Lung Cancer Screening: Why It’s More Than Just a Scan

Mark Block, M.D.
Chief, Division of Thoracic Surgery
Memorial Healthcare System

Sept. 21, 2019
Lung Cancer Screening.....

“...the opportunity to realize the greatest single reduction of cancer mortality in the history of the war on cancer.”

James Mulshine, MD
Associate Provost and Vice President for Research
Rush University Medical Center
Cancer Statistics, 2018

American Cancer Society
Cancer Facts & Figures, 2018
Estimated Cancer Cases, Florida, 2018

Screening tests routine
Estimated Cancer Deaths, Florida, 2018

Screening tests routine
History of Lung Cancer Screening

- Chest x-ray → Negative
- Sputum cytology → Negative
- Chest CT → ?
The Mayo Lung Project

A Perspective

Robert S. Fontana, M.D.

Department of Medicine, Mayo Clinic, Rochester, Minnesota.

BACKGROUND. The Mayo Lung Project (MLP) was a randomized, controlled, clinical trial designed to determine whether intensive radiologic and cytologic screening for lung carcinoma could reduce lung carcinoma mortality significantly.

METHODS. Half the MLP population was encouraged (and reminded) to undergo free chest X-rays and free sputum cytology tests every 4 months for 6 years.

1971 – 1983
N = 9211 men, heavy smokers

Randomized:

CxR + sputum q 4 months

CxR + sputum annually

Cancer, 2000
Mayo Lung Project: Results

Lung Ca Survival

Cumulative Lung Ca Deaths
Discovered Lung Cancers:

- **Study**:
  - Resectable: 120
  - Unresected: 130
- **Control**:
  - Resectable: 70
  - Unresected: 120
Discoverd Lung Cancers:

- Study:
  - Resectable: approximately 50
  - Unresected: approximately 100

- Control:
  - Resectable: approximately 50
  - Unresected: approximately 100

Overdiagnosis
Screening by Chest Radiograph and Lung Cancer Mortality
The Prostate, Lung, Colorectal, and Ovarian (PLCO) Randomized Trial

Martin M. Oken, MD
William G. Hocking, MD
Paul A. Kvale, MD
Gerald L. Andriole, MD
Saundra S. Buys, MD

Context  The effect on mortality of screening for lung cancer with modern chest radiographs is unknown.
Objective  To evaluate the effect on mortality of screening for lung cancer using radiographs in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.
Design, Setting, and Participants Randomized controlled trial that involved 154,901

1993 – 2001
N = 154,901
Age: 55 – 74 years

Randomized:

- Annual CxR (77,445)
- Usual care (77,456)

JAMA, 2011
PLCO: Results

Stage of discovered NSCLCs:

![Bar chart showing the stage of discovered NSCLCs for Screened and Control groups. The chart indicates the number of cases by stage (I, II, III, IV) across the two groups.](chart.png)
PLCO: Results

Cumulative Lung Cancers Detected
PLCO: Results

Cumulative Lung Cancer Deaths
Early Lung Cancer Action Project: overall design and findings from baseline screening

Claudia I Henschke, Dorothy I McCauley, David F Yankelevitz, David P Naidich, Georgeann McGuinness, Olli S Miettinen, Daniel M Libby, Mark W Pasmanter, June Koizumi, Nasser K Aitorki, James P Smith

Summary

Background The Early Lung Cancer Action Project (ELCAP) is designed to evaluate baseline and annual repeat screening by low-radiation-dose computed tomography (low-dose CT) in people at high risk of lung cancer. We report the baseline experience.

Methods ELCAP has enrolled 1000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer, who were medically fit to undergo thoracic surgery. After a structured interview and informed consent, chest radiographs and low-dose CT were done for each participant. The diagnostic

Interpretation Low-dose CT can greatly improve the likelihood of detection of small non-calcified nodules, and thus of lung cancer at an earlier and potentially more curable stage. Although false-positive CT results are common, they can be managed with little use of invasive diagnostic procedures.

Lancet 1999; 354: 99–105
See Commentary page

Introduction

In the USA in 1998, there were an estimated 160 000 deaths from lung cancer and an estimated 172 000 new cases detected. The survival for lung cancer is 19%

N = 1000
Age 60 and over
10 pack-year smoking history
CxR + low-dose Chest CT

Lancet, 1999
ELCAP: Results

Discovered Lung Cancers:

<table>
<thead>
<tr>
<th>Stage</th>
<th>CT</th>
<th>CxR</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Problems with Screening Trials:

- **Overdiagnosis**
  Diagnosis of cancers that would have never become clinically significant

- **Lead-time bias**
Lead-time bias:
Lead-time bias:
Lead-time bias:
Lead-time bias:
Lead-time bias:

3-year survival "advantage"
“The USPSTF concludes that the evidence is insufficient to recommend for or against screening asymptomatic persons....”

Lung Cancer Screening Recommendations (2004)

www.uspreventiveservicestaskforce.org
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

33 Sites
$300,000,000

NEJM, June, 2011
National Lung Screening Trial

- Age 55-75 years
- >30 pack-year smoking history
- Enrolled between 2002-2004
- Annual scans (T0, T1 and T2)
- >4 mm considered positive test

<table>
<thead>
<tr>
<th>Modality</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest CT*</td>
<td>26,722</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>26,732</td>
</tr>
</tbody>
</table>

NEJM, June, 2011
• 20% reduction in deaths from lung cancer
• 20% reduction in deaths from lung cancer

• 6.6% reduction in overall mortality
Cumulative Lung Cancers

Cumulative Deaths from Lung Cancer

NEJM, June 2011
Stage at Diagnosis:

NLST: Stage Shift
Prevalence scan

27.3% positive
NLST: CT Findings

- 27.3% positive
- 3.8% cancer

Prevalence scan
NLST: CT Findings

- **Prevalence scan**
  - 27.3% positive
  - 3.8% cancer

- **Incidence scan**
  - 16.8%
NLST: CT Findings

Prevalence scan
- 27.3% positive
- 3.8% cancer

Incidence scan
- 16.8%
- 5.2% cancer
• Lung cancer incidence = 645/100,000 person-years
• 96% of positive findings were not cancer
LUNG CANCER SCREENING

By Bruce S. Pyenson, Marcia S. Sander, Yiding Jiang, Howard Kahn, and James L. Mulshine

An Actuarial Analysis Shows That Offering Lung Cancer Screening As An Insurance Benefit Would Save Lives At Relatively Low Cost

ABSTRACT Lung cancer screening is not established as a public health practice, yet the results of a recent large randomized controlled trial showed that screening with low-dose spiral computed tomography reduces lung cancer mortality. Using actuarial models, this study estimated the costs and benefits of annual lung cancer screening offered as a commercial insurance benefit in the high-risk US population ages 50–64. Assuming current commercial reimbursement rates for treatment, we found that screening would cost about $1 per insured member per visit. In 2013 dollars, the net life-year benefit would be a

Age 50-64 years, >30 pack-year smoking history

Health Affairs, April 2012
## Cost of Treatment

<table>
<thead>
<tr>
<th>Treatment Year</th>
<th>Stage A</th>
<th>Stage B</th>
<th>Stage C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>$82,087</td>
<td>$132,464</td>
<td>$142,750</td>
</tr>
<tr>
<td>Year 2</td>
<td>$20,159</td>
<td>$42,945</td>
<td>$85,956</td>
</tr>
<tr>
<td>Year 5+</td>
<td>$11,364</td>
<td>$24,209</td>
<td>$48,456</td>
</tr>
</tbody>
</table>

Health Affairs, April, 2012
<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>$1.10</td>
</tr>
<tr>
<td>Colorectal</td>
<td>$0.95</td>
</tr>
<tr>
<td>Breast</td>
<td>$2.50</td>
</tr>
<tr>
<td>Lung</td>
<td>$0.76</td>
</tr>
</tbody>
</table>

Health Affairs, April, 2012
## Cost per Life-year Saved

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Screening Technique</th>
<th>Cost per life-year saved (2012 dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>Pap smear</td>
<td>50,162</td>
</tr>
<tr>
<td>Colorectal</td>
<td>Colonoscopy</td>
<td>18,705</td>
</tr>
<tr>
<td>Breast</td>
<td>Mammography</td>
<td>31,309</td>
</tr>
<tr>
<td>Lung</td>
<td>Low-dose chest CT</td>
<td>11,708 – 26,016</td>
</tr>
</tbody>
</table>

Health Affairs, April, 2012
Cost-Effectiveness of CT Screening in the National Lung Screening Trial

William C. Black, M.D., Ilana F. Gareen, Ph.D., Samir S. Soneji, Ph.D., JoRean D. Sicks, M.S., Emmett B. Keeler, Ph.D., Denise R. Aberle, M.D., Arash Naeim, M.D., Timothy R. Church, Ph.D., Gerard A. Silvestri, M.D., Jeremy Gorelick, Ph.D., and Constantine Gatsonis, Ph.D., for the National Lung Screening Trial Research Team*
### NLST: Cost Analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>147,000</td>
<td>46,000</td>
</tr>
<tr>
<td>Age at Entry (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>152,000</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>48,000</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>54,000</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>117,000</td>
<td></td>
</tr>
<tr>
<td>Smoking Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>615,000</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>43,000</td>
<td></td>
</tr>
</tbody>
</table>

*QALY: Quality adjusted life year

**NEJM, 2014**
Cost-Effectiveness

• Stratified NLST patients into high/low risk based on PLCO_{m2209} score (> 2% risk/6 years).
  • Age, education, smoking history
  • Coexisting COPD, Family history of lung cancer
  • BMI

• Simulated outcomes for
  • High risk, screened
  • High risk, unscreened
  • Low risk, unscreened
In 2004 the USPSTF said:

“...the evidence is insufficient to recommend for or against screening asymptomatic persons....”
Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement

Summary of Recommendation and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age and smoking history.

This is a Grade B recommendation.
Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, MPH, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for lung cancer.

Methods: The USPSTF reviewed the evidence on the efficacy of low-dose computed tomography, chest radiography, and sputum cytologic evaluation for lung cancer screening in asymptomatic persons who are at average or high risk for lung cancer (current or former smokers) and the benefits and harms of these screening tests and of surgical resection of early-stage non-small cell lung cancer. The USPSTF also commissioned modeling studies to provide information about the optimum age at which to begin and end screening, the optimum screening interval, and the relative benefits and harms of different screening strategies.

Population: This recommendation applies to asymptomatic adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years.

Recommendation: The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. (B recommendation)

For author affiliation, see end of text.

* For a list of the members of the USPSTF, see the Appendix (available at www.annals.org).

This article was published online first at www.annals.org on 31 December 2013.

www.annals.org

Dec. 31, 2013
Evidence Lacking to Support or Oppose Low-dose CT Screening for Lung Cancer, Says AAFP

Inability to Make Harms/Benefits Comparison Precludes Definitive Recommendation

January 13, 2014 04:50 pm Cindy Borgmeyer – Citing a paucity of high-quality evidence on which to base a comparison of relative harms and benefits, the AAFP today released an “I” recommendation regarding the routine use of low-dose CT scans in screening high-risk, older smokers for lung cancer.

The Academy’s action puts it at odds with a recommendation issued last month (www.uspreventivenservicestaskforce.org) by the U.S. Preventive Services Task Force (USPSTF).

Jan. 13, 2014
AAFP has reservations.....

“...reviewed the USPSTF's recommendation ... and had significant concern with basing such a far reaching and costly recommendation on a single study."
...about excessive intervention

The risks attendant in such a long-range screening protocol cannot be ignored....

"there's going to be a considerable amount of testing that's going to be required, including some biopsies and some bronchoscopies and some other procedures that have risk to them...."
A shared-decision-making discussion between the clinician and patient should occur regarding the benefits and potential harms of screening for lung cancer.
...most important when talking with these high-risk patients: Don't forget to address the elephant in the room.

"If they're currently smoking, a better thing to do by far is to stop smoking. This is not a substitute for stopping smoking."
Estimated that <5% of eligible patients are screened

Barriers:

- Uncertainty about outcomes
- Concern about overdiagnosis
- Education
- Lack of available screening centers
- Logistics (e.g. SDM visit requirement)
NELSON Lung Screening Trial

- Randomized European trial
- 10 year results presented at IASLC 2018 meeting
- $N = 15,792$

<table>
<thead>
<tr>
<th>Modality</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest CT</td>
<td>7,900</td>
</tr>
<tr>
<td>No screen</td>
<td>7,892</td>
</tr>
</tbody>
</table>
NELSON Lung Screening Trial

- LDCT
- Indeterminate: 2 month f/u for volume doubling time
NELSON Lung Screening Trial

Results:

- Follow-up at 10 years for 93.7% of participants
- 86% compliance rate
- False positive rate = 59.4%

Overall lung cancer detection rate = 3.2%

<table>
<thead>
<tr>
<th>Baseline</th>
<th>1 year</th>
<th>3 years</th>
<th>5 ½ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9%</td>
<td>.08%</td>
<td>1.1%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
NELSON Lung Screening Trial

Results – Lung Cancer Deaths:

214 study arm vs. 157 control arm

LC mortality rate-ratio:

• Men = 0.74 (p = 0.0003)
• Women = 0.61 (p = 0.0054)
Stage shift no different after 1 year, but less favorable after 2 ½ years.
Cost-Effectiveness

Results:

• Reduced number to be screened by 81%
• High risk screening cost $20,724 (Canadian) / QALY
• Higher cost of non-curative care (drug costs, immunotherapy) improve cost-effectiveness
Where do we go from here?

<table>
<thead>
<tr>
<th>Academic</th>
<th>Community</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Further define high risk pool</td>
<td>• Build robust programs</td>
</tr>
<tr>
<td>• Standardize management protocols to reduce variability and cost</td>
<td>• Engage primary physicians</td>
</tr>
<tr>
<td>• Biomarkers</td>
<td>• Outreach, especially to vulnerable and underserved populations</td>
</tr>
<tr>
<td></td>
<td>• Enhance smoking cessation</td>
</tr>
<tr>
<td></td>
<td>• Track results</td>
</tr>
</tbody>
</table>
Why It’s More Than Just a Scan:

• Engagement
• Process
• Management
• Results
<table>
<thead>
<tr>
<th>Category Descriptor</th>
<th>Category Descriptor</th>
<th>Primary Category</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete</td>
<td>-</td>
<td>0</td>
<td>Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed</td>
</tr>
<tr>
<td>Negative</td>
<td>No nodules and definitely benign nodules</td>
<td>1</td>
<td>Continue annual screening with LDCT in 12 months</td>
</tr>
<tr>
<td>Benign Appearance or Behavior</td>
<td>Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth</td>
<td>2</td>
<td>Continue annual screening with LDCT in 12 months</td>
</tr>
<tr>
<td>Probably benign</td>
<td>Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer</td>
<td>3</td>
<td>6 month LDCT</td>
</tr>
<tr>
<td>Suspicious</td>
<td>Findings for which additional diagnostic testing and/or tissue sampling is recommended</td>
<td>4A</td>
<td>3 month LDCT; PET/CT may be used when there is a ≥ 8 mm solid component</td>
</tr>
<tr>
<td>Significant - other</td>
<td>-</td>
<td>S</td>
<td>-</td>
</tr>
<tr>
<td>Prior Lung Cancer</td>
<td>-</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>
“...the opportunity to realize the greatest single reduction of cancer mortality in the history of the war on cancer.”

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