.3%) were ex-smokers.

Table 1. Baseline characteristic of LDCT screened patients

	Total (N=28,807)	Never-smoker (n=12,176)	Ever-smoker (n=16,631)
Sex — No (%)			
Male	20,315 (70.5)	4,432 (36.4)	15,883 (95.5)
Female	8,492 (29.5)	7,744 (63.6)	748 (4.5)
Mean age ± SD, y	52.06 ± 8.9	53.16 ± 9.1	51.3 ± 8.6
Age, year old, n (%)			
40–49	12,958 (45.0)	4,896 (40.2)	8,062 (48.5)
50–59	9,738 (33.8)	4,245 (34.9)	5,493 (33.0)
60–69	4,833 (16.8)	2,335 (19.2)	2,498 (15.0)
70–75	1,278 (4.4)	700 (5.7)	578 (3.5)
Lung-RADS (by baseline LDCT)			
1 or S	25,273 (87.7)	10,958 (90.0)	14,313 (86.1)
2	2,864 (9.9)	950 (7.8)	1,916 (11.5)
3	340 (1.2)	151 (1.2)	189 (1.1)
4A	214 (0.7)	70 (0.6)	144 (0.9)
4B	93 (0.3)	38 (0.3)	55 (0.3)
4X	23 (0.08)	9 (0.07)	14 (0.08)

LDCT = low-dose chest computed tomography, Lung-RADS = Lung Imaging Reporting and Data System

Detection of lung nodules during baseline LDCT according to smoking history

In the never-smoker group at the time of baseline LDCT, 10,958 participants (90.0%) had Lung-RADS category 1 or S lung nodules. Furthermore, 950 (7.8%), 151 (1.2%), 70 (0.6%), 38 (0.3%) and 9 (0.1%) participants had Lung-RADS category 2, 3, 4A, 4B, and 4X lung nodules, respectively.

In the ever-smoker group at the time of baseline LDCT, 14,313 participants (86.1%) had Lung-RADS category 1 or S lung nodules. Furthermore, 1,916 (11.5%), 189 (1.1%), 144 (0.9%), 55 (0.3%) and 14 (0.1%) participants had Lung-RADS category 2, 3, 4A, 4B, and 4X lung nodules, respectively (see Table 1).

Clinical course and characteristics of LCINS and lung cancer in ever-smokers

Lung cancer was detected in 55 of 12,176 patients in the never-smoker group (0.45%) versus in 143 of 16,631 ever-smoker (0.86%) ($p < 0.001$) (Table 2). As expected, lung cancer detection by LDCT was significantly higher in the ever-smoker than never-smoker group.

We also investigated the influence of sex and age on lung cancer. Lung cancer was detected in 0.38% and 0.88% of male never-smokers and ever-smokers, respectively ($p<0.001$). Among female participants, lung cancer was

detected in 0.49% and 0.53% of never-smoker and ever-smoker, respectively ($p = 0.874$). In the never-smoker group, the rate of lung cancer detection in female participants (0.49%) was higher than that in male participants (0.38%), with no statistically significant difference ($p = 0.396$) (see Table 2).

There was no significant difference in age at time of lung cancer detection in either group, except in participants in their 40s. The rate of cancer detection was significantly higher in ever-smokers (1.17%) than in never-smokers (0.16%) in their 40s.

The baseline LDCT screening of never-smokers detected lung cancer in three of the 10,958 (0.03%) in Lung-RADS category 1 or S, 15 of the 950 (1.58%) in category 2, 20 of the 151 (13.25%) in category 3, six of the 70 (8.57%) in category 4A, seven of the 38 (18.42%) in category 4B, and four of the nine (44.44%) in category 4X. Overall, 17 cancers (14.53%) were detected in a total 117 Lung-RADS category 4 nodules. The baseline LDCT screening in ever-smokers detected lung cancer in 57 of the 14,313 (0.40%) in Lung-RADS category 1 or S, 18 of the 1916 (0.94%) in category 2, 20 of the 189 (10.58%) in category 3, 23 of the 144 (15.97%) in category 4A, 15 of the 55 (27.27%) in category 4B, and 10 of the 14 (71.43%) in category 4X. Overall, 48 cancers (22.54%) were detected in a total of 213 Lung-RADS category 4 nodules (see Table 2). Interestingly, the rate of lung cancer detection in those with Lung-RADS category 1 or S was significantly higher in the ever-smoker group ($p < 0.001$), which suggest that more lung cancer in the ever-smoker group was detected at follow-up (interval cancer). We investigated the

characteristics of lung nodules in the never-smoker group intensively (Table 3). The mean size of the nodules was 7.3 mm, and most of the nodules were the ground glass opacity type (55.5%), solid nodule (34.3%), or partial solid nodule (10.1%). Overall, 76.4% of the nodules were single and 65.3% were regular borderline nodules. The mean size of the malignant nodules was significantly larger than that of the noncancerous nodules, and the mean sizes of the partial solid nodule portion and that the irregular border of the malignant nodules were also significantly larger. But there was no difference in the rate of cancer diagnosis according to lung nodule location (p=0.847).

Table 2. Lung cancer detection according to subgroups and Lung-RADS categories at baseline LDCT

Variable	Lung cancer in never-smoker	Lung cancer in ever-smoker	*p Value*
	With Cancer/ Total, n/n (%)		
Total	55 of 12,176 (0.45)	143 of 16,631 (0.86)	<0.001
Sex			
Male	17 of 4,432 (0.38)*	139 of 15,883 (0.88)**	<0.001
Female	38 of 7,744 (0.49)*	4 of 748 (0.53)**	0.784
Age			<0.001
40s	8 of 4,896 (0.16)	94 of 8,062 (1.17)	<0.001
50s	21 of 4,245 (0.49)	27 of 5,493 (0.49)	0.982
60s	22 of 2,335 (0.94)	15 of 2,498 (0.60)	0.173
70s	4 of 700 (0.57)	7 of 578 (1.21)	0.218
Lung-RADS (by baseline LDCT)			<0.001
1 or S	3 of 10,958 (0.03)	57 of 14,313 (0.40)	<0.001
2	15 of 950 (1.58)	18 of 1,916 (0.94)	0.132
3	20 of 151 (13.25)	20 of 189 (10.58)	0.449
4A	6 of 70 (8.57)	23 of 144 (15.97)	0.138
4B	7 of 38 (18.42)	15 of 55 (27.27)	0.323
4X	4 of 9 (44.44)	10 of 14 (71.43)	0.196

* Male never-smoker versus female never-smoker: p=0.396

** Male ever-smoker versus female ever-smoker: p=0.971

Lung-RADS, Lung Imaging Reporting and Data System; LDCT, low-dose chest computed tomography.

Table 3. Baseline characteristics of lung nodules in never-smokers

Characteristics	Total (N=1218)	Lung cancer (N=52)	Not cancer (N=1,166)	*p Value*
Nodule size ± SD, mm	7.29 ± 4.95	13.07 ± 6.95	7.04 ± 4.69	<0.001
Nodule type, n (%)				<0.001
Solid	418 (34.3)	10 (19.2)	408 (35.0)	
Partial solid	123 (10.1)	25 (48.1)	98 (8.4)	
Ground glass opacity	677 (55.5)	17 (32.7)	660 (56.5)	
Location, n (%)				0.847
RUL	372 (30.5)	13 (25.0)	359 (30.8)	
RML	139 (11.4)	5 (9.6)	134 (11.5)	
RLL	271 (22.2)	12 (23.1)	259 (22.2)	
LUL	231 (19.0)	12 (23.1)	219 (18.8)	
LLL	205 (16.8)	10 (19.2)	195 (16.7)	
Nodules (%)				0.117
Single	930 (76.4)	35 (67.3)	895 (76.8)	
Multiple	288 (23.6)	17 (32.7)	271 (23.2)	
Borderline of nodules (%)				<0.001
Regular	795 (65.3)	21 (40.4)	774 (66.4)	

Irregular	423 (34.7)	31 (59.6)	392 (33.6)	
Lung-RADs				<0.001
2	950 (77.8)	15 (28.8)	935 (80.2)	
3	151 (12.4)	20 (38.5)	131 (11.2)	
4A	70 (5.7)	6 (11.5)	64 (5.5)	
4B	38 (3.1)	7 (13.5)	31 (2.7)	
4X	9 (0.7)	4 (7.7)	5 (0.4)	

RUL = Right upper lobe, RML = right middle lobe, RLL = right lower lobe LUL = left upper lobe, LLL = left lower lobe

There were big differences in cancer stage, type of cancer, and treatment modality between the two groups. Of the lung cancers in never-smokers, 92.7% was stage 0 or I, with only 3.6% (two cases) diagnosed in stage IV. On the other hand, in ever-smokers, 63.6% of lung cancers were in stage 0 and I whereas 28% were in stages III or IV. LCINS tended to be in earlier stages than were the cancers in ever-smokers (p=0.004). All the cases of LCINS were adenocarcinomas; meanwhile, the lung cancers in ever-smokers were more heterogeneous: adenocarcinoma (72.7%), squamous cell carcinoma (18.9%), and small cell lung cancer (3.5%) ($p < 0.001$). Surgery was performed more frequently for LCINS (96.4%) than for lung cancer in ever-smoker (75.2%) (see Table 4).

Table 4. Characteristics of lung cancers according to the smoking status

Characteristic	Lung cancer in never-smoker (n=55)	Lung cancer in ever- smoker (n=143)
Cancer diagnosis, n (%)		
Prevalent cancer	52 (94.6)	81 (56.6)
Interval cancer	3 (5.4)	62 (43.4)
Mean interval between baseline screening and diagnosis ± SD, mo	22.7 ± 4.28	42.1 ± 3.48
Stage, n (%)		
0*	7 (12.7)	17 (11.8)
I	44 (80)	74 (51.7)
II	2 (3.6)	12 (8.4)
III	0 (0.0)	15 (10.5)
IV	2 (3.6)	25 (17.5)
Initial treatment, n (%)		
Surgery	53 (96.4)	109 (75.2)
Concurrent chemoradiation	0 (0.0)	6 (4.2)
Chemotherapy	2 (3.6)	24 (16.8)
Best supportive care	0 (0.0)	4 (2.8)

Histologic type, n (%)		
Adenocarcinoma	55 (100.0)	104 (72.7)
Adenocarcinoma in situ	7 (12.7)	17 (16.4)
Minimally invasive adenocarcinoma	11 (20.0)	14 (13.5)
Invasive adenocarcinoma	37 (67.3)	73 (70.2)
Squamous cell carcinoma	0 (0.0)	27 (18.9)
Small cell lung cancer	0 (0.0)	5 (3.5)
Large cell lung cancer	0 (0.0)	2 (1.4)
Poorly differentiated carcinoma	0 (0.0)	3 (2.1)
Other LSCLC	0 (0.0)	2 (1.4)

* Carcinoma in situ (former bronchioloalveolar cell carcinoma)

Survival

One death (1.8%) occurred in 55 cases in the never-smoker group; however, 41 deaths (28.7%) occurred in 143 lung cancer patients in the ever-smoker group. The median follow-up periods for patients with lung cancer were 2.21 years for never-smoker (range 0 – 13 years) and 3.21 years for ever-smoker (range 0 - 12.5 years). The estimated rate of overall survival at 5 years among never-smoker lung cancer was 96% and the rate at 10 years remained 96%. The estimated rate of overall survival at 5 years among ever-smoker with lung

cancer was 67.4% whereas the rate at 10 years was 62.7%. Kaplan-Meier survival estimates with the log-rank test showed that never-smoker with lung cancer had better survival than ever-smokers did ($p < 0.001$) (Figure 2).

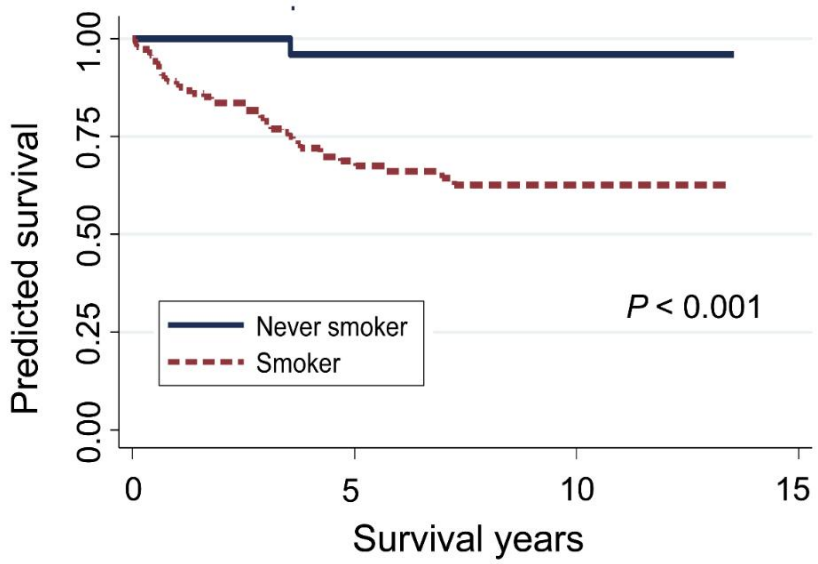

Figure 2. Cumulative survival curves of patients with screening-detected lung cancers, by smoking status.

In the Cox proportional hazard ratio, adjusted for age, sex, cancer stage, and histologic type, smokers had a higher risk of mortality than never-smokers did (HR = 0.09, 95% confidence interval: 0.01-0.74) (Table 5).

Table 5. Hazard ratio (HR) of lung cancer mortality adjusted by Cox

regression

Category	aHR	95% CI	*p-value*
By smoking status[1]			0.026
Smoker	1		
Never-smoker	0.09	0.01-0.74	
By stage[2]			
Stage I	1		
Stage II	3.84	1.13-13.01	0.031
Stage III	8.37	2.99-23.42	<0.001
Stage IV	47.08	18.07-122.71	<0.001

[1] Adjusted by age, sex, cancer stage, histology

[2] Adjusted by age, sex, smoking status, histology

aHR = adjusted hazard ratio

HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio

Discussion

This was a large descriptive study to investigate the role of LDCT in lung cancer screening among never-smokers and ever-smokers. Lung cancer was diagnosed by using LDCT in 0.45% of patients in the never-smoker group and 0.86% in the ever-smoker group. In the NLST, a previous randomized controlled trial (RCT) conducted among heavy smokers, 270 of 26,309 patients (1.0%) were diagnosed in the first (T0) stage of tomography

screening.[17] In the Dutch-Belgian NELSON lung cancer screening trial, the Danish Lung Cancer Screening Trial, the Italian Lung Cancer Screening Trial, and the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays Study, lung cancer was diagnosed in 0.9% [25], 0.8% [26], 1.5% [27], and 3.7% [28] of patients, respectively.

We thought that the rate of 0.45% in the never-smoker group was quite high, although it is lower than the rate reported from the aforementioned lung cancer screening studies targeting heavy smokers. However, the rate of 0.86% in the ever-smoker group was quite similar to those reported in these previous studies even though the amount of smoking in our study was probably lower in comparison. Furthermore, almost 30% of patients who had positive nodules were still being followed-up, with some patients (< 1%) refusing the tissue diagnosis. Therefore, with prolonged follow-up, the rate of cancer detection would likely have increased. The rate of lung cancer detection in never-smoker in this study (0.45%) is quite similar to that reported in another Korean study (0.5%) in which LDCT of 4365 female never-smoker was identified retrospectively from the Korea Cancer Registry Database.[20] In this study, the rate of cancer detection in female never-smokers was 0.49% (see Table 2).

Analysis of the characteristics of lung cancer in both groups revealed some clinically significant findings. First, the higher proportion of prevalent cancer in never-smoker than ever-smoker is important. In never-smokers, 95% of lung cancers were detected in the first nodules found (prevalent cancer)

whereas the remaining 5% of lung cancers (in three of 12,176 screened never-smokers) were interval cancers. However, in ever-smokers, 43% of cancers were interval cancer. The NLST of heavy smokers showed 1.0%, 0.7%, and 0.9% of cancer diagnoses during the initial 3 years of screening with LDCT at 1-year intervals[17]. The cancer in never-smokers seemed to be more indolent than that in ever-smokers. Therefore, screening intervals in never-smokers could be longer than 1 year, which was generally recommended in the heavy smoker group if LDCT showed no significant finding.[17]

Second, most lung cancers in never-smokers were in the early stages (92.7% were in stage 0 or 1) in contrast to those among the ever-smokers (63.6% were in stage 0 or 1), with never-smokers showing excellent survival (in contrast to ever-smokers). This finding strongly suggests the necessity of LDCT screening in never-smokers as well as in ever-smokers, even though the detection rate of lung cancer is lower in never-smokers. The relatively high proportion of adenocarcinoma in situ found in this study deserves further attention. All of the adenocarcinomas in situ in this study were resected (12.7% in never-smoker and 11.8% in ever-smoker were in stage 0) were pure ground glass opacity nodules larger than 15 mm or larger than 10mm with growth of more than 2 mm and were formerly classified as bronchioloalveolar cell carcinoma. Our institute recommended surgical resection for patients with pure ground glass larger than 15 mm or larger than 10mm with growth of more than 2 mm before the NCCN guidelines suggested the follow-up policy.[21] All of the lung cancers in never-smokers were adenocarcinomas; however, squamous cell carcinoma and small cell lung cancer were found in

ever-smokers, even though adenocarcinoma was still the most common pathologic type (72.7%) (see Table 4).

Third, the subgroup analysis of this study revealed no sex difference in the rate of lung cancer detection in never-smokers (in 0.38% of males and 0.49% of females [$p = 0.396$]). No difference was found between female never-smokers (0.49%) and female ever-smokers (0.53%); however, a large difference was found between male never-smoker and male ever-smoker (0.38% versus 0.88%, respectively [$p < 0.001$]). The fact that there was no difference between female never-smokers and ever-smokers might be related to the low amount of smoking among female smokers or the high exposure to secondhand smoke among female never-smokers. However, no data were available to support this interpretation.

Fourth, nodules from Lung-RADS category 2 to 4 were found in 10% of never-smokers and 13.9% of ever-smokers; in contrast, Lung-RADS category 3 and 4 nodules were found in 2.2% of never-smoker and 2.4% of ever-smoker. Most cancers were detected from Lung-RADS category 3 and 4 nodules in both groups, as we expected. It seems reasonable to prolong the screening interval if LDCT shows Lung-RADS category 1 or 2, especially in never-smokers.

Another Korean study suggested that repeating annual LDCT screening for at least 5 years or even longer was unnecessary unless the initial LDCT showed Lung-RADS category 4 findings in female never-smokers.[20] Another RCT from Japan that included never-smokers and light-smokers (the JECS

study) adopted a 5-year interval for computerized tomography (CT) screening.[29]

Finally, in this study, lung cancer mortality was much lower in never-smoker than ever-smoker. The 5-year survival, estimated by Kaplan-Meier curves was also higher in the never-smoker group. Better survival in LCINS is mainly derived from the early detection in never-smokers. However, the HR in smokers was higher than that in never-smokers even after adjustment for age, sex, histologic type, and stage. This result is similar to the results of previous studies.[13, 30-32]

In the Republic of Korea, only 21.7% of all patients with lung cancer had their lung cancer detected as localized disease, with 41.1% detected in stage IV.[7] A comparative study of lung cancer in smokers and never-smokers from an unscreened general population in Singapore showed some significant differences. A higher prevalence of adenocarcinoma was reported in never-smokers than in smokers (current or former smokers), whereas poorer performance status and higher median age at diagnosis were reported in smokers; however, more advanced stage of disease was reported in never-smokers.[14] However, a study from Japan reported that 52% of LCINS detected in a clinic-based screening program were stage I and 35% were stage III B or IV.[13] Kondo et al.[19] investigated the efficacy of CT screening for LCINS and reported that in the CT-screened subgroup, the rate of stage IA cancer was 69.7% whereas that of advanced stage was 6.6%. The rate of lung cancer detected at an advanced stage in CT-screened subgroup was lower than the rates in group screened by radiography (22.1%) and group with screening

prompted by symptoms (61.9%). From several reports described earlier in this article[7, 13, 14, 19] and the present study, we found that case of LCINS detected by CT screening were in an earlier stage than unscreened LCINS. We hopefully expect that LDCT screening in never-smokers will detect lung cancer in early stages and will therefore improve the survival of patients.

This study has some limitations. First, it was not a prospective RCT but a retrospective cohort study in a single center. To overcome the lack of control group, we compared the never-smoker and ever-smoker groups during the same period and in the same center. Second, patients with lung nodule were referred to a pulmonologist according to the NCCN guidelines[21] at that time or based on the Lung-RADS recommendation[22] for further follow-up or diagnostic procedures. However, some of the patients with positive nodules are still being followed-up. Third, the study population was not representative of the general population of the republic of Korea. The participants underwent the health screening at their own expense or sponsored by their employers. Therefore, they are at least in the middle to high socio-economic status. Fourth, amount of smoking was not available for the study population. Almost all participants described their smoking status (never-smoker, ex-smoker and current smoker); however, amount of smoking and duration of smoking cessation were missing for many participants. Furthermore, information on the history of exposure to secondhand smoke was unavailable, although exposure to secondhand smoke has been suggested as the cause of LCINS.[10] Finally, all participants of this study are Koreans. LCINS has shown marked sex and racial differences. In particular, lung cancer has been diagnosed in a

higher proportion of never smokers among East Asian women, including Republic of Korea, Japan and China than in never-smoking women in Europe and the United states. [33, 34] This finding might have influenced the result of this study.

In conclusion, LDCT screening in the never-smoker population has enhanced the detection of a significant number of lung cancer cases. Most LCINS has been detected at a very early stage with added survival benefit. The positive results of NLST in the United States and the NELSON trial may have established the value of LDCT screening for heavy smokers, but future research should consider the value of using LDCT screening in the never-smoker population.

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국문 초록

비흡연자의 조기 폐암 검진에서 저선량 흉부전산화 단층촬영의 역할

서론: 미국 국립 폐암 검진 연구 (NLST) 및 NELSON 연구에서 저선량 흉부 전산화 단층촬영 (LDCT) 을 이용한 폐암 검진이 중증 흡연자의 폐암 사망률을 효과적으로 낮춘 것으로 나타났다. 비흡연자들의 폐암 발병률이 빠르게 증가하고 있으나 비흡연자에서 LDCT의 폐암검진 효과에 대해서는 연구된 결과가 없다. 이 연구는 비흡연자에서 LDCT를 사용한 폐암검진의 결과를 조사했다.

방법: 본 연구는 단일기관의 후향적 코호트 연구로, 2003년 5월부터 2016년 6월까지 LDCT로 폐암 검진을 받은 환자에 대해 분석했다. LDCT 에서 결절이 발견된 경우 Lung Imaging Reporting and Data System criteria에 따라 결절을 분류하였다. 흡연력에 따른 폐암 진단율 및 조직학적 진단, 병기 및 사망 여부가 조사되었다.

결과: 전체 28,807명의 환자 중 12,176은 비흡연자였고 그 중 7744(63.6%)는 여성이었으며 1,218 (10%)의 환자에서 폐 결절이 발견되었다. 비흡연자 중에서 55명(0.45%)의 환자가 폐암으로 진단되었으며 16,631명의 흡연자 중에는 143명 (0.86%)의 환자가 폐암으로 진단되었다. 비흡연자의 폐암에서

51명(92.7%)는 폐암 1기였고, 비흡연자에서 발견된 모든 폐암은 선암이었다.

결론: 비흡연자에서 LDCT는 유의미하게 폐암을 검진하는 데 도움이 되었으며, 대부분의 폐암은 초기 병기에 발견되었다. NLST연구에서 흡연자에 국한하여 폐암검진에서 LDCT의 유용성에 대해서 연구되고 있으므로, 비흡연자에서 LDCT 폐암검진의 효용성에 대한 추가적인 연구가 필요하다.

주요어 : 저선량 흉부 전산화 단층촬영, 비흡연자, 폐암, 폐선암

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