Lung Cancer Screening: Benefits and limitations to its Implementation

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Pulmonary-Critical Care Medicine
University of Iowa
### Lung cancer - Epidemiology

#### Cancer statistics in US - 2011

#### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>240,890</td>
<td>230,460</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>115,060</td>
<td>106,070</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>71,850</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Uninary bladder</td>
<td>52,020</td>
<td>Uterine corpus</td>
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<tr>
<td>Melanoma of the skin</td>
<td>40,010</td>
<td>Thyroid</td>
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<tr>
<td>Kidney &amp; renal pelvis</td>
<td>37,120</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>36,060</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>27,710</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>Leukemia</td>
<td>25,320</td>
<td>Ovary</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,050</td>
<td>Pancreas</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>822,300</strong></td>
<td><strong>774,370</strong></td>
</tr>
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</table>

#### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>85,600</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>Prostate</td>
<td>33,720</td>
<td>Breast</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>25,250</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>Pancreas</td>
<td>19,360</td>
<td>Pancreas</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>13,260</td>
<td>Ovary</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,740</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Esophagus</td>
<td>11,910</td>
<td>Leukemia</td>
</tr>
<tr>
<td>Uninary bladder</td>
<td>10,670</td>
<td>Uterine Corpus</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>9,750</td>
<td>Live &amp; intrahepatic bile duct</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,270</td>
<td>Brain &amp; other nervous system</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>300,430</strong></td>
<td><strong>271,520</strong></td>
</tr>
</tbody>
</table>
Lung cancer - Epidemiology

Number of deaths from lung cancer in US - 2011
Lung cancer - Epidemiology

Lung cancer stage distribution and 5 year survival adjusted to the stage at time of diagnosis in US 2001-2007

- Breast Cancer: 90%
- Colon Cancer: 65%
- Prostate cancer: 100%

Stage Distribution (%) and 5-Year Relative Survival (%)
National Lung Screening Trial (NLST)

53,454 patients

- Age: 55 – 74 years old
- Smoking history: 30 pack year
- Quit within 15 years
- 33 centers in US
- 90% power for 20% difference

Low dose CT (1.5 mSv)
26,722 patients

- Annually x 3
- Follow up for 6 years
- Adherence was > 90%
- 39.1% positive screenings (96.4% false positive)
- Lung ca Incidence: 645 x 100,000 person years
- Early stage lung cancer detected: 50%
- Lung ca deaths: 247 x 100,000 person years (1.33%)

CXR
26,732 patients

- 16% positive screenings (94.5% false positive)
- Lung ca incidence: 572 x 100,000 person years
- Early stage lung cancer detected: 31%
- Lung ca deaths: 309 x 100,000 person years (1.66%)

Reduction in lung cancer mortality:
- Relative 20%
- Absolute 0.3 %
- 3 fewer deaths per 1000 high risk patients
- # needed to screen to prevent 1 death = 320

Lung Cancer Screening: Key points

- **Sensitive test to detect early stage lung cancer**

- **Adequate selection of screening population**

- **Effective treatment of early stage lung cancer**

- **Minimization of risks:**
  - Adequate management of lung nodules
  - Overdiagnosis
  - Radiation
National Lung Screening Trial (NLST)

Cumulative numbers of Lung Cancers and Deaths from Lung Cancer

- Low-dose CT: 120 cases
- Chest radiography

Death from Lung Cancer

- Chest radiography: 87 deaths
- Low-dose CT

Lung Cancer Screening – Population goal

- **Generalizability**
  - NLST population was younger, healthier, > former smokers, surgical candidate: 92.5%
  - Minority population under-represented in NSLT: Blacks (4.5%); Hispanics (1.8%)  > active smoking  > % comorbidities  < surgical resection in early stage LC  

  Minorities → worse outcomes

- **High risk population**
  - COPD → DLCST trial  
  - Current versus former smokers?  
    Am J Respir Crit Care Med. 2016; 193 (5): 534-541
  - Asbestos
  - Previous tobacco related malignancies
Early Stage Lung Cancer Therapy

- 70-80% survival at 5 years
- 3-5% peri-operative mortality

Sublobar resection
Early Stage Lung Cancer Therapy

Stereotactic Body radiation (SBRT)

Radiofrequency Ablation (RFA)

“Non-operable”

Superficial spreading tumor confined to airway wall
Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials


- Patient dataset: - STARS (enrolled 36 pts of 1030)
  - ROSEL (Netherlands, enrolled 22 pts of 960)
## Lung nodule management

### NSLT
- 55% had (+) screening (CXR:16% + LDCT:39%)
- 10% of pts underwent invasive procedure
- Invasive procedures in benign nodules:
  - Non surgical: 10%
  - Surgical: 24%
- Adverse events:
  - Non surgical: 1%
  - Surgical mortality: 1%

### Real life
- **Tanner et al. Chest 2015**
  - 377 pts with SPN (> 8mm; < 20 mm) at 18 sites
  - Invasive procedures in benign nodules
    - Non surgical: 30%
    - Surgical: 35%
  - 45% of low risk nodules had invasive test
- **Wiener et al. JAMA 2014**
  - 300 pts with SPN (≤ 4mm; > 8mm) at 15 VA centers
  - Invasive procedures:
    - Non surgical: 41.3%
    - Surgical resection
  - 45% inconsistent with guidelines (+18% ; - 27%)
Lung Cancer Screening - Limitations

**Overdiagnosis**

- Overall overdiagnosis in the NSLT = 18.5% - (up to 25% in other studies)
- # overdiagnosis cases in 320 needed to screen to prevent 1 death = 1.38
- May change based on specific lung cancer risk & time of follow up
- VDT ≥ 400 days may help identifying slow growing/ indolent tumors

<table>
<thead>
<tr>
<th>Lung Cancer Type</th>
<th>Overdiagnosis, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_A$</td>
</tr>
<tr>
<td>All lung cancers</td>
<td>11.0 (3.2 to 18.2)</td>
</tr>
<tr>
<td>All NSCLC, including BAC and NOS</td>
<td>14.4 (6.1 to 21.8)</td>
</tr>
<tr>
<td>All NSCLC, excluding BAC and including NOS</td>
<td>7.1 (-2.3 to 15.6)</td>
</tr>
<tr>
<td>BAC only</td>
<td>67.6 (53.5 to 78.5)</td>
</tr>
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LC Screening - Limitations

**Radiation risk**

- Radiation dose from LDCT = 1.5 mSV (Standard CT = 8 mSv)
- NSLT average radiation exposure over 3 years = 8 mSV
- #1 radiation associated cancer per 2500 people screened with LDCT
- Radiation exposure is cumulative over lifetime: - Worse for younger population
- 50 mSV / year = 1 additional fatal cancer / year / 500 people exposed
- 55 year old with positive screen every 2 years, 3 full dose CT = 280 mSV at 20 years
  420 mSV at 30 years

McCunney et a. Chest 2014;145:618-624
Bach et. al. JAMA 2012;307:2418-2429
LC Screening – Systematic reviews

- Two systematic reviews: - USPSTF (Humphrey et. al.)
  - ACS + ACCP + ASCO + NCCN (Bach et. al)

- Three RCT: - NLST
  - DANTE * men only, LDCT (n=1276) vs. CXR & sputum
  - DLCST * LDCT (n= 2052 ) vs. usual care
  - Nelson* (Netherlands + Belgium - ongoing)

Bach et. al. JAMA 2012;307:2418-2429
LC Screening – CISNET modeling

- 5 independent models (NLST and PLCO)
- 576 possible clinical scenarios --> 8 scenarios were thought to be efficient
- Most efficient: 55 – 80 years / 30 pack year history / quit within 15 years

LC Screening - Benefits

- “NSLT is the largest and the only RCT that showed a life saving benefit to finding and treating early lung cancer diagnosed by CT screening in a high risk population”

- Cost – effective: $ 81,000 per QALY gained
  - Women ($46,000/QALY) vs. Men ($147,000/QALY)
  - Current smokers ($43,000/QALY) vs. former smokers ($615,000/QALY)
  - Highest two quintiles of risk ($32,000/QALY) vs. Three lowest quintiles ($169,000/QALY)
    - ($52,000/QALY)
    - ($123,000/QALY)
    - ($269,000/QALY)

- Research opportunities
<table>
<thead>
<tr>
<th>Professional Society (Reference)</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>USPSTF (Moyer 2014&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>Grade B: Annual low-dose chest CT scan in high-risk individuals (ages 55-80 y, &lt;br&gt; &gt;30 pack-year current or former smokers who have quit within the past 15 y); may discontinue screening if limited life expectancy or &gt;15 y since quitting smoking&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>ACCP/ASCO (Detterbeck 2013&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>Grade 2B: Annual low-dose chest CT scan in high-risk individuals (ages 55-74 y, &lt;br&gt; &gt;30 pack-year current or former smokers who have quit within the past 15 y), but only in settings that can deliver the comprehensive care provided to NLST participants</td>
</tr>
<tr>
<td>AATS (Jaklitsch 2012&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>Annual low-dose chest CT scan in high-risk individuals (ages 55-79 y with a &lt;br&gt; &gt;30 pack-year smoking history); individuals ages 50-79 y with a 20 pack-year history &lt;br&gt; and added risk &gt;5% of developing LC within 5 y (grade B); &gt;5-year LC survivors (grade C)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>NCCN (National Comprehensive Cancer Network 2014&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>Grade B: Annual low-dose chest CT scan in high-risk individuals (ages 55-79 y and &lt;br&gt; &gt;30 pack-year current or former smokers who have quit within the past 15 y) or aged &lt;br&gt; &gt;50 y with a &gt;20 pack-year history and 1 additional risk factor&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>ACS (Wender 2013&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>Grade B: Annual low-dose chest CT scan in high-risk individuals (ages 55-74 y, &lt;br&gt; &gt;30 pack-year current or former smokers who have quit within the past 15 y) and who are in relative good health</td>
</tr>
<tr>
<td>ALA (American Lung Association, 2014&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>Annual low-dose chest CT scan in high-risk individuals (ages 55-74 y, &lt;br&gt; &gt;30 pack-year current or former smokers who have quit within the past 15 y)</td>
</tr>
</tbody>
</table>

Kanodra et al. *Cancer*. 2015 May 1;121(9):1347-56.
The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to add a lung cancer screening counseling and shared decision making visit, and for appropriate beneficiaries, annual screening for lung cancer with low dose computed tomography (LDCT), as an additional preventive service benefit under the Medicare program only if all of the following criteria are met:

Beneficiary eligibility criteria:

- Age 55 – 77 years
- Asymptomatic (no signs or symptoms of lung cancer);
- Tobacco smoking history of at least 30 pack-years
- Current smoker or one who has quit smoking within the last 15 years
LC Screening Implementation

- Better screening population selection
- Interval between screening
- Better lung nodule management

*Lancet Oncology*, March 18, 2016 (published online)
Lung nodule management - Future

1. Cancer probability
   - Clinical prediction models
   - Biomarkers
     - Exhaled breath analysis
     - Airway epithelial gene expression
     - Ab and micro RNAs
   - Radionomics

2. Surgical risk
   - Sublobar resection
   - SBRT
   - RFA
   - Pulmonary rehab

3. Patient’s preferences
   - Patient centered & shared decision making models research

Risk factors
- Rx features
- PET/CT

Comorbidities
- Lung function
- Conditioning

Cultural factors
- Patient beliefs
A 65-year-old woman presents for follow-up. She has history of COPD (FEV1: 1 liter, 30%; DLCO:35%). She has long-standing dyspnea on exertion associated with chronic cough. There is no family history of lung cancer. She reports smoking one pack of cigarettes per day since 15 years of age. Should you advise lung-cancer screening with low-dose computed tomography (CT)?

- Does she meet criteria for USPSTF recommendations?
  - Age: 55 - 80 ✓
  - Smoking history: ≥ 30 pack year history or quit within 15 years ✓

- Does she meet any exclusion criteria?
  - Operable? X
  - Life expectancy?
A 70-year-old man presents to your clinic inquiring about lung cancer screening. He has history of remote smoking history 30 pack year history but he quit more than 15 years ago. He has mild emphysema, and strong history of asbestos exposure (he was a mechanic and he worked with brakes for 20 years without personal protection equipment). There is no family history of lung cancer. Should you advise lung-cancer screening with low-dose computed tomography (CT)?

Does she meets criteria for USPSTF recommendations?
- Age: 55 - 80 ✓
- Smoking history: ≥ 30 pack year history or quit within 15 years X
Lung Cancer Screening - Limitations

False positives

- Positive screen in NSLT = non calcified nodules > 4 mm and ≤ 30 mm

- 40% in LDCT group and 16% in CXR group after 3 year → 1.8% underwent invasive test

- MDs in the community adhere less to guidelines = Unnecessary tests:
  - Higher cost
  - % complications

- Volumetric assessment may help reducing false positives: “Nelson trial” (>500 mm3 approximately 9.8 mm in greatest dimension; or volume-doubling time <400 days) → 2.6% (+) screens