Screening for lung cancer

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INTRODUCTION

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 [1]. 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 United States. However, the smoking rate in the United States remains high, at 15 percent in 2015 [3], and is increasing in many parts of the world. In addition, 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 [4-7]. Given these facts, screening for lung cancer has been recommended broadly by many expert panels since 2014 for risk groups meeting specific smoking and demographic parameters. However, despite broad recommendations from almost all expert panels, lung cancer screening has been poorly adopted. In fact, it is estimated that only approximately 15 percent of eligible candidates have been screened. This review provides information on the current status of lung cancer screening.

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 possible risk factors for lung cancer".)

Information on the evaluation of abnormal findings as a result of screening is presented elsewhere. (See "Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer".)

EPIDEMIOLOGY

Lung cancer is the leading cause of cancer-related death in adults [8]. Some [8-10] but not all [11] studies suggest that, for any level of smoking, women are at higher risk of developing cancer than men. Worldwide, it is estimated that there are 1.6 million deaths due to lung cancer annually [12]. The American Cancer Society estimates over 234,000 new cases of lung cancer diagnosed yearly and over 154,000 lung cancer-associated deaths in the United States [13].

Clinical outcome for non-small cell lung cancer is directly related to stage at the time of diagnosis. Based on the eighth edition of TNM classification for lung cancer (table 1 and table 2), five-year survival using clinical staging ranges from 92 percent (stage IA1) to no survival (stage IVB) (figure 1); using pathologic staging, five-year survival ranges from 90 to 12 percent (figure 2) [14]. In addition, within early lung cancers (stage I), there is a relationship between tumor size and survival [15,16]. 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. However, 75 percent of patients with lung cancer present with symptoms due to advanced local or metastatic disease that is not amenable to cure [17]. Despite advances in therapy, five-year survival rates average approximately 18 percent for all individuals with lung cancer [13]. (See "Overview of the initial treatment and prognosis of lung cancer" and "Overview of the initial evaluation, diagnosis, and staging of patients with suspected lung cancer" and "Tumor, node, metastasis (TNM) staging system for lung cancer".)

POTENTIAL BENEFITS OF SCREENING

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 [18,19].

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 is properly performed and results properly 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. (See 'National Lung Screening Trial' below and 'Other trials' below.)

Enrollment in lung cancer screening may also positively affect smoking cessation rates. Several studies found that participation in a randomized controlled trial of lung cancer screening with low-dose computed tomography (LDCT) scan was associated with a favorable impact on smoking cessation rates. However, results are mixed as to whether favorable quit rates were associated with being invited to participate in a trial, being screened rather than being in the control group, or having more or less favorable results of screening [20-24].

POTENTIAL HARMS OF SCREENING

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

- **Consequences of evaluating abnormal findings** – Detection of abnormalities that require further evaluation, most of which are benign nodules, may involve needle biopsy and/or surgery, with associated morbidity and mortality [25,26]. In the National Lung Screening Trial (NLST), over 53,000 high-risk individuals were randomly assigned to LDCT scan or chest radiograph screening [27]. 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.

  Implementation of LDCT lung cancer screening in the Veterans Health Administration also provided information about the potential need for follow-up testing [28]. Among the 2106 patients who underwent lung cancer screening, 1184 (56 percent) had lung nodules that had to be tracked (the majority of nodules were <5 mm). A total of 73 patients (3.5 percent of all people screened) had findings suspicious for possible lung cancer and underwent further diagnostic evaluation, with 31 patients (1.5 percent of all people screened) diagnosed with lung cancer.

Approximately 40 percent of screened patients had incidental findings such as emphysema or coronary calcifications. Although incidental findings may not require follow-up testing, they may cause patient worry and may require a clinician to counsel the patient and determine if additional testing is indicated. Findings within the well-organized US Department of Veterans Affairs screening program, which includes older patients, smokers, and many high-risk patients, as well as experts in lung cancer and imaging, may not be generalizable to the general population of smokers and ex-smokers.

A discussion of the diagnostic evaluation of incidental pulmonary nodules is provided elsewhere. (See "Diagnostic evaluation of the incidental pulmonary nodule".)

- **Radiation exposure** – Radiation from serial imaging in a screening program may add independently to the risk of developing cancers, including lung cancer [29]. Since screening typically occurs over several rounds and positive studies require further evaluation, the cumulative radiation dose is also important. (See "Radiation-related risks of imaging", section on 'Effective dose'.)

  In secondary analysis of a LDCT screening program for asymptomatic high-risk smokers age 50 and above who were screened at least annually [30], the estimated median cumulative effective radiation dose after 10 years of screening was 13.0 millisieverts (mSv) for women and 9.3 mSv for men [31]. It was estimated that for every 108 lung cancers discovered by screening, one major cancer would be induced by radiation.

  For LDCT, the estimated effective radiation dose is 1.4 mSv compared with average effective radiation doses of 7 to 8 mSv for one standard-dose diagnostic chest CT and 0.1 mSv for one chest radiograph (posterior-anterior [PA] and lateral) [32]. (See "Radiation-related risks of imaging", section on 'Radiation dose for common imaging examinations and procedures'.)

- **Patient distress** – Prolonged follow-up of nodules, often lasting several years, may cause anxiety related to fear of having lung cancer. Few trials have evaluated patient distress with LDCT screening. A 2014 systematic review of five randomized trials and one cohort study found that LDCT screening may be associated with short-term psychologic discomfort but did not affect distress, worry, or health-related quality of life [33]. False-positive results were associated with short-term increases in distress. A subsequent study evaluated health-related quality of life and anxiety in 2800 patients who were a subset of participants in the NLST [34]. Compared with patients who had negative screens, the study found no differences in outcomes at one and six months in those with false-positive screens or screens with significant incidental findings.

- **Overdiagnosis** – Some cancers identified at screening, if never found, would not have affected morbidity or mortality during the patient's lifetime [35]. Identification of such cancers is referred to as "overdiagnosis." Overdiagnosis 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 [36]. 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 LDCT have estimated the extent of overdiagnosis to range between 13 and 27 percent [37,38].

  Although randomized trials demonstrate that screening with LDCT 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 radiograph group (1060 versus 941) [27]. One study has used the NLST data to estimate an upper limit of overdiagnosis [39], but this model has been criticized for not taking into account lead or length time bias [40,41]. Only long-term follow-up can provide a true estimate of overdiagnosis.

SCREENING MODALITIES

Chest radiograph/sputum cytology not recommended — Screening for lung cancer by chest radiograph and/or sputum cytology is not recommended. There have been at least seven large-scale controlled clinical trials (six randomized, one non-randomized) of chest radiograph screening for lung cancer [42-57]. These studies began as early as 1960, and a 20-year follow-up analysis has been published for one randomized trial [53,58,59]. None of the randomized trials have demonstrated a mortality benefit for chest radiograph screening; however, only the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial compared screening with no screening [60].

The PLCO 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 [61]. Screening for lung cancer consisted of a single posterior-anterior (PA) chest radiograph performed at baseline and annually for three years, while the control group received usual care. This study differs from prior chest radiograph screening trials in several important aspects: the cohort includes males and females 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 radiographs were abnormal, ranging from 11 percent in current smokers to 8 percent in never-smokers [62]. 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 to 84 percent during years 1 through 3 [63]. 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, relative risk [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 six 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 radiograph, 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 low-dose computed tomography (LDCT) screening with chest radiograph 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.)

Low-dose chest CT — Refinements of CT scanning techniques have led to the evaluation of low-dose helical computed tomography (LDCT) for lung cancer screening [64]. New multidetector CT scanners generate high-resolution imaging with significantly less radiation exposure than diagnostic chest CT scanning. 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 estimated effective radiation dose due to LDCT is described elsewhere. (See 'Potential harms of screening' above.)

National Lung Screening Trial — The NLST was a randomized trial comparing annual screening by LDCT scanning with chest radiograph for three years in 53,454 high-risk persons at 33 United States medical centers [27,65-67]. Participants were adults 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 NLST demonstrated that LDCT screening reduced mortality in a high-risk population (based on age and smoking history),

compared with screening by radiograph (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 LDCT to prevent one lung cancer death was 320.

The trial was stopped early after an interim analysis found a statistically significant benefit for LDCT scanning [27]. 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 radiograph 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 radiograph group, yielding a relative mortality reduction of 20 percent (CI 6.8-26.7) 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 radiograph. Over all three screening rounds, 24.2 of LDCT scans and 6.9 percent of radiographs were abnormal. The cumulative rate of false-positive findings was high: 96.4 and 94.5 percent for LDCT and radiograph 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 radiograph screening [67]. 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 radiograph group (table 3).

The rate of detection of lung cancer did not diminish between screening years, suggesting that ongoing screening would be necessary. A retrospective cohort analysis of this study examined the effect of extending the interval of screening for those with an initial negative study [68]. In this study, participants with a negative initial screening LDCT (19,066 out of 26,231) had an overall lower incidence of lung cancer and lung cancer-related mortality than did all participants. The yield of lung cancer diagnosis at the next annual LDCT screening study for these patients was lower compared with all participants (0.34 versus 1.0 percent, respectively). Extrapolating from this, the authors concluded that screening participants with a negative initial LDCT at one year would, at most, result in 28 fewer lung cancer deaths in the annual screening group (decreasing mortality from 212.1 [186.8 to 240.0] per 100,000 person-years to 185.8 [95% CI 162.3-211.9]). Because more frequent screening might cause harm, the study's authors concluded that in subjects with a negative initial screening study, increasing the screening interval from one year might be warranted.

Fewer stage IV cancers were observed in the LDCT group than the chest radiograph group with the second and third screening rounds, suggesting that diagnosis of earlier-stage cancers reduced the occurrence of later-stage lung cancers. Lung cancers detected by screening were mostly stage I or II (70 percent of CT detected and 56.7 percent of radiograph 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 radiograph group; stage IIB to IV cancers were found in 120 versus 112 participants [67]. Thus, the difference in cancer detection between groups was in the increased identification of early-stage cancers with LDCT scan in the first screen. Based on data collected for three years following the screening rounds, sensitivity and specificity were, respectively, 93.8 and 73.4 percent for LDCT and 73.5 and 91.3 percent for radiograph. Additional details about screening rounds 2 and 3 (T1 and T2) and incident lung cancers indicate that 27.9 and 16.8 percent of T1 and T2 LDCT scans, respectively, were positive [69]. 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 radiograph).

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 United States census data, a low complication rate of follow-up procedures may reflect the expertise at the participating academic centers, and radiologic performance and interpretation may not be representative of community-based radiology [70].

Since the control group in the NLST had screening with chest radiograph rather than usual care, findings of the PLCO trial, in which participants were randomly assigned to usual care or annual chest radiography, are pertinent [71]. 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 radiograph screening or usual care (RR 0.94, 95% CI 0.81-1.10).

NELSON trial — The NELSON trial, a randomized LDCT-based lung cancer trial including 15,789 (approximately 84 percent male) current or former smokers aged 50 to 74 in the Netherlands and Belgium, compared LDCT screening at increasing intervals (baseline study and subsequent screenings at years 1.0, 3.0, and 5.5) with no screening [72-75]. The study was 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 estimated cost effectiveness. Unlike other screening studies, five-year lung cancer survivors, a group at very high risk of developing a new lung cancer, were eligible for enrollment. This was the first large-scale randomized trial to compare LDCT screening with no screening.

At 10 years, lung cancer mortality for men was reduced in the screened compared with the control (unscreened) group by 24 percent (RR 0.76; 95% CI 0.62-0.94) [75]. For the smaller group of screened women, there was a 48 percent reduction in mortality at 9 years compared with unscreened women (RR 0.52, 95% CI 0.28-0.94); at 10 years, the reduction persisted but became nonsignificant (RR 0.67, 95% CI 0.38-1.14).

All-cause mortality was not different between the screened and control groups, in contrast to the 6.7 percent reduction in all-cause mortality seen in the NLST. However, unlike the NLST, the NELSON trial was not powered to detect differences in all-cause mortality. (See 'National Lung Screening Trial' above.)

Among screened male participants, 344 lung cancers were diagnosed over 10 years, of which 59 percent (203) were detected on screening examinations. Among the control (unscreened) group, 304 lung cancers were diagnosed over the same period. Among the screened group, lung cancers were more likely to be early stage at the time of diagnosis; 59 percent stage I versus 9 percent stage IV. Among the control (unscreened) group, the reverse was noted; 13.5 percent stage I versus 46 percent stage IV.

Among male participants, at each round of screening, approximately 2 percent of examinations were positive, although 9.2 percent were indeterminate and required interval scanning. Lung cancer was detected in 0.86 percent of those screened, and in 43 percent of those with positive examinations.

Nodule volume had a high discriminatory power, with a cancer frequency of 0.5 percent among nodules smaller than 27 mm^3, 3.1 percent among those with a volume of 27 mm^3 to 206 mm^3, and 17 percent among those larger than 206 mm^3 [76]. A volume cutoff of 27 mm^3 or greater had a sensitivity exceeding 95 percent for the detection of lung cancer.

Using a more extended period of follow-up and comparing screening with an unscreened control group, the NELSON trial can provide accurate estimates of overdiagnosis. At 11 years' follow-up, the excess lung cancer cases were reduced to 18, yielding an overdiagnosis rate of 8.9 percent.

Other trials — Several randomized trials of LDCT screening in Europe 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 radiograph screening) [77].

- The DANTE trial, a randomized trial in Italy that enrolled 2472 male smokers age 60 to 74 years, was 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 radiograph and sputum cytology [78]. Follow-up at an average of 8.35 years from enrollment and after completion of the baseline and annual screens has been reported [79]. Lung cancer was found in 8.2 percent of patients who received LDCT screening and in 6 percent of controls. Although there were more stage I cancers detected in the screened group than in the control group (47 [3.7 percent of lung cancers] versus 16 [1.4 percent of lung cancers]), the numbers of advanced lung cancer cases and lung cancer mortality were the same (543 versus 544 per 100,000 person-years) for both groups. The authors caution that because of the small trial size, it is unlikely to be of sufficient power to detect a mortality difference.

- The Danish Randomized Lung Cancer CT Screening Trial (DLCST) is another randomized trial of 4104 smokers (at least 20 pack-years) age 50 to 70 years [80]. Baseline data found a prevalence of lung cancer of 0.83 percent (17 cases in 2052 participants). Employing the algorithm from the International Early Lung Cancer Action Program (I-ELCAP) study for follow-up of abnormal initial findings on LDCT scan, 9 of the 17 cases were stage I. After five annual screening rounds, there was an increase in the number of stage I to IIB non-small cell lung cancers in the screened group compared with the non-screened group, with no difference in high-stage lung cancer [81]. Long-term results from the DLCST have been reported, with outcomes reported up to five years from the last round of screening LDCT. There was no difference in lung cancer-specific or overall mortality [82]. Compared with the NLST, there are several differences that may account for the lack of benefit seen. Overall, the DLCST population had a lower lung cancer risk, and it has been shown that the benefit of screening is lower in low-risk populations. The definition of an abnormal study in DLCST reduced the false-positive rate but may have resulted in more advanced cancers at time of detection. Lastly, DLCST was underpowered to detect reductions in mortality [82].

- 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) age 49 years or older [83]. It did not find any differences in lung cancer mortality among the groups [84]. However, the trial is judged to be of low quality and at high risk of

bias because of inadequate randomization, the addition of the control group later in the trial, and overall lower risk for lung cancer among participants compared with other trials.

- The German Lung Cancer Screening Intervention Study (LUSI) compared annual LDCT scan for four years with no intervention in 4052 patients 50 to 69 years old with a history of heavy smoking (defined as ≥25 years of smoking at least 15 cigarettes a day or ≥30 years of smoking at least 10 cigarettes a day) [85]. Results from the first three years of follow-up found that in the first round of screening, 22 percent of patients were recalled to be evaluated for suspicious findings. Most recall patients received repeat imaging in three to six months, 1.6 percent of all participants received a biopsy, and there was a 1.1 percent detection rate for cancer. In the second through fourth rounds of screening, the recall rate decreased to 3 to 4 percent, and the detection rate for cancer was about 0.5 percent for each round.

- The UK Lung Cancer Screening (UKLS) pilot trial evaluated the effectiveness of a risk prediction model, strategies for follow-up, and cost-effectiveness of lung cancer screening using a single LDCT screen versus no screening among a high-risk (≥5% risk over five years) population of 4055 patients aged 50 to 75 years [86]. Selection criteria were based on the Liverpool Lung ProjectV2 (LLP_{V2}) risk model that includes smoking duration (cigarette, pipe, cigar), current or prior lung disease, lung cancer history, family history of lung cancer at age <60 years, and occupational exposure to asbestos. Of 1994 participants screened with LDCT, 48 percent had at least one more CT based upon the initial findings, either at 3 or 12 months. Overall, 2.1 percent (42 patients) were diagnosed with lung cancer, 34 at initial screening, and 8 at follow-up within one year. Most cancers (86 percent) were stage I or II [86].

Meta-analysis — In a 2020 meta-analysis of seven trials (including the NLST and NELSON) among over 84,000 patients with a greater than 15 pack-year smoking history, patients screened with LDCT had lower lung cancer mortality (risk ratio [RR] 0.83, 95% CI 0.76-0.91), as well as a nonsignificant relative reduction in overall mortality of 4 percent (RR 0.96, 95% CI 0.92-1.00) compared with other interventions [87]. However, this meta-analysis includes studies of differing quality and different populations.

SYNTHESIZING THE AVAILABLE EVIDENCE

Summary — In summary, randomized controlled trials and cohort studies of screening with chest radiograph or low-dose computed tomography (LDCT) demonstrate:

- Chest radiograph screening does not reduce mortality from lung cancer, although there are limited data in women.
- LDCT screening is significantly more sensitive than chest radiograph for identifying small, asymptomatic lung cancers.
- Chest radiograph and LDCT screening have high rates of "false-positive" (noncancer) 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 National Lung Screening Trial (NLST), a large randomized trial of screening LDCT versus chest radiograph in high-risk individuals, demonstrated a lung cancer mortality benefit of 20 percent, with all-cause mortality reduced by 6.7 percent [27]. 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 [88]. In one model, estimating that 8.6 million people in the United States 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 United States [89]. However, another study suggested that screening-eligible patients in the United States were older and have more comorbidities when compared with NLST participants [90]. The benefits and harms of screening may be different in the screening-eligible patient population compared with the NLST trial.
- The NELSON trial, a large European randomized trial comparing LDCT with a control group receiving no screening, demonstrated a 24 percent reduction in lung cancer deaths with extended follow-up, findings consistent with the NLST. This study, however, was underpowered to assess all-cause mortality. Compared with the NLST, there were significant differences in screening methodology, including volumetric definitions of a positive screening study and longer intervals between screening studies.
- 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. (See 'Cost-effectiveness' below.)

Limitations of the available evidence — Questions remain regarding the optimal screening frequency and duration, appropriate population targets, defining criteria for a "positive"

finding, and identifying diagnostic follow-up protocols that minimize evaluations of false-positive findings [91-93].

- **Older age** – The best evidence regarding screening comes from the NLST, but only 25 percent of participants in the NLST were ≥65 years and none older than 75 [94]. A secondary analysis of the NLST results found that compared with patients <65 years, those ≥65 years were more likely to have false-positive screens but higher prevalence and positive predictive value for cancer (4.9 versus 3.0 percent) [95].

- **Women** – Women were underrepresented in both of the large, randomized trials of lung cancer screening, particularly the NELSON trial. However, there is evidence from studies of chest radiographs, Japanese cohort studies of LDCT, and the NLST suggesting that lung cancer screening may be more effective in women than men [84,96].

- **Radiologic parameters** – The criteria used to define an "abnormal" result affects the risk of cancer and the performance characteristics of a screening program. The NLST identified a noncalcified nodule >4 mm as an abnormality with a high false-positive rate of screening [27]. Studies have suggested that the false-positive rate could be decreased with different radiologic criteria, but it is not clear how to define the optimal parameters for screening.

  There are two basic approaches to determining an abnormal study, each with thresholds for being considered abnormal: linear dimension of size (generally an average of two perpendicular measurements), and nodule volume determined using specialized software. The NELSON trial used semiautomated volume measurements and demonstrated a lower rate of positive studies with a higher positive predictive value. Other factors may also contribute to the improved accuracy seen in the NELSON trial.

  A retrospective interpretation of data from the International Early Lung Cancer Action Program (I-ELCAP) study cohort and NLST suggested that setting a more conservative threshold (eg, >6 mm) would decrease the false-positive rate (resulting in fewer unnecessary procedures or follow-up studies) with minimal impact on the detection of cancers [97,98]. Another retrospective study applied the Lung Imaging Reporting and Data System (Lung-RADS) criteria from the American College of Radiology to the NLST data [99]. The study found a decrease in the false-positive rate but also a concomitant decrease in the sensitivity of screening. Compared with the NLST, the Lung-RADS criteria have a more conservative threshold for a positive baseline screen (>6 mm) and require growth for preexisting nodules.

  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 optimal approach to identifying, defining, and following abnormal studies remains an active area of investigation. The evaluation of a solitary pulmonary nodule is discussed in greater detail separately. (See "Diagnostic evaluation of the incidental pulmonary nodule", section on 'Nodules found on lung cancer screening'.)

- **Risk prediction models** – Trials have selected participants who are considered to be at high risk for lung cancer on the basis of smoking history. However, the benefits from screening could be improved if it were possible to more precisely identify a high-risk population. Risk prediction models that incorporate factors in addition to smoking have been proposed to better identify high-risk groups [102-108]. 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. In addition, how to implement and operationalize individual risk-based screening remains a major challenge.

  There is evidence to suggest that targeting screening to higher-risk individuals could result in greater benefits with lower risks. In a retrospective study using NLST participants, a risk prediction model was used to divide participants into five quintiles [109]. The study found that 88 percent of the screen-prevented lung cancer deaths occurred among participants in the three highest-risk quintiles, and only 1 percent of prevented deaths occurred in the lowest-risk quintile. A model derived from data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial incorporates age, education, body mass index (BMI), family history, history of chronic lung disease, and smoking status, and it performed well with external validation [107,110]. A study applying this model to the PLCO and NLST cohorts suggested that smokers age 66 to 80 years would benefit more from screening than those age 55 to 64 years, and that never-smokers would not benefit from screening [111].

In a subsequent study, an empirical individual risk model incorporating smoking history, family history, presence of lung disease, sex, education, race, and BMI was validated in the PLCO and NLST cohorts and in the United States general population, and compared with US Preventive Services Task Force (USPSTF) and The Centers for Medicare and Medicaid Services (CMS) recommendations for screening [102]. The individual risk assessment model improved both effectiveness and efficiency of screening; if the same number of ever-smokers were screened, individual risk-based screening would avert 20 percent more deaths compared with application of the USPSTF criteria. It would also reduce the number needed to screen to prevent a death

(NNS) by 17 percent. With this approach, there are USPSTF-ineligible individuals with sufficient lung cancer risk who would benefit from screening, replacing 36 percent of USPSTF-eligible, low-risk individuals who are unlikely to benefit from screening. This strategy also results in increasing the number of African Americans and women recommended for screening.

As a final example, 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 [103]. 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.

Cost-effectiveness — Decisions regarding implementation of a lung cancer screening program should in part be based upon a cost-effectiveness analysis of a screening program. Based on the NLST trial, 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) [27].

Modeling studies will be needed to determine actual cost-effectiveness. One analysis, based upon a model designed prior to completion of the NLST, suggested that LDCT screening might decrease lung cancer mortality at 10 years by 18 to 25 percent, at a cost ranging from USD $126,000 to $269,000 per quality-adjusted life year (QALY) [112]. Additionally, the model found that a smoking cessation program was more cost-effective than LDCT screening alone or LDCT screening combined with smoking cessation. Another model, done after the completion of the NLST, estimated LDCT screening would cost $81,000 per QALY [113]. The model noted that estimates varied widely depending on subgroups, with LDCT screening being more cost-effective in women and in groups with a higher risk of lung cancer.

Recommendations by expert groups — Many expert screening groups have incorporated results from the NLST in their recommendations (table 4):

- **American Association for Thoracic Surgery** – The American Association for Thoracic Surgery (AATS) also released guidelines in 2012 that recommend LDCT screening for high-risk individuals who meet the NLST criteria [114]. The AATS guidelines extend the age for screening, advise 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.

- **American College of Chest Physicians, American Society of Clinical Oncology, American Cancer Society** – Guidelines were issued in 2012 from the American College of

Chest Physicians (ACP), the American Society of Clinical Oncology (ASCO) [115-117], and the American Cancer Society (ACS) [118]. These guidelines (table 4) 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.

- **Canadian Task Force on Preventive Health Care** – The Canadian Task Force on Preventive Health Care recommends screening asymptomatic adults age 55 to 74 years with at least a 30 pack-year smoking history who smoke or quit smoking <15 years ago with LDCT every year for three consecutive years [119].

- **National Comprehensive Cancer Network** – The 2022 National Comprehensive Cancer Network (NCCN) guidelines recommend discussion of screening with annual LDCT scan screening for those at high risk [120]. High risk was defined age 50 years or greater with a ≥20 pack-year history of smoking. There is no upper age cutoff; however, LDCT screening is not recommended for individuals with functional status or comorbidity that would prohibit curative-intent therapy. The guidelines state that lung cancer screening should be done within the context of a multidisciplinary program (which may include radiology, pulmonary medicine, internal medicine, thoracic oncology, and/or thoracic surgery) to manage downstream testing.

- **US Preventive Services Task Force** – In 2021, the USPSTF issued new recommendations calling for annual LDCT scan for adults age 50 to 80 years old who are at high risk due to smoking history [121]. Persons are considered at high risk if they have at least a 20 pack-year smoking history and are either current smokers or have quit within the past 15 years. Screening should be discontinued once the individual has not smoked for 15 years or has a limited life expectancy. One of the goals and hopeful consequences of the USPSTF recommendation is to expand lung cancer screening to underserved populations who are at high risk of lung cancer, as well as women.

- 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 LDCT scan, after informing individuals about the risks and benefits of screening [122]. 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 [123].

OUR APPROACH TO COUNSELING FOR SCREENING

Any program of lung cancer screening requires more than low-dose computed tomography (LDCT) capability [124,125]. 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 [126,127].

The National Cancer Institute has developed a guide for patients and clinicians to review the data from the National Lung Screening Trial (NLST) to facilitate communication about the benefits and harms of screening [128].

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 possible risk factors for lung cancer".)
- Lung cancer screening requires an ongoing commitment; cancers are detected on initial and annual follow-up 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 annual 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 and are between the ages of 50 and 80 years old. Persons at increased risk as defined by the 2021 US Preventive Services Task Force (USPSTF) recommendation are those with at least a 20 pack-year smoking history, and either current smokers or former smokers having quit within the past 15 years. Screening should be discontinued once the individual has not smoked for 15 years or has a limited life expectancy.

- 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. As of February 2015, Medicare will cover low-dose helical CT scanning for asymptomatic patients age 55 to 77 years with a history of smoking at least 30 pack-years and, if a former smoker, having quit within the previous 15 years [129]. Orders for screening must also fulfill specific counseling criteria as outlined by the CMS. For former smokers, annual screening should continue until 15 years has elapsed from the date of smoking cessation.

Scheduled cancer screenings may need to be deferred due to intercurrent individual illness or in the setting of a larger public health crises (eg, epidemic or pandemic infectious disease) [130,131].

FUTURE DIRECTIONS

Other modalities and techniques being investigated for lung cancer screening include positron emission tomography (PET), biomarkers, and assessing tumor growth patterns:

- **Positron emission tomography** – At least two studies evaluated annual low-dose computed tomography (LDCT) followed by PET with fluorodeoxyglucose (FDG) for evaluating patients with noncalcified lesions ≥7 mm in diameter, each with similar results [132,133]. In one study, FDG-PET correctly diagnosed 19 of 25 indeterminate nodules [132]. 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.
- **Nonradiographic technologies** – Nonradiographic 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 [134].

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 [135]. The National Lung Screening Trial (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 [136-140].
- Automated image cytometry of sputum [141].
- Fluorescence bronchoscopy [142,143]. (See "Detection of early lung cancer: Autofluorescence bronchoscopy and investigational modalities".)
- Exhaled breath analysis of volatile organic compounds, which appear to be more common in patients with lung cancer [144-146].
- Genomic and proteomic analysis of bronchoscopic samples [147,148].
- Serum protein microarrays for detecting molecular markers [149].

- **Assessing tumor growth patterns** – The Continuous Observation of Smoking (COSMOS) study investigated whether estimation of the volume doubling time (VDT) or growth rate of tumors detected by LDCT scans could be used to determine which tumors may represent indolent cancers and thus potential overdiagnosis [150]. 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.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Screening for lung cancer".)

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 education: Lung cancer screening (The Basics)")
- Beyond the Basics topic (see "Patient education: Lung cancer prevention and screening (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Screening rationale** – Lung cancer is the leading cause of cancer-related death in the United States. Prevention (by preventing smoking and promoting smoking cessation) will have far greater impact on reducing lung cancer mortality than screening. Nonetheless, lung cancer screening with low-dose computed tomography (LDCT) and treatment has been shown to significantly reduce the burden of lung cancer morbidity and mortality. (See 'Introduction' above.)
- **Risks and benefits** – Patients who currently smoke or have a history of smoking should be advised of the risks and benefits of screening for lung cancer (see 'Our approach to counseling for screening' above). The potential harms associated with LDCT include false-

positive imaging requiring follow-up, incidental findings, radiation exposure, anxiety associated with screening and follow-up, and overdiagnosis. (See 'Potential harms of screening' above.)

- **Screening for at risk patients** – For adults age 50 to 80 years old who are at risk of lung cancer due to smoking (at least a 20 pack-year smoking history and are either current smokers or former smokers having quit within the past 15 years), we suggest annual screening with low-dose helical CT (**Grade 2B**). Screening should be discontinued once the individual has not smoked for 15 years or has a limited life expectancy. This advice is in accordance with the 2021 recommendations from the US Preventive Services Task Force (USPSTF). (See 'Our approach to counseling for screening' above.)

  - **Rationale** – Two large randomized trials have shown that screening with LDCT reduces lung cancer mortality in patients at risk due to current or past smoking. (See 'Low-dose chest CT' above.)

- **Screening modalities not recommended** – Plain chest radiograph screening, or radiograph plus sputum cytology, have been shown to be ineffective for lung cancer screening. We recommend **not** screening for lung cancer with chest radiograph (**Grade 1A**). (See 'Chest radiograph/sputum cytology not recommended' above.)

- **Importance of prevention** – All smokers and former smokers should be counseled about the importance of quitting smoking, and offered supportive care in doing so, as well as smoking abstinence. (See 'Our approach to counseling for screening' above.)

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