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Chest radiography surveillance for lung cancer: Results from a National Health Insurance database in South Korea

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ABSTRACT

Background: Lung cancer screening with low-dose computed tomography reduced mortality in selected high risk patients. However, the use of chest radiography for lung cancer screening in Asian populations is still controversial. We investigated the effectiveness of chest radiographic surveillance using a nationwide health service data in South Korea.

Methods: Data from the Korean National Health Insurance Service examinee cohort of 2004 to 2013 were examined, and 63,228 patients with lung cancer were identified, 38,494 (57%) of whom underwent chest radiography screening. The others did not undergo lung cancer screening and were considered as a control group. Clinical data including age, smoking, screening intervals, lung cancer stages, treatments, and survival were collected. Survival gain from surveillance after adjustment for lead-time bias based on the sojourn time was calculated. Cox-proportional hazard analyses were performed to evaluate the effectiveness of screening and to determine the appropriate screening interval for chest radiography surveillance.

Results: Early lung cancer was found in 38% of patients receiving chest radiography versus 26% of those without surveillance. A patient age of more than 65 years (hazard ratio [HR], 1.53; 95% confidence limits [CL], 1.50–1.56), male (HR, 1.66; 95% CL, 1.62–1.70), and high lung cancer stages at the time of diagnosis were independent factors associated with mortality (each, $P < 0.001$). Chest radiography surveillance was a factor for decreasing mortality in female (HR, 0.81; 95% CL, 0.77–0.84, $P < 0.001$), with mortality reduction of 10% at the 3- and 5-year survival time-points. In female patients, chest radiography surveillance at intervals of less than 3 years was an independent predictor of improved survival.

Conclusions: Surveillance chest radiography increased survival in a female screened population in South Korea. Chest radiography intervals of less than 3 years may help to detect lung cancer in female patients.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality in developed countries; however, the clinical presentation and genetic predisposition vary between countries when Asian women are compared with those from North America and Europe [1,2]. In Asia, half of female lung cancers occur in people who have never smoked, and lung cancer is likely to present at a younger age than in North America and Europe [3–5]. Genetic differences in lung cancer are also a considerable factor, with it being likely that up to 35% of lung cancer cases in Asians are adenocarcinomas harboring epidermal growth factor receptor (EGFR) mutations, in contrast to an EGFR positive rate of only 10% in Caucasian patients [6,7].

Since the National Lung Screening Trial (NLST) demonstrated that lung cancer screening with low-dose computed tomography (CT) reduced mortality in selected high risk patients, the importance of CT has been highlighted, and CT has been widely used and planned to be used for lung cancer screening [8–10]. However, CT screening is associated

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with several negative issues, including false positive results, radiation harm, and economic burden [11–13]. In the NLST, suspect findings were detected in 27% of participants, although only 3.8% of these suspected findings were finally diagnosed as lung cancers [8]. This false positive rate leads not only to cost problems, but also triggers anxiety in the affected patients. Moreover, considering the inclusion criteria of the NLST (age 55–74 years; history of smoking at least 30 pack-years; and currently smoking or quit smoking within 15 years), the results of the NLST may not be directly applicable to Asian populations. In CT screening setting, risk stratification and implementation of appropriate follow-up CT intervals are required to reduce screening costs and radiation exposure [14,15].

By contrast, chest radiography is easily performed, has a negligible radiation dose and a low cost. In a previous randomized controlled trial (RCT) with 154,901 participants aged 55–74 years that evaluated the benefit of a chest radiography every year for 4 years, chest radiography did not appear to reduce mortality [16]. However, this study included 85% Caucasian and only 3.6% Asian participants, and the results may not be directly applicable to Asian lung cancer populations. Other RCTs of lung cancer screening using chest radiography failed to show a mortality reduction for radiographic screening, although the trials may have been subject to methodological limitations and a selection bias due to motivated participants [17–21]. Contrastingly, population-based cohort studies performed in Italy and Japan showed mortality reductions of 18–41% with chest radiography screening, and these trials were more likely to reflect real clinical scenarios [22–25]. The U.S. Preventive Service Task Force declared that the evidence for or against screening with chest radiographs is insufficient [26].

The Korean nationwide health service has offered a free biennial chest radiography screening to all residents aged 40 years or more [27], but the efficacy of this mostly biennial chest radiography screening has not been investigated. In this study, we investigated the effect of chest radiography surveillance on survival, using nationwide health service data from South Korea.

2. Materials and methods

2.1. Data sources and study population

Using data from the Korean National Health Insurance Service (NHIS) health examinee cohort, we identified 63,228 adults who were diagnosed with lung cancer between Jan 2004–Dec 2013. The Republic of Korea has a national health coverage system open to all residents; this provides health insurance for up to 97% of Korean people, and all eligible individuals and their dependents are offered the option to undergo a periodic (mostly biennial) general health examination. The National Health Examination followed a standard protocol with examinations being performed at local hospitals. Information on additional exams, including chest radiography, lung cancer diagnosis, and mortality during follow-up (until April 30, 2017), were obtained. The institutional review board of Asan Medical Center (Seoul, Republic of Korea) approved this study (approval number: 2015-0236). Also, the use NHIS database was provided by the NHIS of Korea (approval number: NHIS-2017-4-005). The requirement for informed consent from the NHIS health examinee cohort was waived.

Of 71,593 NHIS participants over the age of 18 years who diagnosed as lung cancer, those who had one or more of the following exclusion criteria were excluded: age at diagnosis $\geq$80 years (n = 2,772), age at diagnosis < 40 years (n = 1,268), and an interval between diagnosis and prior chest radiography of more than 3 years (n = 4,375). A total of 63,228 patients aged 40–79 years were finally included in this study (Fig. 1), and their mean sojourn time was analyzed.

Patients were dichotomized into those receiving chest radiography surveillance or those who received no surveillance. In the patients who received radiography surveillance, at least one chest radiograph was performed before lung cancer diagnosis, while if more than two chest radiography exams had been performed before the lung cancer diagnosis, the intervals of the chest radiography exams during the preceding years were subdivided as follows: < 1 year, $\geq$1 to < 2 years, $\geq$2 to < 3 years, and $\geq$3 years. In the surveillance group, the time interval between the last chest radiography surveillance and the date of lung cancer diagnosis was obtained to calculate the sojourn time.

Although the TNM stages were not available from the NHIS data, the treatment methods used for lung cancers were available, and the information was used to infer the cancer stages. The classifications of patients with respect to the treatment methods are presented in Supplementary Table 1: Class 1, localized stage (TNM IA, IB, and IIA); Class 2, regional stage 1 (TNM IIB); Class 3, regional stage 2 (TNM IIIA, IIIB, and IIIC); and Class 4, metastatic stage (TNM IV).

2.2. Korean cancer registration statistics and Korean National Health and Nutrition Examination survey

As the data from the Korean NHIS only contained information on the surveillance of patients, data from the Korean National Health and Nutrition Examination survey (KNHANES) were presented to assess the demographic features of the population. All KNHANES participants agreed to participate in the original survey through written informed consent. KNHANES is a cross-sectional survey designed to provide information regarding the civilian non-institutionalized Korean population. KNHANES data from 2010 covering 4363 patients from 40 to 79 years of age were included in the analysis. According to the KNHANES data from 2010, 87% of female participants (median age: 56, interquartile range: 48–67) and 14% of male participants were non-smokers. The incidences of other co-morbidities such as stroke, myocardial infarction, or chronic obstructive pulmonary diseases are presented in Supplementary Table 2.

2.3. Clinical outcome events and assessments

The primary outcome of the NHIS examinee cohort was the initial diagnosis of lung cancer at any stage. A secondary outcome was death from any cause. Events were assessed until April 30, 2017. The diagnosis of lung cancer was ascertained on the basis of the International Classification of Diseases 10th Revision codes (for lung cancer, C34, based on KCD-7/ICD-10). Complete recording of all events was assured because the NHIS and National Statistical Office include all Korean subjects.

2.4. Statistical analyses

Continuous data are presented as medians and ranges, and categorical variables as absolute or relative frequencies (percentages). The time intervals between the last chest radiography and the initial diagnosis of lung cancer were noted as the medians and ranges. Survival time was defined from the date of initial lung cancer diagnosis to date of death or end of follow-up (latest: end of study 30 April 2017). To accommodate lead-time bias, which could be shown as the improved survival in the surveillance group resulting from the earlier diagnosis in the disease course, lead-times for patients in the surveillance group were calculated prior to the lung cancer diagnosis. These lead-times were calculated using the parametric model proposed by Duffy et al. [28]. The calculated lead-times in the surveillance group patients were subtracted from the survival times.

Kaplan-Meier survival curves and log rank tests were performed to compare survival rates between surveillance and non-surveillance groups in all patients, male patients only, and female patients only. A Chi-square test was performed to evaluate the effect of appropriate surveillance intervals ($\leq$ 2 years of surveillance interval, i.e., biennial) for detecting early stages of lung cancer (Classes 1 and 2). Apart from the surveillance itself, the surveillance intervals, sex, age, smoking status, and lung cancer stage were also tested as possible indicators for

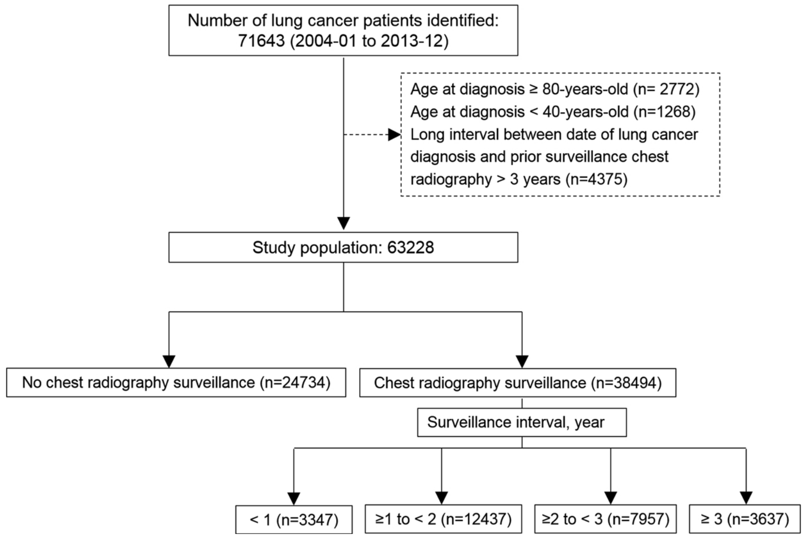

Fig. 1. Flow chart of patient inclusion and details of surveillance.

predicting overall mortality, with univariate and multivariate Cox-proportional hazard regression analysis being used for this analysis. All *P* values were 2-sided, with those < 0.05 being considered as statistically significant. SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

3. Results

3.1. Patients characteristics

The baseline characteristics of all included NHIS subjects are shown in Table 1. From 2004–2013, 63,228 lung cancer patients aged from 40 to 79 years were enrolled in the Korea NHIS database. Among these, 38,494 (60.9%) underwent lung cancer screening with chest radiography. The intervals for the chest radiography surveillance in the 38494 subjects were as follows: < 1 year (n = 3,347), ≥ 1 to < 2 years (n = 12,437), ≥ 2 to < 3 years (n = 7,957), and ≥ 3 years (n = 3,637), while in a further 11,116 (28.9%) subjects, chest radiography surveillance was performed only once before lung cancer diagnosis, and therefore the interval for chest radiography surveillance could not be obtained. The median time interval between the last chest radiograph and lung cancer diagnosis was 9.1 months (interquartile range: 2.5–17.2 months).

The percentage of patients of age > 65 was higher in the surveillance group than in the non-surveillance group in all patients (50.8% vs. 46.2%, $P < 0.001$) and male patients (53.9% vs. 47.5%, $P < 0.001$). In the female patients, the patients' ages were not statistically different between the surveillance and non-surveillance groups. In the female patients with surveillance, most of the patients (88.9%) were never-smokers.

In the surveillance group, the lung cancer stages were lower than in the non-surveillance group, in both the male and female patients ($P < 0.001$, both). Early stage lung cancer (Classes 1 and 2) was found in 38.7% of patients with surveillance and 26.4% of patients without surveillance. Classes 1 and 2 were more frequently detected in patients with appropriate surveillance intervals (< 2 years) than in patients with long screening intervals (≥ 2 years) ($P = 0.006$, Supplementary Table 3).

Table 1
Baseline characteristics of the 63228 lung cancer patients.

Group	All subjects			Male			Female		
Surveillance	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
No. of patients	24,734	38,494		17,524	28,119		7,210	10,375	
Age, median (range)	65 (57–70)	66 (59–71)	< 0.001	65 (58–70)	66 (60–72)	< 0.001	63 (55–71)	64 (56–70)	0.89
≤ 65 year, n (%)	13307 (53.8)	18927 (49.2)	< 0.001	9204 (52.5)	12978 (46.2)	< 0.001	4103 (56.9)	5949 (57.3)	0.57
> 65 year, n (%)	11427 (46.2)	19567 (50.8)		8320 (47.5)	15141 (53.9)		3107 (43.1)	4426 (42.7)	
CXR duration									
Only 1 CXR, y	–	11116 (28.9)		–	8279 (29.4)		–	2837 (27.3)	
< 1	–	3347 (8.7)		–	2741 (9.8)		–	606 (5.8)	
≥ 1 to < 2	–	12437 (32.3)		–	9058 (32.2)		–	3379 (32.6)	
≥ 2 to < 3	–	7957 (20.7)		–	5473 (19.5)		–	2484 (23.9)	
≥ 3	–	3637 (9.5)		–	2568 (9.1)		–	1069 (10.3)	
Class 1	4660 (18.8)	10688 (27.8)	< 0.001	2955 (16.9)	6704 (23.8)	< 0.001	1705 (23.7)	3984 (38.4)	< 0.001
2	1872 (7.6)	4213 (10.9)		1243 (7.1)	2853 (10.2)		629 (8.7)	1360 (13.1)	
3	787 (3.2)	1478 (3.8)		624 (3.6)	1154 (4.1)		163 (2.3)	324 (3.1)	
4	17415 (70.4)	22115 (57.5)		12702 (72.5)	17408 (61.9)		4713 (65.4)	4707 (45.4)	
Smoking status									
Unknown*	24734	491 (1.3)		17524	215 (0.8)		7210	276 (2.7)	
Never smoker	NA	13951 (36.2)		NA	4726 (16.8)		NA	9225 (88.9)	
Ex-smoker	NA	10382 (27.0)		NA	9987 (35.5)		NA	395 (3.8)	
Current smoker	NA	13670 (35.5)		NA	13191 (46.9)		NA	479 (4.6)	

Data are presented as numbers of patients and percentages in parenthesis, if not indicated. *If there was no information regarding smoking status, it was marked as unknown. CXR, chest radiography surveillance; NA, not available.

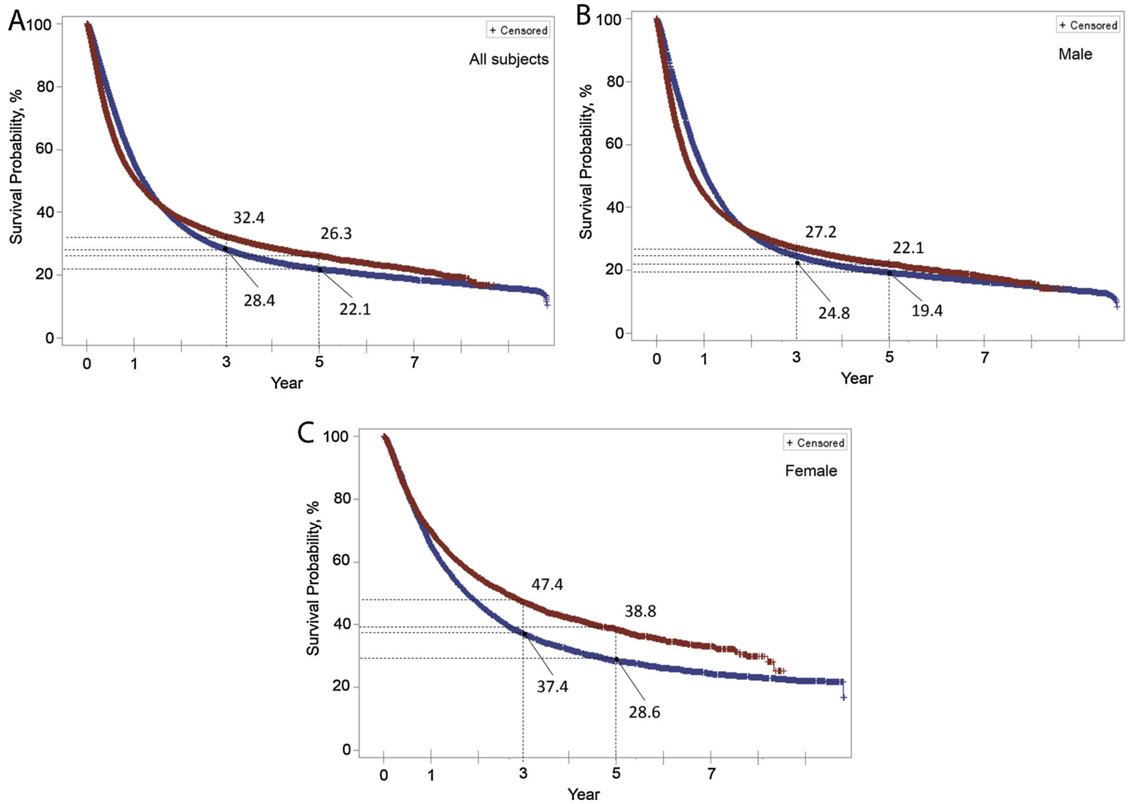

Fig. 2. Kaplan-Meier survival curves of the study population. The observed survival rates of lung cancer patients with (red line) and without chest radiography surveillance (blue line) are shown for (A) all patients, (B) males, and (C) females. Only the female group shows a survival gain ($P < 0.001$) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

3.2. Survival analyses

In total, 62.9% (n = 39,797) of patients died during follow-up. The 3- and 5-year survival rates were higher in the chest radiography surveillance group than in the non-surveillance group (32.4% and 26.3%, respectively, in the surveillance group vs. 28.4% and 22.1% in the non-surveillance group; Fig. 2A), although the differences were not statistically significant. Moreover, the two survival curves crossed-over at a follow-up time of 19.4 months, with the survival rates being lower in the surveillance group before the crossover point. In the male population, the 3- and 5-year survival rates were also higher in the surveillance group (27.2% and 22.1%, respectively, in the surveillance group vs. 24.8% and 19.4%, respectively, in the non-surveillance group) than in the non-surveillance group (Fig. 2B). However, the survival curves also crossed-over at 23.6 months of follow-up; these results need careful interpretation considering the fact that the median ages of the total surveillance and male patients groups were higher than those of the non-surveillance group. In the female group, significant survival benefit was noted in all the follow-up periods studied, with the 3- and 5-year survival rates being 10% higher in the chest radiography surveillance group than in the non-surveillance group (47.4% and 38.8%, respectively, in the surveillance group vs. 37.4% and 28.6%, respectively, in the non-surveillance group; Fig. 2C).

In the univariate analysis, a history of chest radiography surveillance, a patient age > 65, male sex, and advanced lung cancer stages were associated with increased mortality (Table 2). As the patients in the surveillance group were older than those in the non-surveillance group, it is difficult to observe the effect of surveillance itself without the influence of the age effect in all patients and male patients. However, in the female patients, the surveillance group demonstrated a significant survival benefit compared with the non-surveillance group (HR, 0.81; 95% CL, 0.77–0.84; $P < 0.001$).

In the surveillance group, a patient age > 65, male sex, advanced lung cancer stages, smoking status, and chest radiography surveillance intervals were associated with survival (Table 3). Never-smokers at the time of initial diagnosis had a significant survival gain compared with ex-smokers and current smokers (HR, 1.53; 95% CL, 1.48–1.59 for ex-smokers; and HR, 1.64; 95% CL, 1.60–1.70 for current smokers). The effects of a patient age > 65, male sex, advanced lung cancers stages, smoking status, and chest radiography surveillance intervals all remained significant factors in the multivariable analysis.

The subgroup analysis of male and female surveillance groups showed similar results (Supplementary Tables 4 and 5), with the only difference being that the effects of the chest radiograph surveillance intervals of < 1 year, ≥ 1 to < 2 years, and ≥ 2 to < 3 years were not statistically different in the univariate and multivariable analyses on female patients. A surveillance interval of < 3 years had a survival gain compared with an interval of ≥ 3 years (HR, 1.20; 95% CL, 1.12–1.43 for a surveillance interval of ≥ 3 years; Fig. 3).

4. Discussion

In this study, we assessed the effect of chest radiography surveillance in a nationwide population in South Korea. Early stage lung cancer (Classes 1 and 2) was found in 38% of patients receiving chest radiography versus 26% without surveillance. In patients with appropriate surveillance intervals (< 2 years), Classes 1 and 2 were detected more than in patients with long screening intervals (≥ 2 years). Chest radiography surveillance was shown to be a significant factor associated with decreased mortality in female patients, with a mortality reduction of 10% at the 3- and 5-year survival timepoints. In the female patients, chest radiography surveillance with an interval of less than 3 years was associated with improved survival.

According to the Korean national cancer registry for 2015, a total of

Table 2
Univariate analysis of prognostic factors affecting survival using a Cox-proportional hazard model in all, male, and female patients.

		All patients HR	95% CL	*P* value	Male HR	95% CL	*P* value	Female HR	95% CL	*P* value
CXR Surveillance	No	1			1			1		
	Yes	1.03	1.01–1.05	0.01	1.10	1.07–1.12	< 0.001	0.81	0.77–0.84	< 0.001
Age, y	≤65	1			1			1		
	> 65	1.53	1.50–1.56	< 0.001	1.48	1.44–1.51	< 0.001	1.56	1.49–1.62	< 0.001
Sex	Female	1			–	–	–	–	–	–
	Male	1.66	1.62–1.70	< 0.001	–	–	–	–	–	–
Class[a]	1	1		< 0.001	1		< 0.001	1		< 0.001
	2	2.08	1.97–2.20	< 0.001	1.72	1.61–1.83	< 0.001	3.76	3.33–4.26	< 0.001
	3	3.32	3.10–3.55	< 0.001	2.60	2.41–2.79	< 0.001	6.24	5.32–7.31	< 0.001
	4	10.30	9.89–10.72	< 0.001	7.99	7.65–8.36	< 0.001	21.16	19.18–23.34	< 0.001

[a] Class: 1, localized stage (IA, IB, IIA); 2, regional stage (IIB); 3, regional stage (IIIA, IIIB, IIIC); and 4, metastatic stage (IV). CL, confidence limits; CXR, chest radiography; HR, hazard ratio.

Table 3
Prognostic factors affecting patients' survival in the surveillance group according to a Cox-proportional hazard model.

Variables		Univariate HR	95% CL	*P* value	Multivariable HR	95% CL	*P* value
Age, y	≤65	1			1		
	> 65	1.64	1.60–1.69	< 0.001	1.53	1.48–1.59	< 0.001
Class[a]	1	1		< 0.001	1		
	2	2.20	2.04–2.37	< 0.001	2.15	1.96–2.36	< 0.001
	3	3.60	3.29–3.93	< 0.001	3.53	3.16–3.95	< 0.001
	4	11.67	11.05–12.31	< 0.001	11.19	10.45–11.97	< 0.001
Smoking status	Never smoker	1		< 0.001	1		< 0.001
	Ex-smoker	1.53	1.48–1.59	< 0.001	1.18	1.12–1.25	< 0.001
	Current smoker	1.64	1.60–1.70	< 0.001	1.22	1.16–1.29	< 0.001
Sex	Female	1			1		
	Male	1.92	1.85–1.99	< 0.001	1.36	1.29–1.45	< 0.001
CXR duration, y	< 1	1		0.002	1		0.002
	≥1 to < 2	1.04	0.99–1.10	0.14	1.07	1.01–1.13	0.014
	≥2 to < 3	1.05	0.99–1.11	0.11	1.11	1.05–1.17	< 0.001
	≥3	1.13	1.06–1.21	0.0003	1.11	1.04–1.19	0.002

[a] Class: 1, localized stage (IA, IB, IIA); 2, regional stage (IIB); 3, regional stage (IIIA, IIIB, IIIC); and 4, metastatic stage (IV). CL, confidence limits; CXR, chest radiography surveillance; HR, hazard ratio.

24,267 patients (17,015:7,252 = male:female) were newly diagnosed with lung cancer in South Korea in that year. As 13,204 patients were diagnosed with lung cancer in 1999, the incidence of lung cancer has shown a rapid increase [29]. In particular, in 2015 the incidence of female lung cancer had increased by 109% compared with the 3,466 patients diagnosed in 1999. In 1999, the mortality rate for female lung cancer patients was 11.2 per 100,000, and the mortality rate in 2015 increased to 18.5 per 100,000. Moreover, in 2015, 39.3% of male lung cancer patients and 5.5% of female patients were current smokers, which are significantly lower proportions than in the US population. As the incidence of female lung cancer is steadily increasing in South Korea, screening for lung cancer in non-smoker females is considered to be important. Lung cancer in non-smokers is known to be associated with Asian origin, female, and adenocarcinomas. However, until now, lung cancer screening has focused on those patients at high risk, with the criteria for selecting high risk groups focusing on those smokers with a history of over 20–30 pack-years; therefore, screening for lung cancer in the general population including non-smokers should be studied further.

Although the validity of extrapolating the results of the NLST to an Asian population has been reported in a recent study [30], only 2% (116 patients) of the study population were Asian, and the findings may not be representative of Asian lung cancers. Even though the genetic background of Asian in the NLST was similar to that in the general Asian population, the acquired characteristics including eating habits and environmental pollution may be different between the selected population in the NLST and the general Asian population. The percentage of non-smokers is higher in the Japanese population [4], and

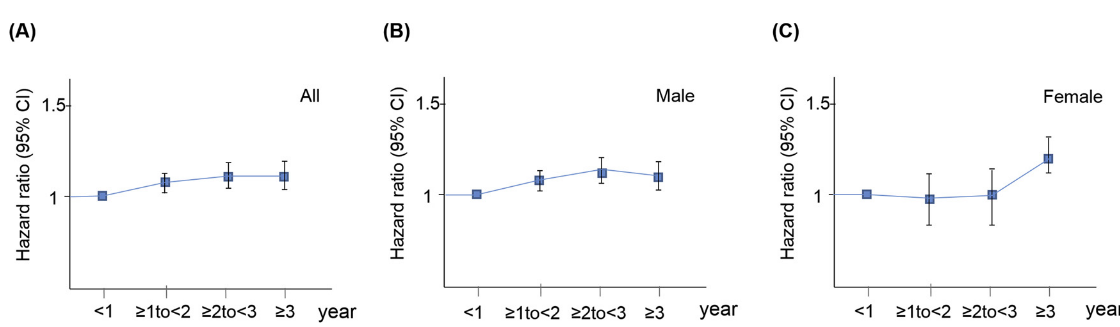

Fig. 3. Hazard ratios for mortality according to the surveillance intervals in (A) all, (B) male, and (C) female patients (multivariable analysis results). The x-axis indicates the surveillance intervals (years). CI, confidence interval.

more than one third of the Korean lung cancer population were never-smokers [3]. Furthermore, air pollution is an increasingly strong contributor to lung cancer among never-smokers in South Korea [31].

In this study, we focused on lung cancer screening of those who never smoked, Asian women, who had substantially slowly growing non-small cell lung cancer (NSCLC). More than one third of the Korean patients with NSCLC were never-smokers. NSCLC in never-smokers has different clinical characteristics and major driver mutations, which are associated with longer overall survival [3]. The differences in the frequency of EGFR mutations and response to gefitinib between Japanese and U.S. patients raise general questions regarding variations in the molecular pathogenesis of cancer in different ethnic, cultural, and geographic groups, and argue for the benefit of population diversity in clinical trials on cancer [6].

Notably, the Kaplan-Meier 3- and 5-year lung cancer survival rates in the female surveillance group were significantly greater (about 10% each) than in the control group, and this survival difference was independently related to chest radiography screening intervals. We consider that our public health policy recommendations for biennial chest radiography screening are suitable and sustainable, especially for females who have never smoked. In the total surveillance and male surveillance groups, the survival gain could not be evaluated because of the influence of the old-age of the surveillance group.

There are several limitations in this study. First, the limitations of observational studies, which include length bias, lead-time bias, and over-diagnosis bias [32]. Statistical methods to adjust for potential lead-time bias have been reported [28] and we used the formula of Duffy et al. However, the surveillance still had the potential for length-time bias. Second, the chest radiography surveillance intervals were variable because of the retrospective study design; however, we used this fact to determine the appropriate chest radiograph interval for deriving a survival gain in both male and female patients. Lastly, TNM lung cancer stages were not available, and therefore we used information on the treatment methods to infer the TNM stages. The strengths of our study include the large nationwide population cohort used to examine the effect of surveillance compared with non-surveillance. The healthy volunteer effect bias was also relatively smaller than in RCTs. Furthermore, this study has generalizability to the Korean population, with the participants being community-based according to the policy of the Health and Welfare of the Republic of Korea, and it may provide insight into Asian lung cancer screening.

In conclusion, although we could not confirm the survival benefit of chest radiography screening in male patients, chest radiography surveillance for the detection of female lung cancer showed decreased mortality, with a mortality reduction of 10% at the 3- and 5-year survival timepoints after lung cancer diagnosis. For the female population, nationwide chest radiography surveillance with intervals of less than 3 years was associated with earlier stage lung cancer and increased surgical resectability, and was an independent predictor of improved survival.

Author contributions

Kim Seulgi who is an expert statistician and Dr Choi C–M had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Kim MY and Choi C–M contributed equally as co-senior authors.

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Critical revision of the manuscript for important intellectual content: S. Park., H.N. Lee., W-J. Ji.

Statistical analysis: S. Kim., H.J. Koo.

Administrative, technical, or material support: S. Kim., D.K. Oh., W-J. Ji.

Study supervision: C–M. Choi., M.Y. Kim.

Final approval of the manuscript: H.J. Koo., C-M. Choi., M.Y. Kim.

Conflict of interest

None.

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Appendix A. Supplementary data

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