Evidence of Benefit Associated With Screening

Screening by low-dose helical computed tomography

Benefits

One large randomized trial reported that screening persons aged 55 to 74 years who have cigarette smoking histories of 30 or more pack-years and who, if they are former smokers, have quit within the last 15 years reduces lung cancer mortality by 20% (95% confidence interval [CI], 6.8–26.7; \( P = .004 \)) and all-cause mortality by 6.7% (95% CI, 1.2–13.6; \( P = .02 \)).[1] An updated analysis showed that the estimated reduction in lung cancer mortality was 16% (95% CI, 5–25).[2]

Magnitude of Effect: 16% relative reduction in lung cancer–specific mortality.

- **Study Design**: Evidence obtained from a randomized controlled trial.
- **Internal Validity**: Good.
- **Consistency**: Not applicable (N/A)—one randomized trial to date.
- **External Validity**: Fair.

Harms

Based on solid evidence, approximately 96% of all positive low-dose helical computed tomography screening exams do not result in a lung cancer diagnosis.[1] False-positive exams may result in unnecessary invasive diagnostic procedures.

Magnitude of Effect: Based on the findings from a large randomized trial, the average false-positive rate per screening round was 23.3%. A total of 0.06% of all false-positive screening results led to a major complication after an invasive procedure performed as diagnostic follow-up to the positive
screening result. Over three screening rounds, 1.8% of participants who did not have lung cancer had an invasive procedure following a positive screening result.

- **Study Design**: Evidence obtained from a randomized controlled trial.
- **Internal Validity**: Good.
- **Consistency**: Good.
- **External Validity**: Fair.

**Evidence of No Benefit Associated With Screening**

**Screening by chest x-ray and/or sputum cytology**

**Benefits**

Based on solid evidence, screening with chest x-ray and/or sputum cytology does not reduce mortality from lung cancer in the general population or in ever-smokers.

**Magnitude of Effect: N/A.**

- **Study Design**: Randomized controlled trials.
- **Internal Validity**: Good.
- **Consistency**: Good.
- **External Validity**: Good.

**Harms**

**False-positive exams**

Based on solid evidence, at least 95% of all positive chest x-ray screening exams do not result in a lung cancer diagnosis. False-positive exams result in unnecessary invasive diagnostic procedures.

- **Study Design**: Randomized controlled trials.
- **Internal Validity**: Good.
- **Consistency**: Good.
- **External Validity**: Good.

**Overdiagnosis**
Based on solid evidence, a modest but non-negligible percentage of lung cancers detected by screening chest x-ray and/or sputum cytology appear to represent overdiagnosed cancer; the magnitude of overdiagnosis appears to be between 5% and 25%. These cancers result in unnecessary diagnostic procedures and also lead to unnecessary treatment. Harms of diagnostic procedures and treatment occur most frequently among long-term and/or heavy smokers because of smoking-associated comorbidities that increase risk propagation.

**Magnitude of Effect:** Between 5% and 25%, depending on characteristics of screened population and screening regimen.

- **Study Design:** Randomized controlled trials.
- **Internal Validity:** Good.
- **Consistency:** Good.
- **External Validity:** Good.

**References**


**Description of the Evidence**

**Background**

**Incidence and mortality**

Lung cancer is the third most common form of noncutaneous cancer in the United States and is the leading cause of cancer death in men and in women. In 2016 alone, it is estimated that 117,920 men and 106,470 women will be diagnosed with lung cancer, and 85,920 men and 72,160 women will die from this disease. The lung cancer death rate rose rapidly over several decades in both sexes, with a persistent decline for men commencing in 1991. From 2008 to 2012, death rates decreased by 3.0% per year in men and by 1.9% per year in women.[1]
Risk Factors

The most important risk factor for lung cancer (as for many other cancers) is tobacco use.[2,3] Cigarette smoking has been definitively established by epidemiologic and preclinical animal experimental data as the primary cause of lung cancer. This causative link has been widely recognized since the 1960s, when national reports in Great Britain and the United States brought the cancer risk of smoking prominently to the public’s attention.[3] The percentages of lung cancers estimated to be caused by tobacco smoking in males and females are 90% and 78%, respectively.

For a complete description of factors associated with an increased or decreased risk of lung cancer, refer to the PDQ summary on Lung Cancer Prevention for more information.

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Screening by low-dose helical computed tomography

There have been intensive efforts to improve lung cancer screening with newer technologies, including low-dose helical computed tomography (LDCT).[4,5] LDCT was shown to be more sensitive than chest radiography. In the Early Lung Cancer Action Project (ELCAP),[5] LDCT detected almost six times as many stage I lung cancers as chest radiography, and most of these tumors were no larger than 1 cm in diameter.

A systematic analysis [6] summarized 13 observational studies of LDCT undertaken between 1993 and 2004 and that included 60 to 5,201 participants. Some Japanese studies included nonsmokers, but the others were limited to current and former smokers. Variability in detection of nodules—between 3% and 51%—may be attributed to several factors:

- The definition of nodules (some studies required a size threshold).
- The CT technology (thin slice detects more and smaller nodules).
- Geographic variation in endemic granulomatous disease.

Overall, lung cancer was diagnosed in 1.1% to 4.7% of screened participants; most of these diagnoses were early-stage disease.[6]
With completion of the National Lung Screening Trial (NLST), there is now evidence that screening with LDCT can reduce lung cancer mortality risk in ever-smokers who have smoked 30 pack-years or more and in former smokers who have quit within the past 15 years. The NLST included 33 centers across the United States. Eligible participants were between the ages of 55 years and 74 years at randomization, had a history of at least 30 pack-years of cigarette smoking, and, if former smokers, had quit within the past 15 years. A total of 53,454 persons were enrolled; 26,722 persons were randomly assigned to receive screening with LDCT, and 26,732 persons were randomly assigned to receive screening with chest x-ray. Any noncalcified nodule found on LDCT measuring at least 4 mm in any diameter and any noncalcified nodule or mass identified on x-ray images were classified as positive, although radiologists had the option of calling a final screen negative if a noncalcified nodule had been stable on the three screening exams. The LDCT group had a substantially higher rate of positive screening tests than did the radiography group (round 1, 27.3% vs. 9.2%; round 2, 27.9% vs. 6.2%; and round 3, 16.8% vs. 5.0%). Overall, 39.1% of participants in the LDCT group and 16.0% in the radiography group had at least one positive screening result. Of those who screened positive, the false-positive rate was 96.4% in the LDCT group and 94.5% in the chest radiography group. This was consistent across all three rounds.[7]

In the LDCT group, 649 cancers were diagnosed after a positive screening test, 44 after a negative screening test, and 367 among participants who either missed the screening or received the diagnosis after the completion of the screening phase. In the radiography group, 279 cancers were diagnosed after a positive screening test, 137 after a negative screening test, and 525 among participants who either missed the screening or received the diagnosis after the completion of the screening phase. Three hundred fifty-six deaths from lung cancer occurred in the LDCT group, and 443 deaths from lung cancer occurred in the chest x-ray group, with a relative reduction in the rate of death from lung cancer of 20% (95% confidence interval [CI], 6.8–26.7) with LDCT screening.[7] An updated analysis showed that the estimated reduction in lung cancer mortality was 16% (95% CI, 5–25).[8] Overall, mortality was reduced by 6.7% (95% CI, 1.2–13.6). The number needed to screen with LDCT to prevent one death from lung cancer was 320.[7]

Since the publication of the results of the NLST, more has been learned about who may benefit the most from screening for lung cancer using LDCT.[9-11] One group of investigators developed an individual risk model to assess who might benefit from screening. The model used additional factors not used as inclusion criteria in the NLST, such as a history of chronic obstructive pulmonary disease,
personal or family history of lung cancer and a more detailed smoking history. More persons would have been eligible to be screened using the trial's criteria as opposed to the inclusion criteria of the NLST without missing patients with cancer. [10] A second group performed a reanalysis of the NLST data and calculated each patient's risk of developing lung cancer and estimated each patient's lung cancer mortality.[11] The investigators then divided the NLST participants into five groups on the basis of risk. The number needed to screen to avoid a lung cancer death in the low-risk group was 5,276; 161 screens were needed in the high-risk group to avoid a lung cancer death. Further, the number of false-positive screens decreased from 1,648 in the lowest quintile of risk to 65 in the highest risk group. The three highest quintiles of risk accounted for 88% of the mortality reduction from screening whereas the lowest quintile accounted for only a 1% reduction in mortality. These studies illustrate possible improvements in determining the population of patients who may benefit the most from screening, potentially reducing the number of false positives, and reducing the potential harm related to the adverse events associated with their evaluation. One other benefit of calculating individual risk is the ability to incorporate the findings into a shared decision-making process so that patients can decide whether to undergo screening.[11]

Other randomized clinical trials (RCTs) of LDCT are under way in a number of countries.[12] The largest is the Dutch-Belgian Randomized Lung Cancer Screening Trial (or NELSON trial). This study differs from the NLST in that the control group does not have chest radiographic screening. Other smaller trials in Europe also compare a nonscreening arm to LDCT. These smaller trials do not appear to be powered to assess mortality as an endpoint, but there is an effort under way to combine the findings from these studies with the NELSON data once it is fully mature. These studies may also be able to assess consistency with the NLST findings. In addition to the data gleaned from ongoing trials, the NLST data are being analyzed to examine other important issues in lung cancer screening, including cost effectiveness, quality of life, and whether screening would benefit individuals younger than those enrolled in the NLST and those with fewer than 30 pack-years of smoking exposure. Data from the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial suggest that, in the absence of screening, the risk of lung cancer death for current smokers who have a smoking history of 20 to 29 pack-years is no different than that of former smokers who have quit within 15 years and have a smoking history of more than 30 pack-years (hazard ratio, 1.07; CI, 0.75–1.5). Although the risk for the former-smokers group is no different than that of the current-smokers group (for whom
LDCT screening is recommended by the U.S. Preventive Services Task Force, the efficacy of screening is unknown in the former-smokers group.[13]

[Note: A Guide has been developed to help patients and physicians assess the benefits and harms of LDCT screening for lung cancer.[14]]

**Screening and smoking cessation**

The target population for lung cancer screening has a high prevalence of current smokers compared with the general population. A lung cancer screening program could potentially impact the likelihood of smoking cessation, theoretically promoting cessation among those screened who have lung abnormalities detected on their screen. Conversely, screening could also be a deterrent to cessation among those with no evidence of lung abnormalities on their screen. The Danish Lung Cancer Screening Trial is a randomized trial that compared LDCT with no intervention among participants aged 50 to 70 years who had at least a 20 pack-year smoking history.[15] The proportion of participants who had quit smoking was monitored every year for 5 years of follow-up and remained virtually identical in the two groups from baseline (CT group and control group each had 23% ex-smokers) until the 5-year follow-up (43% ex-smokers in both groups). The comparison of these two randomized groups indicates that the CT screening program had zero net effect on the likelihood of smoking cessation.

Another report used data from the NLST to address the question of whether the screening result influenced the likelihood of smoking cessation.[16] The NLST compared CT with chest x-ray, and data from both arms were pooled to examine the impact of abnormal findings on the likelihood of smoking cessation. Compared with those who did not have abnormal findings, current smokers who had a screening examination suspicious for lung cancer (but not lung cancer) were significantly more likely to have stopped smoking one year later. The associations with quitting smoking among those who had a major lung abnormality that was not suspicious for lung cancer or a minor abnormality were weaker and not uniformly statistically significant.

The results of these two studies suggest that the net impact of a CT program on smoking cessation is small, if it exists,[15] but that there may be a higher likelihood of smoking cessation among current smokers who have findings suspicious for lung cancer.[16] This is an important research area that needs to be clarified, particularly with evaluation of how a smoking cessation intervention embedded within a screening program might potentiate smoking cessation.
Evidence of No Benefit Associated With Screening

Screening by chest x-ray and/or sputum cytology

The question of lung cancer screening dates back to the 1950s, when rising lung cancer incidence and mortality rates indicated a need for intervention. In response to the emerging lung cancer problem, five studies of chest imaging, two of which were controlled, were undertaken during the 1950s and 1960s.[17-24] Two studies also included sputum cytology.[17-21] The results of these studies suggested no overall benefit of screening, although design limitations prevented the studies from providing definitive evidence.

In the early 1970s, the National Cancer Institute funded the Cooperative Early Lung Cancer Detection Program,[25] which was designed to assess the ability of screening with radiologic chest imaging and sputum cytology to reduce lung cancer mortality in male smokers. The program comprised three separate RCTs, each enrolling about 10,000 male participants aged 45 years and older who smoked at least one pack of cigarettes a day in the previous year. One study was conducted at the Mayo Clinic,[26-28] one at Johns Hopkins University,[29-31] and one at Memorial Sloan-Kettering.[31-34] The Hopkins and Sloan-Kettering studies employed the same design: persons randomly assigned to the intervention arm received sputum cytology every 4 months and annual chest imaging, while persons randomly assigned to the control arm received annual chest imaging. Neither study observed a reduction in lung cancer mortality with screening.[31] The two studies were interpreted as showing no benefit of frequent sputum cytology when added to an annual regimen of chest x-ray.

The design of the Mayo Clinic study (known as the Mayo Lung Project, or MLP), was different. All potential participants were screened with chest imaging and sputum cytology, and those known or suspected to have lung cancer, as well as those in poor health, were excluded. Remaining persons were randomly assigned to either an intervention arm that received chest imaging and sputum cytology every 4 months for 6 years, or to a control arm that received a one-time recommendation at trial entry to receive the same tests on an annual basis. No reduction in lung cancer mortality was observed. The MLP was interpreted in the 1970s as showing no benefit of an intense screening regimen with chest x-ray and sputum cytology.
One RCT of lung cancer screening with chest imaging was conducted in Europe in the 1970s. The Czechoslovakian study began with a prevalence screen (chest imaging and sputum cytology) of 6,364 males aged 40 to 64 years who were current smokers with a lifetime consumption of at least 150,000 cigarettes. All participants except the 18 diagnosed with lung cancer as a result of the prevalence screen were randomly assigned to one of two arms: an intervention arm, which received semi-annual screening for 3 years, or a control arm, which received screening during the third year only. The investigators reported 19 lung cancer deaths in the intervention arm and 13 in the control arm, and concluded that frequent screening was not necessary.

By 1990, the medical community was still unsure about the relationship between screening with chest imaging (using traditional chest x-ray) and lung cancer mortality. Although previous studies showed no benefit, findings were not definitive because of a lack of statistical power. A multiphasic trial with ample statistical power, the PLCO Cancer Screening Trial,[37] began in 1992. PLCO enrolled 154,901 participants aged 55 to 74 years, including women (50%) and never smokers (45%). Half were randomly assigned to screening, and the other half were advised to receive their usual medical care. PLCO had 90% power to detect a 20% reduction in lung cancer mortality.

The lung component of PLCO addressed the question of whether annual single-view (posterior-anterior) chest x-ray was capable of reducing lung cancer mortality as compared with usual medical care. When the study began, all participants randomly assigned to screening were invited to receive a baseline and three annual chest x-ray screens, although the protocol ultimately was changed to screen never-smokers only three times. At 13 years of follow-up, 1,213 lung cancer deaths were observed in the intervention group, compared with 1,230 lung cancer deaths in the usual-care group (mortality relative risk, 0.99; 95% CI, 0.87–1.22). Sub-analyses suggested no differential effect by sex or smoking status.[37]

Given the abundance and consistency of evidence, as well as the lack of benefit observed in the PLCO trial, it is appropriate to conclude that lung cancer screening with chest x-ray and/or sputum cytology, regardless of sex or smoking status, does not reduce lung cancer mortality.

References

**Screening by Low-Dose Helical Computed Tomography**

**False-positive exams**
False-positive exams are particularly problematic in the context of lung cancer screening. Persons most likely to be screened for lung cancer, i.e., heavy smokers, have comorbidities (such as chronic obstructive pulmonary disease and heart disease) that make them poor candidates for certain diagnostic procedures.

False-positive test results must be considered when lung cancer screening with low-dose helical computed tomography (LDCT) is being evaluated. A false-positive test may lead to anxiety and invasive diagnostic procedures, such as percutaneous needle biopsy or thoracotomy. The percentage of false positives findings varies substantially among studies and is primarily attributable to differences in how a positive scan is defined (the size criteria), the thickness of the slice used between cuts (smaller slice thicknesses lead to detection of more nodules) and whether the subject resides in a geographic location where granulomatous disease is highly prevalent. A systematic review of the benefits and harms of CT screening for lung cancer reported that the follow-up of a screen-detected nodule most often included further imaging, which varied among 21 screening trials between 1% and nearly 45%. Positron emission tomography scanning was performed in 2.5% to 5% of patients.[1] The frequency of nonsurgical biopsies or procedures in screening trials ranges from 0.7% to 4.4%. Of those biopsied, there was marked variation in the finding of a benign result (6%–79%). The rate of surgical resection for screen detected nodules in screening trials is between 0.9% and 5.6%. Of patients who underwent surgery, between 6% and 45% had a benign nodule discovered during surgery,[2] a potential harm of lung cancer screening. In the National Lung Screening Trial (NLST), most major complications related to invasive procedures and surgeries occurred in patients diagnosed with lung cancer, with a major complication rate of 14%. Additionally, a complication rate of 4.1 deaths and 4.5 complications per 10,000 diagnostic events can be expected in patients determined to have a benign nodule. The rates of complications from the NLST may not be generalizable to a community setting; participants in the NLST were younger, better educated, and less likely to be current smokers (therefore healthier) than the population of smokers and former smokers in the general U.S. population who would be eligible for screening. Of note, 82% of the participants were enrolled at large academic medical centers and 76% of the enrollees were seen at National Cancer Institute–designated cancer centers. This may account for the extremely low complication rate and surgical mortality (1%) found in the NLST that led the multisociety position paper to strongly recommend that screening be carried out at centers with the same patient-management resources as those in the NLST.[1]
In the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, the percentage of all positive lung cancer screens that were false-positive screens was 98%.[3] When smoking status was considered, the percentage of false positive screens (among all positive screens) was highest in never-smokers (>99%) and lowest in current smokers (95%). After adjustment for smoking, the percentage of false-positive screens did not differ by sex.

**Overdiagnosis**

A less familiar harm is overdiagnosis, the diagnosis of a condition that would not have become clinically significant had it not been detected by screening.[4] Had the patient not been diagnosed with cancer, the patient would have died of other competing comorbidities. In the case of screening with LDCT, overdiagnosis could lead to unnecessary diagnosis of lung cancer requiring some combination of surgery (e.g., lobectomy, chemotherapy, and radiation therapy). Autopsy studies suggest that a significant number of individuals die with lung cancer rather than from it. In one study, about one-sixth of all lung cancers found at autopsy had not been clinically recognized before death.[5] This may be an underestimate; depending on the extent of the autopsy, many small lung cancers that are detectable by CT may go unrecorded in an autopsy record.[6] Studies in Japan provide additional evidence that screening with LDCT could lead to a substantial amount of overdiagnosis.[7] Studies are needed to establish the level of overdiagnosis that might be associated with CT screening for lung cancer. However, in one study the volume-doubling times of 61 lung cancers were estimated using an exponential model and successive CT images. Lesions were classified into three of the following types:

- Type G (ground glass opacity).
- Type GS (focal glass opacity with a solid central component).
- Type S (solid nodule).

The mean-doubling times were 813 days, 457 days, and 149 days for types G, GS, and S, respectively. In this study, annual CT screening identified a large number of slowly growing adenocarcinomas that were not visible on chest x-ray suggesting overdiagnosis.[8]

In a screening trial with more than 5,000 participants, the proportion of cancers that would be considered overdiagnoses was evaluated. Volume-doubling time was used as a surrogate for overdiagnosis. Patients with a calculated volume-doubling time of more than 400 days before surgical resection were considered as having an overdiagnosed cancer.[9] The investigators discovered that 25% of
those ultimately diagnosed with lung cancer met the criteria of an indolent screen-detected nodule, suggesting that one in four cancers in that trial were overdiagnosed.[9] Similar rates of overdiagnosis have been documented in breast cancer. This rate is consistent with previous chest radiograph screening studies and for other solid tumors. The rate of overdiagnosis in the NLST has yet to be calculated, but the study data show a persistent gap of about 120 excess lung cancer cases in the LDCT group compared with the chest radiograph group, although long-term follow-up is needed.[10] Additional evidence of overdiagnosis with LDCT screening was observed in the randomized Danish Lung Cancer Screening Trial. At 10 years of follow-up (5 years after the last screening exam), almost twice as many lung cancers had been diagnosed in the screening group than in the control group (5.1 vs. 2.7 cases per 1,000 person-years or 100 vs. 53 lung cancer cases in 4,104 total participants, respectively); most of the lung cancers were early stage adenocarcinomas, with no statistically significant difference in the number of stage III and IV cancers between the two groups.[11]

About 20 years of follow-up of the Mayo Lung Project (MLP) cohort indicates that 17% of lung cancers diagnosed as the result of an intense regimen of chest x-ray and sputum cytology are overdiagnosed;[12] 585 lung cancers had been diagnosed in the intervention arm as compared with 500 in the usual-care arm. After 13 years of follow-up of the PLCO cohort, 1,696 lung cancers had been diagnosed in the intervention arm as compared with 1,620 lung cancers in the usual-care arm.[13] This suggests that about 6% of cancers diagnosed as the result of annual chest x-ray are overdiagnosed, although that percentage was not significantly different from 0%.

Complications of diagnostic evaluation

In the PLCO,[13] 0.4% of participants with at least one positive screen who had a diagnostic evaluation had a complication associated with a diagnostic procedure. The most common of the 69 complications were pneumothorax (29%), atelectasis (15%), and infection (10%).

Increase in lung cancer mortality

Findings from the MLP hinted at the possibility of an increase in lung cancer mortality for persons screened with an intense regimen of chest x-ray and sputum cytology.[14] At the end of 20 years of follow-up, the lung cancer mortality rate was 4.4 cases per 1,000 deaths in the intervention arm and 3.9 cases per 1,000 deaths in the usual-care arm. The two rates were not statistically different from one another ($P = .09$). No increase in risk was seen in the
intervention arms of the John Hopkins University and Memorial Sloan-Kettering studies (relative risk [RR], 0.88; 95% confidence interval [CI], 0.74–1.05), and the PLCO (RR, 0.99; 95% CI, 0.87–1.22).

**Radiation exposure**

Another potential risk from screening with LDCT is radiation exposure. The average exposure is very low for an LDCT at 1.5 mSv. It is estimated that over a 3-year period of screening, NLST participants have been exposed to an average of 8 mSv of radiation (which accounts for radiation from screens and additional imaging for screen-detected nodules). Modeling from previous work on radiation exposure and the development of cancer suggests that there could be one death per 2,500 screens in those participating in a screening program such as the NLST, although the benefit of screening (1 death avoided per 320 screens) far outweighs the risk. Younger persons and those without a significant risk of lung cancer may be more likely to suffer a radiation-induced lung cancer than may be spared a lung cancer death from screening.[1]

**Screening by Chest X-ray and/or Sputum Cytology**

Unless reported above, data on harms associated with sputum cytology or a combined regimen of sputum cytology and chest x-ray have not been published.

**References**


**Informed Medical Decision Making**

Informed medical decision making is increasingly recommended for individuals who are considering cancer screening. Many different types and formats of decision aids have been studied. (Refer to the PDQ summary on Cancer Screening Overview for more information.)

**Changes to This Summary (11/18/2016)**

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.
Overview

Revised text to state that based on solid evidence, approximately 96% of all positive low-dose helical computed tomography screening exams do not result in a lung cancer diagnosis.

Revised text to describe harms of magnitude of effect from screening by low-dose helical computed tomography based on the findings from a large randomized trial.

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About This PDQ Summary

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about lung cancer screening. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

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Changes to This Summary (11/18/2016)

- Updated: November 18, 2016