What is the target population for lung cancer screening?

Antwerpen, oktober 2012

Rob van Klaveren

November 2010

Lung cancer trial results show mortality benefit with low-dose CT: Twenty percent fewer lung cancer deaths seen among those who were screened with low-dose spiral CT than with chest X-ray.

The National Cancer Institute (NCI) is today releasing initial results from a large-scale test of screening methods to reduce deaths from lung cancer by detecting cancers at relatively early stages.

http://www.cancer.gov/newscenter/pressrelease/NSLTresultRelease

Lung cancer case survival Kaplan Meier curve

Kaplan-Meier curves for lung cancer mortality

20.3% lung cancer mortality reduction
After 6 yrs of follow-up and 3 annual rounds of screening
Compared to CXR screening

Kaplan-Meier curves for all-cause mortality

6.9% all cause mortality reduction

ACCP and ASCO guidelines

• (former)-smokers age 55-74
• > 30 PY’s
• Quit < 15 yrs
• 3 annual screening rounds

• Remark 4: quality metrics should be developed such as those in use for mammography screening which could enhance the benefits and minimize the harms
Gaps in our knowledge

- What will be the effect of CT screening as compared to an anti-smoking policy
- Concern about generalizability of the NLST results (minorities)
- What is the optimal target population
- What is the optimal number of screening rounds and the length of the interval

The effect of CT screening as compared to anti-smoking policy

- Lung Cancer Policy model: Tobacco control versus screening
- Age 30-84 yrs, 1975-2000, annual CT
  - Complete elimination: -28% mortality LC
  - Complete elimination + annual CT screening: -39% mortality LC
  - Conclusion: focus on smoking cessation!

Generalizability of the trial results

- Compared with similar US population, NLST cohort has similar gender distribution and smoking exposure
  - However, NLST participants were
    - Younger
    - Better educated
    - Less likely to be current smokers
    - Less minorities

Comparing NLST with US census population

<table>
<thead>
<tr>
<th></th>
<th>NLST</th>
<th>US Census</th>
</tr>
</thead>
<tbody>
<tr>
<td>Married</td>
<td>66.6</td>
<td>60.9</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; HS</td>
<td>6.1</td>
<td>21.3</td>
</tr>
<tr>
<td>≥ College</td>
<td>31.5</td>
<td>14.4</td>
</tr>
<tr>
<td>Current smoker</td>
<td>48.2</td>
<td>57.1</td>
</tr>
<tr>
<td>Median pack yrs</td>
<td>48.0</td>
<td>47.0</td>
</tr>
</tbody>
</table>

Comparing NLST with eligible US census population

<table>
<thead>
<tr>
<th>53,454 participants</th>
<th>NLST</th>
<th>US Census</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>59.0</td>
<td>58.5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59 (%)</td>
<td>42.8</td>
<td>35.2</td>
</tr>
<tr>
<td>60-64 (%)</td>
<td>30.6</td>
<td>29.3</td>
</tr>
<tr>
<td>65-69 (%)</td>
<td>17.8</td>
<td>20.8</td>
</tr>
<tr>
<td>70-74 (%)</td>
<td>8.8</td>
<td>14.7</td>
</tr>
<tr>
<td>Race</td>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>4.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>1.7</td>
<td>2.4</td>
</tr>
</tbody>
</table>


Oken MW et al JAMA 2011
Generizability of the NLST results

- Cultural factors: knowledge, beliefs, attitudes about the disease/screen process, fatalistic beliefs, mistrust healthcare system, financial burden of screening (lack of insurance), anxiety related to irradiation
- Especially in lower economic status/minorities underutilization of (CT) screening

Jonnalagadda et al. Lung Cancer 2012

The Challenge for Lung Cancer

- Lifetime probability of lung cancer in US
  - 1 in 13 – men
  - 1 in 17 – women
- Lifetime probability of lung cancer in smokers
  - 1 in 6.5 – men
  - 1 in 10 – women

Commonly used definition of a high-risk smoker

- A Lung Cancer incidence > 300/100,000

Other risk factors
**LLP risk model**

### LLP Multivariate model

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-19 years</td>
<td>2.07</td>
<td>1.17 – 3.64</td>
<td>0.01</td>
</tr>
<tr>
<td>20-39 years</td>
<td>4.07</td>
<td>2.51 – 6.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40-59 years</td>
<td>11.67</td>
<td>7.11 – 19.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥60 years</td>
<td>14.56</td>
<td>5.48 – 38.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 years old</td>
<td>2.02</td>
<td>1.18 – 3.45</td>
<td>0.01</td>
</tr>
<tr>
<td>≥60 years old</td>
<td>1.18</td>
<td>0.79 – 1.77</td>
<td>0.41</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1.83</td>
<td>1.26 – 2.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Previous malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asbestos exposure</td>
<td>1.89</td>
<td>1.35 – 2.62</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*model adjusted for most important covariates* 

**LLP-Risk Model Specific examples**

- A man aged 64, 42 years smoking, history of other malignancy, relative with lung cancer aged over 60 at diagnosis, 5-year risk<9.5% - qualifies
- Woman aged 68, 26 years smoking, no other risk factors, 5-year risk ≤ 1.5% - does not qualify
- Man aged 67, never-smoker, relative with lung cancer aged <60 at diagnosis, history of other malignancy and asbestos exposure, 5-year risk≤3.2% - qualifies

**The “upfront risk stratification” approach**

- 

  - Epidemiological factors (ethnic-specific)
  - Molecular epidemiology: Genome-wide association studies, SNPs
  - Non-lung biomarker assessments
    - in blood/serum/plasma/oralbrushings
  - Biomarker assessment in sputum, brushings/biopsy, bronchial washings

**Improvements of LC risk models**

- **LETTERS**
  - A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25

- **REPORT**
  - A Genome-wide Association Study of Lung Cancer Identifies a Region of Chromosome 5p15
    - Associated with Risk for Adenocarcinoma
      - 5p15.33 locus 2 genes, telomerase reverse transcriptase gene
Multivariable Risk Models for Lung Cancer

Never smokers (330 cases/379 controls)  Odds Ratio
• Family History of cancer  2.00
• Environmental tobacco smoke (ETS)  1.80

Former smokers (764 cases/884 controls)
• Emphysema  2.65
• Family History of cancer  1.59
• Dust Exposures  1.59
• Age at smoking cessation - 3rd tertile  1.50
• No Hay fever  1.43

Current smokers (737 cases/738 controls)
• Emphysema  2.13
• Pack-years - 4th quartile  1.85
• Asbestos Exposure  1.51
• No Hay fever  1.49
• Family history (smoking-related cancers)  1.47
• Dust Exposures  1.36

Discriminatory Power of Extended Genetic Model
(n = 1016 cases, 1111 controls)

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
<th>95% CI</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.661</td>
<td>0.64-0.68</td>
<td>—</td>
</tr>
<tr>
<td>* SNP's</td>
<td>0.673</td>
<td>0.65-0.70</td>
<td>0.023</td>
</tr>
</tbody>
</table>

H. Pass, Biomarkers
Where are we?

- Technologies are approaching 90% specificity and sensitivity for early detection markers in training sets
- Technologies vary in complexity, expense and comprehensiveness
- > 2,000 papers on biomarkers
- >99.9% not validated!

- Only biomarkers which can be validated in large cohorts in blinded investigations at designated centers deserve to move towards clinical decision making in high risk cohorts or patients with lung cancer

The Pro’s of upfront stratification

- Provides better cancer risk-estimates than on smoking history alone
- Helps smokers to understand the true nature of their risk and put it into a proper perspective
- Could help to assist counseling smokers to participate in LC screening program
- Will limit LC screening to certain high-risk subgroups
- Cost-effective way to use public health resources

The Con’s

- In general, screening is controversial
- Screening of certain high risk subgroups is even more controversial
  - Gail model for breast cancer screening has been developed for women who underwent 1 screening round and considered to participate in additional rounds
  - License to continue smoking for those at lower risk for lung cancer
- Participation claims based on RCT results
- Biomarker(s) with a very high sensitivity required
- Not for the near future
  - Not yet validated
  - Public education required

The “wide entry” approach

<table>
<thead>
<tr>
<th>Test Negatives (98%)</th>
<th>Based on LC risk model further screening</th>
<th>Interval to be determined</th>
<th>No further screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Positives (2%)</td>
<td>Spiral CT screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk confirmed, further screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biomarkers both for risk and early detection including genetic instability, epigenetic changes, genomic alterations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>False Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>True Positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Pro’s

- all high risk smokers and former smoker invited to undergo at least 1 CT screening round
- Those who are test negative have a very high NPV of 99.7% (95%CI: 99.6-99.8%) and need no rescanning for at least 2-years
- Work-ups limited to test-positives (2%) which is manageable
- Is more “acceptable” than upfront stratification
- Information from 1st screening round can be incorporated into LC risk model

Lung Cancer Risk Prediction to select smokers for screening CT – a model based on the Italian Cosmos Trial


Based on 1st CT scan

- Presence of emphysema on CT
- Nodule type (NS>PS>S)
- Size of the largest NCN
- Strongest predictors of subsequent lung cancer risk
- AUC = 0.744 (moderate)

Results

- 40% of population heavy smokers had < 0.3% annual risk of lung cancer
- During 3-yrs of FU only 10% of LC’s diagnosed
- This population screen interval 3 yrs ?
- Saved 4000 CT scans, avoided surgery for benign nodules in 7, delayed surgery for lung cancer in 10