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Original Article

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Distribution of Lung-RADS categories according to job type in a single shipyard workers

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ABSTRACT

Background: Recently, lung cancer screenings based on age and smoking history using low-dose computed tomography (LDCT) have begun in Korea. This study aimed to evaluate the distribution of lung imaging reporting and data system (Lung-RADS) categories in shipyard workers exposed to lung carcinogens such as nickel, chromium, and welding fumes according to job type, to provide basic data regarding indications for LDCT in shipyard workers.
Methods: This study included 6,326 workers from a single shipyard, who underwent health examinations with LDCT between January 2010 and December 2018. Data on age, smoking status and history, medical history, and job type were investigated. The participants were categorized into high-exposure, low-exposure, and non-exposure job groups based on the estimated exposure level of nickel, chromium, and welding fumes according to job type. Cox proportional hazard regression analysis was used to determine the difference between exposure groups in Lung-RADS category ≥ 3 (3, 4A, and 4B).
Results: Out of all participants, 97 (1.5%) participants were classified into Lung-RADS category ≥ 3 and 7 (0.1%) participants were confirmed as lung cancer. The positive predictive value (ratio of diagnosed lung cancer cases to Lung-RADS category ≥ 3) was 7.2%. The hazard ratio (HR) of Lung-RADS category ≥ 3 was 1.451 (95% confidence interval [CI]: 0.911–2.309) in low-exposure and 1.692 (95% CI: 1.007–2.843) in high-exposure job group. Adjusting for age and pack-years, the HR was statistically significant only in the high-exposure job group (HR: 1.689; 95% CI: 1.004–2.841).
Conclusions: Based on LDCT and Lung-RADS, among male shipyard workers, Lung-RADS category ≥ 3 were significantly higher in the high-exposure job group. Their HR tended to be > 1.0 and was statistically significant in the high-exposure job group. Additional studies should be conducted to establish more elaborate LDCT indications for occupational health examination.

Keywords: Screening for lung cancer; Nickel; Chromium; Welding fume; Lung-RADS

BACKGROUND

According to the Korea Central Cancer Registry statistics, lung cancer was the third most cancer among all cancers in 2017 (second most cancer in men and fifth most cancer in women). The incidence of lung cancer has been increasing worldwide, including in Korea; it

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Abbreviations

ACR: American College of Radiology; ANOVA: analysis of variance; BMI: body mass index; CI: confidence interval; CT: computed tomography; CXR: chest X-ray; HR: hazard ratio; HRCT: high-resolution computed tomography; IARC: International Agency for Research on Cancer; ICER: incremental cost-effectiveness ratio; ILD: interstitial lung disease; LDCT: low-dose computed tomography; Lung-RADS: lung imaging reporting and data system; NCCN: National Comprehensive Cancer Network; NLST: National Lung Screening Trial; OR: odds ratio; PET-CT: positron emission tomography-computed tomography; PPV: positive predictive value; SUS: stainless steel.

Competing interests

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Chung EY. Data curation: Kim YW, Chae CH. Formal analysis: Park HO, Chung EY. Investigation: Chung EY, Woo SJ. Methodology: Park HO, Lee JH. Software: Chung EY, Woo SJ. Validation: Shin YH, Kim CW. Visualization: Son JS, Park SH. Writing - original draft: Chung EY. Writing - review & editing: Chung EY, Shin YH, Kim YW, Chae CH, Son JS, Kim CW, Park HO, Lee JH, Park SH, Woo SJ.

has increased from 13,180 newly diagnosed cases in 1999 to 26,985 newly diagnosed cases in 2017.[1,2] Lung cancer deaths among non-smokers in the US are estimated to be 17,000–26,000 per year, and the causes of these are related to factors such as secondhand smoke, indoor air pollution, and occupational exposure.[3] In 2000, lung cancer due to occupational exposure of all lung cancer deaths is estimated about 10% (88,000 deaths) in men and 5% (14,300 deaths) in women.[4] The International Agency for Research on Cancer (IARC) has announced lists of substances affecting cancer occurrence. Evidence suggest that nickel, chromium, and welding fumes have sufficient lung carcinogenicity (group 1 carcinogen).[5,6] There are various occupations in a shipyard, and they are exposed to various hazardous substances such as nickel, chromium, and welding fume, causing inflammation in the respiratory tract, and eventually causing pneumoconiosis, bronchitis, and chemical pneumonia, and they also reduces lung function and increases the risk of lung cancer.[7-9] In addition, production workers in shipyard had a higher incidence of lung cancer than office workers in shipyard, which cannot exclude the possibility of exposure to dangerous substances.[9]

The 5-year relative survival rate by the Surveillance, Epidemiology and End Results summary stage of lung cancer differs greatly according to the disease stage (69.0% in localized cancer and 39.3% in regional). The survival rate is expected to improve if cancer is detected early.[1] Recently, the National Lung Screening Trial (NLST) conducted in the US reported that performing lung cancer screening using low-dose computed tomography (LDCT) reduced mortality.[10] The American College of Radiology (ACR) reported that the ACR lung imaging reporting and data system (Lung-RADS), a classification system using a larger minimum nodule size than the NLST criteria, was more useful based on several findings—the false-positive rates decreased from 26.6% to 12.0%, positive predictive value (PPV), indicative of the actual proportion of lung cancer patients in the Lung-RADS category ≥ 3 (3, 4A and 4B), increased from 3.8% to 6.9%, and sensitivity decreased from 93.5% to 84.9%, but there was no change in the 5-year disease-specific survival.[11] Based on this finding, guidelines are being established regarding various indications for lung cancer screening. While most guidelines specify individuals aged ≥ 55 years with a smoking history of 30 pack-years as lung cancer screening targets,[12] the guidelines of the National Comprehensive Cancer Network (NCCN) and the American Association for Thoracic Surgery consider history of lung disease, family history of lung cancer, radon exposure, and occupational exposure as additional risk factors.[13,14] Regarding occupational exposure, people in workplaces exposed to lung carcinogens such as nickel and chromium are included, but the presented evidence is insufficient.[13]

Korea has been using LDCT for lung cancer screening and the partially modified ACR Lung-RADS for nodule classification and follow-up observation since 2019.[13,15] The screening is indicated for the high-risk lung cancer group among men and women aged 54–74 years. The high-risk group includes current smokers with ≥ 30 pack-years and other persons mentioned in the Public Notices by the Minister of Health and Welfare. There are no other groups designated as high-risk groups in lung cancer screening, but there might be other high-risk groups once a predictive model is established in future.[15]

According to the 2020 Practical Guidelines of Workers' Health Examination, exposure to lung carcinogens (nickel and chromium) should be examined at least once a year with assessment of the full occupational history, exposure history, and symptoms in addition to specialized health examinations, such as physical examinations, chest X-ray (CXR), and pulmonary function tests. The guidelines stipulate that if an abnormal finding is observed in primary screening, the workers should undergo secondary screening tests such as chest computed

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tomography (CT). Regarding exposure to welding fumes, chest CT is not included in the secondary screening.[16] Age and smoking history are considered in the Korea National Lung Cancer Screening Program, but not the substances with confirmed lung carcinogenicity such as nickel, chromium, and welding fumes.[15] Our study aimed to investigate the differences in Lung-RADS categories based on LDCT in shipyard workers according to their job types. The basic data provided by our study could help establish new criteria for adding occupational history to the Korea National Lung Cancer Screening Program in addition to age and smoking history and develop the LDCT screening criteria in which age and smoking history are considered in specialized health examination during primary screening.

METHODS

Study participants

Our study included 16,938 workers from a single shipyard in Gyeongnam who underwent health examination at a university hospital in Changwon between January 1, 2010, and December 31, 2018. They were classified into exposure and non-exposure groups. The exposure group consisted of workers exposed to nickel, chromium, and welding fumes; these patients underwent specialized health examination. The non-exposure group consisted of workers who did not have occupational exposure to hazardous factors based on assessment of their work environment; these patients did not undergo a specialized health examination. Of the 16,938 workers, female workers were excluded due to their small number (n = 1,394). Additionally, male participants who had missing information such as data job type, medical history, and smoking history (n = 4,754), those who had never undergone LDCT (n = 4,492), and those diagnosed with lung cancer before 2010 (n = 2) were excluded from the study. Finally, 6,326 participants were enrolled (3,106 in the exposure group and 3,220 in the non-exposure group), and a total of 12,672 LDCT results were examined.

General characteristics

The participants' general characteristics data were collected using a self-administered history-taking questionnaire. We used data from the most recent questionnaire survey. Hence, if the answers to medical history and smoking status were “no disease” and “do not smoke,” previous questionnaires were referred to. Age was defined as the age when the participant underwent LDCT for the first time. Regarding smoking history, participants were classified into non-smoking (≤ 5 packs in a lifetime), ex-smoking, and current-smoking groups, and the data in pack-years were computed. Data on medical history (hypertension, diabetes, or tuberculosis) were also collected using the questionnaire. We used the Ministry of Health and Welfare's criteria for high-risk drinking in men to categorize the participants into the high-risk drinking—binge-drinking monthly (≥ 7 glasses of soju in a single drinking session for ≥ 1 time per month in the past year) or high-risk drinking behavior (average alcohol consumption of ≥ 7 glasses of soju in a single drinking session for ≥ 2 times per week). Regarding body mass index (BMI), BMI ≥ 25 kg/m^2 was defined as obesity according the World Health Organization Asia-Pacific guidelines.

Occupation and exposure

The 2018 occupational environment assessment of the shipyard showed that the geometric mean exposure to welding fumes was 0.63 mg/m^3 (maximum value: 41.53 mg/m^3), to nickel was 0.88 $\mu g/m^3$ (maximum value: 73.00 $\mu g/m^3$), and to chromium was 1.38 $\mu g/m^3$ (maximum value: 63.60 $\mu g/m^3$). In the shipyard, CO_2 welding is primarily performed, but stainless steel (SUS) welding is also performed. In SUS welding, the welding electrodes and the base metal contain approximately 18% chromium and 8% nickel, and hence, exposure to nickel and chromium is high.[7,17,18] Regarding CO_2 welding, the accurate level of exposure from the welding electrodes cannot be determined since the wires are made of various materials.[18] However, the 2018 IARC report provides sufficient evidence regarding the lung carcinogenicity of welding fumes[5,19]; hence, CO_2 welding was also defined as a high-risk exposure job.

According to the job type, the exposure group was further divided into the high-exposure job group (welders and tack welders who primarily performed welding jobs and had a high-exposure to nickel, chromium, and welding fumes) and the low-exposure job group (workers performing other jobs, such as piping, outfitting, and production). Workers whose job type changed within 9 years were categorized into a group based on the job type with a longer duration.

LDCT result and Lung-RADS

Since the Korea National Lung Cancer Screening Program uses a modified version of the ACR Lung-RADS for Koreans, LDCT findings were analyzed according to the modified Lung-RADS. The categories of the modified Lung-RADS are the following: category 1, no nodules or definitely benign nodules; category 2, nodules with a very low suspicion of developing lung cancer and a likelihood to be malignant < 1%; category 2b, nodules that may correspond to categories 3 or 4 but are highly suspected to be benign considering the high tuberculosis prevalence in Korea; category 3, nodules with some suspicion of being benign but with a likelihood to be malignant ≥ 1%, requiring follow-up observation; category 4A, nodules suspected to be lung cancer with a likelihood to be malignant of 5%–15%, requiring additional testing or biopsy; and category 4B, nodules suspected to be lung cancer with a likelihood to be malignant > 15%, requiring further testing or biopsy.[15] The study hospital has been using the ACR Lung-RADS since 2017, and thus, nodule size and nodular pattern were confirmed by reviewing LDCT findings. Classifications into Lung-RADS category 2b were limited only to cases where the nodules were benign confirmed by the radiology department. Additionally, a finding other than nodules, such as fibrosis, was coded accordingly if the result was observed at least once. The follow-up of workers categorized into Lung-RADS category ≥ 3 included assessment of high-resolution computed tomography (HRCT) findings, positron emission tomography-computed tomography (PET-CT) findings, outpatient and surgical records. Workers who had never undergone follow-up testing or visited the outpatient clinic after the diagnosis of nodules categorized as Lung-RADS category ≥ 3 were coded as loss to follow-up.

LDCT was performed using SIEMENS SOMATOM Definition AS (Siemens Medical Solutions, Forchheim, Germany) and the following protocol: 120 kVP, 30 mAs (78 mA), rotation 0.5 seconds, collimation 0.6 mm, and pitch 1.0 until October 2017 and 120 kVP, 45 mAs (68 mA), rotation 1 seconds, collimation 0.6 mm, and pitch 1.0 after October 2017. The mean dose length product was 107.37 mGy*cm (74–154 mGy*cm), and the mean estimated effective dose was 2.36 mSv. The same radiologist evaluated all LDCT findings.

Statistical analysis

Continuous variables are reported as means with standard deviations, and categorical variables are reported as frequencies and percentages. Participants were classified into non-exposure, high-exposure job, or low-exposure job groups according to their job type. To examine the distribution of sociodemographic variables and LDCT results, one-way analysis of variance (ANOVA), the χ^2 test, or Fisher's exact test were used depending on the variable type and the number of variables. In addition, the χ^2 test or Fisher's exact test

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were used to examine the distribution of Lung-RADS category ≥ 3, which was considered a positive value in a study conducted to explore the screening effect of the ACR Lung-RADS.[9] Based on the findings, Cox proportional hazards regression was performed to evaluate the difference in the Lung-RADS category ≥ 3 according to exposure level. Regarding time to event, classification into the Lung-RADS category ≥ 3 was defined as the critical event, and data in person-months were used by calculating the time from the first screening to classification to the Lung-RADS category ≥ 3 or the last screening. Hazard ratios (HRs) were compared between groups after adjusting for age and pack-years, the most influential factors for the occurrence of lung cancer. Data were analyzed using the Statistical Package for Social Sciences for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Confidence interval (CI) was set at 95%, and the level of significance was set at $p < 0.05$ in all statistical analyses.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board (IRB) of Samsung Changwon Hospital before implementation (IRB File No. SCMC 2021-02-001).

RESULTS

General characteristics of study participants

Of the 6,326 participants, 3,220, 1,999, 1,107 participants and were categorized into the non-exposure, low-exposure, and high-exposure groups, respectively. The age range across all the participants was wide (22–68 years). The mean age was 39.12 ± 7.63 years, and mean person-months was 27.31 ± 31.31. Regarding the amount of smoking, the maximum pack-years was 92, and the mean pack-years was 9.13 ± 8.85. A total of 149 (2.4%) participants smoked ≥ 20 pack-years, and a total of 2,787 (44.1%) participants were current smokers. There were significant differences in age, person-months, pack-years, and smoking status, among the 3 groups, but not in the group of participants who smoked ≥ 20 pack-years. Of the total participants, 2,116 (33.4%) participants had hypertension, 473 (7.5%) participants had diabetes, 235 (3.7%) participants had tuberculosis, 1,939 (31.0%) participants had high-risk drinking, and 2,707 (42.8%) participants had obesity. Significant differences were found among the 3 groups in most of categories, except for tuberculosis (**Table 1**).

Table 1. General characteristics of study participants

Variables	Total (n = 6,326)	Unexposed (n = 3,220)	Exposed		*p*-value
			Low (n = 1,999)	High (n = 1,107)	
Age (years)	39.12 ± 7.63	38.56 ± 7.74	40.08 ± 7.59	39.01 ± 7.19	< 0.001[a]
Person-months	27.31 ± 31.31	21.64 ± 28.98	32.92 ± 32.40	33.67 ± 32.76	< 0.001[a]
Smoking					
Pack-years	9.13 ± 8.85	8.10 ± 8.35	10.36 ± 9.41	9.89 ± 8.86	< 0.001[a]
Pack-years over 20	149 (2.4)	71 (2.2)	56 (2.8)	22 (2.0)	0.260
Smoking status					0.012
No[b]	1,667 (26.4)	865 (26.9)	496 (24.8)	306 (27.6)	
Ex-smoker	1,872 (29.6)	976 (30.3)	612 (30.6)	284 (25.7)	
Current	2,787 (44.1)	1,379 (42.8)	891 (44.6)	517 (46.7)	
History and others					
Hypertension	2,116 (33.4)	944 (29.3)	768 (38.4)	404 (36.5)	< 0.001
Diabetes	473 (7.5)	216 (6.7)	178 (8.9)	79 (7.1)	0.012
Tuberculosis	235 (3.7)	108 (3.4)	78 (3.9)	49 (4.4)	0.231
At-risk drinking[c]	1,939 (31.0)	510 (16.2)	897 (45.0)	532 (48.1)	< 0.001
BMI over 25 kg/m²	2,707 (42.8)	1,438 (44.7)	842 (42.1)	427 (38.6)	0.002

Data are shown as mean ± standard deviation or number (%). The *p*-value was analyzed by χ^2 test.
[a]The *p*-value was analyzed by one-way analysis of variance; [b]Lifetime smoking history ≤ 5 packs; [c]Monthly binge-drinking (≥ 7 glasses of soju in a single drinking session ≥ 1 time per month in the past 1 year) or high-risk drinking (an average alcohol consumption of ≥ 7 glasses of soju ≥ 2 times per week).

LDCT results of study participants

In total, 12,672 LDCT studies were performed. Of them, 5,819 LDCT studies were performed in 3,220 participants in the non-exposure group (mean studies: 1.81 ± 1.71), 4,367 LDCT studies were performed in 1,999 participants in the low-exposure group (mean studies: 2.18 ± 1.33), and 2,486 LDCT studies were performed in 1,107 participants in the high-exposure group (mean studies: 2.25 ± 1.40). A one-way ANOVA showed that the between-group difference in the distribution was significant ($p < 0.001$).

Regarding the distribution of Lung-RADS categories in all participants, 3,890 (61.5%), 2,227 (35.2%), 112 (1.8%), 52 (0.8%), 26 (0.4%), and 19 (0.3%) participants were categorized into Lung-RADS categories 1, 2, 2b, 3, 4A, and 4B, respectively. The overall distribution of Lung-RADS categories was significantly different among the 3 groups. The χ^2 tests conducted in the individual Lung-RADS categories showed significant between-group differences in all categories, except Lung-RADS category 4 (RADS 1: $p = 0.003$; RADS 2+2b: $p = 0.032$; RADS 3: $p = 0.014$; RADS 4A+4B: $p = 0.194$). Regarding LDCT findings other than the Lung-RADS category, fibrosis was most common finding in 1,417 (22.4%) participants. Additionally, other findings such as emphysema, atelectasis, and tuberculosis sequelae were observed. The distribution of emphysema, atelectasis, tuberculosis sequelae, asbestosis showed significant between-group differences (**Table 2**).

Follow-up of Lung-RADS over 3

Ninety-seven (1.5%) participants were categorized into Lung-RADS category ≥ 3; there were significant differences in the distribution of Lung-RADS category ≥ 3 among the 3 groups ($p = 0.005$). Of the 97 participants, 11 participants were lost to follow-up. Of the remaining 86 participants who were followed up, 79 participants were reclassified into Lung-RADS category ≤ 2b (1, 2, or 2b) after additional testing because either the nodule size remained the same or nodules were confirmed to be benign and 7 participants were diagnosed with lung cancer. In the Lung-RADS category ≥ 3, the overall PPV was 7.2%. The PPV was 5.9% in the

Table 2. Low-dose computed tomography result of study participants

Variables	Total (n = 6,326)	Unexposed (n = 3,220)	Exposed		*p*-value
			Low (n = 1,999)	High (n = 1,107)	
Lung-RADS					0.006
1[b]	3,890 (61.5)	2,045 (63.5)	1,196 (59.8)	649 (58.6)	
2[c]	2,227 (35.2)	1,085 (33.7)	732 (36.6)	410 (37.0)	
2b[d]	112 (1.8)	56 (1.7)	33 (1.7)	23 (2.0)	
3[e]	52 (0.8)	16 (0.5)	23 (1.1)	13 (1.2)	
4A[f]	26 (0.4)	10 (0.3)	11 (0.6)	5 (0.5)	
4B[g]	19 (0.3)	8 (0.2)	4 (0.2)	7 (0.6)	
Other Result					
Fibrosis	1,417 (22.4)	691 (21.5)	469 (23.5)	257 (23.2)	0.187
Emphysema	699 (11.0)	299 (9.3)	253 (12.7)	147 (13.3)	< 0.001
Atelectasis	433 (6.8)	188 (5.8)	166 (8.3)	79 (7.1)	0.003
Tb sequelae	240 (3.8)	96 (3.0)	87 (4.4)	57 (5.1)	0.001
Bronchiectasis	224 (3.5)	109 (3.4)	76 (3.8)	39 (3.5)	0.730
Pneumonia	194 (3.1)	92 (2.9)	64 (3.2)	38 (3.4)	0.578
Active Tb	43 (0.7)	21 (0.7)	10 (0.5)	12 (1.1)	0.160
ILD	15 (0.2)	6 (0.2)	6 (0.3)	3 (0.3)	0.691
Asbestosis	5 (0.1)	0 (0.0)	4 (0.2)	1 (0.1)	0.021[a]

Data are shown as number (%). The *p*-value was analyzed by χ^2 test.
ILD: interstitial lung disease; Lung-RADS: lung imaging reporting and data system; Tb: tuberculosis.
[a]The *p*-value was analyzed by Fisher's exact test; [b]No nodules or definitely benign nodules; [c]Nodules with a very low likelihood of becoming lung cancer; [d]Nodules with a high probability of being benign although they may correspond to Lung-RAD category 3 and 4; [e]Nodules with some likelihood of being benign but requiring follow-up observation; [f]Nodules suspected for lung cancer and requiring additional testing or biopsy, with a probability of malignancy between 5% and 15%; [g]Nodules suspected for lung cancer and requiring further testing or biopsy, with a likelihood of malignancy > 15%.

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Table 3. Follow-up of Lung-RADS category ≥ 3

Variables	Total (n = 6,326)	Unexposed (n = 3,220)	Exposed		*p*-value
			Low (n = 1,999)	High (n = 1,107)	
Lung-RADS ≥ 3	97 (1.5)	34 (1.1)	38 (1.9)	25 (2.7)	0.005[a]
Follow-up					0.466[b]
Lung-RADS ≤ 2b[c]	79 (81.4)	28 (82.4)	35 (92.1)	16 (64.0)	
Cancer	7 (7.2)	2 (5.9)	2 (5.3)	3 (12.0)	
Follow-up loss	11 (11.4)	4 (11.7)	1 (2.6)	6 (24.0)	

Data are shown as number (%).
Lung-RADS: lung imaging reporting and data system.
The *p*-value was analyzed by [a]χ^2 test or [b]Fisher's exact test; [c]Nodules without a change in size on follow-up CT, nodules with a high likelihood of benignity, or newly observed solid nodules small in size.

Table 4. Cox proportional hazard regression test at job exposure and Lung-RADS over 3

Group	Model 1[a]		Model 1[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
Unexposed	1.000		1.000		1.000	
Exposed						
Low	1.451	0.911–2.309	1.327	0.833–2.114	1.303	0.819–2.074
High	1.692	1.007–2.843	1.679	0.999–2.823	1.689	1.004–2.841

Lung-RADS: lung imaging reporting and data system; CI: confidence interval; HR: hazard ratio.
[a]Job risk only; [b]Adjusted for age; [c]Adjusted for age and pack-year.

non-exposure group and 7.9% in the exposure group (5.3% in the low-exposure group and 12.0% in the high-exposure group). The mean age of participants classified into Lung-RADS category ≥ 3 was 43.59 ± 8.21, and the mean pack-years was 15.20 ± 11.85. The between-group difference in the distribution of Lung-RADS category ≥ 3 was not statistically significant according to one-way ANOVA. The Fisher's exact test was used to evaluate follow-up results after excluding the participants lost to follow-up, but the between-group difference was not statistically significant (**Table 3**).

Cox proportional hazard regression test at job exposure and Lung-RADS over 3

A critical event was defined as Lung-RADS category ≥ 3, and Cox proportional hazard regression was performed to evaluate the presence or absence of exposure and its level. Model 1 examined the effect of the job type only. We adjusted for age and pack-years, the 2 most important risk factors for lung cancer, as follows: in Model 2, age was added to Model 1, and in Model 3, age and pack-years were added to Model 1. In Model 1, the HR was 1.451 ($p = 0.117$) and 1.692 ($p = 0.047$) in the low- and high-exposure groups, respectively. In Model 3, which was adjusted for age and pack-years, the HR of the low-exposure group was 1.303, which not statistically significant ($p = 0.264$). In contrast, the HR of the high-exposure group was 1.689, which was statistically significant ($p = 0.048$). Additionally, the HRs of age and pack-years were 1.074 (95% CI: 1.044–1.105) and 1.038 (95% CI: 1.021–1.055), respectively, and both were statistically significant ($p < 0.001$) (**Table 4**).

In addition, a stratified analysis of smoking status was performed in Model 3. First, when pack-years were analyzed by dividing it into 0, less than 20, and more than 20, the HRs of the low- and high-exposure group were 1.279 (95% CI: 0.803–2.037) and 1.647 (95% CI: 0.979–2.773). The HRs of less than 20 and more than 20 pack-years was 0.949 (95% CI: 0.543–1.656) and 2.805 (95% CI: 1.617–4.866). When stratified analyzing by the non-smoking, ex-smoking, and current-smoking group according to smoking status, the HRs of the low- and high-exposure group were 1.323 (95% CI: 0.831–2.106) and 1.699 (95% CI: 1.010–2.857), and HRs of the ex- and current-smoking group were 1.293 (95% CI: 0.727–2.301) and 1.606 (95% CI: 0.931–2.771).

DISCUSSION

The incidence of lung cancer has been increasing in Korea.[1] Compared to the incidence of small cell lung cancer and squamous cell carcinoma, the lung cancer types strongly associated with smoking, that of adenocarcinoma has increased markedly worldwide, including in Korea.[2,20,21] Because adenocarcinoma tends to occur in the peripheral area of the lungs,[2] the role of chest CT is becoming more important than that of bronchoscopy. A meta-analysis based on various studies was conducted to examine the reduction in lung cancer mortality with early diagnosis; lung cancer mortality was not significantly decreased when lung cancer screening was performed using CXR, regardless of whether a sputum culture test was performed.[22] Therefore studies have been conducted to evaluate the use of LDCT, but its effect was not evidenced in European trials such as the detection and screening of early lung cancer with Novel imaging Technology and the Danish Lung Cancer Screening Trial.[12] Recently, the US NLST showed that the lung cancer-specific mortality decreased by approximately 20% and the overall mortality decreased by 6.7% in the LDCT group compared to the CXR group (comparison group).[10] It is speculated that such findings were obtained in the NLST because compared to other trials, the sample size in the NLST was larger, and the NLST had a longer follow-up period and the smoking history criterion was stricter; hence, more lung cancer cases were detected.[10,12]

Although the effect of the LDCT lung cancer screening in reducing mortality has been demonstrated, its cost-effectiveness should be confirmed before using it at the national level. The incremental cost-effectiveness ratio per life year (ICER) refers to the cost required to prolong life by a year, and the ICER of the LDCT lung cancer screening is estimated to be $23,586 in Korea and $52,000 in the US. In Korea, the willingness-to-pay threshold is $27,512, and thus, the Korea National Lung Cancer Screening Program is believed to be cost-effective.[23] Lung cancer screening is performed according to a variety of criteria in other countries too. Additional studies should be performed to develop diverse criteria appropriate to each situation, rather than merely age and smoking history.[24]

The appropriate definition of the high-risk lung cancer group is another area where research is needed to maximize the cost-effectiveness of lung cancer screening. The NCCN guidelines recommend lung cancer screening in persons aged > 50 years with a smoking history of ≥ 20 pack-years and additional risk factors (NCCN group 2 indication) as only 27% of all lung cancer patients would be indicated for screening according to the NLST criteria (age > 55, smoker with a smoking history of ≥ 30 pack-years).[13] The calculated mean relative risk for the development of lung cancer was 1.59 in workplaces with exposure to lung carcinogens such as chromium and nickel,[25] and almost 90% of prevented deaths were observed in persons with a baseline risk of at least 1.24% in the NLST. Thus, it was speculated that lung cancer screening would be effective in NCCN group 2 with a baseline risk of > 1.3%.[13]

Regarding the effect of lung cancer screening in different job types, a study focusing on the incidence of lung cancer in welders and foundry workers among the NLST participants reported that the HR was 1.12 (95% CI: 0.91–1.37) in welders with ≥ 1-year experience and 1.09 (95% CI: 0.85–1.39) in foundry welders with ≥ 1-year experience. In addition, the study reported that the HRs examined separately for each job type were not significant, while the HR of participants who had worked in both jobs was 1.48 (95% CI: 1.08–2.04), showing a significant increased risk of lung cancer.[26] In a study which analyzed the 2000–2013 health screening data of US nuclear weapon workers, the lung cancer screening rate was 1.50% (22 of 1,471, 95% CI: 0.88–2.12) in the workers who met the NLST criteria and 1.36% (27 of 1,979, 95% CI: 0.85–1.87) in the workers who did not meet the NLST criteria and fit the NCCN group 2 indication. The researchers of the study speculated that as the lung cancer detection rates were higher than the NLST's screening rate 1.03% (270 of 26,309, 95% CI: 0.88–1.22), the NCCN group 2 indication, which considers occupational history, might be effective in early detection of lung cancer.[27]

Lung-RADS category ≥ 3 is a group that estimates that the probability of lung cancer is at least 1%.[10,15] For category 3, follow-up LDCT is recommended after 6 months, and for category 4, follow-up tests such as biopsy, HRCT, and PET-CT after 3 months depending on the pattern are recommended.[10] In NLST, 1,763 patients with RADS 3 were found, 108 patients had lung cancer after 7 years of follow-up, and 41 patients died due to lung cancer. The importance of the Lung-RADS category ≥ 3 can be confirmed in that the rates of lung cancer in the 6 month follow-up LDCT group and non-group were 7.5% and 3.1%, and specific lung cancer death was 4.0% and 1.0%.[28] Lung-RADS is classified by the type, shape and size of the nodule. In Korea, the prevalence of tuberculosis is high, and tuberculosis can appear as an uncalcified nodule by forming granulomas in the lungs, which can increase the false-positive rate.[29] When analyzing the results of LDCT in Korea using ACR Lung-RADS, the positive rate in Korea was 16.4% (1,868 of 11,394) and the false-positive rate was 15.9% (1,804 of 11,329). Compared to NLST positive rate 13.6% (3,604 of 26,455) and false-positive rate 12.8% (3,343 of 26,090), the false-positive rate was higher.[29] Therefore, Lung-RADS 2b was newly established to reduce the false-positive rate.

In this study, the HR was > 1.0 in the job groups exposed to nickel, chromium, and welding fumes. The HR in the high-exposure job group, consisting of welders and tack welders, was 1.689 and was statistically significant even after adjusting for age and pack-years. These findings are in line with previous study findings showing that in shipyard workers, exposure to carcinogens such as nickel, chromium, and hard metal dust as well as asbestos exposure were associated with lung cancer[2] and that the odds ratio (OR) of lung cancer in persons with an occupational history of being a welder was 1.44 (95% CI: 1.25–1.67); the OR increased with increasing work experience.[6] In this study, the entire working period from the date of enter the company was checked. Since the subjects are regular workers, the correlation with age was very high (Pearson correlation coefficient 0.810, $p < 0.01$). Therefore, in case of adjusting working period in Model 3 instead of age, HR for working period was significant as 1.059 (95% CI: 1.031–1.087), and the exposure group showed similar results. But adding working period to Model 3, the HR of working period was 1.016 (95% CI: 0.977–1.056), the HR of low-exposure group was 1.258 (95% CI: 0.785–2.015), and the HR of high-exposure group was 1.637 (95% CI: 0.968–2.765), and they were not significant. This is thought to be the result of not properly reflecting job changeover and job change by investigating the entire working period, not the specific job type period. Although it is necessary to assess indices such as mortality reduction to determine the effect of lung cancer screening in practice,[30] it is believed that the current study finding provides evidence supporting the need for LDCT lung cancer screening in welders and tack welders.

The lung cancer pathophysiology is very complicated and has not yet been completely understood. The most representative hypothesis is that normal epithelial cells in the respiratory system become dysplastic if repeatedly exposed to carcinogens such as cigarette smoke. It is speculated that continued exposure to such carcinogens leads to genetic mutation, affecting protein synthesis and interfering with cell cycles, eventually causing cancer.[31] Although the precise mechanism underlying the impact of nickel, chromium, and welding fumes is unknown, it is speculated that repeated exposure to these substances at high concentrations poses a risk via the mechanism mentioned above. This speculation is supported by a patient-control study on 3,418 German lung cancer patients between 1988 and 1996, in which the analysis on the impact of above-median exposures to welding fumes (1.8 $mg/m^3 \times$ years), nickel (9 $\mu g/m^3 \times$ years), and chromium (VI) (1.4 $\mu g/m^3 \times$ years) in lung cancer showed that the OR for welding fumes was 1.55 (95% CI: 1.17–2.05), the OR for nickel was 1.60 (95% CI: 1.21–2.12), and the OR for chromium (VI) was 1.85 (95% CI: 1.35–2.54).[32]

Since it was not possible to confirm the degree of exposure of each subject, it was checked whether there was a difference in exposure between occupation groups using the occupational environment assessment data measured by job type. According to the 2018 occupational environment assessment of the shipyard, 2,429 workers were assessed for welding fumes, 5,792 workers were assessed for nickel, and 5,791 workers were assessed for chromium. In welders and tack welders, the geometric mean exposure to welding fumes was 0.78 ± 0.99 mg/m^3, to nickel was 1.86 ± 6.48 $\mu g/m^3$, and to chromium was 1.47 ± 2.87 $\mu g/m^3$. In workers of all the other job types, such as cutters and production workers, the geometric mean exposure to welding fumes was 0.45 ± 0.49 mg/m^3, to nickel was 0.57 ± 1.73 $\mu g/m^3$, and to chromium was 1.35 ± 1.79 $\mu g/m^3$. When comparing the level of exposure between job type by the independent t-test, there was a statistically significant difference between welding fume and nickel ($p < 0.001$), but not chromium ($p = 0.06$). However, there is an overall difference in exposure to dangerous substances between job type, so we believed that it is appropriate to categorize exposure levels by job type.

Based on job type categorization, the HR tended to be higher in the high-exposure job group (Model 1 HR: 1.692, Model 2 HR: 1.679, Model 3 HR: 1.689) than in the low-exposure job group (Model 1 HR: 1.451, Model 2 HR: 1.327, Model 3 HR: 1.303) in all models. This finding is consistent with previous studies that not only the presence of exposure, but also the level of exposure.[21,32] Therefore, it is believed that lung cancer should be screened not only based on the presence or absence of exposure but also based on more specific criteria such as job type and exposure level.

Lung cancer is a serious public health concern in Korea. It ranked the first in the occupational cancer compensation insurance claims from 2010 to 2016, with 581 of 1,299 claimants being lung cancer patients.[33] However, currently, the Korea National Lung Cancer Screening Program is indicated only for current smokers aged 54–74 years with a smoking history of ≥ 30 pack-years[15]; there is no separate regulation for LDCT screening indications for workers. According to the 2020 Practical Guidelines of Workers' Health Examination, the primary screening in specialized health examination related to lung carcinogens such as nickel and chromium includes history-taking regarding occupational history, exposure history and symptoms, clinical examinations, CXR, and pulmonary function tests. If an abnormal finding is observed in the primary screening, the guidelines recommend a sputum culture test and chest CT. Regarding exposure to welding fumes, chest CT is not included in the secondary screening.[16] Recently, an increasing number of studies have demonstrated the effect of LDCT lung cancer screening.[10,24] Affirmative study findings regarding lung cancer screening of persons exposed to nickel, chromium, and welding fumes were reported.[26] Thus, screening for workers exposed to high-risk substances for which lung carcinogenicity has been demonstrated should be expanded.

First, the addition of a chest CT may be considered in the secondary screening in health examination concerning welding fumes, which is had lung carcinogenicity.[5,19] Second, the effect of lung cancer screening based on NCCN group 2 indication,[11] which considers occupational history, should be investigated. In this study, the distribution of Lung-RADS categories based on LDCT was different according to the job type ($p < 0.001$), and in particular, a significant difference was observed in the distribution of Lung-RADS category ≥ 3 (the category in which the likelihood of lung cancer is ≥ 1%) ($p = 0.005$). These findings are believed to confirm the need for further studies to develop detailed criteria for primary LDCT screening, which considers exposure level and job type as well as age and smoking history like the NCCN lung cancer screening guidelines,[13] rather than the current Workers' Health Examination's primary screening based on the presence or absence of exposure.

A limitation of this study was that indices to evaluate the effect of lung cancer screening in practice were not studied. In our research, the positive value (Lung-RADS category ≥ 3) was significantly high in the high-exposure job group. Also, the PPV, a representative index in assessing the effect of lung cancer screening,[10,11,30] was higher in the exposure group (7.9%) than in the non-exposure group (5.9%), and the PPV in the exposure group was higher than that of the original NLST (3.8%)[10] and that obtained when the NLST results were converted to the ACR Lung-RADS (6.9%).[11] However, the between-group difference in the proportion of loss to follow-up was large, the size of Lung-RADS category ≥ 3 and the number of lung cancer patients were small, and the follow-up was based only on the medical history-taking, outpatient records, and test results; it was not based on accurate data on cancer occurrence. Further, the most important factors, smoking history and occupational history, were assessed using a self-administered questionnaire, and hence, there may have been various confounding variables, including erroneous recall. As for the time-related problem, there is a possibility that there is a risk from the first participation because the time and age of entry into the study are different for each subject, and the mean person-month was short, 27.31 ± 31.31, there were limitations in identifying important pathological changes in individuals. Lastly, because all participants were full-time workers, i.e., eligible for comprehensive health examination, there were possibilities of the effect of healthy workers (that only healthy persons can continue working) and subject bias (that health-conscious persons tend to volunteer to undergo LDCT). Due to these impacts, the mean age of the participants was 39.12 years, and the mean pack-years was 9.13, thus, not meeting the criteria for the NCCN group 2 indication[13] (age > 50 and ≥ 20 pack-years). Thus, there was a limitation in analyzing the actual effect of lung cancer screening due to a small number of cases.

Nevertheless, this study has a few strengths. Because it was a single-institution study, LDCT reading and Lung-RADS assessment were consistent. This study is the first study in South Korea that investigated job type and LDCT Lung-RADS. Further, the sample was large (n = 6,326). Finally, the study used LDCT, the same method used in the Korea National Lung Cancer Screening Program, which will be useful in the future when performing comparative analysis on the results of the Korea National Lung Cancer Screening Program.

CONCLUSIONS

Using the current screening method and diagnostic criterion of the national lung cancer screening, LDCT, and Lung-RADS, this study found that a significantly high proportion of male shipyard workers with occupational exposure to nickel, chromium, and welding

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fumes (exposure group) were classified into Lung-RADS category ≥ 3 and that the risk was increased in the high-exposure group. The effect of the lung cancer screening in the high-exposure group was not demonstrated by the current study finding alone; the need for LDCT lung cancer screening in workers exposed to high levels of nickel, chromium, and welding fumes was confirmed based on previous research (which showed a difference in lung cancer occurrence based on job type) and our study (which showed a difference in Lung-RADS categories according to job type). In the future, prospective research should be conducted to develop a job matrix by the exposure level and evaluate the mortality reduction due to an early lung cancer screening. Thus, it will be possible to establish primary LDCT screening indications in workers exposed to nickel, chromium, and welding fumes.

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