High False-Positive Rate for Lung Cancer Screening

Croswell J, Baker S, Marcus P, et al. Cumulative incidence of false-positive test results in lung cancer screening: a randomized trial. Ann Intern Med 2010;152:505–12.

Study Overview

Objective. To determine the risks of lung cancer screening.

Design. Randomized controlled trial of low-dose computed tomography (CT) versus chest x-ray for lung cancer screening.

Setting and participants. The study was conducted in 6 centers in the United States as a feasibility study for the ongoing National Lung Screening Trial. 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 10 years prior to enrollment. Individuals were excluded if they had a CT within 24 months of enrollment, had prior lung cancer, had prior surgery to remove at least part of a lung, were being treated for any cancer other than nonmelanoma skin cancer, or were participating in another screening trial. 3190 current or former smokers, aged 55 to 74 years, were enrolled. Subjects had a baseline CT or chest x-ray with a repeat study at 1 year and follow-up for up to 2 years. Randomization was stratified by age group, sex, and study center.

Main outcome measures. The primary endpoint was the false-positive rate for screening, defined as a positive test result on CT on chest x-ray with a subsequently negative workup for lung cancer.

Main results. 68% of subjects were between 55 and 64 years old, and 59% were men. 57% were current smokers and most had between a 30 to 59 pack-year smoking history. The cumulative incidence of a false-positive test result on low-dose CT was 21% for 1 screening (95% confidence interval [CI], 19%–23%) and 33% for 2 screenings (95% CI, 31%–35%). The rates for chest x-ray were 9% (95% CI, 8%–11%) and 15% (95% CI, 13%–16%). These results prompted secondary diagnostic tests in 61% of subjects who had a false-positive result on CT and 51% who had a positive result on chest x-ray, and invasive procedures in 7% and 4% of subjects, respectively. Most of the invasive procedures were bronchoscopies; 2% of all subjects had invasive surgical procedures, such as video-assisted thoracic surgery, for benign disease. Older age was associated with increased risk of having a false-positive result on chest x-ray during the follow-up screening; more pack-years was associated with an increased risk of a false-positive result on follow-up screening with CT.

Conclusion. False-positive rates are high for lung cancer screening in asymptomatic individuals.

Commentary

Because three-quarters of lung cancers are metastatic at the time of diagnosis, establishing a technique for early detection is critically needed to decrease the devastating mortality rate from lung cancer [1]. Prior, uncontrolled data for low-dose chest CT screening has shown a promising stage distribution for cancer detected during screening compared with what is currently found in clinical practice [1]. In 5 studies with a total of 13,000 subjects, 55% to 85% of lung cancers detected during a baseline screening examination with CT and 60% to 100% of those detected during annual follow-up were stage I [1]. One recent large U.S. study of 31,567 subjects screened for lung cancer with low-dose CT found 484 cancers, of which 85% were stage I [2].

However, despite the results, these data are limited. Uncontrolled studies cannot control for biases that make indolent cancers more likely to be detected with screening than more aggressive cancers (length–time bias) and that falsely appear to increase survival time because of detection earlier in the course of disease (lead-time bias) [1]. Without randomized controlled trials (RCTs), we cannot know the true benefits of screening and cannot determine whether screening improves the mortality risk from lung cancer. Results from 2 RCTs will be available soon. The National Lung Cancer Screening Trial, for which this present study served as a pilot study, enrolled 50,000 subjects starting in 2002 and will follow subjects through 3 annual screenings. A European RCT with 20,000 subjects should report results later this year.

In its most recent communication about lung cancer screening, the U.S. Preventive Services Task Force found insufficient evidence to recommend or oppose screening asymptomatic individuals for lung cancer [3]. Similarly, the American Cancer Society does not recommend lung cancer screening [4].

Any consideration of screening must also consider the risks of screening. False-positive tests result in unnecessary diagnostic studies or procedures that are costly and can be harmful. Up to 12% of subjects in the prior screening studies required additional testing, such as repeated diagnostic studies and invasive procedures [1,5,6]. Up to 30% of subjects who received invasive procedures after screening were found to have benign lesions. Furthermore, repeated CT scans alone are a major source of exposure to radiation and can have consequences [7]. One study estimated that medical imaging procedures lead to high or very high exposure levels of radiation for 4 million Americans [8], 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 [7]. The negative psychological impact of false-positives also is an important consideration.

Croswell et al have made a significant contribution with this study. They found that one-third of subjects had false-positive results in the CT arm and 15% in the chest x-ray arm. Follow-up diagnostic studies occurred frequently in both groups, with a high rate of invasive tests. The explicit costs of false positives were not estimated, and the psychological impact was not reported. These results call for caution with screening and require that we take a careful cost-benefit assessment before proceeding with widespread screening.

Several limitations were evident with this study. First, follow-up time was limited to 2 years, and it is possible that false-positives were misclassified as such because of insufficient follow-up. Second, false-positive rates varied widely by center. For the highest-risk subjects, false-positive rates for CT varied from 10% to 42% and for chest x-ray, 3% to 19%. These variable rates reveal the subjectivity of classifying a nodule as worthy of additional follow-up diagnostic studies or procedures. Third, the results are dated a bit since testing was done in 2000 to 2002. The technological development with CT scans has been rapid, and additional information is now available with scans that might decrease the need for unnecessary follow-up studies.

Applications for Clinical Practice

High false-positive rates for lung cancer screening, as reported in this study, will be an important consideration when determining whether widespread screening is warranted. The results of ongoing RCTs will provide critical information about the benefits of screening.

—Review by Jason P. Block, MD, MPH

References

1. Mulshine J, Sullivan D. Lung cancer screening. N Engl J Med 2005;352:2714–20.
2. The International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763–71.
3. U.S. Preventive Services Task Force. Lung cancer screening: recommendation statement. May 2004. Agency for Healthcare Research and Quality, Rockville, MD. Accessed at www.ahrq.gov/clinic/3rduspstf/lungcancer/lungcanrs.htm.
4. Smith, RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2008: a review of current American Cancer Society guidelines and cancer screening issues. 2008. CA Cancer J Clin 2008;58:161–79.
5. Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest 2002;122:15–20.
6. Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362:593–7.
7. Brenner D, Hall E. Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007;357:2277–84.
8. Fazel R, Krumholz H, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med 2009;361:849–57.