

Lung Cancer Screening with Low-Dose Helical CT in Korea: Experiences at the Samsung Medical Center

To determine overall detection rates of lung cancer by low-dose CT (LDCT) screening and to compare histopathologic and imaging differences of detected cancers between high- and low-risk groups, this study included 6,406 asymptomatic Korean adults with ≥ 45 yr of age who underwent LDCT for lung cancer screening. All were classified into high- (≥ 20 pack-year smoking; 3,353) and low-risk (3,053; <20 pack-yr smoking and non-smokers) groups. We compared CT findings of detected cancers and detection rates between high- and low-risk. At initial CT, 35% (2,255 of 6,406) had at least one or more non-calcified nodule. Lung cancer detection rates were 0.36% (23 of 6,406). Twenty-one non-small cell lung cancers appeared as solid ($n=14$) or ground-glass opacity (GGO) ($n=7$) nodules. Cancer likelihood was higher in GGO nodules than in solid nodules ($p<0.01$). Fifteen of 23 cancers occurred in high-risk group and 8 in low-risk group ($p=0.215$). Therefore, LDCT screening help detect early stage of lung cancer in asymptomatic Korean population with detection rate of 0.36% on a population basis and may be useful for discovering early lung cancer in low-risk group as well as in high-risk group.

Key Words : Mass Screening; Lung Neoplasms; Tomography, Spiral Computed; Smoking

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INTRODUCTION

Lung cancer is one of the most lethal malignant tumors with more than 1.3 million estimated deaths annually. In the United States, approximately 175,000 new cases are diagnosed each year, 75-80% of which are non-small cell lung cancer (1). In 2004, it has been estimated that there will be 68,200 lung cancer deaths among women and 93,100 among men; there appears to be a leveling off in the incidence of lung cancer and the death rate among males in the U.S.A. although the incidence and mortality in females continues to increase (2).

According to the Korean National Cancer Registry, lung cancer is the second most common malignant tumor following gastric cancer, and accounts for the 11.9% of total number of newly reported cancers (3). Recently, lung cancer death rates have continued to increase since 1999 and lung cancer is the leading cause of all cancer deaths in Korea. Lung cancer death rates of Korean population increased from 17.4 per 100,000 in 1993 to 26.4 per 100,000 in 2003, and accounted for 15.7% of all cancer deaths in 1993 and 20.0% in 2003 (4).

Overall, 5-yr survival rates for lung cancer are about 14% in the United States and ranges from 5.5% to 14% in the Europe (5-7). It has been reported that the 5-yr survival rate after resection of stage IA is more than 70%, whereas that

for stage IV lung cancer is less than 3% (8, 9).

Trials to reduce mortality rates from lung cancer have been performed over many years using various methods (10-13). However, there is no good evidence that screening for lung cancer by using chest radiography or sputum cytology can reduce lung cancer mortality (14). Recently, lung cancer screening using low-dose CT (LDCT) has been reported to be effective at detecting small lung cancer (15-17), thus increasing the expectation that this method will reduce lung cancer mortality. However, in terms of demonstrating definite improvements in cancer mortality, the results of randomized controlled trials using this screening method are awaited (18).

The purpose of our study was to assess the overall detection rates of lung cancers using LDCT screening and to compare differences in the histopathologic and imaging findings of detected cancers between asymptomatic Korean high-risk and low-risk groups.

MATERIALS AND METHODS

Study population

From August 1999 to September 2003, 6,406 individu-

als with ≥ 45 yr of age (mean \pm SD; 55 ± 6.7 , range; 46-85) underwent LDCT for lung cancer screening. Our institutional review board approved the lung cancer screening study, and written informed consent was obtained from all participants for the CT study. All subjects were asymptomatic and none had any history of cancer within the previous 5 yr. They were 5,530 men and 876 women. We evaluated the individual smoking history with the answer sheets for all participants, who were classified into two groups; high-risk group who had smoked 20 pack-years or more and low-risk group who had smoked less than 20 pack-years or who never smoked.

Screening procedure

All scans were performed on multi- or single-slice CT scanners from lung apex to base without contrast enhancement. The scanning parameters were 120 kVp and 48 (60 mA/0.8 sec) or 50 (50 mA/1.0 sec) mAs. CT machines with four different detector numbers were used, namely, single-detector (HiSpeed Advantage scanner, GE Medical Systems, Milwaukee, WI, U.S.A.; pitch 1.7:1, 5-mm thickness reconstruction with 4-mm intervals), four-detector (LightSpeed QXi, GE Medical Systems; 20-mm beam collimation, beam pitch 1.5, 5-mm thickness reconstruction with 4-mm intervals), eight- and 16-detector (LightSpeed Ultra or Ultra16, GE Medical Systems; 20-mm beam collimation, beam pitch 1.375, 5-mm thickness reconstruction with 4-mm intervals).

We evaluated all images shown on lung (window width 1,500 HU, window level -700 HU) and mediastinal (window width 342 HU, window level 56 HU) windows on PACS (Centricity 1.0, General Electric Medical Systems Integrated Imaging Solutions, Mt. Prospect, IL, U.S.A.) monitors using cine mode by one of three chest radiologists (S.C., M.J.C., and K.S.L. with two years, eight years and 15 yr of experience, respectively, in thoracic imaging). We assessed the attenuation, size and number of nodules, which were classified into the three types of attenuation: non-calcified solid, ground-glass opacity or calcified nodule, and were categorized into three groups of size according to their greatest dimensions: < 5 mm, 5-10 mm, and > 10 mm in diameter.

For non-calcified nodules detected on baseline CT scans, we recommended the follow-up protocol: if the detected nodule was solid and 10 mm or more in diameter, immediate intervention (percutaneous needle biopsy, video-assisted thoracoscopic surgery or open lung biopsy) was given to obtain a tissue diagnosis after obtaining thin-section CT scans throughout the nodule (for the marginal and internal nodule characterization of a nodule; volume scanning using multislice CT, 0.8-sec gantry rotation time, 120 kVp, 90 mA, 2.5-mm beam collimation, beam pitch 1.375, 2.5-mm thickness reconstruction with 2.5-mm intervals); if the detected nodule was less than 10 mm in diameter, patients were recommended to have followed-up CT scans 6 months after the initial examination. If the nodule did not show any growth over a follow-up period

of six months, an annual follow-up study was recommended. For ground-glass opacity (GGO) nodules, if more than 10 mm in diameter, immediate intervention was recommended after obtaining thin-section CT scans throughout the nodule, however, if less than 10 mm in diameter, thin-section CT scans were obtained within a short-term follow-up period of 2 months, then after six-months, and annually thereafter.

Of all subjects, 3,638 subjects underwent LDCT scan only once, 1,537 subjects twice, 704 subjects three times and 527 subjects four times or more.

Cancer assessment

During screening studies, when a nodule was suggestive of lung cancer with a diameter exceeding 10 mm, a tissue diagnosis was established by obtaining tumor tissue. For 21 peripheral nodules, tissue diagnosis was made by trans-thoracic needle biopsy in 12 patients, video-assisted thoracoscopic surgery in four, open lung biopsy in two, bronchoscopic biopsy in two, and sputum cytology in one. In two patients with small cell lung cancer, diagnosis was made in each by bronchoscopic biopsy and percutaneous needle biopsy. For all pathologic specimens, one lung pathologist with nine years of experience evaluated all histopathologic specimens.

For staging of non-small cell lung cancers (NSCLC), we used the revised International System for Staging Lung Cancer adopted by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) system (19). For staging of small cell lung cancer (SCLC), we used the system adopted from the Veterans Affairs Research Service Lung Group (20).

We also obtained the tumor doubling time of lung cancer using the maximum diameter and volume of each tumor, which were determined from initial and follow-up CT images. Tumor volume (V) was calculated using the following equation, assuming a spherical form:

$$V = [4/3 \times \pi \times a \times b \times (a+b)/2] \times 1/8$$

where a indicates the maximum tumor diameter and b indicates the minimum tumor diameter. The tumor doubling time (T_d) was calculated using the following equation:

$$T_d = (T - T_0) \times \log 2 / \log V - \log V_0$$

where $T - T_0$ indicates the length of time between two measurements and V_0 and V denote the tumor volumes at these times (21).

For all patients with lung cancers, we assessed the treatment given to the patients and described the follow-up outcomes after treatment when available.

Statistical analysis

Overall lung cancer detection rates were described on an individual basis and on a detected non-calcified nodule basis. Rates were also calculated according to stratified subjects' ages (≥ 45 yr, > 50 yr, or finally > 60 yr). Differences in the preva-

lence of all lung cancers between high- and low-risk groups were compared using the chi-square test. Differences in the prevalence of stage IA cancers between high- and low-risk groups, in the incidence of stage IA cancers between the initial and follow-up screenings, and in the incidence of lung cancers between GGO and solid nodules were compared using the Fisher's exact test. Differences of tumor doubling time in high- and low-risk groups were compared by the Mann-Whitney test. We used the SPSS software package (SPSS 11.0.0, SPSS Inc., Chicago, IL, U.S.A.) and considered to be statistically significant at a *p* value of <0.05.

RESULTS

Of 6,406 subjects, 3,353 subjects belonged to high-risk

group who had smoked 20 pack years or more (39 ± 15.9 pack years). Low-risk group included 3,053 subjects; 1,581 smokers who smoked less than 20 pack-years (13 ± 4.7 pack years) and 1,472 non-smokers. All smokers had the mean smoking history of 33.3 pack years.

Table 1 shows the characteristics of non-calcified nodules detected on LDCT scans. At CT, 35% (2,255 of 6,406) of screened subjects had at least one or more non-calcified nodules ($n=4,037$); 2,085 subjects had 3,783 solid nodules (mean, 1.8 nodules per subject) and 170 subjects 254 GGO nodules (mean, 1.5 nodules per subject).

Table 2 shows the characteristics of lung cancers detected on LDCT scans. Twenty-three primary lung cancers were detected with an overall detection rate of 0.36% (23 of 6,406) on an individual basis and 0.57% (23 of 4,037) on a non-calcified nodule basis. The prevalence of lung cancer according

Table 1. Characteristics of non-calcified nodules detected by low-dose screening CT

Group	Solid				GGO				Total
	<5 mm	5-10 mm	>10 mm	Total	<5 mm	5-10 mm	>10 mm	Total	
High risk	1,887 (950)	191 (144)	28 (26)	2,106 (1120)	46 (21)	65 (50)	26 (23)	137 (94)	2,243 (1,214)
Low risk	1,479 (816)	174 (125)	24 (24)	1,677 (965)	52 (24)	53 (40)	12 (12)	117 (76)	1,794 (1,041)
Total	3,366 (1,766)	365 (269)	52 (50)	3,783 [1.8] (2,085)	98 (45)	118 (90)	38 (35)	254 [1.49] (170)	4,037 [1.79] (2,255)

Numbers in parenthesis are number of subjects and numbers in bracket are number of nodules per person. GGO, ground-glass opacity.

Table 2. Characteristics of detected lung cancers by low-dose screening CT

No.	Sex	Age (yr)	Histologic type	TNM staging	Type of Attenuation	Group	Treatment	Outcome	Size [†] (mm)		Td* (mo)
									Initial	Final	
1	M	73	Adenocarcinoma	T1N0 IA	GGO	High	Lobectomy	Good	9	15	1
2	M	63	Squamous cell ca	T1N0 IA	Solid	High	Lobectomy	Good	29		
3	M	72	Adenocarcinoma	T1N0 IA	GGO	Low	No treatment	Unknown	6	29	8
4	M	61	Squamous cell ca	T2N3 IIIB	Solid	Low	Chemotherapy, Palliative	Death, 1 yr later	32		
5	M	69	Adenocarcinoma	T1N2 IIIA	GGO	High	Lobectomy	RT due to recurrence 1 yr later	18		
6	M	46	Adenocarcinoma	T1N0 IA	Solid	High	Lobectomy	Good	10	17	7
7	M	62	SCLC	Extensive	LAP	Low	Chemotherapy, Palliative	Good	NA		
8	F	60	Adenocarcinoma	T2N3M1 IV	Solid	Low	No treatment	Unknown	42		
9	M	58	Adenocarcinoma	T1N1 IIA	Solid	High	Lobectomy	Good	8	18	3
10	M	47	Squamous cell ca	T3N2 IIIA	Solid	High	No treatment	Unknown	27		
11	M	80	Adenocarcinoma	T3N1 IIIA	Solid	High	No treatment	Death, 3 months later	40		
12	F	56	Adenocarcinoma	T1N0 IA	Solid	Low	Lobectomy	Good	18		
13	M	60	Squamous cell ca	T2N3M1 IV	Solid	High	No treatment	Unknown	34		
14	F	60	Adenocarcinoma	T1N0 IA	Solid	Low	Lobectomy	Good	6	13	3
15	M	54	Adenocarcinoma	T1N0 IA	Solid	Low	Lobectomy	Pneumonectomy, due to recurrence 3 yr later	7	12	49
16	M	53	BAC	T1N0 IA	GGO	High	Lobectomy	Good	9	19	29
17	M	63	BAC	T1N0 IA	GGO	High	Lobectomy	Good	8	13	27
18	M	56	Adenocarcinoma	T1N0 IA	GGO	High	Lobectomy	Good	25		
19	M	48	Adenocarcinoma	T1N0 IA	GGO	High	Lobectomy	Good	10	12	21
20	M	61	Squamous cell ca	T1N0 IA	Solid	Low	Lobectomy	Good	8	13	40
21	M	73	Pleomorphic ca	T1N2 IIIA	Solid	High	Lobectomy	Good	14	16	3
22	M	56	SCLC	Limited	LAP	High	CCRT	Good	NA		
23	M	65	Squamous cell ca	T1N0 IA	Solid	High	Lobectomy	Good	5	10	3

Td*, doubling time in months; Size[†], size of nodule at initial or final follow-up CT, single number denotes diameter at initial CT; LAP, lymphadenopathy; RT, radiation therapy; CCRT, concurrent chemoradiation therapy; GGO, ground-glass opacity; BAC, bronchioloalveolar carcinoma; ca, carcinoma; NA, not applicable.

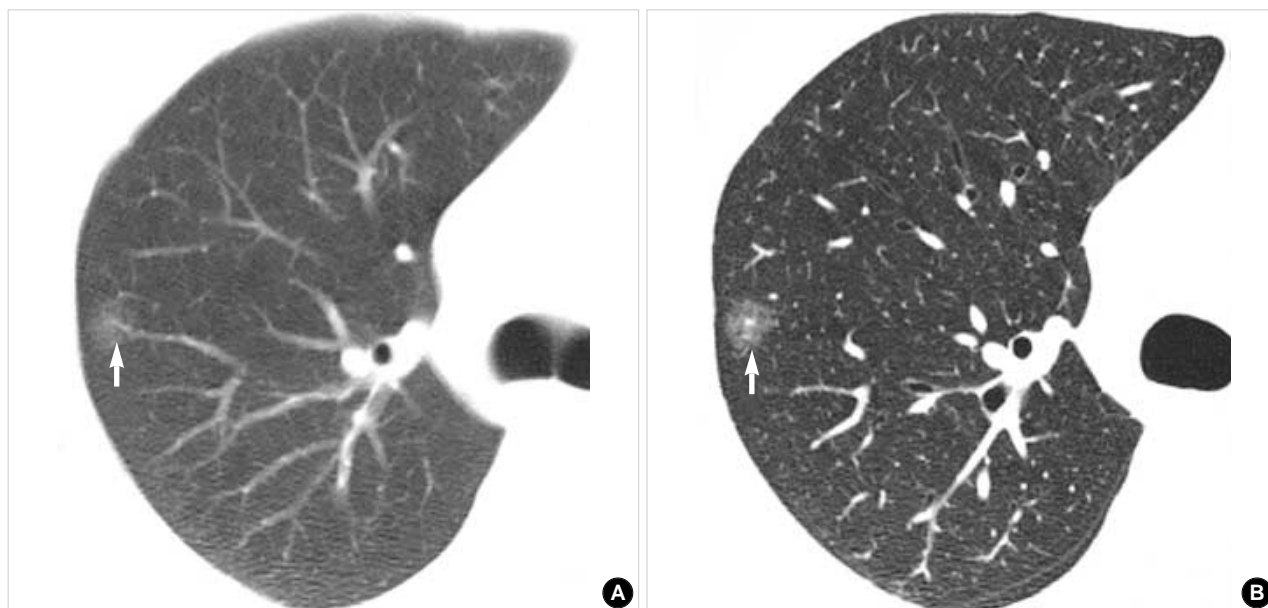


Fig. 1. A 48-yr-old man with adenocarcinoma. (A) Lung window of initial screening low-dose CT scan obtained at level of right upper lobar bronchus shows 10-mm-sized ground-glass opacity nodule (arrow) in right upper lobe. (B) Lung window of thin-section (2.5-mm thickness) CT scan obtained at similar level to A shows clearly ground-glass opacity nature of nodule (arrow). Right upper lobectomy disclosed adenocarcinoma.

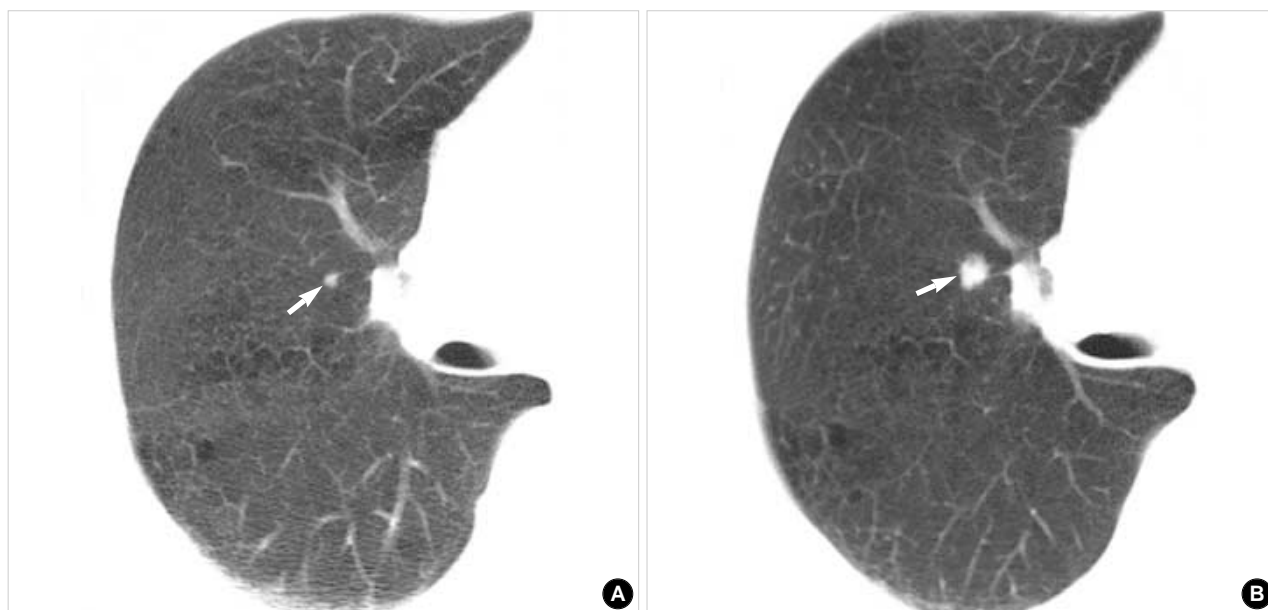


Fig. 2. A 65-yr-old man with squamous cell carcinoma. (A) Lung window of initial screening low-dose CT (5-mm collimation) scan obtained at level of bronchus intermedius shows 5-mm-sized nodule (arrow) in bottom of anterior segment of right upper lobe. (B) Repeat CT scan obtained at same level to and 6 months after A shows interval increase in nodule size (arrow). Right upper lobectomy disclosed squamous cell carcinoma.

to stratified subjects' ages was 0.36% (23 of 6,406) in those of ≥ 45 yr in age, 0.47% (20 of 4,254) in those of >50 yr, and 0.91% (11 of 1,215) in those of >60 yr.

Adenocarcinoma was found in 12 patients (Fig. 1), squamous cell carcinoma in 6 (Fig. 2), bronchioloalveolar carcinoma in two, pleomorphic carcinoma in one and small cell

carcinoma in two.

On CT scans, 21 NSCLCs presented as a solid nodule in 14 patients and GGO in seven. The likelihood of lung cancer was higher in GGO nodules (7 of 254 GGO nodules, 3%) than in solid nodules (14/3,783, 0.4%) ($p < 0.01$) (Fisher's exact test).

The pathologic stages of the 21 NSCLCs were as follows: T1 in 16 (76%) patients, T2 in 3 (14%), and T3 in 2 (10%); N0 in 13 (62%), N1 in 2 (10%), N2 in 3 (14%), and N3 in 3 (14%); and stage IA in 13 (62%), IIA in 1 (5%), IIIA in 4 (19%), IIIB in 1 (5%), and IV in 2 (10%).

Sixty-five percents (15 of 23) of lung cancers occurred in high-risk group and 35% (8 of 23) in low-risk group ($p=0.215$) (chi-square test). Of 13 stage IA NSCLCs, 8 (57% of 14 NSCLCs in high-risk group) were observed in high-risk group and 5 (71% of 7 NSCLCs in low-risk group) in low-risk group ($p=0.656$) (Fisher's exact test).

Of 23 lung cancers, 11 lung cancers were detected during initial screening and 12 during repeat study. In terms of repeat studies, 10 lung cancers were detected during the second follow-up study (mean 25.3 months) and 2 during the third follow-up study (mean 27.3 months). Of 9 NSCLCs detected at initial screening, three (33%) were stage IA cancers, whereas of 12 NSCLCs detected at repeat study, 10 (83%) were stage IA cancers, i.e., stage IA cancers were much more prevalent in the repeat study than in the initial study ($p=0.032$) (Fisher's exact test).

Of the 12 lung cancers for which the tumor doubling time was calculable, the average doubling time was 16 ± 16.7 months (range; 1-49 months). Although this tumor doubling time was twice as long in low-risk (25 ± 23.2 , median; 24, range; 3-49) group as in high-risk (12 ± 11.9 months, median; 5.0, range; 1-29) group, it was not statistically significant ($p=0.368$) (Mann-Whitney test).

Of 23 patients with lung cancer, lobectomy was performed in 15. Two patients underwent chemotherapy. Another patient underwent concurrent chemoradiation therapy. Five patients were discharged without any therapy because they declined

treatment. Seventeen (74%) of 23 patients were still alive for 4 yr, 2 died, and 4 were lost during follow-up studies. Of the 17 living patients, 15 (65% [15/23]) were alive without tumor recurrence.

DISCUSSION

Comparisons in inclusion criteria, screening parameters, and results of LDCT screening for lung cancer are summarized in Table 3 (22-26).

In our study, the proportion (35%) of individuals with non-calcified nodules was higher than that (23%) reported in the Early Lung Cancer Action Project (ELCAP) study (24) and was lower than those (43% and 69%, respectively) reported in the Germany study by Diederich *et al.* (26) and in the Mayo study by Swensen *et al.* (25), respectively. The difference may be due to the 5-mm collimation used in the present study versus 10-mm collimation used in the ELCAP study. However, the lower detection rates in our study compared to those of Mayo and German studies (25, 26), although they used the same 5-mm collimation, cannot be explained simply. Despite Korea has been known for endemic areas of acute or chronic granulomatous disease, the reason for this discrepancy is not clear.

The prevalence of lung cancer in the present study was 0.36% (23 of 6,406) in the study population of ≥ 45 yr in age, 0.47% (20 of 4,254) in that of >50 yr, and 0.91% (11 of 1,215) in that of >60 yr. These results of increasing tendency of cancer detection rates with older age are parallel to those of the German study (26); i.e., 1.5% (12 of 817) in the study population older than 40 yr, 2.3% (12 of 519) in that

Table 3. Comparison of inclusion criteria, screening parameters, and the results of low-dose screening CT at various institutions

	ALCAP (22*)	Shinshu (23*)	ELCAP (24*)	Mayo (25*)	Munster (26*)	SMC
Age (yr)	≥ 40	≥ 40	≥ 60	≥ 50	≥ 40	≥ 45
Smoking habits (pack years)	NL	NL	≥ 10	≥ 20	≥ 20	NL
Period	1993-1998	1996-1998	1993-1999 [†]	1999-2001	1995-1999	1999-2003
CT protocol						
Tube voltage (kVp)	120	120	140	120	120	120
Tube current (mA)	50	25-50	40	40	50 [‡]	48-50 [‡]
Collimation (mm)	10	10	10	5	5	5
Pitch	2	2	2	1.5	2	0.75-1.5
Number of Detector	1	1	1	4	1	1,4,8,16
CT interval (months)	6	12	3, 6, 12	12	3,6,12,24	6, 12
Chest radiograph	Yes	Yes	Yes	No	No	No
Volunteers (total)	1,611	5,483	1,000	1,520	817	6,406
Lung cancer at CT	32 [§] (2.0)	60 (1.1)	33 (3.3)	38 [§] (2.5)	12 [§] (1.5)	23 (0.36)
SCLC	1	3	0	3	1	2
NSCLC	31	57	33	35	11	21
Stage IA	24 (77)	53 (93)	27 (82)	21 (60)	6 (55)	13 (62)

ALCAP, anti-lung cancer association project; ELCAP, early lung cancer action project; SMC, Samsung Medical Center; NL, no limitation; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer. Numbers in parenthesis are percentages.

*, reference number; [†], approximate date that is 6-18 months after baseline screening completed in 1998; [‡], mAs; [§], number of lung cancer detected at low-dose CT; ^{||}, included both lung cancers considered synchronous primary tumors.

older than 50 yr, and 3.9% (8 of 206) in that older than 60 yr. Although the observed prevalence was less in our study, it is clear that the prevalence of lung cancer in younger populations is lower.

Nakata et al. (27) reported that persistent GGO for several months is an indicator of early adenocarcinoma or its precursor. The present study showed that nodules showing GGO on CT scans have a higher risk of harboring lung cancer (2.8%) than solid nodules (0.37%). Additionally, Kakinuma et al. (28) evaluated screening CT-detected pure GGO nodules at follow-up CT and noticed that pure GGO of lung cancer nodule change in size and attenuation over time (GGO nodules increase in size and solid component appears within GGO nodule indicating the evolution of pure bronchioloalveolar carcinoma to adenocarcinoma with bronchioloalveolar carcinoma component). They recommended close follow-up until solid component appears for the management of such a focal GGO. We also emphasize that 'a short-term follow up and immediate intervention with growth' policy are needed for the management of GGO nodules detected by LDCT screening.

In the current study, 13 (62%) of 21 non-small cell lung cancers were stage IA. Stage IA cancers were much more frequently detected in the repeat study than in the initial study ($p=0.032$). The proportion of stage IA cancers in our study was higher than those in the Mayo and German Mayo studies, in which the rates of stage IA were 60% and 55%, respectively (25, 26), but lower than those recorded by the Anti-Lung Cancer Association Project (ALCAP), Shinshu and ELCAP studies, in which the rates of stage IA were 77%, 93%, and 82%, respectively (22-24). The high incidence of stage IA cancer in the ALCAP and Shinshu studies may be due to the fact that more cancers are detected by repeat study, and thus less advanced lung cancers are detected. In fact, in the present study, 57% of detected NSCLCs were discovered by repeat study, and 31% and 9% in the Mayo and German studies (25, 26), respectively; and 58% and 60% in the ALCAP and Shinshu studies (22, 23). Moreover, in ALCAP, Shinshu, ELCAP and our study, most of stage IA cancers can be detected at repeat study. Therefore, we suggest that the repeat screening studies help detect early stage of lung cancer.

Most previous studies have included smokers who have consumed at least 10 packs a year or more (24-26). However, in our study and in the Shinshu study (23), subjects of 45 yr or more of age were included regardless of smoking history. Our study population was classified into high- and low-risk groups according to smoking status and evaluated the respective prevalence of lung cancer accordingly. We found that there were no significant differences in the prevalence of lung cancer, doubling time or stage IA of lung cancers between high- and low-risk groups.

Some limitations of our study should be mentioned. First, not all patients enrolled in this study were on regular and recommended followed-up study, therefore there might be some subjects who had lung cancer after the initial study but

not included in the present study. Second, a single radiologist read images, and thus some nodules might have been missed.

In conclusion, LDCT screening help detect early stage of lung cancer in asymptomatic Korean population with detection rate of 0.36% on a population basis and may be useful for discovering early lung cancer in low-risk group as well as in high-risk group. The possibility of lung cancer is higher when persistent nodular areas of GGO are present at LDCT than when solid nodules are seen, therefore, a careful follow-up study should be scheduled for the detection of early lung cancer.

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