What is the target population for lung cancer screening?

Antwerpen, oktober 2012

Rob van Klaveren
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/NLSTresultRelease
Lung cancer case survival
Kaplan Meier curve

Participants with lung cancer

Years from randomization

Probability of survival: Participants with lung cancer

CT arm
CXR arm
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

Probability of survival: ALL participants

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
Gaps in our knowledge

• Only data from a single US study (NLST):
  – DANTE no mortality reduction after 3-yrs of FU.
  – DLCST: no mortality reduction or stage shift, suggestion for overdiagnosis!
  – EU data (NELSON) awaited
  – PLCO data (n=154,901) CXR=Usual care!

Oken MW et al JAMA 2011
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>
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<tr>
<td>Median pack yrs</td>
<td>48.0</td>
<td>47.0</td>
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</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>

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
“Predictions are risky - especially about the future....”

Yogi Berra

Who could have predicted this outcome?
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

Smokers in the US
Current -21% - 45 million
Former -23% - 49 million

How to identify that fraction of smokers most likely to get lung cancer?
Commonly used definition of a high-risk smoker

- A Lung Cancer incidence > 300/100,000

<table>
<thead>
<tr>
<th>Age at incidence (death—5 years)</th>
<th>30–34</th>
<th>35–39</th>
<th>40–44</th>
<th>45–49</th>
<th>50–54</th>
<th>55–59</th>
<th>60–64</th>
<th>65–69</th>
<th>70–74</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9</td>
<td>42</td>
<td>114</td>
<td>258</td>
<td>362</td>
<td>560</td>
<td>859</td>
<td>574</td>
<td>1372</td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>101</td>
<td>103</td>
<td>192</td>
<td>360</td>
<td>859</td>
<td>574</td>
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<tr>
<td>20</td>
<td>43</td>
<td>83</td>
<td>200</td>
<td>297</td>
<td>652</td>
<td>854</td>
<td>1372</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–39</td>
<td>25</td>
<td>114</td>
<td>218</td>
<td>442</td>
<td>510</td>
<td>1042</td>
<td>1326</td>
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<tr>
<td>40</td>
<td>57</td>
<td>159</td>
<td>254</td>
<td>507</td>
<td>836</td>
<td>1244</td>
<td>1525</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>53</td>
<td>141</td>
<td>220</td>
<td>335</td>
<td>499</td>
<td>999</td>
<td>1469</td>
<td>4067</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>6</td>
<td>19</td>
<td>41</td>
<td>115</td>
<td>206</td>
<td>361</td>
<td>582</td>
<td>909</td>
<td>1118</td>
</tr>
</tbody>
</table>

CPS II data [22].
Number of cigarettes smoked per day
Duration of smoking
Duration of cessation
Age 50-75
Other risk factors

<table>
<thead>
<tr>
<th>Co-variates and lung cancer risk [9,10]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk factors for lung cancer</td>
</tr>
<tr>
<td>Tobacco exposure</td>
</tr>
<tr>
<td>Environmental (radon)</td>
</tr>
<tr>
<td>Occupational exposure (asbestos)</td>
</tr>
<tr>
<td>Genetic factors</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Diet</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
</tr>
<tr>
<td>Family history</td>
</tr>
</tbody>
</table>
Stratification of the high risk population

British Journal of Cancer (2007), 1 – 7
© 2007 Cancer Research UK. All rights reserved 0007 – 0920/07 $30.00
www.bjcancer.com

Full Paper

The LLP risk model: an individual risk prediction model for lung cancer

A Cassidy1,5, JP Myles2,5, M van Tongeren3, RD Page4, T Liloglou1, SW Duffy2 and JK Field3,1

1Ray Castle Lung Cancer Research Programme, University of Liverpool Cancer Research Centre, Liverpool, L3 9TA, UK; 2Cancer Research UK Centre for Epidemiology, Mathematics and Statistics Wolfson Institute of Preventive Medicine, London, EC1M 6BQ, UK; 3Institute of Occupational Medicine, Research Avenue North, Riccarton, Edinburgh, EH14 4AP, UK; 4Department of Thoracic Surgery, The Cardiothoracic Centre, Liverpool, L14 3PE, UK

Using a model-based approach, we estimated the probability that an individual, with a specified combination of risk factors, would develop lung cancer within a 5-year period.
### 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><strong>Cigarette smoker</strong></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><strong>Family history</strong></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><strong>Pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.83</td>
<td>1.26 – 2.64</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Previous malignancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.96</td>
<td>1.22 – 3.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Asbestos exposure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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, clinical factors (ethnic-specific)

Molecular epidemiology: Genome-wide association studies, SNPs

Non-lung biomarker assessments * in blood/serum/plasma/oral brushings

Biomarker assessments* in sputum, brushings / biopsy, bronchial washings

Highest-risk individuals

Biomarkers assessed both for risk and early detection include genomic instability, methylation, mutations, genomics, proteomics

Spiral CT screening

Distribution of participants with lung cancer according to the presence or absence of airway obstruction (AO) and/or emphysema (E).

- No Airway Obstruction or Emphysema: 692 (59%)
- Airway Obstruction and/or Emphysema: 474 (41%)
- Total population: 1,166 (100%)

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Improvements of LC risk models

- Adding DNA repair capacity: no improvement in sensitivity

15q25.1 locus
- CHRNA3 and CHRNA5 nicotine dependence genes; direct relation with carcinogenesis

5p15.33 locus
- 2 genes, telomerase reverse transcriptase gene
# Multivariable Risk Models for Lung Cancer

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

**Former smokers (784 cases/884 controls)**  
- Emphysema  
  - Odds Ratio 2.65  
- Family History of cancer  
  - Odds Ratio 1.59  
- Dust Exposures  
  - Odds Ratio 1.59  
- Age at smoking cessation – 3rd tertile  
  - Odds Ratio 1.50  
- No Hay fever  
  - Odds Ratio 1.45

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

* baseline + chr 15 and 5 SNP’s

<table>
<thead>
<tr>
<th>Score</th>
<th>Poor</th>
<th>Moderate</th>
<th>Good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>80</td>
<td>90</td>
<td>100</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

High-risk smokers and former smoker wide entry criteria based on trial results

Spiral CT screening

Test Negatives (98%)

Based on LC risk model: further screening (interval to be determined) no further screening

Test Positives (2%)

Biomarkers both for risk and early detection including genomic instability, methylation, mutations, genomics, proteomics

False Positive

True Positive
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