New Testing for Lung Cancer Screening

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In this review, the authors discuss past attempts at lung cancer screening, the results of the National Lung Cancer Screening Trial, and innovative tests for lung cancer screening currently being evaluated.

Introduction

Lung cancer is responsible for the largest number of cancer-related deaths worldwide. In the United States in 2011, it was expected that there would be 221,130 new cases of lung cancer, accounting for 14% of all new cancer diagnoses. It was estimated that 156,940 deaths would occur from lung cancer in 2011, accounting for 27% of all cancer deaths.[1]

At the time of presentation, only 16% of patients are diagnosed with a disease stage that has potential for cure by surgical resection. The overall 5-year survivorship for all patients is 15%, despite therapy. However, the 5-year survival for those with pathologic stage I non–small-cell lung cancer (NSCLC) is 58% to 73% after surgery.[2] This significant difference in survivorship makes the identification of early-stage disease desirable. Until recently, however, there had not been a screening test that demonstrated a mortality reduction in lung cancer. In this review, we discuss past attempts at lung cancer screening, the results of the National Lung Cancer Screening Trial (NLST), and innovative tests for lung cancer screening currently being evaluated.

Lung Cancer Testing: The Past

CXR/sputum screening

The first trial using chest radiographs for lung cancer screening was published in 1968. Subjects were randomly assigned to receive a chest x-ray (CXR) every 6 months for 3 years or to receive a baseline and end-of-study CXR; there was no difference in mortality between the two groups.[3] The addition of sputum cytology screening was examined in four subsequent studies published in the 1980s that randomly assigned patients to annual CXR with or without annual sputum cytology; there was again no difference in mortality.[4-7]

Recently, the findings of the lung cancer arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial were reported.[8] This randomized controlled trial enrolled 154,901 participants aged 55 through 74 years at 1 of 10 screening centers across the United States between 1993 and 2001; 77,445 were assigned to annual screening CXR for 4 years and 77,456 to usual care. Participants were followed for a total of 13 years or until December 2009, whichever occurred first. Cancers diagnosed were classified according to histology and as either screen-detected or non-screen-detected (interval or never-screened). Logistic regression analysis was performed to control for smoking status. Cancer stage and tumor histology were similar between the groups. At 13 years of follow up, 1213 lung cancer deaths were observed in the intervention group, compared with 1230 in the usual-care group (mortality relative risk [RR], 0.99; 95% confidence interval [CI], 0.87-1.22). These results clearly demonstrated that a CXR screening program does not improve lung cancer mortality. Despite repeated trials failing to show a mortality benefit with CXR screening for lung cancer, a recent survey of primary care physicians showed that 67% recommended lung cancer screening, and more than 65% of respondents said that they would use CXR over other screening modalities.[9] A follow-up survey completed by 962 primary care physicians showed that 55% had ordered CXR for asymptomatic patients even though this is not a recommendation of any expert group.[10]

Low-dose CT screening

Low-dose CT screening (LDCT), which uses low levels of radiation to generate an image, is faster and...
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Published on Cancer Network (http://www.cancernetwork.com)

less expensive than standard helical CT scanning and detects three times as many lung nodules as chest radiographs. Several single-arm observational cohort studies provided valuable information about the ability to recruit, retain, and screen a large population over multiple years using LDCT but could not provide data on the overall effectiveness of this screening modality.[11-13]

Further investigation with prospective trials demonstrated the potential of LDCT as an effective screening tool. The Mayo Clinic LDCT prospective trial involved annual screening in a high-risk population for 5 years. Lung cancer was identified in 4% of cases, 61% of which were stage I.[14] Similarly, Bach et al combined data from three single-arm studies using LDCT for lung cancer screening and found a detection rate of 4.4%, with 74% of cancers being early-stage.[15] Even with such promising results, these studies by design could not ascertain whether detection of early-stage cancer was truly an indication of a good screening tool that reduced mortality. This has resulted in several randomized controlled trials designed to detect a mortality benefit. The results of the North American National Lung Screening Trial (NLST) have most recently been released, and several other trials, including the NELSON trial (Dutch Belgian randomized lung cancer screening trial) assessing screening with LDCT, are currently underway in Europe.

National Lung Screening Trial

The NLST included 33 centers across the United States. Eligible participants were between ages 55 and 74 years at the time of randomization, had a history of at least 30 pack-years of cigarette smoking, and, if former smokers, had quit within the past 15 years.[16] A total of 53,454 persons were enrolled; 26,722 were randomly assigned to screening with LDCT and 26,732 to screening with CXR. Any noncalcified nodule found on LDCT measuring at least 4 mm in any direction and CXR images with any noncalcified nodule or mass were classified as positive. The LDCT-screened group had a substantially higher rate of positive screening tests compared with 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 radiography group. The false-positive rate was evenly distributed across all three rounds.

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. A total of 356 deaths from lung cancer occurred in the LDCT group and 443 in the CXR group, with a relative reduction in the rate of death from lung cancer of 20.0% with LDCT screening. Overall mortality was reduced by 6.7%. The number needed to screen with LDCT to prevent 1 death from lung cancer was 320, which is comparable to the numbers in studies on screening mammography for breast cancer in women over 50. The National Lung Screening Trial is the first large-scale randomized trial to convincingly demonstrate a mortality benefit for LDCT lung cancer screening in high-risk individuals.

One of the concerns with using LDCT for lung cancer screening is the high rate of test-positive results necessitating further work-up. Investigators from the NELSON study demonstrated that this can be overcome by utilizing semi-automated volumetry software to measure diameter and volume doubling time (VDT). Growth was defined as a change in volume between the first and the second scan of 25% or greater. Nodules meeting growth criteria were then classified into three categories based on VDT (< 400, 400-600, and > 600 days). This approach to nodule management resulted in a decrease in the rate of test-positive results at baseline from 30% to 2%.[17] The final results regarding the reduction in mortality from lung cancer in this trial are pending.

Despite the impressive results from NLST in high-risk adults, generalizing them may be problematic for a number of reasons. Participants in the NLST were enrolled in urban, tertiary care hospitals with expertise in all aspects of cancer care. LDCT studies were interpreted by dedicated chest radiologists with expertise in characterizing nodules and providing appropriate recommendations for follow-up. As a result, few patients required further invasive testing, and radiographic follow-up was sufficient for many.

In contrast, community practice gives rise to the potential for considerable variation in the management of solitary pulmonary nodules identified by screening LDCT. One study demonstrated a two-fold variation among geographic regions in use of CT-guided biopsy, ranging from 14.7 to 36.2 per 100,000 adults. This substantial variation in the management of solitary pulmonary nodules may...
lead to an increased number of invasive procedures with risk of harm. For instance, complications from transthoracic biopsies include a 1% rate of bleeding (with one-third of affected patients requiring transfusion) and a 15% rate of pneumothorax. More than 6% of CT-guided biopsies result in a pneumothorax requiring chest tube drainage, a clinically important complication that results in pain, serial imaging with radiation exposure, and hospitalization.[18] Older patients and those with chronic obstructive pulmonary disease (COPD) have an increased risk of biopsy-related complications that can result in longer length of hospital stay, contributing both to economic cost and higher rates of respiratory failure that can affect long-term health.[18-20] Furthermore, the psychological harm of a positive test result should not be underestimated. This effect has been demonstrated in patients with false-positive results from both breast and prostate cancer screening. A study of women recalled for diagnostic assessment following a mammogram found that those with abnormal findings reported an increase in level of concern regarding cancer that was sustained even a month after a negative result had been reported.[21] Similarly, men with false-positive screening results had increased prostate cancer-related worry and problems with sexual function.[22,23] Another difference between the results of the NLST and community practice is that the mortality from lung cancer surgery was 1% in the NLST, whereas the national average is between 3% and 5% for a lobectomy. While the NLST allowed patients to choose where they had their evaluation and management for screen-detected nodules, it is likely that many were managed at an NLST site with high volume and dedicated thoracic surgery support, both of which have been shown to have better outcomes.[24,25] It is also important to note that while 70 is the average age at lung cancer diagnosis, only 8% of the NLST study population was over the age of 70. Thus it is probable that patients enrolled in this study were younger and healthier than persons likely to participate in broad-based screening programs.

In addition to the difficulty associated with generalizing the study results to the community, difficulties arise from the fact that smokers represent a unique group with potential barriers to lung cancer screening. One study demonstrated that current smokers are less likely than nonsmokers to believe that early cancer detection would result in a good chance of survival. Current smokers are also less likely to consider CT screening for lung cancer (71.2%) than are never-smokers (87.6%). In addition, only half of the current smokers surveyed would opt for surgical resection of a screening-diagnosed cancer.[26] Finally, it is significant that smokers make up 31% of the population below the poverty line, compared with 20% of those at or above the poverty line[27]; as a result, smokers are likely to be more difficult to reach as a target population for large-scale screening in the community.

Currently, most of the major societies either have no recommendation or recommend against screening for lung cancer in a high-risk population.[15,28,29] Representatives of major societies in the cancer community are collectively evaluating cost-efficacy and assembling guidelines for appropriate screening and management of screen-detected abnormalities. The National Comprehensive Cancer Network (NCCN) most recently published its screening recommendations for lung cancer; these recommend screening with LDCT for those determined to be high risk. The NCCN guidelines rate as “category 1” the screening recommendation for high-risk patients with the same demographics as those enrolled in the NLST (age 55 to 74 years, with at least a 30-pack-year smoking history). They also place people who are 50 years of age or older and who have at least a 20-pack-year smoking history and an additional risk factor into the high-risk category, with a 2B recommendation for screening with LDCT.[30] However, there is no evidence to support this recommendation, and we believe it unwise to extend lung cancer screening to persons outside the inclusion criteria of the NLST.

**Lung Cancer Testing: The Present**

**Light-induced fluorescence endoscopy (LIFE)**

A number of endobronchial treatment modalities, including cryotherapy, laser therapy, and photodynamic therapy, have been developed to target small intraepithelial (or preinvasive) neoplastic lesions. Unfortunately, identifying people at risk for and then localizing the endobronchial lesions can present a challenge. When occult lung cancer is detected by sputum cytology alone without radiographic abnormalities, conventional bronchoscopy is the only way to identify the lesion and does so successfully in only 29% of cases.[31] A difference in fluorescence between normal and neoplastic tissue can be used to enhance the ability of bronchoscopy to identify intraepithelial neoplasia.[32-34] In a multicenter trial, the addition of LIFE bronchoscopy to conventional white-light bronchoscopy improved the sensitivity (detection of
at least one lesion) from 37.3% to 75%, but there was no improvement in positive predictive value.[35] While this modality may be superior at localizing tracheobronchial dysplasia, sputum cytology, a study not shown to improve mortality, is needed to identify those harboring dysplastic or malignant lesions.

**Airway epithelial markers**

Based on previous studies that demonstrated airway epithelial cell injury and various genetic mutations in the large airways of current and former smokers without lung cancer,[36-38] DNA microarrays were used to describe the smoking-induced changes in the gene expression of large-airway epithelial cells obtained during bronchoscopy.[39] Spira et al took this work further and performed genetic expression profiling on specimens obtained from the large airways of patients undergoing bronchoscopy to follow up a clinical suspicion of lung cancer.[40] A training set consisting of 77 samples was used to identify an 80-gene biomarker that distinguished between smokers with and without lung cancer. In a test set of 52 samples, the accuracy, sensitivity, and specificity were 83%, 80%, and 84%, respectively. These results were then validated with 35 samples collected prospectively, with similar results. When combined with cytopathologic analysis of airway brushings obtained during bronchoscopy, the biomarker had an increased sensitivity of 95% and a 95% negative predictive value.[40]

The airway epithelial gene expression biomarker was later applied in a clinicogenomic prediction model that combined gene expression and clinical factors.[41] The prediction model was used to predict cancer in three different sample sets and was compared to a clinical prediction model. The combined clinicogenomic prediction model had a sensitivity and negative predictive value of 100% and resulted in a higher specificity and positive predictive value than other models. Currently, there is a large multicenter trial underway to assess the role of this epithelial gene expression model in patients with and without lung cancer. One could envision this technology being useful for helping to predict malignancy in non-calcified pulmonary nodules.

**Serum biomarkers**

Under normal conditions, the immune system is self-tolerant, thereby preventing reactions directed toward the host. Aberrations in this self-tolerance lead to inflammation and/or tissue destruction, as seen in autoimmune diseases. A similar phenomenon is seen in cancer, in which an immune response is initiated by alterations in the tumor itself; this results in the presence of circulating serum antibodies to autologous cellular antigens, also known as tumor-associated antigens (TAA).[42] Several antigens expressed in tumor cells but not at all in normal cells have been identified and likely function as TAAs capable of priming the immune system to recognize the tumor cells.[43] These antibodies have the potential to be detected much earlier than the underlying tumors and therefore hold promise as a target for a diagnostic serologic test.

Recently, a panel of six TAAs was validated in three groups of patients with newly diagnosed lung cancer.[44] These proteins, which include p53, NY-ESO-1, CAGE, SOX2, and Annexin 1, were selected to be part of the panel because of their roles in inducing the production of autoantibodies or immune biomarkers in lung cancer.

Circulating autoantibodies to Annexin 1, a glycoprotein expressed diffusely in lung cancer cells, have been described in patients with NSCLC.[45] Similarly, SOX2, a transcription factor, has been described as inducing an autoantibody response in small-cell lung cancer.[46] NY-ESO-1 is a protein expressed by a number of solid tumors, including those of the lung, liver, and breast.[47] Its function is unknown; however, antibodies to NY-ESO-1 can be detected in serum samples. Increased levels of antibodies to CAGE, a protein thought to act as an oncogene, have also been identified in solid tumors, including gastric, endometrial, and lung cancers.[48] Finally, the first autoantibodies targeting p53, a tumor suppressor gene that is often mutated in a wide variety of cancers, were described in breast cancer.[49]

Serum samples were collected after the diagnosis of lung cancer was made but prior to therapy initiation. The panel was tested in three groups of patients and demonstrated an overall sensitivity of 37% and a specificity of 90%.[44] There was no difference between lung cancer stages. The poor sensitivity suggests that this test may be best used as an adjunct in evaluating high-risk patients.

**Volatile organic compounds**

There is a growing body of literature to support the use of exhaled breath analysis for the diagnosis of lung cancer. The majority of exhaled breath is composed of nitrogen, carbon dioxide, oxygen,
water, and inert gases. The latter trace components are volatile substances that are a result of the
body’s cellular biochemical processes or absorbed from the environment. The measurement of
volatile organic compounds (VOCs) is noninvasive, can be repeated in short intervals, and therefore
has potential as a screening test.
VOCs were first described in lung cancer in 1985 by Gordon and colleagues using a gas
chromatography–mass spectrometry (GC-MS) system.[50] The breath of 12 lung cancer patients was
analyzed and compared with that of controls. A significant difference in the detected level of three
VOCs allowed for a model that had 93% accuracy in identifying persons with lung cancer. Since this
first study, a number of large-scale multicenter studies have been conducted that demonstrate
varying sensitivities and specificities for the use of VOCs to detect lung cancer. Two of these studies
conducted by the same group applied a model of exhaled VOCs for lung cancer screening.[51,52]
The first study compared 87 patients with lung cancer to healthy volunteers using nine VOCs and
demonstrated a sensitivity of 89.6% and a specificity of 82.9%.[52] The next evaluated 193 patients
with lung cancer, again comparing results of 16 exhaled VOCs to results in healthy volunteers, with a
sensitivity of 84.6% and specificity of 80%.[51] Importantly, smoking status did not affect the results,
nor was there a difference in results by stage of lung cancer.

There are two main devices available that have been studied to analyze VOCs in exhaled breath,
each with advantages and disadvantages. GC-MS is very sensitive and can detect and measure
specific VOCs. However, GC-MS devices are more expensive and require more expertise than
gaseous chemical sensing devices.[53] Gaseous chemical sensing devices (also known as electronic
noses) have a high sensitivity, are easy to use, and are portable. They do not, however, obtain
quantitative data and cannot be calibrated.[54]

A colorimetric sensor array using exhaled breath has also been evaluated for the detection of lung
cancer. This sensor uses a disposable cartridge that has 36 spots impregnated with different
chemical compounds that change color when contact is made with an inducing chemical. A total of
143 persons, including both healthy persons and persons with lung cancer, were evaluated with the
sensor, which demonstrated a sensitivity of 73.3% and a specificity of 72.4%.[55]

Interestingly, VOCs can be recognized by dogs. In a double-blinded study, dogs were first trained to
distinguish between the exhaled breath of persons with lung cancer from those without lung cancer.
The dogs then sniffed breath samples from patients that they had not been exposed to previously.
The sensitivity of canine breath detection of lung cancer was 99%, with a specificity of 99%.[56]

Cost-Effectiveness of Screening Procedures

Various models of cost-effectiveness analysis of CT scanning for lung cancer screening have
produced results ranging from highly cost-effective to not cost-effective (estimates range from
$2,500 to $2 million per life-year gained).[57-59] Since the release of the NLST, a microsimulation
model that simulated cohorts of individuals representative of the US population (not calibrated to the
NLST results) suggested that the cost-effectiveness of screening with CT scanning would be strongly
influenced by specific eligibility criteria and the rate of smoking cessation in screening
participants.[60] It should be noted, however, that the only randomized study to assess enrollment in
smoking cessation programs at the time of lung cancer screening showed that screening did not
improve rates of cessation.[61]

Cost-effectiveness analyses from the NLST are currently underway for the use of LDCT for lung
cancer screening. The estimates will vary based on the reproducibility of the study findings in
general practice settings. For example, LDCT will be less cost-effective in populations in which
screening results in more surgery, or in populations that have a higher morbidity or mortality for the
work-up of benign disease. Cost-effectiveness will also be lower if scans performed to follow up
screen-detected nodules are obtained at more frequent intervals than recommended. Alternatively,

Furthermore, life expectancy will be improved if follow-up is conservative, if the morbidity and mortality of
surgery remain low, and if high-risk populations such as current smokers with COPD are screened.
Should screening using LDCT be deemed cost-effective, the question will remain of how to financially
support this technology while continuing to fund programs that have already been shown to be
cost-effective ($5,000 per quality-adjusted life-year to implement the Agency for Healthcare
Research and Quality [AHRQ] smoking cessation guidelines).[62] Reducing smoking initiation or
increasing cessation rates will have benefits in reducing the rate of not only lung cancer but also
coronary artery disease, vascular disease, and the 11 or so other cancers associated with smoking.
An additional consideration is the incorporation of any of the new testing procedures discussed
above into screening strategies. A new technology might further reduce the cost of screening by
preventing the need for surgery and other invasive procedures were it able to identify malignancy in those with screen-detected pulmonary nodules.

**Lung Cancer Testing: The Future**

While the NLST showed an improvement in mortality of 20% in those screened for lung cancer, the number of false-positive results was staggering. It may be that new testing techniques, such as exhaled breath VOCs, the airway epithelial gene expression biomarker, or serum sampling for antibodies, will be included as part of a screening algorithm for lung cancer. For example, one can foresee how a simple breath test could be performed on a high-risk individual, and if positive would raise the possibility of lung cancer and lead to chest CT screening. A negative breath test might prevent CT scans from being performed in those without lung cancer, but allow the screening to miss very few patients with lung cancer.

Similarly, in patients who undergo LDCT for screening and are found to have solitary pulmonary nodules, it might be advantageous to examine exhaled VOCs to determine which patients require further invasive work-up.

While it is recognized that smoking is a major risk factor for lung cancer, only a minority of smokers develop lung cancer—and in patients with lung cancer, approximately 15% are never-smokers. This suggests that to improve our ability to detect lung cancer in those who have it and to avoid testing in those who don’t, we need to better identify those at the highest risk for developing this disease. This may include some combination of airway genetic testing, serum biomarker analysis, and exhaled VOCs, as well as factors yet to be elucidated. The early detection of lung cancer holds great promise, but clinicians and scientists should not consider this issue in a vacuum. Without continued efforts at tobacco control and smoking cessation, significant reductions in the mortality from lung cancer and other smoking-related diseases will not be realized.

**Financial Disclosure:** Drs. Tanner and Silvestri are currently involved in trials sponsored by Allegro Diagnostics that evaluate airway epithelial gene expression in the diagnosis of lung cancer. The authors have no other significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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New Testing for Lung Cancer Screening
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