National Cancer Institute

National Cancer Advisory Board

Indoor Air Pollution from Coal Combustion and Lung Cancer

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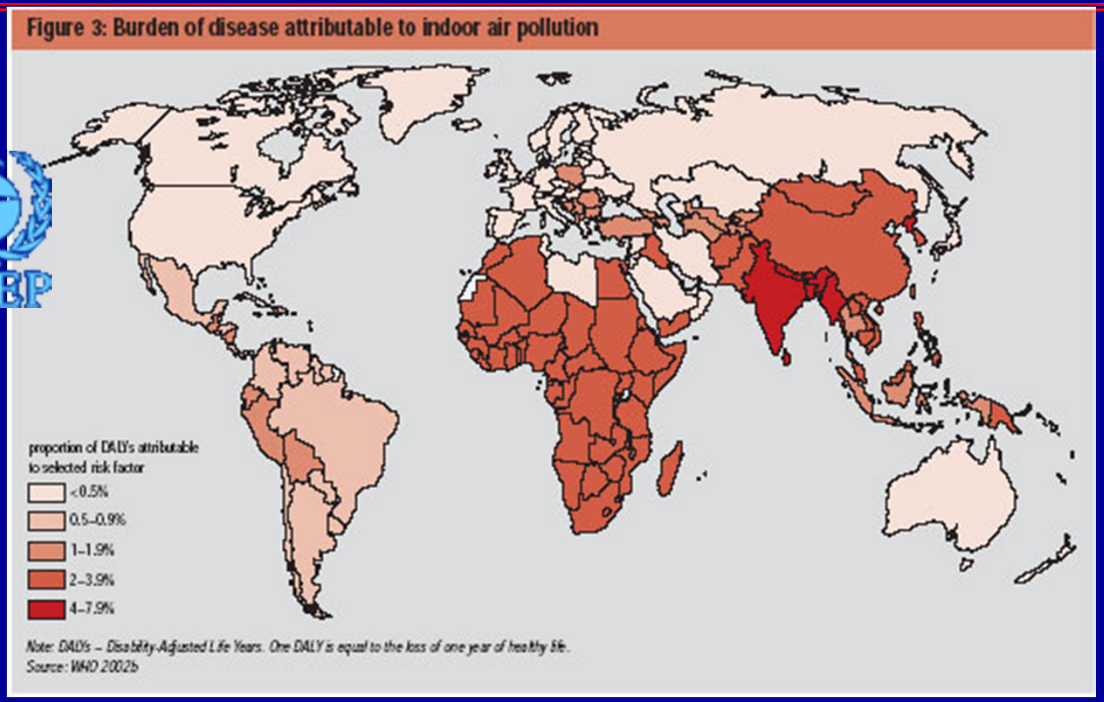
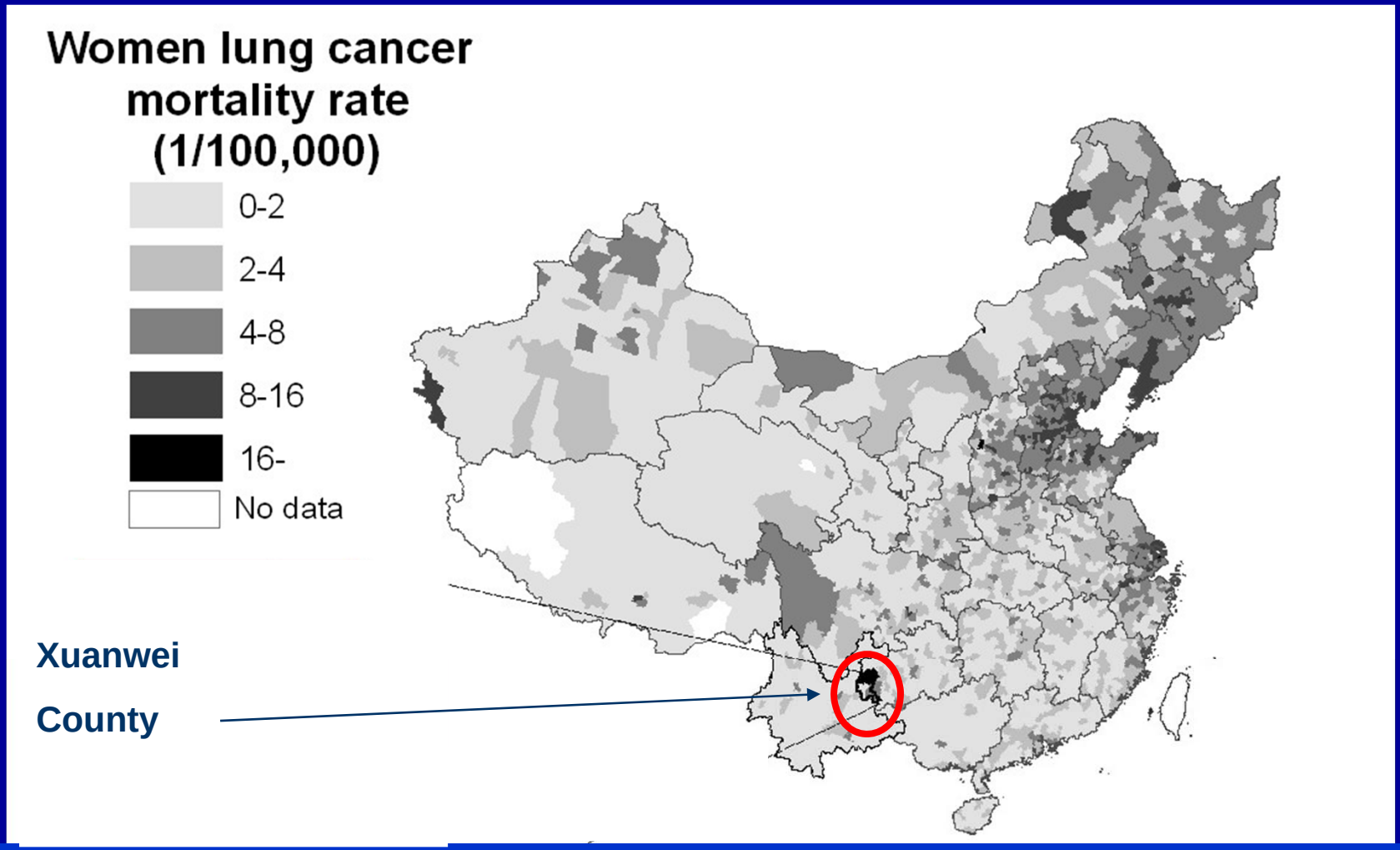
Background: Indoor Air Pollution to Solid Fuels



- 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

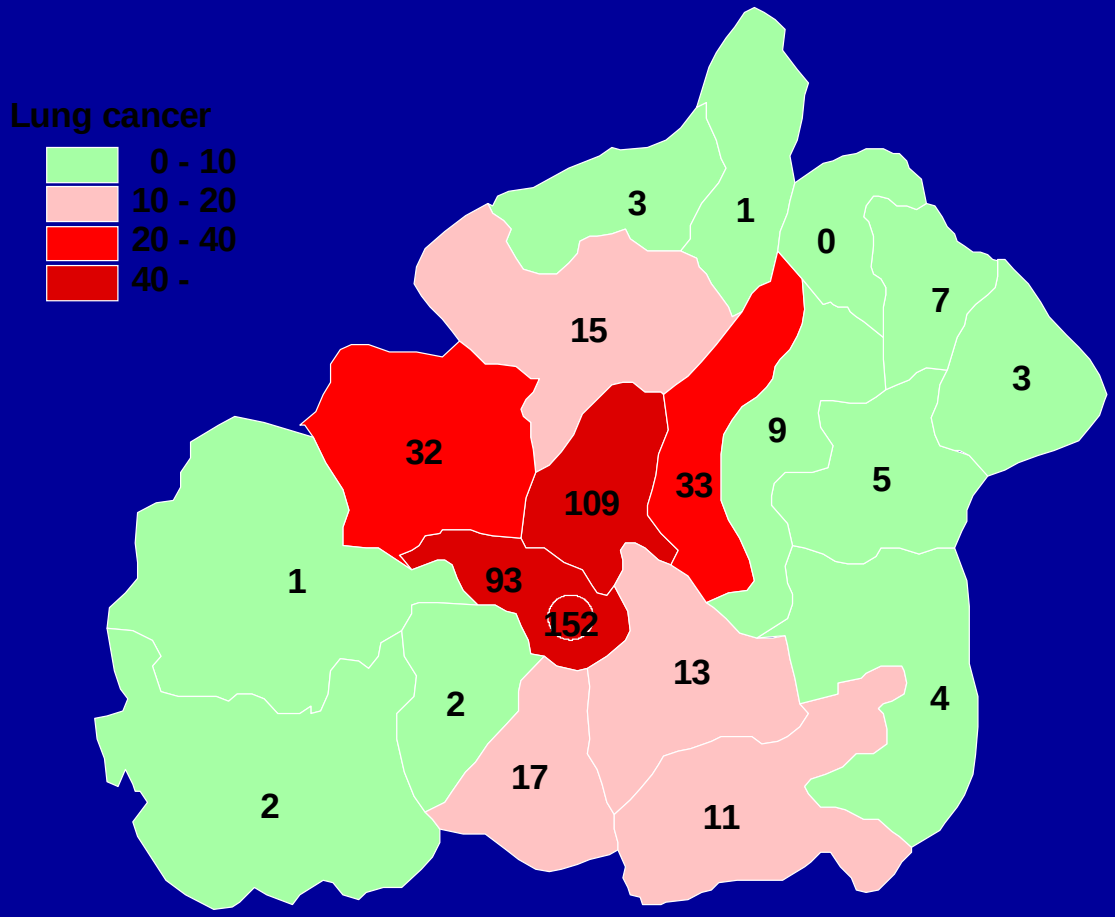


County-specific lung cancer mortality rates (per 100,000, 1973-75)

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

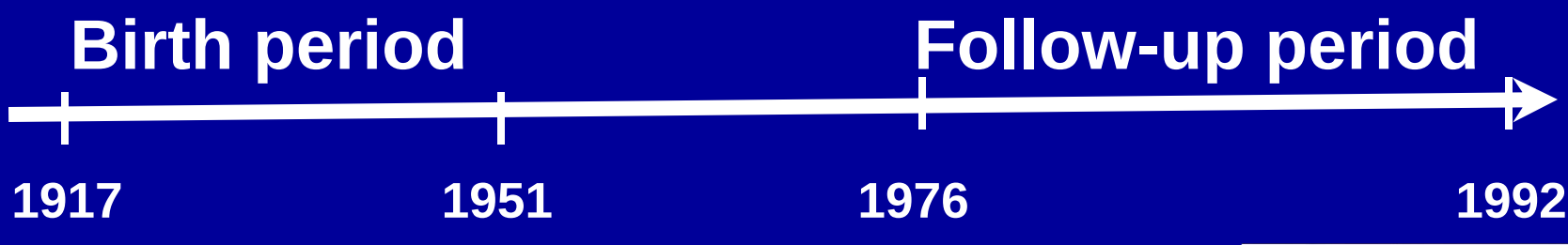
Smoky Coal and Lung Cancer Association

- 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



43,000 subjects

1,900 lung cancer cases

2,700 COPD cases

Lung Cancer Risk by Stove Improvement

Stove improvement	Males RR (95% CI)	*P Value*	Females RR (95% CI)	*P Value*
No stove improvement	1.00 ---		1.00 ---	
Changed to chimney stove	0.59 (0.49-0.71)	<.001	0.54 (0.44-0.65)	<.001

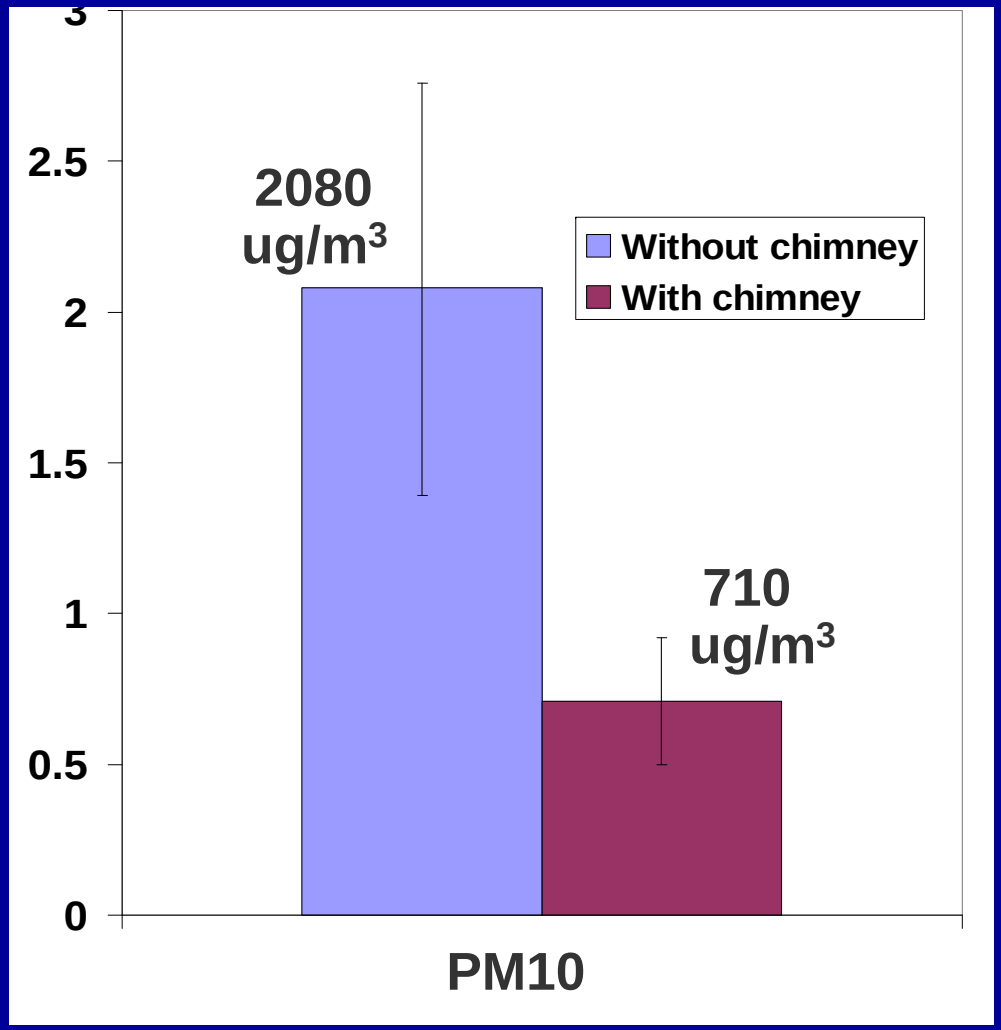
Lan et al., 2002 J Natl Cancer Inst.

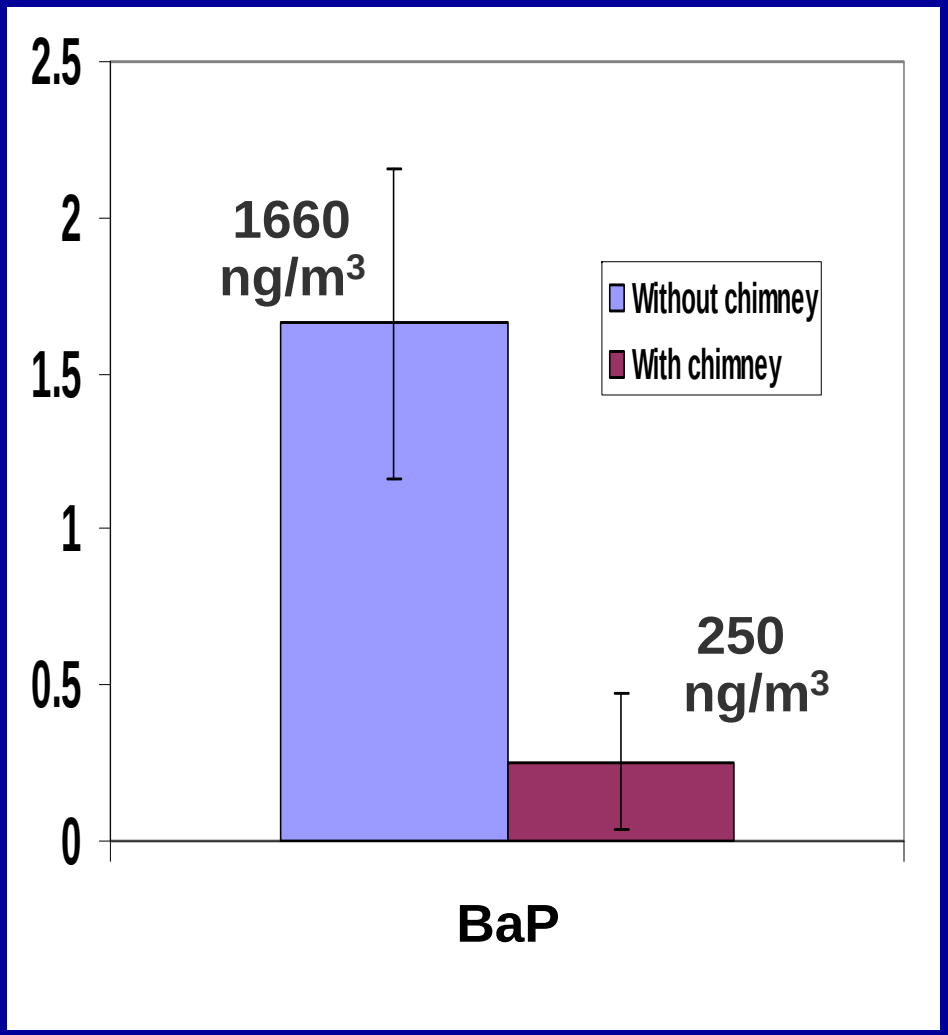
COPD Risk by Stove Improvement

Stove improvement	Males RR (95% CI)	*P Value*	Females RR (95% CI)	*P Value*
No stove improvement	1.00 ---		1.00 ---	
Changed to chimney stove	0.58 (0.49-0.70)	<.001	0.75 (0.62-0.92)	.005

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

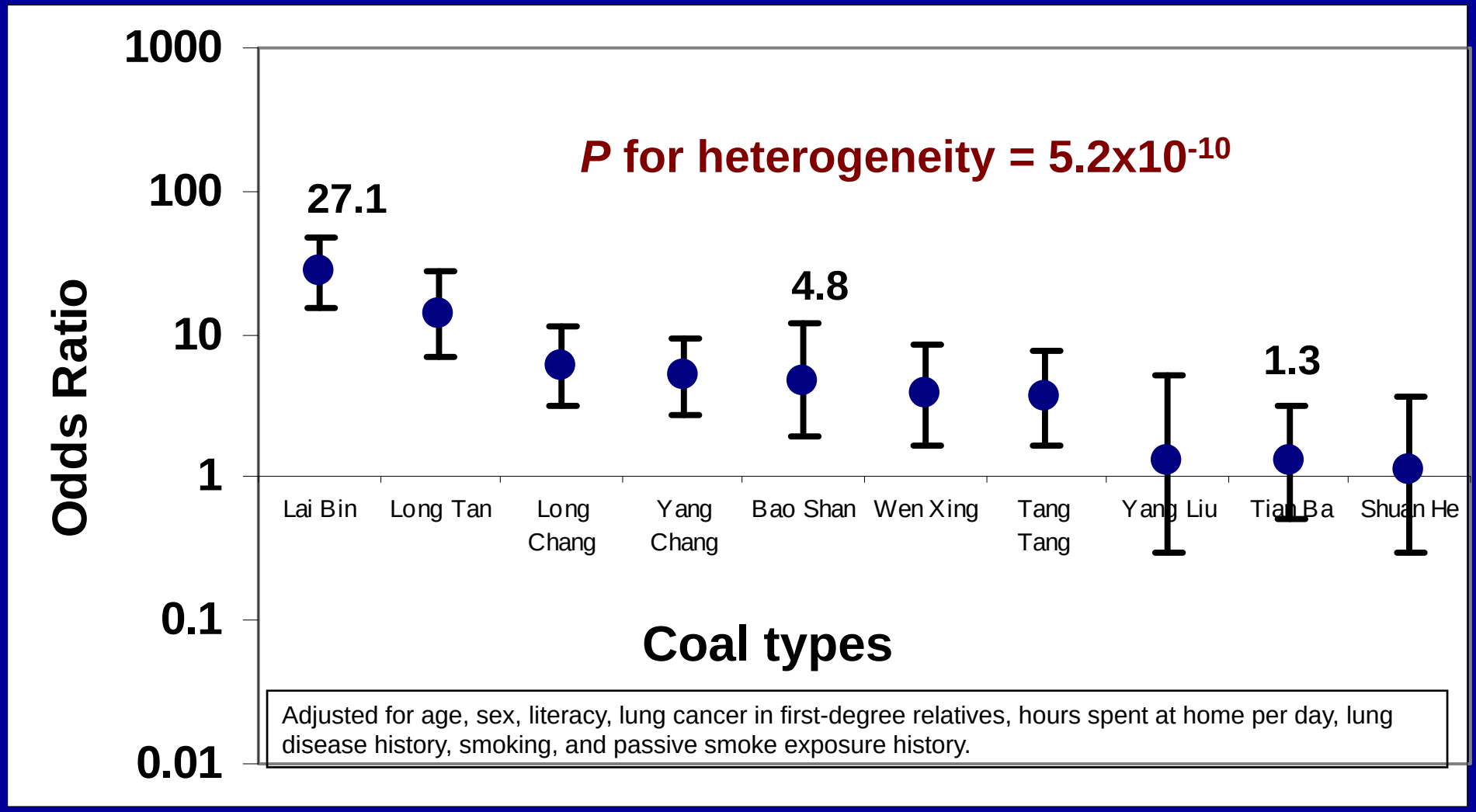
- Cohort study evaluated lung cancer risk from only one type of coal (Lai Bin coal)
- Many other types of coal are used, but risk for coal type has not been quantified
- Wide variation in risk by coal type → wide variation in exposure to PAHs

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



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

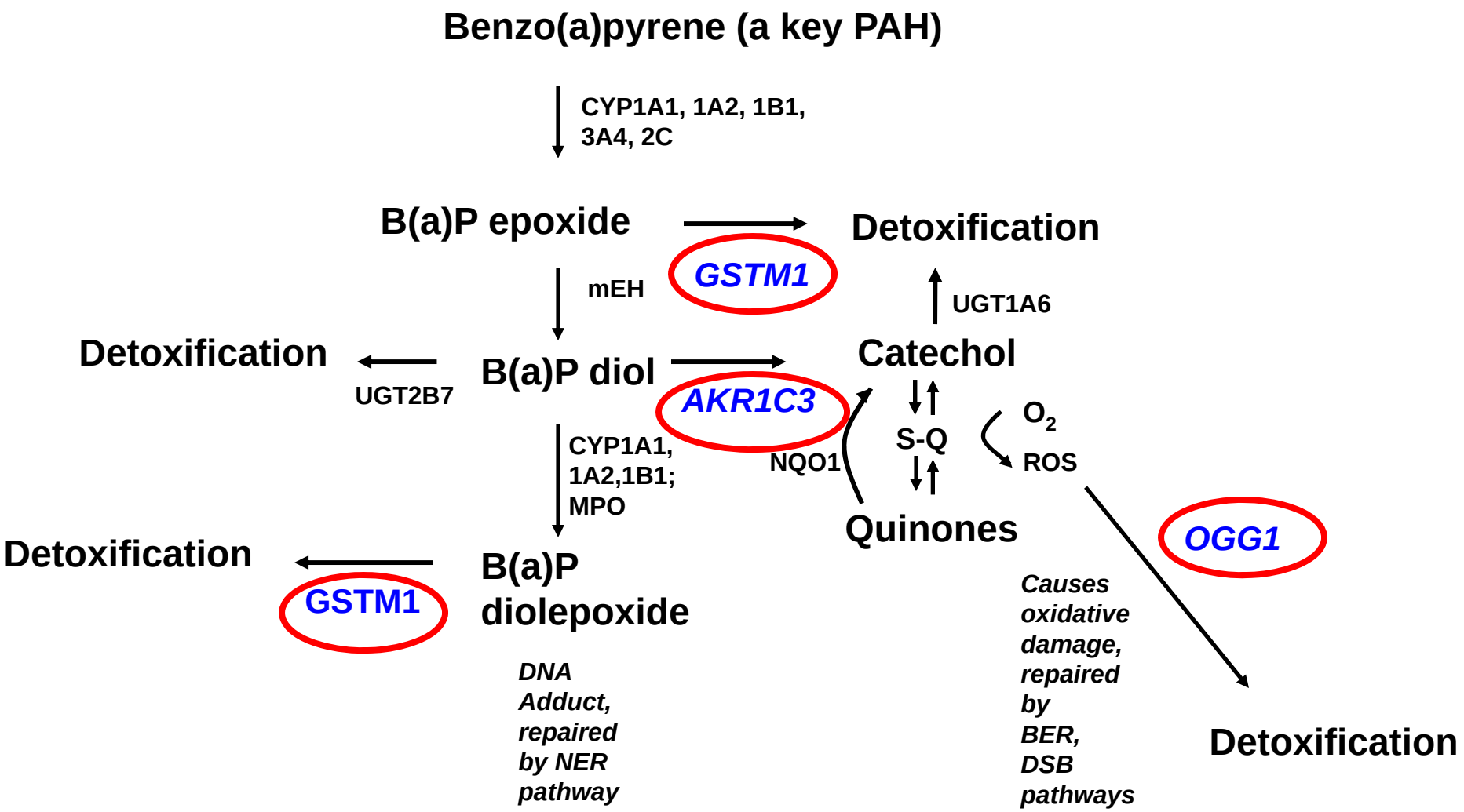
PAH Exposure, Genetic Susceptibility, and Lung Cancer

- 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

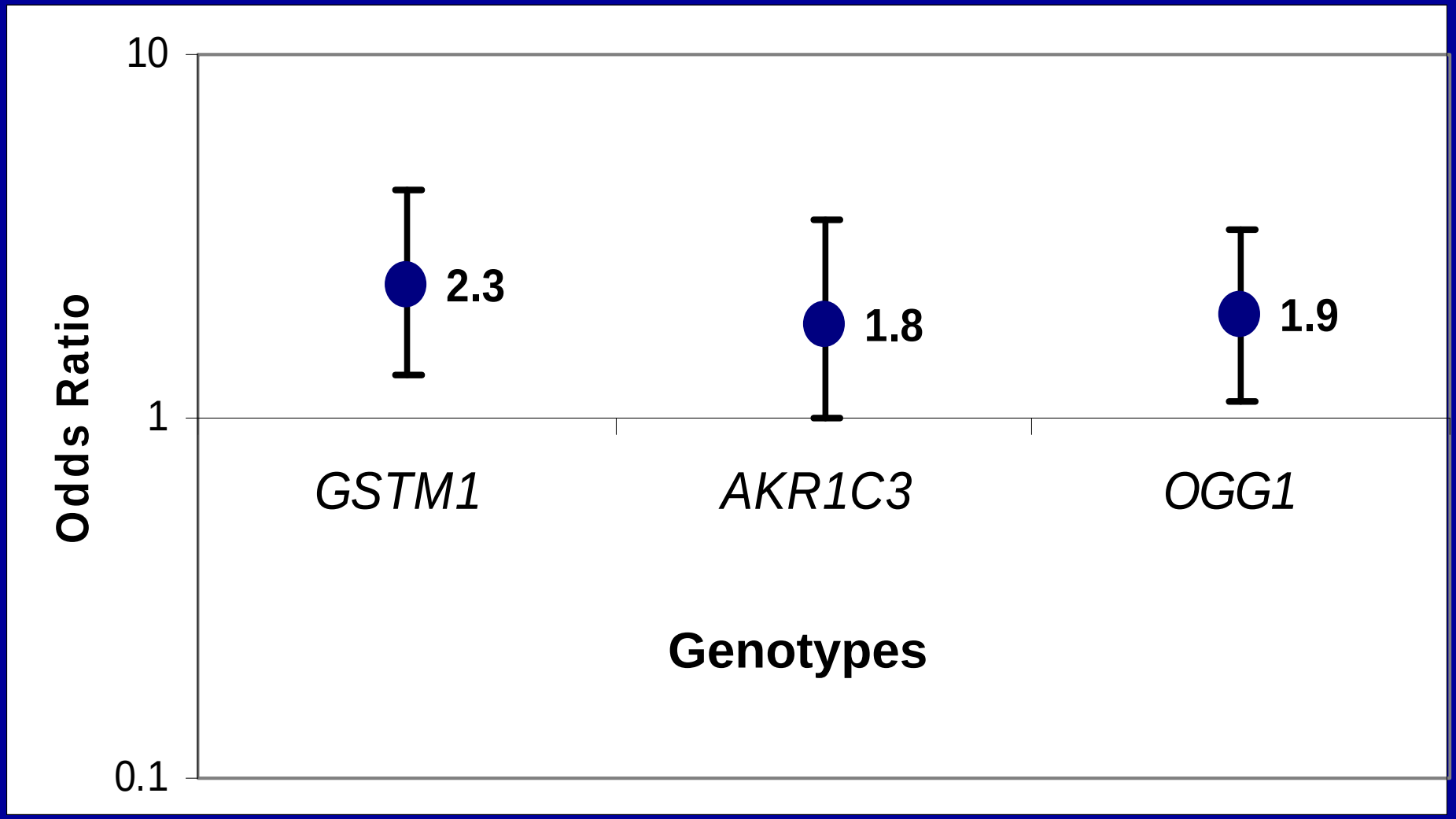
Molecular Epidemiology Case-Control Study

- 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



GSTM1 null, *AKR1C3* (Ex1-70C>G), and *OGG1* (Ex6-315C>G) Genotypes and Lung Cancer Risk



Lan et al., 2004 Carcinogenesis

AKR1C3, *OGG1*, and *GSTM1* Genotypes and Lung Cancer Risk, by Sex and Level of Smoky Coal Use

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

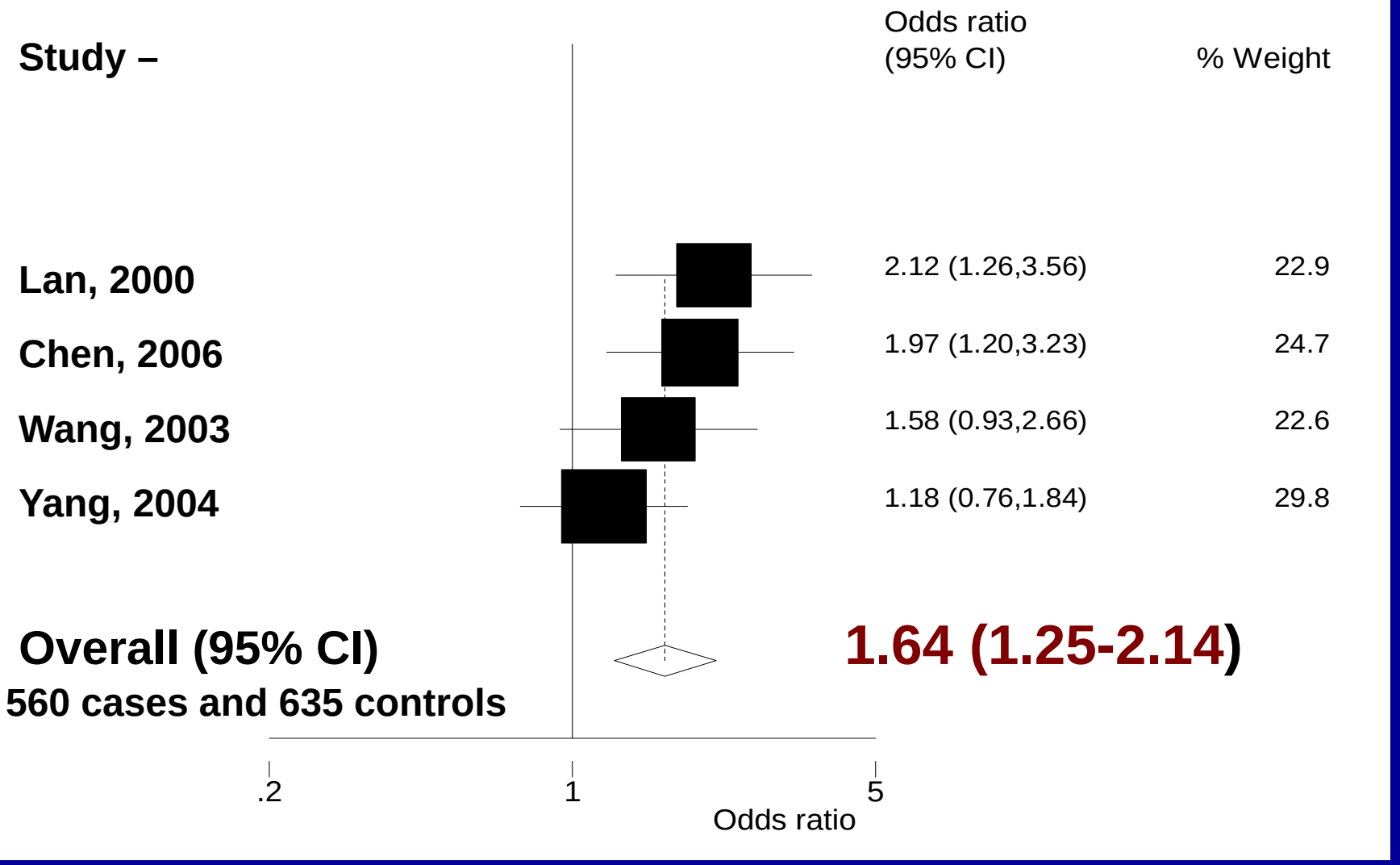
Adjusted for age, pack-year of smoking (for males only)

Lan et al., 2004 Carcinogenesis

Gene-Environment Interaction: *GSTM1* and Smoky Coal Exposure

- Average lifetime exposure: 200 tons
- *GSTM1*-positive subjects:
  1.2-fold per 100 tons
- *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



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

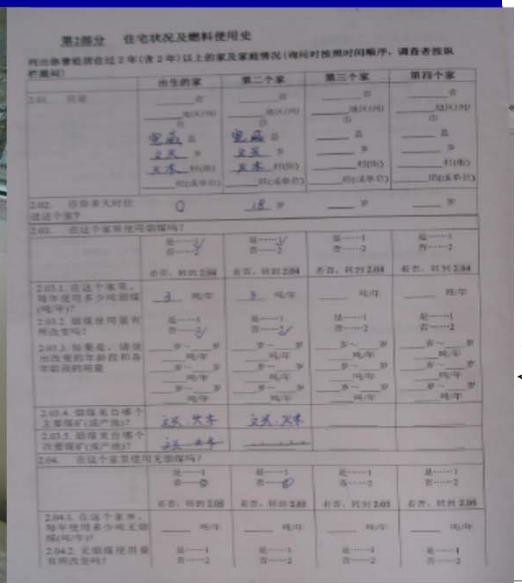
- **Findings being used to develop international WHO Guidelines for Indoor Air Quality and to support improved home ventilation and replacement of coal with cleaner sources of heating and cooking**

Unanswered Questions

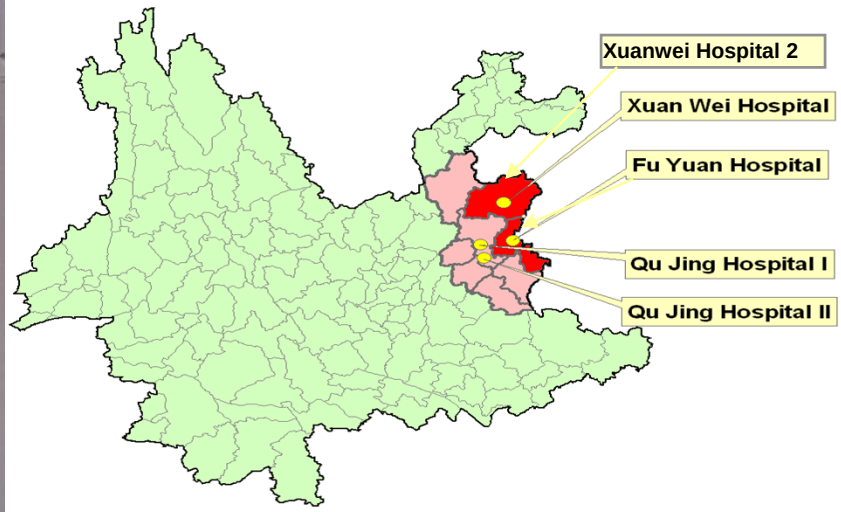
- What is the dose-response relationship between PAH exposure and lung cancer risk?
- What is the role of genetic susceptibility for lung cancer risk overall and as a modifier of the PAH association?

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



Hospitals for the new case-controls study



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

Household coal measurement

Personal air monitoring

Dermal exposure monitoring

Planned Analysis of Lung Cancer among Never Smoking Women in Xuanwei

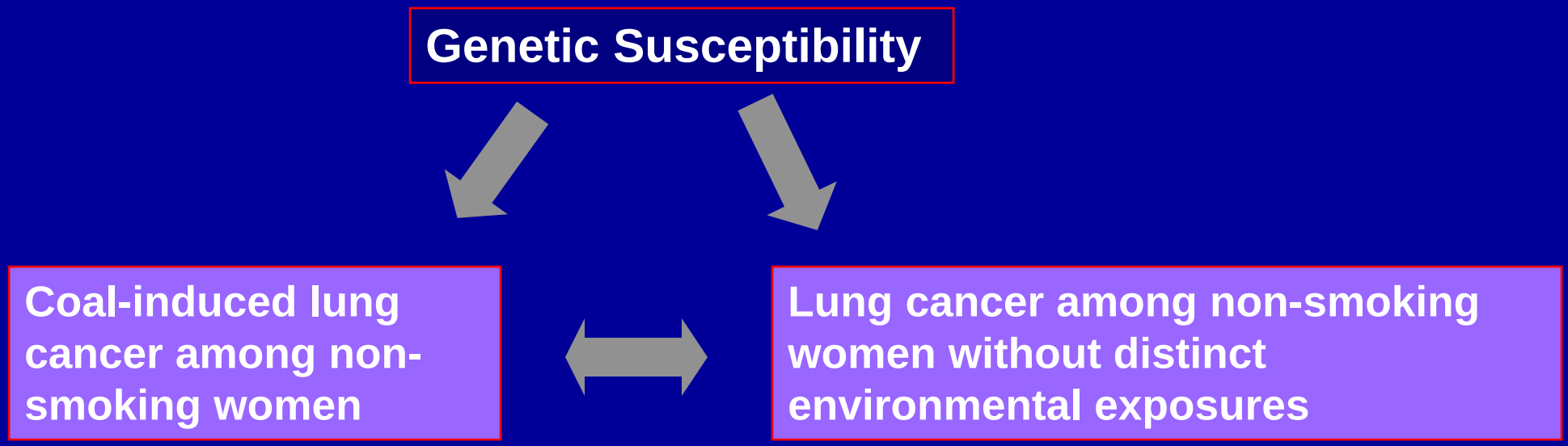
- Estimate exposure to PAHs and particulates
- Genotype SNPs in key genes important for PAH metabolism and DNA repair and for lung cancer etiology
- Analyze main effects of PAH exposure and co-exposures and interactions with genetic variants

Stationary air monitoring

Personal air monitoring

Unanswered Questions

- **Relatively modest sample size**
  - Broad analysis of genetic variants
  - Detecting small gene-environment interactions
- **Generalizability of genetic susceptibility findings?**



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

University of Utrecht: Roel Vermeulen

IARC: Paolo Boffetta, Pierre Hainaut

Aichi Cancer Center Research Institute, Nagoya, Japan: Keitaro Matsuo

Peking Union Medical College Cancer Institute, China: Daxin Lin

Nanjing University, China: Hongbing Shen

China Medical University, China: Baoshen Zhou

Tongji Medical University, China: Tangchun Wu

Seoul National University, South Korea: Yun-Chul Hong

Kyungpook National University, South Korea: : Jae Yong Park

Korea University College of Medicine, South Korea: Yeul Hong Kim

U.S. NCI: Min Shen, Nat Rothman, Dean Hosgood, Neil Caporaso, Aaron Blair, Jay Lubin, Nilanjan Chattergee, Tere Landi, Peggy Tucker, Wong-Ho Chow, Stephen Chanock, Joseph F. Fraumeni, Jr.

Some Questions for NCAB

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?**