All three authors have no conflicts of interest to declare.
Learning Objectives

1. Review the epidemiology of lung cancer.
2. Review the principles of screening programs.
3. Review the latest evidence for and against lung cancer CT screening, including the National Lung Screening Trial and other ongoing trials.
4. Review associated risks, limitations and implementation challenges of lung cancer screening.
Epidemiology

- Lung cancer is most significant cause of cancer-related death globally.
- 27% of all cancer-related death in US.
Epidemiology

- After an initial decline in incidence with public health successes in the 1980s and 90s, lung cancer is now on the rise.
- Mortality no longer declining in males.
- Mortality increasing in females.

Epidemiology

- Survival strongly dependent on early treatment.

Current Mean 5 Year Survival from Diagnosis = 15%
“Principles and Practice of Screening for Disease” (WHO, 1968)

In order for a screening program to be acceptable it must address a:

- Significant public health issue
- Treatable disease with defined practices on who to treat
- Disease with a latent stage where treatment can change outcomes and the progression is understood
- Disease that can be tested for

Additionally, testing must be:

- Acceptable (ie non/minimally invasive)
- Economically sensible
- Continuous, ongoing process
Past Screening Programs

- Chest X-ray (1-3x per year)
- Sputum cytology
- Combined chest X-ray and sputum cytology
Past Screening Programs

- Systematic review of 9 trials (8 RCTs) with 453,965 subjects looked at whether sputum cytology, CXR or CT screening affects lung cancer mortality.

- No significant mortality reduction when screening with chest x-ray and sputum cytology was compared with chest x-ray alone (RR 0.88, 95% CI: 0.74-1.03).

- PLCO trial annual CXR vs no CXR for 4 years (>150,000 participants, age 55-74, general population). No significant mortality reduction. (RR 1.05, 95% CI, 0.98-1.12).

- Conclusion: CXR and/or sputum cytology NOT recommended for screening.

National Lung Screening Trial

- NLST enrolled a high risk population of 53,454 current and former smokers.

- Inclusion criteria:
  - Age 55 to 74
  - >30 pack year history of smoking
  - Current smoker or quit within past 15 years

- Participants were randomized to annual screening with either low-dose helical CT or single-view chest radiograph for three years.

NLST Definition of Positive Findings

- For low-dose CT:
  - All non-calcified nodules with diameters >4 mm.

- For CXR:
  - All non-calcified nodules and masses.

- Radiologist overall opinion (ie hilar adenopathy, pleural disease).

(A) CT image showing ground-glass RUL nodule.
(B) 20 month followup progression to increasingly solid tumor.
(C) Adenocarcinoma on biopsy.

The study was stopped early at a mean follow-up time of 6.5 years.

Lung cancer mortality:
- CT arm 247 per 100,000 person-years
- CXR arm 309 per 100,000 person-years

Relative mortality benefit of 20.0% (95% CI, 6.8 to 26.7; P=0.004).

Ongoing Trials
NELSON Trial

- Dutch Belgian randomised lung cancer screening trial (NELSON).
- Only ongoing trial with sufficient power to detect mortality differences (n=15 822).
- RCT with population similar to NLST.
- Control arm receives usual care (ie no CXR).
- Intervention arm receives CT screen every 1.2 or 2.5 years.

NELSON Trial Registration http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=636
### Other Ongoing Trials

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Number of Patients</th>
<th>Comparison</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DANTE Trial</td>
<td>2472</td>
<td>Annual CT vs Usual Care</td>
<td>Ongoing (interim three year results showed no mortality difference)</td>
</tr>
<tr>
<td>Danish Lung Cancer Screening Trial (DLCST)</td>
<td>4104</td>
<td>Annual CT vs Usual Care</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Multi-centric Italian Lung Detection Trial (MILD)</td>
<td>4099</td>
<td>Annual CT vs Usual Care</td>
<td>Increased mortality in screening arm (low quality study due to inadequate randomization and differences in baseline characteristics)</td>
</tr>
</tbody>
</table>

Other Ongoing Trials

- A large pooled analysis of UKLS, NELSON, MILD, DLCST, ITALUNG, LUSI and DANTE is planned for 2015/16.

NELSON Trial Registration http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=636
Risks and Concerns
Reproducibility

- Academic vs community
- The NLST involved primarily academic centres with fellowship trained thoracic radiologists reading the screening CTs.
- Unknown if applicable on large scale in community hospitals with general radiologists.

False Positives

- False positives (20% after first screening CT, 30% after second).

- 7% of these false positives lead to need for percutaneous, thoracoscopic, open biopsies.

- Significant anxiety associated with false positives in other screening programs (not yet demonstrated for lung cancer screening).


Radiation Dose

- Continued advances in dose reduction allow for minimal radiation exposure (~1.5 mSv per screening CT).
- Potentially >20 years of annual chest CT
- Unclear potential risk for radiation-induced cancer.


Cost Efficacy

- No studies yet evaluate cost effectiveness in Canada’s public health care system.
- Studies in US forecast screening will be cost effective at <$19 000 (USD) per life-year saved.
- By comparison:
  - Biennial breast screening costs $18 999 (USD) per life-year saved
  - Colon cancer screening costs $11 900 (USD) per life-year saved


Some concerns whether effective screening and negative test results could paradoxically reassure smokers, reducing smoking cessation rate.

However, an analysis of current smokers in NELSON found screening had no impact on quit rate.

Organizations Endorsing CT Lung Screening

- American Cancer Society
- American College of Chest Physicians
- American Society of Clinical Oncology
- National Cancer Institute
- US Preventive Services Task Force
- CancerCare Ontario

Conclusion

- Lung cancer screening holds great promise in improving lung cancer mortality.
- Numerous ongoing trials should help to clarify the role of screening for lung cancer.
- It remains to be seen if and how such a program will be implemented in the Canadian setting on a provincial or national level.