Lung Cancer Screening

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Abstract

Keywords

- lung cancer
- screening
- clinical trials
- low dose computed tomography
- chest radiography
- pulmonary nodules
- lung cancer screening program

Lung cancer is the leading cause of cancer death. Although smoking prevention and cessation programs have decreased lung cancer mortality, there remains a large at-risk population. Dismal long-term survival rates persist despite improvements in diagnosis, staging, and treatment. Early efforts to identify an effective screening test have been unsuccessful. Recent advances in multidetector computed tomography have allowed screening studies using low-dose computed tomography (LDCT) to be performed. This set the stage for the National Lung Screening Trial that found that annual LDCT screening benefits individuals at high risk for lung cancer. An understanding of the harmful effects of lung cancer screening is required to help maximize the benefits and decrease the risks of a lung cancer screening program. Although many questions remain regarding LDCT screening, a comprehensive lung cancer screening program of high-risk individuals will increase detection of preclinical and potentially curable disease, creating a new model of lung cancer surveillance and management.

Objectives: Upon completion of this article, the reader will be able to provide an overview of lung cancer screening, discuss the National Lung Screening Trial study, discuss the potential harms of lung cancer screening, and describe the challenges, development, and future of lung cancer screening programs.

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Lung cancer comprises a heterogeneous group of diseases with varied histologies, treatments, and outcomes (► **Fig. 1A–D**).^{1,2} Lung cancer is the leading cause of cancer death among both men and women, with more people dying each year from lung

cancer than cancers of the colon, breast, prostate, and pancreas combined.³ There will be an estimated 160,000 lung cancer deaths in 2012,⁴ accounting for ~28% of all cancer deaths.⁵ Despite being a major contributor to cancer-related mortality, federal funding for lung cancer research is relatively small compared with funding for other major cancers.^{4,6} Smoking is the major risk factor, and it is estimated that smoking accounts for up to 90% of lung cancers.⁷ In the United States, smoking prevention and cessation programs have decreased smoking rates and lung cancer mortality.⁸ However, an estimated 94 million current or former smokers remain at elevated risk for the disease.^{9,10} Although advances in surgical, radiotherapeutic, percutaneous thermal ablative, and chemotherapeutic approaches have been made, the long-term survival from lung cancer remains low.³ Survival rates are stage dependent, where 5-year survival for stage IA lung cancer is 52.2% versus 3.7% for stage IV disease; most patients present with advanced disease.¹¹

Screening

Background

Screening is the periodic examination of a population to detect early stage asymptomatic disease with the goal of

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Figure 1 Lung cancer. (A) Adenocarcinoma: right upper lobe ground-glass nodule (arrow). (B) Squamous cell carcinoma: left upper lobe mass (arrow). (C) Small cell carcinoma: right upper lobe mass (arrow) and mediastinal lymphadenopathy (asterisk). (D) Carcinoid: partially calcified nodule (arrow) associated with the right middle lobe bronchus.

decreasing mortality and increasing survival. An effective screening program of an asymptomatic population must balance the potential benefits versus harmful effects to the individual and population as a whole. Over the past decades, efforts to identify an effective screening test for early lung cancer have been unsuccessful.

Early randomized screening trials that assessed combinations of chest radiography and sputum cytology were able to detect early stage lung cancer but were inconclusive in demonstrating a mortality benefit from such screening.^{12–17} Advances in multidetector computed tomography have made the acquisition of high-resolution volumetric images of the lung using a single breath hold and acceptable levels of radiation exposure a reality. Because of the inherently high contrast between aerated lung and soft tissue, low radiation dose preserves the detection of focal lung lesions despite higher image noise. This allowed imaging-based screening to become the focus of investigation.

Multiple single-arm observational studies provided important information on the performance characteristics of low-dose computed tomography (LDCT) of the lung. These studies showed positivity rates ranging from 5.1% to 51.4%.^{18–25} These initial investigations demonstrated that LDCT screening detects more lung nodules and early stage lung cancers compared with chest radiography. Because these

studies were not designed to address the effects of LDCT screening on lung cancer mortality, multiple randomized control trials were performed, with the largest the National Lung Screening Trial (NLST).

National Lung Screening Trial

The National Cancer Institute funded the NLST to determine whether screening with LDCT compared with chest radiography would reduce mortality from lung cancer among high-risk individuals.²⁶ The NLST enrolled 53,454 current and former smokers across 33 sites in the United States. Eligibility criteria included age range of 55 to 74 years and current or previous smoking history of at least 30 pack-years with former smokers quitting within 15 years. Relative to the general U.S. population that would have been eligible for the trial, NLST participants had comparable gender proportions and smoking intensity as measured by median pack-years of smoking, but the NLST cohort tended to be former smokers, younger, and more educated than the comparable U.S. eligible population, which made them slightly healthier overall (→ **Table 1**).²⁷

Participants were randomized to receive either LDCT or chest X-ray (CXR) annually for three screens. LDCT screening tests were considered positive and potentially related to lung cancer if they revealed at least one noncalcified nodule ≥ 4 mm

Table 1 National Lung Screening Trial cohort

Demographic characteristic	NLST (N = 53,454)
Sex (%):	
Male	59.0
Female	41.0
Smoking status (%):	
Smoker	48.1
Former smoker	51.9
Age (%):	
< 55	< 0.1
55–59	42.8
60–64	30.6
65–69	17.8
70–74	8.8
Education (%):	
> College	31.5
< High school	6.1
Race/Ethnicity (%):	
White	90.8
Black	4.4
Asian	2.0
Hispanic/Latino	1.7

NLST, National Lung Screening Trial.

in longest diameter or any other abnormality suspicious for lung cancer. CXR screens were considered positive when a noncalcified nodule or mass was identified. A recommendation for additional follow-up was made for all positive screens based on trial-wide diagnostic guidelines or at the discretion of the interpreting radiologist. A total of 24.2% of CT screens and 6.9% of CXR screen were positive in the trial. Indeterminate nodules that were stable over all three screens could be considered negative and thus contributed to the decreased screen positivity rates at the third screening examination. Complications from diagnostic follow-up were low overall and were extremely low in participants with positive screens where no lung cancer was diagnosed.^{27,28}

LDCT detected more lung cancers than chest radiography with a greater than twofold increase in the diagnosis of stage IA cancers. Fewer stage III and IV lung cancers were diagnosed in the LDCT arm. Overall, lung cancer–specific mortality rates were 247 per 100,000 person-years in the LDCT arm and 443 per 100,000 person-years in the CXR arm. This resulted in a 20% relative reduction in lung cancer mortality in the LDCT arm (95% confidence interval [CI], 6.8 to 26.7), and an absolute risk reduction in lung cancer death by 4 per 1000 individuals screened. There was a 6.7% reduction in all-cause mortality (95% CI, 1.2 to 13.6) in the LDCT arm relative to CXR.

The NLST trial is the first randomized screening trial for lung cancer to have shown improvements in both disease-specific and all-cause mortality, which indicates screening resulted in no deleterious downstream effects that contributed

to death and that the reduced lung cancer mortality observed with LDCT did not result in deaths from competing causes such as cardiovascular disease. Based on these data, an estimated 320 individuals need to be screened to save one life from lung cancer.²⁸ This compares favorably with screening mammography, in which some estimates suggest that 465 to 601 women must be screened to save one life^{29,30} from breast cancer.

Overall, the NLST made several key observations: A higher number of lung cancers were detected with LDCT than with CXR; a true stage shift was seen with LDCT, such that the absolute number of advanced stage cancers was decreased relative to those found on CXR; a 20% relative mortality reduction was conferred with LDCT relative to CXR, amounting to an absolute risk reduction of 4 individuals per 1000 screened; few significant complications occurred from LDCT screening; and lastly, a 6.7% reduction in all-cause mortality was observed with LDCT. Preliminary cost effectiveness results based on available data suggest that LDCT screening could be cost effective if implemented in a fashion similar to the NLST approach.³¹

Screening Harms

The NLST demonstrated that LDCT screening benefits individuals at high risk for lung cancer. If lung cancer screening is to be effective, its benefits must outweigh its risks or the potential harms of the process. The potential harms of lung cancer screening include radiation-induced cancers, high false positivity rates, and the potential for overdiagnosis.

LDCT screening exposes individuals to increased radiation during baseline and periodic screening and during follow-up for indeterminate nodules. Although individual risk may be acceptable, the large number of individuals who might be screened could translate into measurable population increases in radiation-induced cancers.³⁰ This appears to be true for LDCT screening and lung cancer risk because the risk of radiation-induced lung cancer is highest in middle age (peaking at around 55 years of age) as compared with cancers in other solid organs where the radiation risks are highest at a younger age.³² Radiation risk of carcinogenesis is based on individual organ susceptibility and organ-specific doses. Using slightly higher estimates of dose than were reported in the NLST, Brenner used dose, sex, age, and smoking status to calculate excess relative risks of lung cancer among individuals who undergo annual LDCT screening from age 50 to 75 years. In smoking women, annual LDCT screening conferred a 0.85% (95% CI, 0.28 to 2.2) radiation-related risk of developing lung cancer in addition to the population-based expected risk of 17%, a 5% increase in risk. In smoking men, annual LDCT screening conferred a 0.23% (95% CI, 0.06 to 0.63) radiation-related risk of developing lung cancer in addition to the population-based expected risk of 16%,³³ a 1.5% increase in risk. These calculations likely overestimate radiation risk because of the current use of lower exposures to generate diagnostic images. Additionally, the 20% relative mortality reduction observed with LDCT screening in the NLST population more than offsets the radiation-related increase in risk.

An additional challenge is to communicate effectively the risk of radiation-induced cancers to both referring physicians

and the screening population. Effective dose estimates the participant dose and depends on the acquisition parameters used to acquire the images and where the radiation is being absorbed in the body. Effective dose can then be compared with other medical radiation procedures to provide a context to the referring physician and patient. Conservative estimates of effective dose from the NLST based on representative imaging protocols for average size participants were 1.6 mSv for men and 2.1 mSv for women, with gender differences owing primarily to breast dose in women.³⁴ This can be compared with estimates of annual population radiation dose from all sources averaging 3 mSv at sea level.

An effective screening program should minimize false positivity rates and thus decrease the monetary and emotional costs of unnecessary diagnostic evaluation. The NLST used a one-step interpretation algorithm where a low-dose CT screen was positive in the context of an indeterminate nodule of minimum 4 mm diameter or other abnormality suspicious for lung cancer. In the NLST, there was a 24.2% screen positivity rate for all LDCT, but only 3.6% of the positive LDCT screens resulted in a diagnosis of lung cancer, ultimately demonstrating a positive predictive value <4%. Although few medical complications were associated with the diagnostic evaluation for the positive screens, substantial gains would be achieved by improving the performance characteristics of LDCT screening.²⁸

A higher positive predictive value was seen in the Dutch-Belgian randomized lung cancer screening trial (Nederlands-Leuven Longkanker Screenings Onderzoek [NELSON]). The NELSON trial used a two-step interpretation strategy based on nodule volume: nodules <50 mm³ (5 mm) were negative, nodules >500 mm³ (10 mm) were positive, and nodules ranging from 50 to 500 mm³ (5 to 10 mm) were indeterminate and underwent follow-up LDCT.³⁵ Nodule growth on volumetric analysis at the follow-up scan determined whether the scan was classified as negative or positive. The NELSON trial achieved a sensitivity of 94.6% at prevalence and 96.4% at the incidence screen; a specificity of 98.3% at prevalence and 99.0% at incidence; a positive predictive value of 35.7% at prevalence and 42.2% at incidence; and negative predictive values of 99.9% at both prevalence and incidence screens.³⁵ Resource utilization between the NLST and NELSON trials was comparable for subcentimeter nodule because most of the NLST participants with subcentimeter nodules were evaluated by follow-up imaging. Beyond the improvement of the positive predictive value of a positive screen, the two-step process provides interpretations that are more representative of the true risk of lung cancer in the screened population and conveys that lung cancer screening is a process rather than a single examination.

Another potential harm of LDCT screening is the diagnosis and treatment of a lung cancer that would not progress to cause symptoms or death, or so-called overdiagnosis. Overdiagnosis in lung cancer may result from an indolent cancer that will not result in symptoms or death or from a cancer that is treated or progresses slowly enough that the patient dies of a competing noncancer-related medical condition. That heterogeneous biological behavior of lung cancers may result in the detection of slow-growing tumors is particularly true in

screening programs that diagnose cancer prior to symptoms or signs of disease. Autopsy studies have provided compelling evidence of overdiagnosis by observing clinically silent cancers of prostate and thyroid in individuals who have died from other causes.^{36–38} However, overdiagnosis may not be a significant problem in lung cancer, as in one autopsy series, undiagnosed lung cancer was found in only 0.8% of all autopsies.³⁹ Additionally, estimates from randomized trials suggest that a proportion of screen-detected cancers represent overdiagnosis due to lead time. In the absence of overdiagnosis, once screening concludes, cancer diagnoses should catch up to the screening arm, and the persistence of excess cancers in the screening arm provides evidence of overdiagnosis.⁴⁰ Complicating overdiagnosis in lung cancer screening is the anecdotal observation of a ground-glass nodule that demonstrates long-term stability, which at a random point in time transitions to an aggressive phenotype with invasive or metastatic potential.⁴¹ Currently, there is no CT or other nonimaging method to definitively identify these indolent lesions, although research correlating nodule CT appearance and prognosis is ongoing.

Lung Cancer Screening Program

The NLST provides the randomized control trial evidence of the benefits of LDCT screening for lung cancer relative to the risks.²⁸ This important first step toward the development and implementation of a lung cancer screening program is required, particularly in the controversial arena of medical screening. The widespread acceptance and implementation for LDCT screening will bring about significant new challenges requiring referring physician and patient education, further research, and the development of a multidisciplinary screening program.

Referring physician education is required for the widespread acceptance of LDCT screening. Primary care providers must be educated on the efficacy of lung cancer screening, its benefits and risks, the appropriate screening population, and the management of indeterminate nodules. In addition to education, additional resources must become available to the primary care workflow because primary care providers will be increasingly challenged to allocate their already limited time and resources for lung cancer screening, particularly the burden that high screen positivity rate and the management of indeterminate nodules brings. The development of screening programs will need to incorporate responsibility for communicating with patients and managing their follow-up.

Patient education, particularly of the high-risk population, will be pivotal in the adoption of lung cancer screening programs. The stigma that smokers and patients with lung cancer are responsible for their condition cultivates a variety of personal responses including fatalism and denial^{42–45} that contribute to delays in medical evaluation^{46,47} and potentially for screening. Finally, there are significant well-known differences in the understanding of smoking-related risks and lung cancer among different racial and socio-demographic groups. Individuals from disadvantaged backgrounds are more likely to have misperceptions about their individual

risk of lung cancer, the benefits of surgical resection, and lung cancer mortality.^{48–51} The implementation of an effective lung cancer screening program across all socioeconomic strata will require multiple strategies to educate across diverse socioeconomic groups.

Further lung cancer screening research will be required, including how to optimize the selection criteria for screening. By identifying the risk groups most likely to have preclinical lung cancer, screening effectiveness can be enhanced. Although 80 to 90% of lung cancers occur in tobacco smokers, only 10 to 15% of chronic smokers develop lung cancer.^{52,53} Smokers with chronic obstructive pulmonary disease (COPD) have up to a sixfold increased risk of lung cancer relative to smokers with normal lung function, making COPD the greatest known risk factor for lung cancer in never smokers.^{54,55} Investigators have established that emphysema, as determined on LDCT, is associated with lung cancer independent of airflow obstruction on spirometry.⁵⁶ A separate study observed that the highest frequency of lung cancer was in subjects with both CT-based emphysema and moderate-to-severe spirometric airflow obstruction.⁵⁷ These and future studies will allow for a more comprehensive identification of the highest risk population by phenotyping smokers based on a combination of clinical, spirometric, and imaging features. The imaging phenotypes captured on the screening examination can be further used to stratify patients with indeterminate nodules into varying degrees of diagnostic evaluation. In the future, these multidimensional phenotypes can be combined with molecular biomarkers to construct improved risk models of preclinical lung cancer.

The development of a lung cancer screening program requires a dedicated infrastructure with standardized protocols for image acquisition, quality control, and diagnostic practice. These standardized diagnostic practices will dictate the way radiologists interpret and report screening LDCT

while ensuring ongoing programs of image and clinical quality assurance. The screening program must be able to track screening results and readily communicate and recall positive screens or indeterminate nodules that require further diagnostic evaluation. The implementation of an effective LDCT screening program for lung cancer will require a transdisciplinary team that can offer comprehensive programs of lung cancer surveillance, prevention, and treatment. This team should include diagnostic and interventional radiologists, pathologists, thoracic surgeons, and pulmonologists, and it must be integrated with lung cancer oncology programs.

Conclusion

Prior efforts to identify an effective screening test for early stage lung cancer were unsuccessful despite lung cancer being the leading cause of cancer death worldwide. Advances in multidetector CT allowed imaging-based screening to become the focus of investigation and found that LDCT screening detects more lung nodules and early stage lung cancers relative to CXR. The NLST found that annual LDCT screening benefits individuals at high risk for lung cancer with a reduced relative risk of death from lung cancer by 20% and a reduced absolute risk by 0.33%. An understanding of the harmful effects of lung cancer screening, which include radiation-induced cancers, overdiagnosis, and high false positivity rates, is required to assess the potential impact to the individual and population. Smoking prevention and cessation programs will continue to play an important role in decreasing lung cancer mortality; however, LDCT screening of high-risk individuals will increase detection of preclinical and potentially curable disease, creating a new paradigm of lung cancer surveillance and management. Multiple organizations, including the American Lung Association, have published guidelines and recommendations (►Table 2) for

Table 2 American Lung Association: Low-dose computed tomography lung cancer screening recommendations

Summary of specific recommendations
<ul style="list-style-type: none"> • Low-dose computed tomography screening for those who meet the National Lung Screening Trial criteria: <ul style="list-style-type: none"> ◦ Current or former smokers ◦ 55–74 years of age ◦ 30 pack-years ◦ No history of lung cancer
<ul style="list-style-type: none"> • Emphasis of smoking cessation for patients who undergo screening
<ul style="list-style-type: none"> • Do not use chest X-rays for lung cancer screening
<ul style="list-style-type: none"> • Does not recommend universal lung cancer screening at this time
<ul style="list-style-type: none"> • Develop a toolkit that provides patients with lung disease a comprehensive framework of the lung cancer screening process
<ul style="list-style-type: none"> • Hospitals and screening centers should: <ul style="list-style-type: none"> ◦ Establish ethical policies for advertising and promoting screening programs ◦ Fully educate the public about lung cancer, its risks and prevention, and the importance of patient/physician discussions
<ul style="list-style-type: none"> • Screening should be linked to “best practice” multidisciplinary teams that can provide the needed follow-up for evaluation of nodules

LDCT screening to provide guidance to physicians and patients.⁵⁸ Many questions remain regarding lung cancer screening including cost effectiveness, translation into clinical practice, who should be screened, the frequency and duration of screening, and the optimal management of indeterminate nodules. We hope ongoing and future research will answer these questions to maximize the benefits while reducing the risks of a comprehensive lung cancer screening program.

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