Screening for Lung Cancer with Low-Dose CT Scans Reduces Lung Cancer Mortality

The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 29 Jun 2011. Online publication prior to print.

Study Overview

Objective. To determine whether low-dose computed tomography (CT) screening reduces mortality from lung cancer among patients at high risk for lung cancer.

Design. Randomized controlled trial of low-dose CT versus chest x-ray for lung cancer screening. Subjects were enrolled from 2002 to 2004 in 33 US centers. Participants received 3 annual screenings with either low-dose CT or a single view chest radiograph and were followed for up to 7.5 years. Randomization was stratified by age-group, sex, and study center.

Setting and participants. 53,454 current or former smokers, aged 55 to 74 years. Subjects were included if they were without known lung cancer, had a 30 pack-year or greater smoking history, and were actively smoking or quit smoking less than 15 years prior to enrollment. Individuals were excluded if had a CT within 18 months of enrollment, had prior lung cancer, had hemoptysis, or had unexplained weight loss of 15 pounds in the preceding year.

Main outcome measure. Lung cancer mortality.

Main results. In both arms, 73% of subjects were 55 to 64 years old, and 59% were men. Over 90% of subjects were white, and 48% were current smokers. 90% of subjects were compliant with testing. Over the 3 screening studies, 39.1% of those in the CT arm and 16.0% in the chest x-ray arm had a positive screening result. Over 94% of the positive screening tests were false-positives. 645 lung cancer cases were detected per 100,000 person-years of follow-up in the CT arm with 572 cases per 100,000 person-years in the chest x-ray arm (rate ratio, 1.13 [95% confidence interval {CI}, 1.03–1.23]). Subjects in the CT arm had a 20% lower rate of death

from lung cancer (247 vs. 309 deaths per 100,000 person-years; relative risk reduction of 20% [95% CI, 6.8–26.7]; P = 0.004). The number needed to screen with low-dose CT to prevent 1 death from lung cancer was 320. The low-dose CT group also had a 6.7% lower rate of all-cause mortality (95% CI, 1.2–13.6; P = 0.02). Fewer stage IV cancers were found in the CT group at the second and third screening rounds compared with the chest x-ray group. Overall, 63% of cancers found during CT screening were stage 1A or 1B compared with 58% of cancers found during chest x-ray screening. 457 of the positive screening results in the CT arm that did not result in a cancer diagnosis underwent an invasive procedure compared with 115 in the chest x-ray arm. Adverse events related to screening were low—1.4% and 1.6% in the CT and chest x-ray arms respectively. Among subjects who were not found to have lung cancer, 0.06% and 0.02% of the positive screening tests in the 2 groups were associated with a major complication after an invasive procedure. 11.2% and 8.2% of positive tests among subjects who were found to have lung cancer resulted in a major complication after an invasive procedure.

Conclusion. Low-dose CT scans for lung cancer screening in high-risk subjects resulted in lower lung cancer mortality.

Commentary

Because nearly three-quarters of lung cancers are metastatic at the time of diagnosis, screening for the early detection of lung cancer is desperately needed to somewhat decrease the overwhelming mortality rate from lung cancer [1]. Prior, uncontrolled data from low-dose chest CT screening has shown a promising stage distribution for cancer detected during screening compared with what is seen in typical clinical practice [1,2], with more than ½ of lung cancers detected

being classified as stage 1. The National Lung Cancer Screening Trial (NLST) has long been anticipated to provide more definitive information about the effect of low-dose CT screening among individuals at high risk for developing lung cancer.

This study compared low-dose CT scan to chest x-rays among more than 50,000 current or former smokers who had at least 30 pack-year smoking histories. Low-dose CT scans were associated with a 20% relative reduction in mortality compared with chest x-ray, with an absolute risk reduction of 62 deaths per 100,000 person-years (247 vs. 309 deaths). All-cause mortality was lower in the CT group as well, but this reduction was entirely driven by the reduction in lung cancer deaths. The estimated number needed to screen with low-dose CT to prevent 1 lung cancer death was 320. Positive screening tests were common in this study, with 39% of subjects in the CT arm having a positive result and 16% in the chest x-ray arm. Over 96% of these positive results were false-positives. These false-positive tests led to 457 invasive procedures in the CT arm, more than double that in the chest x-ray group. Few of those invasive procedures were associated with major complications.

The NLST is likely to be the definitive trial of low-dose CT scanning. We will soon get additional information to help interpret the results from the NLST. A smaller series of European randomized controlled trials, with approximately 20,000 subjects, should be completed soon, and further analyses from the NLST, including cost-effectiveness analyses and assessments of the impact of screening on quality of life, are not yet available. In the meantime, we are left with the important results of the NLST to determine whether to embrace low-dose CT scans as a routine part of the prevention arsenal for health care providers and patients.

The trial was meticulous in its construction and implementation and has many important attributes. Adherence to testing was remarkably high at 90%. The dose of radiation was formulated to be quite low, less than 5 times the dose of radiation used for a standard chest CT. The study allowed for subjects and their health care providers to follow up the abnormal results rather than scripting the diagnostic process, a method comparable to how results would be followed in typical clinical practice. The sample size was large though not substantially diverse; over 90% of subjects were white.

Several limitations or questions remain. The radiographic technology used in this study is already outdated. Authors speculate that perhaps more cancers would be detected with newer CT technology, yet false-positive rates may be higher. Also, authors openly discuss the concern that the effect of screening may be different in community settings compared with the mostly academic health center settings where this study was conducted. Higher complication rates from unnecessary invasive procedures in community settings may alter the risk-benefit balance of screening. Further, results presently available cannot rule out the biases that can commonly occur with screening studies, such as more frequent detection of indolent cancers than aggressive cancers with screening (length-time bias) and a false decrease in mortality when a lesion is detected early in the course of disease but ultimate survival is not prolonged (lead-time bias) [1]. These biases are always substantially reduced with longer follow-up, use of mortality (rather than survival time) as the outcome, and a randomized trial design, all of which are utilized in this study. Studying lung cancer specifically with long follow-up especially reduces lead-time bias because the length of survival is low on average. However, the biases are still present to some degree and must be considered when evaluating the results.

How these results are used by clinicians, guideline organizations, and insurers is an open question and may depend on results of the cost-effectiveness analyses that should be forthcoming. In the meantime, the NLST has given low-dose CT screening a boost. It will likely become standard practice for screening of the 7 million Americans who meet the NLST eligibility criteria (55 to 74 years, a 30 pack-year or greater smoking history, actively smoking or quit smoking less than 15 years prior to enrollment). Of note, these eligibility criteria rule out over 90% of smokers. If adopted as a routine screening practice, clinicians will have to carefully counsel patients about the risks and benefits of screening. Repeated exposure to radiation, even at the low doses used in this study (1.5 mSv compared with 8 mSv for standard chest CT scans) from multiple CTs could have long-term implications that cannot be assessed by the NLST [3]. One study estimated that medical imaging procedures lead to high or very high exposure levels of radiation for 4 million Americans [3], and recent estimates suggest that 1.5 to 2% of all

cancers in the United States may be related to exposure to radiation from CT scans [4]. Patients will need to be made aware of the very high false-positive rate and the possibility of unnecessary invasive testing.

Applications for Clinical Practice

Low-dose CT scans for patients at high-risk for lung cancer are associated with a small absolute reduction in mortality that translates into a 20% relative mortality reduction, compared with chest x-rays. Low-dose CT scanning may well become standard screening for patients aged 55 to 74 years with a 30 or greater pack-year smoking history.

—Review by Jason P. Block, MD, MPH

References

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