

Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for lung cancer.

Methods: The USPSTF reviewed the evidence on the efficacy of low-dose computed tomography, chest radiography, and sputum cytologic evaluation for lung cancer screening in asymptomatic persons who are at average or high risk for lung cancer (current or former smokers) and the benefits and harms of these screening tests and of surgical resection of early-stage non-small cell lung cancer. The USPSTF also commissioned modeling studies to provide information about the optimum age at which to begin and end screening, the optimum screening interval, and the relative benefits and harms of different screening strategies.

Population: This recommendation applies to asymptomatic adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.

Recommendation: The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)

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* For a list of the members of the USPSTF, see the **Appendix** (available at www.annals.org).

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The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

See also:

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Related article. 311
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SUMMARY OF RECOMMENDATION AND EVIDENCE

The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)

See the Clinical Considerations section for suggestions for implementation in practice.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

RATIONALE

Importance

Lung cancer is the third most common cancer and the leading cause of cancer-related death in the United States (1). The most important risk factor for lung cancer is smoking, which results in approximately 85% of all U.S. lung cancer cases (2). Although the prevalence of smoking



Figure. Screening for lung cancer: clinical summary of U.S. Preventive Services Task Force recommendation.**Annals of Internal Medicine**

SCREENING FOR LUNG CANCER
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Asymptomatic adults aged 55 to 80 y who have a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 y
Recommendation	Screen annually for lung cancer with low-dose computed tomography. Discontinue screening when the patient has not smoked for 15 y. Grade: B
Risk Assessment	Age, total cumulative exposure to tobacco smoke, and years since quitting smoking are the most important risk factors for lung cancer. Other risk factors include specific occupational exposures, radon exposure, family history, and history of pulmonary fibrosis or chronic obstructive lung disease.
Screening Tests	Low-dose computed tomography has high sensitivity and acceptable specificity for detecting lung cancer in high-risk persons and is the only currently recommended screening test for lung cancer.
Treatment	Non-small cell lung cancer is treated with surgical resection when possible and also with radiation and chemotherapy.
Balance of Benefits and Harms	Annual screening for lung cancer with low-dose computed tomography is of moderate net benefit in asymptomatic persons who are at high risk for lung cancer based on age, total cumulative exposure to tobacco smoke, and years since quitting smoking.
Other Relevant USPSTF Recommendations	The USPSTF has made recommendations on counseling and interventions to prevent tobacco use and tobacco-caused disease. These recommendations are available at www.uspreventiveservicestaskforce.org .

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

has decreased, approximately 37% of U.S. adults are current or former smokers (2). The incidence of lung cancer increases with age and occurs most commonly in persons aged 55 years or older. Increasing age and cumulative exposure to tobacco smoke are the 2 most common risk factors for lung cancer.

Lung cancer has a poor prognosis, and nearly 90% of persons with lung cancer die of the disease. However, early-stage non-small cell lung cancer (NSCLC) has a better prognosis and can be treated with surgical resection.

Detection

Most lung cancer cases are NSCLC, and most screening programs focus on the detection and treatment of early-stage NSCLC. Although chest radiography and sputum cytologic evaluation have been used to screen for lung cancer, LDCT has greater sensitivity for detecting early-stage cancer (3).

Benefits of Detection and Early Treatment

Although lung cancer screening is not an alternative to smoking cessation, the USPSTF found adequate evidence that annual screening for lung cancer with LDCT in a defined population of high-risk persons can prevent a substantial number of lung cancer-related deaths. Direct evidence from a large, well-conducted, randomized, controlled trial (RCT) provides moderate certainty of the

benefit of lung cancer screening with LDCT in this population (4). The magnitude of benefit to the person depends on that person's risk for lung cancer because those who are at highest risk are most likely to benefit. Screening cannot prevent most lung cancer-related deaths, and smoking cessation remains essential.

Harms of Detection and Early Intervention and Treatment

The harms associated with LDCT screening include false-negative and false-positive results, incidental findings, overdiagnosis, and radiation exposure. False-positive LDCT results occur in a substantial proportion of screened persons; 95% of all positive results do not lead to a diagnosis of cancer. In a high-quality screening program, further imaging can resolve most false-positive results; however, some patients may require invasive procedures.

The USPSTF found insufficient evidence on the harms associated with incidental findings. Overdiagnosis of lung cancer occurs, but its precise magnitude is uncertain. A modeling study performed for the USPSTF estimated that 10% to 12% of screen-detected cancer cases are overdiagnosed—that is, they would not have been detected in the patient's lifetime without screening. Radiation harms, including cancer resulting from cumulative exposure to radiation, vary depending on the age at the start of screening;

the number of scans received; and the person's exposure to other sources of radiation, particularly other medical imaging.

USPSTF Assessment

The USPSTF concludes with moderate certainty that annual screening for lung cancer with LDCT is of moderate net benefit in asymptomatic persons who are at high risk for lung cancer based on age, total cumulative exposure to tobacco smoke, and years since quitting smoking. The moderate net benefit of screening depends on limiting screening to persons who are at high risk, the accuracy of image interpretation being similar to that found in the NLST (National Lung Screening Trial), and the resolution of most false-positive results without invasive procedures (4).

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

The risk for lung cancer increases with age and cumulative exposure to tobacco smoke and decreases with time since quitting smoking. The best evidence for the benefit of screening comes from the NLST, which enrolled adults aged 55 to 74 years who had at least a 30 pack-year smoking history and were current smokers or had quit within the past 15 years. As with all screening trials, the NLST tested a specific intervention over a finite period. Because initial eligibility extended through age 74 years and participants received 3 annual screening computed tomographic scans, the oldest participants in the trial were aged 77 years.

The USPSTF used modeling studies to predict the benefits and harms of screening programs that use different screening intervals, age ranges, smoking histories, and times since quitting. A program that annually screens adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years is projected to have a reasonable balance of benefits and harms. The model assumes that persons who achieve 15 years of smoking cessation during the screening program discontinue screening. This model predicts the outcomes of continuing the screening program used in the NLST through age 80 years.

Screening may not be appropriate for patients with substantial comorbid conditions, particularly those at the upper end of the screening age range. The NLST excluded persons who were unlikely to complete curative lung cancer surgery and those with medical conditions that posed a substantial risk for death during the 8-year trial. The baseline characteristics of the NLST showed a relatively healthy sample, and fewer than 10% of enrolled participants were older than 70 years (5). Persons with serious comorbid conditions may experience net harm, no net benefit, or at least substantially less net benefit. Similarly, persons who are unwilling to have curative lung surgery are unlikely to benefit from a screening program.

Assessment of Risk

Age, total exposure to tobacco smoke, and years since quitting smoking are important risk factors for lung cancer and were used to determine eligibility in the NLST. Other risk factors include specific occupational exposures, radon exposure, family history, and history of pulmonary fibrosis or chronic obstructive lung disease. The incidence of lung cancer is relatively low in persons younger than 50 years but increases with age, especially after age 60 years. In current and former smokers, age-specific incidence rates increase with age and cumulative exposure to tobacco smoke.

Smoking cessation substantially reduces a person's risk for developing and dying of lung cancer. Among persons enrolled in the NLST, those who were at highest risk because of additional risk factors or a greater cumulative exposure to tobacco smoke experienced most of the benefit (6). A validated multivariate model showed that persons in the highest 60% of risk accounted for 88% of all deaths preventable by screening.

Screening Tests

Low-dose computed tomography has shown high sensitivity and acceptable specificity for the detection of lung cancer in high-risk persons. Chest radiography and sputum cytologic evaluation have not shown adequate sensitivity or specificity as screening tests. Therefore, LDCT is currently the only recommended screening test for lung cancer.

Treatment

Surgical resection is the current standard of care for localized NSCLC. This type of cancer is treated with surgical resection when possible and also with radiation and chemotherapy. Annual LDCT screening may not be useful for patients with life-limiting comorbid conditions or poor functional status who may not be candidates for surgery.

Other Approaches to Prevention

Smoking cessation is the most important intervention to prevent NSCLC. Advising smokers to stop smoking and preventing nonsmokers from being exposed to tobacco smoke are the most effective ways to decrease the morbidity and mortality associated with lung cancer. Current smokers should be informed of their continuing risk for lung cancer and offered cessation treatments. Screening with LDCT should be viewed as an adjunct to tobacco cessation interventions.

Useful Resources

Clinicians have many resources to help patients stop smoking. The Centers for Disease Control and Prevention has developed a Web site with many such resources, including information on tobacco quit lines, available in several languages (www.cdc.gov/tobacco/campaign/tips). Quit lines provide telephone-based behavioral counseling and support to tobacco users who want to quit smoking. Counseling is provided by trained cessation specialists who follow standardized protocols that may include several ses-

sions and are generally provided at no cost to users. The content has been adapted for specific populations and can be tailored for individual clients. Strong evidence shows that quit lines can expand the use of evidence-based tobacco cessation treatments in populations that may have limited access to treatment options.

Combination therapy with counseling and medications is more effective at increasing cessation rates than either component alone. The U.S. Food and Drug Administration has approved several forms of nicotine replacement therapy (gum, lozenge, transdermal patch, inhaler, and nasal spray), as well as bupropion and varenicline. More information on the treatment of tobacco dependence can be found in the U.S. Public Health Service Reference Guide "Treating Tobacco Use and Dependence: 2008 Update" (available at www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/reference/tobaqrq.pdf). The National Cancer Institute has developed a patient and physician guide for shared decision making for lung cancer screening based on the NLST (available at www.cancer.gov/newscenter/qa/2002/NLSTstudyGuidePatientsPhysicians). This 1-page resource may be a useful communication tool for providers and patients.

In addition, the National Comprehensive Cancer Network has developed guidelines for the follow-up of lung nodules (7). The appropriate follow-up and management of abnormalities found on LDCT scans are important given the high rates of false-positive results and the potential for harms. Lung cancer screening with LDCT should be implemented as part of a program of care, as outlined in the next section.

OTHER CONSIDERATIONS

Implementing a Lung Cancer Screening Program

Screening Eligibility, Screening Intervals, and Starting and Stopping Ages

The NLST, the largest RCT to date with more than 50 000 patients, enrolled participants aged 55 to 74 years at the time of randomization who had a tobacco use history of at least 30 pack-years and were current smokers or had quit within the past 15 years (4). The USPSTF recommends extending the program used in the NLST through age 80 years. Screening should be discontinued once the person has not smoked for 15 years.

The NLST enrolled generally healthy persons, and the findings may not accurately reflect the balance of benefits and harms in those with comorbid conditions. The USPSTF recommends discontinuing screening if a person develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

Clinicians will encounter patients who are interested in screening but do not meet the criteria of high risk for lung cancer as described previously. The balance of benefits and harms of screening may be unfavorable in these lower-

risk patients. Current evidence is lacking on the net benefit of expanding LDCT screening to include lower-risk patients. It is important that persons who are at lower risk for lung cancer be aware of the potential harms of screening. Future improvements in risk assessment tools will help clinicians better individualize patients' risks (6).

Smoking Cessation Counseling

All persons enrolled in a screening program should receive smoking cessation interventions. To be consistent with the USPSTF recommendation on counseling and interventions to prevent tobacco use and tobacco-related disease, persons who are referred to a lung cancer screening program through primary care should receive these interventions before referral. Because many persons may enter screening through pathways other than referral from primary care, the USPSTF encourages incorporating such interventions into the screening program.

Shared Decision Making

Shared decision making is important for the population for whom screening is recommended. The benefit of screening varies with risk because persons who are at higher risk because of smoking history or other risk factors are more likely to benefit. Screening cannot prevent most lung cancer deaths, and smoking cessation remains essential. Lung cancer screening has substantial harms, most notably the risk for false-positive results and incidental findings that lead to a cascade of testing and treatment that may result in more harms, including the anxiety of living with a lesion that may be cancer. Overdiagnosis of lung cancer and the risks of radiation are real harms, although their magnitude is uncertain. The decision to begin screening should be the result of a thorough discussion of the possible benefits, limitations, and known and uncertain harms.

Standardizing LDCT Screening and Follow-up of Abnormal Findings

The evidence for the effectiveness of screening for lung cancer with LDCT comes from RCTs done in large academic medical centers with expertise in using LDCT and diagnosing and managing abnormal lung lesions. Clinical settings that have high rates of diagnostic accuracy using LDCT, appropriate follow-up protocols for positive results, and clear criteria for doing invasive procedures are more likely to duplicate the results found in trials. The USPSTF supports adherence to quality standards for LDCT (8) and establishing protocols to follow up abnormal results, such as those proposed by the National Comprehensive Cancer Network (7). A mechanism should be implemented to ensure adherence to these standards.

In the context of substantial uncertainty about how best to manage individual lesions, as well as the magnitude of some of the harms of screening, the USPSTF encourages the development of a registry to ensure that appropriate

data are collected from screening programs to foster continuous improvement over time. The registry should also compile data on incidental findings and the testing and interventions that occur as a result of these findings.

Research Needs and Gaps

Smoking prevalence and lung cancer incidence are higher among socioeconomically disadvantaged populations, and more research is needed in these groups. In addition, if lung cancer screening with LDCT is implemented more widely in diverse community settings, it is important to evaluate whether variability in follow-up protocols of positive results on LDCT scans results in a different balance of benefits and harms than that observed in RCTs.

More research is also needed on the use of biomarkers to focus LDCT efforts in persons who are at highest risk for lung cancer. The role of biomarkers in accurately discriminating between benign and malignant nodules and in identifying more aggressive disease needs to be determined.

DISCUSSION

Burden of Disease

Lung cancer is the third most common cancer in the United States. Age-adjusted incidence rates per 100 000 persons are higher in men and vary according to the duration of and exposure to tobacco smoke. The most important risk factor for lung cancer is smoking, which results in approximately 85% of all lung cancer cases in the United States. Although the prevalence of smoking has decreased, approximately 37% of U.S. adults are current or former smokers. In 2008, an estimated 7 million U.S. adults aged 55 to 75 years had a 30 pack-year or more smoking history (2).

The incidence of lung cancer increases with age and is most common in adults aged 55 years or older. Lung cancer is the leading cause of cancer-related death in the United States, accounting for approximately 28% of all deaths from cancer. Death from lung cancer is often related to the initial stage of diagnosis. The average 5-year survival rate for lung cancer is among the lowest (17%) of all types of cancer but is higher when the disease is diagnosed at an early stage (52%). However, only 15% of lung cancer cases are diagnosed at such a stage (2).

Scope of Review

To update the 2004 recommendation, the USPSTF commissioned a systematic evidence review to assess the efficacy of LDCT, chest radiography, and sputum cytologic evaluation for lung cancer screening in asymptomatic persons who are at average or high risk for lung cancer (current or former smokers) (3). The review focused on new evidence from RCTs to determine the effectiveness of these screening tests in improving health outcomes. Information about the harms associated with these screening tests was obtained from RCTs and cohort studies. The

benefits and harms associated with surgical resection of early-stage NSCLC were also examined.

In addition to the evidence review, the USPSTF commissioned modeling studies from the Cancer Intervention and Surveillance Modeling Network (CISNET) to provide information about the optimum age at which to begin and end screening, the optimum screening interval, and the relative benefits and harms of different screening strategies (9, 10). The modeling studies complement the evidence from the systematic review.

Accuracy of Screening Tests

The sensitivity of chest radiography for detecting lung cancer varies depending on the size and location of the lesion, image quality of the scan, and skill of the radiologist who interprets the scan. Low-dose computed tomography has emerged as a test with higher sensitivity and specificity for lung cancer than chest radiography. In 2004, the USPSTF found inadequate evidence to recommend for or against screening for lung cancer with LDCT, chest radiography, sputum cytologic evaluation, or a combination of these tests (I statement). Since then, many RCTs have been done and published, resulting in more data on the benefits and harms of screening. Recent data from the NLST showed a sensitivity of 93.8% and specificity of 73.4% for LDCT and a sensitivity of 73.5% and specificity of 91.3% for chest radiography (11). Sputum cytologic evaluation is now rarely used for lung cancer screening, and no studies reported on the test characteristics of this screening method.

Effectiveness of Early Detection and Treatment

Four RCTs reported the effectiveness of LDCT for lung cancer screening. The largest trial, the NLST, showed a reduction in lung cancer mortality of 16% (95% CI, 5.0% to 25.0%) (12) and a reduction in all-cause mortality of 6.7% (CI, 1.2% to 13.6%) (4). This trial included more than 50 000 asymptomatic adults aged 55 to 74 years who had at least a 30 pack-year smoking history.

Participants were current or former smokers and were randomly assigned to LDCT or chest radiography. They received annual testing at baseline and years 1 and 2 and were followed for a median of 6.5 years. After 6 to 7 years of follow-up, 2.06% of patients in the chest radiography group and 1.75% of those in the LDCT group had died of lung cancer, for an absolute difference of 0.31% and a number needed to screen of about 320 (4). The number needed to screen is based on 3 annual screenings; screening the same sample over a longer period will result in a much lower estimate.

In contrast to the NLST, 3 small European trials showed potential harm or no benefit of screening. Two small fair-quality trials, the DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays) trial and the DLCST (Danish Lung Cancer Screening Trial), showed no benefit associated with LDCT compared with no LDCT (13–15).

Table. Screening Scenarios From CISNET Models*

Screening Scenario†				Benefit		Harm‡			CT Screens per Lung Cancer Death Averted, <i>n</i>
Minimum Pack-Years at Screening, <i>n</i>	Minimum Age at Which to Begin Screening, <i>y</i>	Time Since Last Cigarette, <i>y</i>	Population Ever Screened, %	Lung Cancer Deaths Averted, %	Lung Cancer Deaths Averted, <i>n</i>	Total CT Screens, <i>n</i>	Radiation-Induced Lung Cancer Deaths, <i>n</i>	Overdiagnosis, %§	
40	60	25	13.0	11.0	410	171 924	17	11.2	437
40	55	25	13.9	12.3	458	221 606	20	11.1	506
30	60	25	18.8	13.3	495	253 095	21	11.9	534
30	55	15	19.3	14.0	521	286 813	24	9.9	577
20	60	25	24.8	15.4	573	327 024	25	9.8	597
30	55	25	20.4	15.8	588	342 880	25	10.0	609
20	55	25	27.4	17.9	664	455 381	31	10.4	719
10	55	25	36.0	19.4	721	561 744	35	9.5	819

CISNET = Cancer Intervention and Surveillance Modeling Network; CT = computed tomography.

* All scenarios model the results of following a cohort of 100 000 persons from age 45 to 90 *y* or until death from any cause, with a varying number of smokers and former smokers screened on the basis of smoking history, age, and years since stopping smoking. Bold text indicates the screening scenario with a reasonable balance of benefits and harms and that is recommended by the U.S. Preventive Services Task Force.

† In all scenarios, screening is continued through age 80 *y*.

‡ Number of CT screenings is a measure of harm because it relates to the number of patients who will have risk for overdiagnosis and potential consequences from false-positive results.

§ Percentage of screen-detected cancer that is overdiagnosis; that is, cancer that would not have been diagnosed in the patient's lifetime without screening.

However, these were smaller trials (*n* = 2472 and 4104, respectively) that may have had limited power to detect a true benefit.

Of note, the inclusion criteria in the DLCST resulted in younger and healthier participants than in other trials. The relative risk for all-cause mortality in the DLCST was 1.46 (CI, 0.99 to 2.15). This finding raises the possibility of potential harm of screening a young, healthy population. Follow-up in the DLCST was 4.7 years (15). Combined data from the DLCST and the NELSON (Dutch-Belgian Randomised Lung Cancer Screening) trial will be reported soon (2).

When these 3 fair- or good-quality trials were combined in a meta-analysis, the relative risk for lung cancer mortality was 0.81 (CI, 0.72 to 0.91) (2). Another European trial, the MILD (Multicentric Italian Lung Detection) study, was rated as poor quality because of concerns about the adequacy of randomization; its results were not included in the final meta-analysis (16).

Two fair- to good-quality trials found no benefits associated with chest radiography screening (2). The larger of these trials, the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial, evaluated more than 150 000 participants from the general population and found no benefits of this type of screening in this group or in a subgroup that had tobacco smoke exposure (17).

Smaller RCTs from Europe had different eligibility criteria and have not yet duplicated the findings of the NLST; therefore, only moderate certainty exists about the magnitude of benefit from screening (3). As with all screening trials, these studies were done over a limited time frame, with the NLST evaluating the effect of 3 annual screenings. Modeling is required to estimate the effect of screening beyond that evaluated in a clinical trial. Esti-

mates of the results of different screening intervals, ages at which to start and stop screening, and thresholds for smoking history come from modeling studies that CISNET conducted for the USPSTF.

Annual screening with LDCT provides the greatest benefit in decreasing lung cancer mortality compared with biennial or triennial screening (9, 10). The Table shows the results of annual screening strategies between the ages of 55 and 80 years that had a better balance of benefits and harms than other strategies in this age range. Focusing screening efforts on the highest-risk persons, those with at least a 40 pack-year smoking history, results in the lowest number of screening scans per death averted and, therefore, the least harm to patients in terms of risk for overdiagnosis and consequences of false-positive results.

Screening progressively larger proportions of the population by lowering the screening threshold increases the number of deaths averted but with a progressively higher number of screening scans per death averted, therefore increasing harm. The Table shows that increasing the proportion of the population screened from 13% to 36% increases the number of deaths averted by 75% but increases the number of screening scans by 327%, greatly increasing the probability of an untoward event after the evaluation of a false-positive result and the number of radiation-induced cancer deaths. The "bolded" program—screening current or former smokers aged 55 to 80 years who have at least a 30 pack-year smoking history and discontinuing (or not starting) screening after 15 years of smoking abstinence—most closely resembles the strategy applied to participants in the NLST and offers a reasonable balance of benefits and harms.

The CISNET modeling studies show similar life-years gained per death averted and proportion of cancer cases

detected at an early stage across the screening strategies. The modeling studies estimate that 9.5% to 11.9% of screen-detected cancer cases are overdiagnosed—that is, they would not have been detected in the patient's lifetime without screening (9, 10).

Potential Harms of Screening and Treatment

Harms associated with LDCT screening include false-negative and false-positive results, incidental findings, overdiagnosis, radiation exposure, and psychological distress. The sensitivity of LDCT ranged from 80% to 100%, suggesting a false-negative rate of 0% to 20%. The specificity of LDCT ranged from 28% to 100%.

The positive predictive value for lung cancer of an abnormal test result ranged from 2% to 42% (2). As mentioned previously, the NLST is the largest trial of lung cancer screening to date, and recent results showed a sensitivity of 93.8% and specificity of 73.4% for LDCT. In the NLST, the positive predictive value for a positive finding of a pulmonary nodule measuring 4 mm or larger was 3.8% (11).

Over the 3 rounds of screening in the NLST, 24.2% of screening test results were positive; 96.4% of these were false-positives. Most positive test results were followed by additional imaging. Approximately 2.5% of positive test results required additional invasive diagnostic procedures, such as bronchoscopy, needle biopsy, or thoracoscopy. Of the 17 053 positive test results evaluated, there were approximately 61 complications and 6 deaths after a diagnostic procedure. Recently published data from the first round of screening in the NLST showed an average of 1 follow-up scan per positive screening test result. Approximately 1.9% of NLST participants had a biopsy (11).

The most common incidental findings on LDCT were emphysema and coronary artery calcifications. Other pulmonary findings included bronchiectasis, pulmonary fibrosis, carcinoid tumors, and hamartomas. The NLST reported that 7.5% of non-lung cancer abnormalities were clinically significant. None of the studies reported data on the evaluations that may have occurred in response to the incidental findings. Therefore, the harms and benefits associated with incidental findings cannot currently be determined (2).

Overdiagnosis was not formally reported in any study. The NLST found 119 more lung cancer cases in approximately 26 000 participants in the LDCT group than in the chest radiography group after 6.5 years of follow-up, which suggests some overdiagnosis. Recent data from the Italian Continuing Observation of Smoking Subjects cohort study of approximately 5000 participants showed that of the 120 incident cancer cases, 25% were slow-growing or indolent (based on volume-doubling time), thus possibly indicating some overdiagnosis with LDCT (18).

Radiation exposure associated with LDCT ranged from 0.61 to 1.5 mSv per scan. To provide context, annual background radiation exposure in the United States aver-

ages 2.4 mSv, radiation exposure from mammography is 0.7 mSv, and radiation exposure from head computed tomography is 1.7 mSv. The risk for radiation-induced lung cancer depends on the age at which a person begins screening and the amount of cumulative radiation received. On the basis of modeling studies, starting annual LDCT screening before age 50 years may result in more radiation-related lung cancer deaths than starting annual screening after age 50 years (9, 10).

Overall, LDCT screening did not seem to result in substantial long-term psychological distress, although assessment has been limited. No studies reported long-term differences in anxiety or distress levels associated with LDCT in participants.

No RCTs compared treatment of stage IA or IB lung cancer with surgical resection versus no treatment. Surgical resection is the standard of care in the United States for early-stage NSCLC. Studies of symptomatic and unselected patients reported 5-year survival rates associated with surgical resection of 71% to 90% for stage IA cancer and 42% to 75% for stage IB cancer. No RCTs of LDCT screening evaluated the harms associated with screen-detected cancer. Studies that reported the harms of surgical resection were done in patients who were identified in clinical practice and had comorbid conditions (3).

Estimate of Magnitude of Net Benefit

On the basis of data from the systematic evidence review and modeling studies, the USPSTF determined with moderate certainty that annual LDCT screening provides substantial net benefit in persons aged 55 to 80 years at high risk for lung cancer. Evidence from the NLST supports this recommendation because participants in that trial were in this age range and had a similar degree of lung cancer risk from cumulative tobacco exposure. Persons who do not meet the minimum eligibility criteria for the NLST may have less net benefit and more harms from screening (persons aged 55 to 74 years at enrollment who have a ≥ 30 pack-year smoking history and are current smokers or have quit in the past 15 years). For these persons, the absolute benefit of screening is strongly associated with their age and smoking history.

Modeling studies conducted by CISNET investigators for the USPSTF showed that annual LDCT screening yielded the greatest net benefit (compared with biennial or triennial screening) (9, 10). Benefits were measured as percentage of early-stage detection of lung cancer, percentage and absolute number of lung cancer deaths averted, and number of life-years gained. Harms were measured as the number of total LDCT screenings per 100 000 persons and per person, number of cases of overdiagnosed lung cancer, and number of radiation-induced lung cancer deaths. The microsimulation models used standardized data on smoking history and non-lung cancer mortality to simulate the effects of various screening programs on the mortality rate of a U.S. cohort born in 1950. This cohort

was chosen because these persons reach age 63 years (approximate midrange of participants' ages in the NLST) in 2013.

Modeling evidence suggests that an annual screening program starting at age 55 years and ending after age 80 years (in persons who have a 30 pack-year smoking history and currently smoke or have quit in the past 15 years) resulted in approximately 50% of lung cancer cases detected at an early stage (9, 10). This screening protocol would result in a 14% reduction in lung cancer mortality, or an estimated 521 lung cancer deaths prevented per 100 000 persons in the population. The harms associated with this screening protocol are an estimated overdiagnosis of 10% of screen-detected cases and radiation-induced lung cancer deaths of less than 1%. As mentioned previously, a person's absolute net benefit from screening may depend not just on age but functional status and the presence of other comorbid conditions.

How Does Evidence Fit With Biological Understanding?

Lung cancer is a proliferation of malignant cells arising in the tissues or airways of the lungs. In addition to age and exposure to tobacco smoke, other risk factors for lung cancer include family history; chronic obstructive pulmonary disease; pulmonary fibrosis; and exposure to indoor cooking fumes, radon, asbestos, arsenic, chromium, and coal tar. Non-small cell lung cancer is a heterogeneous category that includes adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and undifferentiated carcinoma. Adenocarcinoma is the most common subtype, encompassing 36% of all lung cancer cases.

Currently, 75% of patients with lung cancer present with symptoms of advanced local or metastatic disease that result in a poor prognosis (2). At the earliest stage, median 5-year survival for NSCLC is 77%. Patients with localized disease (defined as cancer limited to the lung without metastasis to other organs or lymph nodes) have a median 5-year survival of 52% compared with 25% for those with regional spread and 4% for those with distant metastasis. Thus, earlier detection and treatment of lung cancer give patients a greater chance for cure.

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 30 July to 26 August 2013. Most of the comments generally agreed with the recommendation statement, although some suggested restricting screening to a higher-risk group and others suggested expanding eligibility criteria beyond those used in the NLST. Many comments expressed concerns about implementation of a screening program, predicting substantially greater harm in the community setting than was found in the NLST. Some comments expressed concern about the cost of implementing a screening program and the potential paradoxical effect of enabling persons to continue smoking with the perception that medical care can mitigate the risks of smoking.

In response to these comments, the USPSTF further emphasized the importance of tobacco cessation as the primary way to prevent lung cancer and provided links to resources that clinicians can use to help their patients quit smoking. A section on implementation of a screening program was added, emphasizing the need for monitoring this implementation, quality assurance in diagnostic imaging, and appropriate follow-up to replicate the benefits observed in the NLST in the general population. The USPSTF also clarified that, in addition to age and smoking history, such risk factors as occupational exposure, family history, and history of other lung diseases are important when assessing patients' risks for lung cancer.

The USPSTF acknowledges the importance of accurately identifying persons who are at highest risk to maximize the benefits and minimize the harms of screening and calls for more research to improve risk assessment tools. The USPSTF did not incorporate the costs of a screening program or the potential savings from a reduction in treatment of advanced lung cancer into the recommendation.

UPDATE OF PREVIOUS USPSTF RECOMMENDATION

This recommendation updates the 2004 recommendation, in which the USPSTF concluded that the evidence was insufficient to recommend for or against screening for lung cancer in asymptomatic persons with LDCT, chest radiography, sputum cytologic evaluation, or a combination of these tests. In the current recommendation, the USPSTF recommends annual screening for lung cancer with LDCT in persons who are at high risk based on age and cumulative tobacco smoke exposure.

RECOMMENDATIONS OF OTHERS

In 2012, the American College of Chest Physicians, the American Society of Clinical Oncology, and the American Thoracic Society (19) recommended screening for lung cancer with LDCT primarily on the basis of results from the NLST, using eligibility criteria that closely modeled those of the NLST (persons aged 55 to 74 years who have a ≥ 30 pack-year smoking history and currently smoke or have quit in the past 15 years). The recommendations also stipulated that screening should be offered only in clinical settings similar to those in the trial.

The American Association for Thoracic Surgery (20) recommends annual screening with LDCT in current and former smokers aged 55 to 79 years who have a 30 pack-year smoking history. It also recommends annual screening starting at age 50 to 79 years in patients who have a 20 pack-year smoking history and additional comorbid conditions that produce a cumulative risk for cancer of at least 5% over the next 5 years. Furthermore, it recommends annual screening in long-term cancer survivors aged 55 to 79 years.

In 2013, the American Cancer Society (21) also began recommending screening for lung cancer with LDCT in

high-risk patients who are in relatively good health and meet the NLST criteria (persons aged 55 to 74 years who have a ≥ 30 pack-year smoking history and currently smoke or have quit in the past 15 years). It recommends against the use of chest radiography and strongly suggests that all adults who receive screening enter an organized screening program that has experience in LDCT.

In addition, the National Comprehensive Cancer Network (7) recommends LDCT screening in selected patients who are at high risk for lung cancer. High risk is defined as persons aged 55 to 74 years who have at least a 30 pack-year smoking history and, if a former smoker, 15 years or less since quitting or persons aged 50 years or older who have at least a 20 pack-year smoking history and 1 additional risk factor. It does not recommend lung cancer screening in persons who are at moderate risk (aged ≥ 50 years and ≥ 20 pack-year smoking history or secondhand smoke exposure but no additional lung cancer risk factors) or low risk (younger than 50 years or smoking history of < 20 pack-years).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

Disclaimer: Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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APPENDIX: U.S. PREVENTIVE SERVICES TASK FORCE

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Virginia A. Moyer, MD, MPH, *Chair* (American Board of Pediatrics, Chapel Hill, North Carolina); Michael L. LeFevre, MD, MSPH, *Co-Vice Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Kirsten Bibbins-Domingo, PhD, MD (University of California, San Francisco, San Francisco, California); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Glenn Flores, MD (University of Texas Southwestern, Dallas, Texas); Francisco A.R. García, MD, MPH

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† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice		
Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	<p>The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as:</p> <ul style="list-style-type: none"> the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. <p>As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.</p>
Low	<p>The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of:</p> <ul style="list-style-type: none"> the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. <p>More information may allow an estimation of effects on health outcomes.</p>

* The USPSTF defines *certainty* as “likelihood that the USPSTF assessment of the net benefit of a preventive service is correct.” The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.