Screening for lung cancer

Authors
Mark E Deffebach, MD
Linda Humphrey, MD

Section Editors
Robert H Fletcher, MD, MSc
James R Jett, MD

Deputy Editor
Lee Park, MD

Disclosures: Mark E Deffebach, MD Nothing to disclose. Linda Humphrey, MD Nothing to disclose. Robert H Fletcher, MD, MSc Grant/Research/Clinical Trial Support: NCI [Screening for colorectal cancer (None. Journal articles, in the future, only). Consultant/Advisory Boards: spouse - Lancet [All (None)]; NCI [Cancer screening (None. Reports to organization)]; ACS [Cancer screening (None. Reports to organization)]. Other Financial Interest: spouse - Wolters Kluwer [clinical epidemiology (Textbook: Clinical Epidemiology, 5th edition)]. James R Jett, MD Grant/Research/Clinical Trial Support: Oncimmune [lung cancer biomarkers (early CDT lung blood test)]; Metabolomx [biomarker lung cancer (breath and urine test in development)]. Consultant/Advisory Boards: Quest Diagnostics [lung cancer biomarkers (blood test in development)]. Lee Park, MD Employee of UpToDate, Inc. Employment (Spouse): Novartis. Equity Ownership/Stock Options (Spouse): Novartis.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Sep 2014. | This topic last updated: Oct 14, 2014.

INTRODUCTION — Lung cancer is the leading cause of cancer-related death among men and women, and the third leading cause of cancer in the United States [1]. Worldwide, lung cancer and lung cancer-related deaths have been increasing in epidemic proportions, largely reflecting increased rates of smoking [2]. Some [3,4], but not all [5], studies suggest that for any level of smoking, women are at higher risk of developing cancer than men. In the year 2013, the American Cancer Society predicts that there will be approximately 224,230 new cases of lung cancer diagnosed, and approximately 159,260 lung cancer-associated deaths in the US [6]. Worldwide, it is estimated that there were 1.4 million deaths in the year 2008 [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 [8]. Despite advances in therapy, five-year survival rates average approximately 16 percent for all individuals with lung cancer [9].

Prevention, rather than screening, is the most effective strategy for reducing the burden of lung cancer in the long term. Most lung cancer is attributed to smoking, including lung cancer in nonsmokers in whom a significant proportion of cancer is attributed to environmental smoke exposure [10]. The promotion of smoking cessation is essential, as cigarette smoking is thought to be causal in 85 to 90 percent of all lung cancer [2]. Progress in smoking cessation is now reflected in declining lung cancer rates and mortality in men in the US. However, the smoking rate in the US remains high, at 19 percent in 2011 [11], and is increasing in many parts of the world. A high percentage of lung cancer occurs in former smokers since the risk for lung cancer does not decline for many years following smoking cessation [12-15].

Screening for lung cancer will be reviewed here. General principles of screening, risk factors associated with the development of lung cancer, and techniques for smoking cessation are discussed separately. (See "Evidence-based approach to prevention" and "Overview of smoking cessation management in adults" and "Cigarette smoking and other risk factors for lung cancer".)

POTENTIAL SCREENING OUTCOMES

Potential benefits — Many characteristics of lung cancer suggest that screening should be effective: high morbidity and mortality; significant prevalence (0.5 to 2.2 percent); identified risk factors allowing targeted screening for high-risk individuals; a lengthy preclinical phase for some types of lung cancer; and evidence that therapy is more effective in early stage disease [16,17]. Clinical outcome for non-small cell lung cancer is directly related to stage at the time of diagnosis, ranging from over 60 percent five-year survival for stage I disease, to less than 5 percent for stage IV disease (table 1 and figure 1) [18]. In addition, within early lung cancers (stage I), there is a relationship between tumor size and survival [19]. Available data are more limited for patients with small cell lung cancer, but also support an improved outcome when disease is diagnosed at an early stage.

The potential of screening to detect early cancers may both increase the overall cure rate and allow more limited surgical resection to achieve cure. However, screening may not accomplish these goals unless it takes place in the context of a multidisciplinary program to ensure that screening results are properly performed, interpreted, and followed-up, and that disease, when detected, is managed appropriately.

The success of lung cancer screening can be assessed using various outcome measures, including cancer detection rates, stage at detection, survival, disease-specific mortality, and overall mortality. For a lethal disease such as lung cancer, which requires invasive procedures for detection and treatment, the most important outcomes to assess are disease-specific and overall mortality.

Potential harms — While screening for lung cancer has the potential benefits of decreased morbidity and mortality from lung cancer, it also has potential harms, which include:

●Detection of abnormalities that require further evaluation, most of which are benign nodules. Evaluation may involve needle biopsy and/or surgery, with associated morbidity and mortality [20,21]. In the National Lung Screening Trial, as an example, over 53,000 high-risk individuals were randomly assigned to low-dose CT (LDCT) scan or chest radiograph screening [22]. Among abnormal results (24.2 percent of LDCT scans and 6.9 percent of radiographs), 96 percent were false positive (that is, did not lead to a diagnosis of lung cancer) and 11 percent of the positive results led to an invasive study. Most positive studies are resolved with imaging and prove to be false-positive exams.

●Radiation from serial imaging in a screening program may add independently to the risk of developing cancers, including lung cancer [23]. The increased radiation exposure associated with spiral LDCT scanning, compared with plain radiographs, may further add to cancer risk [24]. Radiation exposure has been poorly reported in studies, but in the studies that do report this parameter, it ranges from 0.61 to 1.50 mSv. Since screening typically occurs over several rounds and positive studies require further evaluation, the cumulative radiation dose is also important. However, there are limited data on this, with one study reporting cumulative exposure in a screening program of 6 to 7 mSv [25,26]. For comparison, most mammograms entail radiation doses on the order of 0.7 mSv. (See "Radiation-related risks of imaging studies".)

●Prolonged follow-up of nodules, often lasting several years, may cause anxiety related to fear of having lung cancer. Studies of this topic suggest that short-term increased anxiety among individuals with positive-low dose CT scans and decreased anxiety in those with negative LDCTs [1,27].

●Some cancers identified at screening, if never found, would not have affected morbidity or mortality during the patient's lifetime. Identification of such cancers is referred to as "overdiagnosis." (See 'Overdiagnosis with x-ray screening' below and 'Overdiagnosis' below.)

SCREENING WITH CHEST X-RAY/SPUTUM CYTOLOGY — Screening for lung cancer by chest x-ray is not recommended.

No randomized trial has demonstrated a mortality benefit for chest x-ray screening [28]. There have been at least seven large scale controlled clinical trials of chest x-ray screening for lung cancer: six randomized controlled trials [29-43] and one non-randomized controlled trial [44]. These studies began as early as 1960, and a 20-year follow-up analysis has been published for one randomized trial [40,45,46].

PLCO Cancer Screening Trial — The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a large randomized trial (n = 154,942) evaluating the impact of screening individuals aged 55 through 74 for several cancers, including lung cancer [47]. Screening for lung cancer consisted of a single posterior-anterior chest-x-ray performed at baseline and annually for three years, while the control group received usual care. This study differs from prior chest x-ray screening trials in several important aspects: the cohort includes men and women in equal numbers; participants are not specifically high-risk (51.6 percent current or former smokers); and prevalence screening results are included in the trial and analysis, allowing a true comparison of screening with no screening.

At the initial screening, 5991 (8.9 percent) of all chest-x-rays were abnormal, ranging from 11.0 percent in current smokers to 8.0 percent in never smokers [48] After up to three rounds of annual screening (nonsmokers did not participate in the third screening round), participants were followed through 13 years, with a screening adherence of 86.6 percent at baseline and 79.0 to 84.0 percent years one through three [49]. After 13 years of follow-up, there was no significant difference in lung cancer incidence rates between the screening and usual care groups (20.1 and 19.2 per 10,000 person-years, RR 1.05, 95% CI 0.98-1.12), and no difference in lung cancer mortality rates (RR 0.99, 95% CI 0.87-1.22) or stage of disease. Lung cancer incidence was higher in those with prior or current smoking exposure than in nonsmokers, but there was no difference in incidence or mortality between smokers who were in the screening or control groups (RR 0.94; 95% CI 0.18-1.10 after 6 years and RR 0.99; 95% CI 0.87-1.22 after 13 years of follow-up). Only approximately 20 percent of the cancers in the screening group were detected by screening. Thus, annual screening with chest x-ray, compared with usual care, did not reduce lung cancer mortality.

The lung cancer arm of the PLCO trial was designed to be completed in 2015. However, the monitoring board thought that results would be unlikely to change with longer follow-up and that the current findings had public health significance because of the recent report of the National Lung Screening Trial (NLST) that compared LDCT screening with chest x-ray screening in a high-risk population. Data from the PLCO trial were also analyzed for a subset of patients who would meet the criteria for the NLST. (See 'National Lung Screening Trial' below.)

Mayo Lung Project — The Mayo Lung Project was the first North American trial to evaluate the value of intense screening with chest x-ray and sputum cytology in male smokers (n = 10,993) and reported initial results in 1984 [34,40]. All participants underwent prevalence screening (baseline) evaluation with chest x-ray and sputum cytology. Subjects were then randomly assigned to a six-year program of chest x-ray and sputum cytology every four months (incidence screening), or to the control group receiving "usual care" and advised to have an annual chest x-ray.

Prevalence screening identified 91 cancers (0.8 percent). After six years, 206 new cancers were identified in the screening group, and 160 in the control group. After 20 years of follow-up, lung cancer death rates were significantly higher in the screened group (4.4 versus 3.9 deaths per 1000 patient years). Significantly more early cancers were detected in the screened cohort, but there was no reduction in late-stage cancers. Several issues confound these findings: nearly half of the control group had a "screening" chest x-ray during the course of the study; compliance in the intervention group was only 75 percent; and there was no completely unscreened group (baseline prevalence screening detected 91 cases of lung cancer).

Overdiagnosis with x-ray screening — While it is believed that most lung cancers progress to late stage cancer, it has not been proven that all lung malignancies progress [50]. Overdiagnosis occurs when screening detects cancers that would not otherwise have become clinically apparent. In the absence of overdiagnosis and with successful randomization, the number of cases of lung cancer (identified either by screening or clinical presentation) in both control and intervention groups should equalize over time, as cancers in the control group become clinically apparent.

Data from the Mayo Lung Project suggest significant overdiagnosis (or unsuccessful randomization) since a persistent excess of lung cancer in the screened group compared with controls (585 versus 500) was found 16 years after the trial had ended [46]. The PLCO trial, conducted in the general population, identified 76 extra lung cancers after 13 years of follow-up with a cumulative incidence ratio of 1.05 (95% CI 0.98-1.12), suggesting less overdiagnosis than reported in the Mayo Lung Project [49]. Among high-risk (smoking-exposed) PLCO trial participants, the cumulative incidence of lung cancer after six years of follow-up was the same in both the chest x-ray and no chest x-ray groups. Thus, the magnitude of overdiagnosis resulting from chest x-ray screening is currently uncertain.

Case-control studies — Six case-control studies have evaluated the role of chest x-ray screening for lung cancer [51-57]. Five fair-quality Japanese case-control studies suggest benefit with chest x-ray screening among men with smoking exposure and women without direct smoking exposure or of mixed risk. Interpretation of these studies is limited by the potential screening biases associated with non-randomized studies.

SCREENING WITH LOW-DOSE CHEST CT — The lack of a mortality benefit from chest x-ray screening and the refinement of CT scanning techniques led to the evaluation of low-dose helical CT (LDCT) for lung cancer screening [58]. On the basis of randomized trial results, many professional guidelines, as well as UpToDate recommendations, endorse LDCT screening for lung cancer in selected populations at high risk. The National Lung Screening Trial (NLST) was a large, high-quality randomized trial, in which high-risk individuals were screened with LDCT [22]. Results published in 2011 indicate a 20 percent reduction in lung cancer mortality with screening. Additional randomized trials are ongoing. (See 'Recommendations for screening by expert groups' below.)

A 2012 systematic review of the benefits and harms of screening with low-dose CT scan identified the NLST as the only trial from which a mortality benefit could be concluded, with other trials either too small, still preliminary, or with study design flaws precluding meaningful interpretation [59]. Similarly, a 2013 systematic review also found the NLST to provide the best quality available data regarding screening [1].

Low-dose helical CT scanning — New multidetector CT scanners generate high-resolution imaging with radiation exposure significantly less than for diagnostic chest CT scanning. Low-dose CT (LDCT) refers to a noncontrast study obtained with a multidetector CT scanner during a single maximal inspiratory breath-hold with a scanning time under 25 seconds. High-resolution (1.0 to 2.5 mm interval) images are reconstructed using a soft tissue or thin-section algorithm. The overall average effective dose of low-dose CT used in the National Lung Screening Trial was 2 mSv, compared with 7 mSv for a standard-dose diagnostic chest CT examination [60]. (See 'National Lung Screening Trial' below.)

Randomized trials

National Lung Screening Trial — The National Lung Screening Trial (NLST), a randomized trial conducted under the auspices of the National Cancer Institute, compared annual screening by low-dose chest CT scanning with chest x-ray for three years in 53,454 high-risk persons at 33 US medical centers [22,61-63]. Participants were men and women 55 to 74 years of age with a history of at least 30 pack-years of

smoking, and included current smokers and those who had discontinued smoking within 15 years of enrollment.

The trial was stopped in November 2010 after an interim analysis found a statistically-significant benefit for LDCT scanning [22]. At a median follow-up of 6.5 years, there were 645 cases of lung cancer per 100,000 person years (1060 cancers) in the LDCT group, and 572 cases per 100,000 person years (941 cancers) in the chest x-ray group, resulting in an incidence rate ratio of 1.13 (95% CI 1.03-1.23). Per 100,000 person years, there were 247 lung cancer deaths in the CT group and 309 in the x-ray group, yielding a relative mortality reduction of 20 percent (CI 3.8-26.7) and an absolute reduction of 62 lung cancer deaths per 100,000 person years. Importantly, there was also a 6.7 percent (CI 1.2-13.6) relative reduction in all-cause mortality in the LDCT group and an absolute reduction of 74 deaths per 100,000 person years.

Positive findings were defined as a noncalcified nodule ≥4 mm on LDCT scan or any noncalcified nodule on x-ray. Over all three screening rounds, 24.2 and 6.9 percent of participants in the LDCT and x-ray groups respectively had a positive screen. The cumulative rate of false-positive findings was high: 96.4 and 94.5 percent for LDCT and x-ray screening respectively. Follow-up for false-positive findings was at the discretion of the institution, 90.4 and 92.7 percent of false-positive screens led to at least one diagnostic procedure, mostly imaging, but including surgery in 297 patients who had LDCT scan and 121 who had x-ray screening [63]. The rate of adverse events related to complications from the diagnostic work-up was low: among participants with a positive finding, at least one complication occurred in 1.4 percent of the LDCT group and 1.6 percent of the x-ray group (table 2).

The rate of detection of lung cancer did not diminish between screening years, suggesting that ongoing screening would be necessary. However, fewer stage IV cancers were observed in the LDCT group than the chest x-ray group with the second and third screening rounds. Lung cancers detected by screening were mostly stage I or II (70 percent of CT-detected and 56.7 percent of x-ray detected), except for small cell cancers that accounted for less than 10 percent of detected cancers. Chest LDCT identified a preponderance of adenocarcinomas.

More detailed results of the first round of screening (T0) in the NLST show that stage I cancer was detected in 158 participants in the LDCT group and 70 participants in the x-ray group; stage IIB to IV cancers were found in 120 versus 112 participants [63]. Thus, the difference in cancer detection between groups was in the increased identification of early-stage cancers with LDCT scan. Based on data collected for three years following the screening rounds, sensitivity and specificity for LDCT were 93.8 and 73.4 percent and for x-ray were 73.5 and 91.3 percent, respectively. Additional details about screening rounds two and three (T1 and T2) and incident lung cancers indicate that 27.9 and 16.8 percent of T1 and T2 low-dose CT scans, respectively, were positive [64]. The positive predictive value for cancer was 2.4 and 5.2 percent at T1 and T2, respectively. The higher predictive value at T2 was likely related to classification of a nodule that had been stable over three screenings as "negative." Consistent with results from T0, lung cancers detected by LDCT scan were more likely to be stage 1A (at T1, 47.5 percent of cancers identified by LDCT compared with 23.5 percent of those identified by x-ray). The two

annual screenings with LDCT resulted in a decrease in the number of advanced stage cancers and an increase in the number of early stage lung cancers diagnosed.

Generalizability of these findings may be affected by the following factors: trial participants had a higher education level and were younger than tobacco users identified in US census data; a low complication rate of follow-up procedures may reflect the expertise at the participating academic centers; radiologic performance and interpretation may not be representative of community-based radiology [65].

Since the control group in the NLST had screening with chest x-ray rather than usual care, findings of the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial, in which participants were randomly assigned to usual care or annual chest radiography, are pertinent [66]. Results of the PLCO trial were analyzed for the subset of patients who would meet criteria for participation in the NLST. There was no significant difference in mortality at six-year follow-up for the PLCO trial high-risk subset that was assigned to chest x-ray screening or usual care (RR 0.94, 95% CI 0.81-1.10).

In summary, the NLST demonstrated that LDCT screening reduced mortality in a high-risk population, compared with screening by x-ray and, by inference from the PLCO trial data, compared with usual care. For those undergoing at least one screen, the number needed to screen with low-dose CT to prevent one lung cancer death was 320 in the NLST. However, the cost of screening per life saved is unknown but likely to be high, given the high (approximately 95 percent) false-positive rate leading to the need for additional studies, the need for ongoing screening, and the relatively low absolute number of deaths prevented (73 per 100,000 person years). Modeling studies will be needed to determine actual cost effectiveness.

Ongoing trials — Seven randomized trials of low-dose CT screening remain in progress in Europe [67]. These include the NELSON trial, the DANTE trial, the Danish Lung Cancer Screening Trial (DLCST), the Multi-centric Italian Lung Detection Trial (MILD), the Italian Lung cancer Computed Tomography screening trial (ITALUNG), the German Lung Cancer Screening Intervention Study (LUSI), and the United Kingdom Lung Cancer Screening trial (UKLS). The trials differ in recruitment strategies and number of screening rounds, though all include only past or current heavy smokers, and all control groups had no screening (in contrast to the NLST where the control arm had chest x-ray screening). The only individual trial of large enough size to possibly show a mortality reduction is the NELSON trial. However, analysis of pooled data from the seven trials is planned for 2015 to 2016.

●The NELSON trial is a randomized LDCT-based lung cancer trial being conducted in the Netherlands and Belgium; LDCT screening is being compared with no screening in 7557 current or former smokers [68]. The study is powered to detect a 25 percent decrease in lung cancer mortality after 10 years, as well as the effects of screening on quality of life, smoking cessation, and an estimate of cost effectiveness. Unlike other screening studies, five-year lung cancer survivors, a group at very high risk of developing a new lung cancer, are also eligible for enrollment. This is the only large-scale randomized trial to compare LDCT-screening with no screening. Information is available at www.trialregister.nl/trialreg/admin/rctview.asp?TC=636.

A total of 90 subjects (1.2 percent) were found to have lung cancer after two rounds of screening [69]. The proportion of stage I cancers in round one was 64 percent, which is similar to the 59.3 percent from the first round of the NLST, and lower than the 86 percent reported in the I-ELCAP study, an observational study of low-dose CT screening (see 'Observational studies' below). Follow-up for identified nodules was based on initial nodule volume and subsequent change in size to limit invasive testing for false-positive studies; using this protocol, 20 lung cancers were found after two years of follow-up in the 7361 subjects who had initial negative screening.

LDCT screening results (indeterminate versus negative) did not significantly impact the smoking abstinence rate among male smokers in this trial [70]. However, smokers with an indeterminate result on LDCT scanning reported more quit attempts than those with a negative scan.

●The DANTE trial, a randomized trial in Italy that enrolled 2472 male smokers age 60 to 74 years, is designed to assess lung cancer-specific mortality over 10 years, comparing five years of annual screening by single slice spiral LDCT scan or annual clinical follow-up; the control group received baseline screening with chest x-ray and sputum cytology [71]. At initial evaluation, lung cancer was found in 2.2 percent of the LDCT group (71 percent stage I) and 0.67 percent of the controls (50 percent stage I) [72]. Fifteen percent of subjects had an abnormal LDCT, and 4 percent underwent an invasive procedure. Benign pulmonary lesions were found in 19 percent (6 of 32) of the patients who underwent thoracotomy.

Follow-up at an average of 33.7 months from enrollment and after completion of the baseline and annual screens has been reported [73]. Lung cancer was found in 4.7 percent of patients who received LDCT screening and in 2.8 percent of controls. Although there were more stage I cancers in the screened group (54 versus 34 percent), the numbers of advanced lung cancer cases and lung cancer mortality were the same for both screened and control patients. The authors caution that these interim findings should not be considered as definitive evidence that screening is ineffective, but suggest that any effect may be smaller than hoped. It is likely that longer follow-up will be required to detect differences in disease-specific mortality. Additionally, the trial size is small, compared with the NLST, and may not be of sufficient power to detect a mortality difference.

●The Danish Randomized Lung Cancer CT Screening Trial is another randomized trial of 4104 smokers (at least 20 pack-years) aged 50 to 70 years [74]. The trial is coordinated with the NELSON trial so that final results of both studies can be pooled to achieve an 80 percent power to detect a reduction in lung cancer mortality of at least 25 percent. Baseline data from the Danish trial found a prevalence of lung cancer of 0.83 percent (17 cases in 2052 participants), employing the algorithm from the I-ELCAP study for follow-up of abnormal initial findings on LDCT scan, 9 of the 17 cases were stage I. Of the 11 cases considered to be surgically resectable, 8 were amenable to minimally invasive (VATS) technique. The results of this trial after five annual screening rounds show an increase in the number of stage I-IIB non-small cell lung cancers in the screened group, compared with the non-screened group, with no difference in high-stage lung cancer between the groups [75]. The risk of lung cancer comparing LDCT

with no LDCT was RR 2.88 (95% CI 1.85-4.49), but there was no significant difference in lung cancer mortality (RR 1.37, 95% CI 0.63-2.97) or all cause mortality (1.46, 95% CI 0.99-2.15).

●The Multicentric Italian Lung Detection (MILD) study compared annual or biennial LDCT screening with no screening in 4099 smokers (>20 pack-years, current or quit within 10 years) aged 49 years or older [76]. Compared with the control group, all-cause mortality was increased for the annual screening group (RR 1.80, 95% CI 1.56-2.07). However, this trial was judged to be of low quality due to inadequate randomization and differential time to follow-up for control and intervention groups [1].

Observational studies — Several observational studies of low-dose CT scanning have been published and demonstrate that screening with low-dose chest CT can identify early stage asymptomatic lung cancer. The larger observational studies include the Early Lung Cancer Project (ELCAP) [77,78], the International ELCAP [79], the Mayo Clinic CT study [80-83] and the Continuous Observation of Smoking (COSMOS) study [84]. However, results from randomized trials are more pertinent to decisions about screening.

Adverse effects of screening

Overdiagnosis — Overdiagnosis, the detection of lung cancer with screening that would not be clinically apparent in the patient's lifetime, could be expected to have greater impact in screening programs where subjects are at increased risk for other potentially life-threatening comorbidities, as is the case for smokers [85]. The risk for unnecessary invasive studies and therapy for "overdiagnosed" lung cancer might be greatest in this population.

Observational studies of screening for lung cancer with low-dose CT that preceded the NLST trial have estimated the extent of overdiagnosis to range between 13 and 27 percent [86,87].

Although randomized trials demonstrate that screening with low-dose CT scan can reduce lung cancer and all-cause mortality, some cancers detected by screening may still represent overdiagnosis and lead to unnecessarily aggressive treatment. After 6.5 years of follow-up in the NLST, there were 119 more lung cancers identified in the LDCT group compared with the chest x-ray group (1060 versus 941) [22]. One study has used the NLST data to estimate an upper limit of overdiagnosis [88] but this model has been criticized for not taking into account lead or length time bias [89,90]. Only long-term follow up can provide a true estimate of overdiagnosis.

Patient distress — Few trials have evaluated patient distress with low-dose CT screening. A 2014 systematic review of five randomized trials and one cohort study found that low-dose CT screening may be associated with short-term psychologic discomfort but did not affect distress, worry, or health-related quality of life [91]. False-positive results were associated with short-term increases in distress.

RISK PREDICTION MODELS FOR SCREENING — Although trials to date have selected participants who are considered to be at high risk for lung cancer on the basis of current or past smoking history, the relative benefit (with reduction in harm) from screening could be improved if it were possible to more precisely identify a high-risk population for screening. To this end, risk models have been proposed that incorporate factors in addition to smoking [92-96].

●A model derived from data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial incorporates age, education, body mass index, family history, history of chronic lung disease, and smoking status, and it performed well with external validation [96,97].

●Another model, the Liverpool Lung Project (LLP) risk model, incorporates smoking duration, history of pneumonia, history of cancer, family history of lung cancer, and asbestos exposure into a risk score [92]. The model was validated in three independent populations and found to have better discrimination than smoking history or family history alone in identifying high-risk patients.

●In a retrospective study, applying a risk prediction model to divide the participants in the NLST into five quintiles, 88 percent of the screen-prevented lung cancer deaths occurred among the 60 percent of study participants in the three highest risk quintiles, and only 1 percent of prevented deaths occurred in the lowest-risk quintile [98], suggesting that targeting screening to higher-risk individuals could result in greater benefits with lower risks.

Prospective studies are needed, however, to determine whether a population can be readily identified using risk models in which screening would have greater benefit than the 20 percent lung cancer mortality benefit identified in the NLST.

Another parameter that affects the risk of cancer and the performance characteristics of a screening program is the criteria used to define an "abnormal" CT result requiring further investigation. The NLST identified a noncalcified nodule size of >4 mm as an abnormality, but retrospective interpretation of data from the I-ELCAP study cohort suggest that setting a more conservative threshold (>6 mm) might decrease the false-positive rate (resulting in fewer unnecessary procedures or follow-up studies) with minimal impact on the detection of cancers [99]. It is possible that a range of nodule sizes should be considered "abnormal," determined by an individual's specific risks for cancer [100]. A predictive tool has been developed and validated to estimate the probability that a nodule is malignant, based on characteristics of the patient and the nodule in the Pan-Canadian screening study [101]. The investigation of a solitary pulmonary nodule is discussed in greater detail separately. (See "Diagnostic evaluation and management of the solitary pulmonary nodule".)

SYNTHESIZING THE AVAILABLE EVIDENCE — In summary, randomized controlled trials and cohort studies of screening with chest x-ray or low-dose CT (LDCT) demonstrate:

●LDCT screening is significantly more sensitive than chest x-ray for identifying small, asymptomatic lung cancers. Chest x-ray screening does not reduce mortality from lung cancer, although there are limited data in women.

●Chest x-ray and LDCT screening have high rates of "false-positive" (non-cancer) findings leading to additional testing that usually includes serial imaging, but may include invasive procedures. The most common incidental findings are emphysema and coronary artery calcifications.

●The NLST, a large randomized trial of screening LDCT in high-risk individuals, demonstrated a lung cancer mortality benefit of 20 percent, with all cause mortality reduced by 6.7 percent [22]. For the

"typical" NLST participant, screening would prevent 3.9 deaths over six years per 1000 persons, which equates to screening 256 persons annually for three years to prevent one lung cancer death over six years [102]. In one model, estimating that 8.6 million people in the US would have met NLST criteria for screening (based on 2010 data) and assuming full screening implementation, screening could potentially avert 12,000 deaths from lung cancer per year in the US [103].

●The question of cost-effectiveness is a major issue because of the significant costs associated with screening and, especially, follow-up of the many false-positive tests identified with LDCT screening in this trial. Additionally, relatively-low procedural complication rates in the NLST trial may not be reproducible in other settings and, thus, harms may be greater than reported.

Issues remaining to be addressed include cost-effectiveness analysis, screening frequency and duration if screening is undertaken, appropriate population targets, defining criteria for a "positive" finding, and identifying diagnostic follow-up protocols that minimize evaluations of false-positive findings [104] . Finally, more data on potential "overdiagnosis" of lung cancer from screening trials need to be reviewed. Developing a registry of individuals who have been screened, with the potential for tracking long-term follow-up findings and outcomes, will be helpful to inform modifications to current screening recommendations.

Cost-effectiveness — Decisions regarding implementation of a lung cancer screening program based upon the results of the NLST should in part be based upon a cost-effectiveness analysis of a screening program. One analysis, based upon a model designed prior to completion of the NLST, modeled the potential cost-effectiveness of screening by LDCT scan for six different patient cohorts (differing ages and smoking histories) [105]. The modelers also varied whether patients who underwent screening were more likely to quit smoking because of the opportunity for smoking cessation intervention (nicotine replacement plus bupropion) or less likely to quit smoking because of reassurance from a negative test result. Projections from this analysis were that LDCT screening might decrease lung cancer mortality at 10 years by 18 to 25 percent, at a cost ranging from $126,000 to $269,000 per quality adjusted life year (QALY). In comparison, the cost-effective ratios for colorectal and breast cancer screening are $47,700 and $13,000 to $32,000 per QALY, respectively. Additionally, the model found that a smoking cessation program was more cost-effective than LDCT screening alone or LDCT screening combined with smoking cessation.

Recommendations for screening by expert groups — A 2012 systematic review of available evidence was commissioned by the American Cancer Society (ACS), American College of Chest Physicians (ACCP), American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) to serve as a basis for screening guidelines for these societies [59]. Screening guidelines supporting low-dose CT scans for identified high-risk groups, based upon this review, were issued by the NCCN and by the ACCP/ASCO. A 2013 systematic review for the US Preventive Services Task Force (USPSTF) [1] serves as the basis for revised guidelines for the USPSTF [106]. Many expert screening groups have incorporated results from the NLST in their recommendations (table 3). The recommended age cut-off for screening varies between groups, with modeling studies suggesting that extending screening beyond the 74 years of the NLST cohort will provide further benefit [107].

The National Comprehensive Cancer Network (NCCN) issued guidelines for lung cancer screening in October 2011 [108]. These guidelines recommend annual low-dose CT scan screening for those at high risk; they recommend no routine screening for moderate- or low-risk individuals. High risk was defined by the NCCN as age 55 to 74 years with a 30 pack-year history of smoking and, if no longer smoking, smoking cessation within 15 years, or a 20 pack-year history of smoking with one additional risk factor (other than secondhand smoke exposure). Although the guidelines note that the duration of screening is uncertain, they advise a minimum of three scans so that individuals initiating screening at age 74 would stop screening at age 76. The guidelines emphasize that lung cancer screening should be done within the context of a multidisciplinary program (that may include radiology, pulmonary medicine, internal medicine, thoracic oncology, and/or thoracic surgery) to manage downstream testing.

Similar guidelines, incorporating high-risk criteria from the NLST, were issued in 2012 from the American College of Chest Physicians and the American Society of Clinical Oncology [59,109] and from the American Cancer Society in 2013 [110]. These guidelines advise patient counseling on the risks and benefits of screening; the development of a registry to collect data on follow-up testing, smoking behavior, radiation exposure, and patient experience; the development of quality metrics for CT interpretation, similar to quality control for mammography; and also emphasize the importance of smoking cessation. The American Lung Association and the American Association for Thoracic Surgery (AATS) also released guidelines in 2012 that recommend low-dose CT screening for high-risk individuals who meet the NLST criteria. The AATS guidelines extend the age for screening, advising screening for high-risk individuals from age 55 to 79 years and advise initiating screening at age 50 for those with a cumulative risk of 5 percent or greater over the next five years [111]. The US Preventive Services Task Force (USPSTF) revised its guidelines in 2013 based on a systematic review and an analysis of the benefits and harms of lung cancer screening [1,107]. The USPSTF recommends annual low-dose CT scan for high-risk adults 55 to 80 years old (30 pack-year smoking history and current smoker or quit within the past 15 years), with discontinuation of screening once the individual has not smoked for 15 years or has a limited life expectancy [106].

Similar to the US guidelines, a multidisciplinary expert group from France, representing the intergroup for thoracic oncology and French-speaking oncology (the French Intergroup [IFCT] and the Groupe d'Oncologie de Langue Française [GOLF]), advised screening a target population (age 55 to 74 years who have a 30-pack-year smoking history) with low-dose CT scan, after informing individuals about the risks and benefits of screening [112]. The Cancer Care Ontario Programme (CCOP) issued guidelines in 2013 targeting the same group of patients, but suggesting biennial screening after two consecutive years of negative scanning [113].

The International Association for the Study of Lung Cancer (IASLC) chartered an advisory committee in 2011 to work with professional societies who are developing guidelines for screening [114]. The IASLC identified several issues that need to be addressed in guideline development and implementation: defining the optimal population for screening; determining the cost-effectiveness of screening; developing consistent CT screening protocols; defining the optimal work-up for abnormal findings; defining optimal management of screen-detected nodules; determining the optimal screening interval and number of screening rounds; and encouraging data collection and further research to improve

screening outcomes and limit complications. There was consensus that smoking cessation programs need to be integrated into screening programs and that a lung cancer screening program should involve a multidisciplinary team experienced in evaluation and management of early lung cancer.

Counseling for screening — Any program of lung cancer screening requires more than low-dose CT capability. Screening should only be performed when the clinician and patient are committed to pursuing follow-up investigations, including serial imaging and possible surgical lung biopsy and where there is expertise in chest radiography and lung cancer management [115].

The National Cancer Institute has developed a guide for patients and clinicians to review the data from the NLST to facilitate communication about the benefits and harms of screening [116].

Providers need to be experienced in the principles of screening and the management of small lung nodules. If these components are in place and at-risk individuals (mostly through smoking and occupational exposure) are highly motivated to be screened for lung cancer, the following points should be discussed with the patient before beginning screening. Some have advocated formal informed consent including these points:

●Smoking cessation is a more proven and powerful intervention for preventing death and complications from lung cancer and other diseases than screening. (See "Cigarette smoking and other risk factors for lung cancer".)

●Lung cancer screening requires an ongoing commitment; cancers are detected on initial and annual studies, and a single baseline study is insufficient.

●The most likely "positive" result of screening is detection of benign nodules requiring further evaluation, and this evaluation may require invasive studies, possibly even surgery.

For patients who would opt to be screened after appropriate counseling, and pending results of cost-effectiveness analyses and ongoing randomized trials, we suggest screening with low-dose helical CT scanning only for those who meet all of the following criteria:

●Are in general good health.

●Are at increased risk for lung cancer (similar to the risk of the group participating in the NLST trial). High-risk criteria for participation in the NLST were age 55 to 74 years, a history of smoking at least 30 pack-years and, if former smoker, had quit within the previous 15 years.

●Have access to centers whose radiologic, pathologic, surgical, and other treatment capabilities in the management of indeterminate lung lesions are equivalent to those in the NLST trial.

●Understand the possible need for subsequent evaluation of abnormal findings.

●Are able to manage the cost of annual screening. The role of insurance coverage in screening has not been determined following the NLST results and insurance may not cover the cost of screening [117-119].

FUTURE DIRECTIONS

Positron emission tomography — At least two studies evaluated annual low-dose computed tomography (CT) followed by positron emission tomography (PET) with fluorodeoxyglucose (FDG) for evaluating patients with noncalcified lesions ≥7 mm in diameter, each with similar results [120,121]. In one study, FDG-PET correctly diagnosed 19 of 25 indeterminate nodules [120]. The sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET for the diagnosis of malignancy were 69, 91, 90, and 71 percent, respectively. When a negative FDG-PET was followed three months later with a repeat CT, the negative predictive value was 100 percent. If these results are validated by future studies, the simple algorithm employed could have substantial implications for incorporation of PET imaging into large-scale screening programs. (See "Thoracic positron emission tomography" and "Computed tomographic and positron emission tomographic scanning of pulmonary nodules".)

Non-radiographic technologies — Non-radiographic technologies, including identification of molecular and protein-based tumor biomarkers, may also contribute to the early detection of lung cancer. Detection and treatment of small lung tumors (prior to radiographic visualization) may produce superior outcomes, though the possibility of lead-time and other types of bias influencing the assessment of these technologies is great. Outcome benefits must be thoroughly investigated prior to their widespread use [122].

These techniques may also help identify people with significantly higher lung-cancer risk, in whom the likelihood that radiographic studies would detect early-stage lung cancer is increased.

Potential biosamples for biomarker analysis include airway epithelium (including buccal mucosa), sputum, exhaled breath, and blood [123]. The NLST has established a biospecimen repository of blood, sputum, and urine samples serially collected from over 10,000 NLST participants, for future investigation.

Technologies under investigation include:

●Immunostaining or molecular analysis of sputum for tumor markers. As examples, p16 ink4a promoter hypermethylation and p53 mutations have been shown to occur in chronic smokers before there is clinical evidence of neoplasia [124-128].

●Automated image cytometry of sputum [129].

●Fluorescence bronchoscopy [130,131]. (See "Fluorescence bronchoscopy".)

●Exhaled breath analysis of volatile organic compounds, which appear to be more common in patients with lung cancer [132-134].

●Genomic and proteomic analysis of bronchoscopic samples [135,136].

●Serum protein microarrays for detecting molecular markers [137].

Assessing tumor growth patterns — The COSMOS study investigated whether estimation of the volume doubling time (VDT) or growth rate of tumors detected by low-dose CT scans could be used to determine which tumors may represent indolent cancers and thus potential overdiagnosis [138]. VDT was estimated on the basis of change in tumor size with serial scans; a tumor with a VDT <400 days was considered to be fast-growing, 400 to 599 days as slow growing, and >600 days as indolent. VDT correlated with lung cancer mortality rates (9.2 percent per year for fast-growing and 0.9 percent per year for slow-growing or indolent cancers). Ten percent of the cancers identified in the COSMOS cohort had a VDT of 600 days or more, and 25 percent had a VDT of 400 or more days and thus might represent overdiagnosis; such tumors might reasonably be managed with less aggressive intervention.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

●Basics topic (see "Patient information: Lung cancer screening (The Basics)")

●Beyond the Basics topics (see "Patient information: Lung cancer prevention and screening (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

●Lung cancer is the leading cause of cancer-related death. Prevention (promoting smoking cessation) is likely to have far greater impact on lung cancer mortality than is screening. Nonetheless, lung cancer screening has the potential to significantly reduce the burden of lung cancer. (See 'Introduction' above.)

●Early trials of chest x-ray screening in males at high risk for lung cancer found no mortality benefit for x-ray alone or x-ray plus sputum cytology. A large randomized trial (the PLCO trial) of single view chest x-ray in men and women found no decrease in lung cancer incidence or mortality with screening. (See 'Screening with chest x-ray/sputum cytology' above.)

●Low-dose CT (LDCT) refers to a noncontrast study obtained with a multidetector CT scanner during a single maximal inspiratory breath-hold with a scanning time under 25 seconds. Radiation dose exposure is less than a third of a standard-dose diagnostic chest CT examination. (See 'Low-dose helical CT scanning' above.)

●A large randomized trial (NLST) of annual low-dose CT screening in patients with a 30 pack-year history of smoking, including those who quit smoking in the preceding 15 years, demonstrated a decrease in

lung cancer and all-cause mortality. These results have led to revised guidelines from multiple professional organizations. (See 'Randomized trials' above and 'Recommendations for screening by expert groups' above.)

●All patients who smoke should be strongly counselled to quit smoking as the most-effective intervention to reduce the risk of lung cancer. Patients who currently smoke or have a history of smoking should be advised of the risks and benefits of screening for lung cancer (see 'Counseling for screening' above):

•For patients in good health who are thought to have a risk for lung cancer at least as great as those in the NLST and who have access to centers with radiologic, diagnostic, and treatment capabilities similar to those in the NLST, and for whom the cost of screening is not an issue, we suggest annual screening with low-dose helical CT (Grade 2A). High-risk criteria for participation in the NLST were age 55 to 74 years, a history of smoking at least 30 pack-years and, if a former smoker, had quit within the previous 15 years. Consistent with modeling studies subsequent to the NLST and with recommendations from the USPSTF, we also suggest screening for high-risk patients in good health to age 80 (Grade 2C).

•Plain chest x-ray screening has been shown to be ineffective for lung cancer screening. We recommend not screening for lung cancer with chest x-ray (Grade 1A).

REFERENCES

Humphrey LL, Deffebach M, Pappas M, et al. Screening for lung cancer with low-dose computed tomography: a systematic review to update the US Preventive services task force recommendation. Ann Intern Med 2013; 159:411.

Alberg AJ, Samet JM. Epidemiology of lung cancer. Chest 2003; 123:21S.

McDuffie HH, Klaassen DJ, Dosman JA. Men, women and primary lung cancer--a Saskatchewan personal interview study. J Clin Epidemiol 1991; 44:537.

Osann KE, Anton-Culver H, Kurosaki T, Taylor T. Sex differences in lung-cancer risk associated with cigarette smoking. Int J Cancer 1993; 54:44.

Bain C, Feskanich D, Speizer FE, et al. Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst 2004; 96:826.

Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014; 64:9.

Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69.

Molina JR, Adjei AA, Jett JR. Advances in chemotherapy of non-small cell lung cancer. Chest 2006; 130:1211.

Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011; 61:212.

Fontham ET, Correa P, Reynolds P, et al. Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA 1994; 271:1752.

Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults - United States, 2011. MMWR Morb Mortal Wkly Rep 2012; 61:889.

Burns DM. Primary prevention, smoking, and smoking cessation: implications for future trends in lung cancer prevention. Cancer 2000; 89:2506.

Halpern MT, Khan ZM, Young TL, Battista C. Economic model of sustained-release bupropion hydrochloride in health plan and work site smoking-cessation programs. Am J Health Syst Pharm 2000; 57:1421.

Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. J Natl Cancer Inst 1993; 85:457.

Tong L, Spitz MR, Fueger JJ, Amos CA. Lung carcinoma in former smokers. Cancer 1996; 78:1004.

Cole P, Morrison AS. Basic issues in population screening for cancer. J Natl Cancer Inst 1980; 64:1263.

Patz EF Jr, Goodman PC, Bepler G. Screening for lung cancer. N Engl J Med 2000; 343:1627.

Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111:1710.

Flieder DB, Port JL, Korst RJ, et al. Tumor size is a determinant of stage distribution in t1 non-small cell lung cancer. Chest 2005; 128:2304.

Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007; 297:953.

Croswell JM, Baker SG, Marcus PM, et al. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. Ann Intern Med 2010; 152:505.

National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365:395.

Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology 2004; 231:440.

Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007; 357:2277.

Mascalchi M, Belli G, Zappa M, et al. Risk-benefit analysis of X-ray exposure associated with lung cancer screening in the Italung-CT trial. AJR Am J Roentgenol 2006; 187:421.

Mascalchi M, Mazzoni LN, Falchini M, et al. Dose exposure in the ITALUNG trial of lung cancer screening with low-dose CT. Br J Radiol 2012; 85:1134.

van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Long-term effects of lung cancer computed tomography screening on health-related quality of life: the NELSON trial. Eur Respir J 2011; 38:154.

Manser R, Lethaby A, Irving LB, et al. Screening for lung cancer. Cochrane Database Syst Rev 2013; 6:CD001991.

Berlin NI, Buncher CR, Fontana RS, et al. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Results of the initial screen (prevalence). Early lung cancer detection: Introduction. Am Rev Respir Dis 1984; 130:545.

Brett GZ. The value of lung cancer detection by six-monthly chest radiographs. Thorax 1968; 23:414.

Brett GZ. Earlier diagnosis and survival in lung cancer. Br Med J 1969; 4:260.

Dales LG, Friedman GD, Collen MF. Evaluating periodic multiphasic health checkups: a controlled trial. J Chronic Dis 1979; 32:385.

Flehinger BJ, Kimmel M, Polyak T, Melamed MR. Screening for lung cancer. The Mayo Lung Project revisited. Cancer 1993; 72:1573.

Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. Am Rev Respir Dis 1984; 130:561.

Friedman GD, Collen MF, Fireman BH. Multiphasic Health Checkup Evaluation: a 16-year follow-up. J Chronic Dis 1986; 39:453.

Frost JK, Ball WC Jr, Levin ML, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis 1984; 130:549.

Kubik A, Parkin DM, Khlat M, et al. Lack of benefit from semi-annual screening for cancer of the lung: follow-up report of a randomized controlled trial on a population of high-risk males in Czechoslovakia. Int J Cancer 1990; 45:26.

Kubík A, Polák J. Lung cancer detection. Results of a randomized prospective study in Czechoslovakia. Cancer 1986; 57:2427.

Kubík AK, Parkin DM, Zatloukal P. Czech Study on Lung Cancer Screening: post-trial follow-up of lung cancer deaths up to year 15 since enrollment. Cancer 2000; 89:2363.

Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000; 92:1308.

Melamed MR. Lung cancer screening results in the National Cancer Institute New York study. Cancer 2000; 89:2356.

Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. Chest 1984; 86:44.

Stitik FP, Tockman MS. Radiographic screening in the early detection of lung cancer. Radiol Clin North Am 1978; 16:347.

Wilde J. A 10 year follow-up of semi-annual screening for early detection of lung cancer in the Erfurt County, GDR. Eur Respir J 1989; 2:656.

U.S. Preventive Services Task Force. Lung cancer screening: recommendation statement. Ann Intern Med 2004; 140:738.

Marcus PM, Bergstralh EJ, Zweig MH, et al. Extended lung cancer incidence follow-up in the Mayo Lung Project and overdiagnosis. J Natl Cancer Inst 2006; 98:748.

Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. Control Clin Trials 2000; 21:273S.

Oken MM, Marcus PM, Hu P, et al. Baseline chest radiograph for lung cancer detection in the randomized Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. J Natl Cancer Inst 2005; 97:1832.

Oken MM, Hocking WG, Kvale PA, et al. Screening by chest radiograph and lung cancer mortality: the Prostate, Lung, Colorectal, and Ovarian (PLCO) randomized trial. JAMA 2011; 306:1865.

Bach PB. Is our natural-history model of lung cancer wrong? Lancet Oncol 2008; 9:693.

Ebeling K, Nischan P. Screening for lung cancer--results from a case-control study. Int J Cancer 1987; 40:141.

Nishii K, Ueoka H, Kiura K, et al. A case-control study of lung cancer screening in Okayama Prefecture, Japan. Lung Cancer 2001; 34:325.

Okamoto N, Suzuki T, Hasegawa H, et al. Evaluation of a clinic-based screening program for lung cancer with a case-control design in Kanagawa, Japan. Lung Cancer 1999; 25:77.

Sagawa M, Tsubono Y, Saito Y, et al. A case-control study for evaluating the efficacy of mass screening program for lung cancer in Miyagi Prefecture, Japan. Cancer 2001; 92:588.

Sobue T. A case-control study for evaluating lung cancer screening in Japan. Cancer 2000; 89:2392.

Sobue T, Suzuki T, Naruke T. Efficacy of lung cancer screening; comparison of results from a case-control study and a survival analysis. The Japanese Lung Cancer Screening Research Group. Jpn J Cancer Res 1992; 83:424.

Tsukada H, Kurita Y, Yokoyama A, et al. An evaluation of screening for lung cancer in Niigata Prefecture, Japan: a population-based case-control study. Br J Cancer 2001; 85:1326.

Black WC. Computed tomography screening for lung cancer: review of screening principles and update on current status. Cancer 2007; 110:2370.

Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA 2012; 307:2418.

Larke FJ, Kruger RL, Cagnon CH, et al. Estimated radiation dose associated with low-dose chest CT of average-size participants in the National Lung Screening Trial. AJR Am J Roentgenol 2011; 197:1165.

Gohagan J, Marcus P, Fagerstrom R, et al. 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. Chest 2004; 126:114.

National Lung Screening Trial Research Team, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. Radiology 2011; 258:243.

National Lung Screening Trial Research Team, Church TR, Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013; 368:1980.

Aberle DR, DeMello S, Berg CD, et al. Results of the two incidence screenings in the National Lung Screening Trial. N Engl J Med 2013; 369:920.

Silvestri GA. Screening for lung cancer: it works, but does it really work? Ann Intern Med 2011; 155:537.

National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365:395.

Field JK, van Klaveren R, Pedersen JH, et al. European randomized lung cancer screening trials: Post NLST. J Surg Oncol 2013; 108:280.

van Iersel CA, de Koning HJ, Draisma G, et al. 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). Int J Cancer 2007; 120:868.

van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361:2221.

van der Aalst CM, van Klaveren RJ, van den Bergh KA, et al. The impact of a lung cancer computed tomography screening result on smoking abstinence. Eur Respir J 2011; 37:1466.

Infante M, Brambilla G, Lutman F, et al. DANTE: a randomized trial on lung cancer screening with low-dose sprial CT (LDCT): initial announcement. Chest 2003; 124:118S.

Infante M, Lutman FR, Cavuto S, et al. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. Lung Cancer 2008; 59:355.

Infante M, Cavuto S, Lutman FR, et al. A randomized study of lung cancer screening with spiral computed tomography: three-year results from the DANTE trial. Am J Respir Crit Care Med 2009; 180:445.

Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial--overall design and results of the prevalence round. J Thorac Oncol 2009; 4:608.

Saghir Z, Dirksen A, Ashraf H, et al. 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. Thorax 2012; 67:296.

Pastorino U, Rossi M, Rosato V, et al. Annual or biennial CT screening versus observation in heavy smokers: 5-year results of the MILD trial. Eur J Cancer Prev 2012; 21:308.

Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999; 354:99.

Henschke CI, Yankelevitz DF, Libby DM, et al. Early lung cancer action project: annual screening using single-slice helical CT. Ann N Y Acad Sci 2001; 952:124.

International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006; 355:1763.

Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. Radiology 2005; 235:259.

Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002; 165:508.

Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003; 226:756.

McMahon PM, Kong CY, Johnson BE, et al. Estimating long-term effectiveness of lung cancer screening in the Mayo CT screening study. Radiology 2008; 248:278.

Veronesi G, Maisonneuve P, Spaggiari L, et al. Diagnostic performance of low-dose computed tomography screening for lung cancer over five years. J Thorac Oncol 2014; 9:935.

Reich JM. A critical appraisal of overdiagnosis: estimates of its magnitude and implications for lung cancer screening. Thorax 2008; 63:377.

Sone S, Nakayama T, Honda T, et al. Long-term follow-up study of a population-based 1996-1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. Lung Cancer 2007; 58:329.

Lindell RM, Hartman TE, Swensen SJ, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 2007; 242:555.

Patz EF Jr, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med 2014; 174:269.

Couraud S, Greillier L, Milleron B, IFCT Lung Cancer Screening Group. Estimating overdiagnosis in lung cancer screening. JAMA Intern Med 2014; 174:1197.

Gelbman BD, Libby DM. Estimating overdiagnosis in lung cancer screening. JAMA Intern Med 2014; 174:1197.

Slatore CG, Sullivan DR, Pappas M, Humphrey LL. Patient-centered outcomes among lung cancer screening recipients with computed tomography: a systematic review. J Thorac Oncol 2014; 9:927.

Raji OY, Duffy SW, Agbaje OF, et al. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. Ann Intern Med 2012; 157:242.

Cronin KA, Gail MH, Zou Z, et al. Validation of a model of lung cancer risk prediction among smokers. J Natl Cancer Inst 2006; 98:637.

Etzel CJ, Bach PB. Estimating individual risk for lung cancer. Semin Respir Crit Care Med 2011; 32:3.

Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. J Natl Cancer Inst 2007; 99:715.

Tammemagi CM, Pinsky PF, Caporaso NE, et al. Lung cancer risk prediction: Prostate, Lung, Colorectal And Ovarian Cancer Screening Trial models and validation. J Natl Cancer Inst 2011; 103:1058.

Tammemägi MC, Katki HA, Hocking WG, et al. Selection criteria for lung-cancer screening. N Engl J Med 2013; 368:728.

Kovalchik SA, Tammemagi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013; 369:245.

Henschke CI, Yip R, Yankelevitz DF, et al. Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. Ann Intern Med 2013; 158:246.

Lam S, McWilliams A, Mayo J, Tammemagi M. Computed tomography screening for lung cancer: what is a positive screen? Ann Intern Med 2013; 158:289.

McWilliams A, Tammemagi MC, Mayo JR, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med 2013; 369:910.

Bach PB, Gould MK. When the average applies to no one: personalized decision making about potential benefits of lung cancer screening. Ann Intern Med 2012; 157:571.

Ma J, Ward EM, Smith R, Jemal A. Annual number of lung cancer deaths potentially avertable by screening in the United States. Cancer 2013; 119:1381.

Tammemagi MC, Lam S. Screening for lung cancer using low dose computed tomography. BMJ 2014; 348:g2253.

McMahon PM, Kong CY, Bouzan C, et al. Cost-effectiveness of computed tomography screening for lung cancer in the United States. J Thorac Oncol 2011; 6:1841.

U.S. Preventive Services Task Force Recommendation Statement: Screening for Lung Cancer http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfinalrs.htm (Accessed on January 03, 2014).

de Koning HJ, Meza R, Plevritis SK, et al. Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. Ann Intern Med 2014; 160:311.

NCCN Clinical Practice Guidelines in Oncology. Lung cancer screening. Version 1.2012. http://www.nccn.org/professionals/physician_gls/pdf/lung_screening.pdf (Accessed on October 28, 2011).

Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143:e78S.

Wender R, Fontham ET, Barrera E Jr, et al. American Cancer Society lung cancer screening guidelines. CA Cancer J Clin 2013; 63:107.

Jaklitsch MT, Jacobson FL, Austin JH, et al. The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. J Thorac Cardiovasc Surg 2012; 144:33.

Couraud S, Cortot AB, Greillier L, et al. From randomized trials to the clinic: is it time to implement individual lung-cancer screening in clinical practice? A multidisciplinary statement from French experts on behalf of the French intergroup (IFCT) and the groupe d'Oncologie de langue francaise (GOLF). Ann Oncol 2013; 24:586.

Roberts H, Walker-Dilks C, Sivjee K, et al. Screening high-risk populations for lung cancer: guideline recommendations. J Thorac Oncol 2013; 8:1232.

Field JK, Smith RA, Aberle DR, et al. International Association for the Study of Lung Cancer Computed Tomography Screening Workshop 2011 report. J Thorac Oncol 2012; 7:10.

Mulshine JL, D'Amico TA. Issues with implementing a high-quality lung cancer screening program. CA Cancer J Clin 2014; 64:351.

Woloshin S, Schwartz LM, Black WC, Kramer BS. Cancer screening campaigns--getting past uninformative persuasion. N Engl J Med 2012; 367:1677.

Wiener RS. Balancing the Benefits and Harms of Low-Dose Computed Tomography Screening for Lung Cancer: Medicare's Options for Coverage. Ann Intern Med 2014; 161:445.

Sox HC. Implementing lung cancer screening under Medicare: the last chance to get it right? JAMA 2014; 312:1206.

Davis AM, Cifu AS. Lung cancer screening. JAMA 2014; 312:1248.

Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003; 362:593.

Bastarrika G, García-Velloso MJ, Lozano MD, et al. Early lung cancer detection using spiral computed tomography and positron emission tomography. Am J Respir Crit Care Med 2005; 171:1378.

Mulshine JL, Tockman MS, Smart CR. Considerations in the development of lung cancer screening tools. J Natl Cancer Inst 1989; 81:900.

Hensing TA, Salgia R. Molecular biomarkers for future screening of lung cancer. J Surg Oncol 2013; 108:327.

Belinsky SA, Liechty KC, Gentry FD, et al. Promoter hypermethylation of multiple genes in sputum precedes lung cancer incidence in a high-risk cohort. Cancer Res 2006; 66:3338.

Kersting M, Friedl C, Kraus A, et al. Differential frequencies of p16(INK4a) promoter hypermethylation, p53 mutation, and K-ras mutation in exfoliative material mark the development of lung cancer in symptomatic chronic smokers. J Clin Oncol 2000; 18:3221.

Mulshine JL, Scott F. Molecular markers in early cancer detection. New screening tools. Chest 1995; 107:280S.

Ahrendt SA, Chow JT, Xu LH, et al. Molecular detection of tumor cells in bronchoalveolar lavage fluid from patients with early stage lung cancer. J Natl Cancer Inst 1999; 91:332.

Baryshnikova E, Destro A, Infante MV, et al. Molecular alterations in spontaneous sputum of cancer-free heavy smokers: results from a large screening program. Clin Cancer Res 2008; 14:1913.

Henschke CI. Medicine on lung cancer screening: a different paradigm. Am J Respir Crit Care Med 2003; 168:1143.

George PJ. Fluorescence bronchoscopy for the early detection of lung cancer. Thorax 1999; 54:180.

Hirsch FR, Prindiville SA, Miller YE, et al. Fluorescence versus white-light bronchoscopy for detection of preneoplastic lesions: a randomized study. J Natl Cancer Inst 2001; 93:1385.

Phillips M, Gleeson K, Hughes JM, et al. Volatile organic compounds in breath as markers of lung cancer: a cross-sectional study. Lancet 1999; 353:1930.

Phillips M, Cataneo RN, Cummin AR, et al. Detection of lung cancer with volatile markers in the breath. Chest 2003; 123:2115.

Machado RF, Laskowski D, Deffenderfer O, et al. Detection of lung cancer by sensor array analyses of exhaled breath. Am J Respir Crit Care Med 2005; 171:1286.

Petty RD, Nicolson MC, Kerr KM, et al. Gene expression profiling in non-small cell lung cancer: from molecular mechanisms to clinical application. Clin Cancer Res 2004; 10:3237.

Rahman SM, Shyr Y, Yildiz PB, et al. Proteomic patterns of preinvasive bronchial lesions. Am J Respir Crit Care Med 2005; 172:1556.

Zhong L, Hidalgo GE, Stromberg AJ, et al. Using protein microarray as a diagnostic assay for non-small cell lung cancer. Am J Respir Crit Care Med 2005; 172:1308.

Veronesi G, Maisonneuve P, Bellomi M, et al. Estimating overdiagnosis in low-dose computed tomography screening for lung cancer: a cohort study. Ann Intern Med 2012; 157:776.

Topic 7566 Version 48.0