Reanalysis of Radiation and Mesothelioma in the U.S. Transuranium and Uranium Registries

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“Learning from Plutonium and Uranium Workers”
Excess of mesothelioma deaths in the USTUR

"In general, no apparently elevated causes of death except for six cases of mesothelioma....."

"The mesothelioma cases had a documented occupational exposure to asbestos,......"

The Gibb study (Gibb et al. 2013, Am J Public Health. 103 (4): 710-716) examines 7 mesothelioma deaths among 329 deceased registrants in the USTUR.
The Gibb study error

• The Gibb study compares percentage of causes of deaths between the USTUR and the general population in the U.S., and suggests that external radiation at nuclear facilities is associated with an increased risk of mesothelioma.

• The study failed to recognize that the software performed calculations as if there were no mesothelioma deaths in the general population prior to 1999. (a new specific code for mesothelioma defined only in ICD-10).

• Six of seven mesothelioma cases were before 1999.

• The study made an error from the beginning, and its analysis on mesothelioma and radiation was wrong.

Reanalysis with a different approach

- Yes, there is an excess of mesothelioma cases in the USTUR and there are two more cases after the Gibb study (9 cases among 341 deceased registrants).
- Yes, the mean cumulative external radiation dose is higher for mesothelioma group than for other cancer and non-cancer groups.
- The reanalysis aims only to compare the group means statistically.
## Study group descriptions:
LC/lung cancer, OC/other cancer, NC/non-cancer

<table>
<thead>
<tr>
<th></th>
<th>Meso</th>
<th>LC</th>
<th>OC</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Death (range)</td>
<td>54 - 87</td>
<td>48 - 87</td>
<td>31 - 89</td>
<td>25 - 96</td>
</tr>
<tr>
<td>Employment Start (range)</td>
<td>1945 - 64</td>
<td>1942 - 82</td>
<td>1942 - 71</td>
<td>1941 - 83</td>
</tr>
<tr>
<td>Employment Duration (mean)</td>
<td>31.2</td>
<td>23.7</td>
<td>22.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Cumulative External Dose [mSv] (mean)</td>
<td>173.9</td>
<td>105.1</td>
<td>109.7</td>
<td>152.5</td>
</tr>
<tr>
<td>Group Size</td>
<td>9</td>
<td>31</td>
<td>62</td>
<td>185</td>
</tr>
</tbody>
</table>
Different composition of the study groups

• Mesothelioma group has the largest cumulative external radiation dose.

• However, the mesothelioma group tends to be older at the age of death, hired earlier and employed longer than other groups.

• Therefore, age at death, employment start and employment duration are potential factors associated with cumulative external radiation dose.

• Take home message: control
A matched case “control” approach

• A matched case control approach is used to reduce the group differences, so that the mean external radiation doses among groups can be compared.

• For each case of mesothelioma, controls were identified in LC, OC and NC groups matching:
  ✓ Employment duration (± 2.5 years)
  ✓ Employment start (± 5 years)
  ✓ Age at death (± 5 years)
  ✓ Birth year (± 5 years)
Effect of matching

Cumulative External Dose, mSv

- Before Matching
- After Matching

Mesothelioma  Lung Cancer  Other Cancers  Non-Cancers
A permutation paired t-test (PPTT)

• For each paired t-test, one of multiple (4 ~5) matching controls for each case is randomly selected.

• Repeat the procedure 10,000 times, so the inference is based on a large number of paired t-tests.

• 5% of the significant paired t-tests (p ≥ 0.05) is used as a critical level.

<table>
<thead>
<tr>
<th>Case #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meso Cases</td>
<td>294.1</td>
<td>31.6</td>
<td>29.7</td>
<td>426.2</td>
<td>191.7</td>
<td>80.1</td>
<td>126.9</td>
<td>366.1</td>
<td>18.7</td>
</tr>
<tr>
<td>NC control 1</td>
<td>45.9</td>
<td>29.1</td>
<td>161.4</td>
<td>186.6</td>
<td>314.1</td>
<td>41.3</td>
<td>141.4</td>
<td>44.1</td>
<td>521.4</td>
</tr>
<tr>
<td>NC control 2</td>
<td>127.0</td>
<td>131.6</td>
<td>104.1</td>
<td>159.0</td>
<td>61.3</td>
<td>82.0</td>
<td>11.4</td>
<td>230.9</td>
<td>10.4</td>
</tr>
<tr>
<td>NC control 3</td>
<td>39.4</td>
<td>456.3</td>
<td>107.3</td>
<td>384.8</td>
<td>9.2</td>
<td>55.5</td>
<td>141.4</td>
<td>141.4</td>
<td>19.2</td>
</tr>
<tr>
<td>NC control 4</td>
<td>36.5</td>
<td>137.2</td>
<td>133.8</td>
<td>316.5</td>
<td>710.9</td>
<td>209.2</td>
<td>11.4</td>
<td>9.9</td>
<td>39.0</td>
</tr>
<tr>
<td>NC control 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62.3</td>
<td>29.6</td>
<td>11.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results of PPTT

- PPTT was not significant
  - Meso vs. LC
  - Meso vs. OC
- PPTT was significant
  - Meso vs. NC

<table>
<thead>
<tr>
<th>Cumulative External Radiation Dose (mSv)</th>
<th>% of significant Paired t-tests (10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meso vs. LC</td>
<td>0.0</td>
</tr>
<tr>
<td>Meso vs. OC</td>
<td>0.2</td>
</tr>
<tr>
<td>Meso vs. NC</td>
<td>9.0*</td>
</tr>
</tbody>
</table>
Conclusion

• The reanalysis finds that mean cumulative external radiation dose in mesothelioma group is statistically higher than non-cancer group.

• A follow-up conditional logistic regression for the mesothelioma and non-cancer groups shows no association between external radiation and mesothelioma. (results not presented here)

• The reanalysis makes no inference about the U.S. nuclear workers, as the Gibb study did, because the USTUR registrants are not representative of nuclear workers.
Key point of emphasis

• “It is to be emphasized that the present USTR is not an epidemiology study.” (Observation and recommendation of the SAC in November 1979);

• The USTR “does not seek to measure mortality rates for specific diseases in transuranic workers.” (USTR Annual Report, 1982);

• “The use of USTR data for this purpose is scientifically inappropriate and misleading.” (USTR Annual Report, 1983)