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American Cancer Society Lung Cancer Screening Guidelines

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Abstract

Findings from the National Cancer Institute's National Lung Screening Trial established that lung cancer mortality in specific high-risk groups can be reduced by annual screening with low-dose computed tomography. These findings indicate that the adoption of lung cancer screening could save many lives. Based on the results of the National Lung Screening Trial, the American Cancer Society is issuing an initial guideline for lung cancer screening. This guideline recommends that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30-pack-year smoking history and who currently smoke or have quit within the past 15 years. A process of informed and shared decision-making with a clinician related to the potential benefits, limitations, and harms associated with screening for lung cancer with low-dose computed tomography should occur before any decision is made to initiate lung cancer screening. Smoking cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer. Screening should not be viewed as an alternative to smoking cessation.

Keywords

humans; lung neoplasms; mortality; radiography; radiation dosage; randomized controlled trials as topic; risk; risk reduction behavior; x-ray; computed tomography; adverse effects; lung cancer screening

Introduction

In the 20th century, the world population began to experience rising mortality from lung cancer caused by chronic exposure to tobacco smoke. This epidemic of lung cancer deaths is now receding in some nations where tobacco control has reduced smoking, but it is rapidly rising in others.[1] Since the first Surgeon General's report, there has been a concerted effort to reduce the uptake of cigarette smoking and to help smokers to quit, and to determine if screening could reduce the burden of disease among those at high risk of lung cancer due to prolonged cigarette smoking.[2]

On November 4, 2010, the director of the National Cancer Institute (NCI) announced that an ongoing evaluation of the National Lung Screening Trial (NLST) data had shown a statistically significant 20% reduction in lung cancer mortality in a group of adults at high risk of lung cancer who were randomized to receive 3 consecutive annual lung cancer screening examinations (at baseline, year 1, and year 2) with low-dose computed tomography (LDCT) compared with an equivalent-risk group of adults randomized to receive 3 consecutive annual chest x-rays (CXR).[3] An equally important conclusion in the announcement was the conclusion of the NLST's Data Safety and Monitoring Board that "there was no evidence of unforeseen screening effects that warranted acting contrary to the trial's pre-specified monitoring plan." On June 30, 2011, the initial study results of the NLST were published, providing the first evidence from a prospective randomized controlled trial (RCT) that lung cancer screening in a high-risk population was effective in reducing lung cancer deaths.[4]

The purpose of this guideline is to provide clinicians and the public with guidance about screening for lung cancer, and specifically to address: 1) who is and who is not a candidate for lung cancer screening; 2) what is known about the benefits, limitations, and harms associated with lung cancer screening; 3) the importance and key elements of informed and shared decision-making prior to making a decision to undergo lung cancer screening; and (4) specific recommendations about the scfreening process and the importance of smoking cessation for current smokers.

Background

In the United States, lung cancer is the leading cause of death from cancer. This has been observed for men since the mid-1950s and for women since the mid-1980s.[5] Although lung cancer is the third most common cancer diagnosed among men and women (after prostate cancer and breast cancer), the annual burden of disease is larger than that of any other cancer. In 2012, the American Cancer Society estimates that lung cancer will account for 160,340 deaths, which is approximately 28% of all deaths from cancer in the United States.[6] Average 5-year lung cancer survival is among the poorest of all cancers (16.8%), and although 5-year survival is considerably better when the disease is diagnosed while still localized (52.2%), the large majority of patients with lung cancer are diagnosed with regional and distant disease.[7] The estimated direct medical cost of lung cancer was $12.1 billion in the United States in 2010, accounting for approximately 10% of the total medical expenditure on cancer.[8] Another important measure of disease burden when compared with deaths from other cancers is the magnitude of premature mortality. The NCI estimates that US deaths from lung cancer in 2009 accounted for 2,373,200 person-years of life lost, more than 3 times the number of years lost to breast cancer (770,700 person-years) and colorectal cancer (765,300 person-years).[7] This translates to substantially higher indirect costs (or productivity loss) of lung cancer. Of the $134.8 billion indirect cost associated with cancer deaths in 2005, $36.1 billion (or over 25%) was attributable to premature mortality from lung cancer.[8]

The incidence of lung cancer is relatively low before the age of 50 years, but begins to increase rapidly afterward and especially after age 60 years. Overall age-adjusted incidence rates per 100,000 population (2005–2009) are higher in men than women (76.4 vs 52.7), and while age-specific incidence rates are similar in men and women before age 50 years, with increasing age the difference in age-specific rates widens.[7] The magnitude of age-adjusted and age-specific rates is influenced by the underlying prevalence of various lung cancer risk factors, of which prior exposure to tobacco smoke has the greatest influence. Bain et al derived estimates of lung cancer incidence among current and former smokers from 2 prospective cohort studies.[9] Overall rates among female and male current smokers were 253

and 232 per 100,000 person-years, respectively, and 81 and 73 per 100,000 person-years, respectively, among former smokers. Among current and former smokers, age-specific incidence increased with increasing age and number of cigarettes smoked per day. For example, among female current smokers aged 65 years to 69 years who began smoking at age 19 years or younger, lung cancer incidence among those who smoked fewer than 25 cigarettes per day was 641 cases per 100,000 person-years versus 1081 for those who smoked 25 or more cigarettes per day.[9]

Lung cancer mortality rates are similar in magnitude to lung cancer incidence rates due to the high fatality rate from this disease. The age-adjusted death rates (2005–2009) per 100,000 men and women were 65.7 and 39.6, respectively.[7] Like incidence rates, overall population age-adjusted death rates are considerably lower than those estimated specifically for current and former smokers and rates vary with cumulative exposure to tobacco smoke. For example, Bach et al estimated a lung cancer mortality rate of 376 per 100,000 person-years among current and former smokers in the Carotene and Retinol Efficacy Trial (CARET).[10]

Numerous studies have demonstrated that smoking cessation measurably reduces the risk of developing and dying from lung cancer compared with continuing smoking. Using data from the American Cancer Society's Cancer Prevention Study II, Halpern et al examined the effect of age at cessation on the absolute risk of lung cancer death.[11] With increasing age, adults who quit smoking between the ages of 30 years and 49 years experienced only a slightly higher absolute risk of lung cancer death compared with nonsmokers, while adults who quit between ages 50 years and 64 years retained the absolute risk attained at the time of cessation. In a long-term evaluation of British physicians, Doll et al observed progressively greater longevity in former smokers based on their age at cessation. For a cohort of men born around 1920, the 3-fold excess mortality associated with prolonged cigarette smoking was halved by quitting at age 50 years, and was reduced nearly to that of lifelong nonsmokers by quitting at age 30 years.[12]

Death rates from lung cancer have been declining among men since 1984 and among women since 2003[7]; this trend principally is due to tobacco control efforts leading to lower rates of tobacco use and a reduced incidence of lung cancer. However, the accumulation of risk in the US adult population from years of exposure to tobacco smoke among current and former smokers[13] and the stall in the decline in smoking rates in the United States means that a significant lung cancer burden will persist in the nation for the foreseeable future.

The observation that survival was more favorable when lung cancer was diagnosed at an earlier stage by CXR led to efforts in the 1970s and 1980s to determine whether or not screening with CXR with or without sputum cytology was associated with reduced lung cancer mortality. Four prospective RCTs of lung cancer screening were carried out using combinations of CXR and sputum cytology.[14–18] None of these studies showed a significant reduction in lung cancer mortality associated with an invitation to screening. However, the results of these early RCTs were controversial due to a range of methodological shortcomings. Furthermore, CXR both alone and in combination with sputum cytology improved the stage at diagnosis and was associated with more favorable survival, which had also been observed in case-finding series. Still, in spite of limitations in study design, for many years it was widely accepted that lung cancer screening with CXR was not effective. The ACS, which had recommended lung cancer screening with CXR in the 1970s for current and former smokers, withdrew the recommendation in 1980.[19]

The possibility that the negative results from the early lung cancer screening RCTs were due to limitations in the early study designs led to further attempts to properly evaluate CXR,

with the NCI including CXR in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, which was launched in the early 1990s.[20] However, concerns about the limited sensitivity of CXR also led other investigators to explore the potential of lung cancer screening with newer, more sensitive imaging technology. The sensitivity of CXR is dependent on the size and location of the lesion, the image quality, and the skill of the interpreting physician.[21] Failure to detect abnormal lung lesions at a favorable size can occur because the lesions are too small to be seen or are obscured by the mediastinum and other aspects of the chest structure, or because of errors in perception on the part of the interpreter.[22] In contrast, early investigations of screening for lung cancer with LDCT demonstrated considerably greater sensitivity in the detection of small pulmonary nodules.[23–25] In 1999, investigators from the Early Lung Cancer Action Project (ELCAP) published baseline findings comparing lung cancer screening with LDCT and CXR in 1000 volunteers aged 60 years and over with a smoking history of at least 10 pack-years.[25] LDCT identified 233 participants with noncalcified nodules and 27 malignancies, 26 of which were resectable and 23 of which were stage I disease. In contrast, conventional CXR identified 68 noncalcified nodules, 7 of which were malignant and 4 of which were stage I disease. Based on the growing evidence that LDCT might succeed where CXR had failed, investigators in the United States and Europe launched prospective RCTs comparing LDCT with CXR or usual care.[26–32]

Materials and Methods

Following the announcement of the NLST results in late 2010, the ACS joined with the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network (NCCN) to produce a systematic review of the evidence related to lung cancer screening with LDCT.[33] The systematic review focused on 4 key questions:

- What are the potential benefits of screening individuals at high risk of developing lung cancer using LDCT?
- What are the potential harms of screening individuals at high risk of developing lung cancer using LDCT?
- Which groups are likely to benefit or not benefit?
- In what setting is screening likely to be effective?

The literature search and review focused on literature published from January 1996 through April 8, 2012, and reference lists from key articles and recent review articles also were examined for additional citations. Both RCTs and observational studies were included in the review. Eligible studies included RCTs offering LDCT lung cancer screening to one group, or noncomparative cohort studies of LDCT screening that provided at least one of the following outcomes: lung cancer-specific or all-cause mortality, nodule detection rate, frequency of additional imaging, frequency of invasive diagnostic procedures (eg, needle or bronchoscopic biopsy, surgical biopsy, or surgical resection), complications from the evaluation of suspected lung cancer, or the rate of smoking cessation or reinitiation. For the primary endpoints of lung cancer mortality and all-cause mortality, only RCT data were considered, whereas RCT and observational data were considered for other endpoints, particularly those pertaining to screening performance (ie, the false-positive rate, frequency of additional imaging tests, and the biopsy rate), and rates of smoking cessation.[33] Case series, studies not published in English, and studies in which elevated lung cancer risk was due to occupational or environmental exposures were excluded. A total of 591 citations were identified by the search strategy, which yielded 8 RCTs and 13 cohort studies. Additional details related to the methodology are published elsewhere.[33]

Each of the RCTs randomized current or former smokers to a group invited to LDCT screening or a control group who received usual care or, in the case of the NLST, Lung Screening Feasibility Study (LSS), and DEPISCAN (Pilot Study to Evaluate Low Dose Spiral CT Scanning as a Screening Method for Bronchial Carcinoma), the control group received an invitation to CXR. All noncomparative studies screened individuals with LDCT. Risk was based on a combination of age and smoking history, with the lowest minimum exposure being 15 pack-years, but more commonly 20 or more or 30 or more pack-years. In 5 trials, the maximum allowable years since smoking cessation was 10 years, and in 2 trials it was 15 years. All RCTs with the exception of the DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays) trial enrolled both men and women. With the exception of the NLST and the NELSON trial (Dutch-Belgian Randomized Lung Cancer Screening Trial [Dutch acronym: NELSON study]), which has not reported end results, the average trial size is small, and ultimately these trials' contribution to estimating the effect of LDCT screening on lung cancer mortality will be realized in a pooled analysis at some time in the future.[34,35] At this time, there are only 3 RCTs (the NLST, DANTE, and Danish Lung Cancer Screening Study [DLCST]) that have reported on the association between an invitation to screening with LDCT and lung cancer mortality. In developing this guideline, particular weight was given to the NLST based on its larger study size.

Benefits of Screening for Lung Cancer With LDCT

Among the 8 RCTs, only 3 (the NLST, DANTE, and DLCST) have reported mortality results. Although the principal benefit of screening is measured in terms of lung cancer-specific mortality, these 3 trials also have reported all-cause mortality. While disease-specific mortality is the primary endpoint in an RCT of cancer screening, the examination of all-cause mortality as a secondary endpoint is relevant to determine whether or not a reduction in lung cancer-specific mortality may be offset by deaths from other unanticipated causes.[36]

Lung Cancer-Specific Mortality and All-Cause Mortality

In the NLST, there were 247 lung cancer deaths in the LDCT arm and 309 deaths in the CXR arm per 100,000 person-years, with a mean duration of follow-up of 6.5 years, resulting in a 20% difference in the lung cancer death rate between the LDCT arm and the CXR arm (rate ratio [RR], 0.80; 95% confidence interval [95% CI], 0.73–0.93) and a 6.7% reduction in deaths from any cause (RR, 0.93; 95% CI, 0.86–0.99), of which a large fraction was due to fewer deaths from lung cancer.[4] Comparing the 2 arms on the basis of participation in at least one round of screening, the number needed to screen with LDCT at least once over 3 rounds of screening (with a median duration of follow-up of 6.5 years) to save one life was 320.[4] The DANTE trial and the DLCST, each of which is considerably smaller with fewer years of follow-up, have not observed a significant difference in the lung cancer mortality rate or the all-cause mortality rate. The DANTE trial observed 3% fewer lung cancer deaths in the group invited to screening (RR, 0.97; 95% CI, 0.71–1.32) and no difference in all-cause mortality.[37] In the DLCST, there was an excess rate of lung cancer mortality in the invited group (RR, 1.15; 95% CI, 0.83–1.61) and no difference in all-cause mortality.

There is some uncertainty as to whether a 20% difference in lung cancer deaths is the ultimate mortality reduction that can be expected from LDCT screening. First, there were only 3 LDCT examinations given in the NLST: the first at baseline, the second one year after baseline, and the third 2 years after baseline (ie, 3 examinations over a 2-year period). Second, there actually may have been some, albeit small, benefit from CXR that contributed to a smaller difference in the lung cancer death rates between the 2 arms than would have

been observed if the patients in the comparison arm had just received usual care. In both the NLST and the PLCO, there was approximately twice the detection rate of stage I cancers in the group invited to undergo CXR screening compared with the usual-care group or refusers (those who were never screened).[4,38] Furthermore, although the PLCO trial did not observe a statistically significant difference in lung cancer deaths associated with CXR screening, the authors noted that the combination of 4 screening rounds coupled with the long period of follow-up (approximately 12 years) may have diluted the ability to observe a favorable screening effect with CXR. The authors provided estimates that limited the analysis to cases diagnosed within 6 or 7 years of randomization (ie, cases diagnosed during the screening period [3 years] plus an additional 3- to 4-year period representing the upper end of the detectable preclinical phase). Restricting the follow-up period to 3 years results in a screening effect of 11% (RR, 0.89; 95% CI, 0.80–1.00); however, using a 4-year follow-up period results in a screening effect of only 6% (RR, 0.94; 95% CI, 0.84–1.04).[38]

Smoking Cessation

A legitimate concern is that some smokers might use LDCT imaging as an excuse to continue smoking. Although a majority of current smokers who undergo CT screening continue to smoke within the short duration of time that they are contacted after screening, it is not clear what fraction continues smoking due to reassurance from a negative screen or other factors. There also appears to be little supporting evidence that simply undergoing CT screening affects quitting rates.[33] However, evidence from noncomparative studies suggests that an additional benefit of LDCT screening may be a positive effect on smoking cessation among smokers who undergo screening and are counseled to quit smoking. To date, most of these studies have shown higher rates of smoking cessation among those choosing to be screened by LDCT than are seen at the community level in unscreened groups.[39–41] In one study, cessation rates also were higher among those with CT abnormalities creating moderate or high lung cancer suspicion.[42] Vigorous smoking cessation efforts must accompany LDCT screening for adults who are current smokers, and further investigations are warranted to determine best practices for promoting cessation among smokers seeking lung cancer screening.

Limitations and Harms

Adults seeking testing for early lung cancer detection must be informed that screening will not detect all lung cancers, and the detection of a cancer by LDCT does not guarantee that death from lung cancer will be avoided. Harms associated with LDCT screening include anxiety associated with abnormal testing results, additional imaging tests and biopsy procedures associated with false-positive results, and investigations for incidental findings outside of the lung field; in rare instances, serious harms, including hospitalizations and death, can result from diagnostic evaluations in patients with and without lung cancer.

False-Positive Results

One feature of lung cancer screening with LDCT is the relatively high rate of identification of benign, noncalcified nodules. Studies varied in the nodule size thresholds for a positive finding, as well as in the nodule detection rate per round of screening. Most studies reported only the baseline rate or the baseline and round 1 nodule detection rates, with only the NLST reporting rates for 3 rounds of screening. Overall, the average nodule detection rate per round of screening was 20%; at baseline, the nodule rate in the RCTs ranged from 3% to 30%, and in the cohort studies it ranged from 5% to 50%.[33] The recall rate tends to decline in subsequent rounds,[33] and in the NLST it declined between the second and third screening round because stable nodules were no longer considered positive.[4]

In the LDCT arm of the NLST, 27.3% of study subjects experienced a positive test result in the first round of screening, and over 3 screening rounds, 39.1% of individuals experienced at least one abnormal CT scan.[4] According to the American College of Radiology Imaging Network (ACRIN) NLST study protocol, individuals with indeterminate or positive findings based on nodule size were recommended to undergo diagnostic tests or repeat LDCT or limited thin-section CT at varying intervals (3 months, 6 months, 12 months, or 24 months) from the date of the positive screening test based on nodule size and level of suspicion for lung cancer. Thus, some individuals with small nodules with a low suspicion of cancer might have had a second LDCT scan and if there was no change in the nodule, no additional imaging would take place before the next round of screening. If some change in size or appearance was observed, additional interval imaging (at 3 months–6 months) might be scheduled, or more definitive diagnostic tests would be recommended.[43] The large majority of individuals with abnormal LDCT test results required only additional imaging to determine if one or more nodules were growing.

Prior to resolution, false-positive findings can cause anxiety, and lead to additional costs, additional radiation exposures, and invasive procedures. One study reported that indeterminate lung cancer screening test results increased anxiety, but that anxiety diminished over time, a finding similar to what has been observed in breast cancer screening.[44] In the NELSON trial, a battery of health-related quality of life questionnaires were administered longitudinally to measure both short- and long-term effects of LDCT screening among adults with normal and indeterminate results. At 2 months after indeterminate findings were reported, there was a significant increase in lung cancer-specific distress, whereas scores were significantly lower after negative findings.[45] Longer-term evaluation demonstrated that the short-term anxiety associated with an indeterminate finding had resolved, and a second indeterminate finding was not associated with increased lung cancer-specific distress.[46]

At this time, there is insufficient evidence in the medical literature to draw conclusions about the near- and long-term psychological effects of false-positive LDCT findings, although based on the limited evidence from these studies and evidence of some adverse psychological effects of false-positive findings associated with other screening tests, there is reason for concern about the short-term anxiety associated with positive findings and additional testing during intervals between screening examinations.

Invasive Procedures

The rate of invasive procedures among participants with abnormal imaging results who ultimately were determined not to have lung cancer was low: only 2.7%.[4] The rate of complications resulting from a diagnostic procedure following a positive screening test also was relatively low, and was considerably higher in patients with a diagnosis of lung cancer versus those whose abnormality was determined to be benign (11.2% vs 0.06%, respectively).[4]

Invasive procedures may be associated with adverse events, although NLST investigators judged the rate of complications resulting from LDCT examinations as “few and minor.” While the risk of a false-positive screening test is high, few patients (2.7%) who did not have lung cancer also underwent an invasive procedure. Among patients who had a positive screening test and underwent a diagnostic procedure, approximately 1.4% experienced a complication.[4] The complication rate was higher among individuals who ultimately were diagnosed with lung cancer (23.3%) compared with those who had false-positive findings (0.4%). Thus, while the risk of a false-positive screening test result is high, the risk of a biopsy or a major complication following a positive screening test is low.

There were 21 deaths within 60 days of the most invasive diagnostic procedure in the LDCT group, 16 of which occurred following invasive medical interventions and 5 of which occurred in patients who only underwent additional imaging. The majority of these deaths (10 deaths) occurred in patients who underwent an invasive procedure and were found to have lung cancer. Among patients without lung cancer, there were 6 deaths among those patients who underwent an invasive procedure and 5 deaths in patients not found to have lung cancer within 60 days of additional imaging, which presumably were not related to diagnostic procedures. For the entire population undergoing LDCT screening, the risk of death and major complications associated with any diagnostic evaluation for benign findings was 4.1 and 4.5 per 10,000, respectively.[33] Among the 6 deaths in patients without lung cancer, 2 occurred within 60 days of additional imaging only, suggesting they were unlikely to be due to the diagnostic evaluation.[33] It is not known whether these deaths were due to elevated risk from other comorbid conditions. Although the risk of death in the noncancer patients was low (0.024%), the potential for serious adverse events associated with positive LDCT examinations must be discussed with patients considering undergoing screening.

Radiation Risk

There are concerns about radiation exposure from repeat LDCT screening examinations and higher-dose diagnostic evaluations.[47] While there is agreement that there are possible harms of radiation associated with repeated screening examinations and subsequent higher-resolution diagnostic examinations, these risks are not precisely quantifiable. For individuals at a low risk of lung cancer, concerns about radiation exposure become more of a concern relative to the expected benefit versus potential harm.[48] It is known that radiation doses received by subjects in the NLST varied significantly across CT scanners, principally due to variations in the type and generation of CT scanners and the scanner settings.[4] This variation is also common in community practice. There also is concern that if follow-up protocols are not strictly followed, some patients with small, indeterminate nodules may receive higher-dose, high-resolution CT versus recommended LDCT.

With improvements in technology resulting in lower-dose examinations, the risk associated with screening may become less of a concern as new generations of scanners replace older ones, and quality standards for lung cancer screening that include radiation dose criteria for screening examinations are widely propagated.[49]

Incidental Findings

An additional potential harm of lung cancer screening (but also a potential benefit) is the detection by CT of incidental findings outside of the lung. In the NLST, 7.5% of participants in the CT arm were judged to have a clinically significant non–lung-related abnormality, such as cardiac and vascular abnormalities.[4] In some instances, the detection of these abnormalities may lead to health benefits for the patient, but in other instances it will only mean an additional diagnostic process and/or additional anxiety that will be experienced with no health benefit. Without evidence of benefit, the most conservative approach is to assume that the additional diagnostic procedures associated with these findings are harmful. The overall mortality reduction seen in the NLST suggests that that the harm associated with these additional findings does not outweigh the observed mortality benefit of screening.

Overdiagnosis

Overdiagnosis is the detection through screening of a cancer that is not life-threatening and never would have been detected if the patient had not undergone screening. To the degree that some over-diagnosis occurs in lung cancer screening, it represents a harm of screening since an over-diagnosed cancer can be expected to result in overtreatment.

An overdiagnosed cancer does not have any distinguishing features to set it apart from a progressive cancer; thus, overdiagnosis is an epidemiological rather than pathological concept. Estimates of overdiagnosis depend on a careful comparison of expected versus observed incidence rates over time. Thus, estimating the rate of overdiagnosis must distinguish excess incidence from the known effects of screening on lead time, as well as other historical and contemporaneous influences on incidence. The concept of overdiagnosis often is broadened, inappropriately, to include cancers that ultimately would be life-threatening, but are so slow-growing that the patient has a higher likelihood of dying from some other cause first. This definition, while seemingly apt for near-term smoking-related nonlung cancer deaths, still is unworkable for the simple reason that estimates of overdiagnosis would necessarily require arbitrary posttreatment time boundaries and include all incident cases for which a death occurs from another cause.

The most reliable method for estimating the degree to which lung cancer screening results in overdiagnosis is to observe long-term incidence in an RCT, since randomization should produce equivalent comparison groups, one of which nominally receives screening and the other of which receives usual care (ie, ideally, no screening) and thus depicts the natural history of disease progression. Follow-up should occur sufficiently long enough after screening rounds have ceased to compare incidence rates in both groups. If there is no overdiagnosis, the number of incident cancers should be the same in both groups, with the expectation that if screening is effective, the cancers in the invited group will be found earlier and at an earlier stage compared with the control group.

Estimating overdiagnosis from the NLST is complicated by the design of the study, which compared LDCT with CXR. Excess incidence was observed in the early CXR RCTs, leading to estimates that lung cancer screening resulted in rates of overdiagnosis exceeding 20%.[50,51] Given the greater sensitivity of LDCT, some have speculated that lung cancer screening with LDCT will lead to even higher rates of overdiagnosis.[52] However, in the NLST, there was only a 13% difference in the number of cases diagnosed in the LDCT arm versus the CXR arm, and it is still too early in the follow-up period to draw any conclusions about overdiagnosis from this difference. PLCO trial investigators observed a difference in the number of cancers in the experimental group compared with the control group of 4.6%, which is considerably lower than earlier estimates of overdiagnosis associated with CXR.[38] In short, it is impossible at this time to draw definitive conclusions about the magnitude of overdiagnosis associated with lung cancer screening. However, based on the data from the NLST and the PLCO, some overdiagnosis associated with lung cancer screening is a possibility, but likely does not represent a significant fraction of the screen-detected cancers. Additional evidence from prospective RCTs in Europe, where the number of cases in a group invited to screening with LDCT can be compared with a control group offered usual care may eventually provide better estimates of the rate of overdiagnosis associated with lung cancer screening.

Patients Likely to Benefit From Screening

At this time, the evidence from the NLST demonstrates that LDCT screening is beneficial in a population of men and women aged 55 years to 74 years who are in reasonably good health and are current or former smokers (having quit within the past 15 years) with 30 or more pack-years of smoking. The average NLST participant was aged 62 years and had an approximately 50-pack-year history of smoking. Bach et al estimated the 10-year lung cancer risk of the average NLST participant to be 10%, with a range from 2% to over 20%.[33] A this time, subgroup analysis to determine whether or not the benefit of screening varied by age and smoking history is not yet available.[33] As with any screening test, identifying the population to invite to screening is based on the underlying prevalence of

disease; the likelihood that benefits will exceed harms; whether competing causes of death would reduce the potential benefit of an early diagnosis of lung cancer; and, under some health care systems, the cost-effectiveness of the screening strategy. These are questions that cannot be answered at this time.

Effective Screening Setting

A majority of the NLST study sites were NCI-designated cancer centers and large academic medical centers. The NLST established quality parameters for the study: 1) minimum equipment standards; 2) a standard screening protocol, with acquisition variables designed to insure a low-dose examination; and 3) radiologists and technologists completed training in image acquisition and interpretation.[33] While the degree to which the average imaging facility in the United States can deliver the level of care that was delivered in the NLST is not known, it is expected that the level of preparedness to deliver high-quality screening and follow-up is variable across the nation.

Recommendations

Clinicians should ascertain the smoking status and smoking history of their patients aged 55 years to 74 years (Table 1). Clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about lung cancer screening with patients aged 55 years to 74 years who have at least a 30-pack-year smoking history, currently smoke, or have quit within the past 15 years, and who are in relatively good health. Core elements of this discussion should include the following benefits, uncertainties, and harms of screening:

- Benefit: Screening with LDCT has been shown to substantially reduce the risk of dying from lung cancer.
- Limitations: LDCT will not detect all lung cancers or all lung cancers early, and not all patients who have a lung cancer detected by LDCT will avoid death from lung cancer.
- Harms: There is a significant chance of a false-positive result, which will require additional periodic testing and, in some instances, an invasive procedure to determine whether or not an abnormality is lung cancer or some nonlung cancer-related incidental finding. Fewer than 1 in 1000 patients with a false-positive result experience a major complication resulting from a diagnostic workup. Death within 60 days of a diagnostic evaluation has been documented, but is rare and most often occurs in patients with lung cancer.
- Smoking cessation counseling constitutes a high priority for clinical attention for patients who are currently smoking. Current smokers should be informed of their continuing risk of lung cancer, and referred to smoking cessation programs. Screening should not be viewed as an alternative to smoking cessation.
- Eligible patients should make the screening decision together with their health care provider. Helping individuals to clarify their personal values can facilitate effective decision-making:
    - Individuals who value the opportunity to reduce their risk of dying from lung cancer and who are willing to accept the risks and costs associated with having a LDCT and the relatively high likelihood of the need for further tests, even tests that have the rare but real risk of complications and death, may opt to be screened with LDCT every year.

- Individuals who place greater value on avoiding testing that carries a high risk of false-positive results and a small risk of complications, and who understand and accept that they are at a much higher risk of death from lung cancer than from screening complications, may opt not to be screened with LDCT.

- Clinicians should not discuss lung cancer screening with LDCT with patients who do not meet the above criteria. If lung cancer screening is requested, these patients should be informed that at this time, there is too much uncertainty regarding the balance of benefits and harms for individuals at younger or older ages and/ or with less lifetime exposure to tobacco smoke and/or with sufficiently severe lung damage to require oxygen (or other health-related NLST exclusion criteria), and therefore screening is not recommended.
- Adults who choose to be screened should follow the NLST protocol of annual LDCT screening until they reach age 74 years.
- CXR should not be used for cancer screening.
- Wherever possible, adults who choose to undergo lung screening preferably should enter an organized screening program at an institution with expertise in LDCT screening, with access to a multidisciplinary team skilled in the evaluation, diagnosis, and treatment of abnormal lung lesions. If an organized, experienced screening program is not accessible, but the patient strongly wishes to be screened, they should be referred to a center that performs a reasonably high volume of lung CT scans, diagnostic tests, and lung cancer surgeries. If such a setting is not available and the patient is not willing or able to travel to such a setting, the risks of cancer screening may be substantially higher than the observed risks associated with screening in the NLST, and screening is not recommended. Referring physicians should help their patients identify appropriate settings with this expertise.
- At this time, very few government or private insurance programs provide coverage for the initial LDCT preformed for the indication of lung cancer screening. Clinicians who decide to offer screening bear the responsibility of helping patients determine if they will have to pay for the initial test themselves and to help the patient know how much they will have to pay. In light of the firm evidence that screening high-risk individuals can substantially reduce death rates from lung cancer, both private and public health care insurers should expand coverage to include the cost of annual LDCT screening for lung cancer in appropriate high-risk individuals.

Discussion

This guideline provides guidance about lung cancer screening with LDCT to clinicians and their patients who are at risk of developing lung cancer. Other organizations also have issued lung cancer screening guidelines. The American College of Chest Physicians and the American Society of Clinical Oncology suggest that LDCT screening for lung cancer should be offered over both annual screening with CXR or no screening to individuals who would have met the entry criteria for the NLST, but only in settings that can deliver the comprehensive care provided to NLST participants.[33] The American Lung Association recommends annual lung cancer screening with LDCT based on the NLST entry criteria.[53] The NCCN guidelines recommend annual LDCT for adults who meet the NLST entry criteria, and for individuals aged 50 years or older with a smoking history of 20 or more pack-years who have one other known risk factor for lung cancer (family history, significant

exposure to radon, etc).[54] The American Association for Thoracic Surgery guidelines recommend annual lung cancer screening with LDCT for adults aged 55 to 79 years with a 30-pack-year history of smoking, and annual screening beginning at age 50 for adults with a 20-pack-year history who have an additional cumulative risk of developing lung cancer of 5% or greater over the following 5 years.[55] The recommendations from these organizations are conservative and mostly restricted to the NLST study protocol since there are many questions inherent to a lung cancer screening guideline that cannot fully be answered at this time. These include but are not limited to the age to begin and end screening; whether or not the synergy between the age at initiation, duration, and intensity of smoking and current age should be considered; the optimal screening interval; and issues pertaining to the performance characteristics of screening. Each warrants focused attention.

Despite these unresolved issues, the NLST demonstrated that there is an opportunity to reduce deaths from lung cancer in a high-risk group of current and former smokers. Clinicians will now face the challenge of integrating risk assessment into their encounters with patients. Inevitably, they will face the question of how to cope with the patient who does not strictly meet the NLST eligibility criteria, but appears to be at a similar, or seemingly greater, risk of lung cancer compared with the study thresholds. Some examples include the patient who is aged 54 years but with a 45- pack-year smoking history, or the 58-year-old patient with a 50-pack-year history who quit smoking 16 years ago. When confronted with these circumstances, where risk seems to approximate or exceed the NLST eligibility criteria in one category but not another, clinicians will need to use their best judgment in deciding whether to engage the patient in a discussion about screening or not. For those patients who are at substantially lower risk than individuals who were invited to participate in the NLST, clinicians should inform them that screening is not recommended. For these lower-risk patients, the balance of benefits and potential harms may be unfavorable. The NCCN issued screening guidelines in 2011 that endorse screening eligibility based on the NLST criteria, but that also endorse screening in adults at lower risk based on age (aged older than 50 years) and smoking history (smoking history of 20 or more pack-years) in the presence of one additional risk factor for lung cancer (ie, documented high radon exposure, certain occupational exposures, family history of lung cancer, chronic obstructive pulmonary disease, or pulmonary fibrosis).[53] These recommendations extend screening eligibility considerably beyond the NLST criteria and some aspects of these recommendations may be difficult to implement in clinical practice (ie, a history of radon exposure). Ultimately, whether or not eligibility criteria in lung cancer screening guidelines are significantly broadened and, if so, in what manner, will depend on additional research and the development and validation of new risk assessment tools.

Identifying individuals who are eligible for screening in the primary care setting will probably become easier with the “meaningful use” criteria for electronic health records under the recent Health Information Technology for Economic and Clinical Health (HITECH) Act since the meaningful use criteria require clinicians to both screen the smoking status of over 50% of their patients who are aged 13 years or older and track the percentage of patients aged 10 years and older who are current smokers. Nevertheless, many clinicians are not experienced in or prepared to guide patients through the shared decision-making process around screening. Developing this competency is a rapidly emerging obligation for the primary care clinician and their clinical teams. Shared decision-making is highly consistent with the movement to encourage patient-centered care within the medical home environment. Cancer control organizations and specialty societies must devote resources to ensuring that clinicians are prepared to distinguish those patients who are eligible for screening from those who are not, and to support shared decision-making. Failure to adhere to the guidelines will increase harms without the potential for greater benefit.

Conclusions

Now that there is rigorous evidence supporting the value of screening for lung cancer with LDCT, it is important that the implementation of lung cancer screening proceeds in a manner that is focused on maximizing benefits and minimizing harms. At this time, there is sufficient evidence to support screening provided that the patient has undergone a thorough discussion of the benefits, limitations, and risks, and can be screened in a setting with experience in lung cancer screening. Many questions remain to be answered, and an experience base and infrastructure to support population-based lung cancer screening is not yet in place and needs to be built. Additional scientific reports from the NLST and the European trials and evidence from observational studies will contribute to filling in the existing knowledge gaps related to broadening eligibility for lung cancer screening and further define early lung cancer detection protocols. As with other guidelines for cancer screening, we can expect that this initial guideline will be revised as new data become available. Whether community-based screening for lung cancer with LDCT will exceed or fail to achieve the benefit observed in the NLST could be influenced by many factors, and the answer awaits the results of further observation and research.

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TABLE 1

Eligibility Criteria for the National Lung Screening Trial

Age	Ages 55–74 y, with no signs or symptoms of lung cancer.
Smoking history	Active or former smoker with a 30–pack-y history (a pack-y is the equivalent of 1 pack of cigarettes per d per y. One pack per d for 30 y or 2 packs per d for 15 y would both be 30 pack-y).
Active smoker	If active smoker, should also be vigorously urged to enter a smoking cessation program.
Former smoker	If former smoker, must have quit within the past 15 y.
General health exclusions	Life-limiting comorbid conditions. Metallic implants or devices in the chest or back. Requirement for home oxygen supplementation.