Previous pulmonary diseases and risk of lung cancer in Gansu Province, China

Alina V Brenner, Zuoyuan Wang, Ruth A Kleinerman, Longde Wang, Shouzhi Zhang, Catherine Metayer, Katherine Chen, Suwen Lei, Hongxing Cui and Jay H Lubin

Background

Although active smoking is well established as the main cause of lung cancer, there is accumulating evidence that history of prior lung diseases may be an independent risk factor for lung cancer.

Methods

A population-based case-control study in Gansu Province, China identified 886 lung cancer cases (656 male, 230 female) diagnosed between January 1994 and April 1998. A standardized interview collected information on a variety of potential risk factors including a history of physician-diagnosed non-malignant lung diseases (pulmonary tuberculosis, chronic bronchitis/emphysema, asthma, pneumonia), age and year in which each condition was first diagnosed, and any therapy or hospitalization received.

Results

Pulmonary tuberculosis (odds ratio [OR] = 2.1, 95% CI: 1.4–3.1) and chronic bronchitis/emphysema (OR = 1.4, 95% CI: 1.1–1.8) were associated with increased risk of lung cancer, after adjustment for active smoking and socioeconomic status. The OR for asthma (OR = 1.4, 95% CI: 0.9–2.1) and pneumonia (OR = 1.5, 95% CI: 1.0–2.3) were also elevated. The risk of lung cancer remained significant for pulmonary tuberculosis and chronic bronchitis/emphysema when analysis was limited to the pathologically confirmed cases and self-responders.

Conclusions

This study provides additional evidence that previous pulmonary tuberculosis and chronic bronchitis/emphysema are causally related to lung cancer, although the precise mechanism is still unclear. The results for asthma and pneumonia, while suggestive of a positive association, did not reach the traditional level of statistical significance and should be interpreted with caution.

Keywords

Case-control studies, lung neoplasms, tuberculosis, pulmonary, bronchitis, pulmonary emphysema, asthma, pneumonia

Accepted 6 June 2000

Active smoking has been well established as the main risk factor for lung cancer, and more recent studies of lung cancer have sought to identify other aetiological factors, especially among non-smokers. There is accumulating evidence that occupational or domestic exposure to radon may increase cancer risk. There is also evidence of possible relationships between previous non-malignant pulmonary diseases and lung cancer.

Several studies have examined the association between lung cancer occurrence and prior diagnosis of other pulmonary diseases. While not all of these studies yielded statistically significant results, risks for lung cancer were generally elevated for prior diagnosis of pulmonary tuberculosis, chronic bronchitis/emphysema, asthma, and pneumonia. The consistency of the results suggests that one or more of these associations may indeed be causal, since it is unlikely that a systematic bias affected all of these diverse studies similarly. Questions remain about the relationship between prior diagnosed lung disease and lung cancer, in particular, whether the timing of diagnosis of lung disease influences lung cancer risk.

We initiated a comprehensive population-based case-control study of lung cancer in Gansu Province, China to address this and other issues. Although the primary goal of the study was to investigate high levels of exposure to indoor radon and risk of lung cancer, the study generated an extensive database, including information on history of prior pulmonary diseases. A particular strength of this study is its large number of subjects,
both male and female, drawn from a predominantly rural population with little exposure to industrial sources of air pollution, and who had a detailed smoking history. An examination was made within this sample of the association between lung cancer and previous pulmonary disease.

Methods

Case ascertainment

We conducted a population-based case-control study of lung cancer in Pingliang and Qingyang, two prefectures in Gansu Province, China. Cases were aged 30–75 years, diagnosed between January 1994 and April 1998 and were identified retrospectively (1994–1995) and prospectively (1996–1998) from two prefecture hospitals, a company hospital located at a nearby oilfield, 15 county hospitals, and local clinics. We also reviewed records from special anti-tuberculosis reporting stations in the prefectoral hospitals in larger cities, such as Lanzhou, Xi’an, and Yinchuan, and were reviewed for lung cancer diagnosed in residents of the two prefectures. Cases consisted of those with clinical/radiological symptoms suggestive of lung cancer or pathological evidence.

There were 1209 possible lung cancer cases identified in the study area. All lung cancer diagnoses were reviewed by an expert panel that included two oncologists, two radiologists, and one pathologist. Diagnoses of lung cancer were based on clinical/radiological criteria for 60% of cases and pathological evidence (such as broncholiberoptopic biopsy, sputum cytology, lymphatic node biopsy) for 40% of cases. The expert panel ruled out 277 cases leaving 932 cases. Of these, 43 cases could not be located and 3 cases moved out of the study area leaving 886 cases (656 males, 230 females) for analysis.

All case subjects agreed to be interviewed. Mean times from diagnosis to the interview were 4.6 months for cases identified prospectively and 13.5 months for cases identified retrospectively. For subjects who had died, next-of-kin (primarily the spouse) were interviewed. Surrogate interviews were required for 481 cases. For all probable lung cancer cases, an attempt was made to identify vital status at the end of the study period, and we assumed a subject’s death was confirmatory of lung cancer diagnosis.

Control selection

A total of 1968 controls were randomly sampled from the population census list for the two prefectures. Of the identified controls, 6 refused to be interviewed, 62 could not be located, 23 moved out of the study area, 73 died before 1994, 4 became cases, and 35 could not be interviewed before the end of the study and so 1765 controls (1310 males, 455 females) were included.

Controls were frequency matched by gender, 5-year age group, and prefecture. The control selection within each stratum was based on the distribution of lung cancer cases obtained in a 1991 pilot study in the same area.\textsuperscript{15}

Interview

After obtaining informed consent, personal interviews were conducted for all cases and controls by trained interviewers using a structured questionnaire. Interviews were conducted either at home or in the hospital.

Detailed questions were asked about amount of time spent at home; smoking habits, including smoking by other members of the household; housing characteristics; type of fuel used in homes; diet and cooking practices; occupation; pesticide use; reproductive factors for females; and medical histories. Long-term radon detectors were placed in all residences lived in for at least 2 years over the past 30 years. Cases and controls were asked whether a physician had ever advised them that they had specific lung conditions (pulmonary tuberculosis, chronic bronchitis/emphysema, asthma, and pneumonia) and, if so, the age and year in which each condition was first diagnosed and any therapy or hospitalization received for the condition. Because the diagnostic distinction between chronic bronchitis and emphysema is problematic, we combined the two diseases into a single category.

Statistical analysis

Odds ratios (OR) were used to measure the association between lung cancer and the prior lung disease of interest. Unconditional multivariate logistic regression models were used to adjust OR for potential confounding factors included as main effects (age, gender, prefecture, active smoking, passive smoking among non-smokers, radon exposure, socioeconomic status, coal combustion and fumes), and to evaluate effect modification.\textsuperscript{16} There was concern that early symptoms of lung cancer might have been misdiagnosed as a prior lung disease, which could artificially increase the magnitude of any association between prior lung diseases and lung cancer risk. To examine this possibility, we evaluated OR by time interval between diagnosis of the prior lung disease and lung cancer (or date of the interview for controls). All calculations were done using the SAS program.\textsuperscript{17}

Results

Table 1 summarizes the sociodemographic characteristics of the participants. The frequency matching resulted in comparable distributions of cases and controls by gender and prefecture. Although subjects were matched by age, there was a small difference in age distribution, with a higher proportion of younger cases. This difference was due to controls being selected from the 1990 census list based on their ages in 1995. However, because the midpoint of control enrollment was in 1997, the mean age at interview for controls was slightly older than anticipated. The subjects were comparable on marital status. Case subjects had higher socioeconomic status as measured by a higher proportion with education beyond primary level, had a higher income, and were more likely to own goods such as a colour television set. Finally, 54.3% of case responders were next-of-kin compared to 5.8% of the control responders.

Table 2 summarizes OR for developing lung cancer among different categories of smokers, defined by number of cigarettes/pipes smoked per day and number of years smoked. Moderate and heavy smoking was associated with a low but significantly increased risk of lung cancer. The OR and 95% CI for these categories were 1.5 (1.1–2.0) and 2.8 (1.7–4.5), respectively.

Table 3 shows that OR were significantly elevated for all prior lung conditions about which participants were asked. Adjustment for active smoking had no effect on the OR. In addition, adjustment for passive smoking, radon exposure, socioeconomic status, amount
of coal used in home heating and cooking, and smokiness resulting from cooking did not alter these results (not shown).

To examine the time course of the associations, we computed OR by number of years between the reference age (age at diagnosis of lung cancer for cases or age at interview for controls) and age when first diagnosed with the individual lung disease. For all prior lung diseases, OR were significantly elevated in the interval 1–5 years (Table 4). This was especially pronounced for pulmonary tuberculosis, pneumonia and asthma. Similar patterns of OR were observed when the time period was computed within smaller intervals (1–2, 3–5 years) as well. For time intervals greater than 5 years OR exhibited little variation.

For example, for chronic bronchitis/emphysema OR and 95% CI for 1–2, 3–5, 6–10, 11–20, and 21 and more years were 3.0 (1.9–4.8), 2.6 (1.5–4.6), 1.9 (1.1–3.1), 1.3 (0.8–2.0), and 1.3 (0.9–2.0), respectively.

To minimize the distortion of OR by the misclassification of early manifestation of lung cancer as recent pulmonary disease, we included those subjects with prior lung diseases diagnosed within 1–5 years of lung cancer in the reference group. In addition, following the practice of other investigators, we excluded subjects with recent pulmonary diseases from the analysis. Because the number of subjects in the 1–5 year category was small relative to the number in the reference group, the results of both analyses were similar (not shown).

All subsequent analyses included recent lung diseases in the referent category. Relative to no previous pulmonary diseases 0–5 years prior to lung cancer or interview, OR and 95% CI, were 2.1 (1.4–3.1) for pulmonary tuberculosis, 1.4 (1.1–1.8) for chronic bronchitis/emphysema, 1.4 (0.9–2.1) for asthma, and 1.5 (1.0–2.3) for pneumonia. None of the adjustment variables (active or passive smoking, radon exposure, socioeconomic status, coal combustion and fumes) altered these OR (not shown). In
addition, the OR remained unchanged when data were limited to self-responders only.

Table 5 summarizes the analysis of effect modification of the OR for prior lung diseases. All statistical tests of variations of OR across characteristics were non-significant, except for the variations of OR for chronic bronchitis/emphysema by gender ($P = 0.04$), with the OR greater in males, and asthma by prefecture ($P = 0.03$), with OR greater in Pingliang. After additional adjustment for active smoking, the interaction of chronic bronchitis/emphysema and gender as well as asthma and prefecture remained statistically significant. The OR for lung cancer among never-smokers were elevated for all pulmonary diseases except chronic bronchitis/emphysema, and there was no consistent pattern of OR across smoking categories for any of the pulmonary diseases.

A final analysis restricted the case group to the pathologically confirmed cases (40%) or probable cases who had died by the end of the study (43%). The results did not differ from those which included all lung cancer cases (not shown).

**Discussion**

In this population-based case-control study of lung cancer in two prefectures of the Gansu Province of China, we found statistically significant increases in lung cancer risk with previous pulmonary tuberculosis and chronic bronchitis/emphysema. The association between these diseases and lung cancer remained significantly increased after controlling for active smoking and socioeconomic status. The OR for asthma and pneumonia were also consistently elevated, but did not always reach the traditional level of statistical significance, so results must be interpreted more cautiously.

The results for pulmonary tuberculosis support those previous studies which have found a moderate increase in risk of lung cancer among tuberculosis patients, that was not related to treatment with isoniazid, low-dose fractionated radiation, smoking, and socioeconomic status. The association was related to both squamous cell carcinoma and adenocarcinoma. Different mechanisms have been proposed to explain the positive association. It is biologically plausible that chronic inflammatory processes of the lung could enhance the effects of other carcinogenic exposures and/or stimulate cell proliferation and growth. Compromised immune response, which often accompanies chronic inflammatory reaction, may predispose to the development of lung cancer. There is additional evidence from pathological studies that, in the case of inactive tuberculosis, lung carcinoma can evolve directly from pre-existing post-tuberculosis lesions.

Chronic bronchitis/emphysema appeared in our study as a risk factor for lung cancer. Because cigarette smoking has been related to the aetiology of chronic bronchitis and emphysema, it is difficult to demonstrate an independent effect of these non-malignant pulmonary diseases on lung cancer risk. A positive association of chronic bronchitis and emphysema with lung cancer has been reported in several case-control studies and cohort studies. This association was reported mainly among smokers and for squamous-cell or small-cell carcinomas histological types known to be more strongly related to smoking.

In our study, a positive association of these diseases persisted even after adjustment for active smoking:
however, it was not elevated among never-smokers, so it remains possible that the overall association might be due to residual confounding by smoking. However, there is evidence from cohort studies that mucus hypersecretion and chronic airway obstruction, associated with chronic bronchitis/emphysema, are independent risk factors for lung cancer.\textsuperscript{27,28} These pulmonary impairments may reduce the clearance of carcinogens while damaged pulmonary tissue is more susceptible to the effects of carcinogens.\textsuperscript{30} There may also be inherent susceptibility to both lung cancer and obstructive lung disease.\textsuperscript{31}

In our study, the OR for asthma and lung cancer were consistently elevated after adjustment for active smoking but a statistically significant association was not consistently observed. Also, an elevated OR occurred in never-smokers and in females, who are mainly non-smokers, after adjustment for passive tobacco smoking. An association, therefore, seems to be independent of active and passive smoking. This evidence supports the findings of some studies,\textsuperscript{4,8} although the overall epidemiological evidence and association with different histological types is inconclusive.\textsuperscript{4,10,32} It might be related to the complex nature of asthma itself.\textsuperscript{33} Asthma is a separate disease that involves both chronic inflammation of the respiratory tract and bronchial hyperresponsiveness. This makes possible a misclassification of asthma and chronic bronchitis\textsuperscript{33} (which is positively associated with lung cancer) and misclassification of asthma with allergies\textsuperscript{18,34} (some of which have been reported to have a protective effect against lung cancer).

In our study, pneumonia showed a marginally significant association with lung cancer overall and this association was elevated among never smokers. There have been few epidemiological studies that investigated the association between pneumonia and lung cancer risk.\textsuperscript{4,8,10–12} The association has been demonstrated for adenocarcinoma\textsuperscript{10} and other types of lung cancer.\textsuperscript{11} In our study, like others, no differentiation was made between different types of pneumonia or the number of times it had occurred, although there is evidence that interstitial pneumonia is associated with lung cancer.\textsuperscript{35,36} Like pulmonary tuberculosis, pneumonia might result in scar formation in the lungs and the subsequent development of malignancy.\textsuperscript{37}

There are several methodological issues that must be considered in the analysis and interpretation of the results. First, there is a question of smoking as a major confounder and effect modifier of the association between lung cancer and previous

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Characteristic} & \textbf{Pulmonary tuberculosis} & \textbf{Chronic bronchitis/emphysema} & \textbf{Asthma} & \textbf{Pneumonia} \\
\hline
\textbf{Smoking} & & & & \\
Never-smoked & 1.9 (1.0–3.7) & 1.0 (0.6–1.6) & 2.0 (0.9–4.2) & 1.5 (0.7–3.2) \\
Light smokers & 1.5 (0.8–2.7) & 1.6 (1.1–2.4) & 1.0 (0.5–2.0) & 1.1 (0.6–2.2) \\
Moderate smokers & 7.2 (2.0–25.9) & 1.6 (1.0–2.8) & 1.1 (0.4–2.9) & 1.8 (0.8–4.0) \\
Heavy smokers & 4.6 (0.5–41.6) & 0.9 (0.3–2.6) & 1.8 (0.4–8.2) & 3.8 (0.4–38.4) \\
\hline
\textbf{Age (years)} & & & & \\
<45 & 1.6 (0.3–8.0) & 1.9 (0.9–4.3) & 1.6 (0.3–8.2) & 2.6 (0.7–9.3) \\
45–54 & 2.2 (1.2–4.2) & 1.5 (0.9–2.4) & 1.2 (0.6–2.6) & 1.0 (0.5–2.0) \\
55–64 & 1.9 (1.1–3.5) & 1.3 (0.9–1.9) & 1.2 (0.6–2.2) & 1.8 (0.8–3.8) \\
65+ & 2.5 (0.9–7.1) & 1.3 (0.7–2.2) & 2.3 (0.9–5.9) & 2.0 (0.7–5.3) \\
\hline
\textbf{Gender} & & & & \\
Male & 2.4 (1.5–3.8) & 1.2 \textsuperscript{b} (1.2–2.2) & 1.2 (0.7–1.9) & 1.6 (1.0–2.5) \\
Female & 1.5 (0.7–3.0) & 0.8 (0.5–1.4) & 2.2 (0.9–5.3) & 1.3 (0.6–3.1) \\
\hline
\textbf{Prefecture} & & & & \\
Pingliang & 2.1 (1.3–3.6) & 1.6 (1.1–2.2) & 2.2 \textsuperscript{b} (1.2–4.0) & 1.6 (0.8–3.2) \\
Qingyang & 2.1 (1.2–3.7) & 1.2 (0.8–1.7) & 0.9 (0.5–1.7) & 1.4 (0.8–2.4) \\
\hline
\textbf{Education} & & & & \\
<Primary & 1.9 (1.2–3.0) & 1.3 (1.0–1.8) & 1.3 (0.8–2.2) & 1.4 (0.8–2.3) \\
Tech/vocation & 1.4 (0.6–3.0) & 1.4 (0.8–2.4) & 1.2 (0.6–2.8) & 1.8 (0.7–4.2) \\
≥College & 5.0 (0.9–28.4) & 0.8 (0.2–3.8) & NA \textsuperscript{c} & 0.9 (0.1–7.3) \\
\hline
\textbf{Income} & & & & \\
<2000 & 2.0 (0.8–4.5) & 1.1 (0.6–2.0) & 0.9 (0.4–2.2) & 1.1 (0.5–2.3) \\
2000–2999 & 2.8 (1.1–7.0) & 1.6 (0.9–2.9) & 1.1 (0.5–2.7) & 1.0 (0.4–2.3) \\
3000–4399 & 2.1 (1.0–4.2) & 1.2 (0.8–2.1) & 1.8 (0.8–4.1) & 2.8 (1.1–7.3) \\
≥4400 & 1.8 (0.9–3.6) & 1.5 (1.0–2.4) & 2.4 (1.0–6.0) & 2.8 (1.1–7.2) \\
\hline
\textbf{No. of colour TVs} & & & & \\
None & 1.9 (1.2–3.1) & 1.2 (0.9–1.7) & 1.3 (0.8–2.2) & 1.3 (0.7–2.1) \\
At least one & 2.6 (1.2–5.8) & 1.7 (1.0–2.7) & 1.4 (0.6–3.2) & 2.0 (0.9–4.3) \\
\hline
\multicolumn{5}{l}{\textsuperscript{a} Reference group includes subjects with diseases diagnosed within 1–5 years of lung cancer diagnosis/interview.} \\
\multicolumn{5}{l}{\textsuperscript{b} Test of interactions, }\textit{P}<0.05.} \\
\multicolumn{5}{l}{\textsuperscript{c} Not available.} \\
\end{tabular}
\caption{Odds ratios and 95% CI for lung cancer by categories of sociodemographic variables and previous pulmonary diseases}
\end{table}
pulmonary diseases. In this study, active smoking was significantly associated with lung cancer, but the magnitude of the association was low compared to Western studies. However, this result is consistent with other Chinese studies and it has been attributed to the fact that older Chinese smokers in the past may not have smoked persistently, or may have smoked hand-rolled tobacco or pipes resulting in a lower risk than smoking cigarettes. We controlled for active smoking in all analyses, and the overall association is unlikely to be due to the residual confounding given the low risk of lung cancer from smoking and low proportion of heavy smokers in this population. Also, there was no consistent pattern of OR for lung cancer and previous pulmonary diseases across smoking categories that might have suggested residual confounding by smoking. Smoking did not modify the effect of previous pulmonary diseases either, but the test of interactions was of low power so it remains inconclusive whether smoking and previous pulmonary diseases are independent risk factors for lung cancer.

Second, it is possible some patients may have been mis-diagnosed with early symptoms of lung cancer as prior pulmonary disease (which would artificially increase the associations). However, results of the analysis were similar when we included patients with pulmonary diseases diagnosed within 1–5 years before lung cancer in the reference group or when we excluded patients in the 1–5 year interval. Since the 5-year relative survival rate for lung cancer is low, about 7% in China, it seems unlikely that the observed association was entirely due to misdiagnosis of lung cancer.

A third methodological issue involves the accuracy of the lung cancer diagnosis. The main analysis included all pathologically and clinically/radiologically diagnosed lung cancer cases. While pathological confirmation was available for 40% of the cases, the associations between lung cancer and pulmonary tuberculosis and chronic bronchitis/emphysema were still significant when the case group was limited to confirmed cases.

A fourth methodological issue concerns the fact that previous pulmonary diseases were self-reported, since the elevated OR could reflect differential recall bias, as a result of lung cancer patients being more likely to recall previous lung diseases because of their current illness. To minimize recall bias, subjects were asked only about a specific list of lung diseases, and diseases had to be diagnosed by a physician or have resulted in treatment and/or hospitalization. A related issue concerns reporting bias resulting from the fact that 54.3% of the cases were next-of-kin interviews. However, the results were unchanged when the next-of-kin data were excluded from the analysis, suggesting little bias was introduced by this factor.

In summary, this population-based case-control study in Gansu Province, China, provides additional evidence that previous pulmonary tuberculosis and chronic bronchitis/emphysema are causally related to lung cancer, although the precise mechanism is still unclear. The results for asthma and pneumonia, while suggestive of a positive association, should be interpreted with caution.

Acknowledgements
This work was supported by a contract between the United States National Cancer Institute (NO1-CP-50509) and the Laboratory of Industrial Hygiene, Beijing, China. We thank Ms Margaret Pecious and Ms Regina Hur, Westat Inc., for data management and programming support, and Dr Paul Levine, George Washington University, School of Public Health and Health Services, for advice and helpful suggestions. We appreciate data collection efforts accomplished by Shurong Zhang, Bing Shang, Ying Xia, Wenlan Wang, Jisheng Cao, Shujie Lei of the Laboratory of Industrial Hygiene, Ministry of Public Health, People’s Republic of China. We are also grateful to members of the expert review panel, Drs Jiguo Shi, Yuelan Kang, Fuhui Du, Datong Zhao, Yucheng Wang, for reviewing lung cancer diagnoses.

KEY MESSAGES
A population-based case-control study of lung cancer was conducted in Gansu Province, China. Pulmonary tuberculosis and chronic bronchitis/emphysema were significantly associated with lung cancer after adjusting for smoking. Asthma and pneumonia were suggestive of a positive association with lung cancer. History of prior lung disease may be an independent risk factor for lung cancer, although the precise mechanism is unclear.

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