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Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

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The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

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Structured Abstract

Background: Lung cancer is the leading cause of cancer-related death in the United States. However, persons with early lung cancer have lower lung cancer–related mortality than those with extensive disease, suggesting early detection and treatment of lung cancer might be beneficial. Low-dose computed tomography (LDCT) and chest x-ray (CXR) have been studied for early screening, with several new studies reporting results since the last review.

Purpose: To update the 2004 review of screening for lung cancer for the U.S. Preventive Services Task Force.

Data Sources: MEDLINE (2000 to 2012), Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through fourth quarter 2012), Scopus, and reference lists.

Study Selection: English-language randomized, controlled trials or cohort studies that evaluated screening or treatment interventions for lung cancer and reported health outcomes.

Data Extraction: Details about participants, study design, analysis, followup, and results were abstracted; study quality was rated using established criteria, where applicable.

Data Synthesis (Results): Four trials reported the effectiveness of screening with LDCT for lung cancer in patients with personal smoking exposure: one large good-quality trial reported screening was associated with reduced lung cancer and all-cause mortality reductions of 20 percent (95% CI, 6.8 to 27.6) and 6.7 percent (95% CI, 1.2 to 13.6), respectively. Three small European trials (two fair- and one poor-quality) showed no benefit of screening. When the three good- or fair-quality trials were combined in random effects meta-analysis, the relative risk of lung cancer mortality was 0.81 (95% CI, 0.72 to 0.91). One trial evaluated CXR screening in over 150,000 participants from the general population and reported no benefit of screening in this group or in a subset with personal tobacco smoke exposure. The reported sensitivity of LDCT for detecting lung cancer ranged from 80 to 100 percent and specificity from 28 to 100 percent in six studies; each study varied in its reporting method. The harms associated with LDCT screening included radiation exposure ranging from 0.61 to 1.5 mSv per scan, some degree of overdiagnosis of lung cancer that varied by study, and a high rate of false-positive examinations, which were typically resolved with further imaging. Most patients with positive results who underwent an invasive procedure were diagnosed with lung cancer. Smoking cessation was not significantly impacted by screening, although individuals with positive or indeterminate screens showed a trend toward reduced smoking or sustained abstinence. Patients with positive or indeterminate scans had some evidence of short-term increases in anxiety and distress but not long-term in the five studies evaluating this; patients with negative scans had a reduction in distress. Finally, no trials comparing treatment of stage I non-small cell lung cancer (NSCLC) with no treatment have been conducted. However, survival associated with surgical resection was evaluated in 11 studies of mostly symptomatic and unselected patients that have shown 5-year survival rates in the 71 to 90 percent range for stage IA NSCLC and 42 to 75 percent for stage IB NSCLC and that surgical resection is the U.S. standard of care. Harms of treatment of stage I NSCLC were poorly reported and ranged among the studies that reported

them.

Limitations: Three trials were underpowered and of too short of duration to reach conclusions on effectiveness of screening. Overdiagnosis is an important harm of screening but its magnitude is uncertain. No studies of LDCT have reported results in women or minority populations.

Conclusions: Good evidence shows LDCT can significantly reduce mortality from lung cancer. However, there are significant harms associated with screening that must be balanced with the benefits. More efforts to reduce false-positive examinations are of paramount importance and smoking cessation remains the most important approach to reducing lung cancer mortality.

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CHAPTER 1. INTRODUCTION

Purpose of Review and Prior U.S. Preventive Services Task Force Recommendation

The purpose of this report is to update a previous evidence review[1] commissioned by the U.S. Preventive Services Task Force (USPSTF) on screening for lung cancer. In 2004, based on the previous evidence review, the USPSTF found there was insufficient evidence to either recommend for or against routinely screening asymptomatic persons for lung cancer with either low-dose computed tomography (LDCT), chest x-ray (CXR), sputum cytology, or a combination of these tests (I statement).[2]

The previous evidence review assessed six randomized, controlled trials (RCTs) of poor- or fair-quality of CXR screening with or without sputum cytology examination conducted in the 1960s and 1970s among men at high risk for lung cancer because of exposure to tobacco smoking. No studies showed reduced lung cancer mortality among any of the screened participants.[1] However, participants in all studies received some level of screening, limiting conclusions about screening compared with no screening.

The previous evidence review also included five fair-quality case-control studies from Japan of high-risk men and low- or unknown-risk women.[1] All studies found lower odds of dying of lung cancer among those screened periodically with CXR, with odds ratios (ORs) ranging from 0.4 to 0.7. One poor-quality case-control study did not show benefit.[3] Focusing specifically on the efficacy of lung cancer screening in women, the previous evidence review identified a suggestion of benefit from Japanese case-control studies of CXR screening, but found no RCTs evaluating CXR screening in women.

Screening for lung cancer with LDCT was evaluated in six cohort studies included in the previous evidence review. These studies screened both high- and low-risk individuals and found LDCT identified more early-stage lung cancer than CXR or than is typically identified in clinical practice. The previous evidence review identified no RCTs on the use of LDCT screening for lung cancer.

The current evidence review will be used by the USPSTF to update its 2004 recommendation on screening for lung cancer. This update focuses on evidence that has been published since the previous evidence review on the effectiveness of screening asymptomatic men and women for lung cancer, as well as the risks and harms associated with screening. The report will emphasize evidence applicable to typical practice in the United States.

Condition Definitions

Lung cancer is a proliferation of malignant cells arising in the airways or tissues of the lung. Ninety-five percent of lung malignancies are either non-small cell lung cancer (NSCLC) or small

cell carcinoma, with small cell carcinoma accounting for 16 percent of cases. The remaining 5 percent of primary pulmonary malignancies include rare entities such as carcinoid tumor. NSCLC is a heterogeneous designation with subsets including squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and undifferentiated carcinoma. Individual tumors can show features of several of these subtypes. Adenocarcinoma is the most common subtype, encompassing 36 percent of all lung cancers, with squamous cell carcinoma making up 20 percent of cases in a large survey of U.S. lung cancer from 1998 to 2001.[4] The World Health Organization has recently revised the histology classifications for lung cancer, including several new preinvasive lesions within the adenocarcinoma classification.[5]

Lung cancer is staged according to the American Joint Committee by the TNM system. The TNM and stage designations have been recently revised and a new breakdown of early-stage primary cancers into T1a (<2 cm) or T1b (2 to 3 cm) has been added.[6] Stage IA NSCLC is less than or equal to 3 cm in its greatest dimension, does not invade the visceral pleura or bronchus within 3 cm of the main carina, and has no evidence of lymph node or metastatic spread.[7]

Prevalence and Burden of Disease

Lung cancer is the second most commonly occurring cancer in the United States among men and women and the leading cause of cancer-related death.[8] The American Cancer Society (ACS) predicted there would be approximately 226,160 new cases and 160,340 lung cancer–related deaths in the United States in 2012.[4] Notably, lung cancer is expected to account for almost 28 percent of all cancer-related deaths in 2012. Current estimates suggest that almost 7 percent of men and women born today will be diagnosed with lung cancer during their lifetime and almost 6 percent will die from it.[4,9,10] Lung cancer and lung cancer–related deaths have been increasing in epidemic proportions throughout the world, with differences between countries largely explained by differences in smoking rates.[11] Worldwide, it is estimated there were 1.6 million new cases and 1.4 million deaths from lung cancer in 2008.[11] Rates of lung cancer vary by smoking status. In one very large population-based cohort study of approximately 50,000 people ages 40 to 70 years, lung cancer death rates among women and men smoking 20 or more cigarettes per day were 41 and 43 per 1,000 or 16 and 11 percent of all deaths, respectively. Among never smokers, lung cancer mortality was 1.0 and 1.3 per 1,000 for women and men, respectively.[12] As a measure of the burden of lung cancer in the population, lung cancer is the leading cause of years of life lost to cancer in the United States, with an estimate of 15 years of life lost on average per person dying of lung cancer.[13]

Risk Factors

The biggest single risk factor for lung cancer is smoking,[14] causing approximately 85 percent of lung cancers in the United States.[15] Worldwide, smoking accounts for 75 to 80 percent of cases in men and at least 50 percent in women.[11,16] Smoking has been associated most strongly with squamous cell and small cell carcinoma[17] and to a lesser degree with adenocarcinoma, including the bronchioloalveolar subtype.[18]

Utilizing data from 2006 through 2007, the Tobacco Use Supplement Survey from the National Cancer Institute reported 37 percent of adults in the United States as current or former smokers.[19] Although the prevalence of current smoking has declined slowly in recent years, in 2010 it was estimated that 19 percent of U.S. adults were current smokers[20] and that 17 percent of adults will still be current smokers in 2020.[21] Furthermore, it was estimated that in 2008, there were 7 million people in the United States ages 55 to 75 years with at least a 30 pack-year smoking history,[22] the approximate target group for lung cancer screening in most trials published to date. In the United States, a high percentage of lung cancer occurs in former smokers because of the large group of former smokers in the population and because lung cancer risk does not decrease until many years after smoking stops.[23-25] In recent years, the incidence of lung cancer in the United States has been slowly declining, but given these estimates of both current and former cigarette smoking, it is unlikely to decline significantly for many years, and lung cancer will remain a major public health problem in this country and an increasing problem worldwide.

The incidence of lung cancer also significantly increases with age. Other risk factors for lung cancer include family history,[14,15,17] chronic obstructive pulmonary disease,[15,18,26] pulmonary fibrosis,[14] exposure to passive tobacco smoke,[27-29] indoor cooking fumes,[11] environmental radon, and occupational exposures such as asbestos, arsenic, chromium, and coal tar.[15,26] Some studies suggest women are at higher risk for lung cancer than comparably exposed men.[14,28,30,31] In addition to these risk factors, blacks are nearly twice as likely as their white counterparts to have a tobacco-related cancer,[32] suggesting that race/ethnicity may also be a risk factor for lung cancer. There is also some evidence suggesting that the incidence of lung cancer is higher among people of disadvantaged socioeconomic status, although this may be due to unmeasured confounding from smoking.[33,34]

If lung cancer among nonsmokers is considered alone, it would be the seventh leading cause of cancer-related death in the world,[16] and as smoking rates decrease, will represent a larger fraction of lung cancer than is currently the case. Notably, there are major sex, clinicopathologic, and molecular differences in lung cancers arising in nonsmokers and smokers.[16]

Natural History

The rate of progression of lung cancer varies by cell type as well as molecular biology, but generally has a poor prognosis and is the cause of death in more than 90 percent of affected individuals.[35] The 5-year survival rate for all stages combined is approximately 16 percent.[9] Stage at diagnosis is a strong predictor of lung cancer mortality.[7] Unfortunately, 75 percent of patients with lung cancer present with symptoms due to advanced local or metastatic disease that is not amenable to cure.[35]

For patients diagnosed with localized disease (defined as cancer limited to the lung without spread to other organs or lymph nodes), 5-year relative survival is 52 percent compared with 25 and 4 percent for regional (spread to regional lymph nodes) and distant (metastatic) disease, respectively. For the earliest-stage tumors, median 5-year survival is estimated at 77 percent.[7] Currently, however, only 15 percent of lung cancers are diagnosed at an early stage.[4] Accordingly, there is considerable interest in the early detection and treatment of lung cancer in

order to give patients the highest chance for cure.

Rationale for Screening

Lung cancer has many attributes that make it appropriate to consider screening for, including high morbidity and mortality and a relatively high prevalence in high-risk populations. Lung cancer mortality and survival are related to the initial stage of diagnosis, suggesting that treating early may be beneficial; therefore, an effective screening program for the early detection and treatment of lung cancer could have a significant impact on its high mortality rate.

A good screening test for lung cancer should be sensitive, specific, acceptable to patients and providers, and relatively cost-effective. In this regard, LDCT has emerged from observational studies as a promising new technology for diagnosing early lung cancer. In the early 1990s, LDCT was introduced as a screening test with hope that improved sensitivity might improve lung cancer screening outcomes, and several observational studies and RCTs began to evaluate this modality. Thus, with data now being reported from several ongoing trials, it is appropriate to reexamine the literature to date on the outcomes of screening for lung cancer. Current screening efforts are directed toward the early detection of NSCLC, since small cell lung cancer is less common and often grows and spreads too quickly to be reliably detected by intermittent screening.

Interventions/Treatment

Small cell lung cancer and NSCLC are managed differently. While small cell lung cancer is treated as a systemic disease, except in rare instances, the current standard of care for the treatment of localized NSCLC is surgical resection,[27,29,36] whereas advanced NSCLC is often treated with radiation and/or chemotherapy, in addition to surgical resection when possible. For patients with poor performance status, supportive care may be the only appropriate therapy. Detecting and treating early-stage NSCLC is the focus of most screening programs for lung cancer since early treatment can lead to cure of NSCLC.

Current Clinical Practice

Until recently, few patients in the United States were being screened for lung cancer and no professional organizations, including the USPSTF, the ACS, the American College of Chest Physicians (ACCP), and the American Academy of Family Physicians, recommended routine screening. However, since the early 2000s, LDCT for the detection of early lung cancer has been broadly available, and there is evidence that patients and clinicians are already engaging in lung cancer screening.[37-39]

Recommendations of Other Groups

In May 2012, based primarily on results from the National Lung Screening Trial (NLST), several

organizations, including the ACCP, the American Society of Clinical Oncology, and the American Thoracic Society,[40] as well as the National Comprehensive Cancer Network (NCCN)[22] and the American Lung Association[41] recommended lung cancer screening, modeled closely on the NLST, using a LDCT program for individuals ages 55 to 74 years with a 30 pack-year history of cigarette smoking and the ability to partake in organized programs of screening (**Table 1**). The American Association for Thoracic Surgeons recommends screening select groups from ages 50 to 79 years in its recently developed guidelines, which differ slightly from the NLST study population of 54- to 74-year-olds.[42] In January 2013, the ACS also began recommending screening for lung cancer with LDCT.[43] In addition, several patient organizations, such as the Lung Cancer Alliance[44] and the National Lung Cancer Partnership, are currently advocating screening.[45-47]

CHAPTER 2. METHODS

Key Questions and Analytic Framework

Using the methods developed by the USPSTF,[48] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) determined the scope and key questions for this review. Investigators created an analytic framework with the key questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**). The target population for lung cancer screening was asymptomatic men and women at average risk or current and former smokers at high risk.

Key Questions

1. How effective is screening for lung cancer in reducing mortality and morbidity?
   a. How effective is screening in persons at average risk?
   b. How effective is screening in persons at higher risk for lung cancer (e.g., current or former smokers)?
   c. Does effectiveness differ by subgroups (e.g., sex, age, race, presence of comorbid conditions, other lung cancer risk factors)?
2. What are the test characteristics (sensitivity, specificity, predictive value) of screening tests for lung cancer?
   a. How do these test characteristics vary by lung cancer risk?
   b. How are test characteristics different by subgroups (e.g., sex, age, race)?
3. What are the harms associated with lung cancer screening and are there ways to modify harms (e.g., unnecessary biopsy, radiation exposure, overdiagnosis, and psychosocial harms)?
4. How effective is surgical resection for the treatment of early (stage IA) NSCLC?
5. What are the harms associated with surgical resection of early (stage IA) NSCLC?

Key question 1 focuses on direct evidence that screening for lung cancer improves important health outcomes compared with no screening. The remainder of the analytic framework (key questions 2 through 5) evaluates the chain of indirect evidence needed to link screening for lung cancer with improvement in important health outcomes. Links in the chain of indirect evidence include the performance, yield, and acceptability of the screening test for lung cancer; the effectiveness of interventions for reducing morbidity and mortality; and any harms associated with screening and subsequent interventions.

Search Strategies

In conjunction with a research librarian, investigators searched the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the fourth Quarter 2012), MEDLINE (2000 through December 2012), reference lists of papers, and Scopus for relevant English-language studies and systematic reviews. Search strategies are described in

Appendix A1.

Study Selection

At least two reviewers independently evaluated each study to determine eligibility for inclusion. Investigators selected studies on the basis of inclusion and exclusion criteria developed for each key question (**Appendix A2**). Papers were selected for full-text review if they were about lung cancer screening, were relevant to a key question, and met the predefined inclusion criteria. We restricted inclusion to English-language articles and excluded studies only published as abstracts. Studies of nonhuman subjects were also excluded, and studies had to include original data.

For key questions 1, 2, and 3, we included large (n ≥1,000) screening trials and/or studies of adult (age ≥18 years) men and women without signs of lung cancer. The screening interventions were LDCT, CXR, sputum cytology, or a combination of these screening interventions. For key questions 4 and 5, we focused on surgical resection of early (stage I) NSCLC. Outcomes were mortality, morbidity, impact on smoking cessation, quality of life, incidental findings, and harms from screening (such as false-positives, radiation, and overdiagnosis) and treatment. For key questions 4 and 5, we limited our review of treatments to studies involving 500 or more people and those published in the last 12 years, as our interest was in treatment outcomes that are relevant to current practice. Given differences in stage classification, diagnostic procedures used to define stage, and surgical techniques, we determined studies published before those dates would be unlikely to be generalizable to current clinical practice.

Data Abstraction and Quality Rating

For each included study, an investigator abstracted details about the patient population, study design, screening procedure, imaging assessment, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Investigators used criteria developed by the USPSTF[48] to rate the quality of each RCT as good, fair, or poor (**Appendix A3**) if they reported results for both comparison groups. Two investigators independently rated the quality of studies and resolved discrepancies by consensus. Several studies reported their findings in more than one paper. When this occurred, the data reported in this review are from the most recent publication unless unique data were presented in an older publication.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question ("good," "fair," "poor") using methods developed by the USPSTF, based on the number, quality and size of studies, consistency of results between studies, and directness of evidence.[48]

Meta-analyses were conducted to summarize data and obtain more precise estimates on outcomes for trials that were homogeneous enough to provide a meaningful combined estimate.

In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

Only dichotomous outcomes (cancer incidence and mortality and all-cause mortality) were included in meta-analysis and relative risk (RR) was used as the effect measure. All combined effects were estimated using random-effects models.[49] The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[50] Because of the small number of studies, it was not feasible to conduct subgroup analysis and meta-regression to explore heterogeneity. We conducted sensitivity analyses to check the impact of quality on the results. All analyses were performed using Stata/IC 12.0 (StataCorp, College Station, TX).

External Review

The draft report was reviewed by content experts, USPSTF members, AHRQ Project Officers, and collaborative partners (**Appendix A4**). Revisions have been made in response to reviewers' and USPSTF members' comments.

CHAPTER 3. RESULTS

We reviewed 8,149 references from electronic searches, reference list review, and manual searches of recently published studies. After applying inclusion and exclusion criteria, 1,734 full-text papers were reviewed. Of the full-text papers, 63 provided data to answer one or more of the key questions and were included in this evidence review. **Appendix A5** shows the results of our literature search and selection process and **Appendix A6** shows the list of excluded full-text papers.

Description of Randomized, Controlled Trials

We identified seven RCTs that reported results of screening with LDCT[51-57] and two of screening with CXR (**Table 2** and **Appendix B1**).[58,59]

Randomized Trials of Low-Dose Computed Tomography Compared With Chest X-Ray

National Lung Screening Trial

The NLST was a good-quality trial of lung cancer screening comparing LDCT with single-view posterior-anterior (PA) CXR.[54] The NLST enrolled participants from August 2002 through April 2004 at 33 sites in the United States. Asymptomatic men and women ages 55 to 74 years who had at least 30 pack-years of smoking history and were current or former (>15 years since quitting) smokers were eligible. Of the 53,454 subjects enrolled, 26,722 were randomized to LDCT and 26,732 to CXR. Subjects were followed for a median of 6.5 years from randomization (maximum 7.4 years) for the outcomes of lung cancer incidence and all-cause mortality and 5.5 years for lung cancer mortality. Screening was conducted from 2002 to 2006 and participants followed in the trial from 2002 to 2009, when the trial was stopped early; participants are still being followed, however.

Subjects received a baseline evaluation (LDCT or CXR) with annual evaluations at 1 and 2 years. Screening radiology procedures were performed in accordance with a standard protocol. Results and recommendations of interpreting radiologists were reported to the participant and their health care provider within 4 weeks of a positive study; followup of abnormal scans was determined by the subject's individual health care provider. A positive ("suspicious for lung cancer") LDCT scan was one that showed any noncalcified nodule or mass 4 mm or greater in any diameter. A positive CXR image was one showing any noncalcified nodule or mass. Abnormalities such as adenopathy or pleural effusions were also classified as positive findings. Radiology findings suggesting other clinically significant processes were noted but not categorized in the publications to date. Abnormalities that were suspicious for lung cancer were classified as minor if they remained stable after the third round of screening.

The LDCT and CXR groups were both comprised of 59 percent men and 73 percent were ages 55 to 64 years, with a mean age of 61.4 years.[60] At baseline, 48 percent in both groups were current smokers and 52 percent were former smokers, with a mean smoking history of 56 pack-

years.[60]

Overall, adherence to the screening protocol was high: 95 percent in the LDCT group and 93 percent in the CXR group. Contamination was also relatively small; among a subgroup of 500 subjects, 4.3 percent of the participants in the CXR group self-reported that they received a screening CT outside of the study.

Lung Screening Study

The Lung Screening Study (LSS) was a trial of lung cancer screening comparing LDCT with PA CXR designed as a feasibility study in preparation for the NLST.[55] The trial was conducted at six sites in the United States from September 2000 through November 2001 and followup continued into 2002. Men and women ages 55 to 74 years who were current (≥30 pack-years) or former (quit <10 years ago) smokers were enrolled. Of the 3,318 subjects enrolled, 1,660 were randomized to LDCT and 1,658 to CXR. Subjects received a baseline (LDCT or CXR) and one annual evaluation, which were evaluated by 32 different radiologists; abnormalities were evaluated by community providers.

The definition of a positive screen changed between the baseline and annual screens. At baseline, noncalcified nodules 4 mm or greater, as well as several other specific findings (even with nodules <4 mm), were described as positive. At the 1 year examination, any noncalcified nodule 4 mm or greater was considered a positive screen, and other abnormalities could be considered suspicious for lung cancer at the discretion of the radiologist. Thus, the incidence screen involved more radiologist discretion than the baseline screen. Although more participants were randomized, only 1,586 (96% of 1,660) received a baseline LDCT and 1,550 (93% of 1,658) received a baseline CXR.

The overall population was 59 percent male and 68 percent were ages 55 to 64 years, though no mean or median age was reported. At baseline, 58 and 57 percent in the LDCT and CXR groups, respectively, were current smokers and 42 and 43 percent, respectively, were former smokers, with a median smoking history of 54 pack-years.

Randomized Trials of Low-Dose Computed Tomography Compared With No Low-Dose Computed Tomography

Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial

The Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) Trial[51,61] was a fair-quality trial of lung cancer screening comparing the addition of LDCT with a usual care protocol that involved baseline CXR (type not specified) and sputum cytology for all participants. The trial was conducted in Italy from March 2001 through February 2006. Male current or former smokers (≥20 pack-years) ages 60 to 74 years were eligible. Men were excluded if they did not meet eligibility criteria or if they had severe comorbidity or a life expectancy less than 5 years. Participants could have had cancer if treated more than 10 years previously or prior "early " squamous cell cancer of the oral cavity or larynx if treated more than 5 years prior to enrollment.

Of the 2,472 subjects enrolled, 1,276 were randomized to LDCT and 1,196 to usual care. LDCT results were considered positive if they showed noncalcified pulmonary nodules or nonnodular lesions suggestive of malignancy. Generally, abnormalities were followed with interval LDCT or high resolution CT over several months; patients with lesions greater than 6 mm often underwent a trial of antibiotics with followup CT. Other LDCT abnormalities, such as noncalcified nodules 10 mm or greater in diameter or smaller nodules with spiculated margins, or nonnodular lesions that were suggestive of malignancy were also reported.[61] Abnormalities found on screening LDCT were evaluated within the study by a diagnostic algorithm based on the abnormality's size, growth, descriptive characteristics, and response to a trial of antibiotics.

All subjects received a baseline clinical interview and examination, CXR, and 3-day sputum cytology; those in the LDCT group also received LDCT. All subjects were followed annually for approximately 4 years with clinical interviews and physical examinations focused on detecting lung cancer; participants randomized to LDCT also underwent annual LDCT.

This trial included only men; the LDCT group had a mean age of 64 years and the usual care group of 65 years. At baseline, 56 and 57 percent in the LDCT and usual care groups, respectively, were current smokers, with a mean smoking history of 47 pack-years in both groups. The LDCT group had significantly more subjects with respiratory comorbidities at baseline compared with the CXR group (35% vs. 31%; p=0.04).

The final results of this trial have not yet been reported, but preliminary findings with median followup of 34 months were reported in 2009.[51] As of January 2008, 3,612 LDCT scans had been performed,[51] 95 percent of participants had completed baseline questionnaires, and 68 percent had provided baseline sputum samples.[61] At 3 years, equivalent numbers of patients in each group had received an extra CT scan (6.0% and 6.1%) and an extra CXR (19%).

Danish Lung Cancer Screening Trial

The Danish Lung Cancer Screening Trial (DLCST)[62] was a fair-quality trial comparing LDCT with usual care (no lung cancer screening). The DLCST enrolled participants between June 2000 and June 2001 and was conducted from October 2004 through March 2006 in a single center in Denmark. The study was planned to last 5 years, with a baseline LDCT followed by four annual LDCT scans. It was also designed to study predictors of smoking cessation and the effect of LDCT participation on smoking behaviors. The study population involved healthy men and women ages 50 to 70 years who were current or former smokers (≥20 pack-years smoking history). Former smokers must have quit after age 50 years and less than 10 years prior to enrollment in the study. Eligibility required the ability to walk up 36 steps without stopping; exclusions included prior treatment for breast or lung cancer, any cancer within the last 4 years, and any illness that would be expected to shorten life expectancy to less than 10 years. All study participants underwent baseline pulmonary function testing (PFT) and, to confirm smoking status, carbon monoxide level in exhaled air. In addition, all participants had an annual visit with PFTs and health questionnaires.

Nodules 5 mm or greater in diameter were considered positive or indeterminate unless they had benign characteristics. Nodules 5 to 15 mm in size were considered indeterminate and rescanned after 3 months; individuals with nonbenign appearing nodules greater than 15 mm were referred

to chest physicians in two lung cancer diagnostic centers for evaluation. Nodules were considered benign if they appeared benign or were less than 5 mm. Nodules greater than 14 mm and any growing nodules were referred for diagnostic evaluation, as well as "suspicious" nodules. Growth was defined as an increase in volume of at least 25 percent. Volume doubling time (VDT) was used to measure growth rate and supplemented decisionmaking. Rapid VDT increased the suspicion that a nodule might be cancer. Participants needing further evaluation were referred to chest physicians in two specialized centers. Lung cancers in the usual care group were diagnosed and treated by the subject's personal clinician, independent of the study, but this mostly involved the same lung cancer diagnostic centers used in the LDCT group.

Of the 4,104 subjects enrolled, 2,052 were randomized to LDCT and 2,052 to usual care. There were no significant baseline differences between the study groups in mean age (58 years), sex (56% male in LDCT and 55% male in usual care), mean smoking history (36 pack-years), or PFT results (mean forced expiratory volume in 1 second [FEV1], 2.9 in both groups; mean FEV1 % predicted, 93% in LDCT group and 94% in usual care group). Current smokers comprised 75 percent of the LDCT group and former smokers 25 percent. The usual care group included 77 percent current smokers and 23 percent former smokers. The authors noted that followup among the usual care group was not as complete as it was for the LDCT group.

Smoking cessation education for the DLCST involved less than 5 minutes of smoking cessation counseling by a certified smoking cessation nurse at annual visits. PFT results (abnormal and normal) were used to motivate participants to stop smoking. From the publication, it is unclear whether this counseling occurred at the initial visit or only at the annual followup visits.

Multi-Centric Italian Lung Detection

The Multi-centric Italian Lung Detection (MILD) study was a poor-quality trial of lung cancer screening comparing LDCT, either annually or biennially, with usual care (no lung cancer screening).[53] The trial was conducted from September 2005 through January 2011 in a single center in Italy. Eligible subjects were men and women ages 49 years or older who were either current or former (quit ≥10 years ago) smokers with at least 20 pack-years of smoking and no history of cancer within the previous 5 years. Of the 4,099 subjects enrolled, 1,190 were randomized to annual LDCT, 1,186 to biennial LDCT, and 1,723 to usual care, with a median followup of 4.4 years. All subjects in this trial underwent PFT, blood testing, and a program of smoking cessation.

Evaluation of positive or suspicious LDCT scans was coordinated through the study center.[53] Solid lesions with volume of 6 mm^3 or less (diameter of ≤4.8 mm) were considered nonsuspicious. Solid nodules of approximately 5 to 8 mm received further evaluation, typically repeat LDCT at 3 months. Nodules greater than 250 mm^3 were referred for additional evaluation, including positron emission tomography (PET) scanning or biopsy. Computer-aided detection that showed volumetric growth of 25 percent or more was considered suggestive of malignancy.

Participants in all three groups were similar at baseline in age (median of 57, 58, and 57 years for annual, biennial, and usual care, respectively), percent male (68%, 69%, and 63%, respectively), and smoking history (median of 39, 39, and 38 pack-years, respectively). There were more current smokers in the usual care group compared with the annual and biennial group (90% vs.

68 vs. 68%, respectively) and less former smokers (10% vs. 31% vs. 32%, respectively). Fewer participants in the usual care group had a FEV1 percent predicted that was less than 90 percent compared with both the annual and biennial groups (19% vs. 28% vs. 28%, respectively).

This study was rated poor-quality due to significant differences in the LDCT and usual care groups at baseline, raising concerns about the adequacy of randomization. In addition, there was substantially less followup among the usual care group (44.9 vs. 56 months). Finally, the study was underpowered and did not reach its planned size of 10,000 participants.

Nederlands-Leuvens Longkanker Screenings Onderzoek

The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) study is a trial of lung cancer screening comparing LDCT with no screening.[56] The NELSON trial is currently ongoing; it began in 2003 and is being conducted in The Netherlands and Belgium. Male and female former and current smokers ages 50 to 75 years with adequate health status, no chest LDCT in the prior year, and no prior diagnosis of melanoma, renal, or breast cancer were eligible. Unlike other studies, lung cancer survivors (≥5 years) were eligible. To date, 15,588 subjects have been enrolled with one-to-one ratio randomization; screening results for 7,557 participants randomized to the LDCT group have been reported.

The LDCT group received LDCT at years 0, 1, and 3; the control group received no screening. In this trial, LDCT scans utilized volumetric measurements of detected nodules with calculation of VDT for evaluation. A positive test result was defined as a solid nodule with a volume greater than 500 mm^3, a solid, pleural-based nodule with a diameter greater than 10 mm, or a partially solid nodule with solid component measuring greater than 500 mm^3. Positive scans were also defined by VDT; a VDT less than 400 days was considered positive.

The NELSON investigators also assessed characterization and automated detection and measurement of lung nodules detected at screening,[63-67] effect of screening on quality of life,[68,69] smoking cessation during lung cancer screening,[70] and the role of PET scans in evaluation of screen-detected nodules.[71]

Smoking cessation education for the NELSON trial included a standard smoking cessation brochure or a questionnaire requesting tailored smoking cessation information from the Dutch expert center on tobacco control. The standard brochure contained brief information about the advantages of quitting, the barriers to quitting, tips about how to quit smoking and how to prevent smoking relapse, and the possibilities for smoking cessation support. The questionnaire asked about smoking history, previous attempts to quit, attitudes toward smoking cessation, and self-efficacy in smoking abstinence.

Most baseline characteristics, including those for the no screening group, have not been reported to date. The LDCT group was described as 84 percent male with a mean age of 59 years.

ITALUNG

The ITALUNG study was a trial of lung cancer screening comparing LDCT with usual care (no lung cancer screening).[57] The trial began in 2004 in Italy and baseline results were reported in 2009 for the LDCT group only. Enrolled subjects were men and women ages 55 to 69 years who

were either current or former (>10 years since quitting) smokers with at least 20 pack-years of smoking history. Of the 3,206 subjects enrolled, 1,613 were randomized to LDCT and 1,593 to usual care.

Subjects in the LDCT group underwent a baseline scan plus three annual scans. The control group received usual care. All subjects were invited for free access to a smoking cessation program. LDCT was considered positive when it showed at least one noncalcified nodule 5 mm or greater or a nonsolid nodule 10 mm or greater in size. Nodules 8 mm or greater underwent PET scanning. Management of positive screening tests was carried out using followup LDCT, fluorodeoxyglucose PET, fine needle aspiration cytology, or fiber optic bronchoscopy. Subjects with positive screening tests were phoned and invited to meet with a pulmonologist for further assessment.

The overall population was 65 percent male, with a mean age of 64 years, and 65 percent were current smokers, with a median smoking history of 39 pack-years.

Randomized Trials of Chest X-Ray Compared With Usual Care

Mayo Lung Project
The Mayo Lung Project was a fair-quality trial comparing CXR and pooled 3-day sputum cytology examination every 4 months for 6 years (intensive screening) with a control group advised to have annual CXR and sputum cytology examinations (usual care).[1] The trial was conducted from November 1971 through July 1976. There were 10,933 male smokers ages 45 years or older enrolled and after eliminating all cases of prevalent lung cancer (91 participants, or 0.8% prevalence), 4,618 subjects were randomized to intensive screening and 4,593 to usual care.[58]

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
The Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial was a good-quality trial comparing annual CXR with usual care (no screening). Participants were enrolled from 1993 through 2001 and the trial was conducted from 1993 to 2011, with screening carried out from 1993 through 2004. Men and women from the general population ages 55 to 74 years were enrolled. Of the 154,901 subjects enrolled, 77,445 were randomized to PA CXR and 77,456 to usual care, with a median followup of 12 years.[59] The population was approximately 85 percent white, 49 percent male, and 45 percent never smokers. The evaluation of abnormal tests was conducted by participants' personal health care providers, not within the study.

Key Question 1. How Effective Is Screening for Lung Cancer in Reducing Mortality and Morbidity?

Summary

One good-quality trial (n=53,454) of high-risk lung cancer participants with good generalizability found that LDCT compared with CXR conducted over three screens reduced

lung cancer mortality by 20 percent and all-cause mortality by 6.7 percent. Two smaller (n=2,472 and n=5,861) fair-quality European trials of high-risk lung cancer participants showed no benefit associated with LDCT screening compared with no LDCT screening. However, these were small trials with limited power that could have missed a true benefit. One small (n=4,099) poor-quality trial also suggested no benefit from screening with LDCT, and perhaps harm. When the three fair- or good-quality trials were combined in a meta-analysis, the combined RR of lung cancer mortality was 0.81 (95% CI, 0.72 to 0.91). When the poor-quality MILD trial was included, the RR of lung cancer mortality was 0.98 (95% CI, 0.68 to 1.40).

Two trials of screening with CXR compared with either less intense or no screening, one in the general population and one in high-risk individuals, showed no benefit associated with CXR screening. Only one study evaluated or reported findings on lung cancer screening in women and did not show a significant reduction in lung cancer mortality associated with CXR screening. No trials have reported data on lung cancer screening in different racial or ethnic populations. See **Table 3** for a summary of lung cancer outcomes in these trials; for complete details on the RCTs included in this review, see **Appendix B1**, and for the details on their quality ratings, see **Appendix B2**.

Evidence

Low-Dose Computed Tomography

To evaluate the effectiveness of screening for lung cancer with LDCT, we limited our review to RCTs of screening published since the previous evidence review that reported results in both the LDCT and control groups (**Table 2** and **Appendix B1**). We identified seven RCTs that reported results of screening with LDCT; however, only four[51-54] have reported results in both the intervention and control groups (**Appendix B2**).

Comparing low-dose computed tomography with chest x-ray. Only the NLST[54] has reported results for both the intervention and control groups comparing periodic LDCT with CXR. The NLST (n=53,454) reported its findings after the trial was stopped early on review by the data safety monitoring board.[54] After a median followup of 6.5 years for lung cancer incidence and all-cause mortality, the cumulative incidence of lung cancer in the LDCT group was 645 per 100,000 person-years (py) and 572 per 100,000 py in the CXR group; the RR was 1.13 (95% CI, 1.03 to 1.23) for incident lung cancer. Over 5.4 years of followup, lung cancer mortality in the LDCT group was 247 per 100,000 py and 309 per 100,000 py in the CXR group, with a reduction of lung cancer mortality of 20.0 percent (95% CI, 6.8 to 26.7; p=0.004) in the LDCT group. The RR of all-cause mortality was reduced by 6.7 percent (95% CI, 1.2 to 13.6). The authors calculated a number needed to screen (NNS) with LDCT to prevent one lung cancer death as 320 (among those undergoing ≥1 screens). Intention-to-screen analysis determined a NNS of 310 (95% CI, 190 to 840) to prevent one lung cancer death. The NNS to prevent one death from any cause was 219 (95% CI, 112 to 5,000).[54] This corresponds with an absolute risk reduction of lung cancer death of 4.6 (95% CI, 0.2 to 9.0) per 1,000 participants.[85]

Comparing low-dose computed tomography with no low-dose computed tomography. Three randomized trials in four publications comparing periodic LDCT screening with no LDCT screening ("usual care") have reported lung cancer outcomes in both groups.[51-53,61]

Though the final results of the DANTE trial (n=2,472) have not been published, preliminary findings were reported in 2009, with a median followup of 34 months. However, as noted above, followup was longer in the LDCT group by 657 person-months (35.7 months in the LDCT group compared with 31.5 months in the control group).[51] The baseline prevalence of lung cancer was 2.2 percent (28 cases) in participants randomized to LDCT and 0.7 percent (8 cases) in the control group. After approximately 3 years of followup, the cumulative incidence of lung cancer was 4.7 percent (60 cases) for LDCT and 2.9 percent (34 cases) for the control group. The corresponding incidence rate was 1,600 per 100,000 py in the LDCT group and 1,015 per 100,000 py in the usual care (nonLDCT) group. The 3-year cumulative lung cancer mortality rates were 1.6 percent (n=20) in the LDCT group and 1.7 percent (n=20) in the control group, a nonstatistically significant difference. The corresponding lung cancer mortality rates were 558 per 100,000 py in the LDCT group and 597 per 100,000 py in the control group (RR, 0.83 [95% CI, 0.45 to 1.54]). All-cause mortality was also equivalent in both groups at 3 years, with a RR of 0.85 (95% CI, 0.56 to 1.27). All rates are calculated given the person-months of followup appropriate for each study group (rather than the mean). The study had only 80 percent power to show a 35 percent reduction in lung cancer mortality.

In the DLCST (n=4,104), the cumulative incidence of lung cancer in the LDCT group was 0.7 percent (incidence, 706 per 100,000 py) and 0.5 percent (incidence, 245 per 100,000 py) in the usual care group after a median followup of 4.8 years (RR, 2.88 [95% CI, 1.85 to 4.49]).[52] Lung cancer mortality was 0.7 percent (mortality rate, 154 per 100,000 py) in the LDCT group and 0.5 percent (mortality rate, 112 per 100,000 py) in the usual care group, with a RR of 1.37 (95% CI, 0.63 to 2.97). Overall, there were 61 deaths (3%) in the LDCT group (624 per 100,000 py) and 42 deaths (2.1%) in the usual care group (429 per 100,000 py), with a RR of 1.46 (95% CI, 0.99 to 2.15).[52] This study had 80 percent power to show a 20 percent lung cancer mortality reduction after 5 years at the 0.05 p-value level.

In the MILD trial (n=4,099), 25 lung cancers were diagnosed (20 LDCT-detected) in the biennial LDCT group, 34 (29 LDCT-detected) in the annual LDCT group, and 20 in the control group.[53] The incidence rates of lung cancer per 100,000 py were reported as 457 in the LDCT biennial group, 620 in the LDCT annual group, and 311 in the control group (RR, 1.47 [95% CI, 0.82 to 2.64] for biennial vs. control and RR, 1.99 [95% CI, 1.16 to 3.43] for annual vs. control). Lung cancer mortality was not significantly different between the control and screened groups combined after adjustment for age and smoking (hazard ratio [HR], 1.64 [95% CI, 0.67 to 4.01]). When comparing the lung cancer mortality rate among the biennially screened group with the control group, the RR was 1.00 (95% CI, 0.34 to 2.98); among the annual screen group compared with the control group, the lung cancer mortality HR was 1.99 (95% CI, 0.80 to 4.96); however, this is not adjusted for age and smoking. All-cause mortality was not statistically different comparing screened groups combined with the control group (RR, 1.40 [95% CI, 0.82 to 2.38]). However, when comparing the annually screened group with the control group, the all-cause mortality RR was 1.80 (95% CI, 1.03 to 3.13). The RR of all-cause mortality among the biennially screened compared with the control group was 1.17 (95% CI, 0.63 to 2.17). Of note, 10 squamous cell cancers were identified in the annual LDCT group and one in the biennial LDCT group, with similar numbers of adenocarcinomas in each of the LDCT groups; tumor histology was not reported for the control group.[53] As with the DANTE trial, all rates are calculated based on the followup reported for each study group. Again, as noted above, there are

significant concerns about the adequacy of randomization in this study, as well as differences in followup between groups, with substantially more followup in the LDCT groups compared with the usual care group.

Results of pooled analysis. When the three fair- or good-quality studies were combined in a random effects meta-analysis, the RR of lung cancer incidence was 1.63 (95% CI, 0.95 to 2.80) (**Figure 2**); when the poor-quality MILD trial was included, the RR was 1.70 (95% CI, 1.07 to 2.68). For lung cancer mortality, the RR was 0.81 (95% CI, 0.72 to 0.91) (**Figure 3**); when the poor-quality MILD trial was included, the RR was 0.98 (95% CI, 0.68 to 1.40). For all-cause mortality, the RR was 1.02 (95% CI, 0.78 to 1.33) (**Figure 4**); when the poor-quality MILD study was included, the RR was 1.13 (95% CI, 0.84 to 1.53).

Chest X-Ray

To evaluate the effectiveness of screening for lung cancer with CXR, we limited our review to RCTs of screening that reported results in both the CXR and control groups published since the previous evidence review. We identified an update of the Mayo Lung Project of lung cancer screening with quarterly CXR screening conducted in the 1970s,[58] and the first major publication of lung cancer results from the PLCO Screening Trial, which evaluated the effectiveness of screening with annual CXR in reducing lung cancer mortality (**Table 2** and **Appendix B1**).[59]

After 20 years of followup in the Mayo Lung Project, lung cancer mortality rates were 440 per 100,000 py (95% CI, 390 to 490) and 390 per 100,000 py (95% CI, 350 to 440) in the intensive screening group and control group, respectively. In 2006, the results of this trial were updated and continued to show no benefit for intensive versus periodic screening with CXR in reducing lung cancer mortality.[58]

After 6 years of followup in the PLCO Screening Trial, the RR for lung cancer mortality among the entire CXR screened group compared with the usual care group was 0.91 (95% CI, 0.80 to 1.03). After 13 years of followup, the cumulative incidence of lung cancer in the CXR group was 200 per 100,000 py and 192 per 100,000 py in the usual care group. Over the same time period, there were 1,213 lung cancer deaths (140 per 100,000 py) in the CXR group and 1,230 (142 per 100,000 py) in the usual care group, with a RR of 0.99 (95% CI, 0.87 to 1.22). All-cause mortality rates were 1,052 per 100,000 py in the CXR group and 1,071 per 100,000 py in the usual care group, with a RR of 0.98 (95% CI, 0.95 to 1.01) after 13 years of followup.[59]

In addition to the analysis of CXR screening outcomes in the general population, the PLCO Screening Trial also assessed the effectiveness of CXR screening among individuals at high risk of lung cancer by evaluating the outcomes of individuals who would be eligible for the NLST (all current and former smokers ages 55 to 74 years with ≥30 pack-year smoking history). Among the 30,321 individuals meeting these criteria, the cumulative incidence of lung cancer through 6 years of followup was 606 per 100,000 py in the intervention group and 608 per 100,000 py in the control group (RR, 1.00 [95% CI, 0.88 to 1.13]). Over the same period of followup, the lung cancer mortality rates were 361 per 100,000 py in the CXR group and 383 per 100,000 py in the usual care group, with a RR of 0.94 (95% CI, 0.81 to 1.10). This study also evaluated lung cancer mortality associated with screening among women and found a RR of 0.92 (95% CI, 0.81 to 1.06) after 13 years of followup.[59]

Sputum Cytology
The searches did not identify any new studies that evaluated screening for lung cancer with sputum cytology. Sputum cytology was included as part of the study protocol in the DANTE trial, but results on effectiveness have not been reported.[51,61]

Benefits by Subgroup
All of the RCTs of screening with LDCT were conducted in participants at high risk of lung cancer based on participants' history of prior or current smoking. None evaluated low- or average-risk participants. The only CXR trial evaluating annual CXR screening compared with usual care among the general population was the PLCO Screening Trial, which showed no benefit of screening, with a RR of lung cancer death of 0.94 (95% CI, 0.81 to 1.10) after 6 years of followup and 0.99 (95% CI, 0.87 to 1.22) after 13 years of followup.[59] None of the trials of LDCT reported findings by sex or race. Only the PLCO Screening Trial reported findings by sex, as noted above, and found the RR for lung cancer mortality among women from the general population (smokers and nonsmokers) screened annually with CXR was 0.92 (95% CI, 0.81 to 1.06). Data on women smokers enrolled in this trial have not yet been reported.

Key Question 2. What Are the Test Characteristics of Screening Tests for Lung Cancer?

Summary

Sensitivity of LDCT was reported in one trial and five cohort studies and ranged from 80 to 100 percent but was most often greater than 90 percent; however, the method for determining sensitivity varied among studies. Specificity was reported in two RCTs and five cohort studies and ranged from 28 to 100 percent; again the method for determining specificity varied among the studies. The calculated positive predictive value for an abnormal (positive or indeterminate) LDCT scan predicting lung cancer ranged from 2.2 to 42 percent. The calculated positive predictive value of a recommendation for biopsy or surgery based on LDCT for predicting lung cancer ranged from 50 to 92 percent. The sensitivity of CXR for lung cancer was reported in the prior review as 25 percent compared with LDCT, while specificity was not evaluated. No studies reported test parameters for sputum cytology.

Evidence

In the previous evidence review,[1] test characteristics of CXR and LDCT were summarized but not systematically reviewed; test characteristics of sputum cytology testing were not reviewed, although the effectiveness of screening with cytology was. For the current evidence review, data were included from the RCTs described above, as well as eight cohort studies meeting criteria for this review (**Appendix B3**). In addition, when data were not directly reported but were provided, we calculated the positive predictive value of LDCT both for "abnormal" or "suspicious" findings requiring further evaluation and for biopsy (or surgery if biopsy not reported) that resulted from the evaluation of an abnormal or suspicious LDCT.

Low-Dose Computed Tomography

All of the RCTs that reported data contributed to the discussion of test characteristics of LDCT. In addition, we identified eight cohort studies of LDCT that provided data on test characteristics. The findings from the cohort studies are summarized in **Appendix B3**. Because of variable ways of reporting results and/or test parameters, we did not calculate test parameters. It is important to note that there is no defined "gold standard" for evaluating either the sensitivity or specificity of LDCT.

Reported sensitivity of LDCT in prevalence and incidence screens ranged from 80 to 100 percent, with most studies reporting sensitivity greater than 90 percent.[56,86-91] This number reflects variation in the definition of a false-negative. Most studies report a false-negative scan as LDCT that was negative within 1 year or less of the participant developing lung cancer. However, one study defined false-negative scans as those in which a participant developed greater than stage I lung cancer within 1 year of a negative screening scan.[57] In addition, some studies reviewed prior LDCT scans when a nodule was identified on an incidence scan. If the abnormality was seen on a prior LDCT scan, the sensitivity was reported as if the prior scan had identified the nodule.

Specificity was reported in two RCTs[52,56] and five cohort studies.[86,87,89-91] In these studies, specificity ranged from 28[87] to 100 percent.[91] Variability in reporting of specificity can be attributed to heterogeneity in definitions between studies. Some trials report three categories of findings: positive, indeterminate, and negative. Also, some studies reported false-positive examinations as those categorized as "positive" on the screening LDCT scan; indeterminate examinations that were clarified by either treatment of an abnormality or another CT scan within the first few months of the indeterminate LDCT scan were not always considered or reported as false-positive examinations.[56] We considered this type of specificity program or protocol specificity. Further complicating this issue, some studies only reported the number of positive scans or the number of nodules, rather than the number of participants with a positive scan, which is the most important measure in considering potential harms. This issue also complicates the understanding of positive predictive values discussed below.

Chest X-Ray

The previous evidence review assessed the test characteristics of CXR by comparing the findings among patients subjected to both LDCT and CXR and evaluating these parameters using LDCT as the gold standard, which may be problematic because of LDCT's low specificity. In that review, the sensitivity of CXR for detecting lung cancer compared with LDCT was 25 percent.[1] No new studies directly reporting CXR test characteristics were identified by the current evidence review.

Sputum Cytology

As noted above, the previous evidence review did not evaluate the test characteristics of sputum cytology as a screening test for lung cancer, and thus did not provide data on this measure for the current evidence review. The current evidence review did not identify any papers that reported sputum cytology test characteristics published in the medical literature since the previous evidence review. One RCT and two cohort studies included in the current evidence review collected sputum samples from participants,[58,61,89] but no studies formally reported on the test

characteristics of sputum cytology testing. It is likely that the absence of recent data on this topic reflects the fact that sputum cytology has not been studied as a screening method since trials conducted in the mid1970s failed to show benefit from screening with sputum cytology.[1] Accordingly, sputum cytology testing is now rarely used for lung cancer screening.

Test Characteristics by Subgroups
No studies provided data on test characteristics by subgroups other than by risk profile. Since the predictive value of tests will vary with prevalence, all screening tests will have higher predictive value in individuals at higher baseline risk of lung cancer.

Key Question 3. What Are the Harms Associated With Lung Cancer Screening and Are There Ways to Modify Harms?

Summary

Radiation Exposure
Two RCTs and two cohort studies reported radiation associated with one LDCT scan ranging from 0.61 to 1.5 mSv; however, only one study reported cumulative radiation exposure associated with the screening program, which was estimated at 6 to 7 mSv.

False-Positive Examinations and Followup Evaluations
Positive examinations ranged from 9.2 to 51 percent (of participants) in baseline screens, with calculated positive predictive values for abnormal studies ranging from 2.2 to 36 percent; most abnormal scans were resolved with further imaging. Positive examinations were lower in subsequent screens, with positive predictive values for abnormal studies predicting lung cancer of 4 to 42 percent and most abnormal scans were resolved with further imaging. Positive predictive values for abnormal LDCT scans with recommendations for biopsy ranged from 50 to 92 percent.

False Reassurance
The sensitivity of LDCT for detecting lung cancer ranged from 80 to 100 percent, implying a false-negative rate of 0 to 20 percent. The harm of false reassurance was not evaluated in any study.

Overdiagnosis
Overdiagnosis was not formally reported in any study. However, of the four RCTs of LDCT reporting results in both the LDCT and no LDCT groups, overdiagnosis was suggested in one trial showing an excess of 119 lung cancers among 26,722 participants after 6.5 years of followup. Four RCTS reported more early-stage lung cancer in LDCT-screened groups than among the control group but not a smaller number of advanced lung cancers. However, there was insufficient followup in these studies to fully evaluate overdiagnosis. Data from one older trial of lung cancer screening with CXR involving approximately 9,000 high-risk participants showed that after 20 years of followup an excess of lung cancers diagnosed in the screened group persisted. The PLCO Screening Trial of CXR screening in the general population (n=155,000) found 18 excess lung cancers in the CXR group (compared with no CXR) after 6 years of

followup (2 years after screening ended) and 76 lung cancers after 13 years of followup (RR, 1.05 [95% CI, 0.98 to 1.12]); data from the same trial evaluating overdiagnosis only among a high-risk population showed a cumulative incidence of lung cancer of 606 per 100,000 py in the CXR group and 608 per 100,000 py in the usual care group after 6 years of followup (RR, 1.00 [95% CI, 0.88 to 1.13]).

Psychosocial Consequences

Five studies evaluated psychosocial consequences among individuals undergoing LDCT screening. Overall, LDCT screening did not appear to significantly impact overall health-related quality of life and no long-term difference in anxiety was reported, although in the short-term, three studies suggested increased anxiety among those with positive or indeterminate results compared with baseline. Distress was decreased among individuals in one trial with negative results compared with baseline.

Smoking Behavior

RCTs identified no differences in smoking cessation rates, smoking relapse rates, or smoking intensity when comparing individuals randomized to LDCT with no LDCT. In RCTs, smoking behavior among subjects with abnormal scans compared with those with negative scans showed mixed results; one study showed a tendency toward smoking abstinence among those with abnormal scans and one showed no difference. Similar mixed results were seen in cohort studies that compared smoking behaviors among those with abnormal and negative scans. One cohort study suggested that physician referral for patients with abnormal screening LDCT scans (compared with nonreferral for those with negative studies) may result in higher smoking cessation rates.

Incidental Findings

Most of the studies included in this review reported incidental findings. However, there was no standardized approach to reporting these findings. Among the studies of LDCT, nonpulmonary findings were common; infections and other cancers were also diagnosed. Coronary artery calcification was identified in approximately 50 percent of participants in one cohort study evaluating LDCT.

Evidence

Radiation Exposure

One of the direct harms associated with LDCT is radiation exposure. Data on LDCT parameters and radiation exposure in trials of LDCT screening are shown in **Table 4**. Two RCTs and two cohort studies reported the radiation associated with one LDCT scan as ranging from 0.65 to 1.5 mSv. Of the seven RCTs of LDCT screening included in the current evidence review, only the ITALUNG trial accounted for cumulative radiation exposure, using estimates of exposure for specific scanners and techniques employed.[81] In 1,406 subjects randomized to LDCT screening, the four screening LDCT scans accounted for 77 percent of all radiation exposure, and evaluation of abnormal findings with additional CT scans, PET/CT, and CT-guided biopsy accounted for 23 percent. The cumulative exposure from screening over 4 years averaged 6 to 7 mSv. In individual patients screened on a single detector scanner, exposure over 4 years was as high as 21.5 mSv, and with four negative studies on multidetector (MD) CT scanners, as low as

1.9 mSv.[82] MDCT is associated with lower radiation doses than single-detector CT technology. The cumulative effective doses per 1,000 subjects were 3.3 mSv using an MDCT scanner and 5.8 or 7.1 mSv using a single-detector scanner.[81] No studies reported radiation exposure among individuals enrolled in CXR trials. The reported LDCT exposures compare with background radiation exposures in the United States that average 2.4 mSv per year, with significantly higher exposures at higher elevations.[92] Also, to provide context, other imaging radiation exposure rates are approximately 1.7 mSv for head CT, 5 mSv for lumbosacral spine x-ray, and 0.7 mSv for mammography. Notably, a roundtrip flight from New York City to London would be associated with radiation exposure of approximately 0.1 mSv.[92,93]

False-Positive Examinations and Followup Evaluations

The RCTs of LDCT reported the number of noncalcified nodules identified on screening and associated followup evaluations in varying detail. However, the definition of a positive LDCT scan, the categorization of nodules, the methods used to follow nodules, and the method of reporting nodules (by individual or by screen) varied among the studies, making comparisons difficult. In addition, some studies reported all lung cancer and some (NSCLC) only the primary object of screening. Notably also, the evaluations occurring in patients randomized to usual care were rarely reported in the trials that only presented early information on the intervention groups or baseline data.

Since the predictive value of tests will vary with the prevalence of the disease in the population, we have summarized baseline and annual or overall prevalence rates (cumulative incidence) in **Table 5** for both intervention and control groups. In trials of LDCT that reported the prevalence of lung cancer detected at baseline in high-risk populations, the prevalence ranged from 0.6 to 2.2 percent,[52,54,56,61,62,74,82] suggesting different baseline risk for lung cancer or different LDCT program characteristics. Among the cohort studies, reported baseline prevalence ranged from 1.1 to 4.5 percent[58,88,91,96] in high-risk populations. The studies included in the current evidence review vary by number of incidence screens, as well as length of followup, and some only report cumulative incidence or overall rates, making it difficult to compare cumulative incidence rates. These numbers are shown in **Tables 5** and **6**. Two cohort studies conducted in Japanese populations[89,90] evaluated LDCT screening in the general population and reported lower lung cancer prevalence rates of 0.9 to 1.0 percent overall,[89,90] but did not separately report data on prevalence and incidence screens.

One of the most common and important harms to consider in screening for lung cancer is the evaluation of patients with positive scans, which often involves more imaging and sometimes more invasive procedures such as bronchoscopy, fine needle biopsy, and/or surgery. Importantly, surgery is used both for diagnosis and treatment of early-stage lung cancer, making it difficult to separate the two. We attempted to evaluate these harms when they were reported in the studies; however, reporting varied substantially. To address this issue, we examined rates of positive scans and the subsequent evaluation of abnormal scans in both the RCTs[52,54-56] and the cohort studies;[86,88,96,98] this information is summarized in **Tables 5** and **6**. The prevalence of findings defined as "positive" varied between studies. On average, the number of positive examinations was higher on baseline screens and ranged from 9.2 to 39 percent in the RCTs[52,54-56] and 9.8 to 51 percent in the cohort studies,[86,88,91,96] with most in the 10 to 20 percent range. The positive predictive value for an abnormal baseline finding showing cancer ranged from 2.2 to 36 percent

in the RCTs.[55-57,73] Among the cohort studies, the positive predictive value of abnormal baseline scans requiring further evaluations ranged from 4 to 21 percent, meaning that 79 to 96 percent of positive baseline scans did not result in a diagnosis of cancer.[86-88,91] Since most positive scans were resolved by comparison with prior scans or further imaging, we also calculated the positive predictive value for a patient being referred for biopsy in the RCTs as a measure of harm. These positive predictive values ranged from 50 to 81 percent, suggesting that most patients who undergo an invasive procedure, such as biopsy, are diagnosed with lung cancer; in the cohort studies, the positive predictive value for patients referred to biopsy or surgery ranged from 66 to 92 percent.

The NLST was the only RCT that reported complications from diagnostic procedures used to evaluate a positive LDCT scan.[54] In this study, complications from diagnostic procedures were low; the rate of at least one complication was 1.4 percent in the LDCT group and 1.6 percent in the CXR group. Major complications were infrequent in both groups of this study. Among individuals diagnosed with lung cancer, there were 75 major complications in the LDCT group (11.5% of positive screen results determined to be cancer) and 24 in the CXR group (8.6% of positive screen results determined to be cancer) that were associated with invasive diagnostic procedures. However, among individuals with positive studies who were not found to have lung cancer and underwent invasive procedures, there were 12 major complications among LDCT participants (0.1% of positive screen results determined to not be cancer) and four among CXR participants (0.1% of positive screen results determined to not be cancer). Notably, 16 participants in the LDCT group died within 60 days after an invasive procedure (10 of whom had lung cancer), as did 10 (all with lung cancer) in the CXR group. It is not known if the procedure itself was the cause of death and deaths were not reported separately by procedure.

False-Negative Examinations and False Reassurance

The sensitivity of LDCT for detecting lung cancer at baseline was reported in one RCT as 96 percent.[56] Though sensitivity of incidence screens was rarely reported, the NELSON trial reported it as 96 percent.[56] Sensitivity was reported in five cohort studies[56,86,87,89,90] and ranged from 80 to 100 percent. These data imply false-negative examination rates in the range of 4 to 20 percent. We found no studies that evaluated the potential harm associated with false-negative examinations, although this is an important harm to consider given the potential for false reassurance of patients and/or providers, which may delay evaluation of suspicious symptoms in the future.

Overdiagnosis and Overtreatment

One of the most concerning aspects of screening for lung cancer is the issue of possible overdiagnosis and treatment of lung cancer that will not impact a patient's life either due to mild disease that does not progress, cancer that resolves spontaneously, or death from other causes (competing mortality). If screening is effective and does not cause overdiagnosis after an adequate period of followup, both groups of a RCT will have the same number of cancers, but more early-stage and less late-stage (in absolute terms) disease should be found in the screened group. Alternately, finding more cancers in the screened group compared with the control group, especially more early-stage disease with the same number of later-stage disease, would be evidence for overdiagnosis.

While the optimum followup duration for measuring overdiagnosis is not known, the NLST found 119 more lung cancers (1,060 vs. 941) in the LDCT group compared with the CXR group after a median of 6.5 years of followup, suggesting overdiagnosis.[54] In addition, we found evidence in the LDCT trials of more early-stage lung cancers in the LSS, DANTE, MILD, and DLCST trials.[51-53,55] However, with the exception of the NLST, these studies did not report fewer stage III to IV lung cancers in the LDCT group compared either with CXR or usual care.

Recent data from the Italian Continuing Observation of Smoking Subjects cohort study involving 5,203 asymptomatic participants aged 50 years and older describing VDT as a measure of potential overdiagnosis indicates variable VDT among lung cancers diagnosed in a screening program.[99] There were 175 patients diagnosed with lung cancer either with baseline LDCT (n=55) or subsequent LDCT (n=120). Of the 120 incident lung cancers, the authors demonstrated that VDT varies continuously from very slow-growing (VDT ≥600 days) to fast-growing (VDT of 52 days), with 75 percent of the incident lung cancer categorized as fast-growing. The authors suggest that this pool of slow-growing tumors are potentially those that are "overdiagnosed," but note that the growth rate of what appear to be slow-growing (indolent) cancers can increase markedly from one scan to the next, complicating decisions about appropriate followup and treatment of slower-growing lesions. In addition, the lung cancer risk profile of patients with lung cancer in this study correlated with VDT, suggesting that slow-growing cancer is more common in lower-risk people.

Data from the 1970s Mayo Lung Project of quarterly CXR screening compared with less frequent CXR screening over 4 years have shown a persistent excess of lung cancers diagnosed in the CXR group (585 vs. 500) after 20 years of followup (16 years after screening ended) without a reduction in mortality or tumors identified at late stages.[58] Interestingly, in the 16 years after the Mayo Lung Project trial ended, more lung cancer was diagnosed in the CXR group (379 cases) compared with the control group (340 cases), in the absence of a screening program. Data from the PLCO Screening Trial conducted in the general population identified 76 extra lung cancers after 13 years of followup, with a cumulative incidence RR of 1.05 (95% CI, 0.98 to 1.12), suggesting less overdiagnosis. However, data from the PLCO Screening Trial at 6 years of followup (2 years after screening stopped) showed an excess of 18 lung cancers in the CXR group compared with the usual care group.[59] More relevant to screening high-risk individuals, in PLCO participants at high risk of lung cancer due to tobacco exposure, the cumulative incidence of lung cancer after 6 years of followup was the same in both groups: 606 per 100,000 py in the CXR group and 608 per 100,000 py in the usual care group after 6 years of followup (RR, 1.00 [95% CI, 0.88 to 1.13]).

Psychosocial Consequences

Three RCTs (in five publications) of either fair- or good-quality evaluated psychosocial consequences among individuals undergoing lung cancer screening with LDCT.[68,69,77,100,101] Overall, LDCT screening did not appear to significantly impact general health-related quality of life, regardless of whether the screen findings were negative or indeterminate. Similarly, most studies did not find a long-term difference in anxiety, regardless of the screen result. In the short-term after a LDCT, approximately half of the patients reported discomfort about waiting for the results and dread of the results.[68] Measured 2 months after baseline LDCT in the NELSON trial, distress levels increased from baseline after an indeterminate result.[77] Compared with baseline,

distress decreased for subjects with negative LDCT results.[69,77] For subjects in the Pittsburgh Lung Screening Study (PLuSS),[100] compared with baseline, state anxiety increased at 1 to 2 weeks and 6 months after an indeterminate result but returned to baseline 12 months after the LDCT scan. Similarly, for 60 subjects in the Mayo Clinic Project with a family risk of lung cancer who had a nonnegative result, worry increased from baseline in the short-term but returned to baseline 6 months after the LDCT scan.[101] In a report based on the NELSON trial,[69] the only study to compare screened subjects with usual care subjects, health-related quality of life and anxiety were similar 2 years after enrolling in the study for both screened and usual care subjects. This study did report a short-term increase from baseline in distress for subjects who received an indeterminate result after LDCT that returned to baseline 2 years after the baseline scan.

Smoking Behavior

Seven studies, including three RCTs (in four publications)[70,72,80,102] and four cohort studies (in five publications),[103-107] reported smoking behavior changes in lung cancer screening studies and were included (**Table 7**).

Screening versus no screening. Two RCTs compared the effect of LDCT lung cancer screening with no screening on rates of smoking cessation.[62,70] The DLCST found smoking abstinence (defined as >4 weeks of abstinence) rates of 10 and 11 percent in the no screening and LDCT groups, respectively, after 1 year of followup.[62] The NELSON trial reported prolonged smoking abstinence (defined as 7-day point prevalence abstinence and <5 cigarettes since 2 weeks after their quit date) rates of 15 and 13 percent in the no screening and LDCT groups, respectively, after 2 years of followup (p=0.35).[70] The study also reported a non–intention-to-treat analysis among only those who responded to the followup smoking behavior survey. In this analysis, the prolonged abstinence rates were 19 percent in the no screening group and 15 percent in the LDCT group (OR, 1.40 [95% CI, 1.01 to 1.92]; p=0.04), which the authors interpreted as an unfavorable influence of screening on smoking behavior. However, response rates differed significantly among the groups, with a 78 percent response from the no screening group and 91 percent response from the LDCT participants. Because of the significantly different response rates among LDCT and control groups, we believe the most valid measure of smoking cessation comes from evaluating the full sample rather than just the responders.

Relapse rates were only reported in the DLCST,[62] which found baseline former smokers had a relapse rate of 9.3 percent in both the no screening and the LDCT groups after 1 year, assuming nonattendees did not restart smoking. If nonattendees resumed smoking, the relapse rates may have been as high as 21 and 17 percent in the no screening and LDCT groups, respectively. Smoking intensity changes were only reported in the NELSON trial and did not differ between the no screening and LDCT groups.[70] In the no screening group and LDCT groups, respectively, 32 compared with 29 percent maintained baseline smoking intensity, 14 compared with 18 percent increased smoking intensity, and 54 compared with 53 percent decreased smoking intensity.[70]

Comparing positive, indeterminate, and negative results. Two RCTs and two cohort studies in three publications[62,80,104,106] compared the effect of receiving a positive, negative, or indeterminate LDCT screening result on smoking cessation and relapse rates. An additional

study evaluated the effect of physician referral category on these outcomes.[107]

The two RCTs reported on different groups and had varying followup durations, making comparisons difficult. The DLCST demonstrated a tendency toward increased smoking abstinence and decreased relapse rates after 1 year in participants with a positive LDCT result.[62] For baseline smokers with a positive result, the quit rate was 18 versus 11 percent in the group with negative LDCT results (p=0.04). In baseline former smokers with a positive LDCT result, the relapse rate (smoking during the year before followup) was significantly less (4.7%) than for those with a negative result (11%; p<0.01). A second trial (NELSON)[80] reported no statistically significant differences in prolonged smoking abstinence between male baseline smokers who received a negative LDCT screen result and those who received an indeterminate result after 2 years of followup (8.9% vs. 12%, respectively; p=0.19). Prolonged abstinence rates in this study did not differ significantly between participants with a single indeterminate LDCT result and those with multiple indeterminate results, though there was a trend toward higher abstinence rates among participants with multiple indeterminate findings (11% for single indeterminate result and 15% for ≥2 indeterminate results; p=0.26).

Two cohort studies in three publications reported mixed findings for the effect of LDCT screen results on smoking behavior.[104,106] The Mayo Clinic Project cohort study reported increased odds of smoking abstinence among current smokers who received followup recommendations based on the prior year's LDCT scan (OR, 1.37 [95% CI, 1.12 to 1.67]; p=0.002). At 3 years of followup, those who received three recommendations for interim followup had the highest percentage of smoking abstinence (42%). For those that received no recommendations (implying a negative screening LDCT), the smoking abstinence rate was 20 percent. The influence of followup recommendations did not reach statistical significance for relapse rates among former smokers or recent quitters. Another cohort study, the Early Lung Cancer Action Program (ELCAP),[104] reported that a positive LDCT scan was not a significant predictor for prolonged abstinence in participants without a lung cancer diagnosis within 1 year (HR, 1.34 [95% CI, 0.90 to 1.99]). A positive LDCT finding was also not significantly associated with relapse of baseline smokers who quit.

The PLuSS[107] cohort study reported the effect of physician referral category on smoking behavior. LDCT screen results were used to categorize participants by risk (based on the LDCT findings): no referral, other referral, low suspicion (<5% predicted probability for lung cancer), or moderate/high suspicion (>5% predicted probability for lung cancer). The proportion of baseline smokers who were abstinent for more than 30 days at 1 year followup increased with increasing category of risk, from 14 percent in the no referral group to 26 percent in the moderate/high suspicion group (excluding participants who received a lung cancer diagnosis over this period).

Incidental Findings

Most of the studies included in the current evidence review reported incidental findings discovered in the course of screening for lung cancer. As there is no standardized research approach to defining what is considered an important incidental finding in lung cancer screening, investigators varied in what findings they reported. For example, researchers from the PLCO Screening Trial reported the frequency of emphysema and chronic obstructive pulmonary disease

incidentally detected by screening CXR,[59] whereas the majority of other RCTs in the current evidence review did not. Additionally, some studies reported incidental findings by radiographic description, such as lymphadenopathy, but others provided a clinical diagnosis, such as lymphoma. Given the variability in reporting practices between studies and that the reported incidental findings could not always be traced to screening modality (CXR or LDCT), it was not possible to calculate the frequency of incidental findings in a meaningful way.

Among the lung cancer screening RCTs, nonpulmonary nodule lung findings were common and included diagnoses such as bronchiectasis, pulmonary fibrosis, carcinoid tumors, and hamartomas. The NLST reported clinically significant abnormalities other than lung cancer in 7.5 percent of LDCT and 2.1 percent of CXR participants.[54] Notable infections included tuberculosis and fungal diseases. Other cancers discovered in the course of lung cancer screening included esophageal, thyroid, breast, renal, parathyroid, lymphomas, and metastatic cancers, such as colon and renal cell carcinoma. Some studies described cardiovascular findings such as coronary calcifications or aortic aneurysms. The finding of coronary artery calcification was reported in the Toronto ELCAP study and was approximately 50 percent.[86,94] None of the studies reported what evaluations occurred in response to incidental findings.

While we have included this information under the key question dealing with harms for the current evidence review, it is plausible that there may also be some benefit to patients of identifying incidental findings. However, we found no data on either the harms or benefits associated with the incidental findings identified in the studies of screening reported in the current evidence review. Clearly, potential harms and benefits will vary by the finding, the clinical situation, and the patient's perspective.

Key Question 4. How Effective Is the Treatment of Surgical Resection of Early (Stage IA) Non-Small Cell Lung Cancer?

Summary

No RCTs compared treating stage IA or IB lung cancer with surgical resection with no treatment. Five studies from four cohorts in Japan showed 5-year survival rates for resected pathologic stage IA NSCLC ranging from 71 to 90 percent. Five-year survival among cohorts evaluating pathologic stage IB resected lung cancer ranged from 70 to 74 percent. Data from two large U.S. cohorts on 5-year survival among patients with resected stage IA NSCLC showed 5-year survival rates of 58 to 66 percent for stage IA and 55 percent for stage IB lung cancer resected between 1990 and 2000 (**Table 8**).

Evidence

No RCTs that assessed the effectiveness of surgical resection for stage IA NSCLC compared with no treatment were identified. Data from the United States on 5-year survival rates among patients with resected stage I NSCLC come from four studies.[108,110,112,119] Data from the Surveillance Epidemiology and End Results (SEER) Program on 2,090 NSCLC cases less than 1

cm, resected between 1988 and 2005, and comparing lobectomy with sublobectomy showed 67 percent of patients overall were alive at 37 months.[112] A large study (n=10,761) utilizing SEER data of stage IA patients with a median age of 67 years, resected between 1988 and 1997, and a mean followup of 8.3 years, reported overall 5-year survival of 58 percent (63% for women and 53% for men).[108] Another study (n=715) of consecutive patients with pathologic stage I NSCLC, a median age of 67 years, and resected between 1990 and 2000 reported 5-year survival rates of 66 percent for stage IA and 55 percent for stage IB NSCLC.[110] Finally, the most relevant evidence may come from a study of various treatment strategies evaluated in a cohort of 10,923 Medicare patients age 66 years or older diagnosed with stage IA to IB NSCLC between the years of 2001 and 2007. In this study, 2-year overall mortality was 18 percent among patients treated with lobectomy (n=6,531), 25 percent with sublobar resections, 41 percent with stereotactic ablative radiation, 57 percent with conventional radiation, and 73 percent with observation without treatment. In a multivariable adjusted analysis, observation was associated with a higher risk for lung cancer–specific mortality compared with anatomic surgical resection (HR, 3.01 [95% CI, 2.51 to 3.60]) more than 6 months after treatment.[119]

Five studies of four cohorts from Japan with survival data on patients with resected stage IA NSCLC were included.[111,113,116-118] Generally, these studies included from 510 to 12,760 subjects and reported 5-year survival rates for resected stage IA lung cancer ranging from 71 to 90 percent, with the more recent studies consistently showing approximate survival in the 85 to 90 percent range.[111,113,116-118] Because screening often detects stage IB NSCLC, we also report survival rates for resected pathologic stage IB NSCLC. Five-year survival among the cohorts evaluating pathologic stage IB patients ranged from 70 to 74 percent in the more recent studies evaluating survival among these patients.[113,118]

Several comparative studies evaluated secular trends in survival that support significant improvement in 5-year survival rates over time.[116] One large study (n=12,760) of pathologic stage IA patients resected during 2004, 1999, and 1994 reported 5-year survival rates of 89, 83, and 79 percent, respectively. While these numbers likely reflect improved staging technology and surgical technique, they may also show secular changes in patient populations, since widespread lung cancer screening with LDCT was implemented in Japan in the early 2000s.[111]

Two studies from Europe were also identified. In these studies, 5-year survival for stage IA NSCLC ranged from 64 to 67 percent and survival for stage IB from 42 to 49 percent.[109,120] However, these studies reported data collected on patients resected in the 1990s, which is unlikely generalizable to current practice.

While the rates described above from the United States are likely the most generalizable to the United States, it is important to note that these survival rates reflect survival among unselected and presumably symptomatic patients, since, for the most part, there has been little lung cancer screening in the United States during the time periods reviewed. Because of this, the survival rates identified in Japan may represent the “best” estimates for long-term survival from NSCLC under ideal circumstances or are more comparable to a screening population, since screening has been widespread there for many years.

Key Question 5. What Are the Harms Associated With Surgical Resection of Early (Stage IA) Non-Small Cell Lung Cancer?

Summary

None of the RCTs of LDCT screening evaluated the harms associated with resection of screen-detected stage 1A NSCLC. Two cohort studies evaluated the harms associated with resection of stage IA NSCLC. One Japanese study reported one postoperative death among 510 individuals undergoing resection between 1992 and 2001. One Italian study conducted between 1991 and 1994 (n=548) with complete resections of stage I NSCLC reported nine postoperative deaths among those resected. Six studies reported harms among large cohorts of individuals undergoing resection but did not specify results specifically for stage IA NSCLC.

Evidence

The NLST reported 60-day mortality after surgery associated with lung cancer resection of 1 percent; however, this included all resections, not just stage IA or IB resections.[54] To more fully address the harm associated with the treatment of early-stage lung cancer, we included several cohort studies of resection.[108-120] However, of the 13 large studies (n≥500) we reviewed, only two reported on operative complications among patients undergoing surgery for stage IA NSCLC. One study (n=510) reporting outcomes among patients with NSCLC 2 cm or less in diameter undergoing resection in Japan between 1992 and 2001 identified one postoperative death among this cohort.[117] Another trial from Italy (n=548) conducted between 1991 and 1994 and involving the complete resection of patients with stage IA or IB lung cancer reported nine postoperative deaths among those resected.[109]

Six studies reported harms associated with resection in all patients with resected lung cancer, not limited to those with stage IA lung cancer.[109,115-118,120] Among these cohorts, one study reporting on patients resected between 1993 and 1999 in Norway, where resection rates are very low (16%), reported a 30-day postoperative mortality rate of 4.8 percent in the entire cohort.[120] Another study (n=1,465) of consecutive patients of all stages resected in Japan during the years 1985 to 1995 and 1996 to 2002 reported postoperative complication rates of 28 percent in the 1985 to 1995 cohort and 12 percent in the 1996 to 2002 cohort. In-hospital deaths among those resected between 1985 and 1995 were 2 percent and among those resected from 1996 to 2002 were 0.5 percent.[116] More applicable data comes from a large cohort (n=11,663) resected in 2004 in Japan. Among those resected, 4.5 percent had postoperative complications and 0.4 percent operative deaths and 0.4 percent hospital deaths occurred.[118] Notably, these complications were summarized for the entire cohort, including all stages and all degrees of comorbidity and symptomatology. Finally, a study of patients in the United States (n=1,100) undergoing video-assisted thorascopic surgery procedures between 1992 and 2004 reported no intraoperative deaths, nine postoperative deaths (0.8%), and 168 complications, including 56 air leaks, 32 cases of atrial fibrillation, 13 pneumonias, and 13 readmissions.[115] Similar to the large Japanese cohort described above, these data reflect complications and adverse events associated with resection of all stages of lung cancer and symptomatic disease among patients with unknown comorbidities.

Thus, the applicability of these complication rates to screening populations is uncertain.

CHAPTER 4. DISCUSSION

Summary of Review Findings

The personal and public health importance of lung cancer in the United States and worldwide is enormous, and even a small benefit from screening could save many lives. The current evidence review found that in one large (n=53,454) good-quality trial (the NLST) of lung cancer screening with three annual LDCT scans in high-risk individuals ages 55 to 74 years, both lung cancer and all-cause mortality were reduced in the LDCT group compared with those receiving annual CXR screening by 20 and 7 percent, respectively.[54] The absolute lung cancer mortality reduction was 4 per 1,000 people screened. One fair-quality Italian trial conducted among men older than age 60 years suggested reduced lung cancer mortality but did not show statistical significance.[51] Two European trials (one of fair-quality [n=4,104] and one of poor-quality [n=4,099]) in populations of lower risk and younger age showed no benefit of LDCT in reducing lung cancer mortality.[52,53]

We found no evidence to support the use of CXR for lung cancer screening, although data from the PLCO Screening Trial evaluating CXR screening among smokers suggested there might be benefit among high-risk individuals and possibly among women of high and average risk.[59] If there is any benefit of CXR screening, then the benefits of lung cancer screening with LDCT demonstrated by the NLST may be even greater if applied to an unscreened population. We found no new data on sputum cytology for the current evidence review, although sputum samples were collected in some of the studies. **Table 9** summarizes the evidence reviewed in the current review.

Sensitivity of LDCT is relatively high but the specificity varied, with positive predictive values for abnormal LDCT findings ranging from 2.2 to 42 percent, depending on the basis of calculation (by screening round or by including only positive or indeterminate scans). These findings are comparable with other screening modalities, such as breast cancer screening with mammography.[121] The low specificity of screening with LDCT suggests the benefit of screening comes at some cost in terms of positive tests requiring subsequent clinical evaluations. The range of positive or indeterminate findings at baseline screening was high (9% to 51%), and most patients required some type of further evaluation, including clinical examinations, CXR, repeat CT, PET scans, and sometimes biopsy or surgical procedures. However, while lung biopsy is a fairly invasive procedure, the majority of biopsies performed were for cancer, not benign disease, with positive predictive values for invasive procedures or biopsy ranging from 50 to 92 percent. This contrasts with the high number of false-positive examinations requiring further evaluation with imaging or clinical/imaging followup, which were predominantly done for benign disease. Screening with LDCT did not seem to reduce overall quality of life, but was associated with short-term increased worry and distress compared with baseline for those with indeterminate results and decreased distress for those with negative screening results.[68,69,77,100,122] Smoking cessation rates were not affected by screening in seven included studies, although there was a suggestion of reduced smoking among individuals with abnormal screening LDCT scans compared with those with negative LDCT scans. Finally, LDCT detected many incidental findings that were reported in variable ways in the included studies. The most commonly reported findings were emphysema and coronary artery calcifications.

While we found no trials evaluating the effect of surgical resection of early-stage lung cancer on mortality, this treatment is universally recommended and the benefit of this approach can be inferred given the positive results shown in the NLST of screening and early treatment of screen-detected disease.[22] In fact, the NLST results may be the most compelling data to date that surgical resection of NSCLC improves survival, given the absence of RCTs on this topic. These findings were similar to the results of previous reviews. In a recent review conducted on behalf of the ACCP, the authors found no evidence from RCTs on the effectiveness of surgical resection for early-stage disease.[123] In an earlier review for the ACCP, authors conducted a search from the founding date of multiple electronic databases through 2001 that also found no relevant trials.[124] Finally, a Cochrane review of treatment for early-stage NSCLC also found no data from RCTs on the effectiveness of surgical resection of NSCLC.[125] Despite this lack of evidence, surgical resection of stage I lung cancer has a 1A recommendation by the ACCP[123] and is recommended by the NCCN.[22] The strength of these recommendations is based on expected NSCLC growth rates,[126] detailed information from observational studies that show clear differences in early- versus late-stage mortality,[4,7,126] and clinical experience. For patients with early-stage NSCLC who can tolerate its adverse effects, surgical resection is universally felt to be beneficial. It is important to note that prior research evaluating the outcomes of lung cancer treatment and resection show that the best patient outcomes occur when surgery is performed by experienced surgeons in high-volume centers.[127-131] The NCCN recommends that patients with clinical stage I and II NSCLC be evaluated by a thoracic surgical oncologist whose practice prominently focuses on lung cancer, even if patients are being considered for nonsurgical therapies such as percutaneous ablation or stereotactic body radiation therapy.[123]

We evaluated what might account for different findings in the four trials, with the NLST showing a benefit of screening[54] and the three European studies (MILD, DANTE, and DLCST) not showing benefit.[51-53,61] The European studies were small, with sample sizes ranging from 2,472 to 5,861 (compared with 53,454 in NLST), and were inadequately powered to detect benefit outcomes such as lung cancer mortality. The European trials also had shorter followup durations ranging from 3 to 5 years (compared with 6.5 years in NLST), which would impact the power of the studies to show a benefit.

A subtle but important issue in all three European studies is the difference in duration of followup in the LDCT groups compared with the nonLDCT groups. In the MILD trial, this results in a significant difference in risk of lung cancer, lung cancer mortality, and all-cause mortality when true followup time is accounted for in the rate denominators then when a median duration of followup is used for calculating incidence/mortality rates. In the MILD trial, the average followup was 53 months for both groups. However, actual followup duration was 56 months in the LDCT group compared with 45 months in the control group. Thus, it is not surprising there were more lung cancer and other deaths in an older population with nearly an extra year of followup. Similarly, when we adjusted for the true denominator of followup in both the LDCT and control groups in the DANTE trial, rather than a neutral effect on lung cancer mortality, the findings suggested a benefit of screening, although it was not statistically significant. Finally, the DLCST authors note that followup of the control group was less complete than for intervention patients (the difference was not reported), which could bias the study against showing a benefit of LDCT screening as well.

Another consideration when comparing the results of studies either showing or suggesting reduced lung cancer mortality (NLST and DANTE) with those showing no benefit or harm is that the populations screened in the NLST and DANTE trial were older and had more smoking exposure, and thus were at significantly higher risk of lung cancer compared with the DLCST and MILD populations. To better understand this, we compared lung cancer incidence and mortality rates among the control groups in each of the main trials. Notably, lung cancer incidence rates in the NLST and DANTE trial are higher than in the DLCST and MILD studies (**Table 3**). Similarly, the rate of lung cancer mortality is nearly 5-fold higher in the DANTE trial and 3-fold higher in the NLST when compared with either the MILD study or DLCST. All-cause mortality among the control groups in the NLST and DANTE trial was nearly equal and approximately 4-fold higher than the all-cause mortality shown in the DLCST and MILD study. These data indicate that different risk groups were enrolled in these four trials and suggest, but do not prove, that LDCT screening might be more beneficial in higher-risk populations similar to the NLST participants. This has been suggested and modeled in a recent paper where high-risk participants in the NLST were contrasted with the minimally eligible participants.[132] Among high-risk participants, the NNS to save one life from lung cancer over 6 years (3 years of annual screening) was 82 compared with 3,180 for the minimally eligible NLST participant.

Finally, for many of the reasons noted in the Results section, there is reason to have great concern about the randomization of the MILD trial, which impacts the evaluation of its validity. There are important differences in the control and LDCT groups that correlate with each other and suggest systematic differences in the groups randomized to LDCT compared with the control group. This is further suggested by the great differential in followup and the authors' comments suggesting that the control group may have been added at a later time.

Data from other work has described the effect of "sticky diagnosis" bias, which may result in patients with a history of malignancy erroneously being labeled as dying of that malignancy when cause of death is uncertain. This bias may differentially impact screened groups since they typically have more diagnoses of cancer given during a screening trial because of lead time and some degree of overdiagnosis. This is especially true for patients diagnosed with adenocarcinoma, and was demonstrated in the Mayo Lung Project CXR screening trial.[133] Thus, patients diagnosed with lung cancer in the intervention group may be more likely to be coded as dying from lung cancer than individuals in the control group, especially if cause of death is not reviewed blind to intervention or control status or prior diagnoses and in the setting of shorter durations of followup. In addition, all three European studies that showed no benefit or suggested harm from screening involved some degree of intervention in the usual care group (such as clinical evaluation or PFT). Finally, the surgical/medical care of lung cancer likely differs between Europe and the United States.

Differences in study results may also be related to differences in the LDCT method used. For example, in the DANTE trial, 5-mm single-slice spiral CT was used, which might impact the radiographic resolution of the images. In addition, all participants in the DANTE trial had CXR as well as sputum cytology as part of the baseline evaluation, which would effectively reduce the power to detect a difference associated with LDCT, since nine patients in the control group and 16 patients in the LDCT group were diagnosed with lung cancer at baseline with CXR and sputum cytology. This difference in cancers diagnosed in the two groups at baseline also raises

the issue of possible inadequate randomization or sample size, since the baseline risk of cancer diagnosed by either sputum cytology or CXR is nearly two-fold higher in the LDCT group.[61] A feature that differs among the European trials is that these studies tend to have higher positive predictive values associated with abnormal studies. High positive predictive values limit followup and worry among patients, but may also reflect a loss in sensitivity (or propensity for further evaluation) that results in different patient outcomes.

An important and controversial issue in lung cancer screening is the question of overdiagnosis and consequent overtreatment. The relatively high prevalence of unrecognized lung cancer in several studies suggests there is a significant preclinical pool of lung cancer in high-risk populations. Whether all of these tumors would eventually present clinically is uncertain. In addition, there currently is no way to tell which lung cancer has lethal potential and which does not, although LDCT VDT may prove helpful in the future. Thus, all patients diagnosed with lung cancer are typically treated, resulting in harm to patients with nonlethal lung cancer or those with tumors that might naturally regress.

Overdiagnosis is supported by data from the Mayo Lung Project study of CXR screening which, after 20 years of followup, still showed more (585 vs. 500) lung cancer diagnosed in individuals randomized to intense CXR screening compared with the control group.[58] Data from this study also showed increased rates of early tumors in the intensely screened group compared with the control group, without a change in numbers of advanced tumors or subsequent mortality rates, suggesting diagnosis of a pool of indolent tumors.[58] An intriguing finding in the Mayo Lung Project is that in the 16 years after screening ended, there were 39 more lung cancers diagnosed in the intervention group (379 vs. 340), which is difficult to explain. In contrast, the PLCO Screening Trial of CXR screening did not identify significantly more lung cancer in the screened group than in the control group, either in the general population or in the high-risk smoking population over 6 years of followup (808 vs. 790), although there were 76 more lung cancers in the CXR group after 13 years of followup, approximately 9 years after screening ended (1,696 vs. 1,620).[59] While the NLST identified more lung cancer in the LDCT group (1,040 vs. 941), this finding is within the context of results that showed a 20 percent reduction in lung cancer mortality and a 6.7 percent reduction in all-cause mortality, suggesting that even with overdiagnosis, there is benefit to screening that outweighs this potential harm.[54] Other data that supports overdiagnosis comes from the DLCST, which identified more early-stage lung cancers in the LDCT group than in the control group, but no difference in advanced-stage lung cancer between the groups. However, this may relate to shorter duration of followup and less up to date information about lung cancer in the control population.[52] Data from the MILD trial that might support overdiagnosis come from a comparison of the LDCT biennial and annual screened groups.[53] In contrast to many LDCT studies, which have tended to show a preponderance of adenocarcinomas diagnosed in participants undergoing LDCT, the MILD trial showed a 10-fold increase in squamous cell cancers among those who were annually screened, which may suggest there is some degree of overdiagnosis of squamous cell cancer as well. However, given concerns about this study's randomization, these findings must be interpreted cautiously.

Arguments against an important role for overdiagnosis in lung cancer come from autopsy and clinical studies. One study of 15,812 necropsies conducted between the years 1953 and 1982 identified unsuspected "surprise" lung cancer in 68 patients (0.4%) who had died of a multitude

of causes, suggesting a relatively low rate of clinically unrecognized lung cancer.[134] However, autopsy may underestimate rates of lung cancer when compared with LDCT, since the lungs are not always thinly sectioned. Moreover, whether autopsy data are generalizable to living populations is questionable, particularly given selection biases for autopsy. Other data arguing against overdiagnosis come from studies of patients involved in screening programs who were diagnosed with stage I NSCLC and not treated for variable reasons.[135,136] In one study of 45 screen-detected but untreated stage I NSCLC patients, only two patients survived 5 years.[135]

A recent study evaluating the comparative effectiveness of five treatment strategies for stage 1A and 1B NSCLC indicates that among individuals age 66 years and older who were untreated, 30-day mortality was 8.6 percent. Among those untreated, 6-month mortality was 32.8 percent and 2-year mortality was 73.4 percent overall; lung cancer specific mortality at 4 years of followup was 95.4 percent.[119] These data do not support a large pool of indolent lung cancer among patients with clinically-detected lung cancer, which likely differs from screen-detected populations.

Overdiagnosis in lung cancer almost certainly exists but its magnitude is unknown. The optimal followup time to calculate overdiagnosis from LDCT is not known but theoretically is the lead-time of the slowest-growing cancers, though it may be shorter in practice because of competing mortality. Currently, the best way to measure the magnitude of overdiagnosis caused by LDCT will be with continued followup of lung cancer incidence in the NLST (if the participants choose not to continue screening).

One of the most difficult challenges of LDCT screening is the high false-positive rate that results in downstream evaluations, which are associated with cost, anxiety, and risk. Reducing false-positive rates without reducing sensitivity and effectiveness will be one of the major challenges associated with CT screening and will require careful study of current protocols and guidelines. Data from the NELSON trial suggest that positive results requiring followup can be decreased significantly by following indeterminate nodules for VDT.[56] However, what is not yet known from the NELSON trial is whether this protocol will show the same mortality reduction as in the NLST. Clarifying parameters for indeterminate and positive LDCT screens involves a tradeoff between sensitivity and specificity that will require the best judgment of pulmonologists and radiologists and careful study of protocols that yield the highest sensitivity and specificity, since this will greatly impact the cost, risks, and effectiveness of LDCT screening. Technologic approaches to the problem of false-positive tests may also be on the horizon. Notably, in a recent surgical series, resection of benign nodules occurred in 50 to 86 percent of cases,[137,138] highlighting the need for better discrimination of lung cancer nodules from benign nodules preoperatively in all domains. VDT, as well as risk prediction models, may independently, or in combination with biomarkers, improve lung cancer prediction and reduce followup imaging and procedures for people with positive scans, in both screening and clinical settings.

False-positive rates also seem to vary by geographic region, with higher rates in the Midwest that are thought to be related to increased rates of granulomatous diseases. One author also notes that rates of identification of noncalcified nodules is correlated with CT collimation.[139] A Canadian study showed that the number of participants with one or more nodules increased from 36 to 60 percent when scan thickness was decreased from 7 to 1.25 mm.[140]

Although the false-positive rate was high in the studies included in this review, false-positive results from lung cancer screening may have a different effect on patients than false-positive results associated with other types of cancer screening tests. Patients who smoke potentially have some control over their subsequent risk and may be able to more effectively modify their high-risk behavior. Data from our review of smoking cessation associated with positive or indeterminate lung cancer screening results showed mixed results, with some studies suggesting or showing a trend that patients with abnormal results reduced smoking or more frequently remained abstinent.[62,70,106,107]

Radiation exposure is a direct harm of lung cancer screening. It is widely accepted that medical imaging radiation exposure is associated with a real and measurable future risk of cancer.[141] Radiation-associated cancer risk increases with younger age at the time of exposure and cumulative dose, and there may be interaction with other lung cancer risks, such as smoking.[142] The effective dose from one LDCT scan averaged 1.6 mSv in the NLST and varied by a factor of two over the varying number of detectors and manufacturers used.[143] In addition, as doses are adjusted for body weight, the effective dose can further increase by a factor of two.[66] LDCT on a modern 16+ MDCT can have a dose as low as 0.8 mSv. In comparison, a standard diagnostic CXR is 0.02 mSv. Given the high frequency of positive LDCT examinations in the trials to date, it is important to note there is also radiation exposure associated with followup imaging of abnormal LDCT screens. These procedures include diagnostic chest CT with an effective radiation dose of 8 mSv and PET/CT with radiation doses ranging from 7 to 14 mSv.

Estimates of cancer risk associated with medical radiation are based on extrapolations and models derived from observations in atomic bomb survivors and occupational exposures.[144,145] In one modeling study[146] using a LDCT dose of 5.2 mGy (approximately 5.2 mSv) for annual screening from ages 50 to 75 years, the model suggested that the lifetime risk of lung cancer in women would increase by 5 percent and in men by 1.5 percent. Chest radiation would also likely increase the risk of breast cancer among women given prior estimates for the radiation associated with mammography, as well as from childhood radiation exposures.[146] However, data on radiation and breast cancer development suggest most of the harm occurs in women sustaining radiation at ages younger than 30 years, significantly younger than the current age group in which lung cancer screening is being evaluated and considered. Notably, with decreasing LDCT radiation dose and frequency, the risks of subsequent lung cancer are proportionally reduced. This highlights the importance of radiation dose, screening interval and duration, and age at onset of screening in lung cancer screening programs and investigation.

Limitations

This review has several limitations. Some of these are discussed above and relate to limitations of the studies reviewed for this report. It could be argued that the NLST results were obtained in volunteers at mostly large academic centers and that the results are not generalizable to most people who might choose to be screened. However, the large size of this trial and its conduct at several centers in the United States, as well as involvement of community physicians and health care providers, improve the odds that these results are generalizable to a community population. The NLST participants were younger, better educated, and less likely to be current smokers than

the general population in the United States that would be eligible for LDCT screening by the NLST criteria. However, this difference is likely more important to consider if LDCT screening is implemented rather than as a limit to the validity of the NLST results. It is much less likely that the European studies would be generalizable to the United States given their very small size and different clinical practices.

The previous evidence review identified a paucity of screening studies among women and found some evidence to suggest that lung cancer screening might perform differently among women. Unfortunately, in spite of the fact that lung cancer is the leading cause of cancer-related death among women, the current evidence review found very little new information in women. There was a suggestion in the PLCO Screening Trial of possible benefit of CXR screening, but the findings were not statistically significant.[59] Hopefully, some of the trials currently underway will report data separately for women. This is especially important in the NLST, given the high number of participants and the statistical chance of identifying benefit if it exists. There are biological reasons to think that screening among women may be associated with different effectiveness, including the propensity of women to develop adenocarcinomas, which are often more peripheral and may be amenable to limited resection. Similarly, the current evidence review identified no studies of screening that evaluated benefits or harms in different racial and ethnic groups.

The rates of biopsy-associated complications were rarely described in the studies reviewed. In addition, while we attempted to evaluate the benefit and harm associated with the treatment of early-stage lung cancer, we found no RCTs that had evaluated surgical resection versus observation. The harms and benefits of surgical resection of lung cancer reported in this review are derived from large series of treatment in unselected symptomatic patients with stage I NSCLC who were treated surgically. Almost certainly, the harms would be higher in such a group and the benefits likely differ as well, making generalizing these results to a screening population problematic.

We excluded nonEnglish language articles, which could result in language bias, though we identified no nonEnglish language studies that would have met inclusion criteria. We did not search for studies published only as abstracts and could not formally assess for publication bias with graphical or statistical methods because of small numbers of studies for each key question and differences in study design, populations, and outcomes assessed. We found few or no randomized trials for a number of key questions. We therefore included nonrandomized trials, as well as observational studies (for harms), which are more susceptible to bias and confounding than well-conducted randomized trials.

Emerging Issues and Future Research

Over the next several years, the large NELSON trial will be publishing information on the benefits and harms of LDCT screening. In addition, longer followup of the smaller trials that will contribute to the NELSON trial should be available. Finally, more analyses of the NLST will be forthcoming and help define whether there are subgroups that might disproportionately benefit or be harmed with LDCT screening. In addition, new studies of risk modeling which could be

applied to currently screened groups may facilitate identification of patients at higher risk who might benefit differentially from screening with LDCT.[40,147]

At this time in the United States, smoking occurs disproportionately in more disadvantaged groups as measured by socioeconomic status and/or educational level.[60] In addition, there is some evidence that individuals of disadvantaged socioeconomic and insurance status have increased lung cancer incidence as well.[19,33,34] While it is not clear how much these associations are mediated by smoking behaviors, these findings will have important resource allocation and financial implications if lung cancer screening is widely adopted. It is important to continue to evaluate the psychosocial consequences in patients who undergo screening. As noted, patients in trials self-select to undergo screening and may differ in their psychological responses to screening and abnormal or normal results. If screening is implemented, it will be imperative that these issues be studied carefully, especially the impact on smoking behavior. Furthermore, the method and quality of communication between clinicians and patients with nonnegative results in screening trials is likely different than occurs in routine practice.[122] All of these factors could influence the occurrence and magnitude of anxiety and distress that patients in the general population might experience. More research among patients in clinical settings is required to better address these concerns.

There is considerable interest in the use of biomarkers to increase the benefits and minimize the harms of lung cancer screening. The goal of this research is to focus LDCT efforts among individuals at highest risk of disease, provide more accurate discrimination between benign and malignant pulmonary nodules, and to find early indicators of aggressive disease. Many studies have examined the role of biomarkers in these settings. It is beyond the scope of our review to describe all of the potential biomarkers and analytic techniques currently being evaluated, but some that have been studied include exhaled breath biomarkers, such as volatile organic compounds;[148,149] DNA methylation analyses using serum, sputum, or exhaled breath condensate;[150,151] circulating serum microRNA;[152-157] and protein and proteomic analyses (such as haptoglobin and posttranslational glycan modifications of haptoglobin,[158] panel of proteins,[159] and proteomic analyses[160]); autoantibodies for small cell lung cancer;[161] and the use of dogs to detect scent changes.[162] Of note, the NLST collected multiple biologic specimens during enrollment, though no studies have yet reported results.[54]

No studies were found that evaluated the efficacy of using these biomarkers as a screening test. One paper describes a series of steps necessary for biomarker development[163] that will likely guide the clinical relevance of biomarker development. Currently, many biomarker studies have been cross-sectional and most studied in patients with known lung cancer, so it is not known if these biomarkers are present in detectable quantities prior to the development of symptomatic disease. In the near future, it is unlikely that biomarkers will be directly proven to be efficacious at defining at-risk cohorts to target for screening. They may ultimately prove informative in models to assess the baseline risk of developing lung cancer and the potential benefits of LDCT for specific groups.

Biomarkers will likely be found that help distinguish between benign and malignant nodules, the source of the majority of false-positive LDCT findings. However, experts currently recommend serial followup of nodules with repeat CT scans, even for patients with a relatively low risk of

lung cancer.[164] The negative predictive value of these biomarkers will likely need to be very high in order to substantially reduce the number of patients who receive followup imaging or the number of scans these patients receive.

Conclusions

The current evidence review found LDCT screening for lung cancer reduced lung cancer mortality by 20 percent and all-cause mortality by nearly 7 percent in one very large, good-quality study conducted in the United States. The NNS to prevent one lung cancer death in this trial was reported as 320 and the NNS to prevent one death overall was calculated to be 219. This compares with a number needed to invite to screen to prevent one breast cancer death of 1,905 in mammography trials following women ages 40 to 49 years for 11 to 20 years, 1,339 for women ages 50 to 59 years, and 377 for women ages 60 to 69 years.[165] It also compares with a NNS with flexible sigmoidoscopy of 871 to save one life from colon cancer.[166] A small Italian study conducted among a population similar to the NLST population suggested benefit but was not statistically significant. A reduction in lung cancer and all-cause mortality was not shown in two small European trials. However, LDCT identified a high number of patients with positive findings that are not due to lung cancer and require further evaluation, which typically involves more radiation exposure and may cause anxiety among those screened in the short-term, as well as significant costs. New data on CXR screening did not show benefit for CXR in reducing lung cancer deaths, although there was a nonstatistical suggestion of benefit among women. The rates of surgical procedures to evaluate positive findings were variable among the studies reviewed, but generally, most patients undergoing biopsy or surgical procedures were diagnosed with lung cancer. Finally, some patients will likely be diagnosed with and treated for lung cancer that would not have impacted their life (overdiagnosis), which is a net harm to the screened patient. The magnitude of this harm is currently not known. We did not find evidence that LDCT screening reduced smoking rates among those screened, but this will be important to vigilantly monitor and study if LDCT screening is broadly implemented, since smoking cessation is by far the most important intervention for reducing lung cancer risk, as well as improving overall health. More work in public health to reduce smoking rates will be the most important approach to reducing morbidity and mortality from lung cancer. However, in the meantime, given the high number of current and former smokers in the population at risk for lung cancer, work on identifying and treating early-stage lung cancer with screening will hopefully clarify the balance of benefits and harms associated with screening.

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Figure 1. Analytic Framework

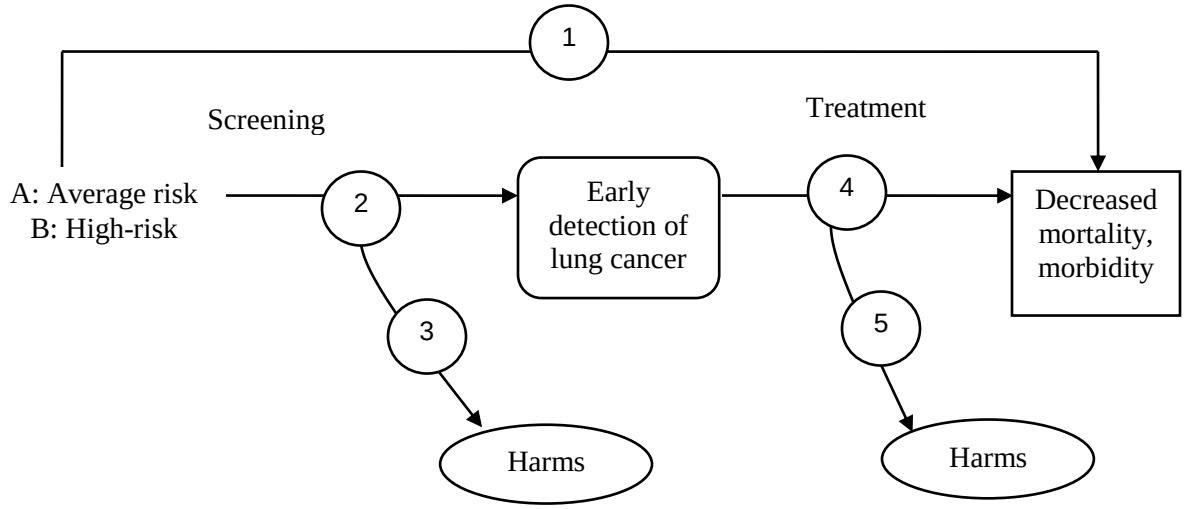
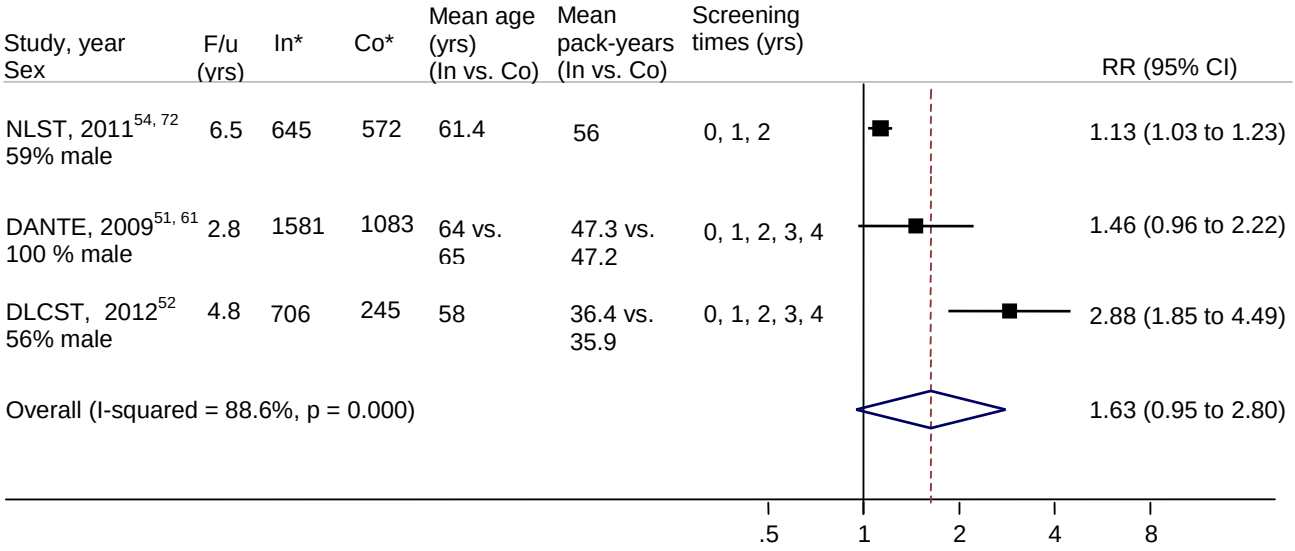


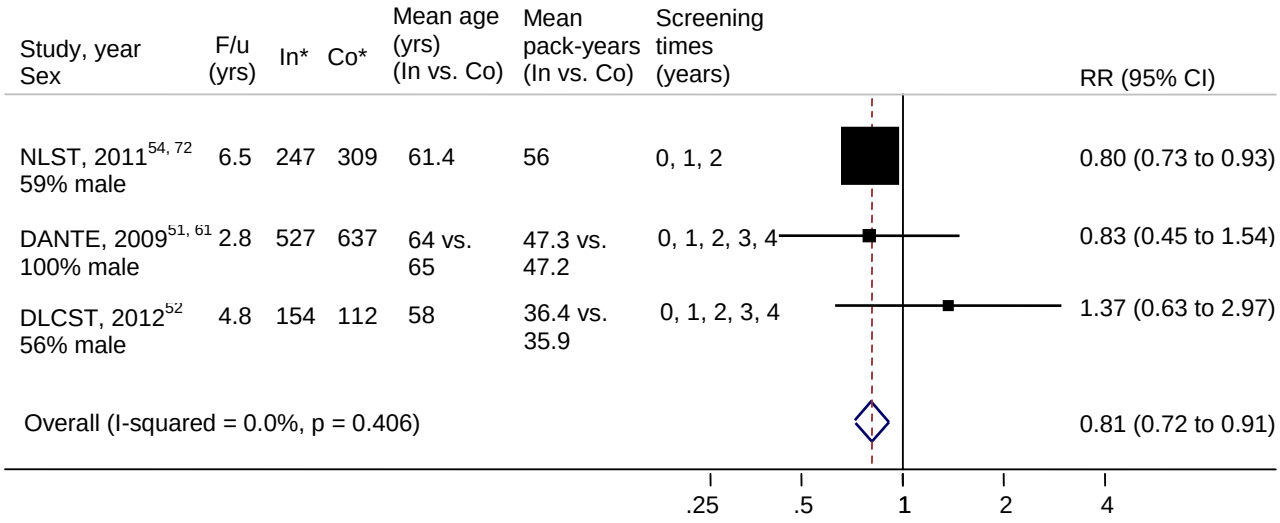
Figure 2. Meta-Analysis of Lung Cancer Incidence



*Per 100,000 person-years

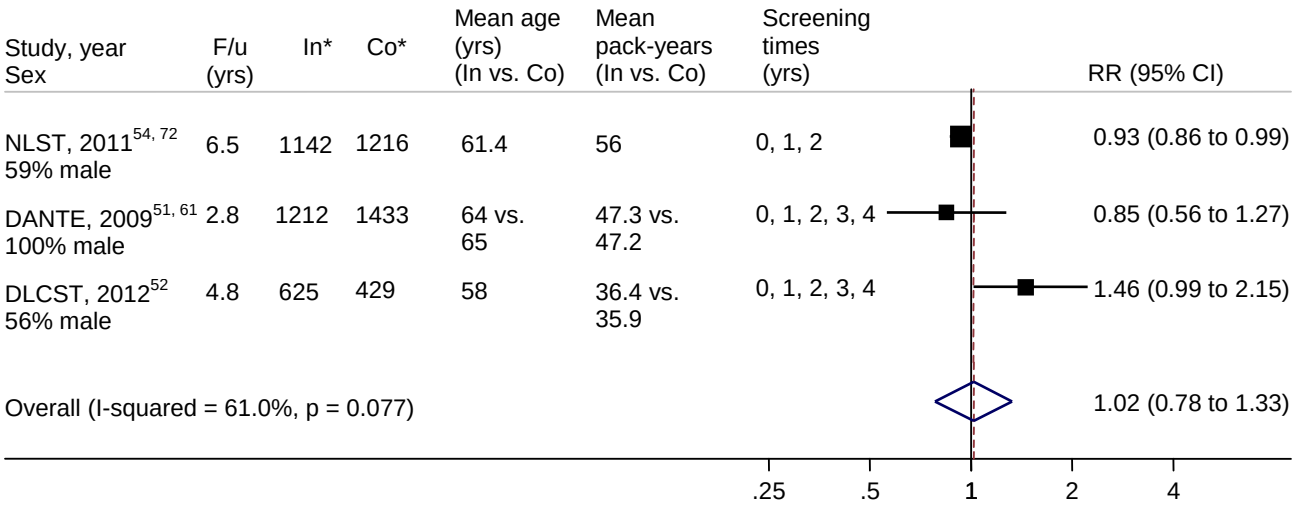
Abbreviations: CI = confidence interval; Co = control; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; F/u = followup; In = intervention; NLST = National Lung Screening Trial; RR = relative risk; vs. = versus; yrs = years

Figure 3. Meta-Analysis of Lung Cancer Mortality



*Per 100,000 person-years
Abbreviations: CI = confidence interval; Co = control; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; F/u = followup; In = intervention; NLST = National Lung Screening Trial; RR = relative risk; vs. = versus; yrs = years

Figure 4. Meta-Analysis of All-Cause Mortality



*Per 100,000 person-years

Abbreviations: CI = confidence interval; Co = control; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; F/u = followup; In = intervention; NLST = National Lung Screening Trial; RR = relative risk; vs. = versus; yrs = years

Table 1. Recommendations of Professional Organizations

Organization, year	Recommendations
American Cancer Society, 2012[43]	The ACS recommends clinicians discuss screening for lung cancer with high-risk patients in relatively good health who meet the NLST criteria (ages 55 to 74 years with ≥30 pack-year smoking history, currently smoke, or have quit ≤15 years ago). Discussion of screening should include the benefits, uncertainties, and harms. The ACS recommends against the use of CXR and strongly suggests all adults undergoing screening enter an organized screening program with experience in LDCT.
American Association for Thoracic Surgery[42]	The Lung Cancer Screening and Surveillance Task Force recommends surveillance with LDCT and annual lung cancer screening for current and former smokers ages 55 to 79 years with a 30 pack-year history of smoking. It also recommends annual screening for long-term lung cancer survivors ages 55 to 79 years. Annual screening should begin at age 50 years for patients with a 20 pack-year history of smoking and additional comorbidity that produces a cumulative risk of developing lung cancer of at least 5% over the next 5 years.
American College of Chest Physicians, American Society of Clinical Oncology, American Thoracic Society[40]	The collaborative work of these organizations recommend lung cancer screening, modeled closely on the NLST, using a LDCT program for individuals ages 55 to 74 years with a 30 pack-year history of cigarette smoking and the ability to partake in organized programs of screening.
American Lung Association, 2012[41]	Recommends LDCT for patients who meet the NLST criteria and recommends against CXR as a method for lung cancer screening.
National Comprehensive Cancer Network Guidelines, 2012[22]	The panel recommends LDCT screening for select patients at high risk of lung cancer based on the NLST results, nonrandomized studies, and observational data. High-risk individuals are defined as: age 55 to 74 years; ≥30 pack-year smoking history; and if they are a former smoker, they have quit ≤15 years ago OR age ≥50 years; ≥20 pack-year smoking history, and one additional risk factor. Moderate-risk (age ≥50 years and ≥20 pack-year history of smoking tobacco or secondhand smoke exposure, but no additional lung cancer risk factors) and low-risk (age <50 years and/or smoking history <20 pack-years) individuals are not recommended for lung cancer screening.

Abbreviations: ACS = American Cancer Society; CXR = chest x-ray; LDCT = low-dose computed tomography; NLST = National Lung Screening Trial

Table 2. Summary of Included Randomized, Controlled Trials

Study, recruitment years	Population	Baseline smoking status (intervention vs. control)	Screening strategy		Total followup	Followup after screening ended
			Number of screening rounds	Screening times (years)		
LDCT vs. CXR						
NLST[54, 72] August 2002–April 2004	N=26,722 vs. 26,732 Ages 55–74 years 59% male	Current: 48% (n=12,862) vs. 48% (12,900) Former: 52% (n=13,860) vs. 52% (n=13,832) Mean pack-years: 56	3	0, 1, 2	Median: 6.5 years Longest: 7.4 years	NR but presumably 4.5 years
LSS[55, 73-75] September 2000–January 2001	N=1660 vs. 1658 Ages 55–74 years 59% male	Current: 58% (n=961) vs. 57% (n=947) Former: 42% (n=699) vs. 43% (n=711) Median pack-years: 54	2	0, 1	NR but approximately 12–24 months	None
LDCT vs. no LDCT						
DANTE[51, 61] 2001–2006	N=1276 vs. 1196 Ages 60–74 years 100% male	Current: 56% (n=714) vs. 57% (n=681) Former: NR Mean pack-years: 47.3 vs. 47.2	5	0, 1, 2, 3, 4	Median: 33.7 months Controls: 31.5 months LDCT: 35.7 months	Unknown (final results pending)
DLCST[52, 62, 76] October 2004–March 2006	N=2052 vs. 2052 Ages 50–70 years 55% male	Current: 75% (n=1545) vs. 77% (n=1579) Former: 25% (n=507) vs. 23% (n=473) Mean pack-years: 36.4 vs. 35.9	5	0, 1, 2, 3, 4	Median person-years: 4.8	NR
MILD[53] September 2005–January 2011	N=2376 (1190 annual, 1186 biennial) vs. 1723 Ages ≥49 years 66% male	Current: 68% (annual) vs. 68% (biennial) vs. 90% (control) Former: 31% (annual) vs. 32% (biennial) vs. 10% (control) Median pack-years: 39 vs. 39 vs. 38	Median number of CT scans (annual vs. biennial): 5 vs. 3	Every 12 months (annual) vs. every 24 months (biennial)	Median: 4.4 years (maximum 6 years in both groups) Controls: 56 months LDCT: 45 months	Recruitment ended January 2011; followup until November 2011
NELSON[56, 63-67, 69-71, 77-80] 1st phase: 2003–NR 2nd phase: October 2005–NR	N=7915 vs. 7907 Ages 50–75 years 84% male	Current: NR Former: NR Mean pack-years: NR, but had to have 15 cigarettes/day for >25 years, or >10 cigarettes/day for >30 years smoking history, and if former smoker, quit ≤10 years ago for inclusion	3	0, 1, 3	2 years	2 years
ITALUNG[57, 81, 82] 2004–NR	N=1406 vs. 1593 Ages 55–69 years 65% male	Current: 65% (n=2078) Former: NR Median pack -years: 39	4	0, 1, 2, 3	Baseline only	NA

Table 2. Summary of Included Randomized, Controlled Trials

Study, recruitment years	Population	Baseline smoking status (intervention vs. control)	Screening strategy		Total followup	Followup after screening ended
			Number of screening rounds	Screening times (years)		
CXR vs. usual care						
PLCO[59, 83, 84] 1993–2001	N=77,445 vs. 77,456 Ages 55–74 50% male	Current: 10% Former: 42% Never: Approximately 45% Mean pack-years: NR	4	0, 1, 2, 3	Median (mean): 11.9 (11.2) years (range: 10–13 years)	NR

Abbreviations: CT = computed tomography; CXR = chest x-ray; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial; DLCST = Danish Lung Cancer Screening Trial; LDCT = low-dose computed tomography; LSS = Lung Screening Study; MILD = Multi-centric Italian Lung Detection; NA = not applicable; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial; NR = not reported; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Table 3. Incidence Rates of Lung Cancer Outcomes

Study	N	Incidence			Lung cancer mortality			All-cause mortality			Duration of followup*
		IN	CO	RR (95% CI)	IN	CO	RR (95% CI)	IN	CO	RR (95% CI)	
LDCT vs. CXR											
NLST[54, 72]	53,454	645	572	1.13 (1.03–1.23)	247	309	0.80 (0.73–0.93)†	1302	1395	0.93 (0.86–0.99)†	6.5
NLST women	41%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
LDCT vs. no LDCT											
DANTE[51, 61]	2472	1600	1015	1.46 (0.96–2.22)†	558	597	0.83 (0.45–1.54)†	1283	1344	0.85 (0.56–1.27)†	2.9 (IN) vs. 2.6 (CO)
DANTE women	0%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DLCST[52]	4104	706	245	2.88 (1.85–4.49)†	154	112	1.37 (0.63–2.97)†	624	429	1.46 (0.99–2.15)†	4.8
DLCST women	45%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
MILD[53]	4099	457‡ 620‖	311	1.47 (0.82–2.64)†,‡ 1.99 (1.16–3.43)†,‖	109‡ 216‖	109	1.00 (0.34–2.98)†,‡ 1.99 (0.80–4.96)†,‖	363‡ 558‖	310	1.17 (0.63–2.17)†,‡ 1.80 (1.03–3.13)†,‖	3.8 (IN) vs. 4.7 (CO)
MILD women	34%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
CXR vs. usual care											
PLCO[59]	154,901	200	192	1.05 (0.98–1.12)	140	142	0.99 (0.87–1.22)	1052	1071	0.98 (0.95–1.01)	11.9
PLCO¶	30,321	606	608	1.00 (0.88–1.13)	361	383	0.94 (0.81–1.10)	NR	NR	NR	6
PLCO women	50.5%	NR	NR	NR	NR	NR	0.92 (0.81–1.06)	NR	NR	NR	11.9

*Data presented as medians in years.
†Data were calculated.
‡Biennial exam group.
‖Annual exam group.
¶NLST-eligible patients only.

Abbreviations: CI = confidence interval; CO = control group; CXR = chest x-ray; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; IN = intervention group; LDCT = low-dose computed tomography; MILD = Multi-centric Italian Lung Detection; NA = not applicable; NLST = National Lung Screening Trial; NR = not reported; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RR = relative risk

Table 4. Computed Tomography Parameters

Study	kV	mAs	Slice width (mm)	Overlap	Multi/single detector	Estimated dose/study (mSv)
Randomized, controlled trials						
NLST[54, 72]	120–140	40–80	1–2.5	Yes	MDCT	1.5
LSS[55, 73-75]	120–140	60–120	NR	NR	NR	NR
DANTE[51, 61]	140	40	5	NR	Both	NR
MILD[53]	120	30	1–5	No	Both	0.7
NELSON[56, 63-67, 69-71, 77-80]	80–90	40–80	1	Yes	MDCT	NR
DLCST[76]	120	40	3 and 1	Yes	16 row MDCT	NR
Cohort studies						
Canada ELCAP[86, 94] September 2003–May 2007	120	40–60	1–1.25	Yes	Variable row 4–64	NR
China ELCAP[95] 2 cohorts: 1993–2002 and 2003–2009	120	80	5	NR	Both	NR
COSMOS[91, 96] October 2004–October 2005	140	30	2.5	NR	8–16 row MDCT	0.8 men 1.0 women
Toyoda et al, 2008[89] August 1998–May 2002	NR	NR	NR	NR	NR	NR
Mayo Lung Project[87] 1999	120	40	5	NR	4 row MDCT	0.65
PLuSS[97] March 2002–November 2006	140	40–60	2.5	NR	NR	NR
Tsushima et al, 2008[90] 2000–2001	120	25	5	NR	MDCT	NR
LUSI[98]	NR	NR	1	Yes	MDCT	1.62–2

Abbreviations: COSMOS = Continuing Observation of Smoking Subjects; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; ELCAP = Early Lung Cancer Action Program; LSS = Lung Screening Study; LUSI = The German Lung Cancer Screening Intervention Trial; MDCT = Multidetector computed tomography; MILD = Multi-centric Italian Lung Detection; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial; NR = not reported; PLuSS = Pittsburgh Lung Screening Study

Table 5. Results of Screening Rounds in Randomized, Controlled Trials*

Author, year	Round screening	Number screened		Study positives, n (%)		Imaging followup					
						CXR, n (%)		CT, n (%)		PET, n (%)	
		IN	CO	IN	CO	IN	CO	IN	CO	IN	CO
NLST[54] Reported by procedure, except where noted	Baseline Round 1 Round 2 Cumulative	26,722	26,732	7191 (27)† 6901 (26)† 4054 (15)† 18,146 (68)† 10,421 (39)	2387 (8.9)† 1482 (5.5)† 1174 (4.4)† 5043 (19)† 4277 (16)	1284 (4.8)† 613 (2.3)† 650 (2.4)† 2547 (9.5)†	867 (3.2)† 381 (1.4)† 365 (1.4)† 1613 (6.0)†	5153 (19)† 2046 (7.7)† 1608 (6.0)† 8807 (33)†	1546 (5.8)† 745 (2.8)† 712 (2.7)† 3003 (11)†	728 (2.7)† 350 (1.3)† 393 (1.5)† 1471 (5.5)†	179 (0.7)† 105 (0.4)† 113 (0.4)† 397 (1.5)†
LSS[55]	Baseline	1660	1658	325 (20)	152 (9.2)	92 (5.5)	68 (4.1)	232 (14)	76 (4.6)	NR	NR
LSS[74]	Annual	1629	1648	295 (18)	145 (8.8)	64 (3.9)	45 (2.7)	140 (8.6)	55 (3.3)	NR	NR
DLCST[52]	Baseline	2052 (2047 had 1st LDCT)	2052	189 (9.2) Baseline recall rate (7.6)	NR	NR	NR	155 (7.6)	NR	NR	NR
	1	1976	1953	117 (5.9)	NR	NR	NR	20 (1.0)	NR	NR	NR
	2	1944	1877	52 (2.7)	NR	NR	NR	24 (1.2)	NR	NR	NR
	3	1982	1838	82 (4.1)	NR	NR	NR	18 (0.1)	NR	NR	NR
	4	1851	1820	72 (3.9)	NR	NR	NR	24 (1.3)	NR	NR	NR
	All annual	96%	93%	198/2054 (9.6)	NR	NR	NR	24	NR	NR	NR
NELSON[56]	Baseline	7557	NR	1451 (19) indeterminate and 119 (1.6) positive; 196 (2.6) referred for further evaluation	NR	55 (0.7)	NR	1438 (19)	NR	0	0
	1	7289	NR	480 (6.6) indeterminate and 90 (1.2) positive; 118 (1.6) referred for further evaluation	NR	35 (0.5)	NR	275 (3.8)	NR	NR	NR
MILD[53]	Overall	Biennial 1186	1723	Biennial 158 (13)	NR	NR	NR	NR	NR	Biennial 34 (2.9)	NR
		Annual 1190		Annual 177 (15)		NR	NR	NR	NR	Annual 49 (4.1)	
ITALUNG[57]	Baseline	1406	1593	426 (30)	NR	NR	NR	366 (26)	NR	59 (4.2)	NR
DANTE[51]	Overall	1276	1196	351 (28) (226 further evaluation)	153 (12.8)	NR	38 (3.2)	199 (16)	22 (1.8)	57 (4.5)	4 (0.3)

Table 5. Results of Screening Rounds in Randomized, Controlled Trials*

Author, year	Biopsy‡, n (%)		Surgery‡, n (%)		Bronchoscopy, n (%)		Screen-detected lung cancer, n (%)		Total lung cancer, n (%)	
	IN	CO	IN	CO	IN	CO	IN	CO	IN	CO
NLST[54]	155‡ (0.6)† 74 (0.3)† 93 (0.3)† 322 (1.2)†	83 (0.3)† 37 (0.1)† 52 (0.2)† 172 (0.6)†	297 (1.1)† 197 (0.7)† 219 (0.8)† 713 (2.7)†	121 (0.5)† 51 (0.2)† 67 (0.3)† 239 (0.9)†	306 (1.1)† 178 (0.7)† 187 (0.7)† 671 (2.5)†	107 (0.4)† 56 (0.2)† 62 (0.2)† 225 (0.8)†	270 (1.0)† 168 (0.6)† 211 (0.8)† 649 (2.4)†	136 (0.5)† 65 (0.2)† 78 (0.3)† 279 (1.0)†	1060 (4.0)† 367 after screening or among those missing LDCT; 44 interval	941 (3.5)† 527 among those missing a screen or after screening ended;137 interval
LSS[75]	63	NR	46 (2.8)	12 (0.7)	29 (1.7)	8 (0.5)	30 (1.8)	7 (0.4)		
LSS[75]	63	NR	18 (1.1)	19 (1.2)	14 (0.9)	8 (0.5)	8 (0.5)	9 (0.5)	40 (2.5)	20 (1.2)
DLCST[52]	NR	NR	NR	NR	NR	NR	17 (0.8)	1 (0.05)		
	2 (0.1)	NR	18 (0.9)	NR	13 (0.7)	NR	11 (0.6)	4 (0.2)		
	NR	NR	NR	NR	NR	NR	13 (0.7)	6 (0.3)		
	NR	NR	NR	NR	NR	NR	12 (0.6)	7 (0.4)		
	NR	NR	NR	NR	NR	NR	16 (0.9)	6 (0.3)		
	NR	NR	NR	NR	NR	NR	69	24	69 (3.8)	24 (1.2)
NELSON[56]	13 (0.2)	NR	92 (1.2) invasive procedures	NR	149 (2.0)	NR	70 (0.9)	NR	74 (1.0)	NR
	3 (0.04)	NR	61 (0.4) invasive procedures	NR	98 (1.3)	NR	54 (0.7)	NR	Uncertain	NR
MILD[53]	NR	NR	NR	NR	NR	NR	20 (1.7)	20 (1.2)	25 (2.1)	20 (1.2)
	NR		NR		NR		29 (2.4)		34 (2.9)	NR
ITALUNG[57]	16 (1.1) FNA	NR	16 (1.1) for treatment	NR	NR	NR	20 (1.4)	NR	20 (1.4)	NR
DANTE[51]	NR	NR	96 (7.5) invasive procedures, 46 (3.6) thoracotomy, 20 (1.6) VATS	36 (3.0) any invasive procedure, 20 (1.7) thoracotomy, 6 (0.5) VATS	NR	NR	47 (3.7)	11 (0.9)	60 (4.7)	34 (2.8)

* Per individual, unless otherwise noted.
†Per test.
‡Per study definition.
Abbreviations: CO = control group; CT = computed tomography; CXR = chest x-ray; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays Trial; DLCST = Danish Lung Cancer Screening Trial; FNA = fine needle aspiration; IN = intervention group; LDCT = low-dose computed tomography; LSS = The Lung Screening Study; MILD = Multi-centric Italian Lung Detection; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial; NR = not reported; PET = positron emission tomography; VATS = video-assisted thoracic surgery

Table 6. Results of Screening Rounds in Cohort Studies

Study	Round of screening	Number screened	Study positives, n (%)	Repeat CT or PET, n (%)	Biopsy*, n (%)	Surgery*, n (%)	Lung cancer, n (%)
Cornell ELCAP[88]	Baseline Repeat	2968 4538	368/2968 (12) 254/4538 (5.6)	NR NR	NR NR	NR NR	79/2968; 77 screen-detected (2.7) 29/4538; 28 screen-detected (0.6)
China ELCAP[95]	Baseline	3582	351/3582 (10)	313/3582 (8.7)	NR	37/3582 (1.0)	34/3582 (0.95); interval cancers NR
Canada ELCAP[86]	Baseline Repeat	3352 2286	600/3352 (18) 259/2286 (11)	NR NR	57/3352 (1.7) 25/2286 (1.1) 78 done	NR	44/3352 (1.3) 21/2286 (0.9); 18 screen-detected
COSMOS[91, 96]	Baseline Round 1	5201 4821	560/5201 (11) 500/4821 (10)	561/5201 (11) NR	NR 101/5201 overall (1.9)	62/5201 (1.2) 46/4821 (0.9)	55/5201 (1.0) 37/4821 (0.8); 36 screen-detected
Mayo Lung Project[87]	Baseline Repeat (4)	1520	780/1520 (51) 1118/1520 (73)	NR NR	NR NR	NR NR	31/1520 (2.0) 35/1520 (2.2); 34 screen-detected
Japan Toyoda et al, 2008[89]	Overall	4689	NR	NR	NR	NR	45/4689 (0.96) - all screen detected
PLuSS[97]	Baseline	3642	1477/3642 (40)	821/3642 (22)	NR	90/3642; 54 for cancer (2.5)	80/3642 (2.2); interval cancers NR
Japan Tsushima et al, 2008[90]	Overall	2486	214/2486 (8.6)	170/2486 HRCT (6.8)	NR	7/2486 (0.3)	8/2486 (0.3); all screen-detected
LUSI[98]	Baseline	2029	540/2029 (27)	NR	31/2029 (1.5)	19/2029 (0.9)	23/2029 (1.1); 22 screen-detected

* Per study definition.

Abbreviations: COSMOS = Continuing Observation of Smoking Subjects; CT = computed tomography; ELCAP = Early Lung Cancer Action Program; HRCT = high-resolution computed tomography; LUSI = The German Lung Cancer Screening Intervention Trial; NR = not reported; PET = positron emission tomography; PLuSS = Pittsburgh Lung Screening Study

Table 7. Smoking Rates

Study	N	Quit rates (for baseline smokers)	Relapse rate	Measure for abstinence
Randomized, controlled trials				
NELSON[70] Random sample of baseline smokers	1284	24 months: CT group: 13% (84/641)* Control group: 15% (96/643)* p=0.35	NR	7 day PPA plus <5 cigarettes since 2 weeks after quit date
NELSON[80] Random sample of baseline smokers in CT group	990	24 months: Negative CT group: 8.9% (46/519)* Indeterminate CT group: 11% (48/419)* p=0.19	NR	7 day PPA plus <5 cigarettes since 2 weeks after quit date
DLCST[62]	4104	12 months: CT group: 11% (174/1545)* Control group: 10% (165/1579)* p=0.47	Former smokers: CT: 9.3% (47/507)*† Control: 9.3% (44/473)*†	>4 weeks PPA
Cohorts from randomized, controlled trials				
NLST[72] LSS	NLST: 169 LSS: 144	1 month: NLST: 6.3% (5/79)*† LSS: 4.8% (4/83)*†	Former smokers: NLST: 4.4% (4/90)*† LSS: 3.3% (2/61)*†	
Cohorts				
ELCAP[104]	2078	Up to 72 months: 14% (103/730)*‡	Recent quitters (during study) with followup: 34% (52/155) Recent quitters (<12 months prior to study): 42% (51/121) Former smokers: 4.4% (54/1227)	30 day PPA
Mayo Lung Project[105] 12-month followup	1475	12 months: 14% (129/901)	Former smokers: 10% (numerator/denominator NR)	PPA
Mayo Lung Project[106] 36-month followup	1520	12 months: 14% (129/926)*† 24 months: 22% (202/926)*† 36 months: 23% (211/926)*† Repeat 7 day PPA x 36 months: 9.3% (86/926)*†	**Recent quitters (during study)** 12 months: NA 24 months: 26% (33/129)*† 36 months: 31% (62/202)*† **Recent quitters (<12 months prior to study)** 12 months: 32% (48/151)*† 24 months: 26% (40/151)*† 36 months: 27% (41/151)*† **Former smokers:** 12 months: 2.3% (10/439)*† 24 months: 2.7% (12/439)*† 36 months: 3.0% (13/439)*†	7 day PPA
PLuSS[107]	2094	12 months: 16% (325/2094)	Recent quitters (during study): 12 months: 12% (244/2094)	>30 day PPA
PALCAD[103]	449	24 months: 19% (59/307)	24 months: 1.6%	PPA

*Intention-to-treat analysis.
†Calculated.
‡Point abstinent with subsequent followup.

Abbreviations: CT = computed tomography; DLCST = Danish Lung Cancer Screening Trial; ELCAP = Early Lung Cancer Action Program; LSS = Lung Screening Study; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial; NR = not reported; PALCAD = ProActive Lung Cancer Detection; PLuSS = Pittsburgh Lung Screening Study; PPA = point prevalence abstinence

Table 8. Survival Benefit and Adverse Events After Treatment of Stage I Lung Cancer

Author, year Recruitment years	Population	Duration of followup	Stage IA (n)	Stage IB (n)	Surgery	5-year survival	Harms
Chang et al, 2007[108] 1988–1997	N=10,761 stage IA 5320 women, 5441 men Median age: 67 years Other: SEER population	NR	10,761	0	Lobectomy: 79% Sublobectomy: 21%	Overall: 58% Women: 63% Men: 53%	NR
Christian et al, 2006[109] 1991–2004	N=1421 NSCLC resection, 548 complete resection stage IA/IB Mean age: 67 years Location: Italy	Median 49 months	250	298	Complete resection	Overall: 57% IA: 67% IB: 49%	9 postoperative deaths
Goodgame et al, 2008[110] 1990–2000	N=715 consecutive patients undergoing resection 46% female 45% adenocarcinoma Location: United States Other: pathologic stage IA/IB Median age: 67 years	4.7 years	378	336	Wedge: 34% Lobectomy: 21% Pneumonectomy: 40%	Overall: 61% IA: 66% IB: 55%	NR
Goya et al, 2005[111] 1994	N=6644 resected NSCLC 70% male Mean age: 64.5 years Location: Japan	At least 5 years	2423	1542	NR	IA: 80% IB: 60% All stages: Men: 49% Women: 62%	NR
Kates et al, 2011[112] 1988–2005	N=2090 resected tumors ≤1 cm Lobectomy vs. sublobectomy Location: United States Other: SEER	37 months	2090	0	1402 lobectomy 688 “limited” resection	64% alive after 37 months Not clear	NR
Maeda et al, 2010[113] 1994–2003	N=713 consecutive, 569 stage I 80% adenocarcinoma 46% female Location: Japan	NR	249	320	Wedge: 14% Lobectomy: 86%	85%	NR
Maeda et al, 2012[114] 1997–2003	N=4668 all stages resected Location: Japan	Retrospective cohort with followup until March 2010	1487	1214	NR by stage	IA: 42% ASC 89% AC 63% SC IB: 19% ASC 65% AC 47% SC	NR

Table 8. Survival Benefit and Adverse Events After Treatment of Stage I Lung Cancer

Author, year Recruitment years	Population	Duration of followup	Stage IA (n)	Stage IB (n)	Surgery	5-year survival	Harms
McKenna et al, 2006[115] 1992–2004	N=1100 patients of all stages undergoing VATS Location: NR	NR but data out to 10 years	561	248	VATS lobectomy	NR	Entire cohort: Benign dissection: 53/1100 (4.8%) Lung cancer: 1015/1100 (92%) No intraoperative deaths 9 postoperative deaths (0.8%) 168 had complications: 56 air leak, 32 atrial fibillation, 13 readmission, 13 pneumonia
Okada et al, 2004[116] 1985–1995 1996–2002	N=1465 consecutive patients, of which 859 stage I Location: Japan Other: NSCLC	103 months early era 41 months later era	523	326	NR by stage	IA: 71% early era 90% later era IB: 63% early era 75% later era	Entire cohort: 6.3% operative deaths Postoperative complications: Early era: 28% Late era: 12% In-hospital deaths: Early era: 2% Late era: 0.5%
Okada et al, 2006[117] 1992–2001	N=510, ≤2 cm undergoing sublobar, lobar, or wedge resection Location: Japan Other: Peripheral NSCLC	72 months	510	0	Wedge: 30 Segmentectomy: 230 Lobectomy: 260	90% 89%	1 operative death (29 days postoperative MI)
Sawabata et al, 2011[118] 2004 1999 1994	N=11,663 (2004), 13,344 (1999), 7393 (1994), 7530 stage I Location: Japan Other: NSCLC undergoing resection in 2004	2–78 months	Pathologic: 2004: 5611 1999: 5007 1994: 2142 Overall: 12,760	Pathologic: 2004: 2398 1999: 2803 1994: 1488 Overall: 6689	NR	2004 IA: 87% IB: 74% 1999 IA: 83% IB: 66% 1994 IA: 79% IB: 66%	Entire cohort: Postoperative complications: 2004: 4.5% 1999: 11% 1994: NR Operative deaths: 2004: 0.4% 1999: 0.9% 1994: 1.4% Hospital death: 2004: 0.4% 1999: 1.1% 1994: 1.7% Cause of death original cancer: 2004: 21% 1999: 25% 1994: 57%

Table 8. Survival Benefit and Adverse Events After Treatment of Stage I Lung Cancer

Author, year Recruitment years	Population	Duration of followup	Stage IA (n)	Stage IB (n)	Surgery	5-year survival	Harms
Shirvani et al, 2012[119] 2001–2007	N=7808 (3582 men; 4226 women) Location: United States Other: SEER	Retrospective cohort with followup through May 2010	6047	1761	Lobectomy: 6531 Sublobar resection: 1277	NR	NR
Strand et al, 2006[120] 1993–1999	N=3211 resected 2061 men, 1150 women (resection rate in country 16%, of which 1375=stage I) Location: Norway	NR	559	816	NR by stage	IA: 64% IB: 42%	Entire cohort 30-day mortality: 4.8%

Abbreviations: AC = adenocarcinoma; ASC = adenosquamous carcinoma; MI = myocardial infarction; NR = not reported; NSCLC = non-small cell lung cancer; SC = squamous cell carcinoma; SEER = Surveillance Epidemiology and End Results; VATS = video-assisted thoracic surgery

Table 9. Summary of Evidence

Number of studies	Design	Limitations	Consistency	Applicability	Overall quality	Findings
Key Question 1. How effective is screening for lung cancer in reducing mortality and morbidity?						
6 studies (7 publications)	RCTs	3 RCTs evaluating LDCT had short followup and were underpowered	Low	High	Fair	• 1 good-quality trial (n=53,454) of high-risk participants with good generalizability showed that LDCT compared with CXR conducted over 3 screens reduced lung cancer mortality by 20% and all-cause mortality by 6.7%. • 3 smaller (n=2472, 4099, and 4104) European trials of fair- and poor-quality included high-risk participants and showed no benefit associated with LDCT screening compared with no LDCT screening. • Meta-analysis of 3 fair- or good-quality trials showed RR of lung cancer mortality of 0.81 (95% CI, 0.72–0.91) and of all-cause mortality of 1.02 (95% CI, 0.78–1.33). • 2 trials of CXR screening compared with no screening (1 in the general population and 1 in high-risk individuals) showed no benefit associated with CXR screening. • 1 study reported findings on screening in women and did not show a significant reduction in lung cancer mortality associated with CXR screening. • No trials reported data on lung cancer screening in different racial or ethnic populations.
Key Question 2. What are the test characteristics (sensitivity, specificity, predictive value) of screening tests for lung cancer?						
15 studies (24 publications)	RCTs Cohort	Variable methods of determining sensitivity and specificity	High	High	Fair	• Sensitivity of LDCT was reported in 1 trial and 5 cohort studies and ranged from 80%–100%. • Specificity of LDCT was reported in 2 RCTs and 5 cohort studies and ranged from 28%–100%. • The calculated positive predictive value for an abnormal (positive or indeterminate) LDCT scan predicting lung cancer ranged from 2.2%–42%. • The sensitivity of CXR for lung cancer was reported in the prior review as 25% when compared with LDCT; specificity was not evaluated. • No studies reported test parameters for sputum cytology.
Key Question 3. What are the harms associated with lung cancer screening and are there ways to modify harms (e.g., unnecessary biopsy, radiation exposure, overdiagnosis, and psychosocial harms)?						
13 studies (32 publications)	RCTs Cohort	Harms variably reported among the studies	Fair	High	Fair	Radiation: • 2 RCTs and 2 cohort studies reported radiation associated with 1 LDCT scan ranged from 0.6 mSv–1.5 mSv. • 1 study reported cumulative radiation exposure associated with its screening program estimated at 6 mSv–7 mSv. False-positive examinations and followup evaluations: • Positive examinations at baseline screen ranged from 9.2%–51% (of participants) with calculated positive predictive values for abnormal scans ranging from 2.2%–36%; most were resolved with further imaging. • Positive examinations were lower in subsequent screens with positive predictive values for abnormal scans predicting lung cancer of 4%–42%; most were resolved with further imaging. • Positive predictive values for abnormal LDCT scans with recommendations for biopsy ranged from 50%–92%. False reassurance: • Sensitivity of LDCT ranged from 80%–100%, implying a false-negative rate of 0%–20%. The harms of false reassurance were not evaluated in any study. Overdiagnosis: • Overdiagnosis was not formally reported in any study. It was suggested in 1 trial of LDCT compared with no LDCT that showed an excess of 119 lung cancers among approximately 26,000 participants after 6.5 years of followup. 3 RCTS with limited followup reported more early-stage lung cancer in LDCT screened groups than among controls but not a smaller number of advanced lung cancer. • 1 older trial of CXR screening of approximately 9000 high-risk participants reported that an excess of lung cancers diagnosed in the screened group persisted after 20 years of followup.

Table 9. Summary of Evidence

Number of studies	Design	Limitations	Consistency	Applicability	Overall quality	Findings
						• 1 trial of CXR screening compared with no screening in the general population (n=155,000) showed 18 excess lung cancers in the screened group after 6 years of followup and 76 excess lung cancers after 13 years of followup (RR, 1.05 [95% CI, 0.98–1.12]); data from the same trial evaluating overdiagnosis among a high-risk population showed a cumulative incidence of lung cancer of 606/100,000 py in the CXR group and 608/100,000 py in the usual care group after 6 years of followup (RR, 1.00 [95% CI, 0.88–1.13]). Psychosocial consequences: • 5 studies showed that LDCT screening did not significantly impact overall health-related quality of life. Most studies reported no long-term difference in anxiety among participants, although 3 studies suggested increased short-term anxiety among those with positive or indeterminate results. Distress was decreased among individuals with negative results (compared with baseline) in 1 trial. Smoking behavior: • 3 RCTs identified no differences in smoking cessation rates, smoking relapse rates, or smoking intensity between LDCT and no LDCT screening groups. • In RCTs, smoking behavior among subjects with abnormal scans and those with negative scans showed mixed results, with 1 study showing a tendency toward smoking abstinence among those with abnormal scans. Mixed results were also seen in cohort studies. • 1 cohort study suggested that physician referral for patients with abnormal screening LDCT may result in higher smoking cessation rates. Incidental findings: • There was no standardized approach to reporting incidental findings. Among LDCT studies, nonpulmonary lung findings were common; infections and other cancers were also diagnosed. Coronary artery calcification was identified in approximately 50% of participants in 1 cohort study evaluating CT scans retrospectively.
Key Question 4. How effective is surgical resection for the treatment of early (stage IA) non-small cell lung cancer?						
12 studies	Cohorts	No RCTs evaluated surgical resection of stage IA or IB NSCLC. All reported survival among patients with clinically-detected lung cancer and not selected for comorbidity	Fair	Moderate	Fair	• No RCTs have compared treating stage IA or IB lung cancer with surgical resection compared with no treatment. • 5 studies from 4 cohorts in Japan showed 5-year survival rates for resected pathologic stage IA NSCLC ranging from 71%–90%. Five-year survival among cohorts evaluating pathologic stage IB resected lung cancer ranged from 70%–74%. • 2 large U.S. cohorts showed 5-year survival rates of 58%–66% for stage IA and 55% for stage IB lung cancer resected between 1990 and 2000.
Key Question 5. What are the harms associated with surgical resection of early (stage IA) non-small cell lung cancer?						
6 studies	Cohorts	Studies reflect harms of surgical resection in patients identified in clinical practice with comorbidities; not necessarily a population eligible for screening	Fair	Low	Fair	• No RCTs of LDCT screening evaluated the harms associated with resection of screen-detected NSCLC. • 2 cohort studies reported harms associated with resection of stage IA NSCLC. 1 Japanese study reported 1 postoperative death among 510 individuals undergoing resection between 1992 and 2001. 1 Italian study reported 9 postoperative deaths among 548 patients with resections of stage I NSCLC between 1991 and 1994. • 6 studies reported harms among large cohorts of individuals undergoing resection but did not specify results specifically for stage IA NSCLC.

Abbreviations: CI = confidence interval; CT = computed tomography; CXR = chest x-ray; LDCT = low-dose computed tomography; NSCLC = non-small cell lung cancer; py = person-years; RCT = randomized, controlled trial; RR = relative risk

Appendix A1. Search Strategies

Screening key questions 1, 2, and 3:

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1947 to 2012>
Search Strategy:
---
1 exp Lung Neoplasms/ (146585)
2 exp Mass Screening/ (85357)
3 screen$.mp. (381192)
4 ((early or earlier or earliest) adj5 (detect$ or diagnos$ or discover$ or find or finding)).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier] (123562)
5 exp early diagnosis/ (9549)
6 2 or 3 or 4 or 5 (492801)
7 1 and 6 (7310)
8 limit 7 to (english language and humans and yr="2000 -Current") (3399)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2012>
Search Strategy:
---
1 ((Lung or lungs or bronchi$ or alveol$ or respiratory tract$ or pulmonar$) adj5 (Neoplas$ or cancer$ or malig$ or tumor$ or tumour$ or carcino$ or adenocarcino$ or metastas$)).mp. [mp=title, full text, keywords] (276)
2 screen$.mp. (2503)
3 ((early or earlier or earliest) adj5 (detect$ or diagnos$ or discover$ or find or finding)).mp. [mp=title, full text, keywords] (132)
4 2 or 3 (2562)
5 1 and 4 (52)

Database: EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2012>
Search Strategy:
---
1 ((Lung or lungs or bronchi$ or alveol$ or respiratory tract$ or pulmonar$) adj5 (Neoplas$ or cancer$ or malig$ or tumor$ or tumour$ or carcino$ or adenocarcino$ or metastas$)).mp. [mp=title, text, subject heading word] (416)
2 screen$.mp. (2484)
3 ((early or earlier or earliest) adj5 (detect$ or diagnos$ or discover$ or find or finding)).mp. [mp=title, text, subject heading word] (259)
4 2 or 3 (2575)
5 1 and 4 (50)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2012>
Search Strategy:
---
1 ((Lung or lungs or bronchi$ or alveol$ or respiratory tract$ or pulmonar$) adj5 (Neoplas$ or cancer$ or malig$ or tumor$ or tumour$ or carcino$ or adenocarcino$ or metastas$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (6652)
2 screen$.mp. (11379)
3 ((early or earlier or earliest) adj5 (detect$ or diagnos$ or discover$ or find or finding)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2242)
4 2 or 3 (13141)
5 1 and 4 (252)

Appendix A1. Search Strategies

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to 2012>
Search Strategy:
---
1 ((Lung or lungs or bronchi$ or alveol$ or respiratory tract$ or pulmonar$) adj5 (Neoplas$ or cancer$ or malig$ or tumor$ or tumour$ or carcino$ or adenocarcino$ or metastas$)).mp. [mp=title, abstract, full text, keywords, caption text] (227)
2 screen$.mp. (3227)
3 ((early or earlier or earliest) adj5 (detect$ or diagnos$ or discover$ or find or finding)).mp. [mp=title, abstract, full text, keywords, caption text] (527)
4 2 or 3 (3431)
5 1 and 4 (142)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to 2012>
Search Strategy:
---
1 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$)).mp. [mp=title, abstract, full text, keywords, caption text] (242)
2 ((x ray$ or radiogra$ or sputum$ or cytolog$) adj5 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. [mp=title, abstract, full text, keywords, caption text] (302)
3 1 and 2 (17)
4 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$) adj7 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. (55)
5 ((chest$ or thorax$ or thoracic$) adj5 (x-ray$ or radiogra$)).mp. [mp=title, abstract, full text, keywords, caption text] (233)
6 4 and 5 (9)
7 sputum.mp. [mp=title, abstract, full text, keywords, caption text] (221)
8 4 and 7 (5)
9 3 or 6 or 8 (23)
10 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$)).mp. [mp=title, abstract, full text, keywords, caption text] (242)
11 ((x ray$ or xray$ or radiogra$ or sputum$) adj5 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. [mp=title, abstract, full text, keywords, caption text] (260)
12 10 and 11 (11)
13 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$) adj7 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. (55)
14 ((chest$ or thorax$ or thoracic$) adj5 (x-ray$ or xray$ or radiogra$)).mp. [mp=title, abstract, full text, keywords, caption text] (236)
15 13 and 14 (9)
16 sputum.mp. [mp=title, abstract, full text, keywords, caption text] (221)
17 13 and 16 (5)
18 12 or 15 or 17 (18)

Database: EBM Reviews - Health Technology Assessment <4th Quarter 2012>
Search Strategy:
---
1 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$)).mp. [mp=title, text, subject heading word] (186)
2 ((x ray$ or radiogra$ or sputum$ or cytolog$) adj5 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. [mp=title, text, subject heading word] (52)
3 1 and 2 (3)
4 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$) adj7 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. (42)

5 ((chest$ or thorax$ or thoracic$) adj5 (x-ray$ or radiogra$)).mp. [mp=title, text, subject heading word] (19)
6 4 and 5 (8)
7 sputum.mp. [mp=title, text, subject heading word] (8)
8 4 and 7 (2)
9 3 or 6 or 8 (8)
10 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$)).mp. [mp=title, text, subject heading word] (186)
11 ((x ray$ or xray$ or radiogra$ or sputum$) adj5 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. [mp=title, text, subject heading word] (26)
12 10 and 11 (3)
13 ((lung$ or pulmonar$ or bronch$ or alveol$) adj5 (cancer$ or carcino$ or adenocarcino$ or malig$ or tumor$ or tumour$ or neopla$) adj7 (test$ or diagno$ or screen$ or find$ or found$ or discover$ or uncover$)).mp. (42)
14 ((chest$ or thorax$ or thoracic$) adj5 (x-ray$ or xray$ or radiogra$)).mp. [mp=title, text, subject heading word] (19)
15 13 and 14 (8)
16 sputum.mp. [mp=title, text, subject heading word] (8)
17 13 and 16 (2)
18 12 or 15 or 17 (8)

Intervention key questions 4 and 5:

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1946 to 2012>
Search Strategy:
---
1 exp Lung Neoplasms/su [Surgery] (21220)
2 (stag$ adj (one or "1" or I or two or "2" or II or 1a or Ia or 1b or Ib or 1c or Ic or 2a or IIa or 2b or IIb)).mp. (54937)
3 ((early or earlier or earliest) adj5 (discover$ or found or find or finding or uncover$ or diagnos$ or detect$ or stage$ or staging)).mp. (239290)
4 2 or 3 (286513)
5 1 and 4 (3023)
6 exp lung neoplasms/ (157194)
7 exp Surgical Procedures, Operative/ (2186270)
8 4 and 6 and 7 (2707)
9 5 or 8 (3945)
10 exp "Outcome and Process Assessment (Health Care)"/ (602752)
11 9 and 10 (748)
12 exp Mortality/ (249169)
13 mo.fs. (367310)
14 12 or 13 (507080)
15 9 and 14 (1650)
16 exp survival analysis/ (150994)
17 9 and 16 (823)
18 exp Postoperative Complications/ (382994)
19 exp Intraoperative Complications/ (33158)
20 18 or 19 (405151)
21 9 and 20 (291)
22 ae.fs. (1238248)
23 ((advers$ or undesir$ or unwant$) adj5 (effect$ or outcome$ or result$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (131512)
24 exp "Wounds and Injuries"/et [Etiology] (109143)
25 22 or 23 or 24 (1394472)
26 9 and 25 (490)
27 exp "Quality of Life"/ (99185)

28 exp Quality-Adjusted Life Years/ (5646)
29 27 or 28 (103891)
30 9 and 29 (49)
31 exp "Costs and Cost Analysis"/ (164677)
32 9 and 31 (34)
33 11 or 15 or 17 or 21 or 26 or 30 or 32 (2450)
34 limit 33 to yr="2000 -Current" (1725)

Appendix A2. Inclusion and Exclusion Criteria

	Include	Exclude
Population	Key questions 1–3: Asymptomatic adults (ages ≥18 years) from large screening trials and/or studies who are generalizeable to the United States Key questions 4–5: Adults (ages ≥18 years) with early (stage IA) non-small cell lung cancer who are generalizeable to the United States	Key questions 1–3: Children Symptoms of lung cancer Prior lung cancer diagnosis Key questions 4–5: Children Not primary lung cancer Greater than stage IA lung cancer
Interventions	Key questions 1–3: Chest x-ray, computed tomography, and/or sputum cytology Key questions 4–5: Surgical resection	Key questions 1–3: No screening Key questions 4–5: Chemotherapy, radiation therapy, and natural therapies
Outcomes	Reduction in morbidity and/or all-cause mortality Reduction in lung cancer mortality/morbidity 5-year and 10-year survival rates Impact on smoking cessation Detection of other abnormalities Quality of life Direct harms from screening and/or treatment interventions	Cost-effectiveness
Study types and designs	Randomized, controlled trials; systematic reviews/meta-analyses; cohorts; case-control studies; and case series Published in or after 2001	Opinions, editorials, case reports, no comparison group Key questions 1–3: Sample size less than 1000 Key questions 4–5: Sample size less than 500
Duration	Key questions 1–3: Any length of duration Key questions 4–5: At least 5 years of followup	Key questions 1–3: None Key Questions 4–5: Less than 5 years of followup

Randomized, Controlled Trials (RCTs)

Criteria:

- Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups; cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies or intention-to-treat analysis for RCTs; for cluster RCTs, correction for correlation coefficient

Definition of ratings based on above criteria:

Good: Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.

Poor: Studies will be graded "poor" if any of the following major limitations exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

Sources: Harris et al, 2001[48]

Appendix A4. List of Reviewers

Expert Reviewers

Peter B. Bach, MD, MAPP, Full Member, Director, Center for Health Policy and Outcomes, Memorial Sloan-Kettering Cancer Center

Harold Sox, MD, Associate Director for Faculty, The Dartmouth Institute, Dartmouth Medical School

David J. Ballard, MD, MSPH, PhD, FACP, Senior Vice President and Chief Quality Officer, Baylor Health Care System, Executive Director and BHCS Endowed Chair, Institute for Health Care Research and Improvement

Federal Reviewers

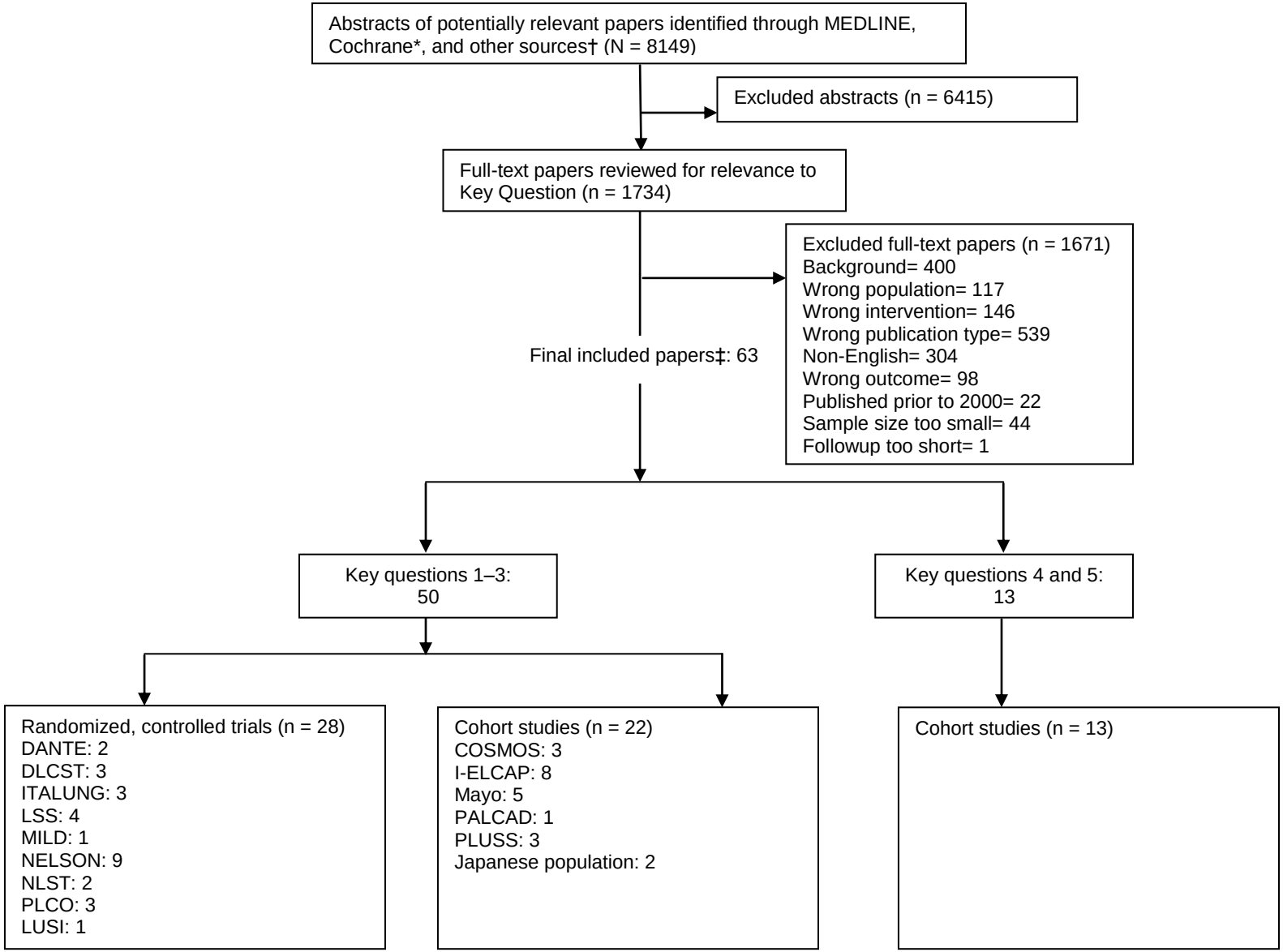
Joseph Chin, MD, Office of Clinical Standards and Quality, Centers for Medicare and Medicaid Services

Barnett Kramer, MD, MPH, Associate Director for Disease Prevention, Director Office of Medical Applications of Research, Office of Disease Prevention, Office of the Director, National Institutes of Health

Linda Kinsinger, MD, MPH, VHA, National Center for Health Promotion and Disease Prevention

Paul Pinsky, PhD, National Institutes of Health

Appendix A5. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Identified from reference lists, hand searching, and suggestions by experts.
‡Studies that provided data and contributed to the body of evidence were considered "included."

Abbreviations: COSMOS = Continuing Observation of Smoking Subjects; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; I-ELCAP = International Early Lung Cancer Action Program; LSS = Lung Screening Study; MILD = Multicentric Italian Lung Detection; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial ; PALCAD = ProActive Lung Cancer Detection; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PLUSS = Pittsburgh Lung Screening Study; SCTS = Spiral Chest Computed Tomography Study

Key to exclusion codes

2	Background
3	Wrong population
4	Wrong intervention
5	Wrong publication
6	Non-English, otherwise relevant
7	Wrong outcome
8	Conducted/Published prior to 2000
9	Followup too short
10	Sample size too small

Listing of excluded papers

Screening for lung cancer. *Med Lett Drugs Ther.* 2001;43(1109):61-62. [PMID: 11468601]
Exclusion code: 5

Smoking cessation counseling needed with spiral CT screening for lung cancer. *Oncology (Williston).* 2002;16(6):816, 839, [PMID: 12088301]
Exclusion code: 5

National Lung Screening Trial (NLST). 2002; http://clinicaltrials.gov/ct/gui/show/NCT00047385;jsessionid=20DAB829F5C5A123FB490104A003A4BA?order=1. Accessed May 23, 2011
Exclusion code: 2

Lung cancer can be diagnosed early. *Health News.* 2005;11(12):14, [PMID: 16419178]
Exclusion code: 5

Screening for cancer: colon, lung and skin cancers. *Harv. Mens Health Watch.* 2005;10(3):1-5, [PMID: 16296122]
Exclusion code: 5

Electronic nose shows promise for detecting early-stage lung cancer. *Disease Management Advisor.* 2005;11(6):71-72, 61, [PMID: 16060297]
Exclusion code: 5

Eleventh international conference on screening for lung cancer. *Clin. Imaging.* 2005;29(4):298-299, [PMID: 15967325]
Exclusion code: 5

Medicare Lung Cancer Screening Benefit Act of 2006. Shaw C, trans. 109th Congress 2006
Exclusion code: 5

Potential new options for lung cancer screening. *Disease Management Advisor.* 2007;13(6):68-70, 61, [PMID: 17595920]
Exclusion code: 2

Can lung cancer screening save lives? *Johns Hopkins Med. Lett. Health After 50.* 2007;19(2):7, [PMID: 17443995]
Exclusion code: 5

Lung cancer screening in women. Women seem to have a special vulnerability to lung cancer, whether they smoke or not. Is it time to be tested? *Harvard Women's Health Watch.* 2007;14(7):1-2, [PMID: 17393589]
Exclusion code: 5

Screening for lung cancer. *Vopr. Onkol.* 2009;55(1):7-14, [PMID: 19435192]
Exclusion code: 6

Clinical implications. *Cancer Treat. Res.* 2010;154:201-214
Exclusion code: 5

Study shows CT scans can reduce lung cancer deaths in smokers. *Mayo Clin Womens Healthsource.* 2011;15(5):3, [PMID: 21467956]
Exclusion code: 5

Why aren't you being screened for lung cancer? Research suggests CT scans may help pinpoint problems early enough to make a difference. *Johns Hopkins Med. Lett. Health After 50.* 2011;23(2):4-5, [PMID: 21523950]
Exclusion code: 5

Abe H, Ishida T, Shiraishi J, et al. Effect of temporal subtraction images on radiologists' detection of lung cancer on CT: results of the observer performance study with use of film computed tomography images. *Acad. Radiol.* 2004;11(12):1337-1343, [PMID: 15596371]
Exclusion code: 7

Abe Y, Hanai K, Nakano M, et al. A computer-aided diagnosis (CAD) system in lung cancer screening with computed tomography. *Anticancer Res.* 2005;25(1B):483-488, [PMID: 15816616]
Exclusion code: 2

Aberle DR, Brown K. Lung cancer screening with CT. *Clin. Chest Med.* 2008;29(1):1-14, v, [PMID: 18267181]
Exclusion code: 5

Aberle DR, Gamsu G, Henschke CI, Naidich DP, Swensen SJ. A consensus statement of the Society of Thoracic Radiology: screening for lung cancer with helical computed tomography. *J. Thorac. Imaging.* 2001;16(1):65-68, [PMID: 11149694]
Exclusion code: 5

ACOG Committee. ACOG committee opinion. Routine cancer screening. Number 247, December 2000. *Int. J._Gynaecol. Obstet.* 2003;82(2):241-245, [PMID: 12926412]
Exclusion code: 2

Adachi H, Maehara T. [Surgical treatment and outcome of multiple primary lung cancers]. *Kyobu Geka - Japanese Journal of Thoracic Surgery.* 2010;63(5):347-351; discussion 351-344, [PMID: 20446600]
Exclusion code: 6

Agarwal M, Brahmanday G, Chmielewski GW, Welsh RJ, Ravikrishnan KP. Age, tumor size, type of surgery, and gender predict survival in early stage (stage I and II) non-small cell lung cancer after surgical resection. *Lung Cancer.* 2010;68(3):398-402, [PMID: 19762109]
Exclusion code: 9

Ahn MI, Gleeson TG, Chan IH, et al. Perifissural nodules seen at CT screening for lung cancer. *Radiology.* 2010;254(3):949-956, [PMID: 20177105]
Exclusion code: 2

Aisner J. CT screening for lung cancer: are we ready for wide-scale application? *Clin. Cancer Res.* 2007;13(17):4951-4953, [PMID: 17785542]
Exclusion code: 5

Ak I, Sivrikoz MC, Entok E, Vardareli E. Discordant findings in patients with non-small-cell lung cancer: absolutely normal bone scans versus disseminated bone metastases on positron-emission tomography/computed tomography. *Eur. J.*

Cardiothorac. Surg. 2010;37(4):792-796, [PMID: 20015657]
Exclusion code: 4

Ak I, Stokkel MP, Pauwels EK. Positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose in oncology. Part II. The clinical value in detecting and staging primary tumours. *J. Cancer Res. Clin. Oncol.* 2000;126(10):560-574, [PMID: 11043393]
Exclusion code: 5

Akata S, Yoshimura M, Nishio R, et al. High-resolution computed tomographic findings of small peripherally located squamous cell carcinoma. *Clin. Imaging.* 2008;32(4):259-263, [PMID: 18603179]
Exclusion code: 4

Aketa A, Yamada G, Aketa K, et al. [Two younger male patients with rapidly progressing pulmonary pleomorphic carcinoma]. *Nihon Kokyuki Gakkai Zasshi.* 2004;42(2):164-169, [PMID: 15007917]
Exclusion code: 6

Akopov AL, Dvorakovskaia IV. [Vascular invasion by tumor in the absence of regional lymph node metastases in patients with locally advanced non-small cell lung cancer]. *Vopr. Onkol.* 2004;50(4):417-420, [PMID: 15605763]
Exclusion code: 6

Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. *J. Soc. Laparoendosc. Surg.* 2007;11(3):368-374, [PMID: 17931521]
Exclusion code: 5

Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest.* 2007;132(3 Suppl):29S-55S, [PMID: 17873159]
Exclusion code: 2

Alexandersson A, Jonsson S, Isaksson HJ, Gudbjartsson T. [Sublobar resection for non-small cell lung cancer in Iceland]. *Laeknabladid.* 2011;97(5):303-308, [PMID: 21586802]
Exclusion code: 6

Alexiou C, Beggs D, Onyeaka P, et al. Pneumonectomy for stage I (T1N0 and T2N0) nonsmall cell lung cancer has potent, adverse impact on survival. *Ann. Thorac. Surg.* 2003;76(4):1023-1028, [PMID: 14529978]
Exclusion code: 10

Alexiou C, Onyeaka CVP, Beggs D, et al. Do women live longer following lung resection for carcinoma? *Eur. J. Cardiothorac. Surg.* 2002;21(2):319-325, [PMID: 11825743]
Exclusion code: 3

Allen JW, Farooq A, O'Brien TF, Osarogiagbon RU. Quality of surgical resection for nonsmall cell lung cancer in a US metropolitan area. *Cancer.* 2011;117(1):134-142, [PMID: 20737568]
Exclusion code: 3

Allen MS, Darling GE, Pechet TTV, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann. Thorac. Surg.* 2006;81(3):1013-1019; discussion 1019-1020, [PMID: 16488712]
Exclusion code: 2

Altorki N, Kent M, Pasmantier M. Detection of early-stage lung cancer: computed tomographic scan or chest radiograph? *J. Thorac. Cardiovasc. Surg.*

2001;121(6):1053-1057, [PMID: 11385370]
Exclusion code: 2

Amann A, Corradi M, Mazzone P, Mutti A. Lung cancer biomarkers in exhaled breath. *Expert Rev Mol Diagn.* 2011;11(2):207-217, [PMID: 21405971]
Exclusion code: 2

Amann A, Ligor M, Ligor T, et al. Analysis of exhaled breath for screening of lung cancer patients. *Memo - Magazine of European Medical Oncology.* Vol 32010:106-112
Exclusion code: 4

Ambrose LF. Lung cancer screening. *CMAJ Canadian Medical Association Journal.* 2009;180(13):1330, [PMID: 19546459]
Exclusion code: 5

Ambrose LF, Healton CG, Idige CR. Letter regarding US Preventive Services Task Force Review of Lung Cancer Screening. In: The Honorable Kathleen Sebelius S, US Department of Health and Human Services, ed. Washington, D.C. 2012
Exclusion code: 2

Ambrose LF, Lopez TJ. Essential Health Benefits Bulletin. In: The Honorable Kathleen Sebelius S, US Department of Health and Human Services, ed. Washington, D.C. 2012
Exclusion code: 2

American Cancer Society. *Cancer Facts and Figures 2000*
Exclusion code: 2

American Cancer Society. *Cancer Facts & Figures 2010*: Atlanta;2010
Exclusion code: 2

American Cancer Society. *Cancer Facts & Figures for African Americans 2011-12.* Atlanta2011Exclusion code: 2

American Cancer Society. *Cancer Facts & Figures 2011*: Atlanta;2011
Exclusion code: 2

American Lung Association. Providing Guidance on Lung Cancer Screening To Patients and Physicians. 2012. http://www.lung.org/finding-cures/research-news/new-screening-guidelines/lung-cancer-screening.pdf. Accessed 30 Sept 2012
Exclusion code: 2

Andersen KB, Dirksen A. [Screening for lung cancer]. *Ugeskr. Laeger.* 2000;162(14):2013, [PMID: 10815513]
Exclusion code: 6

Anderson MW, Goodin C, Zhang Y, et al. Effect of dietary green tea extract and aerosolized difluoromethylornithine during lung tumor progression in A/J strain mice. *Carcinogenesis.* 2008;29(8):1594-1600, [PMID: 18515278]
Exclusion code: 3

Andrade RS, Maddaus MA. Thoracoscopic lobectomy for stage I non-small cell lung cancer. *Semin. Thorac. Cardiovasc. Surg.* 2010;22(1):14-21, [PMID: 20813312]
Exclusion code: 3

Andreas S, Gamarra F, Herth F, et al. Prevention and early detection. *Prävention und früherkennung.* 2011;34(SUPPL. 4):2-10, [PMID: 21677467]
Exclusion code: 6

Andriani F, Conte D, Mastrangelo T, et al. Detecting lung cancer in plasma with the use of multiple genetic markers. *Int. J.*

Cancer. 2004;108(1):91-96, [PMID: 14618621]
Exclusion code: 4

Andriole GL, Reding D, Hayes RB, Prorok PC, Gohagan JK, Committee PS. The prostate, lung, colon, and ovarian (PLCO) cancer screening trial: Status and promise. *Urologic Oncology.* 2004;22(4):358-361, [PMID: 15283897]
Exclusion code: 5

Anglim PP, Alonzo TA, Laird-Offringa IA. DNA methylation-based biomarkers for early detection of non-small cell lung cancer: an update. *Molecular Cancer.* 2008;7:81, [PMID: 18947422]
Exclusion code: 5

Anglim PP, Galler JS, Koss MN, et al. Identification of a panel of sensitive and specific DNA methylation markers for squamous cell lung cancer. *Mol Cancer.* 2008;7:62, [PMID: 18616821]
Exclusion code: 4

Aoki T, Tsuchida M, Watanabe T, et al. Surgical strategy for clinical stage I non-small cell lung cancer in octogenarians. *Eur. J. Cardiothorac. Surg.* 2003;23(4):446-450, [PMID: 12694757]
Exclusion code: 10

Arenberg D, Kazerooni EA. Setting up a lung cancer screening program. *Journal of the National Comprehensive Cancer Network.* 2012;10(2):277-285, [PMID: 22308520]
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Exclusion code: 5

Appendix A6. List of Excluded Full-Text Papers

Brodersen J, Thorsen H, Kreiner S. Consequences of screening in lung cancer: development and dimensionality of a questionnaire. *Value in Health.* 2010;13(5):601-612, [PMID: 20345552]
Exclusion code: 5

Brooks JD. Translational genomics: The challenge of developing cancer biomarkers. *Genome Res.* 2012;22(2):183-187, [PMID: 22301132]
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Exclusion code: 2

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Appendix A6. List of Excluded Full-Text Papers

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Cajoto IV, Prim JMG, Barcala FJG, et al. Reason for a medical visit in the diagnosis of lung cancer. A review of 481 cases. *Motivo de consulta en el diagnóstico de cáncer de pulmón. Revisión de 481 casos.* 2009;209(2):67-72, [PMID: 19798842]
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Carozzi FM, Bisanzi S, Falini P, et al. Molecular profile in body fluids in subjects enrolled in a randomised trial for lung cancer screening: Perspectives of integrated strategies for early diagnosis. *Lung Cancer.* 2010;68(2):216-221, [PMID: 19646775]
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Centre for Reviews and Dissemination. Lung cancer screening: an update for the U.S. Preventive Services Task Force (Provisional abstract): Database of Abstracts of Reviews of Effects; 2011
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Centre for Reviews and Dissemination. Systematic review of baseline low-dose CT lung cancer screening (Structured abstract): Database of Abstracts of Reviews of Effects; 2011
Exclusion code: 2

Centre for Reviews and Dissemination. A systematic review and lessons learned from early lung cancer detection trials using low-dose computed tomography of the chest (Structured abstract): Database of Abstracts of Reviews of Effects; 2011
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Chen C, Chen P, Zhang C-C, Li N, Jin Z-L, Li K. [Clinical characteristics and prognosis of large cell lung cancer]. *Chung-Hua Chung Liu Tsa Chih [Chinese Journal of Oncology]*. 2010;32(12):932-934, [PMID: 21223803]
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Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Population	Risk group	Screening comparison (In vs. Co)	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
National Lung Screening Trial (NLST)					
National Lung Screening Trial Research Team et al, 2011[54] *Reduced lung-cancer mortality with low-dose computed tomographic screening*	Ages 55 to 74 years	Current or former (quit ≤15 years ago) smoker with ≥30 pack-year smoking history	CT vs. CXR: CT: Low-dose (1.5 mSv), multidetector, ≥4 channels CXR: 1 view, PA with deep inspiration	Certified radiologists and technicians by appropriate boards Radiologists trained in image quality and standardized image acquisition NCN ≥4 mm were classified positive, suspicious for lung cancer Adenopathy, effusion could be positive, suspicious Other abnormal findings suggesting clinically important, nonlung cancer diagnosis reported Stability on year 2 scan could be classified as minor rather than positive	Results and recommendations from radiologist to subject's community provider
Lung Screening Study (LSS)					
Gohagan et al, 2004[55] *Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs. chest radiograph: the Lung Screening Study of the National Cancer Institute*	Ages 55 to 74 years	Former or current smokers ≥30 pack-years who quit <10 years prior	LDCT vs. single PA CXR examination	Encouraged via study to be evaluated Diagnostic evaluation assessed by record review	Positive = any nodule ≥4 mm (although varied with time)
Gohagan et al, 2005[74] *Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest x-ray screening for lung cancer*	Ages 55 to 74 years	Former or current smokers ≥30 pack-years who quit <10 years prior	LDCT vs. single PA CXR examination	Encouraged via study to be evaluated Diagnostic evaluation assessed by record review	Positive = any nodule ≥4 mm (although varied with time)
Pinsky et al, 2005[75] *Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen*	Ages 55 to 74 years	Former or current smokers ≥30 pack-years who quit <10 years prior	LDCT vs. single PA CXR examination	Encouraged via study to be evaluated Diagnostic evaluation assessed by record review	Positive = any nodule ≥4 mm (although varied with time)
Croswell et al, 2010[73] *Cumulative incidence of false-positive test results in lung cancer screening*	Ages 55 to 74 years	Former or current smokers ≥30 pack-years who quit <10 years prior	LDCT vs. single PA CXR examination	Encouraged via study to be evaluated Diagnostic evaluation assessed by record review	Positive = any nodule ≥4 mm (although varied with time)

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Population	Risk group	Screening comparison (In vs. Co)	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE)					
Infante et al, 2009[51] *A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial*	Screening vs. none Mean age: 64.3 vs. 64.6 years Current smoker: 56% vs. 57% Mean pack-years: 47.3 vs. 47.2 Prior cancer (considered cured): 1.0% vs. 0.6% Respiratory comorbidity: 35% vs. 31% (p=0.04)	Asymptomatic male current or former smokers with ≥20 pack-years Ages 60 to 74 years	CT vs. annual clinical review	Per study protocol: Case-by-case basis for nonsmooth ≥6 but ≤10 mm lesion that has not regressed after antibiotics on repeat imaging. PET positive nonsmooth ≥10 but ≤20 mm lesion that has not regressed with antibiotics PET positive nonsmooth lesion ≥20 mm Case-by-case for focal ground glass opacities that have not responded to antibiotics or regressed on repeat imaging	Pursued within the study via established diagnostic protocol
Danish Lung Cancer Screening Study (DLCST)					
Pedersen et al, 2009[76] *The Danish Randomized Lung Cancer CT Screening Trial—overall design and results of the prevalence round*	CT vs. control Mean age: 57.9 vs. 57.8 Mean pack-years: 36.4 vs. 35.9 Current/former smokers: 1545/507 vs. 1579/473	Healthy volunteer men and women ages 50 to 70 years Current and former smokers (<10 years and >4 weeks since smoking cessation) with ≥20 pack-years smoking history	LDCT vs. usual care	Imaging assessed and followup imaging within study	Screen-detected findings, single center affiliated with study Control group outside study, but mostly with same specialists
Saghir et al, 2012[52] *CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT*	CT vs. control Mean age: 57.9 vs. 57.8 Mean pack-years: 36.4 vs. 35.9 Current/former smokers: 1545/507 vs. 1579/473	Healthy volunteer men and women ages 50 to 70 years Current and former smokers (<10 years and >4 weeks since smoking cessation) with ≥20 pack-years smoking history	LDCT vs. usual care	All CT scans reviewed by 2 study radiologists, within study protocol	Referred to chest physicians for diagnostic evaluation at 2 lung cancer centers when HRCT, PET-CT, bronchoscopy, and/or biopsy performed In control group, lung cancer diagnosed and treated by the usual clinical practice, which mostly involved the same centers/strategies

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Population	Risk group	Screening comparison (In vs. Co)	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
Ashraf et al, 2008[62] *Smoking habits are unaffected by CT screening at 1-year follow-up in the Danish Lung Cancer Screening Trial*	CT vs. control Mean age: 57.9 vs. 57.8 Mean pack-years: 36.4 vs. 35.9 Current/former smokers: 1545/507 vs. 1579/473	Healthy volunteer men and women ages 50 to 70 years Current and former smokers (<10 years and >4 weeks since smoking cessation) with ≥20 pack-years smoking history	LDCT vs. usual care	Imaging assessed and followup imaging within study	Screen-detected findings, single center affiliated with study Control group outside study, but mostly with same specialists
ITALUNG					
Lopes Pegna et al, 2009[57] *Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT*	Mean age: 64 years (range: 55 to 69)	≥20 pack-years since the last 10 years (former smokers who quit >10 years ago excluded)	CT vs. usual care	5 SCT scanners (1 single row, 4 multirow detectors) Subsequent management per ELCAP study 3 radiologists read first reading, 15 read second	Negative study = no focal findings, <5 mm solid NCN, or <10 mm nonsolid nodule
Mascalchi et al, 2011[82] *Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT*	Mean age: 64 years (range: 55 to 69)	≥20 pack-years since the last 10 years (former smokers who quit >10 years ago excluded)	CT vs. usual care	8 SCT scanners Subsequent management per ELCAP study 3 radiologists read first reading, 15 read second	Negative study = no focal findings, <5 mm solid NCN, or <10 mm nonsolid nodule
Mascalchi et al, 2006[81] *Risk–benefit analysis of x-ray exposure associated with lung cancer screening in the ITALUNG-CT trial*	Mean age: 64 years (range: 55 to 69)	≥20 pack-years since the last 10 years (former smokers who quit >10 years ago excluded)	CT vs. usual care	Followed in study per ELCAP criteria	Negative study = no focal findings, <5 mm solid NCN, or <10 mm non-solid nodule
Multi-centric Italian Lung Detection (MILD)					
Pastorino et al, 2012[53] *Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial*	Age ≥49 years 63% to 68% male 10% former smokers Mean pack-years: 38 to 39	Smokers with a smoking history >20 pack-years or quit <10 years ago	LDCT (annual vs. biennial) vs. usual care	Volumetrics used: <60 mm^3 (4.8 mm) continue 1–2 year schedule 60–250 mm^3 (5 to 8 mm) repeat in 3 months, if <25% increase in volume, resume 1 or 2 year schedule >250 mm^3 (>8 mm) referred for evaluation, generally with PET	Volumetric followup of intermediate nodules PET scan for nodules >250 mm^3 No further description

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Population	Risk group	Screening comparison (In vs. Co)	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON)					
van Iersel et al, 2006[79] *Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON)* Xu et al, 2006[64] *Nodule management protocol of the NELSON randomised lung cancer screening trial* van den Bergh et al, 2009[78] *Informed participation in a randomised controlled trial of computed tomography screening for lung cancer* van Klaveren et al, 2009[56] *Management of lung nodules detected by volume CT scanning*	Median age: 59 years (SD 6) 16% female	Asymptomatic current or former smokers with 15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years smoking history, and if former smoker, quit ≤10 years ago Could have prior lung cancer if >5 years prior and not being treated	CT vs. no screening	Imaging assessment and followup dictated by the study using volumetric indices	Positive test: solid nodule, >500 mm^3 were referred to pulmonologist Positive test: solid, between 50 to 500 mm^3; solid, pleural-based between 5 to 10 mm in diameter, partially solid with nonsolid component >7 mm; partially solid with solid component between 50 to 500 mm^3; or nonsolid, >7 mm diameter: referred for repeat CT scan in 3 to 4 months
van den Bergh et al, 2010[77] *Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON)*	Median age: 59 years (SD 6) 16% female	Asymptomatic current or former smokers with 15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years smoking history, and if former smoker, quit ≤10 years ago Could have prior lung cancer if >5 years prior and not being treated	CT vs. no screening	Imaging assessment and followup dictated by the study using volumetric indices	Positive test: solid nodule, >500 mm^3 were referred to pulmonologist Positive test: solid, between 50 to 500 mm^3; solid, pleural-based between 5 to 10 mm in diameter, partially solid with nonsolid component >7 mm; partially solid with solid component between 50 to 500 mm^3; or nonsolid, >7 mm diameter: referred for repeat CT scan in 3 to 4 months

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Population	Risk group	Screening comparison (In vs. Co)	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
van den Bergh et al, 2011[69] *Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial*	Median age: 59 years (SD 6) 16% female	Asymptomatic current or former smokers with 15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years smoking history, and if former smoker, quit ≤10 years ago Could have prior lung cancer if >5 years prior and not being treated	CT vs. no screening	Imaging assessment and followup dictated by the study using volumetric indices	Positive test: solid nodule, >500 mm^3 were referred to pulmonologist Positive test: solid, between 50 to 500 mm^3; solid, pleural-based between 5 to 10 mm in diameter, partially solid with nonsolid component >7 mm; partially solid with solid component between 50 to 500 mm^3; or nonsolid, >7 mm diameter: referred for repeat CT scan in 3 to 4 months
Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial					
Croswell et al, 2009[73] *Cumulative incidence of false-positive results in repeated, multimodal cancer screening*	CXR vs. usual care Men: 50% vs. 50% White: 86% vs. 85% Current smokers: 10% vs. 10% Former smokers: 42% vs. 42% Never smokers: 45% vs. 44% NLST eligible: 20% vs. 21% Family history: 11% vs. 11%	Those with ≥30 pack-year smoking history; current smokers or quit <15 years ago	CXR vs. usual care	Advised to seek diagnostic evaluation which was decided outside of study; study obtained their records Participants/ health care providers notified of results and evaluation determined by patient with provider	Positive result = nodule, mass, infiltrate, or other abnormality suspicious for lung cancer
Hocking et al, 2010[84] *Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial*	CXR vs. usual care Men: 50% vs. 50% White: 86% vs. 85% Current smokers: 10% vs. 10% Former smokers: 42% vs. 42% Never smokers: 45% vs. 44% NLST eligible: 20% vs. 21% Family history: 11% vs. 11%	Those with ≥30 pack-year smoking history; current smokers or quit <15 years ago	CXR vs. usual care	Advised to seek diagnostic evaluation which was decided outside of study; study obtained their records Participants/ health care providers notified of results and evaluation determined by patient with provider	Positive result = nodule, mass, infiltrate, or other abnormality suspicious for lung cancer

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
National Lung Screening Trial (NLST)					
National Lung Screening Trial Research Team et al, 2011[54] *Reduced lung-cancer mortality with low-dose computed tomographic screening*	Asymptomatic men and women ages 55 to 74 years with ≥30 pack-year smoking history and if former smoker quit ≤15 years ago	Hemoptysis or unexplained >15 lb weight loss in preceding year, chest CT within 18 months	Number approached: NR Number eligible: NR Number enrolled: 53,454 (26,722 vs. 26,732)	United States Multicenter (10 LSS centers and 23 ACRIN centers)	NCI
Lung Screening Study (LSS)					
Gohagan et al, 2004[55] *Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs. chest radiograph: the Lung Screening Study of the National Cancer Institute*	Men and women ages 55 to 74 years with ≥30 pack-year smoking history and quit during <10 years	Prior lung cancer, prior lung surgery, prior chest CT ≤2 years, current treatment for any cancer (other than nonmelanoma skin cancer), participation in another lung cancer screening trial	Number approached: 653,417 Number eligible: 4828 Number enrolled: 3318 (1660 vs. 1658)	6 centers in United States	NCI
Gohagan et al, 2005[74] *Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest x-ray screening for lung cancer*	Men and women ages 55 to 74 years with ≥30 pack-year smoking history and quit during <10 years	Prior lung cancer, prior lung surgery, prior chest CT ≤2 years, current treatment for any cancer (other than nonmelanoma skin cancer), participation in another lung cancer screening trial	Number approached: 653,417 Number eligible: 4828 Number enrolled: 3318 (1660 vs. 1658) Number at 1 year: 2715 (1398 vs. 1317)	6 centers in United States	NCI
Pinsky et al, 2005[75] *Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen*	Men and women ages 55 to 74 years with ≥30 pack-year smoking history and quit during <10 years	Prior lung cancer, prior lung surgery, prior chest CT ≤2 years, current treatment for any cancer (other than nonmelanoma skin cancer), participation in another lung cancer screening trial	Number approached: 653,417 Number eligible: 4828 Number enrolled: 3318 (1660 vs. 1658) Number at 1 year: 2715 (1398 vs. 1317)	6 centers in United States	NCI

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Croswell et al, 2010[73] *Cumulative incidence of false-positive test results in lung cancer screening*	Men and women ages 55 to 74 years with ≥30 pack-year smoking history and quit during <10 years	Prior lung cancer, prior lung surgery, prior chest CT ≤2 years, current treatment for any cancer (other than nonmelanoma skin cancer), participation in another lung cancer screening trial	Number approached: 653,417 Number eligible: 4828 Number enrolled: 3318 (1660 vs. 1658) Number analyzed: 3190 (1610 vs. 1580)	6 centers in United States	NCI
Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE)					
Infante et al, 2009[51] *A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial*	Male current or former smokers with a history of ≥20 pack-years and ages 60 to 74 years	Comorbid conditions carrying a life expectancy of <5 years, a history of previous malignancy treated within 10 years before accrual (exceptions allowed for early laryngeal cancer and nonmelanoma skin cancer if 5-year disease free interval met), or if unable to comply with the followup protocol for any reason	Number approached: 2811 (1403 vs. 1408) Number enrolled: 2472 patients (1276 vs. 196)	Italy, 3 hospitals from same hospital network	Italian Association for the Fight Against Cancer (donations from benefactors and charities directed at financing the study)
Danish Lung Cancer Screening Study (DLCST)					
Pedersen et al, 2009[76] *The Danish Randomized Lung Cancer CT Screening Trial—overall design and results of the prevalence round*	Current or former smokers with history of ≥20 pack-years, ages 50 to 70 years Former smokers who quit smoking after age 50 years and <10 years ago, able to climb 2 flights of stairs without pausing, PFT baseline forced expiratory volume-1 was ≥30% of predicted normal	Body weight >130 kg; previous treatment for lung cancer, breast cancer, malignant melanoma, or hypernephroma; history of any other cancer within previous 5 years; tuberculosis within 2 years; any other serious illness that would shorten life expectancy to <10 years	Number approached: 5861 Number eligible: NR Number enrolled: 4104 (2052 vs. 2052)	Denmark, single site University Hospital, enrolled from October 2004 to March 2006	Danish Ministry of Interior and Health
Saghir et al, 2012[52] *CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT*	Current or former smokers with history of ≥20 pack-years, ages 50 to 70 years Former smokers who quit smoking after age 50 years and <10 years ago, able to climb 2 flights of stairs without pausing, PFT baseline forced expiratory volume-1 was ≥30% of predicted normal	Body weight >130 kg; previous treatment for lung cancer, breast cancer, malignant melanoma, or hypernephroma; history of any other cancer within previous 5 years; tuberculosis within 2 years; any other serious illness that would shorten life expectancy to <10 years	Number approached: 5861 Number eligible: NR Number enrolled: 4104 (2052 vs. 2052)	Denmark, single site University Hospital, enrolled from October 2004 to March 2006	Danish Ministry of Interior and Health

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Ashraf et al, 2008[62] *Smoking habits are unaffected by CT screening at 1-year follow-up in the Danish Lung Cancer Screening Trial*	Current or former smokers with history of ≥20 pack-years, ages 50 to 70 years Former smokers who quit smoking after age 50 years and <10 years ago, able to climb 2 flights of stairs without pausing, PFT baseline forced expiratory volume-1 was ≥30% of predicted normal	Body weight >130 kg; previous treatment for lung cancer, breast cancer, malignant melanoma, or hypernephroma; history of any other cancer within previous 5 years; tuberculosis within 2 years; any other serious illness that would shorten life expectancy to <10 years	Number approached: 5861 Number eligible: NR Number enrolled: 4104 (2052 vs. 2052)	Denmark, single site University Hospital, enrolled from October 2004 to March 2006	Government grant
ITALUNG					
Lopes Pegna et al, 2009[57] *Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT*	≥20 pack-years since the last 10 years	History of cancer and inability to tolerate lung cancer resection surgery, former smokers who quit >10 years ago	Number approached: 71,232 Number eligible: NR Number enrolled: 1613 (1406 vs. 1593)	Italy, general population	Regional Health Public Authority
Mascalchi et al, 2011[82] *Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT*	≥20 pack-years since the last 10 years	History of cancer and inability to tolerate lung cancer resection surgery, former smokers who quit >10 years ago	Number approached: 71,232 Number eligible: NR Number enrolled: 1613 (1406 vs. 1593)	Italy, general population	Regional Health Public Authority
Mascalchi et al, 2006[81] *Risk–benefit analysis of x-ray exposure associated with lung cancer screening in the ITALUNG-CT trial*	≥20 pack-years since the last 10 years	History of cancer and inability to tolerate lung cancer resection surgery, former smokers who quit >10 years ago	Number approached: NR Number eligible: NR Number analyzed: 60 (210 CT scans)	Italy, general population	Health Department of the Region of Tuscany, Italian League Against Tumors, and the Ministry of Education, Universities, and Research
Multi-centric Italian Lung Detection (MILD)					
Pastorino et al, 2012[53] *Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial*	Smokers ages ≥49 years with ≥20 pack-year smoking history or if former smoker quit <10 years ago	History of cancer in past 5 years	Number approached: NR Number eligible: NR Number enrolled: 4099 (1190 vs. 1186 vs. 1723)	Single institution, Milan	Foundations and Ministry of Health

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON)					
van Iersel et al, 2006[79] *Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON)* Xu et al, 2006[64] *Nodule management protocol of the NELSON randomised lung cancer screening trial* van den Bergh et al, 2009[78] *Informed participation in a randomised controlled trial of computed tomography screening for lung cancer* van Klaveren et al, 2009[56] *Management of lung nodules detected by volume CT scanning*	Men born between 1928 and 1956 who smoked >15 cigarettes/day during >25 years or smoked >10 cigarettes/day during >30 years, current or former smokers who quit smoking ≤10 years ago	Moderate or bad self-reported health who were unable to climb 2 flights of stairs; body weight ≥140 kg; current or past renal cancer, melanoma, or breast cancer; lung cancer diagnosed <5 years ago or ≥5 years ago but still under treatment; chest CT examination <1 year before starting study	Number approached: 548,489 Number eligible: NR Number enrolled: 15,822 (7907 vs. 7915)	Belgium, the Netherlands, Denmark	Netherlands Organisation of Health Research and Development, Dutch Cancer Society, Health Insurance Innovation Foundation, Siemens Germany, Roche Diagnostics, G. Ph. Verhagen Stichting, Rotterdam Oncologic Thoracic Study Group, Erasmus Trust Fund, Stichting tegen Kanker, Vlaamse Liga tegen Kanker, and LOGO Leuven
van den Bergh et al, 2010[77] *Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON)*	Men born between 1928 and 1956 who smoked >15 cigarettes/day during >25 years or smoked >10 cigarettes/day during >30 years, current or former smokers who quit smoking ≤10 years ago Consecutive sample of 733 patients in CT group sent surveys on health related quality of life	Moderate or bad self-reported health who were unable to climb 2 flights of stairs; body weight ≥140 kg; current or past renal cancer, melanoma, or breast cancer; lung cancer diagnosed <5 years ago or ≥5 years ago but still under treatment; chest CT examination <1 year before starting study	Number approached:692 sent 1st survey, 685 sent 2nd survey, 667 sent 3rd survey, 684 sent 4th survey Number eligible: NR Number analyzed: 630 returned 1st survey, 641 returned 2nd survey, 620 returned 3rd survey, 600 returned 4th survey	The Netherlands/ Belgium	Netherlands Organisation of Health Research and Development, Dutch Cancer Society, Health Insurance Innovation Foundation, Siemens Germany, Roche Diagnostics, G. Ph. Verhagen Stichting, Rotterdam Oncologic Thoracic Study Group, Erasmus Trust Fund, Stichting tegen Kanker, Vlaamse Liga tegen Kanker, and

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
					LOGO Leuven
van den Bergh et al, 2011[69] *Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial*	Men born between 1928 and 1956 who smoked >15 cigarettes/day during >25 years or smoked >10 cigarettes/day during >30 years, current or former smokers who quit smoking ≤10 years ago Consecutive sample of 733 patients in CT group sent surveys on health related quality of life	Moderate or bad self-reported health who were unable to climb 2 flights of stairs; body weight ≥140 kg; current or past renal cancer, melanoma, or breast cancer; lung cancer diagnosed <5 years ago or ≥5 years ago but still under treatment; chest CT examination <1 year before starting study	Number approached: 1466 sent 1st survey, 684 sent 2nd survey, 1180 sent 3rd survey, 684 sent 4th survey Number eligible: NR Number analyzed:1288 returned 1st survey (90% vs. 86%), 600 returned 2nd survey, 931 returned 3rd survey (89% vs. 65%),600 returned 4th survey	The Netherlands/ Belgium	Netherlands Organisation of Health Research and Development, Dutch Cancer Society, Health Insurance Innovation Foundation, Siemens Germany, Roche Diagnostics, G. Ph. Verhagen Stichting, Rotterdam Oncologic Thoracic Study Group, Erasmus Trust Fund, Stichting tegen Kanker, Vlaamse Liga tegen Kanker, and LOGO Leuven
Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial					
Croswell et al, 2009[73] *Cumulative incidence of false-positive results in repeated, multimodal cancer screening*	Men and women ages 55 to 74 years, eligible for NLST	History of a PLCO cancer, prior pneumonectomy, current cancer treatment	Number approached: NR Number eligible: NR Number enrolled: 154,901 (77,445 vs. 77,456) Number with false-positives in intervention: 11,851 (6320 men and 5531 women)	10 centers	NCI

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Hocking et al, 2010[84] *Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial*	Men and women ages 55 to 74 years, eligible for NLST	History of a PLCO cancer, prior pneumonectomy, current cancer treatment	Number approached: NR Number eligible: NR Number enrolled: 154,901 (77,445 vs. 77,456) Number with false-positives in intervention: 11,851 (6320 men and 5531 women)	10 centers	NCI

Author, year, title	Results		Sensitivity
	Intervention	Control	
National Lung Screening Trial (NLST)			
National Lung Screening Trial Research Team et al, 2011[54] *Reduced lung-cancer mortality with low-dose computed tomographic screening*	Lung cancer mortality: 356 (247/100,000 py); RR, 20% (95% CI, 6.8 to 27%) Overall mortality: 1877; RR, 6.7% (95% CI, 1.2 to 14%) Adherence to screening: 95% Positive screen (T0, T1, T2, total patients): 27%, 28%, 17%, 39% Incidence: 1060 (645/100,000 py)	Lung cancer mortality: 443 (309/100,000 py) Overall mortality: 1998 Adherence to screening: 93% Positive screen (T0, T1, T2, total patients): 9.2%, 6.2%, 5.0%, 16% Incidence: 941 (572/100,000 py)	NR
Lung Screening Study (LSS)			
Gohagan et al, 2004[55] *Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs. chest radiograph: the Lung Screening Study of the National Cancer Institute*	Positive: 325/1586 Any procedure: 309 Clinical evaluation: 244 Comparison with prior: 155 Chest CT: 232 CXR: 92 PFT: 73 Any invasive procedure: 53 Lung cancer: 30 Lung cancer incidence: 1.9% Stage I: 16 (53%) Stage IV: 3 (10%) Adenocarcinoma: 19 (63%)	Positive: 152/1550 Any procedure: 140 Clinical evaluation: 71 Comparison with prior: 71 Chest CT: 76 CXR: 68 PFT: 20 Any invasive procedure: 15 Lung cancer: 7 Lung cancer incidence: 0.5% Stage I: 6 (86%) Stage IV: 0 Adenocarcinoma: 3 (43%)	Baseline: PPV CXR or CT: 9.2% CT: 30 lung cancers and 325 positive exams CXR: 7 lung cancers and 152 positive exams Sensitivity: NR at baseline

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Results		Sensitivity
	Intervention	Control	
Gohagan et al, 2005[74] *Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest x-ray screening for lung cancer*	Year 1 results: Positive: 360 Followup status known: 351 Any procedure: 332 Comparison with prior imaging: 231 CXR: 64 Chest CT: 140 PFT: 70 Bronchoscopy: 14 Biopsy/resection: 18 Lung cancer: 8 (0.6%) Cumulative results: Positive: 35% Screen-detected lung cancer: 38/40 (2 interval cancer) Stage I: 48%	Year 1 results: Positive: 115 Followup status known: 111 Any procedure: 101 Comparison with prior imaging: 57 CXR: 45 Chest CT: 55 PFT: 14 Bronchoscopy: 8 Biopsy/resection: 10 Lung cancer: 9 (0.7%) Cumulative results: Positive: 16% Screen-detected lung cancer: 16/20 (4 interval cancer) Stage I: 40%	NR
Pinsky et al, 2005[75] *Diagnostic procedures after a positive spiral computed tomography lung carcinoma screen*	After 1st positive screen (n=522) <u>Highest level procedure</u> Biopsy/resection: 63 (12%) Invasive procedure without resection: 5 (1%) Chest CT: 287 (55%) Other (PET/MRI): 10 (2%) PFT/sputum cytology: 31 (6%) CXR: 26 (5%) Comparison with other imaging: 63 (12%) Clinical exam: 21 (4%) No evaluation: 16 (3%) <u>Findings</u> Lung cancer: 37 Other lung diseases: 114 COPD/emphysema: 59 Pulmonary fibrosis: 31 Renal cancer: 1	NR	NR
Croswell et al, 2010[73] *Cumulative incidence of false-positive test results in lung cancer screening*	Received ≥1 false-positive: 506 (31%) Baseline risk false-positive: 21% 1st incident screen false-positive: 33%	Received ≥1 false-positive: 216 (14%) Baseline risk false-positive: 9% 1st incident screen false-positive: 15% Baseline false-negative: 4	NR

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Results		Sensitivity
	Intervention	Control	
Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE)			
Infante et al, 2009[51] *A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial*	All-cause mortality: 46 (3.6%) Lung cancer mortality: 20 (1.6%) Other mortality causes: 26 (2.0%) Patients with lung cancers: 60 (4.7%) Total number of lung cancers: 63 (4.9%) Stage IA: 20 (1.6%) All stage I: 33 (2.6%) Stage II: 4 (0.3%) Stage IIIA: 7 (0.6%) Stage IIIB: 6 (0.5%) Stage IV: 11 (0.9%) Any abnormality on CT or CXR: 351 (28%) Additional CT: 199 (16%) Diagnostic PET: 57 (4.5%) Any investigation: 226 (18%) Any invasive procedure: 96 (7.5%) Histology: 6 (0.5%) Small cell: 57 (4.4%)	All-cause mortality: 45 (3.8%) p=0.83 Lung cancer mortality: 20 (1.7%) p=0.84 Other mortality causes: 25 (2.1%) p=0.93 Patients with lung cancers: 34 (2.8%) p=0.02 Total number of lung cancers: 36 (3.0%) Stage IA: 4 (0.3%) All stage I: 12 (1.0%) p=0.004 Stage II: 2 (0.2%) Stage IIIA: 4 (0.3%) Stage IIIB: 3 (0.3%) Stage IV: 14 (1.2%) Any abnormality on CT or CXR: 22 (1.8%) Additional CT: 4 (0.3%) Diagnostic PET: 153 (13%) p=0.001 Any investigation: 36 (3.0%) p<0.0001 Any invasive procedure: 2 (0.2%) Histology: 34 (2.8%) Small cell: NR	NR
Danish Lung Cancer Screening Study (DLCST)			
Pedersen et al, 2009[76] *The Danish Randomized Lung Cancer CT Screening Trial—overall design and results of the prevalence round*	Prevalence round LDCT	NR	NR in study 189/2052 (9.2%) with study requiring followup 17 cases of lung cancer detected 7.9% false-positive
Saghir et al, 2012[52] *CT screening for lung cancer brings forward early disease. The randomised Danish Lung Cancer Screening Trial: status after five annual screening rounds with low-dose CT*	<u>Overall</u> 69 lung cancers 3 small cell 66 NSCLC 44 stage I or II 21 stage III or IV 53 pathologically identified within 1 year of CT first seen on 1 interval cancer Deaths: 61 (3.0%) Lung cancer death: 15 (0.7%) <u>All 5 rounds</u> 1029 nodules 560 baseline 469 incidence 611 individuals with nodules/5 years 198 (of 9800 scans) referred for diagnostic evaluation 7 VATS benign Baseline false-positive rate: 7.9%	24 lung cancers 6 extensive SCLC 17 NSCLC 8 stage I or II 16 stage III or IV Deaths: 42 (2.1%); p=0.059 Lung cancer death: 11 (0.5%); p=0.42	NR 1 interval cancer diagnosed after 3rd incidence screen

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Results		Sensitivity
	Intervention	Control	
	Annual false-positive rate range: 1.6% to 2.0%		
Ashraf et al, 2008[62] *Smoking habits are unaffected by CT screening at 1-year follow-up in the Danish Lung Cancer Screening Trial*	Quit rate: 174/1545 Relapse rate: 85/507	Quit rate: 165/1579 Relapse rate: 98/473	NR
ITALUNG			
Lopes Pegna et al, 2009[57] *Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT*	639 nodules in 426 subjects 366 followup CT, 4/5 with increased nodule size had PET 59 had PET, bronchus in 18 16 FNA biopsy in 15 subjects 12 FNA biopsy positive for lung cancer, 2 indeterminate (later lung cancer), 1 benign 20 with lung cancer, 1 with 2 primary NSCLC: 86%; 10 stage I, 8 stage IA 17 cancer in 16 subjects surgically resected; 1 resection for a benign lesion 16 had cancer after baseline screen 5 had cancer after 1 year followup	NR	NR
Mascalchi et al, 2011[82] *Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT*	1406 baseline CT 3924 annual screen CT 990 followup CT for 6320 total 879 of 6320 scans on single-detector 95 PETs for 90 patients 59 suspicious nodules at baseline, 36 during annual screen 38 CT-guided biopsies in 34 patients Mean collective effective dose: 8.75 Sv to 9.36 Sv Mean effective dose per patient over 4 years: 6.2 mSv to 6.8 mSv Mean number of radiation-induced cancers: 0.12 to 0.33 per 1000 patients (0.12 to 0.13 per 1000 men; 0.31 to 0.33 per 1000 women)	NR	NR
Mascalchi et al, 2006[81] *Risk–benefit analysis of x-ray exposure associated with lung cancer screening in the ITALUNG-CT trial*	Actual radiation dose: Multidetector CT: 0.49 mSv/year Single-slice CT: 1.9 mSv/year Projected radiation dose in full ITALUNG (assumed 10% of subjects would have indeterminate nodules): Multidetector CT: 0.83 mSv/year Single-slice CT: 1.78 mSv/year Lung cancer risk from radiation: Multidetector CT: 11.7/100,000 Single-slice CT: 24.9/100,000	NR	NA

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Results		Sensitivity
	Intervention	Control	
Multi-centric Italian Lung Detection (MILD)			
Pastorino et al, 2012[53] *Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial*	Positive baseline CT: 177 vs. 158 Recall rates: 14% vs. 15% Lung cancer incidence: 34 (662/100,000 py) vs. 25 (457/100,000 py) Stage IA lung cancer: 59% vs. 55% Stage IV lung cancer: 17% vs. 15%	Lung cancer incidence: 20 (216/100,000 py) Stage IA lung cancer: NR Stage IV lung cancer: NR	NR
Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON)			
van Iersel et al, 2006[79] *Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON)* Xu et al, 2006[64] *Nodule management protocol of the NELSON randomised lung cancer screening trial* van den Bergh et al, 2009[78] *Informed participation in a randomised controlled trial of computed tomography screening for lung cancer* van Klaveren et al, 2009[56] *Management of lung nodules detected by volume CT scanning*	Overall 127 (1.6%) diagnosed with lung cancer 3 with interval diagnosis between round 1 and 2 <u>Round 1</u> Negative scan: 5987 (79%) Indeterminate scan: 1451 (19%) Positive scan: 119 (1.6%) Total positive after followup imaging: 196 (2.6%) 70 (35%) with diagnosis of lung cancer <u>Round 2</u> Negative scan: 6719 (92%) Indeterminate scan: 480 (6.6%) Positive scan: 90 (1.2%) Total positive after followup imaging: 128 (1.8%) 54 (42%) with diagnosis of lung cancer <u>Combining both rounds</u> Positive scan: 209 (2.7 %)	NR	For diagnosis of lung cancer Round 1: 95% (95% CI, 87 to 98) Round 2: 96% (95% CI, 87 to 99)
van den Bergh et al, 2010[77] *Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON)*	Mean scores (total, negative result, indeterminate) <u>HRQOL: SF-12 T0 vs. T3</u> SF-12 PCS: 49.5 vs. 50.0 Neg: 49.7 vs. 50.3 Ind: 48.5 vs. 48.9 SF-12 MCS: 51.9 vs. 51.6 Neg: 51.9 vs. 51.6 Ind: 51.8 vs. 51.9 <u>EuroQOL (EQ)-5D T0 vs. T1 vs. T2 vs. T3</u> EQ-5D: 79.3 vs. 78.3 vs. 79.1 vs. 78.4 Neg: 79.4 vs. 78.7 vs. 79.4 vs. 79.2 Ind: 79.1 vs. 76.8 vs. 78.3 vs. 75.0 <u>STAI-6</u> STAI-6: 33.2 vs. 34.6 vs. 32.7 vs. 33.0	NR	NR

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Results		Sensitivity
	Intervention	Control	
	Neg: 33.1 vs. 34.4 vs. 32.5 vs. 32.6 Ind: 33.6 vs. 35.2 vs. 33.5 vs. 34.8 IES IES-D: 4.2 vs. 5.9 vs. 4.5 vs. 3.6 Neg: 4.1 vs. 5.8 vs. 4.5 vs. 2.4 Ind: 4.5 vs. 6.3 vs. 4.9 vs. 8.3		
van den Bergh et al, 2011[69] *Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial*	At T0 and T2 no significant differences in HRQOL scores over time between groups or between the indeterminate or negative 2nd-round screening. There was a temporary increase in IES scores after an indeterminate baseline result: T0: mean 4.0 (95% CI, 2.8 to 5.3) T1: mean 7.8 (95% CI, 6.5 to 9.0) T2: mean 4.5 (95% CI, 3.3 to 5.8) At 2-year followup, the HRQOL of screened subjects was similar to that of control subjects, the unfavorable short-term effects of an indeterminate baseline screening result had resolved, and an indeterminate result at the 2nd screening round had no impact on HRQOL	NR	NR
Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial			
Croswell et al, 2009[73] *Cumulative incidence of false-positive results in repeated, multimodal cancer screening*	Cumulative incidence-false positive (men vs. women) Underwent repeated screening: 3216 vs. 2907 Underwent other imaging: 1466 vs. 1498 Underwent minimally invasive procedure: 52 vs. 56 Underwent moderately invasive procedure: 77 vs. 93 Underwent major surgical procedure: 35 vs. 40 Cumulative risk false-positive after 4 screens: 22% vs. 22%	NR	NR
Hocking et al, 2010[84] *Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial*	Positive scans: 7.5% Lung cancer diagnosis: 306 (284 NSCLC) 147 interval 62 among nonscreened PPV: 1.7%	NR	Calculated: 66% for NSCLC

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

Author, year, title	Results		Sensitivity
	Intervention	Control	
National Lung Screening Trial Research Team et al, 2011[54] *Reduced lung-cancer mortality with low-dose computed tomographic screening*	Positive CXRs: Baseline: 8.9% Round 1: 7.1% Round 2: 6.6% Round 3: 7.0% Cumulative lung cancer: 7.5% Lung cancer incidence: 20.1/10,000 py Screening period # lung cancer: 505 (307 screen-detected) Interval: 198 (39%) Lung cancer never screened: 193 (during screening period) 13 years followup: 1696 cancers (307 screen-detected) Lung cancers diagnosed after screening ended: 998 Stage I: 32% Stage III or IV: 373/1696 (22%) Cumulative death: 1213 Cumulative incidence: 14/100,000 py Lung cancer mortality: RR, 0.99 (95% CI, 0.87 to 1.22) Lung cancer mortality women: RR, 0.92 (95% CI, 0.81 to 1.06) Lung cancer mortality men: RR, 1.02 (95% CI, 0.92 to 1.13) RR late-stage lung cancer after 6 years: 0.88 (95% CI, 0.78 to 0.99) RR late-stage lung cancer after 7 years: 0.94 (95% CI, 0.84 to 1.05) Other deaths: 12% <u>Among the NLST eligible group</u> RR lung cancer: 1.0 (95% CI, 0.89 to 1.13) RR lung cancer death: 0.94 (95% CI, 0.81 to 1.10) <u>Restricting analysis to lung cancer diagnosis within 6 years of screening</u> Lung cancer mortality: RR, 0.89 (95% CI, 0.80 to 1.00) Lung cancer: 518 Lung cancer deaths: 316 Cumulative incidence lung cancer: 606/100,000 py Cumulative lung cancer mortality: 361/100,000 py	Lung cancer incidence: 19.2/10,000 py Stage I: 27% Stage III or IV: 895/1620 (55%) Cumulative death: 1230 Cumulative lung cancer mortality: 14.2/100,000 py Other deaths: 12% Lung cancer: 520 Lung cancer deaths: 334 Cumulative incidence lung cancer: 608/100,000 py Cumulative lung cancer mortality: 383/100,000 py	307/505 during screening period

Abbreviations: ACRIN = American College of Radiology Imaging Network; ARDS = acute respiratory distress syndrome; CI = confidence interval; Co = control group; COPD = chronic obstructive pulmonary disease; CT = computed tomography; CXR = chest x-ray; DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; DVT = deep venous thrombosis; EBUS = endobronchial ultrasound; ELCAP = Early Lung Cancer Action Program; EUS = endoscopic ultrasound; FNA = fine needle aspiration; HRCT = high-resolution computed tomography; HRQOL = health-related quality of life; IES = Impact of Event Scale; In = intervention; LDCT = low-dose computed tomography; LSS = Lung Screening Study; MCS = Mental Health Composite Score; MILD = Multi-centric Italian Lung Detection; MRI = magnetic resonance imaging; NA = not applicable; NCI = National Cancer Institute; NCN = noncalcified nodule; NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek; NLST = National Lung Screening Trial; NSCLC = non-small cell lung cancer; NR = not reported; PA = posteranterior; PCS = Physical Health Composite Scores;

Appendix B1. Evidence Table of Included Randomized, Controlled Trials

PET = positron emission tomography; PFT = pulmonary function testing; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PPV = positive predictive value; py = person-years; RR = relative risk; SCLC = small-cell lung cancer; SCT = spiral computed tomography; SD = standard deviation; SF-12 = 12-item Health Survey; STAI = Spielberger State-Trait Anxiety Inventory; sV = short volume; VATS = video-assisted thoracic surgery

Appendix B2. Quality Rating Table of Included Studies

Study	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Maintain Comparable Groups?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
NLST[54]	Yes	Yes	Yes	Yes	Yes	Mortality outcome: Yes Incidence outcome: No	NR
DANTE[51]	Yes	Unclear, allocation concealment reported but participants randomized during phone interview	No, 35% with pulmonary problems in LDCT and 31% in controls	No, nearly twice the dropout rate in the controls vs. LDCT (166 vs. 91)	Yes	Unclear	NR
DLCST[76, 52]	Yes	Unclear	Yes	Yes	Yes	Unclear	NR
MILD[53]	Probably not	Yes	No; more obstructive pulmonary disease among LDCT compared with controls (81% vs. 72%), more current smokers in the control groups (90% vs. 68%), fewer former smokers in the LDCT group compared with controls (31% vs. 10%)	Not comparable	Yes	Mortality outcome: Yes Incidence outcome: No	NR
PLCO[59]	Yes	Unclear	Yes	Unclear	Yes	Mortality outcome: Yes Incidence outcome: Unclear	No
Mayo[87]	Yes	Unclear	Unclear	Unclear	Yes	No	No

Study	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to followup: differential/high	Intention-to-screen analysis	Post-randomization exclusions	Outcomes prespecified	Funding source	External validity	Quality Rating
NLST[54]	No	Yes	No	Yes	Yes	Yes	NIH	Good	Good
DANTE[51]	No	Yes	Less followup in controls (31.5 months in controls vs. 35.7 months in LDCT group)	Yes	No	Yes	Italian Association for the Fight Against Cancer	Fair (only men)	Fair
DLCST[76, 52]	No	Yes	Study reports less complete followup among controls	Yes	No	Yes	Government grant	Good	Fair
MILD[53]	No	Yes	Significant differences in followup time (44.9 months in controls vs. 56 months in LDCT group)	Yes	No	Yes	Italian Association for Cancer Research; Italian Ministry of Health, the Lombardy Region; and the Cariplo Foundation	Good	Poor
PLCO[59]	No	Yes	No	Yes	Yes	Yes	NCI	Good	Good
Mayo[87]	No	Yes	No	Yes	No	Yes	NCI and Mayo Clinic	Good	Fair

Abbreviations: DANTE = Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays; DLCST = Danish Lung Cancer Screening Trial; LDCT = low-dose computed tomography; LSS = Lung Screening Study; MILD = Multi-centric Italian Lung Detection; NCI = National Cancer Institute; NIH = National Institutes of Health; NLST = National Lung Screening Trial; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Population	Risk Group	Screening intervention	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
Continuing Observation of Smoking Subjects (COSMOS)					
Veronesi et al, 2008[96] *Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program*	Median pack-years: 44 Mean age: 57.7 years 64% men 80% current smokers	Smoking history ≥20 pack-years, if former smoker quit <10 years ago	LDCT High speed multirow detector or 16 slice	Within the study	Within the study: Nodules ≥5 mm repeat CT 1 year Nodules ≥5 to 8 mm repeat CT 3 to 6 months Nodules ≥8 mm or growing CT-PET Nodules growing or CT-PET positive biopsy
Veronesi et al, 2008[91] *Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules*	Median pack-years: 44 Mean age: 57.7 years 64% men 80% current smokers	Smoking history ≥20 pack-years, if former smoker quit <10 years ago	LDCT High speed multirow detector or 16 slice	Within the study	Within the study: Nodules ≥5 mm repeat CT 1 year Nodules ≥5 to 8 mm repeat CT 3 to 6 months Nodules ≥8 mm or growing CT-PET Nodules growing or CT-PET positive biopsy
Japan Studies					
Toyoda et al, 2008[89] *Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography*	NR	Cohort includes anyone with ≥1 LDCT	LDCT vs. CXR	Individuals with positive studies asked to followup at Osaka Medical Center	Participants with positive studies asked to undergo further evaluation at Osaka Medical Center and all patients with positive CXR were asked to undergo CT
Tsushima et al, 2008[90] *Radiological diagnosis of small pulmonary nodules detected on low-dose screening computed tomography*	Mean age: 51 years 39% female	High-risk men (70% ever smokers) and medium-risk women (11% ever smokers)	LDCT multislice	Within study	Within study
International Early Lung Cancer Action Program (I-ELCAP)					
Henschke et al, 2004[88] *CT screening for lung cancer: assessing a regimen's diagnostic performance*	ELCAP 1: 46% women ELCAP 2: Median age: 59 years 52% women Median pack-years: 32	ELCAP 1 ≥10 pack-years high-risk ELCAP 2 ≥1 pack-year	CXR in ELCAP 1	Most in screening center	Most in screening center
Henschke et al, 2006[31] I-ELCAP Investigators *Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer*	Median age: 67 years Median pack-years: 47	Asymptomatic current or former smokers, not otherwise described	Baseline and repeat LDCT	Protocol specified a diagnostic approach Indications for biopsy: Tumor growth Positive PET Nodules ≥15 mm Antibiotics 1 month out No response to CT	ELCAP protocol: specified a common regimen of screening. The definition of positive and the diagnostic evaluation differed for the baseline and annual screening. Evaluations conducted in each study center and recommendations for diagnostic workup were made to the participant and the referring physician.

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Population	Risk Group	Screening intervention	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
Henschke et al, 2006[167] I-ELCAP Investigators *Survival of patients with stage I lung cancer detected on CT screening*	Median age: 61 years Median pack-years: 30	History of smoking or occupational exposure with increased risk or secondhand smoke	Baseline plus annual LDCT	Recommendations made to community physicians	For baseline screen: a positive result defined as identifying ≥1 solid or partially solid nodule ≥5 mm; ≥1 nonsolid NCN ≥8 mm or solid endobronchial nodule For annual screens: positive result was any new NCN
Shemesh et al, 2006[168] *Frequency of coronary artery calcification on low-dose computed tomography screening for lung cancer*	ELCAP population, otherwise not described	High risk smokers	CXR	Most in screening center	Most in screening center
Menezes et al, 2010[86] *Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience* Wagnetz et al, 2012[94] *Screening for lung cancer: implication of lung biopsy recommendations*	Median age: 60 years (range: 50 to 83) Median pack-years: 30 54% female	High-risk smokers with ≥10 pack-years smoking history	CT Variable row detector configuration (4 to 64)	Recommendations within protocol to community providers	Positive: NCN ≥5 mm or 1 nonsolid nodule ≥8 mm Nodules or nodules <5 mm considered of unlikely clinical significance Biopsy recommended for nodules >15 mm immediately or after 1 month of antibiotics
Liu et al, 2011[95] *The outcome differences of CT screening for lung cancer pre and post following an algorithm in Zhuhai, China*	Zhuhai city 1994 to 2002: 70% nonsmokers 2003 to 2009: 71% nonsmokers	Moderate	1994 to 2002: single slice CT 2003 to 2009: 16 MDCT	Up to 2002, image interpretation based on morphology and growth Semiautomatic volumetric software used after 2003	1994–2002 high suspicion: recommended surgery moderate suspicion: PET 2003–2009 ELCAP protocol
Lung Cancer Screening Intervention trial (LUSI)					
Becker et al, 2012[98] *Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round*	46% ages 50–54 years 28% ages 60–69 years 2622 men; 1430 women 62% current smokers	Current or former (quit <10 years ago) smokers with ≥25 years smoking of ≥15 cigarettes/day or ≥30 years smoking of ≥10 cigarettes/day	LDCT (multidetector, 4 annual) vs. no screening	Nodules <5 mm evaluate annually Nodules 5–7 mm evaluate every 6 months Nodules 8–10 mm evaluate every 3 months Immediate recall for >10 mm nodules	Contact physician of choice
Mayo Clinic					
Swensen et al, 2005[87] *CT Screening for lung cancer: five-year prospective experience*	788 men; 732 women 61% current smokers Median pack-years: 45 (range: 20 to 230)	Current or former (quit <10 years ago) smokers with ≥20 pack-years	CT (4-detector row helical CT, at low-dose)	Mayo Clinic	Mayo Clinic

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Population	Risk Group	Screening intervention	Imaging evaluation strategy	Suspicious abnormality finding evaluation strategy
Marcus et al, 2006[58] *Extended lung cancer Incidence follow-up in the Mayo Lung Project and over-diagnosis*	NR	High risk	CXR with sputum cytology either every 4 months vs. usual care	SCT at Mayo Clinic	Mayo Clinic
Sincirope et al, 2010[101] *Perceptions of lung cancer risk and beliefs in screening accuracy of spiral computed tomography among high-risk lung cancer family members*	NR	1st-degree relative with lung cancer and ≥3 blood relatives with lung cancer	SCT	SCT at Mayo Clinic	Mayo Clinic
Pittsburgh Lung Screening Study (PLuSS)					
Wilson et al, 2008[97] *The Pittsburgh Lung Screening Study*	Mean age: 59 years 51% men, 49% women Mean pack-years: 47 60% current smokers	Current or former (quit <10 years ago) smokers with ≥half a pack/day history for 25 years	CT	Screening study results reported to patient and personal physician described as low, moderate, or high risk of being malignant. Study physicians an option. Only imaging within study is initial and 1 year LDCT.	Followup evaluation in the community
Byrne et al, 2008[100] *Anxiety, fear of cancer, and perceived risk of cancer following lung cancer screening*	Mean age: 59 years 51% men, 49% women Mean pack-years: 47 60% current smokers	Current or former (quit <10 years ago) smokers with ≥half a pack/day history for 25 years	CT	Screening study results reported to patient and personal physician described as low, moderate, or high risk of being malignant. Study physicians an option. Only imaging within study is initial and 1 year LDCT.	Followup evaluation in the community

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Continuing Observation of Smoking Subjects (COSMOS)					
Veronesi et al, 2008[96] *Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program*	Asymptomatic men and women ages >50 years with a ≥20 pack-year history; current or prior smokers who quit <10 years ago	Prior malignant disease (except nonmelanoma skin cancer)	Number approached: NR Number eligible: NR Number enrolled: 5200	Italy	NR

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Veronesi et al, 2008[91] *Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules*	Asymptomatic men and women ages >50 years with a ≥20 pack-year history; current or prior smokers who quit <10 years ago	Prior malignant disease (except nonmelanoma skin cancer)	Number approached: NR Number eligible: NR Number enrolled: 5200	Italy	NR
Japan Studies					
Toyoda et al, 2008[89] *Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography*	All residents from Osaka between 1998 and 2000, smokers recommended to undergo LDCT and sputum cytology	Past or suspected lung cancer	Number approached: NR Number eligible: NR Number enrolled: 18,070 (4689 vs. 13,381)	Japan	Ministry of Health, Labor, and Welfare Japan
Tsushima et al, 2008[90] *Radiological diagnosis of small pulmonary nodules detected on low-dose screening computed tomography*	All population, NR	NR	Number approached: NR Number eligible: NR Number enrolled: 2486	Japan	NR
International Early Lung Cancer Action Program (I-ELCAP)					
Henschke et al, 2004[88] *CT screening for lung cancer: assessing a regimen's diagnostic performance*	ELCAP 1 Ages ≥60 years with a smoking history of ≥10 pack-years ELCAP 2 Ages ≥40 years with a smoking history of ≥1 pack-years	CT scan <3 years prior	Number approached: NR Number eligible: NR Number analyzed: 1000 (ELCAP 1) and 1968 (ELCAP 2)	United States	NCI
Henschke et al, 2006[31] I-ELCAP Investigators *Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer*	Asymptomatic past or current smokers ages ≥40 years fit for surgery	History of cancer	Number approached: NR Number eligible: NR Number enrolled: 14,435 (6296 women vs. 8139 men)	International study involving many countries, including the United States	NIH, many supporting institutions
Henschke et al, 2006[167] I-ELCAP Investigators *Survival of patients with stage I lung cancer detected on CT screening*	Asymptomatic adults ages >40 years with a history of smoking or occupational exposure with increased risk or secondhand smoke	NR	Number approached: NR Number eligible: NR Number enrolled: 31,567	International: Europe, United States, Japan, China, Israel	NIH, DOE, New York City
Shemesh et al, 2006[168] *Frequency of coronary artery calcification on low-dose computed tomography screening*	ELCAP 1 Ages ≥60 years with a smoking history of ≥10 pack-years ELCAP 2 Ages ≥40 years with a smoking	CT scan <3 years prior	Number approached: NR Number eligible: NR Number enrolled: 4250	United States	NCI

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
for lung cancer	history of ≥1 pack-year				
Menezes et al, 2010[86] *Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience* Wagnetz et al, 2012[94] *Screening for lung cancer: implication of lung biopsy recommendations*	Asymptomatic, ages ≥50 years, and ≥10 pack-year smoking history	Prior cancer (except nonmelanoma skin cancer) and poor health	Number approached: NR Number eligible: NR Number enrolled: 3352	Canada	Princess Margaret Foundation
Liu et al, 2011[95] *The outcome differences of CT screening for lung cancer pre and post following an algorithm in Zhuhai, China*	Government workers age ≥40 years	NR	Number approached: NR Number eligible: NR Number analyzed: 3348 (1994 to 2002) and 3582 (2003 to 2009)	Zhuhai City, China	NR
Lung Cancer Screening Intervention trial (LUSI)					
Becker et al, 2012[98] *Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round*	Current or former (quit <10 years ago) male and female smokers with ≥25 years smoking of ≥15 cigarettes/day or ≥30 years smoking of ≥10 cigarettes/day, ages 50 to 69 years	Cancer diagnosis within the past 5 years, medical circumstances preventing surgical treatment in case of a lung cancer diagnosis in screening, serious illness shortening life expectancy below 10 years	Number approached: 292,440 Number eligible: 4913 Number enrolled: 4052 Number analyzed: 2029	Germany	German Research Foundation and Dietmar-Hopp-Stiftung, members of the German Center for Lung Research by the German Research Ministry
Mayo Clinic					
Swensen et al, 2005[87] *CT Screening for lung cancer: five-year prospective experience*	Current or former (quit <10 years ago) smokers with ≥20 pack-years history, age >50 years	On supplemental O_2, history of cancer within 5 years, mentally incompetent, unable to undergo lung resection surgery, and <5-year life expectancy	Number approached: NR Number eligible: NR Number enrolled: 1520	United States, single site at Mayo Clinic	NCI and Mayo Clinic
Marcus et al, 2006[58] *Extended lung cancer Incidence follow-up in the Mayo Lung Project and over-diagnosis*	Male smokers who had tested negative for lung cancer with CXR and/or sputum cytology at baseline judged to have life expectancy of ≥5 years and sufficient respiratory reserve to undergo lobectomy if needed	Tested positive for lung cancer on CXR	Number approached: NR Number eligible: NR Number enrolled: 9121 (4618 vs. 4503)	Mayo Clinic	NCI

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Inclusion criteria	Exclusion criteria	Number of subjects	Country and setting	Sponsor
Sincirope et al, 2010[101] *Perceptions of lung cancer risk and beliefs in screening accuracy of spiral computed tomography among high-risk lung cancer family members*	Ages >30 years, 1st-degree relative with lung cancer and ≥3 blood relatives with lung cancer and current medical insurance	Personal history of lung cancer	Number approached: NR Number eligible: 371 Number enrolled: 60	United States, single site at Mayo Clinic	NCI
Pittsburgh Lung Screening Study (PLuSS)					
Wilson et al, 2008[97] *The Pittsburgh Lung Screening Study*	Current or former (quit <10 years ago) smoker with ≥half a pack/day history for 25 years, and symptoms were allowed	Prior history of lung cancer, chest CT within past year, weight >400 lbs, and other lung cancer screening	Number approached: 9386 Number eligible: 5034 Number enrolled: 3642	United States, single site in Pittsburgh	University of Pittsburgh Cancer Institute via NCI
Byrne et al, 2008[100] *Anxiety, fear of cancer, and perceived risk of cancer following lung cancer screening*	Current or former (quit <10 years ago) smoker with ≥half a pack/day history for 25 years, and symptoms were allowed	Prior history of lung cancer, chest CT within past year, weight >400 lbs, and other lung cancer screening	Number approached: 9386 Number eligible: 5034 Number enrolled: 3642 Number analyzed: 341	United States, single site in Pittsburgh	University of Pittsburgh Cancer Institute via NCI

Author, year, title	Results	Sensitivity	Specificity
Continuing Observation of Smoking Subjects (COSMOS)			
Veronesi et al, 2008[96] *Difficulties encountered managing nodules detected during a computed tomography lung cancer screening program*	43% NCN 106 invasive procedures: 15 for benign disease 91 lung cancers, of which 71% stage I (89 screen-detected) 79/91 curative surgery 24-month survival (85%) Interval cancer: NR *This paper defines false-negative as any cancer beyond stage I at diagnosis	91%	100%
Veronesi et al, 2008[91] *Lung cancer screening with low-dose computed tomography: a non-invasive diagnostic protocol for baseline lung nodules*	2198 at baseline had ≥1 NCN ≤5 mm 354 (6.8%) had ≥1 NCN 5.1 to 8 mm 206 had nodules >8 mm 504/5201 had ≥1 indeterminate nodule recalled for ≥1 additional evaluations 55 cancers diagnosed at baseline 36 cancers diagnosed at year 1 1 interval cancer after 1st incidence screening Among 36 cancers diagnosed at 2nd screen, 24 had prevalent nodule 1st year prior, 12 had new malignancy Baseline cancers: 79 Incidence: 13 Stage I: 66%	91% 1 interval cancer after incidence screen 36 cancers detected on incidence screen, of which 24 on baseline	100%

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Results	Sensitivity	Specificity
Japan Studies			
Toyoda et al, 2008[89] *Sensitivity and specificity of lung cancer screening using chest low-dose computed tomography*	40 cancers 5 interval cancer LDCT	Overall: 89% Smokers: 84% Nonsmokers: 100% Adenocarcinoma LDCT: 100% Nonadenocarcinoma: 62% Women: 85% Men: 91%	LDCT: 93% CXR: 97% LDCT baseline: 91% LDCT annual: 96% Men LDCT: 92% Women: 94% Smokers: 92% Nonsmokers: 94%
Tsushima et al, 2008[90] *Radiological diagnosis of small pulmonary nodules detected on low-dose screening computed tomography*	2486 scans Negative: 2132 Seminegative: 140/354 (14%) patients with nodules Semipositive: 111 Positive: 103 HRCT: 1837 cancers 3/7 cancers in nonsmoking women	100%	97% PPV LDCT: 9.9%
International Early Lung Cancer Action Program (I-ELCAP)			
Henschke et al, 2004[88] *CT screening for lung cancer: assessing a regimen's diagnostic performance*	Baseline (positive result: ≥1 solid/part solid nodule ≥5 mm; semi positive: <5 mm NCN): 368 nodules 79 lung cancer 2 interval 77 screen-detected 75 stage I 65 adenocarcinoma Repeat screen (any new or growing nodule; interval cancer = lung cancer diagnosis within 1 year of prior CT): N=4538 254 nodules (6%) 29 lung cancer 1 interval 27 stage I 17 adenocarcinoma	Baseline: 77/79 (97%)* Annual: 28/29 (97%)*	Baseline: 2889/3178 (91%) 11 screen 254 abnormal 29 false-positive: 225 TN: 286/3085 Annual: 2860/3085 (93%) 4538 screens 254 abnormal 29 lung cancer False-positive: 225 TN: 4509
Henschke et al, 2006[31] I-ELCAP Investigators *Women's susceptibility to tobacco carcinogens and survival after diagnosis of lung cancer*	Lung cancer: 156 Stage I: 139 Resection: 125 Lung cancer deaths: NR Carcinoid: 8 Adenocarcinoma: 114 Squamous: 22 Large cell: 5 Small cell: 4 Other NSCLC, not specified: 3	NR	NR

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Results	Sensitivity	Specificity
Henschke et al, 2006[167] I-ELCAP Investigators *Survival of patients with stage I lung cancer detected on CT screening*	Baseline (n=31,567) 4186 with concerning nodule (13%) 405 lung cancer (prevalence 1.3%) 5 interval cancers among 27,381 without nodule Annual (n=484 diagnosed cancers) 1460 new nodules (5%) 74 lung cancer (prevalence 0.3%) Interval cancers (n=484 diagnosed cancers) 411 resected, 57 radiation therapy, chemoprevention or both 16 no treatment Operative mortality: 0.5% (2/411) 412 stage I 39 died 75/484 with lung cancer died, including 2 who died ≤4 weeks before surgery	Baseline: 4186/4191 (99%) Annual: 100%	NR
Shemesh et al, 2006[168] *Frequency of coronary artery calcification on low-dose computed tomography screening for lung cancer*	CAC score 2: 1544 (36%) Positive CAC: 2706 (64%) Frequency of positive CAC: 66% in former vs. 62% in current smokers CAC increased with age and was higher in men	NA	NA
Menezes et al, 2010[86] *Lung cancer screening using low-dose computed tomography in at-risk individuals: the Toronto experience* Wagnetz et al, 2012[94] *Screening for lung cancer: implication of lung biopsy recommendations*	Nodules: Positive: 600/3352 (18%) CT with contrast: 12 1-month followup: 44 3-month followup: 521 6-month followup: 3 Biopsy (within 6 months): 57 Lung cancer: 44 (13% previous) ≥1 repeat CT: 2686 (range: 1 to 5) 65 total cancers 3 interval (false-negative) 48/65 women 56/65 prevalent 6/65 incident 3/65 interval Stage Stage I: 42/65 Stage II: 4 Stage III/IV: 10 Pathology Adenocarcinoma: 44 Squamous: 9 Small cell: 4 Unknown: 1 Carcinoid: 1	1 year: 88% For NSCLC: 89%	99%

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Results	Sensitivity	Specificity
Liu et al, 2011[95] *The outcome differences of CT screening for lung cancer pre and post following an algorithm in Zhuhai, China*	1994 to 2002 cohort 36 screen-detected cancers with 1 interval cancer 6.2% had nodules ≥5 mm 67% stage I 35 contrast CT scans 9 PET scans Cumulative incidence: 0.9% 2003 to 2009 cohort 34 cancers with no interval cancers 9.8% had nodule ≥5 mm 91% stage I 89 contrast CT scans Lung cancer diagnosis: 0.9%	NR	NR
Lung Cancer Screening Intervention trial (LUSI)			
Becker et al, 2012[98] *Randomized study on early detection of lung cancer with MSCT in Germany: study design and results of the first screening round*	2029 initial screens 1488 (73%) negative 540 (27%) suspicious -31% solitary -35% 2–4 nodules -27% 5–9 nodules -7% >10 nodules 393 (19%) 5–7 mm nodules -72 “cleared” and back to normal 78 (5%) 8–10 mm nodules -7 “cleared” and back to normal 69 (5%) >10 mm nodules -11 “cleared” and back to normal 22 lung cancers diagnosed in first round -4 in 5–7 mm nodules -1 in 8–10 mm nodules -17 in >10 mm nodules 1 interval cancer from round 1 to 2, stage IV adenocarcinoma	NR	NR
Mayo Clinic			
Swensen et al, 2005[87] *CT Screening for lung cancer: five-year prospective experience*	2038 nodules <4 mm; 1034 (4 to 7 mm); 268 (8 to 20 mm); 16 (>20 mm) Subjects with prevalence nodules: 780 False-positive rate: 92% to 96%; 69% with ≥1 Prevalent lung cancer stage: N=31; IA: 20, IB: 2, IIA: 4, IIIA: 2, IV: 1, SCLC: 2 Incident/interval lung cancer stage: N=35; IA: 16, IB: 1, IIA: 2, IIB: 2, IIIA: 4, IIIB: 2, IV: 0, unknown: 2, SCLC: 6 Mortality: overall: 48; lung cancer: 9 (of 5481.5 py) Volume doubling time: of 48 cancers with info, mean VDT: 518 days (SD, 1094); 13 tumors with VDT more than 400 days (11/13 in women)	3 interval cancers 63/66: 95%	NR
Marcus et al, 2006[58] *Extended lung cancer Incidence follow-up in the Mayo Lung Project and over-diagnosis*	At the end of the study (1983) 206 lung cancers diagnosed in intervention, after followup (1999) 379 more lung cancers diagnosed in intervention group	NR	NA

Appendix B3. Evidence Table of Included Cohort Studies

Author, year, title	Results	Sensitivity	Specificity
Sincirope et al, 2010[101] *Perceptions of lung cancer risk and beliefs in screening accuracy of spiral computed tomography among high-risk lung cancer family members*	Baseline vs. 1 month negative vs. 1 month nonnegative vs. 6 month negative vs. 6 month nonnegative Cancer thoughts (some): 65% vs. 54% vs. 87% vs. 59% vs. 69% Mood affected by results (some): 34% vs. 29% vs. 27% vs. 21% vs. 31% Daily activity affected (some): 8% vs. 3% vs. 0% vs. 6% vs. 6% Cancer concern (concern): 94% vs. 89% vs. 100% vs. 91% vs. 94% Perceived comparative cancer risk (higher): 76% vs. 74% vs. 69% vs. 57% vs. 81% Perceived absolute cancer risk (likely): 64% vs. 63% vs. 75% vs. 66% vs. 75%	NR	NR
Pittsburgh Lung Screening Study (PLuSS)			
Wilson et al, 2008[97] *The Pittsburgh Lung Screening Study*	80 cases of lung cancer (2.2% cumulative incidence [95% CI, 1.7 to 2.2) 11 small cell (45% limited stage) 69 NSCLC Stage I: 58% Stage II: 17% Stage III: 30% Stage IV: 7% Initial LDCT: 1477 (41%) with abnormality and referred for further evaluation (40 [1.1%] high, 182 [5%] moderate, 1255 [85%] low); 1070 imaging studies in 821 subjects in year after initial LDCT; 82 subjects with significant incidental finding	NR	NR
Byrne et al, 2008[100] *Anxiety, fear of cancer, and perceived risk of cancer following lung cancer screening*	Negative vs. indeterminate vs. suspicious State anxiety Initial: 35.9 vs. 34.4 vs. 32.6 Post: 35.9 vs. 37.7 vs. 38.3 6 months: 34.4 vs. 37.3 vs. 32.6 12 months: 35.1 vs. 35.3 vs. 35.1 Trait anxiety Initial: 37.0 vs. 36.7 vs. 33.9 Post: 36.6 vs. 37.5 vs. 36.6 6 months: 35.7 vs. 36.7 vs. 35.4 12 months: 35.8 vs. 36.3 vs. 35.0 Cancer fear Initial: 7.0 vs. 7.2 vs. 6.4 Post: 7.0 vs. 7.5 vs. 8.5 6 months: 6.5 vs. 7.1 vs. 7.4 12 months: 6.7 vs. 7.1 vs. 7.1 Perceived risk (%) Objective: <1 vs. 1 to 5 vs. 15 to 20 Initial: 17 vs. 19 vs. 19 Post: 11 vs. 20 vs. 35 6 months: 13 vs. 15 vs. 30 12 months: 13 vs. 19 vs. 31	NR	NR

*Calculated.

Appendix B3. Evidence Table of Included Cohort Studies

Abbreviations: CAC = coronary artery calcification; CI = confidence interval; COSMOS = Continuing Observation of Smoking Subjects; CT = computed tomography; CXR = chest x-ray; DOE = Department of Education; ELCAP = Early Lung Cancer Action Program; HRCT = high-resolution computed tomography; I-ELCAP = International Early Lung Cancer Action Program; FNA = fine needle aspiration; LDCT = low-dose computed tomography; LUSI = Lung Cancer Screening Intervention; MDCT = multidetector row computed tomography; NA = not applicable; NCI = National Cancer Institute; NCN = noncalcified nodule; NIH = National Institutes of Health; NR = not reported; NSCLC = non-small cell lung cancer; py = person years; PET = positron emission tomography; PLuSS = Pittsburgh Lung Screening Study; PPV = positive predictive value; SCLC = small cell lung cancer; SCT = spiral computed tomography; SD = standard deviation; TN = true negative; VATS = video-assisted thoracic surgery; VDT = volume doubling time