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ORIGINAL ARTICLE

Performance of Low-dose CT Screening for Detecting Lung Cancer at the Early Stage and the Estimated Tumor Growth Rate According to the Smoking Status/Age

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ABSTRACT —— ***Objectives.*** To assess the utility of low-dose spiral chest CT (LDCT) screening for detecting lung cancer at the early stage and to examine the tumor volume doubling time (TVDT) according to the smoking status and age. ***Methods.*** A total of 295 patients who participated in an LDCT screening program for citizens of Nagano, Japan between 2000 and 2010 were examined with respect to the incidence, prognosis-related features (tumor size, proportion of clinical stage I tumors and histopathology) and TVDT of the lesions. ***Results.*** 1) The prevalence rate of lung cancer was similarly high in all smoking categories (504 per 100,000 subjects for the entire group), especially high in the elderly subjects (＞50 years) and low in the patients in their 40's, seen only in non-smokers. The annual incidence was 84 in all subjects, being particularly low in the non-smokers and zero in the 40-year-old group. 2) The ratio of the prevalence cancer/annual repeat cancer was 6.0 (504/84), with 4.1 for smokers and 11.0 for non-smokers. 3) The prognosis-related features were significantly different between the smokers and non-smokers, with smokers having a larger tumor size and lower proportion of c-stage I lesions. 4) The mean TVDT for all 69 analyzed lesions was 459 days, with 364 days for smokers and 606 days for non-smokers. The TVDT values were shorter in the elderly smokers but longer in the elderly non-smokers, and varied widely in the current and non-smokers, while remaining within narrow limits in the ex- and passive smokers. 5) The rate of possible over-diagnosis (TVDT ＞400 days) was 17% in smokers and 44% in non-smokers. ***Summary and Conclusions.*** 1) Compared with the findings of US studies, the rate of detection of lung cancer was lower in the Japanese smokers, while the prognosis-related features were similar in the two populations, although more favorable features were identified in the Japanese non-smokers. 2) The high rate of prevalence cancer, irrespective of the smoking status, with nearly 45% of patients having tumors ＞14 mm, stresses the importance of prevalence CT screening for both smokers and non-smokers. The prevalence of lung cancer was fairly high in the subjects ＞50 years of age, thus justifying the use of cost-effective screening. The detection of lung cancer in 40-year-old patients among the non-smoking subjects only requires further examinations. 3) For non-smokers, the lower incidence with more favorable prognosis-related features／TVDT of lung cancer stresses the importance of performing repeat scans at an inter-screening interval of ＞1 year. 4) Hence, in general, annual repeat screening for smokers and biennial screening for non-smokers appear to be appropriate for detecting the majority of lung cancers measuring ＜14 mm. However, based on the TVDT results obtained in this study, the detection of lung cancer measuring ＜14 mm is expected to fail in some proportion of 60- and 70-year-old smokers on annual repeat screening and 60-year-old non-smokers on biennial repeat screening, and it is necessary to identify specific risk factors rationally supporting the more frequent use of CT scans in these patients in order to avoid detecting cancer in the late stage. In contrast, no failure to detect lesions ＜14 mm is expected using triennial and quadrennial scans in 70- and 50-year-old non-smokers, respec-

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tively (although the number of 50-year-old patients in this study was limited), and triennial repeat screening appears to be appropriate for these subgroups. 5) The variety of TVDT values observed according to the smoking status/age should be taken into account when planning chest CT screening in the community and performing work-up studies to estimate the degree of tumor growth in the hospital.

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KEY WORDS —— Lung cancer, Screening, Computed tomography (CT), Tumor volume doubling time, Chest

INTRODUCTION

Low-dose spiral chest CT (LDCT) screening allows for the detection of small lung nodules, with potential improvements in the treatment outcomes.[1-3] In Japan, such screening techniques have gradually evolved into optional procedures on annual health check examinations, which include the participation of both smokers and non-smokers, thus reflecting the high level of social interest in lowering mortality from lung cancer. However, little information regarding the performance of CT scans is available to help individuals, consulting physicians and/or health planners at local municipalities to continue such screening.

In this report, we describe the utility of LDCT screening for detecting lung cancer at the small/early stage and the estimated tumor volume doubling time (TVDT) according to the smoking status/age.

BACKGROUND

Lung cancer is the leading cause of cancer death in Japan. However, several studies have indicated that the risk of mortality associated with smoking is lower in Asians than in Caucasians.[4,5] For example, there is a lower risk of lung cancer death among smokers and a higher risk among non-smokers in Japan than in the US. Notably, the relative risk (RR) adjusted for age and area for current smokers compared with non-smokers in Japan is 4.5 (in men) and 4.2 (in women), compared with the much higher rate of 23.2 (men) and 12.8 (women) in the Cancer Prevention Study (CPS)-II in the US, with a crude incidence rate (CIR) per 100,000 person-years for middle-aged non-, former and current smokers in Japan during the period of 1990-1999 of 30.7, 83.3 and 128.3 for men and 21.9, 75.7 and 74.5 for women, respectively. In addition, the death rate from lung cancer among never-smokers is higher in men than in women and in East Asians residing in Korea and Japan (but not the US) than that observed in individuals of European descent. As to the prognosis after treatment of lung cancer in non-smokers versus smokers, a Japanese study of 267 surgically treated patients with adenocarcinoma noted only a slight difference in the 5-year survival rates (smokers: 45%, non-smokers: 55%).[6] Similarly, one US study of 4,546 patients with lung cancer who received primary medical and surgical treatment noted little difference in the long-term survival rates between smokers and non-smokers and reported a dismal prognosis for patients in the advanced stage of cancer.[7]

LDCT screening programs have been shown to be effective for detecting small lung cancer lesions, resulting in subsequently improved post-treatment survival rates.[1,2,8,9] However, it is important to consider relevant biases when evaluating the results of CT screening programs, including lead time, length time and over-diagnosis bias.[10]

OBJECTIVES

To retrospectively examine 295 lung cancers detected on LDCT screening, with a special focus on the rate of detection, prognosis-related factors (proportion of small lesions (<14 mm in size), proportion of clinical (c) stage I lesions, histopathology) and to examine the TVDT values according to the smoking status and patient age. We set an arbitrary target tumor size of <14 mm for presumed highly curable cancers based on the results of previous studies,[9,11-15] recognizing that: 1) lung cancers <10 mm in size are highly curable and 2) many subsolid density lesions measuring <14 mm in size are also highly curable, although 3) using this criterion, a proportion of solid tumors may grow to an unintended stage higher than stage I.

MATERIALS AND METHODS

Subjects

We started a mobile LDCT screening program for lung

cancer in 2000 as part of annual health care examinations for citizens, following our initial trial.[16] Information regarding the procedure, including the potential benefits of early detection and disadvantages of exposure to radiation, was provided by leaflets and we recommended initial CT scans for subjects ≥40 years of age and repeat scans annually for smokers (as generally recommended in other screening programs[1]) and after a couple of years of no screening for non-smokers (with a maximum interval of 1,095 days, i.e., three years, as there is little empirical evidence with respect to the appropriate interval for repeat screening in non-cancer patients). We tentatively suggested this interval based on the findings of our initial study on the TVDT of lung cancer,[17] in which a significantly longer mean TVDT value was noted in non-smokers (607 ± 392 days, mean ± SD) than in smokers (292 ± 297 days) [for further rationalization of the suggestion of triennial screening for non-smokers, we expected that the majority of lung cancers would be detected at an early stage even with an interval of nearly three years, because for 3-mm nodules with a shortest TVDT of 215 days (i.e. 607 − 392 days, mean−SD, shown in our previous study) among non-smokers an interval of 1,433 days (3.9 years) was required, when calculated according to the modified Schwartz equation[17] (see below), to grow to 14 mm (our arbitrarily defined tumor size for achieving a favorable treatment outcome)]. However, the interval of our screening program was in fact selected by the health care plan of the local government and the preference of the individual, and the local governments apparently did not select the screening interval based on the patient's smoking status.

From 2000 through 2010, 88,758 subjects (46,861 men/41,897 women) underwent 49,786 initial scans and 38,972 repeat scans, including 23,699 annual, 6,571 biennial, 5,379 triennial and 3,323 quadrennial (or with an interval of more years) scans. The majority of smokers [current or ex-smokers (who had stopped smoking for >5 years)] were men (87% for both the initial and repeat scans), while the majority of non-smokers [passive smokers (living in the same house with a smoker) and non-smokers (having smoked fewer than 100 cigarettes during their lifetime)] were women (80% and 79% for the initial and repeat scans, respectively).

CT image acquisition and interpretation

A van housing a four-detector row CT scanner (CT-Robusto, Hitachi Medical, Tokyo) was parked at local municipalities to perform CT scans without the intravenous injection of contrast medium. The scanning parameters were as follows: 120 kVp, 25.0 mAs (effective), beam pitch = 1.25 and slice thickness = 10 mm.[18] A panel of radiologists and pulmonologists interpreted the CT images on two monochrome high-resolution cathode ray tube (CRT) monitors using a reporting system (PAXiS viewer, Kissei Comtec, Matsumoto, Japan). Patients with suspicious lesions were advised to undergo a work-up examination at a public/local hospital. The results of the work-up examinations/treatment, reported by the physician in charge of the management of the patient, were indexed and maintained by a health promotion corporation, as legislated in 2004. Information obtained from the database was submitted for the analysis in this study. The study protocol was approved by the Institutional Ethics Committee. Due to the retrospective nature of the study design, a waiver for patient informed consent was granted by the committee.

Data analysis

The pathologists reviewed the histopathology reports to determine the classification of the tumors based on the 1999/2004 WHO/IASLC classification. Clinical staging was performed based on the 2009 IASLC staging system.[19,20] The radiologist retrospectively measured the tumor size using a light pen on the CRT monitors, and enlarged node(s) with a short axis of >10 mm on the screening CT images was defined as exhibiting positive nodal involvement. The TVDT was calculated using the modified Schwartz equation[17,18,21]: $TVDT = t \times \log 2 / \{\log (Vt/V0)\}$, where t is the interval between two CT scans, $V0$ is the tumor volume on the initial CT scan and Vt is the tumor volume on the last CT scan, with $V = (\pi/6) \times a^2 b$, where a is the maximum transverse diameter and b is the perpendicular dimension. All tumors with negative findings on preceding screening CT scans were presumed to be 3 × 3 mm in size for the calculation of the TVDT, as adopted in our previous reports.[2,8,17] This presumption of an invisible tumor size at 3 mm is based on the results of our previous retrospective analysis of the dimensions of a detectable tumor size on low-dose screening CT images.[17]

The TVDT values were sub-classified into five levels according to clinical significance, including very short (VS, range: <54 days), short (S, 55-218 days), medium (M, 219-400 days), long (L, 401-1,499 days) and extremely

Table 1. Number and Proportion of Lung Cancers on the Initial and Annual Repeat Screening Examinations Stratified According to Age and the Smoking Status

Smoking status	n	Patients (n) per 100,000 participants by age (year)				
		40-49	50-59	60-69	>70	Total
Prevalence lung cancer, including misclassified and misdiagnosed cases at initial screening						
current smokers	61	0	237	510	1,188	424
ex-smokers	39	0	240	550	772	518
Subtotal; smoker group	100	0	238	525	964	457
passive smokers	27	0	328	550	1,401	523
non-smokers	124	272	336	578	805	546
Sub-total; non-smoker group	151	210	334	573	876	542
TOTAL	251	104	291	552	912	504
Incidence lung cancer at annual repeat scans						
current smokers	10	0	44	55	307	106
ex-smokers	5	0	0	62	232	122
Subtotal; smoker group	15	0	35	57	275	111
passive smokers	2	0	226	0	279	116
non-smokers	3	0	0	26	74	35
Subtotal; non-smoker group	5	0	52	22	98	49
TOTAL	20	0	42	41	199	84

The prevalence of cancer was similarly high for all smoking categories, while the elderly subjects >50 years of age exhibited an increasingly higher rate in accordance with age. The annual repeat cancer rate was low, specifically being lowest for non-smokers.

long (eL, ≥1,500 days), with subdivision of the S category into S1 (55 to 112 days), S2 (113-163 days) and S3 (164-218 days). The longest period for each level of VS, S1, S2 and S3, i.e., 54, 112, 163 and 218 days, corresponded to a time required for a 3-mm nodule to grow to 14 mm (our arbitrarily defined tumor size for achieving a favorable treatment outcome) of 364 (within one year), 729 (-2 years), 1,094 (-3 years) and 1,459 days (-4 years), respectively. The longest period for level M, 400 days, is the traditionally used upper limit for genuine lung cancer.[21]

The tumor size and TVDT values were analyzed according to the smoking status using a one-way analysis of variance (ANOVA). The proportion of c-stage I lesions detected on screening, the smoking status, histopathology and the TVDT level according to the smoking status and age group were analyzed using frequency tables and the χ^2 test. P values of <0.05 were considered to be statistically significant. The statistical analyses were performed using the MedCalc software program.[22]

RESULTS

Number of cancer lesions detected on screening

The work-up examinations, which were available as of January 1, 2011, identified 306 lung cancers. Excluding one patient with a hilar mass and 10 patients with insufficient information, 295 cancers were examined, comprising 251 initial cancers (including 28 lesions misclassified or misdiagnosed in the initial round and four lesions with an indistinct tumor margin) and 44 repeat cancers (including 20 lesions on annual repeat screening).

The prevalence was similarly high for all smoking categories, with 504 for the entire patient group (Table 1, upper half). Meanwhile, the rate in elderly subjects >50 years of age increased with age, and lung cancers among 40- to 49-year-old patients were seen in non-smokers only.

The annual repeat cancer rate was low (lower half of Table 1), with 84 lesions in the entire patient group, specifically being lowest at 35 for non-smokers.

Prognosis-related features

The mean tumor size was larger in the smokers ($p = 0.063$, initial scans) (Table 2). The proportion of tumors smaller than 14 mm (our arbitrarily defined target tumor size) was 55% in smokers and 57% in non-smokers on the initial CT scans and 67% and 100%, respectively, on the annual repeat scans. The proportion of c-stage I lesions was lower in the smokers than in the non-smokers (76% vs. 90%, $p = 0.0053$, for initial cancers and 87% vs. 100%, $p = 0.9826$, for annual repeat cancers, re-

Table 2. Size and Proportion of Clinical Stage I Lesions According to the Timing of Screening and the Smoking Status

	n [%]	Tumor size (mm)		c-stage I	Proportion of c-stage I (%) for tumor size range [proportion of tumor size range among subtotal cancers]		
		Median (mean)	Range		<14 mm	15-20 mm	>21 mm
Initial screen	247 [100%]	13.3 (15.2)		85% (209/247)	97% (134/138) [56%]	96% (46/48) [19%]	48% (29/61) [25%]
Smokers	97 [100%]	13.8 (16.7)	0.4-57.4	76% (74/97)	91% (48/53) [55%]	90% (18/20) [21%]	29% (7/24) [25%]
Non-smokers	150 [100%]	12.0 (14.4)	1.8-52	90% (135/150)	100% (85/85) [57%]	100% (28/28) [19%]	59% (22/37) [25%]
Annual repeat screen	20 [100%]	10.4 (14.0)		90% (18/20)	100% (15/15) [75%]	100% (1/1) [5%]	50% (2/4) [20%]
Smokers	15 [100%]	11.3 (15.2)	5-36.9	87% (13/15)	100% (10/10) [67%]	100% (1/1) [7%]	50% (2/4) [27%]
Non-smokers	5 [100%]	9.7 (10.1)	7.7-13.5	100% (5/5)	100% (5/5) [100%]	NA*	NA*

The mean tumor size was smaller among the initial cancers in the non-smokers. Specifically, the proportion of lesions with a tumor size smaller than 14 mm was 55% in the smokers and 57% in the non-smokers on the initial CT scans and 67% and 100% on the annual repeat scans, respectively. The proportion of c-stage I lesions was lower in the smokers than the non-smokers on the annual repeat scans. *: not applicable.

spectively). The histopathology classification of the 100 initial cancers in the smokers included 62 (62%) adenocarcinomas (ADC), 14 (14%) squamous cell carcinomas (SCC), four (4%) large cell carcinomas (LCC), two (2%) small cell carcinomas (SCLC) and 18 (18%) lung cancers, not otherwise specified (LC-NOS), while that of the 151 initial cancers in the non-smokers included 142 (94.0%) ADC, one (0.7%) adenosquamous carcinoma and eight (5.3%) LC-NOS lesions. Of the 26 repeat cancers in smokers, there were 16 (61.5%) ADC lesions, five (19.2%) SCC lesions, one (3.8%) LCC lesion, three (11.5%) SCLC lesions and one (3.8%) LC-NOS lesion. Meanwhile, the 18 repeat cancers in the non-smokers included 17 (94.4%) ADC lesions and one (5.6%) LC-NOS lesion. In order to simplify the analysis using histopathology we divided the patients into three groups: ADC, non-ADC (with SCC, LCC, SCLC and others) and LC-NOS. The distribution of the histopathology was significantly different between the smokers and non-smokers (initial cancers, $p < 0.0001$, annual repeat cancers, $p = 0.4153$ (Table 3); repeat cancers from scans performed at an interval of one or more years [n = 44 (information not shown in the table), $p = 0.0263$].

ADC was the most common cancer, with a higher frequency on the initial scans and in non-smokers. The proportion of c-stage >I lesions was higher in the non-ADC and LC-NOS groups among smokers and zero among non-smokers on the repeat scans.

TVDT according to the smoking status, age and histopathology

Excluding two lesions with an indistinct tumor margin, TVDT data were available for 70 cancers. After further excluding a far outlier identified according to the outlier detection method using Grubbs right-sided test (alpha level, $p = 0.05$), the mean TVDT of the remaining 69 cancers was 459 days, with 364 days in smokers and 606 days in non-smokers ($p < 0.084$) (upper part of Table 4). Specifically, the mean TVDT in current smokers was 453 days, which was longer than the 187 days observed in ex-smokers, while the mean TVDT in passive smokers (871 days) was longer than that observed in non-smokers (473 days) ($p < 0.05$, Student-Newman-Keuls test for all pairwise comparisons). The subdivided categories of the TVDT values (right part of Table 4) showed a wide distribution pattern in the current smokers and non-smokers versus as deviated/partial pattern in the ex-smokers and passive smokers. The TVDT was >400 days (level L and eL, possible over-diagnosis[21]) in 17% (7/42) of the smokers and 44% (12/27) of the non-smokers.

The analysis of the TVDT values according to the smoking status/age (middle rows of Table 4) showed a shorter mean TVDT value in the elderly smokers versus a longer mean TVDT value in the elderly non-smokers. Specifically, the TVDT categories were mostly VS through M in the smokers 70- group, whereas a smaller proportion of VS/S1 values and larger proportion of M-eL values were seen in the smokers 60- and L groups among the smokers 50- group only, and no VS values were noted in the non-smokers group. Consequently, the annual repeat CT scans were expected to identify lung cancers of smaller size (less than 14 mm) in most of the smokers, excluding 11% of the 70-year-old and 7% of the 60-year-old patients. On the other hand,

Table 3. Histopathology According to the Timing of Screening and the Smoking Status and Proportion of Clinical Stage >I Lesions According to the Timing of Screening, the Smoking Status and Histopathology

	ADC	Non-ADC	LC-NOS	subtotal
Smoking		Number of patients (percentage)		
All patients	213 (80%)	27 (10%)	27 (10%)	267 (100%)
Prevalence patients	202 (82%)	19 (8%)	26 (11%)	247 (100%)
smokers	(62%)	(20%)	(19%)	97 (100%)
non-smokers	(95%)	(0%)	(5%)	150 (100%)
Annual repeat patients	11 (55%)	8 (40%)	1 (5%)	20 (100%)
smokers	(47%)	(47%)	(5%)	15 (100%)
non-smokers	4 (80%)	(20%)	(0%)	5 (100%)
Proportion of c-stage >I		Percentage		
All patients	9%	30%	48%	15% (40/267)
Prevalence patients	9%	37%	46%	15% (38/247)
smokers	10%	37%	56%	24% (23/97)
non-smokers	9%	NA	25%	10% (15/150)
Annual repeat patients	0%	13%	100%	10% (2/20)
smokers	0%	14%	100%	13% (2/15)
non-smokers	0%	0%	NA	0% (0/5)

ADC: adenocarcinoma, LC-NOS: lung cancer, not otherwise specified.

The distribution of histopathology was significantly different between the smokers and non-smokers. Adenocarcinoma was the most common cancer, with a higher frequency on the initial scans and in non-smokers. The proportion of c-stage >I lesions was higher in the non-ADC and LC-NOS groups among smokers and zero among non-smokers on the repeat scans.

for non-smokers, the rate of screening failure of lung cancer at < 14 mm in size in the 60-year-old non-smokers was expected to be 22% on the biennial scans and 33% on the triennial scans (combination of biennial and triennial scans), and triennial repeat CT scans were expected to identify all lung cancer lesions smaller than 14 mm in the 50- and 70-year-old patients. The rate of screening failure was expected to be high on the quadrennial repeat CT scans.

The analysis of the TVDT values according to the histopathology (bottom rows of Table 4) showed shorter TVDT values in the non-ADC (n = 14; mean, 173 days) and LC-NOS (n = 4; 119 days) groups than in the ADC group (n = 51; 521 days) ($p < 0.05$, Student-Newman-Keuls test for all pairwise comparisons).

DISCUSSION

The present study examined patients older than 40 years of age, comprising a total of 251 cancers identified on the initial scans and 44 cancers detected on the repeat scans (including 20 cancers on the annual repeat scans). A similarly high prevalence of lung cancer was observed, rather unexpectedly, in all smoking categories. The highest prevalence of lung cancer was noted among the 50- to 70-year-old subjects. However, lung cancer was identified in only some of the 40- to 49-year-old non-smokers, compared to none of the smokers in the same age group (Table 1). This finding is in agreement with the results of a previous study that noted a higher mortality rate among Asian non-smokers (living in Japan and Korea, but not in the US) than in Western citizens,[5] as well as other studies identifying lung cancer in a few young female non-smokers.[23-25]

Table 5 shows the results of a comparison of the findings of the current study and previous Western studies, which included only smokers. The prevalence rates were higher in the Western studies than in our smokers (2.0-5.5 times[1,3,21,26,27]), with the exception of the Danish Lung Cancer Screening Trial (DLCST) .[28] The Western studies[1,26,27] also showed higher annual incidence rates than that observed in our population (2.5-6.7 times). The ratio of the prevalence cancer/annual repeat cancer was 4.1 in the smokers (and 11.1 in the non-smokers) in our study, compared with 4.8 to 3.6 observed in the US studies[21,27] and only approximately 1.2 and 1.1 in the European studies.[26,28] The high ratio seen in our non-smokers

Table 4. TVDT Values According to the Smoking Status, Age Group and Histology

	n (%)	Mean	TVDT, number of patients (percentage)						
			VS*	S1*	S2*	S3*	M*	L*	eL*
All cancers	69 (100%)	459 days	4 (6)	15 (22)	5 (7)	7 (10)	19 (28)	14 (20)	5 (7)
Smoking status									
Smokers	42 (100)	364	(10)	(31)	(10)	(7)	(26)	(12)	(5)
current-smokers	28 (100)	453	(11)	(32)	(7)	(7)	(18)	(18)	(7)
ex-smokers	14 (100)	187	(7)	(29)	(14)	(7)	(43)	(0)	(0)
Non-smokers	27 (100)	606	(0)	(7)	(4)	(15)	(30)	(33)	(11)
passive-smokers	9 (100)	871	(0)	(0)	(0)	(11)	(33)	(33)	(22)
non-smokers	18 (100)	473	(0)	(11)	(6)	(17)	(28)	(33)	(6)
Smoker-group/age									
smokers-70-	27 (100)	245	(11)	(41)	(7)	(11)	(22)	(4)	(4)
smokers-60-	14 (100)	385	(7)	(14)	(14)	(0)	(36)	(21)	(7)
smokers-50-	1 (100)	969	(0)	(0)	(0)	(0)	(0)	(100)	(0)
non-smokers-70-	15 (100)	733	(0)	(0)	(0)	(13)	(33)	(40)	(13)
non-smokers-60-	9 (100)	505	(0)	(22)	(11)	(22)	(0)	(33)	(11)
non-smokers-50-	3 (100)	273	(0)	(0)	(0)	(0)	(100)	(0)	(0)
Histology									
ADC	51 (100)	521	(4)	(10)	(8)	(8)	(35)	(25)	(10)
non-ADC	14 (100)	173	(7)	(64)	(7)	(7)	(7)	(7)	(0)
LC-NOS	4 (100)	119	(25)	(25)	(0)	(50)	(0)	(0)	(0)

*Data are the number of patients (percentage). VS: very short (TVDT <54 days), S: short (55-218 days), M: medium (219-400 days), L: long (401-1,499 days), eL: extremely long (≥1,500 days), with subdivisions of S1 (55 to 112 days), S2 (113-163 days) and S3 (164-218 days) (see the meaning of subdivision at the data analysis in the text).

The mean TVDT value was shorter in the smokers than in the non-smokers. Specifically, the TVDT values were longer in current smokers than in ex-smokers and in passive smokers than in non-smokers. The subdivided categories of the TVDT values showed a wide distribution pattern in the current smokers (from level VS through eL) and non-smokers (from S1 through eL) compared to a deviated/partial pattern in the ex-smokers (a low proportion of VS and more slow growing cancers, L and eL) and passive smokers (from S3 through eL without fast growing cancers, from VS through S2). The analysis of the TVDT values according to the smoking status/age showed the shortest mean TVDT value in the elderly smokers, whereas a longer mean TVDT value was observed in the elderly non-smokers. The TVDT values were also short in the non-ADC and LC-NOS groups and long in the ADC group.

Table 5. Diagnostic Performance of Different CT Screening Programs

Study	Participants (n) baseline; repeat	LC (n) baseline; repeat	LC per 100,000 participants baseline; repeat	Median size (mm) baseline; repeat	c-Stage I (%) baseline; repeat	% of all cancers baseline; repeat		TVDT (days) median (mean)
						ADC	non-ADC	
Present study, 2000-2010	49,786; 23,699	251; 20	504; 84	13.0; 10.4				257 (459)
smokers	21,905; 13,523	100; 15	457; 111	13.8; 11.3	76; 87	62; 47	20; 47	164 (364)
non-smokers	27,881; 10,176	151; 5	542; 49	12.0; 9.7	90; 100	95; 80	0; 20	348 (606)
I-ELCAP, 1993-2005[1,29]	31,567; 27,456	410; 74	1,299; 270	13; 9	85	70; 47	20; 47	98
NY-ELCAP, 2000-2003[27]	6,295; 6,014	101; 20	1,604; 333	14; 8	91; 85	65; 35	27; 60	
Mayo Lung study, 1999-2004[21]	1,520	31; 34 (4 rounds)	2,039; 559	12.0; 10	71; 50	61; 18	23; 50	166 (688)
NLST, 2002-2010[3]	26,722	1,060	645		50	36.3	40.8	
NELSON, 2003-2006[26]	7,557; 7,289	70; 54	926; 741		64; 74 (p-stage)			
DLCST 2004-2006[28]	2,052	8; 29 (5 rounds)	390; 353		NSCLC, 53; 67	67	24	

Comparison of the results of the current study with those of previous Western studies that included only smokers. The rates of cancer were higher in the Western studies than our smokers, with the exception of the Danish Lung Cancer Screening Trial (DLCST). The Western studies also showed higher annual incidence rates than that observed in our smokers. In contrast, few differences were seen in the prognosis-related features between the Japanese smokers and the subjects of the Western studies. The Japanese non-smokers showed a higher proportion of c-stage I and ADC lesions and a longer mean TVDT value than the smokers.

presumably reflects a greater proportion of slow-growing tumors among the initially detected cancers, which demonstrated wider variation in the growth rate; the equilibrium at the initial scans was presumably reached due to the accumulation of slowly growing cancers during the preceding years, while more rapidly growing cancers passed away from the screening field due to cancer advancement. On the other hand, the low ratios reported in the European studies suggest that the majority of cancers identified in these studies were rapidly growing, with a narrow range of growth rates; in such cases, it may be difficult to detect cancers at a small, early stage.

As shown in Table 5, there were few differences in the prognosis-related features between our smokers and that observed in the Western studies. For example, the tumor size was similar in our study and the US studies. In addition, the proportion of c-stage I lesions in our study was within the range reported in the Western studies, as was the proportion of ADC/non-ADC lesions. Moreover, the TVDT values in our study were similar to that observed in the Mayo Lung study[21] and slightly longer than that noted in the I-ELCAP trial.[29] Compared with that seen in the smokers, our non-smokers exhibited a higher proportion of c-stage I lesions in addition to a significantly different distribution of the histopathology type, with a higher proportion of ADC lesions and a longer mean TVDT value ($p<0.05$).

In the present study, we examined the distribution of the TVDT values according to the smoking status and noted a wide distribution in the current and non-smokers compared to a narrow/more deviated distribution in the ex- and passive smokers. VS was less frequently observed in the ex-smokers than the current smokers, likely representing the favorable effects of smoking cessation; however, it should be noted that no L or eL lesions (i.e., slowly growing tumors) were observed in the ex-smokers. Although, unfortunately, the incidence of lung cancer was relatively high in the passive smokers, a longer mean TVDT value was noted in the passive smokers than in the non-smokers. To the best of our knowledge, similar important findings have not been reported previously and should be taken into account when planning screening and designing work-up studies to estimate the degree of tumor growth (Table 4).

The analysis of the TVDT values according to the smoking status/age showed a shorter mean TVDT value in the elderly smokers versus a longer mean TVDT value in the elderly non-smokers. Specifically, the TVDT categories were mostly VS through M in the smokers 70- group, whereas a smaller proportion of VS/S1 values was seen in the smokers 60- group and only L values were observed in the smokers 50- group. In addition, no VS values were detected among the non-smokers. Consequently, the annual repeat CT scans were expected to identify lung cancers with a size less than 14 mm in the majority of smokers, excluding 11% of the 70-year-old and 7% of the 60-year-old patients (to avoid detection of these overgrown cancers, it is necessary to identify specific risk factors to rationally support the more frequent use of CT scans, Table 4, smoking status/age). On the other hand, for non-smokers, the rate of screening failure in detecting tumors measuring <14 mm on the biennial repeat scans was expected to be 22% in the 60-year-old patients, while no cases of screening failure were seen in the 70- (even on triennial scans) and 50-year-old (on the quadrennial scans, although the number of patients was limited) subjects.

In the present study, the TVDT was <100 days and >400 days in 33% and 17% of the smokers, respectively. These rates were 33% and 27% in the Mayo Clinic study[24] and 50% and 3% in the I-ELCAP study,[29] respectively. Because cancer lesions with a TVDT of >400 days are sometimes not defined as genuine cancers,[21] concern regarding the potential for over-diagnosis (i.e., the detection of cancer that does not affect the patient's life span if left untreated[10]) may be slightly higher in our study and the Mayo Clinic study than the I-ELCAP trial. It is anticipated that recently introduced volumetric software analyses[30] will enhance the management of such patients on future work-up examinations by increasing the availability of 3D quantitative data for the volume/mass of tumors on thin-section CT images.

The major strength of this study is the population sample, which included passive and non-smokers, as the current literature lacks information on these subjects. Using an arbitrarily defined tumor size, we were able to evaluate the performance of our CT screening program for detecting lung cancer at the small/early stage. Our findings also described the tumor growth rates stratified according to the smoking status and age. Notwithstanding the above strengths, our study has the follow-

ing limitations. 1) The tumors were evaluated on LDCT scan images with a slice thickness of 10 mm, which made it difficult to measure the CT values accurately. For this reason, our analysis did not include data for the tumor density pattern or CT values. 2) Our study population included a small number of 40-year-old patients and lacked data for repeat scans in this subgroup, which resulted in some ambiguity regarding the incidence of lung cancers in young never-smokers. 3) The lack of follow-up is associated with uncertainty with respect to interval cases. 4) Finally, because this study was based on a local screening program in Japan, the data must be refined in accordance with similar programs conducted in other geographic regions with patients exhibiting different age-, sex- and race-specific risks.

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REFERENCES

1. International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, Libby DM, Pasmantier MW, Smith JP, et al. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med.* 2006;355:1763-1771.
2. Sone S, Nakayama T, Honda T, Tsushima K, Li F, Haniuda M, et al. Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. *Lung Cancer.* 2007;58:329-341.
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011;365:395-409.
4. Sobue T, Yamamoto S, Hara M, Sasazuki S, Sasaki S, Tsugane S, et al. Cigarette smoking and subsequent risk of lung cancer by histologic type in middle-aged Japanese men and women: The JPHC study. *Int J Cancer.* 2002;99:245-251.
5. 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:e185. doi: 10.1371/journal.pmed.0050185
6. Sobue T, Suzuki T, Fujimoto I, Doi O, Tateishi R, Sato T. Prognostic factors for surgically treated lung adenocarcinoma patients, with special reference to smoking habit. *Jpn J Cancer Res.* 1991;82:33-39.
7. Meguid RA, Hooker CM, Harris J, Xu L, Westra WH, Sherwood JT, et al. Long-term survival outcomes by smoking status in surgical and nonsurgical patients with non-small cell lung cancer: comparing never smokers and current smokers. *Chest.* 2010;138:500-509.
8. 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.
9. Henschke CI, Yankelevitz DF, Miettinen OS, International Early Lung Cancer Action Program Investigators. Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size. *Arch Intern Med.* 2006;166:321-325.
10. Patz EF Jr, Goodman PC, Bepler G. Screening for lung cancer. *N Engl J Med.* 2000;343:1627-1633.
11. Gajra A, Newman N, Gamble GP, Abraham NZ, Kohman LJ, Graziano SL. Impact of tumor size on survival in stage IA non-small cell lung cancer: a case for subdividing stage IA disease. *Lung Cancer.* 2003;42:51-57.
12. Watanabe S, Oda M, Go T, Tsunezuka Y, Ohta Y, Watanabe Y, et al. Should mediastinal node dissection be routinely undertaken in patients with peripheral small-sized (2 cm or less) lung cancer? Retrospective analysis of 225 patients. *Eur J Cardiothorac Surg.* 2001;20:1007-1011.
13. Miller DL, Rowland CM, Deschamps C, Allen MS, Trastek VF, Pairolero PC. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. *Ann Thorac Surg.* 2002;73:1545-1551.
14. Lee PC, Korst RJ, Port JL, Kerem Y, Kansler AL, Altorki NK. Long-term survival and recurrence in patients with resected non-small cell lung cancer 1 cm or less in size. *J Thorac Cardiovasc Surg.* 2006;132:1382-1388.
15. Suzuki K, Yokose T, Yoshida J, Nishimura M, Takahashi K, Nagai K, et al. Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. *Ann Thorac Surg.* 2000;69:893-897.
16. 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;351:1242-1245.
17. Hasegawa M, Sone S, Takashima S, Li F, Yang ZG, Maruyama Y, et al. Growth rate of small lung cancers detected on mass CT screening. *Br J Radiol.* 2000;73:1252-1259.
18. Sone S, Matsumoto T, Honda T, Tsushima K, Takayama F, Hanaoka T, et al. HRCT features of small peripheral lung carcinomas detected in a low-dose CT screening program. *Acad Radiol.* 2010;17:75-83.
19. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. *World Health Organization classification of tumours:*

pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: LARC; 2004:35-44.
20. Goldstraw P. The 7th Edition of TNM in Lung Cancer: what now? *J Thorac Oncol*. 2009;4:671-673.
21. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Tazelaar HD, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology*. 2007;242: 555-562.
22. MedCalc for windows, version 12.2.1.0 (MedCalc Software, Mariakerke, Belgium).
23. Thomas L, Doyle LA, Edelman MJ. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. *Chest*. 2005;128:370-381.
24. Nordquist LT, Simon GR, Cantor A, Alberts WM, Bepler G. Improved survival in never-smokers vs current smokers with primary adenocarcinoma of the lung. *Chest*. 2004;126:347-351.
25. Subramanian J, Velcheti V, Gao F, Govindan R. Presentation and stage-specific outcomes of lifelong never-smokers with non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2007;2:827-830.
26. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nickaerts K, Vernhout R, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med*. 2009; 361:2221-2229.
27. New York Early Lung Cancer Action Project Investigators. CT Screening for lung cancer: diagnoses resulting from the New York Early Lung Cancer Action Project. *Radiology*. 2007;243:239-249.
28. Saghir D, Dirksen A, Ashraf H, Bach KS, Brodersen J, Clementsen PF, et al. CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT. *Thorax*. 2012;67:296-301.
29. Henschke CI, Yankelevitz DF, Yip R, Reeves AP, Farooqi A, Xu D, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. *Radiology*. 2012; 263:578-583.
30. Sone S, Hanaoka T, Ogata H, Takayama F, Watanabe T, Haniuda M, et al. Small peripheral lung carcinomas with five-year post-surgical follow-up: assessment by semi-automated volumetric measurement of tumour size, CT value and growth rate on TSCT. *Eur Radiol*. 2012;22:104-119.