Did death certificates and a mortality review committee agree on lung cancer cause of death in the National Lung Screening Trial?

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May 22, 2012
Cause of death in cancer screening RCTs

• Primary outcome in cancer screening RCTs is disease-specific mortality

• Accurate assignment of underlying cause of death (COD) is critical

• Two options for COD assignment
  – Mortality review committee (aka death review)
    • More resource-intensive but thought to be more accurate
  – Death certificates (DC)
    • Less resource-intensive but thought to be less accurate
Death review

• Most cancer screening RCTs have used some form of death review

• Is it worth the effort?

• Doria-Rose et al (Clin Trials, 2010)
  – Compared DCs to death review
  – Dichotomous* underlying COD for 4 cancer screening RCTs (lung (2), breast, colorectal)
  – Kappa >= 0.85 for all

*Example: lung cancer versus not lung cancer
National Lung Screening Trial (NLST)

• RCT of lung cancer screening with low dose CT versus chest x-ray
  – Heavy and/or long-term smokers
  – Significant 20% lung cancer mortality reduction

• Death review committee
  – 5 MDs, including an MD-epidemiologist
  – Members blinded to arm assignment
  – Determined whether underlying COD was lung cancer (versus not lung cancer)
Selection for death review

- Subset of deaths
- Selected by a pre-determined algorithm
Deaths selected for review by algorithm

- Deaths with any DC COD that were most likely to represent a death due to lung cancer (either directly or indirectly)
- Deaths that might have been erroneously assigned a DC lung cancer COD
- Deaths within six months of a screen suspicious for lung cancer
- Deaths within 60 days of certain lung cancer diagnostic evaluation procedures
Death review steps

Records only, no DC

With respect to LC dx (versus non-LC dx)
Analyses

• Gold standard: death review

• Outcome of interest: lung cancer COD
  – Versus COD other than lung cancer

• Performance characteristics of the death certificate COD assignment

• Re-ran final interim analysis
  – Published findings used best available information
  – Would use of DC data only change the conclusion of the study?
Agreement and kappa

<table>
<thead>
<tr>
<th>Death certificate</th>
<th>Lung cancer</th>
<th>Not lung cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>855 (52)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Not lung cancer</td>
<td>84 (5)</td>
<td>685 (42)</td>
</tr>
</tbody>
</table>

Agreement: 94%
Kappa: 87%

1643 (42% of all deaths)
### Performance characteristics

#### Death review

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- Sensitivity: 91%
- Specificity: 98%
- PPV: 98%
- NPV*: 89%

*DC appears to have missed 9% of lung cancer deaths (adverse effects of diagnosis or treatment?*)

Total deaths: 1643 (42% of all deaths)
## Difference by study arm?

<table>
<thead>
<tr>
<th></th>
<th>LDCT (n=825)</th>
<th>Chest x–ray (n=818)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agreement</td>
<td>0.94</td>
<td>0.93</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.89</td>
<td>0.86</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.92</td>
<td>0.91</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td>PPV</td>
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Lung cancer mortality reduction
(Final interim analysis)

<table>
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<tr>
<th>Best available information*</th>
<th>DC only</th>
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<tr>
<td><strong>20.0%</strong></td>
<td><strong>18.0%</strong></td>
</tr>
<tr>
<td>95% CI: 6.8-26.7</td>
<td>95% CI: 4.2-25.0</td>
</tr>
</tbody>
</table>

*Death review COD for those reviewed; DC COD for others
Limitations

• About 75% of deaths with a DC COD other than lung cancer (~2079) were not reviewed
  – COD was considered (by the algorithm) unlikely to have been in error with respect to lung cancer death
  – If these deaths had been reviewed and assigned a COD other than lung cancer:
    • Specificity would have been 99%
    • NPV would have been 97%
Limitations

• Generalizability of these findings is limited to lung cancer in persons who meet NLST eligibility criteria
Conclusion

• When assigning lung cancer COD among heavy/long-term smokers, death certificates provide sufficiently accurate information.
Acknowledgements

• My co-authors
  – Ilana F. Gareen, V. Paul Doria-Rose, Jennifer Rosenbaum, Kathy Clingan, Kristen Keating, Brenda Brewer, Heather Rozjabek, Joshua Rathmell, Tony Miller

• The Endpoint Verification Team
  – Tony Miller (Chair), Martin Edelman, Bill Evans, Bob Fontana, Mitch Machtay
Thank you!
DC lung cancer deaths reassigned to other COD by death review

• N=19

• Reassigned to:
  – Other malignancies: 8
  – Respiratory: 6
  – CVD: 3
  – Pneumonia: 1
  – Dementia: 1
DC non-lung-cancer deaths reassigned to lung cancer COD by death review

- N=84

- Reassigned to:
  - Other malignancies: 32
  - CVD: 22
  - Respiratory: 13
  - Other: 13
  - Complications of medical or surgical care: 3

- Pending at close of study: 1