

EDITORIAL



Better Evidence about Screening for Lung Cancer

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In October 2010, the National Cancer Institute (NCI) announced that patients who were randomly assigned to screening with low-dose computed tomography (CT) had fewer deaths from lung cancer than did patients randomly assigned to screening with chest radiography. The first report of the NCI-sponsored National Lung Screening Trial (NLST) in a peer-reviewed medical journal appears in this issue of the *Journal*.¹

Eligible participants were between 55 and 74 years of age and had a history of heavy smoking. They were screened once a year for 3 years and were then followed for 3.5 additional years with no screening. At each round of screening, results suggestive of lung cancer were nearly three times as common in participants assigned to low-dose CT as in those assigned to radiography, but only 2 to 7% of these suspicious results proved to be lung cancer. Invasive diagnostic procedures were few, suggesting that diagnostic CT and comparison with prior images usually sufficed to rule out lung cancer in participants with suspicious screening findings. Diagnoses of lung cancer after the screening period had ended were more common among participants who had been assigned to screening with chest radiography than among those who had been assigned to screening with low-dose CT, suggesting that radiography missed cancers during the screening period. Cancers discovered after a positive low-dose CT screening test were more likely to be early stage and less likely to be late stage than were those discovered after chest radiography. There were 247 deaths from lung cancer per 100,000 person-years of follow-up after screening with low-dose CT and 309 per 100,000 person-years after screening with chest radiography.

The conduct of the study left a little room for concern that systematic differences between the two study groups could have affected the results (internal validity). The groups had similar characteristics at baseline, and only 3% of the participants in the low-dose CT group and 4% in the radiography group were lost to follow-up. However, there were two systematic differences in adherence to the study protocol. First, as shown in Figure 1 of the article, although adherence to each screening was 90% or greater in each group, it was 3 percentage points lower for the second and third radiography screenings than for the corresponding low-dose CT screenings. Because more participants in the radiography group missed one or two screenings, the radiography group had more time in which a lung cancer could metastasize before it was detected. Second, participants in the low-dose CT group were much less likely than those in the radiography group to have a diagnostic workup after a positive result in the second and third round of screening (Table 3 of the article), which might have led to fewer screening-related diagnoses of early-stage lung cancer after low-dose CT. The potential effect of these two differences in study conduct seems to be too small to nullify the large effect of low-dose CT screening on lung-cancer mortality.

The applicability of the results to typical practice (external validity) is mixed. Diagnostic workup and treatment did take place in the community. However, the images were interpreted by radiologists at the screening center, who had extra training in the interpretation of low-dose CT scans and presumably a heavy low-dose CT workload. Moreover, trial participants were younger and had a higher level of education than a ran-

dom sample of smokers 55 to 74 years of age, which might have increased adherence to the study protocol.²

Overdiagnosis is a concern in screening for cancer. Overdiagnosis occurs when a test detects a cancer that would otherwise have remained occult, either because it regressed or did not grow or because the patient died before it was diagnosed.³ In a large, randomized trial comparing two screening tests, the proportion of patients in whom cancer ultimately develops should be the same in the two study groups. A difference that persists suggests that one test is detecting cancers that would never grow large enough to be detected by the other test. Overdiagnosis is a problem because predicting which early-stage cancers will not progress is in an early stage of development,^{4,5} so that everyone with screen-detected cancer receives treatment that some do not need. Overdiagnosis biases case-based measures (e.g., case fatality rate) but not the population-based measures used in the NLST.

Overdiagnosis probably occurred in the NLST. After 6 years of observation, there were 1060 lung cancers in the low-dose CT group and 941 in the radiography group. Presumably, some cancers in the radiography group would have been detectable by low-dose CT but grew too slowly to be detected by radiography during the 6.5 years of observation. The report of the Mayo Lung Project provides strong evidence that radiographic screening causes overdiagnosis of lung cancer.⁶ At the end of the follow-up phase in the Mayo study, 46 more lung cancers were diagnosed in the group screened with radiography and sputum cytologic analysis than in the unscreened group. This gap did not close, as would be expected if undetected cancers in the unscreened group continued to grow; the gap grew and then leveled off at 69 additional lung cancers in the screened group at 12 and 16 years. The Mayo study shows that 10 to 15 additional years of follow-up will be necessary to test the hypothesis that low-dose CT in the NLST led to overdiagnosis. If the difference in the number of cancers in the two groups of the NLST persists, overdiagnosis in the low-dose CT group is the likely explanation.

The incidence of lung cancer was similar at the three low-dose CT screenings (Table 3 of the article), which implies that a negative result of low-dose CT screening did not substantially re-

duce the probability that the next round would detect cancer. Lung cancer was also diagnosed frequently during the 3 years of follow-up after the third low-dose CT screening. Apparently, every year, there are many lung cancers that first become detectable that year. This observation, together with the overall NLST results, suggests that continuing to screen high-risk individuals annually will provide a net benefit, at least until deaths from coexisting chronic diseases limit the gains in life expectancy from screening.

The NLST results show that three annual rounds of low-dose CT screening reduce mortality from lung cancer, and that the rate of death associated with diagnostic procedures is low. How should policy makers (those responsible for screening guidelines, practice measures, and insurance coverage) respond to this important result? According to the authors, 7 million U.S. adults meet the entry criteria for the NLST,¹ and an estimated 94 million U.S. adults are current or former smokers. With either target population, a national screening program of annual low-dose CT would be very expensive, which is why I agree with the authors that policy makers should wait for more information before endorsing lung-cancer screening programs.

Policymakers should wait for cost-effectiveness analyses of the NLST data, further follow-up data to determine the amount of overdiagnosis in the NLST, and, perhaps, identification of biologic markers of cancers that do not progress.^{4,5} Modeling should provide estimates of the effect of longer periods of annual screening and the effect of better adherence to screening and diagnostic evaluation. Systematic reviews that include other, smaller lung-cancer screening trials will provide an overview of the entire body of evidence. Finally, it may be possible to define subgroups of smokers who are at higher or lower risk for lung cancer and tailor the screening strategy accordingly.

Individual patients at high risk for lung cancer who seek low-dose CT screening and their primary care physicians should inform themselves fully, and current smokers should also receive redoubled assistance in their attempts to quit smoking. They should know the number of patients needed to screen to avoid one lung-cancer death, the limited amount of information that can be gained from one screening test, the potential for

overdiagnosis and other harms, and the reduction in the risk of lung cancer after smoking cessation. The NLST investigators report newly proven benefits to balance against harms and costs, so that physicians and patients can now have much better information than before on which to base their discussions about lung-cancer screening.

The findings of the NLST regarding lung-cancer mortality signal the beginning of the end of one era of research on lung-cancer screening and the start of another. The focus will shift to informing the difficult patient-centered and policy decisions that are yet to come.

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