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Lung Cancer Screening: Past, Present and Future

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Introduction

Lung cancer is the leading cause of cancer death for men and women in the United States and worldwide [12]. The most effective way to decrease lung cancer morbidity and mortality would be to significantly alter current smoking patterns. Unfortunately, while smoking decreased dramatically in the 1960's and 1970's, the smoking rate more recently has plateaued. For the past 10 years, roughly 20% of the population have been being active smokers [3]. The high mortality rate for lung cancer is heavily influenced by the fact that most cases are diagnosed at an advanced stage and cure is no longer an option, in contrast to cancers such as breast and colon which have effective screening tests. Seventy percent of lung cancers are stage III or IV at the time of diagnosis and the 5 year mortality for lung cancer has remained relatively unchanged for the past 40 years, while survival for most other cancers has steadily improved [2].

Outside of reducing cigarette smoking rates, arguably the most important factor which impacts lung cancer mortality has been the absence of an effective screening test to diagnose early stage, curable disease. Effective cancer screening is based on the premise that lethal malignancies can be found before they are symptomatic and when therapy can be curative. Over the past 4 decades, numerous lung cancer screening trials, primarily using serial chest x-rays or computed tomography (CT) scans, have been conducted. Despite initial negative studies, the recent publication of the National Lung Screening Trial (NLST) demonstrated improved lung cancer survival in participants screened with serial low dose CT scans and is the first trial showing screening can decrease lung cancer mortality. This trial suggests that large scale successful screening for lung cancer is possible.

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Lung Cancer Screening by Chest X-Ray

Studies of lung cancer screening began in the 1970's with several examining the efficacy of serial chest x-rays with or without sputum cytology analysis to diagnose early stage lung cancer and decrease lung cancer mortality. The first randomized controlled trial was the Mayo Clinic trial which randomized 9,211 males, age 45 or older who had smoked at least 20 cigarettes a day in the past year. All patients underwent an initial "prevalence screen" chest x-ray and sputum cytology examination followed by a chest x-ray and sputum cytology every 4 months for the screening group versus "routine recommendations" of yearly chest x-ray and sputum cytology in the control arm. While the screening group had more lung cancers, and specifically more stage I lung cancers, diagnosed and resected, there was no difference in lung cancer mortality [4,5]. Similar findings were observed in two other chest x-ray screening trials. The Johns Hopkins Lung Project and the Czechoslovakian experience each randomized patients to some combination of serial chest x-rays and sputum cytology versus yearly chest x-ray [6,7]. Again, both found a difference in early stage lung cancers diagnosed but no difference in mortality.

These initial screening studies highlight the importance of using mortality as an end-point in cancer screening trials and the problem of overdiagnosis bias. Overdiagnosis refers to the identification of cancers which do not progress or influence mortality. In an adequately powered, randomized controlled trial, the incidence of cancer should be equal in both the screening and control arms. If cancer occurs more frequently in the screening arm, it suggests that the difference in cancer diagnoses represents cancers which would not advance to the point of causing death. Overdiagnosis results in unneeded, often invasive tests and treatments. The Mayo Lung Project is an example of overdiagnosis. After 8.5 years of follow up, 206 cancers were diagnosed in the screening arm compared with 160 in the control arm. After 12 years of follow up, that difference had shrunk, but was still apparent, with 585 cancers diagnosed in the screening arm and 500 in the control arm. That there was no difference in cancer mortality further supports the likelihood that those excess cancers were the product of overdiagnosis.

The most recent trial of CXR screening was the Prostate, Lung, Colorectal and Ovarian (PLCO) trial. This trial differs from previous chest x-ray screening studies in its large size (154,901 total participants) and the control arm of the study did not undergo either baseline or annual chest x-rays [8]. Importantly, PLCO was a screening trial for multiple cancers and a requirement of a smoking history was not an inclusion criterion, making it a study of screening in a general population, not a high risk population. Starting in 1993, men and women aged 55 to 74 in the study group underwent annual screening for 4 years. The "usual care" group consisted patients given no specific recommendation regarding screening. There was high adherence to screening in the screening arm and a low rate of chest x-rays in the usual care arm. The PLCO trial demonstrated no effect of annual chest x-ray screening on diagnosing lung cancer, no difference on lung cancer stage or histology and no difference on lung cancer mortality through 13 years of follow up. A sub-analysis of the efficacy of yearly chest x-ray screening including only patients at higher risk of lung cancer (i.e. at least 30 pack year smoking history who were either current smokers or had quit within the previous 15 years) also demonstrated no effect on lung cancer incidence or lung cancer mortality.

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Many of the cancers were diagnosed during the follow up period, after active radiographic screening had ended, raising the question of whether a screening period of more than 4 years would have been more effective. An analysis limited to the period during which screening occurred, however, confirmed no increase in lung cancers diagnosed by annual chest x-rays. The PLCO trial provides a possible final confirmation that annual chest x-rays have no impact on lung cancer diagnosis or mortality when compared to no screening.

Overdiagnosis was less apparent in the PLCO trial, with a smaller difference in lung cancer rates between the screened and usual care arms (1,696 in the chest x-ray group vs. 1620 in the usual care arm at study end). This difference when compared to the Mayo Clinic Project might result from screening chest x-rays that were performed more frequently in the Mayo Clinic trail compared the PLCO trial; every four months vs. yearly. Additionally, in the Mayo Clinic trial all patients had initial chest x-rays to diagnose and exclude prevalence lung cancers at the time of study entry, following which patients were randomized to either screening or control arms. In the PLCO trial, patients were randomized prior to any chest x-ray evaluation and the usual care arm did not receive imaging as part of the protocol.

Lung Cancer Screening By Computed Tomography

Chest x-rays diagnosed more early stage lung cancers; however, chest x-ray screening did not decrease the number of late stage cancers compared with the control group, resulting in similar overall mortality rates. The emergence of CT scanning created new hope for effective lung cancer screening, as chest CTs have increased resolution compared to chest x-rays, resulting in increased sensitivity for diagnosing small cancers. This raised the possibility that chest CT scans could identify early stage lung cancer before they progressed to advanced stage disease.

The initial trials of chest CT screening for lung cancer primarily consisted of single arm, observational studies which investigated the utility of low dose CT (LDCT) scans to diagnose early stage cancer. LDCTs expose patients to less than a quarter of the radiation than a conventional CT scan of the chest, 1.5 versus 7 milliseiverts (mSv) [9]. Two studies performed in Japan included up to 6,000 people with a low lung cancer risk (minimal or no smoking history). While the prevalence of lung cancer in these studies was less than 1%, they confirmed that LDCT scans detect more cancers and benign nodules than chest x-rays [10,11].

Investigators at the Mayo Clinic enrolled 1,520 high risk subjects, defined as at least 20 pack year smoking history and participants could not have quit smoking more than 10 years prior to enrollment, in a prospective study in which participants underwent 5 annual LDCT scans (one prevalence scan followed by 4 yearly incidence scans [12]. After these 4 years, 1,118 participants (74%) had nodules of at least 4 mm detected by LDCT. Sixty-six participants (4%) were ultimately diagnosed with lung cancer. Of these, 61% were stage I with a lung cancer mortality rate of 2.8%. While these numbers seem encouraging, the authors note that this was not significantly different from the mortality rates in the chest x-ray Mayo Lung Project. The authors concluded that LDCT scans could detect early stage lung cancers but had no significant effect on mortality. These findings raised the concern that, similar to chest

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x-rays, LDCTs might diagnose more early stage lung cancers without decreasing late stage cancer rates, resulting in overdiagnosis with no effect on mortality. Interestingly, 26% percent of patients had nodules missed on the baseline scan (false negative rate). Additionally, the authors noted a high rate of benign disease (false positive rate) and warned about potential complications and expense incurred in the work up of these benign lesions.

The Early Lung Cancer Action Program (ELCAP) screened patients age 60 or older with at least a 10 pack-year history of cigarette smoking with LDCT [13,14]. The baseline scan (31,567 participants) detected a pulmonary nodule in 4186 (13%) participants and the subsequent annual incidence scans (27,456 total annual screens) found a new nodule in 1,460 (5%) participants. Of these, nodules found on baseline scans were confirmed as lung cancer in 405 patients or 1.2% of all baseline screening tests and 9.7% of positive baseline screens (i.e. nodule identified). Of the incidence screens, 74 proved to be cancer for a rate of 0.2% of all incidence screens and 5.1% of positive incidence screens. An additional 13 cases of lymphoma or metastasis from a distant, non-pulmonary site were also diagnosed by either baseline or annual chest LDCT. The vast majority of lung cancers diagnosed (85%) were stage I and the estimated 10 year survival rate of this sub-group was 88%. A biopsy was performed in 535 patients, of which 92% were proved to be cancer with benign disease in the remaining 8%. These results are striking in the rate of stage I cancers diagnosed, the estimated low mortality of associated with early diagnosis and the arguably low rate of biopsy for benign processes. However, the absence of a control group ultimately limits this study.

The DANTE trial was a randomized, controlled lung cancer screening trial comparing 5 annual LDCTs to no screening [15] . The trial included 2,811 men, aged 60 - 75 years old with at least a 20 pack year history of smoking and half of the participants were randomized to the screening arm and half to the control arm. Subjects were followed for a median of 33.7 months. Similar to previous screening studies, there was a significant increase in lung cancers diagnosed with screening LDCTs (60 vs. 34). However, the two arms had similar rates of advanced lung cancer and screening again no effect on lung cancer specific or all-cause mortality. The rate of invasive procedures (e.g. video assisted thorascopic surgery) was significantly higher in the screening compared to the control arm. Like prior single arm LDCT trials, DANTE indicated that lung cancer screening with LDCT scans might result in overdiagnosis, a high false positive rate and likely leads to unnecessary procedures that do not affect mortality. Though the DANTE trial was an advance over prior LDCT studies in that it included a control group, interpretation of its results is hampered by its small size.

The National Lung Screening Trial-Improved Survival with LDCT

The National Lung Screening Trial (NLST) is the first large, randomized, controlled trial of screening using LDCT in patients at high risk for lung cancer. The trial enrolled 53,454 participants (men and women) between 55 and 74 years of age with at least a 30 pack year history of smoking and, if not a current smoker, subjects must have quit within the previous 15 years [16]. Participants were enrolled between August 2002 and April 2004 during which the screening group (26,723 subjects) underwent an initial prevalence scan followed by two annual incidence scans. The control group (26,733 subjects) underwent yearly chest x-rays.

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The median follow up of patients in both arms was 6.5 years and the maximum follow up was 7.4 years. Over 90% of participants in each arm followed the protocol both years of screening.

Over two years, 24.2% of scans in the LDCT group and 6.9% of chest x-rays in the control group were classified as abnormal (i.e. positive). Of these, 96.4% were ultimately found to be false positives in the LDCT arm compared to 94.5% in the CXR arm. During the two years of screening, 649 lung cancers were diagnosed in the LDCT group compared to 279 lung cancers detected in the chest x-ray group. At the completion of follow-up, 1,060 and 941 lung cancers had been diagnosed in the LDCT and chest x-ray groups respectively. The LDCT participants were more likely to have stage I or II cancer than those who were screened with chest x-rays**.** Lung cancer mortality was 247 per 100,000 person years in the LDCT and 309 per 100,000 person years in the chest x-ray groups. The relative risk of lung cancer mortality was decreased 20.3% by LDCT screening (95% CI, 6.8% to 26.7% P=0.004) and the number needed to screen to prevent one lung cancer death with LDCT was 320. This study was the first trial to demonstrate that lung cancer screening with CT scans can decrease mortality.

Potential Risks of LDCT Screening

Though the NLST demonstrated that LDCT screening can improve survival in patients at risk for lung cancer, screening opens patients to the risk of radiation exposure as well as increased cost and physical and emotional morbidity associated with follow up of identified nodules. Increased radiation exposure secondary to LDCT screening is a concern given the heightened risk of cancer secondary to radiation. As stated above, the dose of radiation with an LDCT is 1.5 mSv compared to a dose of 7 mSv from a conventional chest CT [9]. However, a positive scan usually results in further imaging, including diagnostic CT or positron emission tomography (PET) scanning, raising the cumulative radiation exposure. Even given this, it has been estimated that in high risk patients (as defined by NLST), the benefits of LDCT screening outweigh risks of radiation induced cancer [17]. However, in people at low risk of lung cancer, for example nonsmokers or younger individuals, the risks of radiation-induced cancer likely are greater than the risk of lung cancer [18].

The evaluation of clinically inconsequential processes found by LDCT is an additional risk of screening. Given the increase in lung cancers detected by LDCT compared to chest x-ray during NLST, overdiagnosis of cancers that do not affect mortality is again likely. It is notable that most of the increase in lung cancers diagnosed by LDCT in the NLST consisted of bronchioloalveolar carcinomas (BAC); LDCT diagnosed 119 more cancers than chest x-rays and 75 of these were BACs. In contrast, other histologic forms of lung cancer were diagnosed at similar rates in both the LDCT and the chest x-ray arms. True BAC, newly classified as adenocarcinoma in situ (AIS), is a slowly growing process with little impact on mortality[19,20]. The evaluation and treatment of cancers which likely would not affect mortality exposes patients to un-needed risk and cost. In addition, the evaluation of nodules ultimately found to be benign further raises concerns for excess morbidity and expense. In the NLST, the rate of serious complications resulting from invasive diagnostic and therapeutic procedures for patients who ultimately did not have cancer was 15%. However,

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the entry criteria for NLST included participants at higher risk for lung cancer when compared with other LDCT trials. Lung cancer occurs frequently in patients outside the age range of NLST and with fewer pack years of smoking [21] and when applied to a population defined by a broader risk profile, LDCT screening likely would detect more lung cancers but also more benign processes (false positives). The Fleischner Society, which has created guidelines for the evaluation and management of pulmonary nodules (Table 1), broadly categorizes patients as high risk if they have "a history of smoking or other known risk factors" [22].

Given the inherent risks of LDCT screening, there is a need to define more accurately the "at risk" population that would most benefit from screening. NLST data suggest that screening is efficacious in a high risk population, but a uniform definition of high risk does not exist. Several models have been created to help predict risk of developing lung cancer in a given individual, using clinical risk factors such as smoking history, age, asbestos exposure and prior history of malignancy [23-25]. Use of these models can further define a population at risk who might benefit from screening. Even within the inclusion criteria of the NLST, the predicted rate of lung cancer is not uniform, and increases with age, smoking history and exposure to other lung cancer risk factors. For example, Bach and Gould have calculated that when applied to a person with a high risk of lung cancer (e.g. older person with 110 pack year history of smoking), the number needed to screen to prevent a cancer death is 82 while for a person meeting NLST study criteria but with minimal risk (e.g. age 55, 30 pack year history, recently quit smoking), the number needed to screen to prevent a single cancer death is 1,236 [26]. When screening is applied to a very low risk population of 40 year old non-smokers, over 35,000 people would require LDCT screening to prevent one death [26].

Clearly a better method to define risk of lung cancer is needed. The identification and use of biomarkers of lung cancer might refine the population of those high risk patients who would most benefit from screening, thereby increasing specificity and decreasing the number of benign nodules identified by CT. One tool to improve specificity of CT screening for lung cancer screening is nodule volume doubling time. The Dutch-Belgian lung cancer screening trial studied the change in nodule volume over time, as measured on CT scans, as a mechanism of differentiating benign from malignant nodules. This strategy is based on the idea that cancers increase in size at a greater rate than benign processes. The authors determined that a long volume doubling time (greater than 400 days) predicted benign disease and might be used to reduce invasive follow-up diagnostic testing. Additionally, biologic markers, including changes in gene expression patterns [27], exhaled breath analysis for volatile compounds [28], serum measurement of proteins [29] and tumor autoantibodies [30] have all been studies as possible diagnostic tools for early detection of lung cancer and may help define a high risk population that might benefit from screening.

Conclusion

The NLST proved that LDCT screening for lung cancer decreases mortality. Based on existing data, the American College of Chest Physicians and the American Society of Clinical Oncology created a clinical practice guideline for lung cancer screening using LDCT (Table 2) [17]. However, several questions remain regarding how a screening program

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might be implemented. First, the optimal interval of screening is unknown. Most LDCT trials have investigated yearly screening; however how more or less frequent screening would affect the sensitivity and specificity of LDCT screening is unclear. Additionally, how long to screen individuals remains unknown. The NLST had similar rates of lung cancer incidence in each of the three years of screening, as well as during the follow up period after screening, suggesting that a longer screening period would continue to diagnose new lung cancers. Almost certainly, the NLST will result in increased LDCT screening for lung cancer. How this affects lung cancer mortality in general practice remains to be seen.

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- The NLST proved that LDCT screening for lung cancer decreases mortality.
- Most LDCT trials have investigated yearly screening
- How more or less frequent screening would affect the sensitivity and specificity of LDCT screening is unclear.
- How long to screen individuals remains unknown.
- Almost certainly, the NLST will result in increased LDCT screening for lung cancer.

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Table 1

Fleischner Society Guidelines for the Evaluation of Non-calcified Pulmonary Nodules Detected Incidentally by Nonscreening CT

Nodule Size (mm) *	**≤ 4**	**>4-6**	**>6-8**	**>8**
Low- Risk Patient *	No follow-up needed. §	Repeat CT at 12 months. If unchanged, no further follow-up. °	Repeat CT at 6-12 months and 18-24 months if no change.	Repeat CT at 3, 9, and 24 months, dynamic contrast-enhanced CT, PET, and/or biopsy.
High- Risk Patient †	Repeat CT at 12 months. If no unchanged, no further follow-up. °	Repeat CT at 6-12 months and 18-24 months if no change. °	Repeat CT at 3-6 months and 9-12 and 24 months if no change.	Same as for low-risk patient.

” Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.

Adapted from [22]

*Minimal or absent history of smoking and of other known risk factors.

†History of smoking or of other known risk factors.

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Table 2

Recommendations From the American College of Chest Physicians and the American Society of Clinical Oncology on the Role of CT Screening for Lung Cancer

Recommendation #1
Annual screening should be offered over both annual screening with chest radiograph or no screening to smokers and former smokers aged 55 to 74 who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years. Screening should only be done by centers that can deliver the evaluation and care provided to National Lung Screening Trial (NLST) participants. (Grade of recommendation:2B.)
Recommendation #2
No CT screening should not be performed for individuals who have accumulated fewer than 30 pack-years of smoking are either younger than 55 years or older than 74 years, or for individuals who quit smoking more than 15 years ago, or for individuals with severe comorbidities that would preclude potentially curative treatment and limit life expectancy. (Grade of recommendation:2C.)

Adapted from [17]