Lung Cancer Screening
Promise and Pitfalls

Christine D. Berg, M.D.
Chief, Early Detection Research Group
Division of Cancer Prevention
Lung Cancer

Only 7% cured in 1971: only 15% cured today.
What has helped with other solid tumors?
CI SNET Breast Cancer Group
Impact of Screening and Treatment
Berry et al. *NEJM* 2005;353:1784-1792

US actual
Women 40–79
Mortality rate/100,000
What would help most for lung cancer?

SMOKING CESSATION

U.S. population with direct smoking exposure:
- 46.5 million former smokers
- 45.1 million current smokers

CDC MMWR 10/27/06
Percentage of persons age ≥18 years who were current cigarette smokers, by sex and age groups

<table>
<thead>
<tr>
<th>Age groups (yrs)</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States (2005)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>28.0 (±3.0)</td>
<td>20.7 (±2.4)</td>
<td>24.4 (±2.0)</td>
</tr>
<tr>
<td>25-44</td>
<td>26.8 (±1.4)</td>
<td>21.4 (±1.2)</td>
<td>24.1 (±1.0)</td>
</tr>
<tr>
<td>45-64</td>
<td>25.2 (±1.5)</td>
<td>18.8 (±1.1)</td>
<td>21.9 (±0.9)</td>
</tr>
<tr>
<td>≥65</td>
<td>8.9 (±1.3)</td>
<td>8.3 (±1.0)</td>
<td>8.6 (±0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>23.9 (±1.0)</td>
<td>18.1 (±0.7)</td>
<td>20.9 (±0.6)</td>
</tr>
<tr>
<td>Maryland (2005)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19.7 (±1.9)</td>
<td>18.4 (±1.4)</td>
<td>19.0 (±1.2)</td>
</tr>
</tbody>
</table>

CDC MMWR 10/27/06
Effects of stopping smoking at various ages on the cumulative risk (%) of death from lung cancer up to age 75, at death rates for men in UK in 1990. Nonsmoker rates were taken from US prospective study of mortality.

Peto R, BMJ, 2000
Rationale for Lung Cancer Screening

- Smoking cessation helps, but residual risk remains
  - Quit at age 50 risk by age 75 is 6%
- Improved *survival* with early stage disease
  - 5-Yr Survival all comers: 15%
  - Resected clinical Stage I: 92% per I-ELCAP; 75 % SEER
- Why not start screening high-risk individuals now?
  - Dr. Henschke’s estimate that CT screening could reduce deaths by 80 % is “an outrageous and implausible claim.”
  - But … “it really got people to pay attention.”
  - Dr. Peter Bach, NYT Tuesday, October 31, 2006
Distinguishing *Benefit* from *Bias*

- In screening, survival endpoints are confounded by:
  - **Lead-time:** Earlier detection prolongs survival independent of delay in death
  - **Length:** Screening selects for more indolent cancers
  - **Overdiagnosis:** Detecting cancer that is not lethal

- Prolonged survival ≠ mortality reduction
Current Data
from
CXR & CT Screening Studies
Mayo Lung Cancer Screening Project

9211 Study Participants

Screened Group
CXR & pooled sputum
q 4 months

- Lung Cancers=206
  - Stage I & II (resected) 83 (40%)
  - Late-stage (unresected) 123 (60%)

Standard care recommendation at study entry

- Lung Cancers=160
  - Stage I & II (resected) 41 (25%)
  - Late-stage (unresected) 119 (75%)

Marcus, JNCI, 2000
Mayo Lung Project
Lung Cancer Survival

Screened (n=206)
Usual care (n=160)

Years Since Diagnosis

Marcus, JNCI 2000
Mayo Lung Project
Cumulative Lung Cancer Deaths

Screened (n=337)
Usual care (n=303)

Marcus, JNCI 2000
Overdiagnosis exists

CXR not effective in reducing mortality

Problems:

- Study underpowered for a realistic result, 10% mortality decrease could have been missed
- Contamination and compliance

PLCO launched
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Screening vs. No Screening

- Multicenter RCT involving 154,942 men and women aged 55-74
  - 1:1 randomization to CXR screening vs. no screening
  - Smokers: CXR at baseline and then annually for 3 screens
  - Non-smokers: CXR annually for 3 screens
- Primary endpoint: lung cancer-specific mortality
# PLCO Prevalence Screen Results


<table>
<thead>
<tr>
<th>Participant group (n = 77,465)</th>
<th>Cancers per 1000 screens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smokers</td>
<td>6.3</td>
</tr>
<tr>
<td>Former smokers</td>
<td>Stratified</td>
</tr>
<tr>
<td>If smoked within prior 15 yrs</td>
<td>4.9</td>
</tr>
<tr>
<td>If did not smoke within prior 15 yrs</td>
<td>1.1</td>
</tr>
<tr>
<td>Never smokers</td>
<td>0.4</td>
</tr>
</tbody>
</table>

- 126 lung cancers were screen-diagnosed
  - 55 (44%) were Stage I, representing 52% of the 107 NSCLCs diagnosed
    - Of 14 cancers in never smokers, 12 = adenocarcinoma |12 in women
- Overall rates highest for older age groups, smokers and men
- Data re: mortality benefit from CXR screening are forthcoming
Spiral (Helical) CT

Pitch = 1

Pitch > 1

Pitch = \frac{\text{Table travel per revolution}}{\text{Collimation Width}}

\text{Acquired Slice Spacing (C to C)}

\text{Slice Thickness}
Low-Dose Helical CT

- Allows entire chest to be surveyed in a single breathhold
  - Time: approximately 7 - 15 seconds
  - Reduces motion artifact
  - Eliminates respiratory misregistration
- Narrower slice thickness
- Hourly throughput - 4 patients per hour
- Radiation dose one tenth of diagnostic CT
What do we see on CT? 
Definition of terms

- **GGO (non-solid):** Nodule with hazy increased lung attenuation which does not obscure underlying bronchovascular markings.

- **Mixed (part-solid):** Nodules containing both ground glass and solid components

- **Solid (soft tissue):** Nodules with attenuation obscuring the bronchovascular structures
Nodules may be very subtle on screening CXR.
Corresponding helical CT confirms nodule in RUL
Downstream Effects of CT Screening

- Radiation carcinogenesis
  - screening & consequent diagnostic tests: CT, PET

- Additional minimally invasive procedures
  - Percutaneous Lung FNA
  - Bronchoscopy
  - VATS

- Thoracotomy for benign disease
  - Is there an acceptable percentage?
  - Potential post-operative morbidity & mortality

- Evaluation for other observations: cardiac, renal, liver, adrenal disease
## Summary of Selected Cohort Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Criteria</th>
<th>N</th>
<th>[+ ] Screens</th>
<th>Total Cancers</th>
<th>Stage I NSCLC</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELCAP 2001 CT + CXR</td>
<td>60+ Yr 10 Pk Yr</td>
<td>Yr 0: 1000 Yr 1: 841 Yr 2: 343 Baseline 233 (23.3%) Incidence 40 (3.4%)</td>
<td>Baseline: 31 (3.1%) Incidence: 07 Interval: 2</td>
<td>Baseline: 23 (74%) Incidence: 5 (55%)</td>
<td>All with cancer alive at 2.5 Yrs; 5 deaths other causes No mortality data</td>
<td></td>
</tr>
<tr>
<td>Swensen CT annual x 5 yrs</td>
<td>50+ Yr 20 PkYr Quit &lt;10Yr</td>
<td>Yr 0 1520 Yr 1:1478 Yr 2:1438 Overall &gt;95% Baseline: 782 (51%) Incidence: 9.3-13.5%</td>
<td>Baseline: 31 (2%) Incidence: 32 Interval: 3</td>
<td>Baseline: 20 (65%) Incid: 17 (61%)</td>
<td>42 deaths overall: 09 lung ca (1.6) 33 all cause (6.0) [per 1000 person-Yr]</td>
<td></td>
</tr>
<tr>
<td>I-ELCAP</td>
<td>Site Specific</td>
<td>Yr 0: 31,567 Incid: 27,456 Baseline 4186 (13%) Incidence: 1460 (5%)</td>
<td>Baseline: 405 Incidence: 74 Interval: 5</td>
<td>Baseline: Incidence: Total: 347 (72%)</td>
<td>F/U = median 3.3 Yrs Estimates: -Overall 80% 10 Yr -Resected cStage 1 92%</td>
<td></td>
</tr>
</tbody>
</table>
Mayo Helical CT Study

- 1520 participants; baseline and 4 annual screens
- 1118 (74%) had 3356 uncalcified nodules
- 68 lung cancers in 66 participants
- Lung cancer mortality rates compared with MLP in similar age and sex subset
  - Incidence lung cancer mortality: 2.8 vs 2.0 per 1000 person-years
International Early Lung Cancer Action Project

- Prospective, international, multi-institutional study
- 31,567 patients at high risk for lung cancer screened
  - Azumi Health Care Program, Japan
    - 3,087 (10%) current or former smokers
    - 3,299 (10%) non-smokers
- Criteria for enrollment varied by institution
- 27,456 annual screens (second; what about later?)

31,567 baseline screens; 27,456 annual

Low-dose CT per ELCAP protocol

- Definition of a positive changed
  - Baseline 13% positive (original ELCAP)
  - Annual 5% positive

Diagnostic work-up recommended but decision as to how to proceed left to individual and their physician

535 participants had biopsy as recommended in protocol; 2 deaths within 4 weeks in lung cancer patients after surgery

- No comment as to how many biopsies done outside protocol
Baseline: 31,567
- 4186 nodules qualifying as positive result (13%)
- 405 lung cancer
- 5 interim diagnoses of lung cancer

Annual repeat: 27,456
- 1460 new nodule (5%)
- 74 lung cancer; no interim

Total lung cancers 484 out of 535 biopsies
- 90.5% positivity rate
- 412 (85%) Clinical Stage I
Figure 2. Kaplan–Meier Survival Curves for 484 Participants with Lung Cancer and 302 Participants with Clinical Stage I Cancer Resected within 1 Month after Diagnosis.

The diagnoses were made on the basis of CT screening at baseline combined with cycles of annual CT.

Lessons From CT Observational Trials

- Detected prevalence rate: 0.40 – 2.7%
  - Age is strong risk factor (> 60 years)
  - Pack year smoking history
- Nodule detection rate variable on CT: 5.1% - 51.4%
  - Function of [a] definition of “nodule” and [b] CT slice thickness
  - Benign nodules = majority of detected nodules: ~90%
- CT results in higher lung cancer detection than CXR
  - ≥ 3-fold higher detection rate vs CXR; excess cancers early stage
  - 2-3 fold selective oversampling of adenocarcinoma
  - Stage shift not yet been shown
National Lung Screening Trial

- Determine effect on lung cancer mortality
  - 90% power, $\alpha$ of 5%, to detect a 20% difference
- Determine magnitude if any of stage shift
- Delineate adverse events
- Determine the ratio between risks and benefits
  - Thoracotomies for benign disease
  - Diagnostic radiation exposure in individuals without cancer; estimate radiation carcinogenesis
Definition of High Risk Participants

- Males and females
- 55-74 Yrs
- Asymptomatic current or former smokers $\geq 30$ pack yrs
- Former smokers must have quit within $\leq 15$ yrs
- No prior Hx lung cancer
- No Hx any cancer within past 5 years
- No chest CT w/in prior 18 months
NLST Trial Design

53,464 High-Risk Subjects

Randomize

CT Arm
CXR Arm

3 annual screens: T0, T1, T2
Trial Time posts

CT Arm

Randomize

CXR Arm

T₀

02 03 04 05 06 07 08 09 10

1st Interim Analysis

2nd Interim Analysis

3rd Interim Analysis

Final Analysis

Follow up
# Trial-Wide Participant Demographics

N = 53,464

<table>
<thead>
<tr>
<th>Category</th>
<th>CT #</th>
<th>CT %</th>
<th>CXR #</th>
<th>CXR %</th>
<th>Total #</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>GENDER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15776</td>
<td>59.0%</td>
<td>15769</td>
<td>59.0%</td>
<td>31545</td>
<td>59.0%</td>
</tr>
<tr>
<td>Female</td>
<td>10951</td>
<td>41.0%</td>
<td>10968</td>
<td>41.0%</td>
<td>21919</td>
<td>41.0%</td>
</tr>
<tr>
<td>EDUCATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS or Less</td>
<td>7913</td>
<td>29.7%</td>
<td>8047</td>
<td>30.2%</td>
<td>15960</td>
<td>29.9%</td>
</tr>
<tr>
<td>More than HS</td>
<td>18212</td>
<td>68.2%</td>
<td>18053</td>
<td>67.5%</td>
<td>36265</td>
<td>67.8%</td>
</tr>
<tr>
<td>SMOKING</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>12884</td>
<td>48.2%</td>
<td>12921</td>
<td>48.3%</td>
<td>25805</td>
<td>48.3%</td>
</tr>
<tr>
<td>Former</td>
<td>13837</td>
<td>51.8%</td>
<td>13805</td>
<td>51.6%</td>
<td>27642</td>
<td>51.7%</td>
</tr>
</tbody>
</table>
## Minority Accrual

<table>
<thead>
<tr>
<th>Category</th>
<th>LSS-NLST % Pts</th>
<th>ACRIN-NLST % Pts</th>
<th>ALL % Ppts</th>
<th>Population of eligible persons %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RACE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89.9</td>
<td>92.3</td>
<td>90.8</td>
<td>91.7</td>
</tr>
<tr>
<td>African American</td>
<td>3.7</td>
<td>5.8</td>
<td>4.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Asian</td>
<td>2.9</td>
<td>0.6</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>American Indian</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Indian/Alaskan</td>
<td>0.5</td>
<td>&lt; 0.1</td>
<td>0.4</td>
<td>-</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>1.7</td>
<td>0.5</td>
<td>1.3</td>
<td>-</td>
</tr>
<tr>
<td>More than one race</td>
<td>1.0</td>
<td>0.4</td>
<td>0.7</td>
<td>-</td>
</tr>
<tr>
<td><strong>ETHNICITY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.0</td>
<td>1.3</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>96.9</td>
<td>98.5</td>
<td>97.5</td>
<td>96.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>1.1</td>
<td>0.3</td>
<td>0.8</td>
<td>-</td>
</tr>
</tbody>
</table>

* Estimates derived from the Tobacco Use Supplement of the Current Population Survey (Census Department) for 1998 & 1999. Eligibility defined as: age 55-74; ≥ 30 pack yr smoking history; and current or former smoker of ≤ 15 yrs.
### Screening Exam Compliance (as of June 30, 2006)

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Spiral CT</th>
<th>Chest X-ray</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected</td>
<td>Screened</td>
<td>Expected</td>
</tr>
<tr>
<td>T0</td>
<td>26,715</td>
<td>98.5%</td>
<td>26,728</td>
</tr>
<tr>
<td>T1</td>
<td>26,334</td>
<td>93.9%</td>
<td>26,429</td>
</tr>
<tr>
<td>T2</td>
<td>26,014</td>
<td>91.3%</td>
<td>26,160</td>
</tr>
</tbody>
</table>

- By sex: Female CXR slightly lower than male CXR
- By age group: consistent
- By race/ethnicity: AA, Hispanic is lower than White at T1, T2
NLST Image Standardization and QC

Image Interpretation & Diagnostic Pathways
ACRIN/NLST CT Technique

<table>
<thead>
<tr>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>kV</td>
</tr>
<tr>
<td>Gantry Rotation Time</td>
</tr>
<tr>
<td>mA (Regular patient-Large patient values)</td>
</tr>
<tr>
<td>mAs (Reg-Lg)                (^1)</td>
</tr>
<tr>
<td>Scanner effective mAs(^2) (Reg-Lg)</td>
</tr>
<tr>
<td>Detector Collimation (mm) - T</td>
</tr>
<tr>
<td>Number of active channels - N</td>
</tr>
<tr>
<td>Detector Configuration - N x T</td>
</tr>
<tr>
<td>Collimation (on operator console)</td>
</tr>
<tr>
<td>Table incrementation (mm/rotation) - I</td>
</tr>
<tr>
<td>Pitch ([mm/rotation] /beam collimation) - I/NT</td>
</tr>
<tr>
<td>Table Speed (mm/second)</td>
</tr>
<tr>
<td>Scan Time (40 cm thorax)</td>
</tr>
<tr>
<td>Nominal Reconstructed Slice Width</td>
</tr>
<tr>
<td>Reconstruction Interval (^3)</td>
</tr>
<tr>
<td>Reconstruction Algorithm (^3)</td>
</tr>
<tr>
<td># Images/Data set (40 cm thorax)</td>
</tr>
<tr>
<td>CTDI(_\text{vol}) (Dose in mGy) (^4)</td>
</tr>
</tbody>
</table>

---

**NLST-ACRIN N Physics Committee**

- **CT Technique Chart**
  - Standardized 18 parameters
  - 14 different CT scanners
  - 4 manufacturers: 4-64 channel
- **Equipment certification annually**
- **Bi-monthly CT phantom calibration**
- **CXR techniques from CRFs reviewed**
Interpretation Results

- [−] Screen
  
  No significant findings – or – minimal findings not significant for lung cancer

- [−] Screen
  
  Significant findings unrelated to lung cancer
  
  [Some form of diagnostic recommendation required; e.g., echocardiogram for suspected pulmonary hypertension]

- [+] Screen
  
  Findings potentially related to lung cancer
  
  [diagnostic recommendation of some form required]
Non-calcified nodule(s)
Record slice #; lobe, diameters; margins, attenuation

Micronodules < 4 mm

Benign or calcified nodules

Other major findings:

- Atelectasis, segmental or greater
- Pleural thickening | effusion
- Hilar | mediastinal adenopathy
- Significant cardiovascular abnormality (CM, CAD, AV Ca++)
- Interstitial fibrosis
- Significant other findings above diaphragm
- Significant findings below diaphragm
1 Pure ground glass nodules can be followed-up at 6-12 months if < 10 mm.
2 Some nodules 4-10 mm may go directly to biopsy or other tests in ABNORMAL pathways.
3 No growth is defined as < 15% increase in overall diameter OR no ↑ in solid component.
ABNORMAL Pathways: Nodules >10 mm

- Biopsy: Percutaneous, Bronchoscopic, Thoracoscopic, Open

Solid, Mixed or GG Nodule >10 mm

- DCE-CT
- FDG-PET

- Low Dose TSCT at 3-4 Months¹

- Enhanced <15 HU
- Enhanced ≥15 HU
- ↑ Activity
- No ↑ Activity

- TSCT at 6-12 months
- Biopsy -OR- Definitive Management
- TSCT at 6-12 months

¹ Reserved for nodules considered highly likely to be BENIGN [polygonal shape, 3D shape ratio > 1.78]
WHAT’S THE RISK?

ASSUMING AN INCREMENTAL CANCER MORTALITY RISK OF 5% / Sv, AND A LINEAR, NO THRESHOLD, DOSE RELATIONSHIP, YIELDS

CXR @ 0.033 mSv = INCREMENTAL RISK OF 0.00017% (1/600,000)

CT @ 2.2 mSv = INCREMENTAL RISK OF 0.011% (1/9,000; 67/600,000)
Society of Thoracic Radiology
Physician Responsibility

- Discuss benefits and risks of spiral CT screening
- Warn the subject that a negative screen does not preclude development of lung cancer
- Ensure that the subject knows that some lung cancers may not be amenable to detection by CT screening
- Ensure that the subject is contacted with results of the CT screening
- Ensure that appropriate physicians are available to council and treat the patient with a positive result
- Ensure that patients understand the problem of the number of small lung nodules that are benign and the implications thereof.