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REVIEW ARTICLE

Efficacy of low-dose computed tomography screening for lung cancer: the current state of evidence of mortality reduction

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Abstract The interim and final results of randomized controlled trials on the efficacy of lung cancer computed tomography (CT) screening have been reported recently from Western countries. The outcome of the National Lung Screening Trial (NLST) demonstrated the efficacy of low-dose thoracic CT screening for heavy smokers; however, other studies have found no apparent reduction in the mortality rate, and the outcome of the NELSON study is awaited. To date, a few studies have reported on the efficacy of lung cancer CT screening for non-/light smokers. A report from the Hitachi district, which is an ecological/time series study where non-/light smokers account for approximately half of the CT screening examinees, was published in 2012, with an outcome suggesting efficacy. Currently, a randomized controlled trial (JECS Study) is underway in Japan with non-/light smokers as the subjects, and this trial is very important in terms of cancer prevention.

Keywords Lung cancer · Cancer screening · Thoracic CT screening · Efficacy · JECS study

Introduction

The Japanese Guidelines for Lung Cancer Screening [1] indicate that the current lung cancer screening system in Japan is effective for reducing mortality when the quality of the screening system is sufficiently high; however, the efficacy of computed tomography (CT) screening for lung cancer has not been proven.

The interim [2, 3] and final results [4–6] of randomized controlled trials on the efficacy of lung cancer CT screening have been reported recently in Western countries (Table 1), including the mortality reduction observed in the National Lung Screening Trial (NLST) in 2011 [7]. In Japan, the ecological/time series study in the Hitachi district was the first study to suggest a mortality reduction effect of CT screening for lung cancer in a population including non-/light smokers [8]. In this paper, we review the current evidence regarding the efficacy of lung cancer CT screening in Japan and in other countries.

Prior to the NLST report

Lung cancer screening by chest CT using standard doses is problematic because of radiation exposure, so the current guidelines [1] advise against this type of screening for healthy individuals. To resolve the issue of radiation exposure, low-dose chest CT screening was introduced and developed, with substantial advances in CT technologies evolving over time [9–11].

The initial reports of low-dose chest CT screening include the results of the "Anti-Lung Cancer Association" by Kaneko et al. [12], the Nagano Group by Sone et al. [13], and the Early Lung Cancer Action Project (ELCAP) by Henschke et al. [14]. With these and successive reports, the detection rate of lung cancer, rate of stage I diseases, and survival rate of patients with detected lung cancer have all been shown to be much higher with CT screening than with chest X-ray screening [15, 16]. However, the efficacy of cancer screening cannot be proven by comparing the

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Table 1 Recent and ongoing randomized controlled trials to evaluate the efficacy of low-dose thoracic computed tomography screening for lung cancer

Study	Country	Control	Screening interval (years)	Screening rounds	Follow-up period after randomization (years)	Number of participant (study:control)	Age	Smoking index	Relative risk for Lung cancer death	References
NLST	USA	Chest X-ray	1	3	5–7	53454 (1:1)	55–74	600≦	0.80	[7]
DLCST	Denmark	None	1	5	4–5.5	4104 (1:1)	50–70	400≦	1.36*	[4]
DANTE	Italy	None	1	5	6	2472 (1:1)	60–75	400≦	0.99	[2, 6]
MILD	Italy	None	1/2	5/3	4.4	4099 (2:2:3)	49–	400≦	1.49*	[5]
NELSON	Belgium/Nederland	None	1, 2, 2.5	4	8.2	15822 (1:1)	50–75	300–375≦		[24–26]
ITALUNG	Italy	None	1	4	6	3206 (1:1)	55–69	400≦		[22]
LUSI	Germany	None	1	5		4052 (1:1)	50–69	300–375≦		[3]
UKLS	UK	None		1	10	4055 (1:1)	50–75	LLP_{V2}**		[21]
Depiscan	France	Chest X-ray	1	2		765 (1:1)	50–75	300≦		[23]
JECS study	Japan	Chest X-ray	5	2	10	1455 (1:1)	50-64***	<600		[35]

* Roughly estimated

** LLP_{V2} (Liverpool Lung Project model version 2) is a multivariate evaluating risk model, including smoking status and prior pulmonary diseases

*** 50–70, after March 2016

survival rate and detection rate; instead, the mortality rate of lung cancer must be considered [17, 18].

Until the mid-2000s, no reports had evaluated the mortality reduction achieved by chest CT screening. The first report evaluating the mortality reduction was published in 2005. In this report, the mortality rate of lung cancer in chest CT screenees at the Mayo Clinic was compared with that in the participants of the Mayo Lung Project (MLP; a randomized controlled trial that evaluated the mortality reducing effect of lung cancer screening with chest X-ray and sputum cytology) from the 1970s [19]. The mortality rate of lung cancer in the CT screening group was calculated with only CT screening examinees who were selected with the same conditions as the MLP participants. The mortality rate of lung cancer was 2.8/1000 person-years in the CT screening group vs. 2.0/1000 person-years in the MLP participants. This difference was not significant, despite the higher mortality rate in the CT screening group.

In 2007, a model analysis was carried out with CT screening examinees as the subjects in three institutions in the US and Italy, and the outcome comparing the value predicted using a model with the actual value was reported [20]. The actual number of lung cancers detected was approximately 3-fold the predicted number, and the actual number of resected lung cancers was approximately 10-fold. However, the number of advanced cancers was 1.3-fold the predicted number, and the number of deaths caused by lung cancer was 0.98-fold, with almost no difference. These findings indicate that, although the number of cancers detected and operations increased, the number of deaths caused by advanced cancer did not decline.

In 2009, the initial outcome of the DANTE Trial, a randomized controlled trial in Italy, was reported [2]. This study involved approximately 2400 participants aged 60–74 years with pack-years of ≥20, randomly assigned to one of two groups. CT screening was then conducted once a year for 5 years in only the CT group. After the initial 3 years, the number of stage I lung cancers and bronchioloalveolar carcinoma (BAC; lepidic pattern in the current classification) had increased in the CT group vs. the control group; however, the number of stage IIIB-IV lung cancers and the number of deaths caused by lung cancer were substantially the same, with an outcome similar to that in the model analysis reported earlier.

These outcomes would have been expected if the lung cancers discovered by CT screening had been a result of "overdiagnosis (lung cancer not related to death) [17, 18]". However, the Mayo study was a very small-scale study, and this report from the DANTE study was an interim result, so the evidence level of these studies is not high.

The NLST report

Despite the preponderance of negative reports initially about the effect of reducing the mortality rate by lung cancer screening using low-dose CT, the situation changed dramatically after the outcome of the NLST was reported in 2011 [7]. The NLST involved randomly allocating male and female current smokers and ex-smokers who had quit smoking within the past 15 years, all with pack-years of ≥30 and 55–74 years old, into two groups each: a study group and a control group. The study groups were then invited to undergo low-dose chest CT once a year for 3 years, while the control group was invited to undergo chest X-ray once a year for 3 years. The plan was to monitor both groups for the subsequent 7 years.

The conditions for exclusion were a history of lung cancer, recent prominent weight loss, and chest CT screening carried out within the past 18 months. All of the non-calcified nodules with a maximum diameter of ≥4 mm were judged "screening-positive (need further examination)" along with pleural effusion and lymphadenopathy; however, if no changes had been observed the past two times, then at the third screening, it was decided that further examination was not required. Death certificates and the National Death Index were used to determine the cause of death by the team investigating the cause of death (blinded to the allocation status). Test-related and treatment-related deaths were regarded as deaths from lung cancer.

Registration commenced at 33 institutes in the US from August, 2002 and had finished by April, 2004 (final screening was in September 2007), with 53,454 participants collected. This was the number of participants determined to be necessary to indicate an effect of reducing death by 21% with a power of 90%. The male-to-female ratio of participants was 6:4, with 55- to 64-year-old accounting for more than 70% of the population. A total of 90% of the population were Caucasian, and the ratio of current smokers to ex-smokers was roughly 1:1. The compliance (screening rate) of the study and control groups was both highly maintained, at almost 90%. Because of the rule requiring further examination as mentioned above (non-calcified nodules having a maximum diameter of ≥4 mm), the ratio of screening-positive was high, at 24.2% in the study group (CT group) and 6.9% in the control group (X-ray group); however, among the cases requiring further examination, lung cancer was not found in 96.4% of the study group and 94.5% of the control group.

Regarding the analysis of prognoses until December 31, 2009, the lung cancer detection rates in the study and control groups were 645 and 572 per 100 000 person-years, respectively, with a significantly higher rate in the study group. The lung cancer mortality rates in the study and control groups were 247 and 309 per 100,000 person-years, respectively, with an effective reduced mortality rate for lung cancer in the CT group of 20.0%, significantly different from the control group ($p = 0.004$). Furthermore, 320 screening participants were deemed required to see a decrease of one death caused by lung cancer. The effective reduction in death by all causes was also calculated, revealing a reduction of 6.7% in the CT group vs. the X-ray group ($p = 0.02$). Given these outcomes, it was concluded that the NLST should be "stopped due to futility"; that is, "the study should be discontinued, because the outcome will not change even if the study is continued as preliminarily stipulated". The findings from this study were dramatic, and since then, the proportion of researchers who consider CT screening for smokers to be effective has risen sharply; however, a number of problems associated with CT screening remain to be addressed.

After the NLST report

After the NLST report, it was expected that subsequent randomized controlled trials would follow up on the NLST outcome to confirm that CT screening for heavy smokers is, indeed, effective. Unfortunately, no studies confirming this outcome have yet been conducted.

The outcome of the DLCST conducted in Denmark, which randomly allocated 4104 heavy-smoking men and women into groups receiving either CT screening once a year for 5 years or no screening, was reported in 2012 [4]. This study, which involved a follow-up ranging from 4 to 5.5 years (including the study periods) for each participant, revealed that the number of detected lung cancers and the number of patients with stage I–II diseases were higher in the screening group than in the non-screening group. However, there was no significant difference between the groups in the number of stage III–IV cases detected. Furthermore, although the difference was not significant, the number of deaths caused by lung cancer was higher in the CT screening group than in the non-screening group.

The outcome of the MILD conducted in Italy was also reported in 2012 [5]. In this study, 4099 heavy-smoking men and women were allocated randomly into groups receiving either CT screening once-every 2 years ($n = 1186$), CT screening every year ($n = 1190$), or no screening ($n = 1723$), with a median follow-up period of 4.4 years and a maximum of 6 years (the median number of CT screenings was three in the once-every-2-years group and five in the once-a-year group). The lung cancer detection rates in the non-screening, once-every-2-years, and once-every-year groups were 311, 457, and 620 per 100,000 person-years, respectively, indicating a significantly higher rate in the once-a-year group than in the other groups. However, the mortality rates from lung cancer in the non-screening, once-every-2-years, and once-every-year groups were 109, 109, and 216 per 100,000 person-years, respectively, and the all-cause mortality rates were 310, 363, and 558 per 100,000 person-years, respectively. These values were higher in the screening groups than in the non-screening group, but not significantly.

The outcome after long-term follow-up from the DANTE study was reported in 2015 [5], but even after a long-term follow-up period of 8.35 years, the findings were similar to those in the initial report, with a relative risk of death from lung cancer of 0.993 (95% confidence interval 0.688–1.433) and almost no effects of CT screening in reducing death from lung cancer.

The problems remaining after the NLST and subsequent studies

The NLST was the first randomized controlled trial indicating the efficacy of CT screening and evoked a substantial international response. The NLST was led by the National Cancer Institute (NCI), which is deliberate in introducing screening. It may, therefore, be surmised that the study was conducted appropriately and received sufficient examination. While the outcome is not likely to change significantly in the future, many issues still need to be addressed.

First, the only report that found CT to be effective was that of the NLST, with the relative risk substantially ≥ 1 in other small-scale RCTs. Currently, among several RCTs being conducted in Europe [3, 21–23] (Table 1), the NELSON study, a large-scale RCT, is reaching its final stages in The Netherlands and Belgium [24–26]. If the outcome of the NELSON study leads to a conclusion of "effective for reducing death" again, the efficacy of CT for smokers may be considered established; however, if the outcome is negative, further chaos will ensue.

Second, the percentage of people requiring further examination was very high (24.2%) in the NLST, which was a significant disadvantage. Since the NELSON study is proceeding while trying to keep the rate of "further examination required" under 5%, the outcome of this study is awaited.

Third, a detailed analysis recently published following the NLST found that the relative risk of lung cancer death among men and among past smokers exceeds 0.9 [27]. Another report indicated that the incidence and mortality of the T0 (initial screening)-negative screenees were considerably lower than those of others [28]. A cost-benefit analysis should be conducted, including whether expensive screening modalities, such as CT, should be performed annually in such groups.

The rationale of low-dose CT lung cancer screening in non-/light smokers

Including the NLST, almost all studies examining the efficacy of chest CT screening in Western countries have targeted heavy smokers. Many researchers believe that CT screening should not be performed in non-/light smokers because of the balance of benefit vs. harm [29]. The NCI, which sponsored the NLST, also "advised the public not to extrapolate the results to other populations [30]". However, chest CT screening has been conducted in non-/light smokers in Japan for many years. With our experience in Japan, cancer cases detected by CT screening among non-/light smokers had extremely good prognoses [15, 16]. Is CT screening for these populations actually invalid?

It has become clear that the nature of a given disease can vary greatly by race [31], such as with respect to the ratio of EGFR genetic mutations in primary pulmonary adenocarcinomas [32]. According to a report by Thun et al. [33], not only is the lung cancer prevalence different in Asians, Europeans, and African–Americans, but the effect of gender and smoking history is also very different among these populations. The difference in the mortality associated with lung cancer in smokers vs. non-smokers is much less in Asians than in Europeans. Particularly in Asian women, the tendency is remarkable and the difference in mortality in smokers vs. non-smokers is only twofold. Indeed, in Western countries, lung cancer is regarded as a disease of men and smokers; however, in Asian countries, such as Japan, preventing "lung cancer deaths in women and non-smokers" is one of the essential countermeasures for cancer prevention. Accordingly, investigating the efficacy of low-dose CT lung cancer screening in non-/light smokers in Japan is of great importance.

The efficacy of low-dose CT lung cancer screening in non-/light smokers

Although many articles have been published in Japan on analyses with CT-detected lung cancers, including non-/light smokers [34, 35], a little evidence has been reported supporting the efficacy of CT screening for non-/light smokers. Nakayama et al. presented some results of their cohort study in several meetings [36], but the overall results have not yet been published in the English literature. Among the few studies available on this subject, the ecological/time series study of the Hitachi district reported by Nawa et al. [8] suggests a few affirmative outcomes.

In the Hitachi district, CT screening began in 1998, with screening conducted in a total of 31426 people aged 50–79 years, by March 2009 (average 2.6 times/person). This population accounts for approximately 45% of the entire population of those aged 50–79 years in the Hitachi district, indicating that this district has a very high rate of participation in low-dose CT lung cancer screening among all regions in Japan. The smoking rate of CT screening examinees was 74.1% in men and 8.3% in women (46.2%

overall), with more than half of the examinees being non-smokers. The mortality rate associated with lung cancer in the Hitachi district and that in the whole of Japan were compared, and the standardized mortality ratio (SMR) was calculated. No significant differences in lung cancer mortality were noted between the Hitachi district and the whole of Japan during the pre-introductory phase (1995–1999) or the introductory phase (2000–2004); however, the lung cancer mortality during the developed phase (2005–2009) differed remarkably between the Hitachi district and the whole of Japan, with the SMR of 0.76 (95% CI 0.67–0.86, $p < 0.001$), which was a significant decline from that across the whole of Japan. In the analysis limited to women, non-smokers accounted for ≥90% of the examinees, and a significant decline in SMR was also observed, at 0.74 (95% CI 0.56–0.97).

The outcome of the Hitachi study suggests that CT screening may lead to a decline in the mortality rate associated with lung cancer for non-smokers as well as smokers. However, there are several limitations to this ecological study, and the evidence level is still not very high. Currently, a randomized controlled trial on non-/light smokers is being conducted in Japan by Sagawa et al. (Japanese randomized trial for evaluating the efficacy of low-dose thoracic CT screening for lung cancer: JECS Study) with the support of the Japan Agency for Medical Research and Development (AMED). The protocol of the JECS Study was described previously [37]. Briefly, 35,000 participants 50–64 years of age (after protocol revision in March 2016, 27,000 participants 50–70 years of age) with a smoking history under 30 pack-years were randomly assigned individually into two groups. The intervention group was invited to have low-dose thoracic CT done in the first year and the sixth year, whereas the control group was invited to have chest X-ray done in the first year. The participants in both groups were also encouraged to undertake routine lung cancer screening using chest X-ray annually. After the 10-year follow-up period, lung cancer mortality in each group will be compared. Although a large number of participants is required, this JECS study must be completed to confirm the efficacy of low-dose chest CT screening in non-/light smokers.

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Compliance with ethical standards

Conflict of interest We declare no conflict of interest in association with this study.

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