Background: Indoor Air Pollution to Solid Fuels

- Half of the world’s population is exposed to smoke from cooking or heating with solid fuels.
- 800 million people still use coal in their homes.
- Indoor air pollution from solid fuel use → the eighth largest risk factor for global disease.

Coal:
- For cooking and heating in China
- For generating electricity in many countries
Lung Cancer Mortality Rates in Xuanwei Are Among the Highest in China

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

- Rural county
- Semi-mountainous region
- Very stable population
- < 0.1% of females smoke
- > 70% of males smoke
Commune Specific Lung Cancer Mortality Rates, Xuanwei County (per 100,000, 1973-75)
Unique Opportunity for Investigating Lung Cancer and Indoor Air Pollution

- Wide range of lung cancer mortality rates across Xuanwei communes
- Very stable population with life-time exposure to smoky coal
Indoor Air Pollution to Solid Fuels, Genetic Susceptibility, and Lung Cancer in Xuanwei, China

- **Initial work**
  - Impact of intervention (stove improvement) on lung cancer risk *(cohort study)*
  - Coal type and lung cancer *(case-control study)*
  - Impact of genetic variation lung cancer risk and potential interactions with smoky coal and PAH exposure *(molecular case-control study)*

- **New Case-control study**
Fire pits replaced with chimney stoves → reduced exposure to coal combustion

Did reduced exposure to coal combustion reduce risk of lung cancer and chronic obstructive pulmonary disease (COPD)?
Retrospective Cohort Study

Goal: To test whether incidence rates of lung cancer and COPD decreased in subjects using coal who changed from a fire pit to a chimney stove.

Birth period  Follow-up period

1917           1951           1976           1992

43,000 subjects
1,900 lung cancer cases
2,700 COPD cases
# Lung Cancer Risk by Stove Improvement

<table>
<thead>
<tr>
<th>Stove improvement</th>
<th>Males RR (95% CI)</th>
<th>P Value</th>
<th>Females RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stove improvement</td>
<td>1.00 ---</td>
<td>1.00 ---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changed to chimney stove</td>
<td>0.59 (0.49-0.71)</td>
<td>&lt;.001</td>
<td>0.54 (0.44-0.65)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Lan et al., 2002 J Natl Cancer Inst.
## COPD Risk by Stove Improvement

<table>
<thead>
<tr>
<th>Stove improvement</th>
<th>Males RR (95% CI)</th>
<th>P Value</th>
<th>Females RR (95% CI)</th>
<th>P Value</th>
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<tr>
<td>No stove improvement</td>
<td>1.00 ---</td>
<td></td>
<td>1.00 ---</td>
<td></td>
</tr>
<tr>
<td>Changed to chimney stove</td>
<td><strong>0.58 (0.49-0.70)</strong></td>
<td>&lt;.001</td>
<td><strong>0.75 (0.62-0.92)</strong></td>
<td>.005</td>
</tr>
</tbody>
</table>

Chapman et al., 2005 BMJ
Indoor Airborne Concentrations of Particulate Matter (PM10) and Benzo(a)pyrene (BaP) by Stove Type Xuanwei

Lan et al., 2002 J Natl Cancer Inst.
Conclusion

- Strong evidence of a causal association between smoky coal exposure and lung cancer and COPD risk

- First evidence of the health benefits of stove improvement in households using coal or biomass fuel
Coal Type Matters

- Cohort study evaluated lung cancer risk from only one type of coal (Lai Bin coal)

- Many other types of coal are used, but risk for coal type has not been quantified

- Wide variation in risk by coal type → wide variation in exposure to PAHs
Population-based Case-control Study

Goal: To evaluate the association between coal type and lung cancer risk

- Population-based case-control study carried out 1985-1990
- 498 incident cases, 498 individually-matched on age, sex to controls
- Participation rates > 95% for cases and controls
Odds Ratios of Lung Cancer and Coal Type

*P for heterogeneity = 5.2x10^{-10}*

Adjusted for age, sex, literacy, lung cancer in first-degree relatives, hours spent at home per day, lung disease history, smoking, and passive smoke exposure history.

Lan et al., 2008, Int J of Cancer
Conclusion

- First etiologic study lung cancer risk varies markedly by coal type.
- Limited air monitoring data emissions from coal with the highest lung cancer risk had the highest PAH levels.
PAH Exposure, Genetic Susceptibility, and Lung Cancer

- Evidence indicates that PAHs are the key agents in the pathogenesis of lung cancer

- Substantial genetic variation in genes that activate and detoxify PAHs and repair DNA damage play key role in Xuanwei
Molecular Epidemiology Case-Control Study

- Population-based case-control study, carried out in 1995-96
- 122 incident lung cancer cases and 122 controls individually matched on age and sex
- Participation rates > 95% in cases and controls
- Collected buccal cell and sputum samples
- First epidemiologic study collected biologic samples in this region
Key Pathways in Benzo(a)pyrene Metabolism

Benzo(a)pyrene (a key PAH)

\[ \text{CYP1A1, 1A2, 1B1, } \]
\[ \text{3A4, 2C} \]

\[ \text{B(a)P epoxide} \]
\[ \rightarrow \]
\[ \text{GSTM1} \]
\[ \text{mEH} \]

\[ \text{B(a)P diol} \]
\[ \rightarrow \]
\[ \text{UGT1A6} \]
\[ \text{S-Q} \]
\[ \text{ROS} \]
\[ \text{O}_2 \]
\[ \text{Quinones} \]

\[ \text{CYP1A1, 1A2, 1B1; MPO} \]
\[ \text{NQO1} \]

\[ \text{AKR1C3} \]

\[ \text{Detoxification} \]

\[ \text{DNA Adduct, repaired by NER pathway} \]

\[ \text{Detoxification} \]

\[ \text{OGG1} \]

\[ \text{Catechol} \]

\[ \text{Detoxification} \]

\[ \text{Detoxification} \]

\[ \text{Causes oxidative damage, repaired by BER, DSB pathways} \]
GSTM1 null, AKR1C3 (Ex1-70C>G), and OGG1 (Ex6-315C>G) Genotypes and Lung Cancer Risk

![Graph showing odds ratios for GSTM1, AKR1C3, and OGG1 genotypes.](Lan et al., 2004 Carcinogenesis)
### AKR1C3, OGG1, and GSTM1 Genotypes and Lung Cancer Risk, by Sex and Level of Smoky Coal Use

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Females</th>
<th></th>
<th>Males</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Smoky coal use (tons)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;130</td>
<td>&gt;=130</td>
<td>&lt;130</td>
</tr>
<tr>
<td><strong>AKR1C3 (Ex1-70C&gt;G)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG vs CC+GC</td>
<td>1.00</td>
<td>12.9 (2.2-107.8)</td>
<td>1.5</td>
<td>0.9 (0.2-5.0)</td>
</tr>
<tr>
<td></td>
<td>(0.2-5.8)</td>
<td></td>
<td>(0.5-4.4)</td>
<td></td>
</tr>
<tr>
<td><strong>OGG1 (Ex6-315C&gt;G)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG+GC vs CC</td>
<td>1.3</td>
<td>5.7 (1.1-34.2)</td>
<td>1.1</td>
<td>2.0 (0.7-5.6)</td>
</tr>
<tr>
<td></td>
<td>(0.3-5.3)</td>
<td></td>
<td>(0.5-2.9)</td>
<td></td>
</tr>
<tr>
<td><strong>GSTM1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Null vs positive</td>
<td>2.2</td>
<td>4.9 (1.3-18.2)</td>
<td>1.5</td>
<td>2.7 (1.0-7.4)</td>
</tr>
<tr>
<td></td>
<td>(0.5-9.3)</td>
<td></td>
<td>(0.6-3.7)</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, pack-year of smoking (for males only)

Lan et al., 2004 Carcinogenesis
Gene-Environment Interaction: 
\( \text{GSTM1} \) and Smoky Coal Exposure

- Average lifetime exposure: 200 tons
- \( \text{GSTM1} \)-positive subjects: 1.2-fold per 100 tons
- \( \text{GSTM1} \)-null genotype subjects: 2.4-fold per 100 tons
- Multiplicative interaction, \( P = 0.05 \)
### GSTM1 Genotype and Lung Cancer in Asian Populations with Indoor Exposure to Coal Combustion Products: A Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lan, 2000</td>
<td>2.12 (1.26,3.56)</td>
<td>22.9</td>
</tr>
<tr>
<td>Chen, 2006</td>
<td>1.97 (1.20,3.23)</td>
<td>24.7</td>
</tr>
<tr>
<td>Wang, 2003</td>
<td>1.58 (0.93,2.66)</td>
<td>22.6</td>
</tr>
<tr>
<td>Yang, 2004</td>
<td>1.18 (0.76,1.84)</td>
<td>29.8</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.64 (1.25-2.14)</td>
<td></td>
</tr>
</tbody>
</table>

560 cases and 635 controls

Hosgood et al., 2007 Mutat Res.
Conclusions of Initial Xuanwei Lung Cancer Studies

- Smoky coal with high levels of PAH is the main cause of lung cancer
- Variants in genes involved in activation and detoxification of PAHs may modify the smoky coal-lung cancer association, particularly in women
Impact of Research Findings

- WHO IARC monograph Volume 95 (2006)
  Classified indoor emissions from household combustion of coal as “carcinogenic to humans - Group 1”

- WHO IARC monograph Volume 100E (2009)
  Combustion of coal reaffirmed as carcinogenic to humans

- Findings being used to develop international WHO Guidelines for Indoor Air Quality and to support improved home ventilation and replacement of coal with cleaner sources of heating and cooking
Unanswered Questions

- What is the dose-response relationship between PAH exposure and lung cancer risk?
- What is the role of genetic susceptibility for lung cancer risk overall and as a modifier of the PAH association?
New Hospital-Based Case-Control of Lung Cancer among Never Smoking Women (2006-2009)

- 750 newly diagnosed never smoking female cases
  750 female controls

- Biological sample collection of blood, sputum, buccal cells

- Questionnaire collects extensive information on lifetime exposure to smoky coal, potential confounders
Exposure Assessment Study

- **Goal:** To characterize indoor exposure to key components of coal combustion products in a sample of 150 households at two times in a year.

- **Measure**
  - Personal and area air PM2.5 and PAHs, dermal and dietary PAH exposures
  - Co-exposures (e.g., metals, nitro-PAHs)

Background air monitoring

Personal air monitoring

Dermal exposure monitoring

Household coal measurement
Planned Analysis of Lung Cancer among Never Smoking Women in Xuanwei

- Estimate exposure to PAHs and particulates
- Genotype SNPs in key genes important for PAH metabolism and DNA repair and for lung cancer etiology
- Analyze main effects of PAH exposure and co-exposures and interactions with genetic variants
Unanswered Questions

- Relatively modest sample size
  - Broad analysis of genetic variants
  - Detecting small gene-environment interactions

- Generalizability of genetic susceptibility findings?

Genetic Susceptibility

Coal-induced lung cancer among non-smoking women

Lung cancer among non-smoking women without distinct environmental exposures
Project to Assess Etiology of Lung Cancer among Never Smoking Females in Asia

- Consortium of lung cancer studies of never smoking females in Asia
  - 6 studies in China
  - 4 studies in Korea
  - 2 studies in Taiwan
  - 1 study in Japan
  - 1 study in Singapore
  - A total of 6,000 never smoking female lung cancer cases and 6,000 controls among never smoking females
- About 50% have used coal before for cooking and heating
Project to Assess Etiology of Lung Cancer among Never Smoking Females in Asia

- Analyze risk of lung cancer for coal and other environmental carcinogens
  - Environmental tobacco smoke
  - Cooking fumes

- Genome-wide scan → genetic variants that further our understanding of the relationship between
  - Coal exposure
  - Other sources of indoor air pollution
  - Lung cancer
Indoor Air Pollution from Coal Combustion

- Data will be used to better estimate dose-response relationship between coal use, other sources of indoor pollution, and risk of lung cancer among nonsmokers overall and susceptible subgroups of the population.

- Findings should help further develop environmental regulatory policy to reduce burden of lung cancer from environmental exposures.
Collaborators

China CDC: Xingzhou He, Linwei Tian
China EPA: Fusheng Wei
U.S. EPA: Robert Chapman, Judy Mumford
Boston University: Avi Spira
University of Utah: Richard Cawthon
Vanderbilt University: William Pao, Wei Zheng
Memorial Sloan-Kettering Cancer Center: Robert Klein
UC Berkeley: Kathy Hammond, Steve Rappaport
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China Medical University, China: Baoshen Zhou
Tongji Medical University, China: Tangchun Wu
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Kyungpook National University, South Korea: Jae Yong Park
Korea University College of Medicine, South Korea: Yeul Hong Kim

In occupational and environmental epidemiology, what should be the role of NCI in -

• Responding to Congressional and other mandates, and in tackling controversial issues?

• Launching international studies that provide unique opportunities for research (natural experiments)?

• The risk assessment process vis-à-vis other federal agencies?