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Cost-effectiveness of the Introduction of Low-dose CT Screening in Japanese Smokers Aged 55 to 74 Years Old

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ABSTRACT

The validity of low-dose CT screening for lung cancer in heavy smokers was supported by the results of National Lung Screening Trials (NLST) conducted in the U.S.A. The present study investigated the appropriateness of the introduction of low-dose CT screening for lung cancer in Japanese smokers aged between 55 and 74 years old, in terms of cost-effectiveness and age. To examine changes in the shift from conventional chest radiography (CR) to low-dose CT (LDCT) screening for lung cancer, we estimated the incremental cost-effectiveness ratio (ICER) using Iinuma's mathematical model, and also conducted sensitivity analysis to determine the requirements for the introduction of a population-based screening. As the result, the incremental cost for one life-year saved was one million yen or lower when the costs of the screening were 8,000 and 6,000 yen and the recall rate was 10% for male and female smokers aged 55 to 59 years old, respectively. The recall rate was smaller when the interval between cancer screenings was two years, and the subjects were males. The higher the age of the subject, the smaller the incremental cost. In conclusion, at present, the mean cost of the LDCT test is approximately 10,000 yen in Japan. With a reduction in this cost by a few thousand yen, all Japanese smokers aged 55 to 74 years will be able to undergo LDCT screening for lung cancer annually.

Key words: *Lung cancer, Low-dose CT screening, Smoker, Cost-effectiveness*

Japan has become a super-aging society, with the proportion of its elderly population to the total exceeding 21% as of 2007[5)]. With the aging of the population, a sharp increase in mortality due to malignant neoplasms has become a serious issue. Lung cancer is the first and second leading cause of death for males and females, respectively, and the number of deaths in 2012 was 71,518 in Japan.

For detection of lung cancer at an early stage, screening using chest radiography (CR) is currently conducted. In addition to this, the introduction of low-dose computed tomography (LDCT) with greater diagnostic capability than CR is also being considered[13)]. In a LDCT scan, the radiation dose is approximately 2 mSV or lower[16)] and one-fifth to one tenth of the radiation dose of conventional chest CT scans. The National Lung Screening Trial (NLST)[1)] is a randomized control study (RCT) conducted in the U.S.A. to compare the effects on the reduction of mortality of heavy smokers between CR and LDCT screening. The results suggested that the mortality of the LDCT group was 20% lower than that of the CR group[1)].

After the establishment of the validity of LDCT, its cost-effectiveness should also be investigated as an important task to adopt it to population-based screening. In Japan, Iinuma[3)] analyzed the cost-effectiveness of LDCT conducted on Japanese people aged 35 to 84 years old, based on the NLST.

The purpose of this study was to investigate the appropriate age and costs of LDCT lung cancer screening in subjects who are smokers aged 55 to 74 in terms of cost-effectiveness by using Iinuma's mathematical model. We also calculated the incremental cost and incremental cost-effectiveness ratio following the shift from CR to LDCT lung

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cancer screenings and demonstrated the appropriate age of subjects for whom LDCT should be introduced, the cost and recall rate of the LDCT screening.

MATERIALS AND METHODS

Study Population

The subjects were Japanese smokers aged 55 to 74 years old as of 2006. They were categorized by gender and age (55 to 59, 60 to 64, 65 to 69, and 70 to 74 years old), and the analyses described below were conducted on these groups.

Estimation of number of lung cancer patients in the smoking group

The number of smokers was calculated based on the national population census in 2005 and the smoking rates by gender and ten-year age group in 2006[7]. Let i be index of sex and age, i.e. i=1 for 55-59 y.o. male, i=2 for 60-64 y.o. male,..., i=4 for 70-74 y.o. male, i=5 for 55-59 y.o. female,..., and i=8 for 70-74 y.o. female. The number of lung cancer patients by gender and five-year age group ($N_i(SmLc)$) was estimated based on the relative risk of lung cancer to the number of Japanese smokers (RR)[14], using the following formula on the assumption that RR is not dependent on sex and age:

$$N_i(SmLc) = N_i(Lc) \times \{RR \times N_i(Sm)\} \,/\, \{N_i(Ge)+(RR-1)\times N_i(Sm)\},$$

where $N_i(Lc)$, $N_i(Sm)$, $N_i(Ge)$ are the number of people with lung cancer, number of smokers, and the number of population by gender and five-year age group, respectively.

Calculation of the incremental cost-effectiveness ratio after the introduction of LDCT

The number of lives that could be saved and incremental cost following the shift from CR to LDCT were estimated using Iinuma's calculation model[3]. $N_i(SmLc)$, $M(ELc)$, $M(ALc)$ are the number of smokers with lung cancer by gender and five-year age group, mortality due to early lung cancer and mortality due to advanced lung cancer (not dependent on sex and age), respectively. The sex- and age-specific number of deaths due to lung cancer in each cancer screening ($D_i(Lc)$) was calculated as follows:

$$D_i(Lc) = N_i(SmLc) \times \{P(ELc)\times M(ELc)+P(ALc)\times M(ALc)\},$$

where $P(ELc)$ and $P(ALc)$ are the percentages of early lung cancer and advanced lung cancer (not dependent on sex and age), respectively. $C(Sc)$, $C(Ts)$, $C(ELc)$, $C(ALc)$ are the costs of each (CR or LDCT) screening, the thorough screening, the treatment of early lung cancer, and the treatment of advanced lung cancer, respectively. Here we use the term "Over-diagnosis (OD)" as the proportion of cases in which cancer diagnosis and treatment were provided for patients who would have died of causes other than cancer. The total cost ($C_i(Total)$) by gender and five-year age group was calculated by the number of smokers with lung cancer by gender and five-year age group ($N_i(SmLc)$), as follows:

$$C_i(Total) = N_i(Sm)\times\{C(Sc)+R(Ts)\times C(Ts)\} \,/\, In + N_i(SmLc)\times\{P(ELc)\times(1+OD)\times C(ELc)+ P(ALc)\times C(ALc)\},$$

where $R(Ts)$, In, $P(ELc)$, $P(ALc)$ are the rate of requiring thorough screenings, the interval between cancer screenings, percentage of early lung cancer in each screening group, and percentage of advanced lung cancer in each screening group, respectively.

The number of deaths in LDCT and its total cost were subtracted by the number of deaths in CR and its total cost to calculate the number of lives saved and the incremental cost as a result of the introduction of LDCT. The formulas were based on the assumption that all OD cases in the cancer screening group had early lung cancer and their life expectancy could not be extended. The ratios of the numbers of people who underwent each type of cancer screening and died of lung cancer were calculated to determine the relative risk of death due to lung cancer.

The incremental cost was divided by the number of lives that could be saved or gained life expectancy (the product of the number of saved lives and mean life expectancy) to calculate the incremental cost-effectiveness ratio (incremental costs per person saved and per year of gained life expectancy). Table 1 shows the parameters used to calculate the incremental cost-effectiveness ratio and their sources. The population, the number of people with lung cancer, and mean life expectancy were calculated based on the population determined by the national population census[5], national estimates from the regional cancer registries[15], and the simple life table[6]. The cost of the thorough screening was set to 20,000 yen, which is the same as the cost of the thin-slice CT used in Iinuma's study[3].

The gender- and age-specific smoking rates from the National Health and Nutrition Survey in 2010 were used[7]. As data on relative risks of lung cancer among smokers, comprehensive data on relative risks of lung cancer obtained by Wakai's meta-analysis were adopted[14]. Data on the proportions of early- and advanced-stage lung cancer in each group were obtained from the pathological condition-specific distribution chart of lung cancer identified by cancer screening in examinees who had been registered in the Anti-Lung Cancer

Table 1. Indicators used for analyses with one unknown (1)

	Item				Reference values	Temporary values: Minimum values	Temporary values: Maximum values	References
Fixed	Population (1,000)	$N_i(Ge)$	Males	55-59 years old	5,361			5)
			Males	60-64 years old	3,962			
			Males	65-69 years old	3,644			
			Males	70-74 years old	3,132			
			Females	55-59 years old	5,464			
			Females	60-64 years old	4,181			
			Females	65-69 years old	3,980			
			Females	70-74 years old	3,682			
	Number of lung cancer patients (persons)	$N_i(Lc)$	Males	55-59 years old	4,490			15)
			Males	60-64 years old	5,933			
			Males	65-69 years old	7,781			
			Males	70-74 years old	11,021			
			Females	55-59 years old	2,162			
			Females	60-64 years old	2,248			
			Females	65-69 years old	2,915			
			Females	70-74 years old	4,098			
	Mean life expectancy (years)		Males	55-59 years old	24.91			6)
			Males	60-64 years old	20.81			
			Males	65-69 years old	16.92			
			Males	70-74 years old	13.30			
			Females	55-59 years old	30.64			
			Females	60-64 years old	26.12			
			Females	65-69 years old	21.69			
			Females	70-74 years old	17.46			
	Cost of the thorough screening (yen)	$C(Ts)$			20,000			3)
Variable	Smoking rate (%)		Males	55-59 years old	40	35	45	7)
			Males	60-64 years old	25	20	30	
			Males	65-69 years old	25	20	30	
			Males	70-74 years old	15	10	20	
			Females	55-59 years old	10	5	15	
			Females	60-64 years old	5	3	10	
			Females	65-69 years old	5	3	10	
			Females	70-74 years old	2	1	5	
	Relative risk of lung cancer among smokers	RR	Males		4.39	3.92	4.92	14)
			Females		2.79	2.44	3.20	
	Percentage of early (advanced) lung cancer (%)	$P(ELc),P(ALc)$	CR		50 (50)	40 (60)	60 (40)	4)
			LDCT		85 (15)	75 (25)	95 (05)	3)
	Mortality due to lung cancer (%)	$M(ELc)$	Early cancer		30	20	30	15)
		$M(ALc)$	Advanced cancer		85	75	85	
	Cost of the screening(yen)	$C(Sc)$	CR		1,500			12)
			LDCT		10,000	5,000	15,000	9)
	Rate of requiring thorough screening (%)	$R(CR\text{-}Ts)$	CR		7	3	15	2)
		$R(LDCT\text{-}Ts)$	LDCT		20	5	35	
	Interval between screening (years)	In	CR		1			
			LDCT		1	1	2	
	Overdiagnosis (%)	OD	CR		0			
			LDCT		10	0	30	3)
	Cost of the treatment for lung cancer (10,000 yen)	$C(ELc)$	Early cancer		150	100	200	10)
		$C(ALc)$	Advanced cancer		300	200	500	

Association (ALCA), an organization for membership-based cancer screening, implemented since 1975[4]. The 5-year survival rate of lung cancer in the demographic statistics for 2011 was adopted[15] for mortality. The cost of CR cancer screening was set to 1,500 yen, as reported by Tanaka[12], and that of LDCT to 10,000 yen, as suggested by Nakayama[9]. The ODs of CR and LDCT cancer tests were 0 and 30%, respectively, which is consistent with the study conducted by Iinuma[3]. The costs for the treatment of early and advanced lung cancer were set to 1,500,000 and 3,000,000 yen, respectively, based on a receipts analysis study conducted by Nawa[10]. The rate of requiring thorough screenings published in the guidelines for the management of the accuracy of CT tests (the first edition) was used[2].

Assessment of the incremental cost-effectiveness ratio

For the assessment of the incremental cost-effectiveness ratio, the incremental cost per year of gained life expectancy was set to one million yen or lower, as a requirement for the introduction of LDCT. This is the maximum limit for the cost that can be allotted to save one person per year, taking into account the economic situation in Japan.

The validity of the incremental cost-effectiveness ratio (sensitivity analysis)

In the present study, sensitivity analyses with one and two unknowns were conducted to examine the validity of the calculated incremental cost-effectiveness ratio for a subject whose ICER is around one million yen.

Table 1 shows the minimum and maximum parameters used for the sensitivity analysis with one unknown. Sensitivity analyses of the population, number of people with lung cancer, mean life expectancy, and cost of the thorough screening were not conducted, and they were defined as fixed parameters.

The ranges of changes in the parameters were decided as follows. The range of the smoking rate was ± 5%. The range of the relative risk of lung cancer among smokers was the 95% confidence interval. The range of the ratios between early- and advanced-stage lung cancer cases in the groups was ± 10%. The lung cancer mortality in 2011 was defined as the maximum mortality[15], and 90% of the maximum mortality was defined as the minimum mortality. The cost of the CR test was fixed, and the minimum and maximum costs of LDCT were set to 10,000 and 15,000 yen, respectively, based on the results of a national questionnaire survey[9]. The OD for CR was set to 0%, which is consistent with the study by Iinuma[3], and the minimum and maximum ODs for LDCT were 0 and 30%, respectively. The medical expenses for the treatment of lung cancer in the early and advanced stages were one to two and two to five million yen, respectively. The rate of requiring thorough screenings was based on the estimated rates by gender and age group, as shown in Table 2. The estimated rates of requiring thorough screenings by gender and age group were calculated using the rate of requiring CR thorough screenings by gender and five-year age group[7] and the rate of elderly examinees requiring thorough screenings published in the guidelines for the management of the accuracy of CT tests[2]. The rate of requiring LDCT thorough screenings by gender and five-year age group in the general population ($R_i(Ge\text{-}LDCT\text{-}Ts)$) was estimated using the following formula:

$$R_i(Ge\text{-}LDCT\text{-}Ts) = \{R(LDCT\text{-}Ts) \,/\, R(CR\text{-}Ts)\} \times R_i(Ge\text{-}CR\text{-}Ts),$$

where, $R(LDCT\text{-}Ts)$, $R(CR\text{-}Ts)$, $R(Ge\text{-}CR\text{-}Ts)$ are the rates of requiring thorough screenings among elderly patients who had undergone LDCT: 8% or lower, the rate of requiring thorough screenings among the total population who had undergone lung cancer screenings: 2.90%, rate of requiring

Table 2. Indicators used for analyses with one unknown (2) : Estimated rates of requiring thorough examinations in the smoking groups

		Estimated rate of requiring thorough examinations (%)			
		General population		Smokers	
		CR group	LDCT group	CR group	LDCT group
Males	55-59 years old	2.35	6.48	4.36	12.03
Males	60-64 years old	3.03	8.36	6.90	19.02
Males	65-69 years old	3.39	9.35	7.72	21.28
Males	70-74 years old	3.88	10.70	11.14	30.73
Females	55-59 years old	1.78	4.91	4.19	11.55
Females	60-64 years old	2.12	5.85	5.47	15.10
Females	65-69 years old	2.41	6.65	6.22	17.17
Females	70-74 years old	2.90	8.00	7.81	21.55

thorough screenings among the general population by gender and five-year age group who had undergone CR, respectively.

Let $N_i(Sm\text{-}Ts)$ and $N_i(Ge\text{-}Ts)$ be numbers of smokers and general population with lung cancer by gender and five-year age group, respectively. Then, in order to estimate the rate of requiring thorough screenings by gender and five-year age group for the smoking group ($R_i(Sm\text{-}LDCT\text{-}Ts)$), the rate was assigned to the following formula:

$$R_i(Sm\text{-}LDCT\text{-}Ts) = \{N_i(Sm\text{-}Ts) / N_i(Sm)\} / \{N_i(Ge\text{-}Ts) / N_i(Ge)\} \times R_i(Ge\text{-}LDCT\text{-}Ts).$$

As a result of the sensitivity analysis with one unknown, the ranges of values for some items were significantly wide, and sensitivity analysis with two unknowns of these items was conducted. Table 3 shows the indicators used for the sensitivity analysis with two unknowns.

RESULTS

Incremental cost-effectiveness ratio after the introduction of LDCT

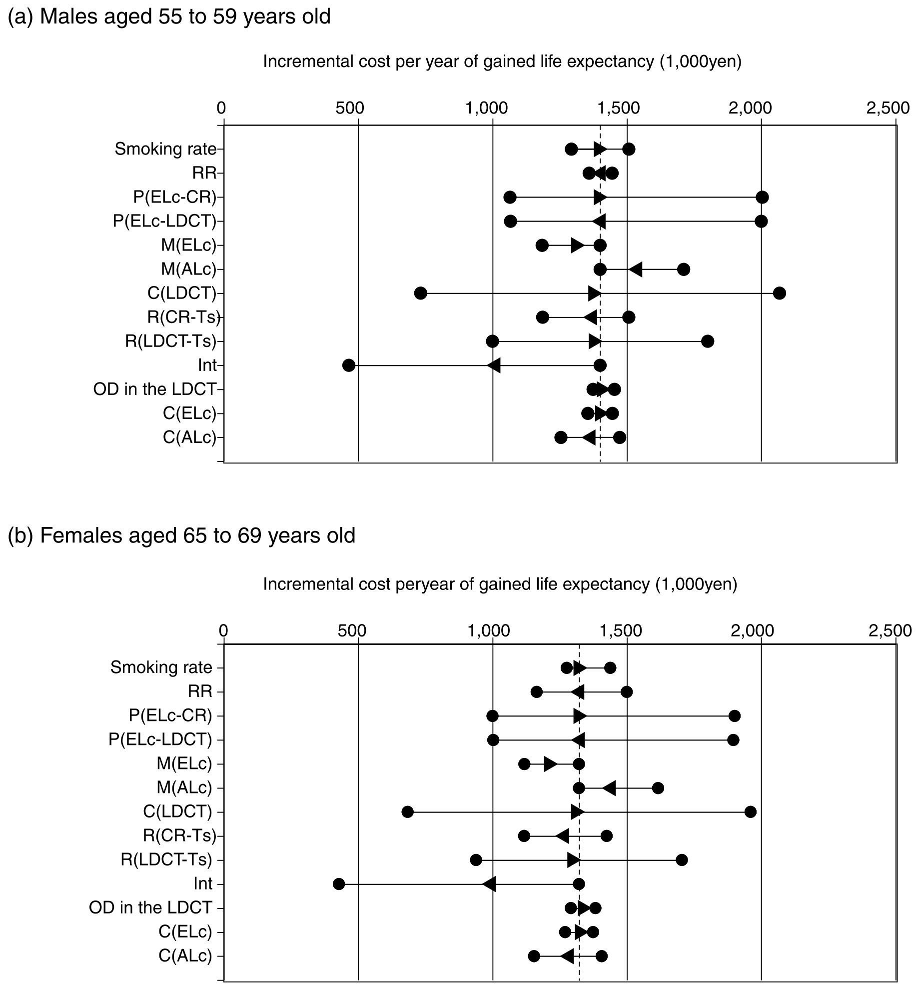
Table 4 shows the incremental cost-effectiveness ratio following the introduction of LDCT and its associated indicators. The ratio of the relative risk of lung cancer death of the CR to LDCT group was 0.67. The higher the age of the subject, the smaller the incremental cost-effectiveness ratio, and the ratio was larger in the female group. As the incremental cost per year of gained life expectancy was about one million yen or lower, LDCT could be

Table 3. Indicators used for analyses with two unknowns

	Item				Temporary values: Temporary values	Temporary values: Minimum values	Temporary values: Maximum values	References
Fixed	Population (1,000)	$N_i(Ge)$			Same as in Table 1			5)
	Number of lung cancer patients (persons)	$N_i(Lc)$			Same as in Table 1			15)
	Life expectancy (years)				Same as in Table 1			6)
	Smoking rate (%)		Males	55-59 years old	40.30			7)
			Males	60-64 years old	27.40			
			Males	65-69 years old	27.40			
			Males	70-74 years old	15.60			
			Females	55-59 years old	10.40			
			Females	60-64 years old	4.50			
			Females	65-69 years old	4.50			
			Females	70-74 years old	2.00			
	Relative risk of lung cancer among smokers	*RR*	Males Females		4.39 2.79			14)
	Mortality due to lung cancer (%)	$M(ELc)$ $M(ALc)$	Early cancer Advanced cancer		28.30 85.00			15)
	Cost of the thorough screening(yen)	$C(Ts)$			Same as in Table 1			3)
	Overdiagnosis (%)	*OD*	CR LDCT		0 30			3)
	Cost of the treatment for lung cancer (10,000 yen)	$C(ELc)$ $C(ALc)$	Early cancer Advanced cancer		160 320			10)
	Percentage of early (advanced) lung cancer (%)	$P(ELc)$,$P(ALc)$	CR annually LDCT annually LDCT every 2 years		50 (50) 85 (15) 80 (20)			4)
Variable	Cost of the screening (yen)	$C(Ts)$	CR LDCT		1,500 10,000	 5,000	 15,000	12) 9)
	Rate requiring thorough screening (%)	$R(CR\text{-}Ts)$ $R(LDCT\text{-}Ts)$	CR LDCT		7 20	3 5	15 35	2)

Table 4. Incremental cost following the introduction of low-dose CT and its related indicators

		Relative risk of death due to pulmonary cancer	Number of lives saved (persons)	Gained life Expectancy (years)	Incremental cost (million yen)	Incremental cost per life saved (thousand yen)	Incremental cost per year of gained life expectancy (thousand yen)
Male	55-59 years old	0.67	644	17,453	22,473	34,884	1,400
Male	60-64 years old	0.67	678	14,119	9,594	14,140	679
Male	65-69 years old	0.67	890	15,055	8,275	9,300	550
Male	70-74 years old	0.67	926	12,317	3,302	3,566	268
Female	55-59 years old	0.67	98	3,018	5,862	59,515	1,942
Female	60-64 years old	0.67	55	1,447	2,206	39,813	1,524
Female	65-69 years old	0.67	72	1,558	2,061	28,678	1,322
Female	70-74 years old	0.67	43	742	730	17,168	983



RR, Relative risk of lung cancer among smokers;
P(ELc-CR), Proportion of early cancer in the CR group;
P(ELc-LDCT), Proportion of early cancer in the LDCT group;
M(ELc), Mortality due to early lung cancer;
M(ALc), Mortality due to advanced lung cancer;
C(LDCT), Cost of the examination in the LDCT group;
R(CR-Ts), Rate of requiring thorough examinations in the CR group;
R(LDCT-Ts), Rate of requiring thorough examinations in the LDCT group;
Int, Interval between examinations in the LDCT group;
C(ELc), Cost for the treatment of early lung cancer;
C(ALc), Cost for the treatment of advanced lung cancer

Fig. 1. Incremental cost per year of gained life expectancy (sensitivity analysis with one unknown)

The dotted line indicates the incremental cost when the parameters were set to the reference values, and the horizontal bars indicate changes in the incremental cost when the parameters changed in the range shown in Table 1. The arrow indicates change of the ICER when the parameter changed from minimum to maximum.

introduced for male and female smokers aged 55 and 65 (or 70) years or older, respectively. Therefore, we conducted sensitivity analysis for a 55-59 y.o. male and a 65-69 y.o. female to discuss the target age for screening.

Validity of the incremental cost-effectiveness ratio I: One way Sensitivity analysis

The graph in Fig. 1 shows the range of the incremental cost for one year of gained life expectancy for males aged 55 to 59 years old and females aged 65 to 69 years old when there were changes in the parameters.

As for the following parameters: the ratios between early- and advanced-stage lung cancer cases in the groups, cost of the LDCT cancer screening, rate of requiring thorough screenings in the LDCT group, and interval between LDCT screenings, the incremental cost for one year of gained life expectancy for both males and females became higher than 500,000 yen, or 50% of one million, when there were changes in the parameters. For both male and female elderly groups, the ranges of values when the cost for the treatment of advanced lung cancer was adopted as the parameter were wider than when other items were used as the parameters.

Validity of the incremental cost-effectiveness ratio II: Two way sensitivity analysis

The ratios of the relative risk of lung cancer death between people who had undergone CR and LDCT lung cancer screenings at intervals of one and two years were 0.65 and 0.70, respectively. The higher the age, the smaller the incremental cost-effectiveness ratio, and it was larger in the female group.

When the costs of the LDCT cancer screening were 8,000 and 6,000 yen and the rate of requiring thorough screenings was 10%, the incremental cost for one year of gained life expectancy for male and female smokers, aged 55 to 59 years old, who had undergone LDCT annually was one million yen or lower, respectively (Table 5 (a) and (b)).

When the cost of the LDCT cancer screening was 10,000 yen (national mean: 9,971 yen) and the rate of requiring thorough screenings was approximately 20%, the incremental cost for one year of gained life expectancy was one million yen or lower if male and female subjects who had undergone LDCT annually were 60 and 70 years or older, respectively (Table 5 (c) and (d)).

When LDCT cancer screenings were conducted every two years, the incremental cost per year of gained life expectancy was one million yen or lower for most males and females aged 55 years old. The incremental cost per year of gained life expectancy was below zero for some elderly males.

DISCUSSION

In the present study, we estimated the incremental cost-effectiveness ratio following the introduction of LDCT for lung cancer screening using a mathematical model. The cost-effectiveness of LDCT in Japan has already been analyzed by Iinuma[3]. Iinuma reported the incremental cost-effectiveness ratio following the introduction of LDCT screening for the group of people who had not undergone lung cancer screening, including non-smokers. On the other hand, we estimated the incremental cost-effectiveness ratio between conventional CR and LDCT only for smokers who were 55-74 years old. We could also estimate requirements for the introduction of LDCT to lung cancer screenings by sensitivity analysis.

The results of the one way sensitivity analysis suggested that the incremental cost for one year of life-years saved after shifting from CR to LDCT was significantly influenced by the following four factors: the ratios between early- and advanced-stage lung cancer patients in the groups, cost of the LDCT lung cancer screening, recall rate of the LDCT group, and the interval between LDCT screenings.

For the present estimation, we used the ratios between early- and advanced-stage lung cancer cases from ALCA's report[4] and the results of a study conducted by Iinuma based on ALCA's report[3]. We considered these data were appropriate for the present study since people who underwent lung cancer screenings conducted by the ALCA were heavy smokers. However, since the ratios between early- and advanced-stage lung cancer cases are the most significant factor influencing cost-effectiveness, if more accurate data on the ratios are obtained from surveys involving multiple health care institutions, more accurate estimation may be possible.

Cost of the treatment for pulmonary cancer is important in cost-effectiveness analysis. One factor for deciding cost-effectiveness in screening is low cost for early medical treatment. In Iinuma's study[3], the cost of the treatment for early cancer was 1,000,000 yen, and that for advanced cancer was 5,000,000 yen. However, the cost of the treatment for early cancer might be too low, and it may lead to the bias that LDCT has a propensity to superior cost-effectiveness. Thus we adapted medical cost in Nawa's receipts analysis into a cost-effectiveness analysis and used cost in Iinuma's study for sensitivity analysis. However, judging by the results of the sensitivity analysis, variation in cost of treatment does not infect ICER, relatively.

According to the results of two way sensitivity analysis, a requirement for the introduction of low-dose CT lung cancer screenings for smokers

Table 5. Sensitivity analysis with two unknowns/incremental cost per one year of gained life expectancy (thousand yen)

(a) Males aged 55 to 59 years old, LDCT conducted annually

		Cost of the examination (yen)										
		5,000	6,000	7,000	8,000	9,000	10,000	11,000	12,000	13,000	14,000	15,000
Rate of requiring thorough examinations (%)	5.00	442	572	702	832	962	1,092	1,223	1,353	1,483	1,613	1,743
	10.00	572	702	832	962	1,092	1,223	1,353	1,483	1,613	1,743	1,874
	15.00	702	832	962	1,092	1,223	1,353	1,483	1,613	1,743	1,874	2,004
	20.00	832	962	1,092	1,223	1,353	1,483	1,613	1,743	1,874	2,004	2,134
	25.00	962	1,092	1,223	1,353	1,483	1,613	1,743	1,874	2,004	2,134	2,264
	30.00	1,092	1,223	1,353	1,483	1,613	1,743	1,874	2,004	2,134	2,264	2,394
	35.00	1,223	1,353	1,483	1,613	1,743	1,874	2,004	2,134	2,264	2,394	2,524

(b) Females aged 55 to 59 years old, LDCT conducted annually

		Cost of the examination (yen)										
		5,000	6,000	7,000	8,000	9,000	10,000	11,000	12,000	13,000	14,000	15,000
Rate of requiring thorough examinations (%)	5.00	622	799	976	1,152	1,329	1,506	1,682	1,859	2,036	2,212	2,389
	10.00	799	976	1,152	1,329	1,506	1,682	1,859	2,036	2,212	2,389	2,566
	15.00	976	1,152	1,329	1,506	1,682	1,859	2,036	2,212	2,389	2,566	2,743
	20.00	1,152	1,329	1,506	1,682	1,859	2,036	2,212	2,389	2,566	2,743	2,919
	25.00	1,329	1,506	1,682	1,859	2,036	2,212	2,389	2,566	2,743	2,919	3,096
	30.00	1,506	1,682	1,859	2,036	2,212	2,389	2,566	2,743	2,919	3,096	3,273
	35.00	1,682	1,859	2,036	2,212	2,389	2,566	2,743	2,919	3,096	3,273	3,449

(c) Males aged 60 to 64 years old, LDCT conducted annually

		Cost of the examination (yen)										
		5,000	6,000	7,000	8,000	9,000	10,000	11,000	12,000	13,000	14,000	15,000
Rate of requiring thorough examinations (%)	5.00	185	256	327	398	469	540	611	682	753	824	895
	10.00	256	327	398	469	540	611	682	753	824	895	966
	15.00	327	398	469	540	611	682	753	824	895	966	1,037
	20.00	398	469	540	611	682	753	824	895	966	1,037	1,108
	25.00	469	540	611	682	753	824	895	966	1,037	1,108	1,180
	30.00	540	611	682	753	824	895	966	1,037	1,108	1,180	1,251
	35.00	611	682	753	824	895	966	1,037	1,108	1,180	1,251	1,322

(d) Females aged 70 to 74 years old, LDCT conducted annually

		Cost of the examination (yen)										
		5,000	6,000	7,000	8,000	9,000	10,000	11,000	12,000	13,000	14,000	15,000
Rate of requiring thorough examinations (%)	5.00	239	335	432	528	624	720	817	913	1,009	1,105	1,202
	10.00	335	432	528	624	720	817	913	1,009	1,105	1,202	1,298
	15.00	432	528	624	720	817	913	1,009	1,105	1,202	1,298	1,394
	20.00	528	624	720	817	913	1,009	1,105	1,202	1,298	1,394	1,490
	25.00	624	720	817	913	1,009	1,105	1,202	1,298	1,394	1,490	1,587
	30.00	720	817	913	1,009	1,105	1,202	1,298	1,394	1,490	1,587	1,683
	35.00	817	913	1,009	1,105	1,202	1,298	1,394	1,490	1,587	1,683	1,779

The shaded area indicates one million yen or lower.

was screening costs of 8,000 yen and a recall rate of 10% for male smokers aged 55 to 59 years old and 6,000 yen and 0% for male smokers aged 55 to 59 years old, respectively.

To determine the age at which low-dose CT lung cancer screenings can be introduced, we estimated the incremental cost-effectiveness ratio under the following conditions: a screening interval of one year, a screening cost of 10,000 yen (almost the same amount as the national mean: 9,971 yen)[9], and a recall rate of 20% (an estimated rate in this study). Consequently, it was suggested that LDCT for lung cancer can be introduced for male and female smokers aged 60 and 70 years or older, respectively.

In the case of LDCT at an interval of two years, regardless of the screening cost and recall rate, the incremental cost for one year of life-years saved was one million yen or lower for male and female smokers aged 55 years or older, and its cost- effectiveness was considered significantly high. Furthermore, when LDCT lung cancer screenings are conducted every two years, the ratio of the relative risk of cancer death between people who have undergone CR and LDCT is 0.70, and LDCT cancer screening is significantly effective for reducing the mortality due to lung cancer.

The present study has several limitations. Firstly, we analyzed cost-effectiveness only in smokers aged 55 years or older because we selected groups in which the mortality of lung cancer was reduced by NLST. On the premise that we introduce the LDCT screening to population-based screening, it may be difficult to define subjects as only smokers with public funds. Therefore, we should estimate the effect of LDCT screening on mortality reduction and cost-effectiveness in both smokers and non-smokers. However, it is considered of value that discussing about introduction of smoker's screening as a kind of screening for the high-risk group. Secondly, although we assumed the response rate to undergoing lung cancer screening was 100% in the present study, the current rate is about 20%[7]. Therefore, we should analyze the effects of the response rate on cost-effectiveness. Thirdly, relative risk is not available by sex and 5-years age group. Mortality in cancer patients was estimated as a 5-year survival rate. It may be said that the saved or gained life expectancy in the present study is rough. Finally, we assumed that the incremental cost for one life-year saved was one million yen or lower. According to a previous study[11], the amount one person can afford to pay per 1 quality-adjusted life years (QALY) is six to seven million yen. Therefore, we may adopt one million yen or higher for the incremental cost for one life-years saved; and it may enable the lowering of the age of subjects for whom LDCT can be introduced.

We must also keep in mind that cost in this study contains only the medical fee and screening and does not contain welfare cost and health expenditure, when we apply this study to public health policy. It is also necessary to discuss the goal of smoking rate reduction from the view of the cost-effectiveness. We should also explain that control strategy of LDCT in the present study is CR. The result of a cost-effectiveness analysis might change depending on the choice of control strategy. From the results of several studies of cost-effectiveness, the introduction of screening should be discussed.

In conclusion, LDCT could be introduced for male and female smokers aged 55 and 65 (or 70) years or older, respectively. Furthermore, the present study elucidates the requirements for the introduction of LDCT cancer screening including the age, cost of the LDCT screening, and interval between screenings. We believe that our results provide useful data for developing implementation methods and policies, including the selection of subjects and determination of screening costs.

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