Lung Cancer and Indoor Air Pollution in Xuan Wei, China: Exposure Assessment, Etiology, and Intervention

Roel Vermeulen, PhD
IRAS, Environmental Epidemiology Division
Utrecht University, the Netherlands

Julius Center, Health Sciences and Primary Care
University Medical Center Utrecht, The Netherlands
Indoor Air Pollution to Solid Fuels

• Half of the world’s population is exposed to smoke from cooking or heating with solid fuels

• Indoor air pollution from solid fuel use → the eighth largest risk factor for global disease (2nd environmental factor)
National Household Solid Fuel Use, 2000

- Low income countries:
  - Female: 4.0
  - Males: 6.0E-3
  - DALYs (millions): 16
- Middle income countries:
  - Female: 3.5
  - Males: 4.3E-3
  - DALYs (millions): 17
- High income countries:
  - Female: 6.0E-3
  - Males: 4.3E-3
  - DALYs (millions): 4.0

DALYs (millions) range from 0 to 20.
Xuan Wei; A special case of solid fuel exposure
Lung Cancer Mortality Rates in Xuanwei are among the Highest in China

Xuan Wei County

County-specific lung cancer mortality rates (per 100,000, 1973-75)
Xuanwei

- Rural county
- Semi-mountainous region of Yunnan Province
- >90% of the population are farmers
- Very stable population
- <0.1% of females smoke
- >70% of males smoke
Risk estimates of lung cancer associated with household coal use

Hosgood et al., 2011
What is special about Xuan Wei?

- Type of coal?
- Type of stoves?
- Population?
Lung cancer mortality in XW

- Associated with “smoky coal”
  - Bituminous coal
  - So-called for the smoke released upon combustion

- Formed at permian-triassic boundary
  - Permian extinction event

- Smokeless coal
  - Anthracite coal

<table>
<thead>
<tr>
<th>Sex and smoking status</th>
<th>Smoky Coal</th>
<th>Smokeless Coal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>450</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(355 to 545)</td>
<td></td>
</tr>
<tr>
<td>Ever smoked</td>
<td>488</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>(459 to 518)</td>
<td>(5.7 to 21.1)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>527</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>(496 to 558)</td>
<td>(1.0 to 9.4)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Deaths from lung cancer among individuals ages less than 70 years in Xuanwei cohort 1976-96, stratified by type of coal used, sex, and smoking habit (Baron-Adesi et al. 2012)

*Age standardised mortality per 100,000 person years. The age structure of the group of smokeless coal users (n=9962) was used as the standard population.
Variation within smoky coal users
What is special about XuanWei?

- Type of coal ✔
- Type of stoves? ✗
- Population?
Primary hypotheses regarding lung cancer

- PAH hypothesis
  - Multiple recognized carcinogens
  - High personal exposure observed among smoky coal users

- Quartz hypothesis
  - Recognized carcinogen
  - Identified in coal samples
  - Personal exposure unknown

- Interaction between individual components?

Coal Analyses

- Coal samples collected directly from the homes of participants

- 116 smoky
  - 63 Xuanwei
  - 51 Fuyuan

- 29 smokeless
  - 7 Xuanwei
  - 22 Fuyuan

Downward et al., 2014
Hydrocarbon release of Coal

- Clear difference between smoky and smokeless coals
- Base differences in hydrocarbon material as would be expected when comparing bituminous to anthracite coal

<table>
<thead>
<tr>
<th>Major Coal Type</th>
<th>N</th>
<th>S1 (mgHC/g coal)</th>
<th>S2 (mgHC/g coal)</th>
<th>Tmax (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoky</td>
<td>116</td>
<td>2.2*</td>
<td>71.5*</td>
<td>460*</td>
</tr>
<tr>
<td>Smokeless</td>
<td>29</td>
<td>0.3</td>
<td>8.4</td>
<td>581</td>
</tr>
</tbody>
</table>
## Hydrocarbon release of Smoky Coal

<table>
<thead>
<tr>
<th>County</th>
<th>Coal Sup-type</th>
<th>Coal Mine</th>
<th>N</th>
<th>S1 (mgHC/g coal)</th>
<th>S2 (mgHC/g coal)</th>
<th>Tmax (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xuanwei</td>
<td>Coking Coal</td>
<td></td>
<td>65</td>
<td>2.35</td>
<td>73.24</td>
<td>462</td>
</tr>
<tr>
<td>Azhi</td>
<td></td>
<td></td>
<td>15</td>
<td>2.34*</td>
<td>73.24*</td>
<td>462*</td>
</tr>
<tr>
<td>Baoshan</td>
<td></td>
<td></td>
<td>5</td>
<td>2.24</td>
<td>61.59</td>
<td>463</td>
</tr>
<tr>
<td>Laibin</td>
<td></td>
<td></td>
<td>14</td>
<td>2.23</td>
<td>76.14</td>
<td>460</td>
</tr>
<tr>
<td>TangTang</td>
<td></td>
<td></td>
<td>22</td>
<td>1.62</td>
<td>61.98</td>
<td>464</td>
</tr>
<tr>
<td>Yangchang</td>
<td></td>
<td></td>
<td>7</td>
<td>4.03</td>
<td>138.69</td>
<td>443</td>
</tr>
<tr>
<td>Fuyuan</td>
<td>Coking Coal</td>
<td></td>
<td>51</td>
<td>1.95</td>
<td>68.86+</td>
<td>452+</td>
</tr>
<tr>
<td>Daping</td>
<td></td>
<td></td>
<td>4</td>
<td>2.34</td>
<td>33.9</td>
<td>458.5</td>
</tr>
<tr>
<td>Enhong</td>
<td></td>
<td></td>
<td>4</td>
<td>1.73</td>
<td>40.53</td>
<td>469.5</td>
</tr>
<tr>
<td>Haidan</td>
<td></td>
<td></td>
<td>6</td>
<td>1.78</td>
<td>46.75</td>
<td>468</td>
</tr>
<tr>
<td>Zude</td>
<td></td>
<td></td>
<td>1</td>
<td>4.21</td>
<td>61.02</td>
<td>473</td>
</tr>
<tr>
<td>1/3 Coking</td>
<td></td>
<td></td>
<td>8</td>
<td>1.98</td>
<td>52.35</td>
<td>459*</td>
</tr>
<tr>
<td>Bagong</td>
<td></td>
<td></td>
<td>5</td>
<td>1.7</td>
<td>47.19</td>
<td>465</td>
</tr>
<tr>
<td>Dahe</td>
<td></td>
<td></td>
<td>3</td>
<td>3.08</td>
<td>80.18</td>
<td>445</td>
</tr>
<tr>
<td>Gas Fat</td>
<td></td>
<td></td>
<td>23</td>
<td>1.97</td>
<td>131.87</td>
<td>433</td>
</tr>
<tr>
<td>Housuo</td>
<td></td>
<td></td>
<td>20</td>
<td>2.03</td>
<td>138.44</td>
<td>433.5</td>
</tr>
<tr>
<td>Qingyun</td>
<td></td>
<td></td>
<td>3</td>
<td>1.62</td>
<td>110.4</td>
<td>431</td>
</tr>
<tr>
<td>Meagre Lean</td>
<td></td>
<td>Gumu</td>
<td>1</td>
<td>3.83</td>
<td>53.43</td>
<td>469</td>
</tr>
</tbody>
</table>
Quartz contents coal

- SEM reveals elevated quartz in smoky coal compared to smokeless coal
- Including quartz of size <9.6µm (respirable fraction)

<table>
<thead>
<tr>
<th>Coal Type</th>
<th>N</th>
<th>Total Quartz (% of coal)</th>
<th>Respirable Quartz (% of coal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoky</td>
<td>19</td>
<td>4.58*</td>
<td>1.92*</td>
</tr>
<tr>
<td>Smokeless</td>
<td>6</td>
<td>2.24</td>
<td>0.6</td>
</tr>
</tbody>
</table>
## PAH exposure in air (ng/m$^3$)

<table>
<thead>
<tr>
<th></th>
<th>Smoky coal</th>
<th></th>
<th>Smokeless coal</th>
<th></th>
<th>Wood</th>
<th></th>
<th>Plant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM</td>
<td>GM</td>
<td>GSD</td>
<td>AM</td>
<td>GM</td>
<td>GSD</td>
<td>AM</td>
</tr>
<tr>
<td>Smoky Coal</td>
<td>74.4</td>
<td>44.8</td>
<td>2.7</td>
<td>15.1</td>
<td>10.5*</td>
<td>2.5</td>
<td>66.6</td>
</tr>
<tr>
<td></td>
<td>50.2</td>
<td>38.1</td>
<td>2.1</td>
<td>5.6</td>
<td>5.5</td>
<td>1.3</td>
<td>73.4</td>
</tr>
<tr>
<td></td>
<td>224.5</td>
<td>160.3</td>
<td>2.4</td>
<td>13.8</td>
<td>9.3*</td>
<td>2.7</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>41.5</td>
<td>31.5</td>
<td>2.2</td>
<td>19.3</td>
<td>14.2</td>
<td>2.4</td>
<td>78.4</td>
</tr>
<tr>
<td>Portable Stove</td>
<td>186.4</td>
<td>151.5†</td>
<td>2.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50.2</td>
</tr>
<tr>
<td></td>
<td>85.7</td>
<td>48.9</td>
<td>3.1</td>
<td>10.6</td>
<td>-</td>
<td>-</td>
<td>159.5</td>
</tr>
<tr>
<td>Unventilated Stove</td>
<td>13.2</td>
<td>7.7</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
| Downward et al., Submitted

Downward et al., Submitted

Universiteit Utrecht
Quartz in indoor air

<table>
<thead>
<tr>
<th>Fuel Type</th>
<th>% Detects(n)</th>
<th>% Non-detects(n)</th>
<th>Total n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoky Coal</td>
<td>14% (11)</td>
<td>86% (69)</td>
<td>80</td>
</tr>
<tr>
<td>Smokeless Coal</td>
<td>0% (0)</td>
<td>100% (17)</td>
<td>17</td>
</tr>
<tr>
<td>Other Coal</td>
<td>12% (2)</td>
<td>88% (15)</td>
<td>17</td>
</tr>
<tr>
<td>Wood</td>
<td>11% (1)</td>
<td>89% (8)</td>
<td>9</td>
</tr>
<tr>
<td>Plant</td>
<td>20% (1)</td>
<td>80% (4)</td>
<td>5</td>
</tr>
<tr>
<td>Other Fuel</td>
<td>10% (3)</td>
<td>90% (27)</td>
<td>30</td>
</tr>
</tbody>
</table>

LOD 0.2μg/m³

- Quartz in the coal ends up in the non-respirable fraction of the ash

Downward et al., submitted
Key Pathways in B(a)P Metabolism

Benzo(a)pyrene

\[ \text{B(a)P epoxide} \xrightarrow{\text{CYP1A1, 1A2, 1B1, 3A4, 2C}} \]

\[ \text{B(a)P diol} \xrightarrow{\text{mEH}} \]

\[ \text{B(a)P diolepoxide} \xrightarrow{\text{GSTM1}} \]

Detoxification

\[ \text{B(a)P diolepoxide} \xrightarrow{\text{UGT2B7}} \]

DNA Adduct, repaired by NER pathway

Detoxification

\[ \text{CYP1A1, 1A2, 1B1; MPO} \]

\[ \text{NQO1} \]

\[ \text{O2} \]

\[ \text{ROS} \]

\[ \text{OGG1} \]

Detoxification

Causes oxidative damage, repaired by BER, DSB pathways

Detoxification

\[ \text{UGT1A6} \]
GSTM1 Null Genotype

- **GSTM1** null genotype $\rightarrow$ lack of GSTM1 enzyme activity

- Results in decreased detoxification of PAH metabolites
### GSTM1 Genotype and Lung Cancer Risk

<table>
<thead>
<tr>
<th>GSTM1</th>
<th>Case N (%)</th>
<th>Control N (%)</th>
<th>OR(^a) (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>40(32.8)</td>
<td>62(49.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Null</td>
<td>82(67.2)</td>
<td>60(50.8)</td>
<td>2.3 (1.3-4.2)</td>
</tr>
</tbody>
</table>

\(^a\) ORs and 95% CIs adjusted for total smoky coal use without ventilation, pack-years, COPD, and family history of lung cancer by multiple conditional logistic regression.

Lan et al., 2000 CEBP
Aldo-keto Reductase Family 1, Member C3 (AKR1C3 Gln5His)

- AKR1C3-Gln5His polymorphism (Exon 1)
- Produces a change from glutamine → histidine
- A shift from a neutral to a basic amino acid
# AKR1C3-Gln5His Polymorphism and Lung Cancer Risk

Lan et al., 2004 Carcinogenesis

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Case N (%)</th>
<th>Controls N (%)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>His/His + His/Gln</td>
<td>22 (19)</td>
<td>33 (29)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>94 (81)</td>
<td>79 (71)</td>
<td>1.8 (1.0-3.5)</td>
</tr>
</tbody>
</table>
**OGG1 (Oxoguanine glycosylase 1)**

Ser326Cys polymorphism

- OGG1 repairs 8-oxo-7,8-dihydroguanine (8oxoG)
- **OGG1 Ser326Cys polymorphism (Exon 6)**
- Repair activity of OGG1-Ser326 has been shown to be > OGG1-Cys326
**OGG1 Ser326Cys Polymorphism and Lung Cancer Risk**

<table>
<thead>
<tr>
<th>OGG1 Genotype</th>
<th>Case N (%)</th>
<th>Control N (%)</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ser/Ser</td>
<td>37 (31)</td>
<td>51 (47)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ser/Cys +Cys/Cys</td>
<td>81 (69)</td>
<td>58 (53)</td>
<td>1.9 (1.1-3.3)</td>
</tr>
</tbody>
</table>

ORs and 95%CIs obtained by logistic regression analysis adjusted for age, sex, pack-year of smoking.

Lan et al., 2004
Carcinogenesis
Primary hypotheses regarding lung cancer

- PAH hypothesis
  - Multiple recognized carcinogens
  - High personal exposure observed among smoky coal users
  - Gene-environment interaction with key genes in BaP metabolism

  - Exposures however not high enough to explain the high excess risks?
    - Armstrong and Gibbs derived a ERC curve for BaP exposure and lung cancer among coke oven workers, which predicted a relative risk of 2.68 at 100 μg/m3 BaP years using a power risk-curve -> RR ~ 8

Open questions

• Causative agent: organic fraction of smoky coal

• Agent/Agent interactions?

• Timing of exposure?

![Graph showing hazard ratio versus age at starting cooking](chart.png)
Engineering Interventions to Reduce Health Burden from Household Solid Fuel Use

- **Ventilation changes**
  - Chimneys on stoves
  - Placement of stoves outside
  - Improved home ventilation

- **Stoves changes**
  - Using existing biomass fuels, e.g., “gasifier” stoves
  - Using processed biomass, e.g., pellet stoves
  - Improve efficiency

- **Fuel Changes**
Stove improvement programs

• Stove improvement programs were implemented in the mid-eighties

Fire pit  Portable stove  Vented stoves
## Reduction in IAP exposure

<table>
<thead>
<tr>
<th></th>
<th>Smoky coal</th>
<th></th>
<th></th>
<th>Smokeless coal</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM</td>
<td>GM</td>
<td>GSD</td>
<td>AM</td>
<td>GM</td>
<td>GSD</td>
</tr>
<tr>
<td>Smoky Coal</td>
<td>74.4</td>
<td>44.8</td>
<td>2.7</td>
<td>15.1</td>
<td>10.5*</td>
<td>2.5</td>
</tr>
<tr>
<td>Ventilated Stove</td>
<td>50.2</td>
<td>38.1</td>
<td>2.1</td>
<td>5.6</td>
<td>5.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Unventilated Stove</td>
<td>224.5</td>
<td>160.3</td>
<td>2.4</td>
<td>13.8</td>
<td>9.3*</td>
<td>2.7</td>
</tr>
<tr>
<td>Portable Stove</td>
<td>41.5</td>
<td>31.5</td>
<td>2.2</td>
<td>19.3</td>
<td>14.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Firepit</td>
<td>186.4</td>
<td>151.5†</td>
<td>2.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mixed Ventilation</td>
<td>85.7</td>
<td>48.9</td>
<td>3.1</td>
<td>10.6</td>
<td>10.6</td>
<td>-</td>
</tr>
<tr>
<td>Unknown</td>
<td>13.2</td>
<td>7.7</td>
<td>3.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Stove Improvement and Lung Cancer in Xuanwei, China
Product-limit survival plot – Probability of not having lung cancer

Vented stoves

Males

\[ P < 0.001 \]

Females

\[ P < 0.001 \]

Portable stoves

Lan et al., 2002 J Natl Cancer Inst.

Hosgood et al., 2008
Initiation of a New Hospital-Based Case-Control of Lung Cancer among Nonsmoking Women (2006-2008)

- Enroll 1000 newly diagnosed non-smoking female cases and 1000 female controls
- Biological sample collection: collect blood, sputum, buccal cells
- Questionnaire collects extensive information on lifetime exposure to smoky coal and potential confounders
- Detailed exposure assessment in 140 households (36 villages)
  - Personal
  - Stationary

Hospitals for the new case-controls study:

- Xuan Wei Hospital
- Fu Yuan Hospital
- Qu Jing Hospital I
- Qu Jing Hospital II
Collaborators

China CDC: Xingzhou He

China EPA: Fusheng Wei

U.S. EPA: Robert Chapman, Judy Mumford

University of Utrecht: Boris Reiss, Kees Meliefste, George Downward

UC Berkeley: Kathy Hammond

Chinese University of Hong Kong: Linwei Tian

U.S. NCI: Qing Lan, Min Shen, Nat Rothman, Neil Caporaso, Aaron Blair, Jay Lubin, Michael Alavanja, Stephen Chanock