LUNG CANCER SCREENING WITH LOW-DOSE CT

ALYSSA CREWS, PA-S3
UNIVERSITY OF OKLAHOMA SCHOOL OF COMMUNITY MEDICINE
PHYSICIAN ASSISTANT PROGRAM
TULSA, OK
LEARNING OBJECTIVES

1. Describe current literature regarding utilizing low-dose CT to screen for lung cancer.
2. Explain the risks and benefits of CT screening.
3. Review recommendations for lung cancer screening, including who should undergo such screening.
The NLST was funded by the National Cancer Institute in an effort to reduce lung cancer mortality in those patients who are at high risk, by comparing the new low-dose helical CT with more traditional methods of screening for lung cancer.\(^1\)

Screening however, is not a replacement for smoking cessation.
DEFINITIONS

- **Current smoker**: anyone with a smoking history of 30 pack years
- **Former smoker**: anyone who has quit smoking within the last 15 years
- **Low-dose CT**: CT that has a radiation exposure of approximately 1.0-1.5mSv, compared to 8mSv with a diagnostic chest CT
- **False positive**: anything suspicious for lung cancer found on screening exam that did not result in a lung cancer diagnosis.
- **True positive**: nodule or mass found on screening exam that resulted in a lung cancer diagnosis.
- **Over diagnosis**: detection of a slow-growing lung cancer that would not have been clinically apparent.
Cigarette smoking is the leading cause of preventable morbidity and mortality in the United States.\(^1\)

- Estimated 94 million current or former cigarette smokers.
- In 2008 smoking rates were highest among men, Native Americans, and those with less than a high school diploma.
- Lung cancer followed a similar trend with higher rates in men, particularly African American men, residents of the Southern portion of the US, and those over age 60.
LUNG CANCER RELATED COSTS

- Lung cancer related health costs are sky rocketing
  - Estimated to be greater than $12 billion in 2012.
  - Approximately 20% of Medicare’s cancer related costs each year.
  - The high costs could potentially be reduced by early diagnosis and treatment, thus the reason for investigating better screening methods.
No reliable screening method that decreased mortality rates.\textsuperscript{1}

Chest radiographs and sputum cytology were studied most commonly.

Serum biochemical markers and bronchial brushing were also studied.
Diagnosis of lung cancer limited by size, location, and quality of image.

Not very accurate for detecting central lung cancers.

Both the Mayo lung Project and the Prostate Lung Colorectal Ovarian Cancer Screening Trial (PLCO) determined that chest radiographs and sputum cytology were not reliable screening methods in regards to decreasing mortality.\textsuperscript{9,10}
MAYO LUNG PROJECT

- 10,000 men with a high risk of developing lung cancer
- Initial chest radiograph to rule out current lung cancer
- Control group: received chest radiographs and sputum cytology once per year
- Experimental group: chest radiographs and sputum cytology every four months for six years
- Conclusion: More frequent chest radiographs and sputum cytology resulted in increased lung cancer detection and increased resectability of tumors, but did not reduce mortality.
## Table 1. Incidence of Lung Cancer: Mayo Lung Project Lung Cancer Cases and Deaths by Cell Type

<table>
<thead>
<tr>
<th>Cell type of cancer</th>
<th>Group screened every 4 mo</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Deaths</td>
</tr>
<tr>
<td>Squamous</td>
<td>68 (33%)</td>
<td>28</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>61</td>
<td>40</td>
</tr>
<tr>
<td>Large cell</td>
<td>29</td>
<td>18</td>
</tr>
<tr>
<td>Small cell</td>
<td>48 (23%)</td>
<td>36</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>206</td>
<td>122</td>
</tr>
</tbody>
</table>
PROSTATE LUNG COLORECTAL OVARIAN CANCER SCREENING TRIAL

- 154,942 men and women 55-74 years of age.
- Fairly extensive exclusion criteria
- Control group: 70,477 participants received no screening measures.
- Experimental group: 77,465 participants received annual PA chest radiographs for three years.
- Results: Lung cancer deaths totaled 1,213 in the experimental group and 1,230 in the experimental group.
- Conclusion: Chest radiographs are not a reliable screening method due to high false positives and no decreased in mortality.
PLCO TRIAL: LUNG CANCER MORTALITY

Figure 3. Lung Cancer Mortality by Year

- Intervention group
- Usual care group

<table>
<thead>
<tr>
<th>Time Since Randomization, y</th>
<th>Intervention group Cumulative deaths</th>
<th>Intervention group Cumulative person-years</th>
<th>Usual care group Cumulative deaths</th>
<th>Usual care group Cumulative person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>77,268</td>
<td>30</td>
<td>77,268</td>
</tr>
<tr>
<td>1</td>
<td>113</td>
<td>154,053</td>
<td>111</td>
<td>154,053</td>
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<tr>
<td>2</td>
<td>196</td>
<td>230,270</td>
<td>198</td>
<td>230,270</td>
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<tr>
<td>3</td>
<td>292</td>
<td>305,833</td>
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<tr>
<td>4</td>
<td>378</td>
<td>380,691</td>
<td>425</td>
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<tr>
<td>5</td>
<td>480</td>
<td>454,773</td>
<td>527</td>
<td>454,773</td>
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<tr>
<td>6</td>
<td>582</td>
<td>527,937</td>
<td>639</td>
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<tr>
<td>7</td>
<td>711</td>
<td>600,004</td>
<td>761</td>
<td>600,004</td>
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<tr>
<td>8</td>
<td>838</td>
<td>670,274</td>
<td>884</td>
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<tr>
<td>9</td>
<td>937</td>
<td>735,086</td>
<td>987</td>
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<tr>
<td>10</td>
<td>1,070</td>
<td>789,540</td>
<td>1,076</td>
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<tr>
<td>11</td>
<td>1,150</td>
<td>832,441</td>
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<tr>
<td>12</td>
<td>1,213</td>
<td>864,227</td>
<td>1,230</td>
<td>864,227</td>
</tr>
</tbody>
</table>
Due to evidence that screening for lung cancer with chest radiographs and sputum cytology does not decrease mortality, combined with the high false positive rates, the following agencies all distributed statements recommending against routine screening:  

- National Cancer Institute
- American Cancer Society
- US Preventative Services Task Force
- Society of Thoracic Radiology
FORMATION OF NLST

- Formed by the National Cancer Institute in 2002
- Due to several observational studies showing that low-dose CT scans detected more nodules than did chest radiographs.
Enrolled current smokers, men and women, 55-74 years of age with a 30 pack-year smoking history, or who had quit smoking in the last fifteen years. 1,15

Exclusion criteria: previous diagnosis of lung cancer, hemoptysis, 15 pound weight loss or more in the past year, or CT in the past 18 months.

Designed to have sex distribution and pack-year smoking history similar to the general population.
53,454 participants randomly divided into two groups:

- Control: chest radiograph at 0, 12, and 24 months
- Experimental: CT at 0, 12 and 24 months

Images were then interpreted and compared to previous results
At least one positive screening:
- 39% in the CT group
- 16% in chest radiograph group

Diagnosis of lung cancer
- CT group: 1060 cases (645/100,000 person years)
- Chest radiograph group: 941 cases (572/100,000 person years)

Deaths due to lung cancer:
- 356 in CT group (247/100,000 person years)
- 443 in chest radiograph group (309/100,000 person years)
**Figure 1. Cumulative Numbers of Lung Cancers and of Deaths from Lung Cancer.**

The number of lung cancers (Panel A) includes lung cancers that were diagnosed from the date of randomization through December 31, 2009. The number of deaths from lung cancer (Panel B) includes deaths that occurred from the date of randomization through January 15, 2009.
RESULTS AND CONCLUSION OF NLST

- Relative reduction in lung cancer mortality of 20.0% in the low-dose CT group.\(^1\)
- The rate of death from any cause was reduced by 6.7%.
- More incidences of lung cancer were diagnosed during the three year follow-up period in the chest radiograph group than in the CT group.\(^{17}\)
DANISH LUNG CANCER SCREENING TRIAL (DLCST)

- Evaluated low-dose CT as a screening tool for reducing lung cancer mortality.
- Enrolled men and women ages 50-70 with a 20 pack-year smoking history who had quit smoking after age 50 or within ten years.
- Very detailed inclusion and exclusion criteria
- Control group: 2,052 participants that received annual lung function test and questionnaires about health status, smoking habits, and psychological impact of screening.\(^1\)
- Experimental group: 2,052 participants that received a baseline CT, followed by four annual CT scans, annual lung function tests, and above questionnaire.
CT scans were considered negative if there were no nodules, nodules <5mm, or nodules between 5 and 15 mm with a benign appearance.

Nodules between 5 and 15mm that did not appear benign were reevaluated in three months by repeat CT scan.

CT scans were considered positive if nodules were > 15mm, had increased in size by 25%. Those participants were then sent for further diagnostic workup. ¹⁸
DLCST RESULTS

- 69 cases of lung cancer were diagnosed in the experimental group, while only 24 cases were diagnosed in the control group.
- The CT group had significantly more cases of lung cancer detected, and of those, more were of lower stage.
- No statistical difference in mortality was seen at the time of the conclusion of the trial, but is expected to be seen in the near future.  
- Final results are expected sometime this year (2015), which will allow for a 4-5 year follow-up, similar to that of the NLST follow-up time frame.
TIMELINE FOR GROWTH OF LUNG CANCER

Figure 1. Timeline of lung cancer progression by number of tumor doublings and volume doubling rate. The volume doubling rate (measured in days) was calculated using the formula $DR = \left( t \cdot \ln 2 \right) / \ln \left( d_2/d_1 \right)$, where $t$ equals time in days, $d_1$ is the diameter at first scan, and $d_2$ the diameter at second scan. The size of initial lung cancer cell for all calculations was 1,000 μm. Although the size of a lung cancer cell may vary significantly, this will affect only the time from first cell division to first possible detection, not the time between detection and other clinical events.
RISKS AND BENEFITS OF CT SCREENING

- **Benefits:**
  - Increased rate of lung cancer detection
  - Cancer detected at an earlier stage

- **Risks:**
  - High number of false positives - which can lead to an expensive, unnecessary work-up.\(^{19,20}\)
    - Work-up includes additional imaging, bronchoscopy and even biopsy, which all carry their own set of risks.
  - In the NLST, risk of death from further diagnostic evaluation was 4.1/ 10,000 patients, while the risk of complications was 4.5/ 10,000 patients.\(^{19}\)
  - Radiation exposure
  - Severe emotional distress:
    - One study found that 46% of people experienced psychological distress while waiting for the result of the screening test.
Radiation exposure is also a concern.
- NLST exposed patients to about 8mSv over the course of the screening period
- Approximately one death due to radiation exposure would occur for every 2,500 people screened. 19

Radiation induced breast cancer is a major risk factor for women.
- For women 30-32 who have never smoked, the risk of breast cancer due to radiation is 6/10,000 women screened.
- For women 50-52, the risk is 4/10,000 women screened
- Annual screening with low-dose CT for adults 55-80 with a 30 pack-year smoking history.  
- Discontinue screening after the patient has stopped smoking for 15 years.
- Low-dose CT is the only screening test recommended for lung cancer.
- Discuss tobacco prevention and cessation strategies
AMERICAN CANCER SOCIETY RECOMMENDATION

- Annual screening with low-dose CT for adults 55-74 with greater than or equal to a 30 pack-year smoking history who are current smokers or who have quit smoking within the last 15 years and are in reasonably good health.\(^5\)

- Discuss benefits and risks of screening prior to initiation of annual screening.

- Discussing smoking cessation should remain a high priority, while explaining the further risk of lung cancer.

- Exclusion criteria: metallic implants in chest or back, need for home oxygen, life-limiting comorbid conditions.
First, Annual screening with low-dose CT for smokers and former smokers ages 55-74 with 30 pack-year smoking history, who continue to smoke or who have quit smoking within the last 15 years. 

- Explain all risks and benefits so patient can make informed decision
- Reinforce that screening is not a substitute for smoking cessation
- Second, those younger than 55 and older than 74 with smoking history of less than 30 pack-years or who quit more than 15 years ago, and those with comorbidities that would limit life expectancy, should not undergo screening with low-dose CT.
- NLST showed a mortality reduction of 20% and 6.3 fewer deaths per 10,000 person years when using the low-dose CT for screening.¹

- Lung cancer is responsible for an estimated average expected years of life lost around 13.78 years.

- Estimated annual years of life lost due to lung cancer in the U.S is more than 3 million years.
COST AND COST-EFFECTIVENESS OF LOW-DOSE CT

- Out of pocket cost is advertised to be $99- $1,000.
- Initial cost may be relatively low, the costs related to follow-up and treatment has a predicted impact on annual national health expenditure to be from $1.3 to $2 billion, if screening was to reach 55-74% of those eligible.
- Compared to no screening, it is estimated that CT screening would cost an additional $1,631/ person.
- Most cost effective for current smokers, those with higher risk of lung cancer and the elderly. 23
- Per the Affordable Care Act, preventative services given grade A or B recommendation by USPSTF are not required to be covered by Medicare.

- Medicare Evidence Development and Coverage Advisory Committee stated concerns about high false positive rates and cumulative risk of radiation exposure.

- However, in 2015 the committee distributed a statement saying they will cover annual lung cancer screening with low-dose CT for those beneficiaries who are 55-77 years old who currently smoke or who have quit within the last 15 years, and who have a smoking history of 30 pack-years.

- This will allow for covered screening of the most high risk populations.
CONCLUSIONS

- Although the American Cancer Society, USPSTF, American College of Chest Physicians and American Society of Clinical Oncology all produced slightly different recommendations, the overall consensus is that low-dose CT should be used for annual lung cancer screening.

- Health care providers need to determine which of their patients will qualify for such screening.

- Annual screening should be encouraged after a discussion of the risk and benefits of screening.


