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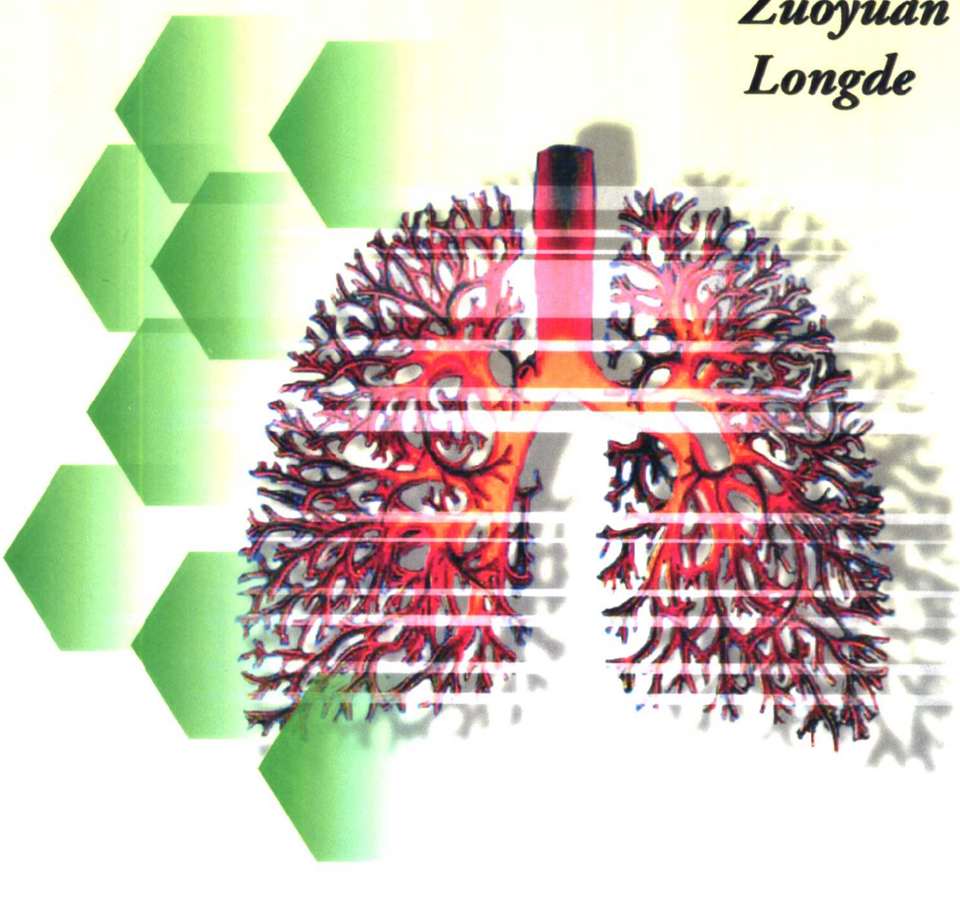

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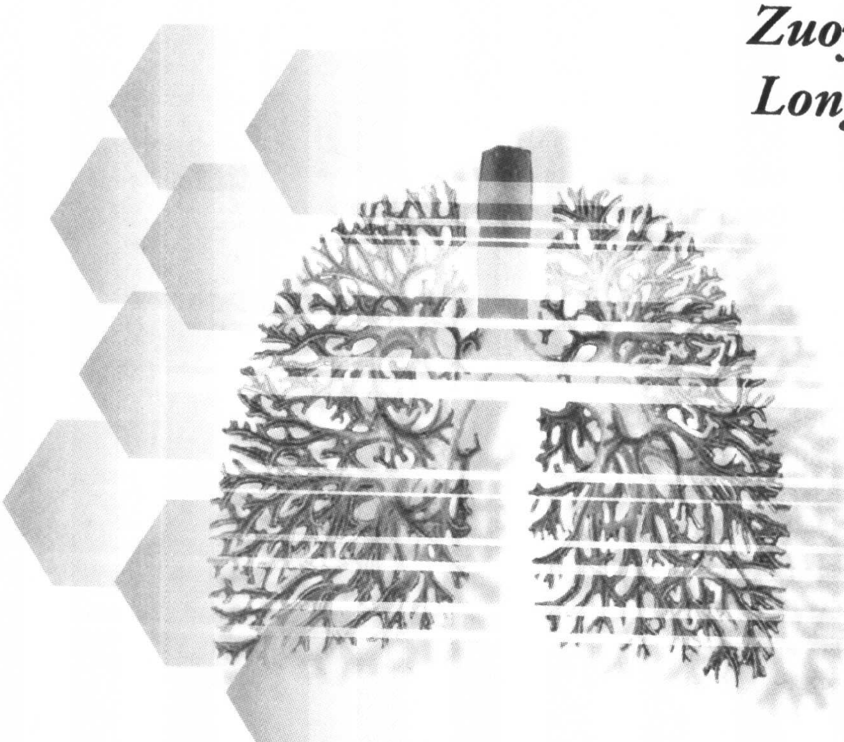

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Epidemiologic Study of Lung Cancer

Mr. Zuoyuan Wang was born in Xianghe County, Hebei Province, China. He graduated from the Chinese University of Science and Technology in 1965, and then started his work in the Laboratory of Industrial Hygiene, Ministry of Health, China. As visiting scholar, he spent two years in Georgia Institute of Technology, Atlanta, USA (1980–1982) and half year in Australian Radiation Laboratory (1993–1994). He used to be a member of Committee 4, ICRP (1984–1992) and Laboratory Director (1983–1993). He is the Principle Investigator of Gansu Epidemiology Study, that is a joint project with National Cancer Institute, USA.

Epidemiologic Study of Lung Cancer

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Preface

The main content of this book is concerned with an epidemiological study of lung cancer, which was conducted in Pingliang and Qingyang Prefectures of Gansu Province, China during 1994 – 1998. This is a joint project of Laboratory of Industrial Hygiene, Ministry of Health, China and National Cancer Institute, National Institute of Health, USA. Good cooperation between Chinese and American scientists and their hard works made the program successful. Results from the epidemiological study will be great contributor to etiology of lung cancer. There are many environmental factors, which could cause lung cancer, such as smoking, arsenic, asbestos, particle, chloromethyl ethers, radon progeny and other agents. Especially the radon and its progeny are omnipresent in dwellings, schools, working place and everywhere. Although the fact, that exposure of radon and its daughters is one of the causes of lung cancer, has been identified in mine environment, but little is known about effect of indoor radon level from epidemiological point of view. The Gansu lung cancer study fills in the gaps in area of effects of indoor radon exposure.

Papers from Gansu lung cancer study collected in the book concern with some aspects of lung cancer etiology: indoor radon, smoking, cooking oil, particles from coal and biomass combustion, previous pulmonary diseases, reproductive factors and others. The book would be helpful in progress of setting national standards of indoor air pollution. It also collects some papers from other studies concerning lung cancer, radiation effects, natural radiation and so on. These papers reflect research activities in each field in China.

Gansu lung cancer study got a lot of assistance from local Government, especially from Health Department of Gansu Province, Health Department of Pingliang and Qingyang Prefectures, Health Bureau of each county (city) as well as from local investigators. All of them make important contribution to the joint study. It is our pleasure to recommend the book to you. Hope it will be useful.

Zuoyuan Wang
Longde Wang
May, 2003

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Part I

Lung Cancer and High Levels of Indoor Radon — General aspects of a population based case-control study in Gansu, China

Zuoyuan Wang, Jay D. Lubin, Longde Wang,
Ruth A. Kleinermen, John D. Boice, Jr.

***Keywords*:** Lung cancer; Indoor radon; Case-control study; Gansu Province

1. BACKGROUND

Studies of underground miners have consistently demonstrated an elevated risk of lung cancer with increasing levels of radon and its decay products [1, 2]. During the 1980s, it became apparent that radon levels in some residential dwellings could be substantial. The presence of this recognized carcinogen in indoor air raised concern that radon might be an important cause of lung cancer in the general population, among both smokers and non-smokers. Based on extrapolation from studies of underground miners, approximately 7000 – 43000 lung cancer deaths per year in the US may be attributable to indoor radon exposure [2, 3].

Risk estimated from miner studies, however, may not be directly applicable to residential settings. There are several important differences between radon exposure in a mine and in a home environment [4]. These differences include radon concentration levels and the relative proportions of radon and its decay products, the presence of dust and other contaminants, and the level of physical activity. Differences also exist in the extent of tobacco use among miners and the general population. Further, although some homes may reach levels that are present in some underground mines, generally average lifetime exposure to indoor radon is substantially lower than the cumulative exposures associated with mining activities. In addition, miner studies only include relatively young and healthy men, but residents in homes include women, children and the elderly.

Studies of indoor exposure to radon are needed to validate the use of miner-bases models for risk assessment. Additional scientific issues associated with radon exposure that should be addressed include: 1) Whether exposures to radon concentrations commonly found in homes pose demonstrable health risk. 2) Whether long duration of radon exposure, potentially a lifetime, add to lung cancer burden. 3) Whether lung cancer risk in female due to radon exposure is similar to males. 4) Whether exposure to tobacco smoke or to other contaminants of indoor air, such as the combustion by-products of cooking and heating, influence lung cancer risk due to radon.

Ecological studies show mixed correlations between estimates of radon exposure and lung cancer rates. These studies, however, are essentially non-informative with regard to demonstrating or quantifying a radon risk because exposure to individuals is not known and confounded by that smoking is a serious problem [5]. Six analytic studies of lung cancer, including long-term radon measurements in the home, have been published, with weak positive associations reported in New Jersey [6] and Stockholm, Sweden [7], ambiguous results in a Finnish study [8], and weak negative associations found in Shenyang, China [9] and Winning, Canada [10]. A joint analysis of data from New Jersey, Shenyang and Stockholm indicates that the studies are consistent with each other, consistent with extrapolation from miners, and consistent with no effect of exposure [2]. Low exposure to radon and uncertainty in exposure assessment may have accounted for the failure of these studies to find an effect. Another Swedish study [11] reported positive findings for lung cancer risk and estimated cumulative and time-weighted residential exposure to radon.

A significant limitation of many studies of indoor radon conducted thus far has been the limited range of indoor radon concentration with few studies including homes with high exposures [12]. To address this limitation, a comprehensive population-based case-control study of lung cancer and high levels of indoor radon in Gansu Province was conducted. Pingliang and Qingyang Prefectures have been identified where a high percentage of the population lives in cave dwellings, where indoor radon levels are relatively high due in part to the limited ventilation. These prefectures in Gansu Province thus provide a unique opportunity to evaluate the effect of indoor radon on lung cancer risk in a stable population.

The population in Pingliang and Qingyang Prefectures for studying the effects of indoor exposure to radon on lung cancer risk has special features. 1) It is a large, stable population, almost half of which live in cave dwellings. 2) It has high indoor radon concentrations (arithmetic mean, 220.5 Bq/m^3) with a wide range of exposures (3.7 – 3418.8 Bq/m^3). There are very few other sources of air pollution in the study area. 3) There is an extensive health system throughout the two Prefectures to identify lung cancers.

The broad range of radon exposures in dwellings of study area is such that estimated cumulative exposure in some residents overlap the range of exposure observed in miners, exceeding 50 – 60 working-level months (WLM)—a cumulative exposure associated with an elevated lung cancer risk in miners [13].

All lung cancer cases diagnosed over a more than four-year period (01/01/94 – 03/31/98) and twice as many population controls were selected from Pingliang and Qingyang Prefectures in Gansu Province. Every effort was made to obtain histological confirmation for all cases. Subjects are interviewed to obtain a 30-year residential history. Data collected included the amount of time spent at home, characteristics of each home such as to ventilation and type of heating fuel, smoking habits including any passive smoking exposure, other potential sources of indoor air pollution, methods of food preparation and diet, occupation and history of respiratory diseases. Exposure assessment involves placement of two radon detectors in each home lived in for 2 or more years over the past 30 years. Other indoor air pollutants were also assessed. Some homes were sampled and measured for CO_2, SO_2, NO_x, PAH and TSP. Radon detectors were sent back to Landauer, Inc. US for processing. Local public health authorities for remediation notified all homeowners with high radon level-more than 400 Bq/m^3.

2. STUDY AREA AND POPULATION

The population-based case-control study in Pingliang and Qingyang offers the opportunity to overcome the limitations in previous studies. The study area concerns two prefectures, including 15 counties. The total area is 38048.1 km^2 and the population is 4076979 (in 1990, Table 1). Transportation is a major problem for conducting epidemiological investigation in this vast and rural area. Two minibuses and four motorbikes were needed to interview subjects and place and retrieve radon detectors. Approximately 1.6 million people (40% – 50% of the population) live in cave dwellings, the reminder live in standard houses or small two floor buildings. There are six basic housing types in the study area. 1) The Underground Cave Dwelling (UGCD) is typically built by digging a large pit, about 30 × 30 meters wide and 20 meters deep, to serve as a courtyard, and individual "cave" rooms at the level of the courtyard are then dug horizontally into the side walls as deep as 10 – 20 meters. One residence may have as many as seven "cave" rooms emanating as spokes off the control space. Rainwater in the courtyard will flow into a deep permeable well, which is located in the center of the courtyard. 2) Open-cut Cave Dwellings (OCCD) are similar to the UGCD, but they are near to big ravines and rainwater in the courtyard is channeled into the ravine. 3) The Ground Cave Dwelling (GCD) is a cave room usually dug into the side of a hill. 4) The Aboveground Cave Dwelling (AGCD), "cave" is built on ground with loess. 5) The Standard Aboveground Dwelling (SAGD) is a typical house in north China built with brick, adobe and wood. 6) The building or tower dwelling is a common apartment or a small two-floor tower dwelling. All of these housing types are depicted in Fig. 1. Most of the cave dwellings have electricity. Additionally, because the population is stable and "cave" homes have changed little over the past hundred years, past exposure to radon can be accurately estimated for individuals.

Table 1 Geographic area and populations in Pingliang and Qingyang Prefectures in 1990

County	Area (km^2)	Population		
		Total	Male	Female
Pingliang Pref.	***11142***	***1909419***	***992389***	***917030***
Pingliang	1936	386325	200025	186300
Jingchuan	1462	293069	152416	140653
Lingtai	1992	209723	110399	99324
Chongxin	850	83566	43578	39988
Huating	1183	161981	86126	75855
Zhuanglang	1527	362260	187959	174301
Jingning	2192	412495	211886	200609
Qingyang Pref.	***27119***	***2167560***	***1123495***	***1044063***
Xifeng City	996	270435	139100	131335
Qingyang	2673	275461	144645	130816
Huanxian	9236	286243	149059	137184
Huachi	3776	111245	57930	53315
Heshui	2976	141945	73297	68648
Zhengning	1326	199385	103808	85577
Ningxian	2633	447095	230373	216722
Zhenyuan	3500	435751	225285	210466
Total	***38261***	***4076979***	***2115886***	***1961093***

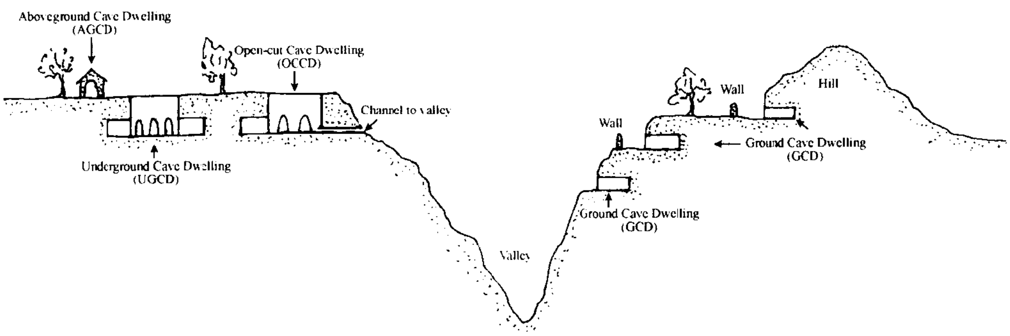

Fig. 1 Sketch Map of Cave Dwelling Location

The study area is primarily rural, and there are few industrial or other sources of air pollution. In large part, dry kindling is used for heating and cooking fuel, although where transportation is available, coal is used. Because of the previously reported associations between lung cancer and exposure to coal-combustion products such as polycyclic aromatic hydrocarbons (PAH)[13], indoor air pollution was also evaluated. Most of residents in study area are engaged in farming activities and there is some exposure to pesticides, which was also evaluated. Dietary habit and exposure to vapors from cooking oil were investigated also.

Although rural, the study area is well served by local clinics and hospitals. A rapid reporting system for lung cancer was integrated into the existing system for identifying and treating tuberculosis (TB). Prior lung disease including tuberculosis, chronic bronchitis, emphysema and pneumonia has been linked to lung cancer [14, 15]. Thus, prior lung disease was also investigated in our study.

The study includes both male and female subjects in order to provide an opportunity to evaluate radon effects for each gender under similar conditions. Most of the adult men smoke locally grown tobacco in long-stem pipes, whereas very few women smoked any sources of tobacco. Passive smoking was evaluated to the extent possible.

3. PILOT STUDY AND STATISTIC POWER

Our research group conducted a pilot study in Pingliang and Qingyang Prefectures between February and August 1993. The number of lung cancer cases diagnosed in the one-year period (1991) was determined and the range of radon exposures in a sample of underground and aboveground homes was estimated. This served as the computational base for statistical power and sample size. The age/gender distribution of lung cancer cases identified over the one-year period is presented in Table 2. Radon detectors (long-term, alpha-track detectors) were placed in 49 homes for one year to estimate indoor radon levels. The results are listed in Table 3. Lung cancer mortality rates in Gansu are considerably lower than those in Beijing—the capital of China. Mortality rates for lung cancer for females in Qingyang and Pingliang Prefectures, where a higher proportion of the population live in underground dwellings, however, are both higher than those in the entire Province, although only the rates for males in Qingyang are higher than for entire province (Table 4).

Table 2 Lung cancers diagnosed during the pilot study from January 1 to December 31, 1991

Age at diagnosis	Pingliang		Qingyang		Total	
	Male	Female	Male	Female	Male	Female
<30	1	0	3	0	4	0
30 –	0	0	4	1	4	1
35 –	2	1	8	1	10	2
40 –	5	1	7	4	12	5
45 –	17	7	12	4	28	11
50 –	11	6	13	5	24	11
55 –	16	8	11	4	27	7
60 –	12	4	22	5	34	9
65 –	6	5	16	2	22	7
70 –	5	2	8	1	11	3
75 +	2	0	0	0	2	0
Total	**77**	**34**	**104**	**27**	**178**	**56**

Table 3 Radon concentration measured in the pilot study[a] **Unit: Bq/m^3**

Type[b]	No.	Arithmetic		Geometric		Range
		Mean	SD	Mean	SD	
UGCD	14	162.8	51.8	155.4	48.1	81.4 - 377.4
OCCD	15	155.4	25.9	151.7	44.4	103.6 - 310.8
GCD	14	196.1	70.3	188.7	51.8	107.3 - 603.1
AGCD	4	107.3	18.5	103.6	44.4	66.6 - 148.0
Total	**47**	**166.5**	**11.2**	**159.1**	**51.8**	**66.6 - 603.1**

[a]-Results omit data from two presumed anomalous readings
[b]-Dwelling types include:
UGCD-Under-Ground Cave Dwelling
OCCD-Open-Cut Cave Dwelling
GCD-Ground Cave Dwelling
AGCD-Above-Ground Cave Dwelling

Table 4 Mortality rates of lung cancer cases in 1980 in Gansu **Unit: $1/10^5$**

Area	Male				Female			
	CMR[a]	CSMR[b]	WSMR[c]	CUMR[d]	CMR	CSMR	WSMR	CUMR
Gansu	2.45	2.48	3.54	0.42	1.31	1.14	1.59	0.18
Pingliang	1.57	1.74	1.96	0.24	1.91	1.94	2.15	0.24
Qingyang	3.05	3.46	4.53	0.57	1.40	1.68	2.50	0.27

Data of mortality rates of lung cancer are from Cancer Control Office, Ministry of Health, China 1980.
[a]-crude mortality rate
[b]-mortality rate standardized to Chinese population
[c]-mortality rate standardized to the world population
[d]-cumulative mortality rate

Power calculations were carried out base on long-term radon concentration measurements from the pilot study (mean = 181.3 Bq/m^3). Subjects were assumed to be 65 years old and to have accumulated 30 years of radon exposure with a 5-year lag interval. All calculations were based on $\alpha = 0.05$ level tests; tests of radon exposure effects and trends in risk were one-sided. The National Academy of Sciences [16] estimates that excess relative risk (ERR) increases by 1.34% - 1.50% per WLM. Living at 37 Bq/m^3 = 1 pCi/l for 30 years results in a total exposure of approximately 6 WLM (0.2 WLM/yr × 30 yr). This translates into an ERR of 0.08 - 0.09per pCi/l - 30 yr. Based on 2,700 subjects, the study has a power of 0.98 of detecting a RR of 1.6, which is associated with the lowest exposure-level category.

4. ASCERTAINMENT OF LUNG CANCER CASE

According to the collaborative study proposal, approximately 900 lung cancer cases (675 males, 225 females) were recommended which meant that 225 cases should be ascertained each year for four years. Lung cancer cases were thus retrospectively (January 1 to December 31, 1994) and prospectively (January 1, 1995 to December 31, 1997) identified from the prefecture hospitals, 15 county hospitals, local clinics and one oilfield hospital. In addition, hospitals in Xi'an City, Yinchuan City and Lanzhou City were checked for lung cancers diagnosed in Pingliang and Qingyang residents. Lung cancer cases were slected to be 30 – 74 years old, and residing in either Pingliang or Qingyang Prefecture at the time of their lung cancer diagnosis.

Local investigators contacted hospitals and local clinics monthly during the years 1995 – 1997 to collect materials on lung cancer cases. For each possible lung cancer cases, investigators recorded name, address, date of birth or age, gender, date and place of first diagnosis and treatment, as well as information on the method of diagnosis (X-ray, sputum cytology or histology), histological classification, tumor location, vital status and names of relatives if the case died. Investigators also collected information on the medical file, X-ray films, pathology slides and other evidence of lung cancer for the use in case review.

Bronchoscope examinations were encouraged for all prospectively identified living lung cancer cases. Benefits to the patients include possible earlier and accurately diagnosis of lung cancer, as well as access to additional treatment options. For this purpose, three bronchoscope machines were supplied to the prefecture hospitals and oilfield hospital.

All lung cancer cases diagnosed in different hospital and clinics were to be reviewed by the Expert Review Panel, consisting of two oncologists, two radiologists and one pathologist from the Department of Health, Government of Gansu Province. The Experts Panel carefully considered all information of case history, physical signs, clinical symptom and chest X-ray examination results (posteroanterior and lateral films or fluoroscopy) before pathological review of the lung cancer specimen. Certainly cytological or histological evidence is always of prime importance in any lung cancer review, if such material exists. However, the results of cytological examination can be influenced by technical factors that blur interpretation.

The expert review panel followed standardized criteria in reviewing each lung cancer case.

4.1. Pathological review

If a presumed lung cancer case reported by local investigator met one of the following criteria, he/she could be confirmed as a lung cancer case.

- Cancer cells are identified in pulmonary tissue, which is moved surgically.
- Cancer cells are identified in living specimen, which is taken by exploratory thoracotomy, needle biopsy and fibrobronchoscopy.
- Cancer cells are identified in living specimen, which is taken from metastatic sites (such as lymph node in neck and axilla), chest wall, pleura or subcutaneous nodules, if other primary tumor is excluded in clinic.

4.2. Cytological review

If cytological examination of specimen, which is from sputa, bronchial washing,