Screening for Lung Cancer
- State of the Art

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Objectives

- Review current evidence for lung cancer screening
- Tools for Lung cancer screening
- Implementing a screening program
- Challenges and controversies of lung cancer screening
The Problem - Worldwide

- 1.6 million cases worldwide (13% of all cancer)
- 1.3 million deaths (20%)
- Demographic variations
  - More in Eastern Europe and China
- India
  - 950,000 cases
  - 630,000 deaths
  - Underdiagnosed, initially as Tuberculosis
  - Squamous histology
Risk Factors

• Occupational exposure (PAR 9-15%)
  – **Tobacco**
  – Asbestos (RR of ~ 5)
  – Tar, Metals (arsenic, chromium, nickel)
• Radon (PAR 10%)
• Pre-existing lung disease
  – COPD
  – Fibrotic lung disease
• Dietary factors
• Genetic predisposition
Trends in Cigarette Smoking

Prevalence

Cigarettes per day

FIGURE. Percentage of daily* and some-day† smokers among persons aged ≥18 years, by number of cigarettes smoked per day and year — National Health Interview Survey, United States, 1993–2004

*Current smokers who reported smoking every day.
†Current smokers who reported smoking some days.
Tobacco Use in the US, 1900-2005

Per capita cigarette consumption

*Male lung cancer death rate

*Female lung cancer death rate

*Age-adjusted to 2000 US standard population.

Screening Principles

• High prevalence of detectable disease in asymptomatic patients

• Detect disease that responds better to early vs. late treatment

• Provide benefits in treating the small number of patients diagnosed with disease, outweighing the harm associated with screening a large number of healthy individuals
Lung Cancer – Projected incidence in the US

Lung Ca >225,000

NSCLC 180,000

STAGE I-III 100,000

STAGE II 50,000

STAGE III 50,000

STAGE IV 80,000

EXT 30,000

SCLC 45,000

LTD 15,000
Screening Goals—Amplify smoking cessation benefit

Prevent Deaths
Early Detection
Minimize Harms

- Amplify smoking cessation benefit
- Prevent Deaths
- Early Detection
- Minimize Harms
Earlier Efforts at Screening – No benefit

• Initial populations studies
  – Doll and Hill: British doctors study
• Mayo Lung Project
  – Age > 45 with 1 pack/day
• Czech Study
  – Age 40 - 64
• Johns Hopkins/ Sloan Kettering Trial
Low Dose CT Scan CAN detect lung cancer at Early Stage
National Lung Screening Trial

NCI/ACRIN 2002-2004

54,000

Age 55-74 30pyr

CT

CXR

Year 0 1 2 3 4 5 6 7

National cancer Institute (NCI)
American College of Radiology Imaging Network (ACRIN)
20% reduction in lung cancer mortality
7% reduction in overall mortality

Number Needed to Screen – 320
“Liquid Biopsy”

Circulating Tumor Cell chip

- Detection of cancer cells in peripheral blood

![Diagram showing a chip with anti-cytokeratin stain and genomic DNA extraction processes.]

100% sensitivity!
Exhaled Breath Condensate
Volatile Organic Compounds (VOC)

- Tumor cells modify protein expression, that causes peroxidation of cell membrane and releases different VOC signature.

Breath samples were taken from healthy individuals.

Unaffected by Stage of disease or tobacco

From Phillips, Clinica Chimica Acta, 2008
AutoFlorescence Bronchoscopy

- Based on difference in florescence between normal and neoplastic epithelium
- Highly sensitive and more specific than white light bronchoscopy to detect dysplasia
- Applies more to central lesions
Airway Epithelial Cell Biomarkers

- Sample is obtained from the bronchial epithelium
- Based on theory of “field carcinogenesis”
- Sensitivity and specificity > 80%
- Nasal sample
Implementing a Feasible Screening Program

Feasibility

Lower cost

High risk population

LDCT
Integrated Program
Duration

High cancer detection

Adherence
Education
Key Elements of a Screening Program

- Behaviour
- Medical
- Pulmonary
- Radiology
- Surgery
- Oncology
- Patient counselling
- Medical community
- Physicians
- Navigators
- Team
- Education
- Nodule Clinic
- Smoking Cessation
- Smoking
- Nodule
- Clinic

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- Smoking
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- Clinic

- Behaviour
- Medical
Subject Selection
## Societal Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Tobacco</th>
<th>Other Risk factors</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am Col Chest Physicians Am So Clin Oncology (ACCP/ASCO)</td>
<td>55-74</td>
<td>&gt; 30 pyr</td>
<td></td>
<td>Not defined</td>
</tr>
<tr>
<td></td>
<td>50-74</td>
<td>&gt; 20 pyr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-79</td>
<td>&gt; 30 pyr</td>
<td>H/o cancer, lung disease, family</td>
<td>Lifelong</td>
</tr>
<tr>
<td></td>
<td>50-79</td>
<td>&gt; 20 pyr</td>
<td>Occupational, radon</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Am Asso for Thoracic Surgery (AATS)</td>
<td>55-79</td>
<td>&gt; 30 pyr</td>
<td>Cumulative risk &gt;5%</td>
<td>Lifelong</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>55-74</td>
<td>&gt; 30 pyr</td>
<td></td>
<td>Till 74</td>
</tr>
</tbody>
</table>

**USPTF:** 55-80 yrs, 30 pyr.  Stop once quit >15 yrs
Risk Prediction Model Based Selection

• Several lung cancer risk prediction models
  • Spitz, Liverpool Lung Project, Etzel etc.
• Modified PLCO: Increased risk predictors:
  • ↑ Age
  • ↑ Tobacco exposure
  • ↑ COPD
  • ↑ Family history of lung cancer
  • ↑ Personal history of lung cancer
  • ↓ BMI
  • ↓ Education
Modified PLCO Model

<table>
<thead>
<tr>
<th></th>
<th>NLST criteria</th>
<th>PLCO\textsubscript{2012}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>71.1%</td>
<td>83.0%</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Specificity</td>
<td>62.7%</td>
<td>62.9%</td>
<td>p=0.536</td>
</tr>
<tr>
<td>PPV</td>
<td>3.4%</td>
<td>4.0%</td>
<td>p=0.011</td>
</tr>
</tbody>
</table>

- PLCO model missed 115 cancers relative to 196 cancers missed by NLST criteria – 41% fewer.
- [C:\Documents and Settings\rxk032\Desktop\LCAriskCalculatorSMKonly-Tammemagi-2SEP13-Locked.xlsx](C:\Documents and Settings\rxk032\Desktop\LCAriskCalculatorSMKonly-Tammemagi-2SEP13-Locked.xlsx)
Implementing the Model
The Pulmonologist Gatekeeper Model

- Patient
- PCP
- Scripted Screening intake
- Pulmonologist Visit
- Biopsy/Surgery
- Imaging
- LDCT
- Rescheduled
- Screening Rescheduled
- Patient Navigator
Advantages of the Pulmonary Model

• Subjects meet a pulmonary physician **BEFORE** screen study
  – Ensures compliance to criteria (NLST)
  – **Reassurance** to individuals not meeting criteria
  – Promotes patient education
  – Chance to discuss implications of findings if detected same day
  – Reduces patient anxiety
Challenges and Controversies of Screening
Limitations of CT screening

- High False positives
- Limited detection of endobronchial or central tumors
- Small cell cancers are not detected early
- Harmful effects of Radiation
  - Projected 1 new cancer for every 2000 spiral CT scans performed
- COST: Not covered by most insurance carriers
Risks of Screening – Procedural

- 16 deaths occurred in LDCT group (vs 10 in CXR group) within 60 days after an invasive diagnostic test was performed.

- Expect more procedures
  - Higher complication rates

<table>
<thead>
<tr>
<th></th>
<th>LDCT</th>
<th>CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive screens</td>
<td>24%</td>
<td>6.9</td>
</tr>
<tr>
<td>Major complications</td>
<td>0.06%</td>
<td>0.02%</td>
</tr>
<tr>
<td>False positives</td>
<td>96%</td>
<td>94%</td>
</tr>
</tbody>
</table>
Controversies of Screening

• Cost effectiveness yet to be determined
  – 3.5 million screening eligible persons
  – >$2 billion / year (assuming 75% screening rate – 95% in NLST)

• Duration of Screening

• Psychological concerns

• Overdiagnosis
  – Cancers that otherwise would not have been detected during an individuals lifetime
  – NLST: Overdiagnosis rate of 13% (1-1060/941)
    • Will be higher in the community

Goulart et al JNCCN 2012;10:267-275
**Cost-effectiveness**

- Higher risk population
- High Quit rates
- High surgical effectiveness
- Less frequent scans

<table>
<thead>
<tr>
<th>Increases</th>
<th>Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Higher false positives</td>
<td>- Higher complications</td>
</tr>
<tr>
<td>- More futile procedures</td>
<td>- ? Radiation Risks</td>
</tr>
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<td></td>
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</tr>
</tbody>
</table>
**Practice Variation - Number Needed to Screen will Vary**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Risk Factors</th>
<th>Deaths From Lung Cancer (Without Screening) per 1000 Persons, n</th>
<th>Deaths From Lung Cancer (With Screening) per 1000 Persons, n</th>
<th>Lung Cancer Deaths Averted per 1000 Persons, n</th>
<th>Persons Needed to Be Screened Annually for 3 y to Prevent 1 Death From Lung Cancer Over 6 y, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Typical” participant in the NLST</td>
<td>62-year-old male current 1.5-PPD smoker for 35 y</td>
<td>19.5</td>
<td>15.6</td>
<td>3.9</td>
<td>256</td>
</tr>
<tr>
<td>Minimum eligible participant in the NLST</td>
<td>55-year-old female former 1-PPD smoker for 30 y who just quit</td>
<td>4.0</td>
<td>3.2</td>
<td>0.8</td>
<td>1236</td>
</tr>
<tr>
<td>High-risk participant eligible for the NLST</td>
<td>70-year-old current 2-PPD smoker for 55 y</td>
<td>60.9</td>
<td>48.7</td>
<td>12.2</td>
<td>82</td>
</tr>
<tr>
<td>Minimum eligible participant by NCCN guidelines</td>
<td>50-year-old male former 1-PPD smoker for 20 y who quit 10 y ago with an occupational asbestos exposure history</td>
<td>1.6</td>
<td>1.3</td>
<td>0.3</td>
<td>3180</td>
</tr>
<tr>
<td>Low-risk eligible participant for Sequola Hospital lung screening program</td>
<td>40-year-old female former 1-PPD smoker for 10 y who quit 15 y ago</td>
<td>0.10</td>
<td>0.08</td>
<td>0.02</td>
<td>35 186</td>
</tr>
</tbody>
</table>

*Table. Projected Likelihood Over 6 Years of Lung Cancer Death With or Without Screening per 1000 Persons Screened*

*Peter Bach. Ann Intern Med. 16 October 2012;157(8):571-573*
Recent Data from a High Volume center

- FREE scans
- 3 lung cancers diagnosed
- 25% had nodules
- No data on complications

Table 2. Patient demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Overall</th>
<th>NLST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>386 (77%)</td>
<td>114 (23%)</td>
<td>500</td>
<td>~26,000</td>
</tr>
<tr>
<td>Average age (y)</td>
<td>63</td>
<td>60.5</td>
<td>62.5</td>
<td>61.4</td>
</tr>
<tr>
<td>Smoking history</td>
<td>50.1</td>
<td>39.7</td>
<td>47.7</td>
<td>56</td>
</tr>
<tr>
<td>Pack-years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>53.4%</td>
<td>42.1%</td>
<td>51.2%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Note: NLST = National Lung Screening Trial.
The “Complete” Screen

• Radiographic, Bronchoscopic and Chemical Screen
  – Low dose CT
  – Autoflorescence Bronchoscopy
  – Possible Autoantibody testing
  – Possible Airway epithelium sampling
  – Use of Exhaled Volatile Compounds
Summary

Prevention, rather than screening, is the most effective strategy for reducing the burden of lung cancer.