Review Article

Screening for lung cancer using low-dose computed tomography: concerns about the application in low-risk individuals

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Abstract: Low-dose computed tomography (LDCT) has been increasingly accepted as an efficient screening method for high-risk individuals to reduce lung cancer mortality. However, there remains a gap of knowledge in the practical implementation of screening on a larger scale, especially for low-risk individuals. The aim of this study is to initiate discussion through an evidence-based analysis and provide valuable suggestions on LDCT screening for lung cancer in clinical practice. Among previously published randomized controlled trials (RCTs), the National Lung Screening Trial (NLST) is the only one demonstrating positive results in a high-risk population of old age and heavy smokers. It is also shown that the potential harms include false-positive findings, radiation exposure etc., but its magnitude is uncertain. In the meantime, the current risk stratification system is inadequate, and is difficult to define selection criteria. Thus, the efficacy of LDCT in lung cancer screening needs to be confirmed in future trials, and the procedure should not be proposed to individuals without comparable risk to those in the NLST. Furthermore, there is a lack of evidence to support the expansion of LDCT screening to low-risk individuals. Therefore, recommendation of LDCT screening for these patients could be premature in clinical practice although some of them might be missed based on current definition of risk factors. Further studies and advances in risk assessment tools are urgently needed to address the concerns about lung cancer screening in order to improve the outcomes of lung cancer.

Keywords: Lung neoplasm; risk; screening; spiral computed tomography

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Introduction

Lung cancer is the leading cause of cancer mortality, accounting for approximately 28% of all cancer-related deaths (1). The current estimate suggests that approximately 7% of the population born today will be diagnosed with lung cancer in their lifetime, and approximately 6% will die of it (SEER Cancer Statistics Review, 2014). According to GLOBOCAN 2012, 35.78% of all newly diagnosed lung cancer cases and 37.56% deaths of lung cancer occur in China. Moreover, the disease is projected to be the sixth leading cause of death worldwide and the third in high-income countries in 2030 (2). Thus, it is a major public health problem.

Despite the development of new therapeutic agents and technologies, the 5-year survival rate of 6% to 18% for lung cancer (3) has not improved significantly over the past 20 years (4). Nevertheless, when the disease is diagnosed at an early stage, its 5-year survival rate is up to 67% (5). However, only 16% of lung cancer patients are diagnosed at early stages (1), whereas 61% of women with breast cancer and 91% of men with prostate cancer are diagnosed at early stage, owing to improvements in early detection and treatment. Consequently, the mortality rates for breast and prostate cancers have decreased from their peaks by 34% and 45%, respectively (1). Therefore, reliable detection and treatment of lung cancer in its earlier stages is a promising approach to improving the prognosis of lung cancer.

Screening for lung cancer dates back to 1968 in the United Kingdom, and several screening methods were tried, including chest X-ray (CXR), CXR with sputum cytology, serum biomarker testing, and fiber optic examination of the bronchial passages. However, these methods yielded limited efficacy in survival improvement, possible owing to the disease's clinical and pathologic heterogeneity (6). In 2011, the initial results of the National Lung Screening Trial (NLST) (7) were published, reporting a relative 20% reduction in lung cancer-specific deaths among high-risk participants undergoing low-dose computed tomography (LDCT) compared to those receiving CXR. The acquisition variables of LDCT were chosen to reduce exposure to an average effective dose of 1.5 mSv. The criteria for high-risk participants of the NLST included patients aged between 55 to 74 years, those currently smoking 30 pack-year, or former smokers who quit within the past 15 years.

The NLST trial was acclaimed as a major breakthrough in lung cancer screening. As a result, lung cancer screening using LDCT was recommended by various organizations, including the American Association of Thoracic Surgery (8,9), American College of Chest Physicians, American Society of Clinical Oncology, American Thoracic Society (10), National Comprehensive Cancer Network, American Lung Association, American Cancer Society (11), and the United States Preventive Services Task Force. Although a major push for primary care providers to incorporate lung cancer screening using LDCT into their practices is expected, clinicians inevitably encounter patients who are interested in screening but do not meet the previously described high-risk criteria. Thus, the question remains whether it is rational to screen as many people as quickly as possible or how these screening candidates should be wisely selected. As it is uncertain if people who do not meet the NLST inclusion criteria have a low risk of developing lung cancer and whether they benefit from screening, the potential harms associated with the procedure and its balance among cost, risks, and benefits should be carefully considered. In the present article, we systematically review the practical aspects of lung cancer screening using LDCT to provide an evidence-based analysis for whether LDCT screening should be expanded to the low-risk population.

Is there sufficient evidence to support lung cancer screening using LDCT?

We conducted a systematic review of current literature on the harms and benefits of lung cancer screening using LDCT and found 107 relevant clinical trials. Mass lung cancer screening programs using CT have been active since the mid-nineties in Japan (12-14), and many uncontrolled studies were launched during the following years in western countries (15-20).

All these studies demonstrated that screening with spiral CT allowed the detection of a high proportion of early-stage lung cancer cases. Furthermore, the International Early Lung Cancer Action Project reported a 10-year survival rate of 92% in patients with resectable stage I disease, whereas that of the whole study cohort was 80% (21). However, it was not a randomized controlled trial (RCT), and thus inevitably affected by cofounders. Therefore, we decided to focus our search on RCTs, in which the benefit of screening in terms of mortality reduction was directly compared between the study and control groups. The following 11 RCTs were found and their data were reviewed.

(I) LSS: Lung Screening Study (22-24);
(II) NLST (7,25);
(III) DANTE: Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays (26,27);
(IV) DLCST: Danish Lung Cancer Screening Trial (28,29);
(V) MILD: Multicentric Italian Lung Detection study (30);
(VI) NELSON: Nederlands-Leuvens Longkanker Screenings Onderzoek trial, or Dutch-Belgian Lung Cancer Screening Trial (31,32);
(VII) ITALUNG: Italian Lung Cancer Computed Tomography Screening Trial (33,34);
(VIII) Depiscan: a French pilot lung screening RCT (35);
(IX) LUSI: German lung cancer screening intervention study (36);
(X) UKLS: United Kingdom Lung Screening Trial (37);
(XI) JECS: Japanese randomized trial for evaluating the Efficacy of low-dose thoracic CT screening for lung cancer in non-smokers and smokers of 30 pack-years aged 50-64 years (38).

The NLST (7,25) was the largest study, comparing LDCT with CXR for lung cancer screening. The results indicated a reduction of 20% [95% confidence interval (CI), 6.8-26.7; P=0.004] in lung cancer-specific mortality and reduction of 6.7% (95% CI, 1.2-13.6; P=0.02) in all-cause mortality. The chance of dying from lung cancer was 0.33% lower for the LDCT group over the study period, and that is 1 lung cancer-specific death was prevented for every 310 individuals being screened. The other 10 smaller RCTs on

lung cancer screening using LDCT were conducted or are ongoing in the United States, Europe and Japan. To date, results from four studies, LSS, DANTE, DLCST, and MILD, have been reported. DANTE, DLCST, and MILD were conducted in Europe, whereas LSS was a pilot study of the subsequent NLST. Therefore, we only summarized results from NLST, DANTE, DLCST, and MILD in *Table 1*. However, all three European trials reported no mortality reduction benefit from LDCT lung cancer screening. The reasons for the inconsistent results have been previously discussed in several reviews (39,40). As shown in *Table 1*, a wide variability in the controls, sample size, demographic characteristics (sex and age), smoking history, tomogram thickness, screening intervals and duration, and follow-up duration might account for the different outcomes.

In addition, most screening studies were conducted in academic institutes or large hospitals with the participation of specialized thoracic radiologists and certified thoracic surgeons, which raises concerns about the effectiveness of screening in the community or at smaller facilities. Therefore, although LDCT screening appears promising, it is also a means of clinical intervention in its infancy with many unanswered questions, including the optimal time for screening initiation, duration, and intervals. Furthermore, other issues such as overdiagnosis, risk definition, patient selection, and financial burden also need to be carefully addressed. Although ongoing randomized trials might help resolve some of these matters and validate the NLST results, future studies are warranted to provide a definitive answer regarding the impact of LDCT screening on lung cancer-specific mortality at the population level.

Is it rational to offer LDCT screening for lung cancer to low-risk individuals?

The NLST reported that three annual rounds of LDCT screening resulted in a 20% relative decrease in death from lung cancer among high-risk participants, as compared to CXR. Further stratification of the participants into five risk categories using a validated prediction model showed that those with the lowest risk (the first quintile) accounted for only 1% of the prevented lung cancer-specific deaths, whereas 88% of the death prevention was from participants with a higher risk (the third to fifth quintiles) (41). Such a result indicated that individuals with a lower risk might benefit less from LDCT screening. Furthermore, the following potential limitations and harms associated with LDCT screening needed to be recognized:

(I) False-positive results: the average nodular detection rate was 20% in the NLST, but varied from 3% (42) to 30% (ITALUNG) in RCTs and 5% (16,43-45) to 51% (20,46) in cohort studies. In the NLST, 96.4% of the positive results in the low-dose CT group were false positive results across the three rounds and other studies reported that more than 90% of the nodules were benign (7,10,22,23,28,29,31-35);

(II) Radiation exposure: the effective dose of radiation from LDCT is estimated to be 1.5 mSv per examination, but it may vary in clinical practice. Furthermore, nodule detection might require more imaging procedures, such as diagnostic chest CT (about 8 mSv) (47) or positron emission tomography-CT (about 14 mSv) (47-49), which increases the total exposure and accounts for most radiation doses in these screening studies;

(III) Additional invasive procedures: in the NLST, 73% of patients with benign lesions had invasive nonsurgical procedures (7); 1.2% underwent invasive procedure such as needle biopsy or bronchoscopy, and 0.7% underwent thoracoscopy or mediastinoscopy (7). The percentage of unnecessary surgeries was 13% in DANTE and around 2% in other studies (50);

(IV) Death and complications: the frequency of death occurring within 2 months of a diagnostic evaluation of a detected finding was 8 per 10,000 individuals screened using LDCT and 5 per 10,000 of those who received chest radiography in the NLST. The majority of complications occurred after surgical procedures. In the total studied population, the risks of death and major complications following diagnostic events for benign nodules was higher in the LDCT group than in the chest radiography group (4.1 and 4.5 per 10,000 *vs.* 1.1 and 1.5 per 10,000, respectively) (50).

(V) Overdiagnosis: overdiagnosis is the detection of an extra quota of indolent tumors that would have no impact on patients' life expectancy even if undiagnosed. Although early RCTs of CXR suggested that lung cancer screening resulted in an overdiagnosis rate of exceeding 25% (51,52), it is impossible to estimate the definitive magnitude of overdiagnosis from the NLST because of the study design comparing LDCT and CXR. More evidence from prospective RCTs may eventually

Table 1 Summary of previously published randomized clinical trials on low-dose computed tomography screening for lung cancer

Trial name	Group (LDCT *vs.* control)	Recruitment years	N (LDCT *vs.* control)	Sex (F/M)	Eligibility criteria	Tomogram thickness (mm)	Screening intervals	Screening duration	Follow-up	Outcomes	Citations
NLST	LDCT *vs.* CXR	2002-2004	26,722 *vs.* 26,732	41/59	Age: 55-74 y; current or former (<15 years since quitting) smokers (≥30 pack-years)	1-2.5	0, 1, 2	3 y	6.5 y	Lung cancer specific mortality: reduction of 20.0% (95% CI, 6.8-26.7; P=0.004); all-cause mortality: reduction of 6.7% (95% CI, 1.2-13.6; P=0.02)	(7,25)
DANTE	LDCT *vs.* no screening	2001-2006	1,276 *vs.* 1,196	0/100	Age: 60-74 y; current or former smokers (≥20 pack-years)	5	0, 1, 2, 3, 4	5 y	2.8 y	LDCT *vs.* control number (%); lung cancer specific mortality: 20 (1.6) *vs.* 20 (1.7); all-cause mortality: 46 (3.6) *vs.* 45 (3.8)	(26,27)
DLCST	LDCT *vs.* no screening	2004-2006	2,052 *vs.* 2,052	44/56	Age: 50-70 y; current or former smokers (≥20 pack-years)	3 or 1	0, 1, 2, 3, 4	5 y	4.8 y	LDCT *vs.* control number (%); lung cancer specific mortality: 15 (0.7) *vs.* 11 (0.5); all-cause mortality: 61 (3.0) *vs.* 42 (2.1)	(28,29)
MILD	LDCT (annual or biennial) *vs.* observation	2005-2011	2,376 (1,190 annual, 1,186 biennial) *vs.* 1,723	34/66	Age: ≥49 y; current or former (quit <10 years ago) smokers (≥20 pack-years)	1-5	0, 1, 2, 3, 4	5 y	4.4 y	LDCT *vs.* control lung cancer specific mortality: HR =1.64 (95% CI, 0.67-4.01; P=0.21); all-cause mortality: HR =1.40 (95% CI, 0.82-2.38; P=0.13).	(30)

LDCT, low-dose computed tomography; F, female; M, male; y, years; CI, confidence interval; HR, hazard ratio; NLST, National Lung Screening Trial; DANTE, Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST, Danish Lung Cancer Screening Trial; MILD, Multicentric Italian Lung Detection.

provide an estimate of overdiagnosis rate;

(VI) Stage detection shifting: there is considerable interest in shifting detection to stages during which intervention could be curative. Screening did not reduce lung cancer stages detected after the first round, and only a slight decrease was reported in stage III and IV diseases detected in the third round compared with those found after the first round (37.8% *vs*. 30.4%) (7);

(VII) Psychological effect: false-positive findings and overdiagnosed tumors can cause anxiety. The NELSON trial results suggested that short-term lung cancer-specific distress was significantly high, but long-term evaluation indicated the resolution of such short-term anxiety; however, a second indeterminate finding was not associated with increased lung cancer-specific distress (53,54).

In addition to the above-mentioned limitations, there are other uncertainties regarding the harms and benefits of LDCT screening. An analysis of the NLST data using predicating models indicated that approximately 1 cancer death might be caused by radiation from imaging per 2,500 individuals screened (10), and the lung cancer-specific death prevention benefit was greater than the radiation risk that might manifest 10 to 20 years later. However, it would be less favorable for younger individuals or those with a low risk of developing lung cancer (10). Therefore, the NLST findings should be neither minimized nor overstated when more data on LDCT screening are due to be reported in the near future. Additionally, considerable risks must be overcome before LDCT can be widely offered as a preventative screening method to those at risk of developing lung cancer. Currently, LDCT may not be cost-effective when provided to individuals with a low risk of lung cancer development, especially in a setting that might involve higher frequency of unnecessary interventions and procedures. Thus, for optimal cost-effectiveness, individuals with a sufficiently high risk of developing lung cancer need to be identified so that the benefit-to-harm ratio of the screening can be maximized (55).

Is there a clear definition of high and low risk for lung cancer development?

As shown in the NLST, screening using LDCT prevented the greatest number of deaths among participants who were at the highest risk for the disease, whereas the number of prevented death was very limited for those at the lowest risk. These findings provided the empirical support for risk-based targeting for such screening. Although it is generally agreed that screening should be limited to high-risk individuals for whom the potential benefits of LDCT screening would outweigh its harms, the exact definition of such a high-risk population is unclear.

Most available recommendations are based on the NLST high-risk criteria, which focus only on patients' age and smoking history. Although such a definition of risk was practical for the purpose of a clinical trial, it is not as useful for screening target selection because certain valuable predictors are omitted. Smoking accounts for 80% of the worldwide lung cancer burden in men and at least 50% of that in women (56); however, approximately 85% of heavy smokers do not develop lung cancer (57). Moreover, the NLST enrolled a younger and healthier population with only 8.8% of the study participants in the oldest category (70-74 years) (7), which might challenge the generalization of the study results to that age group. This particular point cannot be overstated, as the average age of lung cancer diagnosis is 70 years, and it should make clinicians wary of applying the mortality statistics for surgery to individuals in the oldest group.

In addition, other risk factors associated with lung cancer includes second-hand smoking (58); exposure to solid fuel smoke (59) or outdoor particulate matter (60); occupational exposures (61); family history (62); genetic polymorphisms such as those in tumor protein p53, excision repair cross-complementation group 1, or methylenetetrahydrofolate reductase (63-65); radon (66); other pulmonary diseases (67); and sex differences (68). Furthermore, it would be politically problematic to offer publicly funded medical interventions solely to heavy smokers, when non-/light smokers might also be at a high risk owing to other environmental, occupational, and genetic factors. Meanwhile, the low detection rate for prevalent and especially incident lung cancers are key elements in explaining the high cost-effectiveness ratio of lung cancer screening using LDCT alone. This clearly indicates the need for multidimensional integrated strategies to increase the rate of screen-detected lung cancers with LDCT, possibly via the inclusion of subjects with other risk factors besides smoking history and age.

Multiple lung cancer risk prediction models with good performance have been established to facilitate such strategies. An accurate risk prediction model is more efficient in identifying individuals who are likely to develop lung cancer and die from the disease than simple factors such as age and pack-years of smoking. Currently,

there have been many lung cancer risk prediction models developed. Different models have included variable risk factors which could be categorized into epidemiology factors, clinical factors as well as genetic and molecular biomarkers. We picked out the most popularly studied models, and list the risk factors incorporated in each model (shown in *Table 2*).

Although the validation of these models shows moderate to high discrimination and calibration, there are certain limitations that can affect their accuracy and application. First, Maisonneuve *et al*. found that the common epidemiological risk factors had relatively low discriminatory power to predict the possibility of lung cancer development; therefore, clinical factors as well as genetic and molecular biomarkers were used to develop models, but their validation was insufficient (73). Second, the study participants selected to validate these models might not be adequately representative for generalization. For example, the participants in the Tammemagi model were 55-74 years of age at the time of enrollment and in general, were of higher socioeconomic status than the general population, possibly resulting in a healthy volunteer effect and limiting the model's external generalizability (69). Third, categorization of continuous data could lead to loss of information and predictive ability, as used in the Bach and Liverpool Lung Project models which divided continuous smoking history data into four categories (71,75). Fourth, selection of predictive variables for entry into the multivariable models was based on a P value of less than 0.05 in univariate analysis, which could result in important predictors being left out more often than when a less stringent P value cut-off was used, such as in the Spitz model (78).

Currently, no prediction model is utilized in clinical settings. Among the clinical trials on lung cancer screening, only the UKLS applied a prediction model for selection criteria. The better understanding of lung cancer and identification of more potential risk factors could make screening for the disease more accurate and complex at the same time, and the current prediction models could certainly be improved. Therefore, it is difficult to provide an accurate definition of high or low risk for lung cancer. Only the screening guidelines issued by the NCCN in 2011 defined low-risk individuals as those aged <50 years and/or having a smoking history of <20 pack-years, and lung cancer screening was not recommended for these (6). The incorporation of other well-known risk factors has not been studied. Thus, there is currently no evidence to suggest a re-assessment of screening selection criteria. In order to identify individuals for whom the harm/benefit balance of LDCT screening is favorable, a good risk prediction model for lung cancer is certainly needed.

How should we address the current and future implementation of LDCT screening?

The international debate on whether to implement CT lung cancer screening programs is ongoing with unresolved issues. To date, screening programs have reported that 6-34% of all patients with benign lesions have undergone surgical treatment. Such variability is due primarily to the different protocols used and providers' experience. Therefore, only the adoption of a shared protocol and experienced multidisciplinary teams may ensure the lowest possible rate of futile procedures.

An international review of lung cancer screening was conducted during a workshop convened by the International Association for the Study of Lung Cancer, and its report was published (84) after that of the NLST results. The workshop participants provided six recommendations for future priorities: to identify high-risk individuals for lung cancer CT screening programs, to develop radiological guidelines for use in developing national screening programs, to create guidelines for the clinical work-up of indeterminate nodules resulting from CT screening programs, to develop guidelines for pathology reporting of nodules from lung cancer CT screening programs, to make recommendations for surgical and therapeutic interventions of suspicious nodules identified through lung cancer CT screening programs, and to integrate smoking cessation practices into future national lung cancer CT screening programs. However, optimum resolutions of the issues are still awaited.

The ongoing RCTs are likely to provide further evidence for mortality reduction advantage of CT screening and its cost-effectiveness. They might also offer a better insight into risk stratification of the general population who need to be screened and a robust radiological protocol to reduce false-positive results and help with management decisions about indeterminate nodules. Additionally, in-depth data are now emerging from the use of minimally surgical approaches, especially video-assisted thoracoscopic surgery for small CT-identified nodules. All these factors will contribute greatly to reducing the harms and increasing the benefits of CT screening. In the meantime, we need to prepare for lung cancer screening with an integrated smoking cessation policy because this combined

Table 2 Risk factors incorporated in the risk models for lung cancer

Models	Risk factors						Citations
	Epidemiology factors				Clinical factors	Genetic and molecular biomarkers	
	Socio-demographic factors	Medical history	Environmental/ occupational exposures	Smoking history			
Tammemagi model	Age, BMI, education, race, sex	COPD, chest radiography in past 3 years, family history of lung cancer		Duration, quit time, smoking status, smoking, intensity, pack-years, smoked			(69,70)
Bach model	Age, education, race, sex,		Asbestos	Duration, quit time, smoking status, smoking, intensity			(71-74)
LLP model	Age, sex	Pneumonia, family history of lung cancer, prior diagnosis of malignant tumor	Asbestos	Duration			(75)
Etzel model	Sex	Hay fever, COPD	Asbestos, dust, environmental tobacco smoke	Duration, smoking status, smoking intensity, pack-years smoked			(76)
Park model	Age, BMI, physical activity	Family history of cancer, fasting glucose level		Smoking status, smoking intensity, age at smoking initiation			(77)
Spitz model	Age	Emphysema, hay fever, family history of cancer	Asbestos, dust	Smoking status, pack-years smoked, years of cessation, age at smoking initiation, age at smoking cessation			(78)
EPIC model	Age, BMI, education, sex	Asthma, hay fever, family history of cancer	Polycyclic aromatic hydrocarbons, silica, metal, asbestos	Smoking status pack-years smoked, years of cessation, age at smoking initiation, age at smoking cessation		Chr 15q25, Chr 5p15	(79)
Hippisley-Cox model	Sex	COPD, prior cancer, Townsend deprivation score	Asbestos	Smoking status, smoking intensity	Current hemoptysis, current appetite loss, current weight-loss, cough in last year, hemoglobin <11 g/dL in the last year		(80)

Table 2 (*continued*)

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Models	Risk factors						Citations
	Epidemiology factors				Clinical factors	Genetic and molecular biomarkers	
	Socio-demographic factors	Medical history	Environmental/ occupational exposures	Smoking history			
Iyen-Omofoman model	Age, sex	COPD, respiratory tract infection, Townsend score		Smoking status, smoking intensity	Hemoptysis, cough, chest/shoulder pain, dyspnea, weight loss, voice hoarseness, chest infections, No. of general practitioner consultations		(81)
Expanded Spitz model		Emphysema, hay fever, family cancer history	Dusts, asbestos	Smoking status, pack-years smoked, age stopped smoking		DNA repair capacity, bleomycin sensitivity	(82)
Improved LLP model		Pneumonia, previous tumor, family history of cancer, goodness-of-fit statistic	Asbestos	Duration		SEZ6L genotype marker	(83)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; LLP, Liverpool Lung Project; EPIC, European Prospective Investigation into Cancer and Nutrition.

approach might save more lives than any other lung cancer intervention in the near future.

Conclusions

The high incidence and mortality of lung cancer highlights the need for ongoing prevention and control strategy to reduce the disease burden. Although LDCT showed promising results in the NLST trial and has become a recommendation for lung cancer screening in many guidelines, there are still debates on its cost-effectiveness. The value of LDCT in lung cancer screening for high-risk individuals should be confirmed in more trials. Currently, the procedure is not recommended for low-risk patients, although some might be missed based on the current definition of risk factors. The accurate definition of risk factors and better predictive models are particularly important for future lung cancer screening trials. Further studies are urgently needed to solve the problems involved in lung cancer screening in order to improve the disease's outcomes.

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