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An evaluation of chest X-ray screening for lung cancer in gunma prefecture, Japan: a population-based case–control study

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Abstract

In order to evaluate the efficacy of annual chest X-ray screening for lung cancer, a case–control study was conducted in Gunma Prefecture, Japan. Population-based annual lung cancer screening programmes have been conducted by the local government in Gunma Prefecture since the mid-1970s. A total of 121 case subjects, including 91 high-risk males and 30 non-high-risk females between the ages of 40 and 79 years who died of lung cancer from 1992 to 1997 were evaluated. A total of 536 controls (3–5 controls for each case) were matched to case subjects by gender, year of birth, address and smoking habits. Controls were selected from screening programme lists provided by the local governments. All case subjects were also included on these lists. The smoking-adjusted odds ratio (OR) of lung cancer death for those subjects screened within 12 months prior to diagnosis versus those not screened was 0.68 (95% confidence interval (CI): 0.44–1.05; $P=0.084$). When the analysis was conducted without matching case and control subjects by smoking habits, the OR was 0.79 (95% CI: 0.53–1.18). When stratified by histological type, the OR was 0.62 (95% CI: 0.31–1.24) for adenocarcinoma, and 1.01 (95% CI: 0.44–2.31) for squamous cell carcinoma. The results of this study suggest 20–30% of deaths attributable to lung cancer, especially adenocarcinoma, might be prevented by annual chest X-rays.

Keywords: Lung cancer; Screening; Case–control study

1. Introduction

Currently, there is little evidence to indicate that annual chest X-ray examinations (CXE) can significantly reduce mortality from lung cancer. The Mayo Lung Project (MLP) is one of the largest randomised lung cancer studies in the world. The MLP compared results of regular lung cancer screening (consisting of chest X-ray and sputum cytology) every 4 months with sporadic screening every year, and did not show a reduction in mortality [1]. It must be noted, however, that the MLP had several methodological problems, including compliance of only 75% of the screened group, contamination of 50% of the control group, and limited statistical power (a 48% probability of detecting a 20% reduction in lung cancer mortality) [1]. The Johns Hopkins Lung Project (JHLP) as well as the Memorial Sloan-Kettering Lung Project (MSKLP) investigated the effect of sputum cytology screening (in conjunction with CXE) on lung cancer mortality. Both studies failed to yield conclusive results [2,3]. Survival rates for both control groups (CXE only and CXE with sputum cytology) in each study (5-year survival of 35% in the JHLP and 8-year survival of 20% in the MSKLP) were each higher than the 5-year survival rate of 10% reported in the Surveillance, Epidemiology and End Results (SEER) programme in the United States [4].

Marcus and colleagues recently reported that extended follow-up of MLP participants did not reveal decreased mortality from lung cancer in the screened group, although a case survival difference was observed [5]. The authors stated that the MLP's methodological problems could not have masked a true mortality benefit

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and that the findings of improved survival in the screened arm could be explained by 'lead time bias' and 'overdiagnosis bias'. However, some problems, not explained by these biases, still remained in the follow-up data. For example, there was a higher incidence of adenocarcinoma in the screened group (59 cases) compared with the control group (38 cases), but a survival benefit was not observed among patients with adenocarcinoma in the screened arm [6]. Therefore, results from the MLP must be carefully interpreted.

Conversely, in a case–control study conducted in Japan in the 1980s, Sobue and colleagues found that lung cancer screening could reduce mortality by 28% [7]. However, this association was not statistically significant. In a more recent study, Okamoto and colleagues reported that annual screening could significantly reduce lung cancer mortality by 46% [8].

The present study, based on a case–control model, was designed to evaluate the efficacy of chest X-ray screening in reducing mortality due to lung cancer. Observational studies, including case–control studies, are subject to bias. It was therefore important for our study to be designed to reduce bias [9].

2. Patients and methods

2.1. Study setting

The Japanese government, under the Tuberculosis Control Law, has offered annual chest X-ray screening to all residents aged 16 years or older since the 1950s. Local governments and employers define and manage these screening programmes. The study area consisted of four municipalities in Gunma Prefecture, where lung cancer screening programmes have been conducted for residents aged 40 years or older by the local government since the mid-1970s. These programmes were based on the aforementioned tuberculosis screening system.

2.2. Screening programme

All residents aged 40 years or over were mailed invitations to the screening programme from the local government. Screening consisted of a chest X-ray in the posteroanterior view obtained by miniature photofluorography with a mirror camera. The energy of the X-ray beam was 120–140 kV. The fluorescent image was intensified through a mirror lens and photographed on a 100×100 mm ortho-type film. Chest X-ray films were independently examined by two medical doctors who specialised in miniature chest X-ray interpretation. Any abnormal findings were verified by reviewing the patient's films from previous years, except when these films were not available. Further examinations were conducted for cases with suspected lung cancer. These tests included conventional chest X-ray, tomography, and bronchoscopy.

This screening system is considered to be the standard for lung cancer screening programmes in Japan. On the other hand, tuberculosis screening programmes offered by employers usually do not have adequate quality control (low energy of X-beam, lack of review of previous films, etc.).

2.3. Source population

In this study, the source population was defined as all residents, aged 40 years or over, who were either self-employed (farmers, retailers, etc.) or unemployed (retired people, etc.). Although all residents are listed on the local government's screening programme lists, employed residents are rarely screened by governmental agencies because employers offer other screening programmes, for tuberculosis. Since the list for each screening programme was created independently by each municipality, data collection for each area was initiated at different times. Data collection from one municipality began in 1991, two municipalities began in 1992, and another municipality began in 1993. Data collection continued in all participating municipalities until 1996. These lists were used in the selection of case and control subjects.

At the beginning of the study period, 45 642 male and 47 072 female residents between the ages of 40 and 79 years who were either unemployed or self-employed were defined as the source population. As attendance rates for fixed cohorts could not be obtained for each year, dynamic cohort attendance rates, for individuals aged 40–79 years, were calculated from annual local government reports (Table 1). These calculated rates were considerably higher than average lung cancer screening attendance rates in Japan.

2.4. Case subject identification

Case subjects were defined based on the following criteria:

A. The subject lived in the study area and was included on the screening programme list from the beginning of the study period;
B. The subject was diagnosed with lung cancer during the study period;
C. The subject died of lung cancer between the age of 40 and 79 years;
D. The subject was not employed for at least 12 months prior to lung cancer diagnosis.

Case subjects could not be directly selected from the screening programme lists because death certificates

Table 1
Study population and screening attendance rates during the study period

	Study population at the beginning of the study period	Screening attendance rates during the study period (%)				
		1992	1993	1994	1995	1996
Ohta City	63 361	57.2	61.3	60.9	52.0	51.8
Ojima[a]	7226	–	89.4	84.4	85.5	86.5
Nitta	13 931	77.1	82.1	84.1	84.0	85.0
Yabuzuka	8196	81.0	84.7	87.1	85.2	84.7
Total	92 714	62.7	68.7	68.5	62.4	62.4

[a] Data analysis began here in 1993.

were not included with computerised screening programme data. Therefore, potential cases were first identified through the examination of death certificates. Based on the information from the death certificates, cases that met the above qualifications (B–D) were then confirmed on the screening programme lists.

A medical record review was performed to determine whether individuals met the case subject criteria [10] and to exclude individuals whose examinations were given due to symptoms possibly related to lung cancer, which would lead to a bias in estimating screening efficacy [11].

The rates of non-smoking in males and smoking in females are quite low in Japan. Therefore, in order to increase the efficiency of matched control identification on the basis of smoking habits, cases were limited to high-risk males and non-high-risk females. The definition of high-risk was 600 or more on the smoking index (average number of cigarettes smoked per day multiplied by the number of years of regular smoking). Ex-smokers were included in the study, regardless of when they had quit smoking.

A total of 382 deaths due to lung cancer, based on the cause of death indicated on the death certificate, were identified from all residents in the study area between April 1992 and May 1997 (Table 2). Of them, 261 case candidates were excluded for the following reasons.

83 cases were excluded because they were either aged less than 40 years or more than 79 years at the time of death. For the remaining 299 case candidates, information about smoking habits, histological type, date of diagnosis, and date of appearance of symptoms related to lung cancer were collected from previous medical records and/or interviews with a family member. Cough or sputum continuing for only a few weeks, most likely due to a cold, was not regarded as a symptom related to lung cancer. 15 cases were excluded after medical record review revealed that the actual cause of death was another disease, such as pulmonary metastasis of a

Table 2
Flowchart of the identification process for case and control subjects

Case subjects	
Death certificate due to lung cancer	382 subjects
extract	
those who under 40 or over 79 years old at the time of diagnosis	83
those whose deaths were not validated from lung cancer	24
those who were diagnosed before the study period	68
those who may have had another screening [a]	61
those who belonged to the non-high-risk male or high-risk female groups	21
those who could not be matched with a control	4
Total remaining	121 subjects
Control subjects	
Matched control candidates with each case subjects (gender, year of birth, address)	1300 subjects
extract	
those who were not living before the diagnosis of corresponding case[b]	68
those who may have had another screening[c]	130
those whose smoking habits could not be obtained[d]	224
those who belonged to the non-high-risk male or high-risk female groups	240
those whose order was beyond the 5th control to the corresponding case	102
Total remaining	536 subjects

[a] Those who were employed within 12 months prior to the date of diagnosis had a chance to participate in another chest X-ray screening programme.

[b] Nine of them had moved into the study area after the corresponding case had been diagnosed and 59 died or moved out before the corresponding case had been diagnosed.

[c] Those who were employed within 12 months prior to the date of diagnosis of the corresponding case had a chance to participate in another chest X-ray screening programme.

[d] Sixteen deceased control families refused to answer and 208 control candidates could not be contacted.

different cancer. The date of lung cancer diagnosis could not be determined due to loss of previous medical records for another 9 cases. An additional 68 case candidates were found to have been diagnosed before the study period and were excluded because prior screening histories could not be obtained. 61 other cases were excluded because they had been employed during the 12 months prior to diagnosis. Smoking indexes were calculated from medical records for the remaining 146 case candidates. Among the males, 16 cases were excluded because they were determined to be in the non-high-risk group. 5 female case candidates were also excluded because they were in the high-risk group. 4 additional cases were excluded because matched controls could not be found (Table 2).

A total of 121 cases met all the criteria for case subjects and were considered suitable for this study.

2.5. Control subject identification

For each case subject, between 10 and 18 control candidates were selected from the screening programme lists. These control candidates were matched with a case subject by gender, year of birth (within 2 years) and address (administrative district). When enough control candidates could not be found in the same district as the corresponding case, control candidates were selected from adjacent districts.

In total, 1300 control candidates were selected. Of these candidates, 198 were excluded for the following reasons. 9 were excluded because they had moved into the study area after their corresponding case had been diagnosed. 59 additional control candidates were excluded because they had either died or moved out of the study area before their corresponding case had been diagnosed. An additional 130 were excluded because they were employed within the 12-month period prior to when their corresponding case was diagnosed.

The remaining 1102 control candidates were contacted by telephone or by mail and asked to answer a number of questions regarding their smoking habits until 5 appropriate control subjects for each case were obtained. When the control candidates were unavailable, the questions were put to their families. 16 deceased control candidates, whose families refused to answer the questions, were excluded. Another 208 control candidates were excluded because they could not be contacted by mail or by phone. Additionally, 235 males were excluded because they belonged to the non-high-risk group, and 5 females were excluded because they belonged to the high-risk group. Finally, in order to keep the number of matched controls for each case subject within five, 102 excess control candidates were excluded (Table 2).

Of the 1300 control candidates initially selected, 536 were included as controls in the study. The control subjects were matched with the 121 case subjects as follows: 5 matched control subjects were found for 80 case subjects, 4 matched control subjects were found for 25 case subjects, and 3 or fewer matched control subjects were found for 16 case subjects.

2.6. Screening histories of cases and controls

Screening histories were reviewed for the 121 sets of subjects (121 case subjects and 536 control subjects), for the same calendar period, up to 48 months prior to the diagnosis of each lung cancer case. Screening histories were obtained from the files kept at the local government offices. Screening tests completed after the diagnosis of the case subject were not counted as screened histories. The screening test that led to the diagnosis of lung cancer was included in the overall screening history. Screening histories during the 12, 24, 36, and 48 months prior to the diagnosis of lung cancer were compared.

2.7. Data analysis

Conditional logistic regression models for matched sets were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of lung cancer deaths for those screened compared with those not screened [12]. Although control subjects were matched with each case by gender, year of birth, address and smoking habits, they were not matched based on cigarette consumption, which is the most important risk factor for lung cancer death. Therefore, smoking adjusted ORs were calculated by including eight dichotomous variables on the smoking index (1–199, 200–399, 400–599, 600–799, 800–999, 1000–1199, 1200–1399, 1400–1599, and 1600 or more) in the model [4,5]. Smoking indexes for control subjects were calculated based on the number of years smoked up to the time when the corresponding case was diagnosed. Screening histories were divided into two categories, 'screened' and 'not screened', based on whether or not the study subjects had been screened within 12, 24, 36 and 48 months before each case was diagnosed. Odds ratios were also calculated according to gender and histological type.

All analyses were completed using the PHREG Procedure, available in the SAS (Ver. 6.07) package.

3. Results

The histological type and reason for cancer detection in the case subjects are shown in Table 3. Adenocarcinoma was the predominant type of cancer in both males and females and 20 cases (16.5%) were diagnosed solely on a clinical and/or CXE basis. 28 lung cancer cases (23.1% of all case subjects) were detected by screening.

Table 3
Distribution of histological type and reason for cancer detection in the case subjects

	Male (%)	Female (%)
Histological type		
Adenocarcinoma	35 (38.5)	17 (56.7)
Squamous cell carcinoma	28 (30.8)	6 (20.0)
Small cell carcinoma	10 (11.0)	1 (3.3)
Large cell carcinoma	0 (0)	1 (3.3)
Other[a]	2 (2.2)	1 (3.3)
Unknown	16 (17.6)	4 (13.3)
Cause of detection		
Symptom	57 (62.6)	16 (53.3)
Other disease[b]	15 (16.5)	5 (16.7)
Lung cancer screening	19 (20.9)	9 (30.0)
Total	91 (100.0)	30 (100.0)

[a] Adenosquamous cell carcinoma.
[b] Chest X-ray examination for follow-up of other disease.

Unfortunately, the total number of screening-detected lung cancers in the study area as well as the total number of lung cancer cases could not be obtained because a cancer registry has not been conducted in Gunma Prefecture.

The age and smoking index distributions for both cases and controls are shown in Table 4. Although the age range for this study was between 40 and 79 years, nearly half the subjects were more than 70 years old. Smoking indexes among male case subjects were significantly higher than among male controls ($P=0.0051$).

Table 5 shows the ORs of death due to lung cancer for screened versus unscreened subjects for comparative screening periods of 12, 24, 36 and 48 months. The smoking index-adjusted OR of death from lung cancer within 12 months before the date of diagnosis was 0.68 (95% CI: 0.44–1.05; $P=0.084$). When the period for comparing screening histories was extended to 36 months, the OR changed slightly to 0.70.

ORs according to gender and histological type are shown in Table 6. For males, the smoking index-adjusted OR within 12 months prior to the date of diagnosis was 0.74 (95% CI: 0.46–1.22); for females, it was 0.47 (95% CI: 0.18–1.24). Although the 95% CIs overlapped, the OR for females was lower than that for males. Stratified by histological type, the smoking index-adjusted OR was 0.62 (95% CI: 0.31–1.24) for adenocarcinoma, and 1.01 (95% CI: 0.44–2.31) for squamous cell carcinoma.

4. Discussion

This study was designed to evaluate the efficacy of lung cancer screening based on annual chest X-ray examinations. Although the results of this study were unable to reach statistical significance, the results suggest that an annual miniature chest X-ray examination could reduce lung cancer mortality by 20–30%.

The ORs according to histological type reflect the fact that chest X-ray examinations were the only screening tool used in this study. The OR for squamous cell carcinoma, which is usually detected at an early stage by sputum cytology, was 1.01. However, the OR for adenocarcinoma, for which a chest X-ray examination is necessary, was 0.62 (95% CI: 0.31–1.24). The results of this study suggest that annual chest X-ray examinations may not be useful for squamous cell carcinoma, but may help prevent death from lung adenocarcinoma.

Table 4
Ages and smoking indexes of case subjects and control subjects

	Male		Female	
	Case subjects (%)	Control subjects (%)	Case subjects (%)	Control subjects (%)
Age (years)				
40–49	1 (1.1)	3 (0.8)	2 (6.7)	11 (8.1)
50–59	7 (7.7)	30 (7.5)	5 (16.7)	17 (12.5)
60–69	38 (41.8)	187 (46.8)	4 (13.3)	17 (12.5)
70–74	30 (33.0)	121 (30.3)	7 (23.3)	42 (30.9)
75–79	15 (16.5)	59 (14.8)	12 (40.0)	49 (36.0)
Smoking index[a]				
0	0 (0.0)	0 (0.0)	30 (100.0)	132 (97.1)
1–599	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.9)
600–799	18 (19.8)	129 (32.3)	0 (0.0)	0 (0.0)
800–1199	50 (54.9)	218 (54.5)	0 (0.0)	0 (0.0)
1200–1599	8 (8.8)	28 (7.0)	0 (0.0)	0 (0.0)
1600+	15 (16.5)	25 (6.3)	0 (0.0)	0 (0.0)
Total	91 (100.0)	400 (100.0)	30 (100.0)	136 (100.0)

[a] Smoking indexes of male case subjects were significantly higher than those of male control subjects ($P=0.0051$).

Table 5
Smoking-adjusted ORs of lung cancer death for screened versus non-screened patients, according to the period of time screening histories were compared with diagnosis (matched by gender, year of birth, smoking habits)

Months before diagnosis	Number of		Screened (%)		ORs	95% CI
	Case subjects	Control subjects	Case subjects	Control subjects		
0–12	121	536	57.9	67.2	0.68	0.44–1.05**
0–24	111	473	68.5	75.9	0.67	0.40–1.10
0–36	82	340	76.8	81.8	0.70	0.38–1.33
0–48	50	197	82.0	81.2	1.02	0.42–2.48

ORs, odds ratios; 95% CI: 95% confidence intervals.
*$P=0.065$; **$P=0.084$.

Soda and colleagues reported that the sensitivity of adenocarcinoma was 85% and that of squamous cell carcinoma was 52% in a lung cancer screening programme in Nagasaki, Japan [13]. Flehinger and colleagues used a mathematical model to calculate that the mean duration of stage I adenocarcinoma was more than 4 years [14]. Since the detectable preclinical phase is so long, adenocarcinoma is ideally suited for detection by chest X-ray screening. In three randomised control trials (RCT) sponsored by the National Cancer Institute in the United States, all of the participants were male heavy smokers, in whom squamous cell carcinoma and small cell carcinoma were the predominant types of lung cancer [1–3]. However, in Japan, adenocarcinoma is the most common type of lung cancer [15]. Therefore, better results can be expected from chest X-ray screening in Japan than in the United States.

In Japan, approximately 13% of the female population smokes and only 4.4% of all cancers and 15.6% of lung cancers in females are attributable to smoking [16]. Non-high risk females were included in this analysis, instead of high-risk females, due to the lack of information on strong risk factors and preventative strategies for low risk women. Results obtained for non-high risk females showed an almost 50% protective effect of screening on mortality. These results reflect the high percentage (56.7% of female cases) of adenocarcinoma.

In case–control studies, various biases often unavoidably confound the study results. Weiss and Lazovich indicated that short follow-up periods of incident cases led to overestimation of the screening efficacy by the ‘lead-time bias’. This occurs because screening detected cases are diagnosed at earlier stages and therefore have longer intervals between time of diagnosis and death. A short follow-up period might miss these fatal cases [17]. In this study, the follow-up period after diagnosis of the case subjects was relatively short (maximum 4 years) because screening records could not be obtained prior to 1994. Although survival times for lung cancer patients are relatively short, our study may not have captured all of the screening detected lung cancer deaths.

In this study, 7 of the 70 case subjects screened within 12 months before diagnosis had symptoms related to lung cancer prior to their screening visits (1 for severe coughing, 1 for bloody sputum, 5 for pain due to bone metastasis). 6 additional case subjects had been notified of suspicions that they might have lung cancer prior to their screening visits. Pisani and colleagues pointed out those individuals were presumably using the screening programme as a diagnostic service [18]. As recommended by Weiss [19], an additional analysis was performed, regarding such screening visits as ‘not screened’. The smoking-adjusted OR of lung cancer

Table 6
Smoking-adjusted ORs of lung cancer death for those screened within 12 months versus non-screened by gender and histological type

	Number of		Screened (%)		Smoking-adjusted ORs	95% CI
	Case subjects	Control subjects	Case subjects	Control subjects		
Gender						
Male	91	400	57.9	67.2	0.74	0.46–1.22
Female	30	136	68.5	75.9	0.47	0.18–1.24
Histological type[a]						
Squamous	34	153	67.7	66.0	1.01	0.44–2.31
Adeno	52	228	53.9	64.0	0.62	0.31–1.24

ORs; odds ratios; 95% CI, 95% confidence intervals; Squamous, squamous cell carcinoma; Adeno, adenocarcinoma.
[a] ORs for other than squamous cell carcinoma and adenocarcinoma were not estimated due to the limited number of sets.

death for those screened within 12 months before diagnosis in this analysis was calculated at 0.41, a significant reduction of the risk for lung cancer death (95% CI: 0.26–0.64). Theoretically, screening visits by control subjects with symptoms possibly due to lung cancer should also be counted as 'not screened'. Unfortunately, the reasons why control subjects visited screening programmes were not available. However, none of the control subjects in this study were diagnosed with lung cancer during the study period and none of them were notified of suspected lung cancer prior to their screening visits. Furthermore, we only excluded case subjects with severe symptoms because slight respiratory symptoms, such as cough or sputum, are usual even in healthy people and we speculated that most people would not intend to have an X-ray due to such symptoms. Therefore, screening visits by control subjects with symptoms were not considered important to our outcome. Taking these results into consideration, the OR of 0.68 observed in the main analysis of this study probably underestimated the true efficacy of CXE screening on mortality from lung cancer.

Connor and colleagues found an invitation system and time scale impact on the OR, using a microsimulation approach [20]. If a population was invited for screening on their birthday, this leads to an underestimation of the efficacy of screening if calendar time is used to compare the screening histories. The present study, however, is unlikely to be subject to this bias because the population was invited not on their birthday, but on a day selected by each local community.

In the process of identifying control subjects, control candidates who could not be matched by smoking habits were excluded. The screening attendance rate of those who were excluded (58.3%) was lower than that of matched control subjects (67.2%). Since excluding these control candidates from the analysis might cause sampling bias to overestimate screening efficacy, an analysis without smoking adjustment, matched by only gender, year of birth, and administrative district, was performed for the 121 case subjects and 1102 control subjects. The OR without smoking adjustment was 0.79 (95% CI: 0.53–1.18). Although matching case and control subjects by smoking habits increased comparability between the two groups, it may have caused some overestimation of the efficacy of screening on mortality from lung cancer.

Based on mortality and incidence data, smoking cessation has led to a decline in lung cancer deaths for males in the United States [21]. However, former smokers, whose numbers are growing, still run a high risk of developing lung cancer years after they quit smoking. Additional preventative strategies would be of great value for former smokers [22]. Helical computed tomography (CT) may be a more useful screening modality than chest X-rays [23], but as yet there is no evidence to indicate such screening would reduce lung cancer mortality. It will take a long time to confirm the efficacy of helical CT screening and to accept this technique into mainstream medical practice. It must be concluded that when the results of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial to assess modern chest X-ray examinations is published [24], lung cancer screening based on an annual chest X-ray examination should be reconsidered as one of the preventative strategies.

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