Targeted CT Screening for Lung Cancer using Absolute Risk Prediction

Stephanie A. Kovalchik
skovalch@rand.org

FHCRC 2014 Risk Prediction Symposium

June 11, 2014
Outline

• Lung Cancer Epidemiology and Screening
• Screening Benefit and Absolute Risk
• Absolute Risk Model for Lung Cancer Mortality
  ◦ Development
  ◦ Validation
  ◦ Utility
• Model Generalizability
• Implications for Screening Guidelines
• Summary & Remaining Research Questions
Collaborators

Martin Tammemagi  Brock University
Christine Berg  National Cancer Institute
Neil Caporaso  National Cancer Institute
Tom Riley  Information Management Services
Mary Korch  Information Management Services
Gerard Silvestri  Medical University of South Carolina
Anil Chaturvedi  National Cancer Institute
Hormuzd Katki  National Cancer Institute
# Leading Causes of Cancer Death, U.S. 2012

## Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>87,750</td>
<td>72,590</td>
</tr>
<tr>
<td>Prostate</td>
<td>28,170</td>
<td>39,510</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,470</td>
<td>25,220</td>
</tr>
<tr>
<td>Pancreas</td>
<td>18,850</td>
<td>18,540</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>13,980</td>
<td>15,500</td>
</tr>
<tr>
<td>Leukemia</td>
<td>13,500</td>
<td>10,040</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,040</td>
<td>8,620</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>10,510</td>
<td>8,010</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>10,320</td>
<td>6,570</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>8,650</td>
<td>5,980</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>301,820</strong></td>
<td><strong>275,370</strong></td>
</tr>
</tbody>
</table>

Rationale & Modalities for Lung Cancer Screening

- High morbidity and mortality
- High prevalence in high-risk groups
- Early detection is associated with improved survival

<table>
<thead>
<tr>
<th>Modality</th>
<th>Proven Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Cytology</td>
<td>No</td>
</tr>
<tr>
<td>Chest X-ray (CXR)</td>
<td>No</td>
</tr>
<tr>
<td>Low-Dose CT</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Source: University Hospitals Seidman Cancer Center
Why Screen if You Can Prevent?

Source: Moolgavkar et al. JNCI 2012.
Why Screen if You Can Prevent?

Source: Moolgavkar et al. *JNCI* 2012.

Prevention efforts should remain the priority. However, complete prevention may not be attainable.
CT Efficacy: National Lung Screening Trial (NLST)

**Trial Design**

<table>
<thead>
<tr>
<th>Period of Enrollment</th>
<th>2002-2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Region</td>
<td>United States</td>
</tr>
<tr>
<td>Randomized, Two-arm, with</td>
<td>LDCT = 26,722</td>
</tr>
<tr>
<td>Equal Allocation</td>
<td>CXR = 26,732</td>
</tr>
<tr>
<td>Screening Schedule</td>
<td>3 annual rounds</td>
</tr>
</tbody>
</table>

**Strict Entry Criteria**

→ 55-74 years old
→ Current or former smokers with ≥ 30 pack-years
→ Former smokers must have quit within 15 years
20% Overall Reduction in Lung-Cancer Mortality

Do All Smokers Benefit from Screening?
Problem Statement

- The NLST proved the efficacy of CT screening, but it remains unclear which smokers should be recommended for screening.

- The decision to screen requires knowledge about a smoker’s expected net benefit with screening.

Net Benefit = Benefit - Harm
Factors Influencing Net Benefit

Net Benefit = Benefit - Harm

Lung Cancer Screening

- Potential Benefits
  - Identify early stage lung cancer
  - Identify other lung diseases

- Potential Harms
  - False positive
  - Serious complication of diagnostic follow-up
  - Adverse effects of treatment (e.g. radiation-induced cancers)
Principle of Benefit and Absolute Risk

- **Absolute risk** is the probability that disease occurs within a particular time interval, accounting for individual risk factors and competing events.

<table>
<thead>
<tr>
<th>Baseline Risk</th>
<th>Reduced Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>→ 0.2%</td>
</tr>
<tr>
<td>10%</td>
<td>→ 2.0%</td>
</tr>
<tr>
<td>20%</td>
<td>→ 4.0%</td>
</tr>
</tbody>
</table>

- Screening’s benefit is directly proportional to an individual’s absolute risk of lung cancer death.
Technical Definition of Absolute Risk

\[ T \rightarrow \text{Time to primary event} \]
\[ [t_0, t_1) \rightarrow \text{Projection interval} \]
\[ \lambda_p(u; x) = \text{Hazard function of primary event} \]
\[ \lambda_c(u; x) = \text{Hazard function of competing event} \]

\[
P(T < t_1 | T \geq t_0, x) = \int_{t_0}^{t_1} \lambda_p(u; x) S(t_0, u; x) du,
\]

where

\[
S(t_0, u; x) = \exp\{-\int_{t_0}^{u} (\lambda_p(v; x) + \lambda_c(v; x)) dv\}.
\]
Absolute Risk versus Relative Risk/Odds Ratio

- The relative risk and odds ratio focus on comparisons between the risk of two different types of patients.
- **Absolute risk** is concerned with the disease probability for a specific patient.

| Absolute Risk | \( P(D = 1|X_0) \) |
|---------------|-----------------|
| Relative Risk | \( \frac{P(D = 1|X_0)}{P(D = 1|X_1)} \) |
| Odds Ratio    | \( \frac{P(D=1|X_0)(1-P(D=1|X_1))}{P(D=1|X_1)(1-P(D=1|X_0))} \) |
How greatly did the benefit of CT screening vary among NLST participants?
Absolute Risk Model for Lung Cancer Death

- **Development**
  - Data
  - Predictor selection
  - Model form & estimation
  - Inference

- **Validation**
  - Data
  - Calibration
  - Discrimination
  - Risk Distribution

- **Clinical Utility**
Development Data

- NLST CXR Group (n=26,554)
- Lung cancer death in the ‘absence’ of screening

Predictor Selection

- Candidate covariates from published models of lung cancer risk
  - Demographic factors
  - Smoking behavior
  - Pre-existing conditions

- Particular desire for parsimony and interpretability
- Lasso Cox proportional hazards model
Absoute Risk Estimation

Given predictors \( x \), the probability of an event between time \( t_0 \) and \( t_1 \) is

\[
\hat{P}(T < t_1 | T \geq t_0, x) = \frac{\int_{t_0}^{t_1} \hat{S}_p(u) \hat{r}_p(x) \hat{S}_c(u) \hat{r}_c(x) \hat{r}_p(x) d\hat{\Lambda}_p(u)}{\{ \hat{S}_p(t_0) \hat{r}_p(x) \hat{S}_c(t_0) \hat{r}_c(x) \}}
\]

- \( \hat{r}_j(x) = \) hazard ratio for \( j \)th event
- \( \hat{S}_j(t) = j \)th event’s baseline survival beyond \( t \)
- \( \hat{\Lambda}_j(t) = j \)th event’s baseline cumulative hazard to \( t \)
Effect of Competing Risks (1)
Effect of Competing Risks (2)

Absolute Risk

Risk(T0, T1)

Individual A

Individual B
Absolute Risk Estimation Approaches

- **Baseline Hazard**
  - Nelson-Aalen (Cohort)
  - Attributable risk from disease registry (Case-control)

- **Hazard Ratio**
  - Cox proportional hazards (Cohort)
  - Logistic regression (Case-control)
## Selected Covariates and Hazard Ratios

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Lung Cancer Mortality</th>
<th>Competing Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.08</td>
<td>1.09</td>
</tr>
<tr>
<td>Female</td>
<td>—</td>
<td>0.51</td>
</tr>
<tr>
<td>Race</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>White</td>
<td>—</td>
<td>1.00</td>
</tr>
<tr>
<td>Black</td>
<td>2.22</td>
<td>—</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.34</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>1.21</td>
<td>—</td>
</tr>
<tr>
<td>BMI - 25 (linear)</td>
<td>0.94</td>
<td>0.98</td>
</tr>
<tr>
<td>BMI - 25 (quadratic)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Pack-year</td>
<td>1.02</td>
<td>1.01</td>
</tr>
<tr>
<td>Quit years</td>
<td>0.62</td>
<td>0.76</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.56</td>
<td>1.52</td>
</tr>
<tr>
<td>Family history</td>
<td>1.27</td>
<td>—</td>
</tr>
</tbody>
</table>
Validation Data

- Independent of development data (external validation)
- PLCO CXR group
- 15,114 NLST-eligible and 22,649 ineligible smokers

Validation Measures

- Calibration
- Discrimination
- Risk Distribution
Validation — Discrimination

**Overall ROC plot**
- Sensitivity vs. 1-Specificity
- AUC: 0.80

**NLST Eligibles ROC plot**
- Sensitivity vs. 1-Specificity
- AUC: 0.72

**NLST Ineligibles ROC plot**
- Sensitivity vs. 1-Specificity
- AUC: 0.77
Validation —Risk Distribution (1)

Lung Cancer Death 5-YR Risk Distribution - NLST Eligibles

- Non-Cases
- Cases

Predicted Risk

Percentage

0-0.01
0.01-0.02
0.02-0.03
0.03-0.04
0.04-0.05
0.05-0.06
>0.06

Predicted Risk
Validation — Risk Distribution (2)

Predictiveness Curve - NLST Eligibles

Cumulative percentage

Predicted risks

Predicted risks

Cumulative percentage

0.00

0.05

0.10

0.15

0.0

0.2

0.4

0.6

0.8

1.0

0.0

0.2

0.4

0.6

0.8

1.0
Clinical Utility
## Summary of Outcomes by Risk Quintiles

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>5-Year Risk Range</th>
<th>Sample Size</th>
<th>Lung Cancers Total</th>
<th>Lung Cancers Stage 1 (%)</th>
<th>Lung Cancer Total</th>
<th>Cancer Deaths Averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>0.15-0.55%</td>
<td>5,276</td>
<td>71</td>
<td>40 (56)</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Q2</td>
<td>0.56-0.84%</td>
<td>5,310</td>
<td>105</td>
<td>59 (56)</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Q3</td>
<td>0.85-1.23%</td>
<td>5,396</td>
<td>182</td>
<td>84 (46)</td>
<td>45</td>
<td>13</td>
</tr>
<tr>
<td>Q4</td>
<td>1.24-2.00%</td>
<td>5,314</td>
<td>263</td>
<td>132 (50)</td>
<td>73</td>
<td>31</td>
</tr>
<tr>
<td>Q5</td>
<td>&gt;2.00%</td>
<td>5,308</td>
<td>462</td>
<td>215 (47)</td>
<td>181</td>
<td>33</td>
</tr>
</tbody>
</table>
Lung Cancer Mortality Risk Difference

Prevented Deaths Per 10,000 Person-Years

Risk Groups

Q1 0.15-0.55  Q2 0.56-0.84  Q3 0.85-1.23  Q4 1.24-2.00  Q5 >2.00

LC Mortality Model
Bach 2003
Spitz 2007
LLP 2008
Tammemagi 2011
Next, we summarize screening outcomes using 5 different risk thresholds (Q5, Q4, . . . , Q1).

Outcome Measures in LDCT Group

- LDCT-prevented lung cancer deaths
- Numbers needed to screen
- Persons with a false positive screen
- Ratio of LDCT-prevented deaths to persons with false positive screen
Outcomes by Risk Threshold

A. Cumulative Number Of Prevented Lung Cancer Deaths

B. Cumulative Numbers Needed To Screen To Prevent One Lung Cancer Death

C. Cumulative Number Of Persons With False Positive Screen

D. Cumulative False Positives Per Prevented Lung Cancer Death
Model Generalizability
NLST Eligibles are a Small Subset of the US Smoking Population

US Population of Former or Current Smokers, ~98 Million Adults

- Are there high-risk smokers among ineligibles?
- Could the lung cancer mortality model help identify them?
## Relevance for Lung Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>Organization</th>
<th>Primary Recommended Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>AATS</td>
<td>55-79 years, NLST-eligible smokers with no quit-year condition</td>
</tr>
<tr>
<td>ACCP/ASCO</td>
<td>NLST-eligible</td>
</tr>
<tr>
<td>ACS</td>
<td>NLST-eligible</td>
</tr>
<tr>
<td>NCCN</td>
<td>NLST-eligible</td>
</tr>
<tr>
<td>USPSTF (draft)</td>
<td>55-79 years, otherwise NLST-eligible</td>
</tr>
</tbody>
</table>

- Current guidelines are largely defined by NLST eligibility

- **However**
  - We have seen that NLST eligibles include some low-risk smokers
  - It is unknown whether NLST ineligibles include high-risk smokers
Generalizing the Lung Cancer Mortality Model

**Objective:** We sought to determine whether we could extend the lung cancer mortality prediction model to current 50-80 year-old U.S. smokers.

**Data:** Model development in unscreened smokers of the PLCO trial; Validation in 50-80 year-old smokers of the 1997-2001 National Health Interview Survey (NHIS).

**Methods:** We refined the NLST lung cancer model with data from a broader population of unscreened smokers and examined the accuracy and discriminatory power of 5-year lung cancer mortality predictions for the 50-80 year-old U.S. smoking population represented by the NHIS.
<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Risk (%)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLST Eligible, Ages 50–80</td>
<td>0.1–0.79%</td>
<td>13,535</td>
<td>6.6</td>
<td></td>
<td></td>
<td></td>
<td>206,141</td>
</tr>
<tr>
<td>Q1</td>
<td>0.8–1.19%</td>
<td>21,356</td>
<td>10.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>1.3–1.89%</td>
<td>32,740</td>
<td>15.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>1.9–3.2%</td>
<td>48,612</td>
<td>23.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>&gt;3.2%</td>
<td>89,898</td>
<td>43.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>206,141</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLST Ineligible, Ages 50–80</td>
<td>0.02–0.13%</td>
<td>4,131</td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td>246,796</td>
</tr>
<tr>
<td>Q1</td>
<td>0.15–0.30%</td>
<td>14,688</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.32–0.56%</td>
<td>25,238</td>
<td>10.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>0.58–1.17%</td>
<td>51,940</td>
<td>21.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>&gt;1.17%</td>
<td>150,799</td>
<td>61.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>246,796</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Smokers, Ages 50–80</td>
<td>0.02–0.18%</td>
<td>5,688</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
<td>452,937</td>
</tr>
<tr>
<td>Q1</td>
<td>0.20–0.41%</td>
<td>27,054</td>
<td>6.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>0.43–0.82%</td>
<td>57,860</td>
<td>12.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>0.84–1.77%</td>
<td>99,013</td>
<td>21.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4</td>
<td>&gt;1.77%</td>
<td>263,322</td>
<td>58.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>452,937</td>
<td>100.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Expected/Observed**

- Q1: 0.77 [0.37, 1.63]
- Q2: 0.86 [0.44, 1.68]
- Q3: 0.84 [0.55, 1.29]
- Q4: 0.88 [0.64, 1.21]
- Q5: 0.99 [0.78, 1.26]

**95% CI**

- Q1: 1.11 [0.30, 4.17]
- Q2: 0.81 [0.42, 1.58]
- Q3: 0.89 [0.55, 1.44]
- Q4: 0.81 [0.57, 1.15]
- Q5: 1.14 [0.94, 1.39]

**Expected/Observed**

- Q1: 1.34 [0.41, 4.34]
- Q2: 0.77 [0.48, 1.26]
- Q3: 0.75 [0.53, 1.05]
- Q4: 0.87 [0.66, 1.14]
- Q5: 1.08 [0.94, 1.24]

**95% CI**

- Q1: 0.97 [0.86, 1.09]
Distribution of Lung Cancer Death Burden

Recommendation based on USPSTF draft guidelines.
Lung Cancer Mortality Risk Distribution

Risk Percentiles of USPSTF Recommended Population

- <25th: 2.2 (25%)
- 25–50th: 2.2 (25%) 3.4 (10%)
- 51–75th: 2.2 (25%) 1.8 (5%)
- >75th: 2.2 (25%) 0.7 (2%)
Summary

• An absolute risk model for lung cancer death identified clinically significant variation in risk among NLST-eligible smokers.

• Nearly 90% of prevented lung cancer deaths occurred among the 60% of smokers at highest risk, while almost no prevented deaths occurred for the 20% at lowest risk.

• These findings support a shift away from subgroups to model-based risk assessment.

• Based on the principle that the NLST findings can be generalized to smokers of similar risk, we conclude that risk-targeted screening of 50-80 year-old smokers could capture more preventable lung-cancer deaths than USPSTF recommendations.
Open Research Questions

• How do we develop risk models for the general population using data from clinical trials?

• How should external validation be used to guide model refinement?

• When related risk models are available, how should these be used to improve risk prediction?

• In the design of risk-based screening programs, how do we determine cutpoints for recommending screening?
Further Reading


Influence-Based Variance (1)

Let \( \Delta_i(.) \) denote the influence associated with the \( i \)th observation and let \( \theta_k \) be the \( k \)th parameter of the absolute risk estimate \( \hat{P}(t_0, t_1; x) \).

The Taylor deviates for the absolute risk estimate are

\[
\Delta_i\{\hat{P}(t_0, t_1; x)\} = \sum_{k=1}^{K} \sum_{u \in (t_0, t_1]} \frac{\partial \hat{P}(t_0, t_1; x)}{\partial \theta_k(u)} \Delta_i\{\theta_k(u)\}, \quad (1)
\]
Influence-Based Variance (2)

Given the Taylor deviates, the variance estimate for $\hat{P}(t_0, t_1; x)$ is

$$\hat{\text{Var}}[\hat{P}(t_0, t_1; x)] = \sum_i \left( \Delta_i\{\hat{P}(t_0, t_1; x)\} - \bar{\Delta}_i\{\hat{P}(t_0, t_1; x)\} \right)^2$$

(2)

where $\bar{\Delta}_i\{\hat{P}(t_0, t_1; x)\} = n^{-1} \sum_i \Delta_i\{\hat{P}(t_0, t_1; x)\}$ is the average Taylor deviate.