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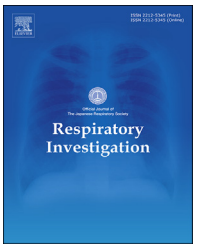

Original article

Results of 10-year mobile low-dose computed tomography screenings for lung cancer in Shimane, Japan

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ABSTRACT

Background: Some randomized controlled trials have evaluated the effects of low-dose computed tomography (CT) screening on lung cancer mortality in heavy smokers. Based on the results of those trials, our CT screening program recommended screening for people aged ≥40 years with a history of smoking. This retrospective study aimed to verify the validity of our CT screening program and elucidate the current state of CT screening program.

Methods: We retrospectively examined lung cancer detection in 25,189 participants who underwent chest CT screening by a mobile low-dose CT screening unit in the 10-year period from April 2009 to March 2019. Participants were recruited at Japan Agricultural Cooperatives (JA) Shimane Kouseiren. Participants requested CT screening for lung cancer. CT images were read by two pulmonologists.

Results: Lung cancer was identified in 82 of the 25,189 participants over 10 years, an overall lung cancer detection rate (percentage of lung cancers detected among all participants) of 0.33%. Lung cancer among never smokers accounted for 54.9% of the detected cases. The lung cancer detection rate was similar for smokers versus never smokers. The stage IA detection rate (percentage of stage IA lung cancers among all lung cancers detected) was 62%, while the stage IV detection rate was 10%.

Conclusions: Chest CT detected lung cancer in never smokers as well as current or former smokers. Our CT screening program was not effective for never smokers; thus, further study of the effectiveness of CT screening in never smokers is needed.

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1. Introduction

Lung cancer is the leading cause of cancer death in Japan. Reducing lung cancer mortality is one of Japan's top public health and medical care priorities. Efforts to de cancer at an early stage are expected to contribute to reducing its mortality. Cancer screening in Japan includes organized and opportunistic screening. Early lung cancer detection efforts using chest X-rays have been promoted as organized screening [1–3], but their effectiveness has been limited. Therefore, there is a perceived need for screening that detects lung cancer sooner.

Lung cancer screening using computed tomography (CT) was first attempted in Japan in 1993. Kaneko et al. [4] and Sone et al. [5] reported in the 1990s that low-dose CT screening has excellent ability to detect early lung cancer. In Japan, multiple randomized controlled trials (RCTs) [6–8] evaluated the effectiveness of CT screening. The National Lung Screening Trial (NLST) [6], the largest lung cancer trial conducted to date in the United States, showed that CT screening reduces lung cancer mortality. NLST targeted approximately 53,000 people aged 55–74 years with a history of heavy smoking (≥30 pack-years). Lung cancer mortality was reduced by 20% and all-cause mortality was reduced by 7% in the group who underwent low-dose chest CT for lung cancer screening; both reductions were statistically significant. Based on this result, lung cancer screening using low-dose CT has been included in public screenings in the United States since 2015.

The results of a Dutch-Belgian lung cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) were reported in 2020 [9]. This population-based RCT with 15,822 participants targeted people with a smoking history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years. Lung cancer mortality was reduced by 24% in the group that underwent low-dose CT examinations versus the group that did not undergo CT examinations. Two large RCTs showing the effectiveness of low-dose CT lung cancer screening have been published to date; however, few have examined the effectiveness of CT screening in never smokers [10,11]. Lung cancer mortality rates among never smokers are very low among Westerners, but lung cancer mortality rates are known to be high among Asian never smokers, including those in Japan [12]. Thus, in Japan and the rest of Asia, it will be necessary to verify the effectiveness of CT screening in never smokers in the future.

In Japan, results from the NLST and NELSON were positively accepted, but CT examinations are still performed opportunistically because they are recommended for middle-aged and elderly people with a history of heavy smoking. Our department formed a CT screening group (Japan Agricultural Cooperatives [JA] Shimane Kouseiren Lung CT with JA Shimane Kouseiren [known collectively as JASKLCT]). Since 2009, we have conducted opportunistic chest CT screenings using a mobile low-dose CT screening unit for the early detection of lung cancer. Here we report the results of 10 years of CT screenings.

2. Patients and methods

2.1. Participant recruitment

JA Shimane Kouseiren has a screening division that conducts a wide range of screening services. This screening division sends information about CT screenings to JA Shimane Kouseiren members in each municipality in Shimane Prefecture and recommends CT screening. In addition, it is possible to add CT screening as an option to occupational medicine examinations conducted by JA Shimane Kouseiren. JA Shimane Kouseiren also provides information on CT screenings to users of facilities it co-sponsors. Those who wish to undergo a CT screening can apply to JA Shimane Kouseiren and schedule the examination at a mobile low-dose CT screening unit at a designated date and time. No indications were required for those who wished to undergo the screening. After the announcement of the NLST results in 2011, our CT screening program recommended screening for individuals aged 40 years old or older with a history of smoking. However, it was difficult to completely apply the NLST results in the Japanese setting, so never smokers were allowed to participate if desired.

2.2. CT protocol

All screenings were performed using a car-mounted 4-row multi-slice CT scanner (ELCOS, Hitachi-city, Ibaraki, Japan). The imaging conditions were 120 kV tube voltage, 50 mA tube current, and 5-mm collimation. We performed the CT scans

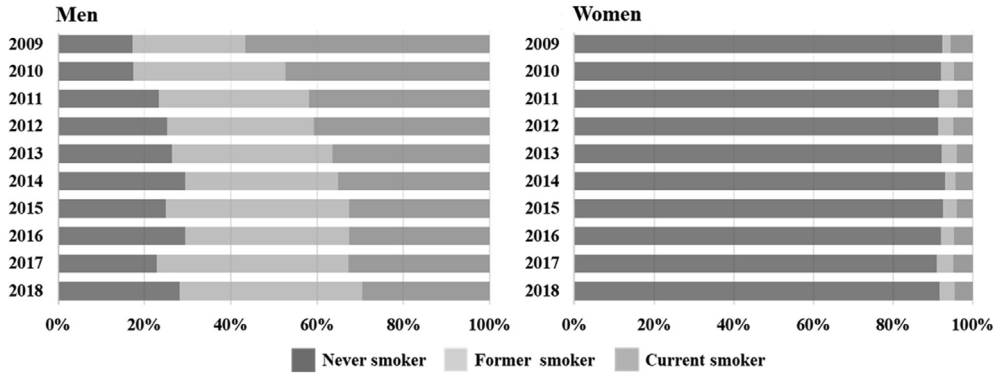

Fig. 1 – Smoking status of the study participants. Current or former smokers accounted for more than 50% of male participants except in 2009. Female participants were mostly never smokers, with less than 10% being current smokers.

from the apex of the lungs to below the diaphragm. The radiation exposure dose was approximately 1.0 mSv. The CT images were created using iterative reconstruction.

2.3. Detection of candidate nodules

The CT images were read by two pulmonologists separately for the primary and final evaluations. Physicians performing the final evaluation were board-certified by the Japanese Society of CT Screening or the Japanese Respiratory Society. The pulmonologists did not use computer-aided detection. Mean evaluation time was 1–2 min per CT examination. The judgment of lung nodule shadows detected by the CT screening was based on the third edition of the Pulmonary Nodule Judgment Criteria for Lung Cancer Screening by Low-Dose CT and Concept of Follow-up by the Japanese Society of CT Screening [13] until 2011 and on the fourth edition [14] starting in 2012. The lung nodule management algorithm was based on the Guidelines for Pulmonary Nodules Management, Version 3 by the Japanese Society of CT Screening (Supplementary 1).

If the CT images did not yield positive findings, the participant received a "no abnormality" notification and instructed that subsequent CT screenings were optional.

2.4. Definite diagnosis

If any lesion required a more detailed examination, JASKLCT mailed the results to the participants and recommended a visit to a hospital to see a doctor who was board-certified by the Japanese Respiratory Society. A high-resolution CT was performed at the specialty hospital, Followed by a histological examination was performed as needed. Histopathologically diagnosed lung cancer was defined as a confirmed case. Doctors who were board-certified by the Japanese Respiratory Society at that hospital filled out a report form with information about lesion location, lesion size, histology, stage (postoperative stage for those treated surgically), and treatment details for each confirmed case of lung cancer.

3. Results

3.1. Overview

Over the 10-year period, a total of 25,189 individuals underwent screenings (13,686 men, 10,503 women) (Table 1). The number of participants increased each year, reaching nearly 4000 in 2016. The median participant age was 57 (range, 21–87) and 58 (range, 21–89) years in 2009 and 2010, with participants under 50 years of age accounting for nearly 30% of all screening participants. Since 2011, the median age has been between 61 and 67 years; 85% of participants have been over 50 years of age.

3.2. Smoking status

Fig. 1 shows the participants' smoking status. Current or former smokers accounted for more than 50% of the male participants except in 2009. Most females were never smokers, with less than 10% being current smokers.

3.3. Lung cancer detection

Over the 10-year screening period, 2518 (10.0%) participants required detailed examinations, of whom 847 were required to undergo a detailed examination due to suspected lung cancer (Table 2). Of the participants with suspected lung cancer, 82 were diagnosed with lung cancer at a hospital with doctors who were board-certified by the Japanese Respiratory Society for an overall cancer detection rate of 0.33%. Of the participants with suspected lung cancer, 9.7% actually received the diagnosis. Lung cancer occurred in 46 men and 36 women, with a median age of 69 (range, 45–89) years. There were 37 (45.1%) cases of lung cancer among current and former smokers (Table 3). Table 4 shows detected lung cancers by smoking status. Lung cancer in current and former smokers was more common in men, while lung cancer in never smokers was more common among women. Since most female participants were never smokers, the observed detection rate of lung cancer was similar for both smokers and never smokers by smoking status. Some advanced lung cancers were detected in male smokers. The most common histological type of lung cancer, adenocarcinoma, was found in 66 participants (81%). Squamous cell carcinoma was found in nine participants (11%). By Union for International Cancer Control stage (seventh edition) criteria, there were 52 stage IA cases and eight stage IB cases. Stage I cancer accounted for 73% of all lung cancer cases, but there were 8 (10%) stage IV cases (Supplementary 2).

4. Discussion

JACKLCT has conducted low-dose CT screenings using a mobile low-dose CT screening unit since 2009 aiming for the early detection of lung cancer. Based on the NLST results, our CT screening program recommended that people aged ≥40 years with a history of smoking undergo screening. However, most of the study's female participants were never smokers. Lung cancer was detected in never smokers as well as current or

Table 1 – Characteristics of screening participants by year.

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Number of participants	1112	1280	1794	2512	2594	2954	2170	3903	2818	4052	25,189
Male sex (n)	632	733	865	1552	1484	1647	1133	2084	1381	2175	13,686
Female sex (n)	480	547	929	960	1110	1307	1037	1819	1437	1877	10,503
Median age, range (years)	57 (21–87)	58 (21–89)	63 (23–90)	61 (23–92)	63 (22–90)	66 (23–92)	67 (24–91)	67 (31–95)	67 (40–94)	67 (39–95)	61 (21–95)
Aged over 40 years (n)	1014	1159	1695	2409	2532	2948	2169	3900	2818	4051	24,695

Table 2 – Number of participants who required a detailed examination.

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Number of participants who required detailed examination, n (% of all participants)	240 (21.6)	274 (21.4)	378 (21.1)	323 (12.8)	170 (6.6)	376 (12.7)	205 (9.4)	404 (10.3)	230 (8.2)	322 (7.9)	2518 (10.0)
Number of participants with suspected lung cancer, n (% of all participants)	16 (1.4)	48 (3.8)	82 (4.6)	77 (3.1)	71 (2.7)	129 (4.4)	84 (3.9)	165 (4.2)	91 (3.2)	84 (2.1)	847 (3.4)

former smokers. Although no conclusions have been reached regarding the effectiveness of CT screening in never smokers, lung cancer detection rates are reportedly high in female never smokers in Japan [15,16]. The effectiveness of CT screening in never smokers was also reported by some cohort studies [10,11]. These results suggest that it might be more appropriate to recommended CT screenings in Japan according to age rather than smoking history. An RCT of low-dose lung CT screenings in groups who are not at high risk (smoking index <600) is currently underway [17]. Our current CT screening program might not be effective for never smokers, and it is possible that it might require modification according to the findings of that RCT.

At the beginning of the screening period, the number of participants was small, approximately 1000 per year. However, since the NLST results were published in 2011, the JASKLCT aimed to improve public awareness of the CT screening. As a result, the number of participants increased. The overall required detailed examination rate for screening was 10.0%. This rate is higher than the target values of 8% or less for the initial screening and 5% or less for repeated screening recommended in the first edition of the Japanese Society of CT Screening Quality Management guidelines. The reason for the high required rate of detailed examinations is that clinically significant findings other than pulmonary nodules (e.g., emphysematous changes in symptomatic smokers, symptomatic interstitial shadows, suspected thyroid tumors, and aorta aneurysm) detected by screening also required detailed examinations. The required detailed examination rate for suspected lung cancer only was 3.4%, which met the target value of the guidelines. In addition, the examination accuracy of this screening was considered appropriate. The lung cancer detection rate was 0.36%, comparable to those of previous reports [15,16,18,19] (Table 5). Since young people in their 20s and 30s were included, the lung cancer detection rate was examined in participants in their 40s or above but did not change (Table 3).

The JACKLCT CT screening program is characterized by the following three points: (1) cooperation with JA Shimane Kouseiren, (2) use of a mobile low-dose CT screening unit, and (3) interpretation by two pulmonologists. By cooperating with the health examination division of JA Shimane Kouseiren, the JASKLCT encouraged union members to undergo consultations and added CT screening as an option during occupational health examinations conducted by the health examination division to ensure the recruitment of a wide range of participants.

The mobile low-dose CT screening unit made it possible to provide mobile individuals who have difficulty undergoing examinations during hospital business hours an opportunity to undergo CT screening. Shimane Prefecture spans 230 km from east to west, and there are substantially fewer medical institutions in the western part of the prefecture than in the eastern part. Thus, the mobile low-dose CT screening unit provided opportunities for medical examinations to people in areas with limited access to medical institutions.

CT images are usually interpreted by radiologists; the evaluation of CT images by two pulmonologists is rare. Pulmonologists commonly determine which cases required further examination or treatment for respiratory diseases other than lung cancer based on clinical practice. As a result, the early treatment for diseases such as chronic obstructive pulmonary disease and interstitial pneumonia has become possible. In this study, the interpretation by two pulmonologists made it possible to perform these CT screening as an extension of the respiratory examination.

This study also clarified some problems with the JASKLCT screening protocol. The first is participant age, while the second is advanced-stage lung cancer detection. In 2009 and 2010, the CT screenings were conducted without any age restrictions; the median age was 57 (range, 21–87) and 58 (range, 21–89) years, respectively; many young participants were included. Since 2011, CT screenings have been recommended for people aged 60 years or older, who are considered to be at

Table 3 – Lung cancer detection.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Number of lung cancers detected (n)	1	4	10	6	9	17	10	10	10	5	82
Male sex (n)	0	3	2	3	6	13	6	5	4	4	46
Female sex (n)	1	1	8	3	3	4	4	5	6	1	36
Lung cancer detection rate (%)	0.09	0.31	0.56	0.25	0.35	0.58	0.46	0.26	0.35	0.12	0.33
Lung cancer detection rate in participants aged >40 years (%)	0.10	0.34	0.59	0.24	0.36	0.58	0.46	0.26	0.35	0.12	0.33
Current and former smokers with detected lung cancer, n (% of participants with lung cancer detected)	0 (0.0)	2 (50.0)	2 (20.0)	3 (50.0)	6 (66.7)	8 (47.1)	6 (60.0)	4 (40.0)	3 (30.0)	3 (66.7)	37 (45.1)

Table 4 – Lung cancer detection by sex and smoking status.

	Male		Female	
	Non-smoker	Smoker	Non-smoker	Smoker
Cases of lung cancer detected (n)	9	37	32	4
Rate of cancer detection by smoking status (%)	0.26	0.36	0.33	0.43
Stage (I/II/III/IV)	9/0/0/0	19/8/3/6; unknown: 1	28/1/1/2	4/0/0/0
Median age (years)	72.5	62.5	65.5	75

Table 5 – Comparison with previous reports.

	Age (years)	Cancer detection rate (%) First screening Repeated screening	Stage IA detection rate (%) First screening Repeated screening
Sobue et al. [16]	40–79	0.87	71
		0.28	82
Sone et al. [13]	40+	0.42	91
		0.45	86
Henschke et al. [17]	60+	2.7	81
		0.59	71
Nawa et al. [14]	50–69	0.44	78
		0.07	100
Hamaguchi et al. (current study)	21–95	0.33	63

high risk for lung cancer. A low lung cancer detection rate has been reported for CT screenings conducted mainly in young people with a median age of 40 years [20]. Thus, it is necessary to maintain the median age as 60 years or older to maintain the detection rate in our screening program. One problem with the JASKLCT screening was that approximately 10% of participants were in their 20s and 30s (Table 1). Considering that the minimum age of lung cancer detected by screening is 45 years and the issue of radiation exposure, it is necessary to set a minimum age for screening.

Regarding lung cancer detection, the rate of stage IA lung cancer cases in this study was 63%, slightly lower than previously reported (Table 5). A certain number of stage IV lung cancers were also detected each year, with no decreasing trend. One possible reason for the discovery of advanced cancers is that new participants were undergoing examinations every year. In the JASKLCT screening program, about 20% of all participants were new each year. In addition, interval cancer might have affected the high detection rate of stage IV lung cancer cases. The screening program did not set any rules regarding the inter-screening interval. The number of progressive cancer cases tends to decrease after repeated screening, but the number of advanced cancers may not have decreased because some participants were only screened a few times. It will be necessary to determine an appropriate screening interval in the future.

5. Conclusion

Here we examined the results of 10 years of CT screening using a mobile low-dose CT screening unit in Shimane Prefecture for detecting lung cancer. This study clarified that lung cancer can be detected in never smokers as well as current or former smokers. However, CT screening program was based on NLST results, which may not be effective for never smokers. We believe that it is necessary to continue studying the effectiveness of CT screening in never smokers, as our program may require modification accordingly. Problems with this screening program, such as how to manage young people who wish to undergo CT screening and the inter-screening interval, require addressing. To ensure high-precision CT screenings, the JASKLCT will continue to review its results and lung cancer detection rate annually. We are also working on quality control by examining the program's performance.

Conflict of Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resinv.2021.10.001.

REFERENCES

[1] Nishii K, Ueoka H, Kiura K, Kodani T, Tabata M, Shibayama T, et al. A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer 2001;34:325–32.
[2] Okamoto N, Suzuki T, Hasegawa H, Gotoh T, Hagiwara S, Sekimoto M, et al. Evaluation of a clinic-based screening

program for lung cancer with a case-control design in Kanagawa, Japan. Lung Cancer 1999;25:77–85.
[3] Tsukada H, Kurita Y, Yokoyama A, Wakai S, Nakayama T, Sagawa M, et al. An evaluation of screening for lung cancer in Niigata Prefecture, Japan: a population-based case-control study. Br J Cancer 2001;85:1326–31.
[4] Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral Lung cancer screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798–802.
[5] Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–5.
[6] Aberle DR, Adams AMBC, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening - the national lung screening trial research team. N Engl J Med 2011;365:395–409.
[7] Van Iersel CA, De Koning HJ, Draisma G, Mali WPTM, Scholten ET, Nackaerts K, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer 2007;120:868–74.
[8] Field JK, Van Klaveren R, Pedersen JH, Pastorino U, Paci E, Becker N, et al. European randomized lung cancer screening trials: post NLST. J Surg Oncol 2013;108:280–6.
[9] De Koning HJ, Van Der Aalst CM, De Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020;382:503–13.
[10] Nawa T, Nakagawa T, Mizoue T, Kusano S, Chonan T, Hayashihara K, et al. A decrease in lung cancer mortality following the introduction of low-dose chest CT screening in Hitachi, Japan. Lung Cancer 2012;78:225–8.
[11] Nawa T, Fukui K, Nakayama T, Sagawa M, Nakagawa T, Ichimura H, et al. A population-based cohort study to evaluate the effectiveness of lung cancer screening using low-dose CT in Hitachi city, Japan. Jpn J Clin Oncol 2019;49:130–6.
[12] Thun MJ, Hannan LM, Adams-Campbell LL, Boffetta P, Buring JE, Feskanich D, et al. Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. PLoS Med 2008;5:1357–71.
[13] The Japanese Society of CT Screening. https://www.jscts.org/pdf/guideline/gls3rd120719.pdf. [Accessed 27 September 2021].
[14] The Japanese Society of CT Screening. https://www.jscts.org/pdf/guideline/gls4th201611.pdf. [Accessed 27 September 2021].
[15] Sone S, Li F, Yang ZG, Honda T, Maruyama Y, Takashima S, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001;84:25–32.
[16] Nawa T, Nakagawa T, Kusano S, Kawasaki Y, Sugawara Y, Nakata H. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow up studies. Chest 2002;122:15–20.
[17] Sagawa M, Nakayama T, Tanaka M, Sakuma T, Sobue T. A randomized controlled trial on the efficacy of thoracic CT screening for lung cancer in neversmokers and smokers of <30 pack-years aged 50-64 years (JECS study): research design. Jpn J Clin Oncol 2012;42:1219–21.
[18] Sobue T, Moriyama N, Kaneko M, Kusumoto M, Kobayashi T, Tsuchiya R, et al. Screening for lung cancer with low-dose helical computed tomography: anti-Lung Cancer Association project. J Clin Oncol 2002;20:911–20.
[19] Henschke CI, Naidich DP, Yankelevitz DF, McGuinness G, McCauley DI, Smith JP, et al. Early lung cancer action project: initial findings on repeat screening. Cancer 2001;92:153–9.
[20] Yokochi T. Practical management of low-dose lung CT screening, in the case of health support center WELPO. J Thorac CT screen 2016;23:13–25 [in Japanese].