Lung cancer screening
Past, present and the future

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Pulmonary Critical Care and Sleep Medicine
Disclosures

• Research Grant for PAH from UT
• Dean’s grant
• Advisory board for UT, Actelion and Gilead
Objectives

1. Explain the rationale for lung cancer screening.
2. Identify the population who should be screened and why.
3. Discuss the potential pitfalls of screening.
<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>% of Men</th>
<th>Number of Deaths Men</th>
<th>% of Women</th>
<th>Number of Deaths Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>28%</td>
<td>306,920</td>
<td>26%</td>
<td>273,430</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td></td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
<td></td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>6%</td>
<td></td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
<td></td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td></td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
<td></td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td></td>
<td>25%</td>
<td></td>
</tr>
</tbody>
</table>
Estimated New Cancer Cases* in the US in 2013

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>854,790</td>
<td>805,500</td>
</tr>
</tbody>
</table>

- **Men**
  - Prostate: 28%
  - Lung & bronchus: 14%
  - Colon & rectum: 9%
  - Urinary bladder: 6%
  - Melanoma of skin: 5%
  - Kidney & renal pelvis: 5%
  - Non-Hodgkin lymphoma: 4%
  - Oral cavity: 3%
  - Leukemia: 3%
  - Pancreas: 3%
  - All Other Sites: 20%

- **Women**
  - Breast: 29%
  - Lung & bronchus: 14%
  - Colon & rectum: 9%
  - Uterine corpus: 6%
  - Thyroid: 6%
  - Non-Hodgkin lymphoma: 4%
  - Melanoma of skin: 4%
  - Kidney & renal pelvis: 3%
  - Pancreas: 3%
  - Ovary: 3%
  - All Other Sites: 19%

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.*
Cancer Death Rates* Among Men, US, 1930-2009

*Age-adjusted to the 2000 US standard population.
Cancer Death Rates* Among Women, US, 1930-2009

*Age-adjusted to the 2000 US standard population.

### The Lifetime Probability of Developing Cancer for Men, 2007-2009*

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 2</td>
</tr>
<tr>
<td>Prostate</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>1 in 13</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1 in 19</td>
</tr>
<tr>
<td>Urinary bladder†</td>
<td>1 in 26</td>
</tr>
<tr>
<td>Melanoma§</td>
<td>1 in 35</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 43</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 in 49</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 63</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>1 in 66</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 in 92</td>
</tr>
</tbody>
</table>

* For those free of cancer at beginning of age interval.
† All sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
§ Statistic for white men.
# The Lifetime Probability of Developing Cancer for Women, 2007-2009*

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>1 in 21</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>1 in 38</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 52</td>
</tr>
<tr>
<td>Urinary bladder‡</td>
<td>1 in 87</td>
</tr>
<tr>
<td>Melanoma§</td>
<td>1 in 54</td>
</tr>
<tr>
<td>Ovary</td>
<td>1 in 72</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 in 69</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td>1 in 147</td>
</tr>
</tbody>
</table>

* For those free of cancer at beginning of age interval.
† All sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
§ Statistic for white women.

Trends in Tobacco Use and Lung Cancer Death Rates* in the US

*Age-adjusted to 2000 US standard population.

Definition

Screening can be defined as the systematic testing of individuals who are asymptomatic with respect to some target disease. The purpose of screening is to prevent, interrupt, or delay the development of advanced disease in the subset with a pre-clinical form of the target disease through early detection and treatment.

Hillman et al. JACR 2004;1(11):861-864
Screening vs Diagnosis

Non-patients
Asymptomatic
Test non-diagnostic
Low prevalence

Patients
Symptomatic
Test diagnostic
High prevalence
Timeline of Disease

Onset of Disease  |  Detectable by Test  |  Signs or Symptoms  |  Death from Disease or Other causes
Critical Point

The point in the natural history of disease before which therapy is more effective.
Death from Disease or Other causes

Signs or Symptoms

Detectable by Test

Onset of Disease

Screening Effective

DPCP

Critical Point

Death from Disease or Other causes
Screening Ineffective

Onset of Disease → Detectable by Test → Signs or Symptoms → Death from Disease or Other causes

Critical Point

DPCP
Screening Unnecessary

Onset of Disease
Detectable by Test
Signs or Symptoms
Death from Disease or Other causes

DPCP

Critical Point
Mountain CF. Chest 1986;89(suppl):225-233.
Mayo Clinic Project

<table>
<thead>
<tr>
<th></th>
<th>Screened (CXR + SC)</th>
<th>Control (Usual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>4,618</td>
<td>4,593</td>
</tr>
<tr>
<td>Incident cases</td>
<td>206</td>
<td>160</td>
</tr>
<tr>
<td>% resectable</td>
<td>46</td>
<td>31</td>
</tr>
<tr>
<td>% five-year survival</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td>Lung cancer deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relative risk(^2) (95%CI)</td>
<td></td>
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\(^1\) 91 prevalent cases and 1631 others excluded before randomization
\(^2\) based on cumulative lung cancer mortality at eleven year
# Mayo Clinic Project

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<td>115</td>
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$^1$ 91 prevalent cases and 1631 others excluded before randomization

$^2$ based on cumulative lung cancer mortality at eleven year
## Screen Detected Cases ELCAP


<table>
<thead>
<tr>
<th>Stage</th>
<th>&lt; 10 mm</th>
<th>11-20 mm</th>
<th>20+ mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>13</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>0</td>
<td>2</td>
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## Screen Detected Cases ELCAP


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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
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Estimated five-year survival 80% vs 13% in SEER
Biases of Early Detection

- Lead time bias
- Length bias
- Overdiagnosis bias
Lead Time Bias

WITHOUT TEST

WITH TEST

Signs or symptoms

Death from Disease

Positive test

SURVIVAL

LEAD TIME
Length Bias

Rapidly progressive

Slowly progressive

TEST

TIME
Length Bias

TEST

Rapidly progressive

Slowly progressive

TIME
Length Bias

Rapidly progressive

Slowly progressive

TEST

TIME
Tumor Histology ELCAP

25 Prevalent Cases

• Adenocarcinoma (18)
• Bronchioloalveolar carcinoma (3)
• Mixed squamous adenocarcinoma (3)
• Squamous cell carcinoma (1)
• Atypical carcinoid (1)

The diagnosis of a condition that would not have become clinically significant had it not been detected.
Growth Rate of Lung Cancer


- Median DT 181 days
- 22% DT >= 465 days
- 94% >= 1 yr grow 0.5-3.0 cm
## Lung Ca Screening in Japan

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Lung cancers</th>
<th>Rate (1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>6295</td>
<td>29</td>
</tr>
<tr>
<td>NonSmokers</td>
<td>7491</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>13786</td>
<td>60</td>
</tr>
</tbody>
</table>

Effects of Overdiagnosis

• Falsely increases sensitivity of test
• Falsely increases PPV of test
• Falsely increases incidence
• Falsely improves stage distribution
• Falsely improves case survival
• Does not decrease pop mortality
Benefits from Screening

- ↓ Anxiety about dz (TN)
- ↓ Morb & mort from dz
- ↓ Morb & mort from rx
  - lobectomy vs pneumonectomy
Harms from Screening

- Direct effect of test (radiation)
- Anxiety about dz (FP)
- Morb & mort from workup
- Overdiagnosis
Patient Population

• High risk for preclinical disease
• No clinical signs or symp of disease
• Willing and able to undergo screening or not
• Willing and able to undergo workup and rx
• Willing and able to undergo follow-up
Endpoints

• Deaths from target disease
• Deaths from any cause
• Stage of target disease at dx
• Adverse events
• Quality of life
• Resource utilization
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive, effective</td>
<td>Major benefit. Death postponed, morbidity decreased</td>
</tr>
<tr>
<td>True positive, ineffective</td>
<td>Knowledge vs longer dx &amp; rx</td>
</tr>
<tr>
<td>True negative</td>
<td>Reassurance</td>
</tr>
<tr>
<td>False positive</td>
<td>Harm. Work up</td>
</tr>
<tr>
<td>False negative</td>
<td>Possibly delayed dx</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td>Moderate to major harm. False labeling and rx</td>
</tr>
</tbody>
</table>
Lung Cancer Screening

- Screening with low-dose CT screening vs. CXR reduces overall and lung cancer mortality
  (National Lung Screening Trial Research Team. NEJM 2011;365:395)
Lung Cancer Screening

• NLST randomly assigned 53,454 adults 55-74, 30+ pack-years, smoked within past 15 years
  – Three annual screenings with either CT or CXR
  – Median follow up 6.5 years
Lung Cancer Screening

• NLST testing results
  – Compliance > 90%
  – ≥ 1 positive test in 39% CT, 16% CXR
    • False positive results in 96% CT, 95% CXR
  – Higher cancer incidence with CT (1060 vs. 941)
    • Rate ratio 1.13 (95% CI 1.03-1.23)
**Lung Cancer Screening**

- **NLST outcomes**
  - Decreased lung cancer mortality (356 vs. 443)
    - Relative reduction 20% (95% CI 6.8-26.7)
    - Absolute reduction 62/100,000 py
      - Number needed to screen: 320
  - Decreased overall mortality (1877 vs. 2000)
    - Relative reduction 6.7% (95% CI 1.2-13.6)
Lung Cancer Screening

- Screening with CXR vs. usual care was ineffective
  (Oken MM. JAMA 2011;306:1865)
Lung Cancer Screening

• PLCO randomly assigned 154,901 adults aged 55 through 74 to annual CXR for 4 years vs. usual care
• Followed for 13 years
• Cumulative lung cancer mortality
  – 14.0/10,000 py screening group vs. 14.2/10,000 py control group
  – Rate ratio: 0.99 (95% CI 0.87-1.22)
Lung Cancer Screening

- PCLO randomly assigned 154,901 adults aged 55 through 74 to annual CXR for 4 years vs. usual care
- Followed for 13 years
- Cumulative lung cancer mortality
  - 14.0/10,000 py screening group vs. 14.2/10,000 py control group
  - Rate ratio: 0.99 (95% CI 0.87-1.22)
  - 45% never smokers
Lung Cancer Screening

• Screening with CXR was ineffective in 30,341 subjects meeting NSLT criteria
  – 30+ pack year, smoked within past 15 years
  – Cumulative lung cancer mortality was 36.1/10,000 py screening group vs. 38.3/10,000 py controls
    • Rate ratio: 0.94 (0.81-1.10)

• Reasonable to conclude that CT screening is more effective than usual care
Lung Cancer Screening

• Translating research into practice
  – Efficacy (NSLT) vs. Effectiveness (real-world)
Lung Cancer Screening

• Patient selection
  – 90% NHW, 1.8% Hispanic
  – Volunteers
    • Younger, more educated, more ex-smokers than Census survey of eligible subjects
Lung Cancer Screening

• Screening
  – Low-dose CT scanners available
  – Experienced radiologists
    • Measures of agreement not presented
    • Clinical judgment important
Lung Cancer Screening

• Complications from invasive diagnostic evaluation procedures infrequent
  • At least one major complication: 10.8%
  • Death following procedure: 1.4%
• No treatment complication data presented
• Requires appropriate multidisciplinary teams
Lung Cancer Screening

• Implementation
  – 7 million eligible Americans
    • Smoking history, comorbidity, lung function
    • Duration and frequency of screening
  – Harms of CT scanning
    • Radiation, adventitious findings
Lung Cancer Screening

- USPSTF recommendations
  - Smoking cessation counseling: “A” (2009)
    - 85% of cancers among smokers attributed to smoking
    - Based on the available evidence, the Task Force recommends screening people who are at high risk for lung cancer with annual low-dose CT scans, which can prevent a substantial number of lung cancer-related deaths. This is a grade B draft recommendation (2013)
Lung Cancer Screening

• Next steps
  – Awaiting cost-effectiveness analyses
    • Effect on quality of life
    • Comparison with smoking cessation
  – Awaiting guidelines
  – Health care systems evaluating feasibility
Implications for Practice

- American Lung Association Lung Cancer Screening Committee guidance statement
  - Support low-dose CT screening for those people who meet the criteria for the NSLT....
  - Smoking cessation should be continuously emphasized....

Should You Get a Lung Cancer Screening?

Are you a **CURRENT** or **former smoker** between **55 & 74 years old**?

Do you have a **smoking history** of at least **30 PACK-YEARS**?

(for example, one pack a day for 30 years or two packs a day for 15 years, etc.)

According to American Cancer Society (ACS) guidelines, if you answer “yes” to both of these questions, it’s important to talk to your doctor about undergoing a lung cancer screening. UF Health physicians in Jacksonville offer lung cancer screenings using a safe, low-dose CT scan as recommended by the ACS.

At UF Health Jacksonville, specialists in radiology, pulmonology and surgery who work as a team to help ensure the best possible outcomes for our patients. For more information about our services, visit us online at UFHealthJax.org/cancer/lung. To make an appointment for a consultation and screening, call 904-266-8677.

Currently, lung cancer screenings are not covered by all health insurance plans. Contact your carrier for more information.
References