

Ingested Arsenic, Cigarette Smoking, and Lung Cancer Risk

A Follow-up Study in Arseniasis-Endemic Areas in Taiwan

Chi-Ling Chen, PhD

Lin-I Hsu, PhD

Hung-Yi Chiou, PhD

Yu-Mei Hsueh, PhD

Shu-Yuan Chen, PhD

Meei-Maan Wu, PhD

Chien-Jen Chen, ScD

for the Blackfoot Disease
Study Group

ARSENIC IS A NATURALLY OCCURRING element in soil. Medicinal use of arsenic for the treatment of leukemia and psoriasis, occupational exposure via inhalation, and drinking arsenic-contaminated water are important sources of arsenic exposure. The International Agency for Research on Cancer¹ documented that inorganic arsenic compounds are skin and lung carcinogens in humans. Recent epidemiologic studies² have shown that arsenic exposure via drinking water was associated with an increased risk of lung cancer.

Residents of the southwestern and northeastern coasts of Taiwan had been drinking well water contaminated with a high concentration of arsenic before the establishment of the public tap water system.^{3,4} They were found to have an increased risk of cancers, including lung cancer.² Our previous study² followed up residents of the southwestern coast for 7 years and found a sig-

Context Arsenic has been documented as a lung carcinogen in humans in only a few follow-up studies, which were limited by a small number of cases or the lack of information on cigarette smoking.

Objectives To elucidate the dose-response relationship between ingested arsenic and lung cancer and to assess the effect of cigarette smoking on the arsenic-lung cancer association.

Design, Setting, and Participants A total of 2503 residents in southwestern and 8088 in northeastern arseniasis-endemic areas in Taiwan were followed up for an average period of 8 years. Information on arsenic exposure, cigarette smoking, and other risk factors was collected at enrollment through standardized questionnaire interview.

Main Outcome Measures The incidence of lung cancer was ascertained through linkage with national cancer registry profiles in Taiwan (January 1985-December 2000). The joint effect of arsenic and cigarette smoking was estimated by both etiologic fraction and synergy index.

Results There were 139 newly diagnosed lung cancer cases during a follow-up period of 83 783 person-years. After adjustment for cigarette smoking and other risk factors, there was a monotonic trend of lung cancer risk by arsenic level in drinking water of less than 10 to 700 $\mu\text{g/L}$ or more ($P < .001$). The relative risk was 3.29 (95% confidence interval, 1.60-6.78) for the highest arsenic level compared with the lowest. The etiologic fraction of lung cancer attributable to the joint exposure of ingested arsenic and cigarette smoking ranged from 32% to 55%. The synergy indices ranged from 1.62 to 2.52, indicating a synergistic effect of ingested arsenic and cigarette smoking on lung cancer.

Conclusions There was a significant dose-response trend of ingested arsenic on lung cancer risk, which was more prominent among cigarette smokers. The risk assessment of lung cancer induced by ingested arsenic should take cigarette smoking into consideration.

JAMA. 2004;292:2984-2990

www.jama.com

See also pp 2977 and 3026.

nificant dose-response relationship between cumulative arsenic exposure and risk of lung cancer (relative risk [RR], 4.01; 95% confidence interval [CI], 1.00-16.12; for the highest level of arsenic exposure [≥ 20 mg/L per year]) compared with unexposed residents. However, there were only 27 lung cancer cases identified; hence, the

Author Affiliations: Graduate Institute of Epidemiology, College of Public Health, National Taiwan University (Drs C.-L. Chen, Hsu, and C.-J. Chen), School of Public Health, Taipei Medical University (Drs Chiou, Hsueh, and Wu), and Division of Biostatistics and Bioinformatics, National Health Research Institute (Dr S.-Y. Chen), Taipei, Taiwan.

A complete list of the Blackfoot Disease Study Group appears at the end of this article.

Corresponding Author: Chien-Jen Chen, ScD, College of Public Health, National Taiwan University, 1 Jen-Ai Rd, Section 1, Taipei 10018, Taiwan (cjchen@ha.mc.ntu.edu.tw).

arsenic-exposed residents could only be divided into 3 groups.

Cigarette smoking has been found to be a major cause of lung cancer during the past 50 years, and it was estimated that quitting cigarette smoking may prevent more than 90% of lung cancers.⁵ A meta-analysis⁶ of studies on occupational arsenic exposure via inhalation found a synergistic effect of cigarette smoking and arsenic on lung cancer, and 30% to 54% of lung cancer cases were attributable to both exposures. A population-based case-control study reported an odds ratio (OR) of 32.0 (95% CI, 7.2-198.0) for cigarette smokers who had an ingested arsenic exposure level of 200 µg/L or higher compared with nonsmokers exposed to an arsenic level of less than 49 µg/L.² The OR was much higher than that for cigarette smoking alone (OR, 6.1; 95% CI, 1.3-39.2; for cigarette smokers compared with nonsmokers) and elevated arsenic exposure alone (OR, 8.0; 95% CI, 1.7-52.3; for arsenic exposure of ≥ 200 µg/L compared with < 49 µg/L).

This study combined 2 study cohorts recruited from southwestern and northeastern Taiwan with 10591 residents who had been followed up for an average of 8 years in an effort to elucidate the dose-response relationship between ingested arsenic exposure and lung cancer risk. The larger number of study participants, longer period of follow-up with more incident lung cancer cases, and wider range of arsenic exposure levels provided us with a unique opportunity to further investigate the modifying effect of cigarette smoking on the association between ingested arsenic and lung cancer.

METHODS

A total of 2503 residents in southwestern and 8088 in northeastern arseniasis-endemic areas of Taiwan were followed up for an average period of 8 years. Information on arsenic exposure, cigarette smoking, and other risk factors was collected at enrollment through standardized questionnaire interview, whereas the incident lung cancer cases were identified through link-

age with a national cancer registry in Taiwan. The joint effect of arsenic and cigarette smoking was estimated by both etiologic fraction and synergy index. All participants provided oral or written informed consent to participate in this study, and the data collection procedures were reviewed and approved by the institutional review board of the College of Public Health, National Taiwan University, Taipei.

Study Areas

This study recruited study participants from 2 arseniasis-endemic areas in Taiwan: one included the 4 townships of Peimen, Hsuehchia, Putai, and Ichu on the southwestern coast, and the other included the 4 townships of Tungshan, Chuangwei, Chiaohsi, and Wuchieh in the northeastern Lanyang Basin.^{3,4} Residents in the southwestern endemic area had consumed artesian well water (100-300 m in depth) because of the high salinity of shallow well water (6-8 m in depth) for more than 50 years before the implementation of the tap water supply system in the early 1960s.⁷ The estimated amount of ingested arsenic mainly from drinking water was as high as 1 mg/d in this area.⁸ Residents in the northeastern endemic area had consumed water from shallow wells (< 40 m in depth) since the late 1940s through the early 1990s, when the tap water system was implemented. Arsenic levels in well water in the northeastern Lanyang Basin ranged from less than 0.15 µg/L (undetectable) to more than 3000 µg/L.⁴

Study Cohorts

Southwestern Cohort. Participants in 2 studies conducted in the arseniasis-endemic area of southwestern Taiwan were followed up in the current study, and a detailed description of the recruitment procedure for both studies has been reported previously.^{2,9} The first study included 257 patients with blackfoot disease (a unique peripheral arterial disease characterized by systemic atherosclerosis and dry gangrene of extremities in arseniasis-endemic areas) and 753 healthy community controls

matched for age, sex, and residential townships. The second study included 1571 residents in 3 villages of Putai Township, including Homei, Fuh-sin, and Hsinming, where the prevalence of blackfoot disease was the highest. Among these 2581 residents, 25 participated in both studies, and since national identification numbers were used for linkage with the national cancer registry profiles, the 53 (42 incomplete and 11 missing) without these numbers were also excluded from the analyses, resulting in 2503 study participants for the southwestern cohort.

Northeastern Cohort. The enrollment of study participants from the northeastern arseniasis-endemic area has been described in detail elsewhere.⁴ Briefly, a total of 8102 residents from 4586 households of 18 villages participated in the baseline home interview from 1991 to 1994. The national identification numbers were missing for 14 participants; therefore, 8088 study participants remained in the northeastern cohort.

Arsenic Exposure

Southwestern Cohort. A structured questionnaire was developed to obtain detailed information on sociodemographic characteristics, residential and occupational history, history of drinking well water, and cigarette smoking and alcohol consumption by 2 well-trained public health nurses. For every study participant, both residential history and duration of drinking artesian well water were used to derive the cumulative arsenic exposure. Since only a few wells were in the same village, those who lived in each village shared these wells. Therefore, the median arsenic level of well water in a specific village tested in the early 1960s¹⁰ was used as the arsenic concentration. Migration from one village to another also occurred, and the arsenic concentration in well water from different villages varied; thus, lifetime cumulative exposure was the best method of estimation, because it took into account not only arsenic concentration in well water, but also duration of drinking wa-

ter. The lifetime cumulative arsenic exposure was obtained by multiplying the median arsenic concentration in 1 specific village by the duration of consuming artesian well water in that village and summing the values across the entire period when residing in the arseniasis-endemic area. Because residents in the northeastern cohort had their own well, from which they had drunk water for more than 50 years, the arsenic exposure could be estimated by direct testing of their well water.⁴ To be compatible with this, we decided to use average arsenic concentration as a measurement of arsenic exposure, and this was calculated by dividing the lifetime cumulative arsenic exposure by the total years of drinking artesian well water. Arsenic exposures were available only for those who have complete information on arsenic exposure throughout their lifetime. If the median level of arsenic

concentration was unknown for any village where a given study participant lived, the arsenic exposures of the study participant were classified as unknown, resulting in 775 study participants with unknown arsenic exposures.

Northeastern Cohort. Four well-trained local public health nurses conducted personal interviews with the same questionnaire developed for the southwestern cohort. There were a total of 3216 water samples (82.4%) collected from individual wells of 3901 households during the home interview. Because the wells of 685 households were no longer existent, the arsenic exposure of 1198 residents was classified as unknown.⁴

For both study areas, we used a similar water sampling technique, and although the analysis methods differed (Natelson method¹¹ for southwestern

cohort and Hydride Generation Atomic Absorption Spectrophotometer method² for northeastern cohort), it was found that the results were highly correlated.¹² The detection limits were 30 and 0.15 µg/L for the southwestern and northeastern cohorts, respectively.^{2,9} Among 1973 study participants with unknown arsenic exposure, 42% were men, with a mean age of 57.6 years; this was compatible with those who had arsenic exposure information.

Identification of Lung Cancer Cases

Each participant's unique national identification number was used to link with the computerized national cancer registry profiles in Taiwan to identify newly diagnosed lung cancer cases between January 1, 1985, and December 31, 2000. The cancer registry system was implemented in 1978 in Taiwan and was considered a nationwide cancer

Table 1. Average Arsenic Level in Well Water, Age at Recruitment, and Follow-up Period in the Southwestern and Northeastern Cohorts*

Risk Factor	Southwestern Cohort		
	Blackfoot Disease Cases and Matched Controls	Residents in 3 Arseniasis-Hyperendemic Villages	Northeastern Cohort
Average arsenic level in well water, µg/L			
<10	277 (29.5)	219 (14.0)	2288 (28.3)
10-99.9	60 (6.4)	8 (0.5)	3002 (37.1)
100-299.9	43 (4.6)	34 (2.2)	909 (11.2)
300-699.9	148 (15.7)	108 (6.9)	441 (5.5)
≥700	9 (1.0)	822 (52.6)	250 (3.1)
Unknown	403 (42.9)	372 (23.8)	1198 (14.8)
Mean (SD)	182.99 (253.5)	592.88 (324.0)	117.26 (297.2)
Age at recruitment, mean (SD), y	59.7 (10.5)	48.8 (11.1)	59.1 (11.0)
Male	449 (47.8)	705 (45.1)	4053 (50.1)
Female	491 (52.2)	858 (54.9)	4035 (49.9)
Cigarette smoking†			
Never	649 (69.0)	1164 (74.5)	4821 (59.6)
Past	49 (5.2)	49 (3.1)	997 (12.3)
Current	242 (25.7)	350 (22.4)	2268 (28.1)
Habitual alcohol consumption‡			
No	822 (87.5)	1356 (86.8)	6540 (80.9)
Yes	118 (12.5)	206 (13.2)	1533 (19.0)
Years of schooling§			
0	393 (41.8)	558 (35.7)	2268 (28.0)
1-6	480 (51.1)	741 (47.4)	4776 (59.1)
>6	58 (6.2)	260 (16.6)	593 (7.3)
Follow-up years, mean (SD)	11.5 (5.2)	11.3 (2.5)	6.9 (1.6)

*Data are number (percent) of study participants unless otherwise indicated.

†Two residents of the northeastern cohort had unknown cigarette smoking status.

‡One resident of the southwestern cohort and 15 of the northeastern cohort had unknown habitual alcohol consumption.

§Thirteen residents of the southwestern cohort and 451 of the northeastern cohort had unknown years of schooling.

registry system with updated, accurate, and complete information.

Statistical Analyses

Follow-up person-years for each participant were calculated from the date of questionnaire interview to the date of cancer diagnosis, death, or December 31, 2000, whichever came first. Average arsenic concentration was arbitrarily divided into less than 10, 10 through 99.9, 100 through 299.9, 300 through 699.9, and 700 µg/L or higher so that there were enough lung cancer cases in each category. Measurements of cigarette smoking included smoking status (never, current, or past), numbers of cigarettes smoked per day, total years of cigarettes smoked, and cumulative exposure of cigarette smoking (pack-years). We defined past smokers as those who quit smoking at recruitment and current smokers as those who were still smoking at interview. The RRs and 95% CIs were estimated by Cox proportional hazards regression models. The adjustment variables in the final model included age (continuous), sex, years of schooling (0, 1-6, or >6 years), study cohort (black-foot disease cases and matched controls of the southwestern coast, residents in arseniasis-hyperendemic villages of the southwestern coast, and residents of Lanyang Basin on the northeastern coast), cigarette smoking status (never, past, or current), and habitual alcohol consumption (no or yes). All analyses were performed with Stata statistical software (version 7.0, Stata Corp, College Station, Tex).

The joint effect of arsenic and cigarette smoke was estimated by 2 indices of synergism. The first index was the etiologic fraction, which indicated the percentage of cases with both exposures that was due to the synergism¹³ ($[(RR_{11} - RR_{01} - RR_{10} + RR_{00})/RR_{11}]$). The range of departure from additivity was estimated from the 95% CI of the etiologic fraction based on the methods described by Walker.¹³ The second index was the synergy index, which was the ratio between the observed excess risk in those with exposures to 2 risk fac-

tors ($RR_{11} - 1$) and the excess risk predicted under simple additivity (the sum of 2 excess risks with only exposure to 1 risk factor, ie, $[RR_{10} - 1] + [RR_{01} - 1]$).¹⁴ A synergy index greater than 1 indicated the synergistic effect of 2 risk factors on a disease.

RESULTS

A total of 83 783 person-years were observed during the follow-up period from January 1, 1985, to December 31, 2000. There were 139 newly developed lung cancers, yielding an incidence of 165.9 per 100 000 person-years. TABLE 1 com-

Table 2. Follow-up Person-Years and Newly Diagnosed Lung Cancer Cases by Age at Recruitment, Sex, Years of Schooling, Habitual Alcohol Consumption, and Cigarette Smoking

Risk Factor	Follow-up Person-Years	Newly Diagnosed Lung Cancer Cases (n = 139)	Age- and Sex-Adjusted RR (95% CI)*
Age at recruitment, y†			
<50	25 507	15	1.00 (Referent)
50-54	14 898	20	2.35 (1.20-4.59)
55-59	13 807	21	2.60 (1.34-5.05)
60-64	11 828	36	5.32 (2.90-9.75)
≥65	17 744	47	4.87 (2.71-8.77)
Sex‡			
Male	39 870	100	1.00 (Referent)
Female	43 913	39	0.35 (0.24-0.50)
Years of schooling			
0	24 563	34	1.00 (Referent)
1-6	48 045	91	1.52 (0.98-2.36)
>6	8126	6	0.64 (0.26-1.60)
Habitual alcohol consumption			
No	69 938	96	1.00 (Referent)
Yes	13 735	43	1.51 (1.02-2.23)
Cigarette smoking at recruitment			
Never	54 513	44	1.00 (Referent)
Past	7443	23	3.60 (1.78-7.27)
Current	21 729	71	4.19 (2.28-7.70)
Years of cigarette smoking§			
0	54 513	44	1.00 (Referent)
1-35	15 117	29	3.27 (1.66-6.43)
>35	13 281	63	4.95 (2.57-9.51)
Cigarettes smoked per day			
0	54 513	44	1.00 (Referent)
1-19	11 325	29	3.08 (1.57-6.04)
≥20	17 946	66	5.00 (2.63-9.51)
Pack-years of cigarette smoking¶			
0	54 513	44	1.00 (Referent)
1-25	12 016	26	3.26 (1.65-6.43)
>25	16 193	66	4.98 (2.60-9.56)
Average arsenic levels in well water, µg/L			
<10	21 677	27	1.00 (Referent)
10-99	21 201	31	1.15 (0.69-1.94)
100-299	7053	17	2.04 (1.11-3.75)
300-699	5675	18	2.65 (1.46-4.82)
≥700	10 843	26	2.50 (1.42-4.40)
Unknown	17 334	20	0.98 (0.55-1.74)

Abbreviations: CI, confidence interval; RR, relative risk.

*P for trend <.001. Those without an average arsenic level in well water were excluded from the trend test.

†Adjusted for sex.

‡Adjusted for age in 1-year increment.

§Eleven study participants of the southwestern cohort and 118 of the northeastern cohort had unknown duration of cigarette smoking.

||Two study participants of the northeastern cohort had unknown quantity of cigarette smoking.

¶Eleven study participants of the southwestern cohort and 147 of the northeastern cohort had unknown data.

INGESTED ARSENIC, CIGARETTE SMOKING, AND LUNG CANCER RISK

compares the average arsenic exposure level, age at recruitment, sex, years of schooling, cigarette smoking and alcohol consumption status at enrollment, and fol-

low-up years among the 3 groups of study participants in the 2 cohorts. The average arsenic exposure level was highest among residents who lived in arse-

niasis-hyperendemic southwestern villages and lowest among those who lived in the northeastern endemic area. Most of the southwestern cohort consumed an average arsenic level greater than 100 µg/L, and most of the northeastern cohort consumed an average arsenic level less than 100 µg/L. The mean age at recruitment was lowest among residents in arseniasis-hyperendemic villages, and the sex distribution was similar in the 3 groups. Residents in the northeastern cohort reported the highest percentage of cigarette smoking and alcohol consumption. The average follow-up years were similar in the 2 study groups of the southwestern cohort (11 years) and shorter in the northeastern cohort (7 years).

TABLE 2 gives the numbers of person-years of follow-up and lung cancer cases by age at recruitment, sex, years of schooling, habitual alcohol consumption, and cigarette smoking. Since the RRs associated with various risk factors were similar in the different study cohorts, only pooled data are given in Table 2. Older age, male sex, and habitual alcohol consumption were associated with an increased risk of lung cancer, whereas years of schooling was not. Compared with nonsmokers, those who smoked cigarettes at recruitment had an increased risk of lung cancer (RR, 4.19; 95% CI, 2.28-7.70). Significant dose-response trends were observed for the duration (years), quantity (cigarettes smoked per day), and cumulative exposure (pack-years) of cigarette smoking, showing a 5-fold risk for the highest exposure group. A significant dose-response trend ($P < .001$) associated with increasing levels of arsenic exposure and risk of lung cancer was found with only age and sex adjustment.

Past and current smokers had a 4-fold risk of lung cancer compared with nonsmokers after adjustment for other risk factors, including ingested arsenic exposure (TABLE 3). Similarly, after adjustment for other risk factors, including cigarette smoking, a significant dose-response trend was found for arsenic exposure ($P < .001$). The RR as-

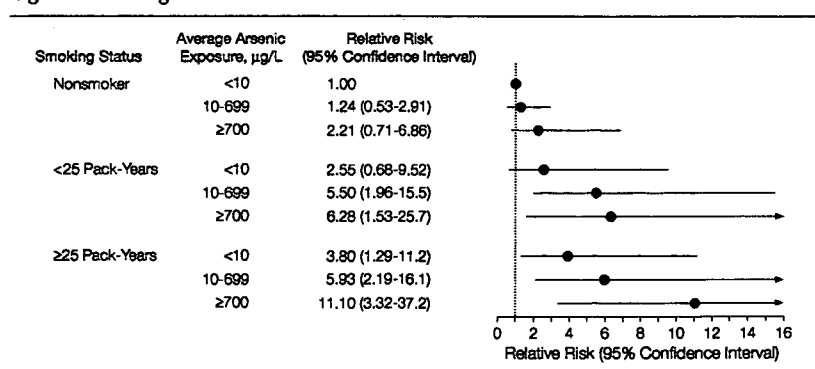
Table 3. Multivariate-Adjusted Relative Risk of Lung Cancer for Various Risk Factors Among Residents in Arseniasis-Endemic Areas in Taiwan*

Risk Factor	Multivariate-Adjusted RR (95% CI)*
Age in 1-year increment	1.06 (1.04-1.08)
Sex	
Male	1.00 (Referent)
Female	1.31 (0.66-2.59)
Cigarette smoking status at recruitment	
Never	1.00 (Referent)
Past	4.03 (1.92-8.44)
Current	4.39 (2.30-8.39)
Cohort	
Southwestern cohort	
Blackfoot disease cases and controls	1.00 (Referent)
Residents in arseniasis-hyperendemic villages	1.16 (0.50-2.66)
Northeastern cohort	1.33 (0.67-2.63)
Years of schooling	
0	1.00 (Referent)
1-6	1.63 (1.04-2.56)
>6	0.87 (0.35-2.19)
Habitual alcohol consumption	
No	1.00 (Referent)
Yes	1.15 (0.77-1.73)
Average arsenic level in well water, µg/L	
<10	1.00 (Referent)
10-99	1.09 (0.63-1.91)
100-299	2.28 (1.22-4.27)
300-699	3.03 (1.62-5.69)
≥700	3.29 (1.60-6.78)
Unknown	1.10 (0.60-2.03)

Abbreviations: CI, confidence interval; RR, relative risk.

* P for trend $< .001$. Those without an average arsenic level in well water were excluded from the trend test.

Figure. Relative Risks of Lung Cancer by Average Arsenic Exposure and Pack-Years of Cigarette Smoking



Relative risks and 95% confidence intervals are shown. The reference group was study participants who were exposed to the lowest level of arsenic (<10 µg/L) and never smoked cigarettes. Data have been adjusted for age at recruitment, sex, years of schooling, and habitual alcohol consumption in a proportional hazards analysis.

sociated with the highest arsenic level (≥ 700 $\mu\text{g/L}$) was 3.29 (95% CI, 1.60-6.78) after adjusting for age, sex, cigarette smoking status at recruitment, years of schooling, habitual alcohol consumption, and the cohort where they were originally recruited.

Among nonsmokers, those who were exposed to the highest arsenic level (≥ 700 $\mu\text{g/L}$) had an RR of lung cancer around 2-fold (RR, 2.21; 95% CI, 0.71-6.86) when compared with those with the lowest level (< 10 $\mu\text{g/L}$) (FIGURE). Among participants with the lowest arsenic level, those who had the highest cumulative cigarette smoking exposure had a 4-fold risk of lung cancer (RR, 3.80; 95% CI, 1.29-11.2) compared with nonsmokers. When compared with nonsmokers with an arsenic exposure level less than 10 $\mu\text{g/L}$, those who consumed well water with an arsenic level of 700 $\mu\text{g/L}$ or more and smoked for more than 25 pack-years had a more than 11-fold risk of lung cancer (RR, 11.1; 95% CI, 3.32-37.2). Similar results were found when duration and quantity of cigarette smoking were used as indicators of cigarette smoking (data not shown). In addition, the etiologic fractions of lung cancer due to joint effect of cigarette smoking and ingested arsenic ranged from 0.32 to 0.55. In other words, 32% to 55% of lung cancer cases were attributable to both arsenic exposure and cigarette smoking. Furthermore, all synergy indices were greater than 1 (range, 1.62-2.52), indicating the existence of synergism in an additive way (TABLE 4). However, the multiplicative interaction was not statistically significant (data not shown).

COMMENT

The association between ingested arsenic and lung cancer mortality was first reported through both ecologic correlation studies^{5,7} and a case-control study² conducted in the southwestern arseniasis-endemic area of Taiwan. The only follow-up study was based on the southwestern cohort of the current study with a 7-year follow-up period and 27 lung cancer cases. A 4-fold risk

(95% CI, 1.00-16.12) was found for the highest cumulative arsenic exposure (≥ 20 mg/L per year) compared with the unexposed.² In this study with a longer follow-up period and more lung cancer cases, we confirmed the elevated risk of lung cancer associated with arsenic exposure. In addition, we found a significant dose-response relationship in finer categories of arsenic exposure from less than 10 to 700 $\mu\text{g/L}$ or more. Similar results were found in a hospital-based case-control study (OR, 8.9; 95% CI, 4.0-19.6; for an average arsenic concentration of 200-400 $\mu\text{g/L}$ compared with < 10 $\mu\text{g/L}$).¹⁰

The lung cancer risk among those with the highest exposures to cigarette smoking and arsenic could be as high as 11-fold when compared with nonsmokers with the lowest arsenic exposure. Approximately 32% to 55% of lung cancer cases were estimated to be attributable to the combined effect of cigarette smoking and ingested arsenic, depending on the levels of both exposures. The synergy indices ranged from 1.62 to 2.52, which were all above 1, indicating a synergistic effect under an additive scale. This finding was consistent with a meta-analysis⁶ of occupational arsenic exposure via inhalation and cigarette smoking, with 30% to 50% of lung cancer cases attributable to both exposures. Other studies² also provided evidence of synergism between ingested arsenic and smoking but did not quantify the etiologic fraction.

Because lung cancer is a rare disease, we followed up all study participants to increase statistical power to detect a significant association at minimal exposure levels. Because most northeastern residents were at lower arsenic exposure levels and southwestern residents were at higher levels, we were able to stratify arsenic exposures into finer categories. The detection limits for arsenic analysis methods were also different in the 2 study areas (30 $\mu\text{g/L}$ for the southwestern cohort and < 0.15 $\mu\text{g/L}$ for the northeastern cohort), but the arsenic concentration ranged from 350 to 1140 $\mu\text{g/L}$ in the southwestern study area and less than 0.15 to 3590 $\mu\text{g/L}$ in the north-

Table 4. Synergy Indices and Etiologic Fractions of Average Arsenic Exposure and Cumulative Cigarette Smoking on the Risk of Lung Cancer in Arseniasis-Endemic Areas in Taiwan

Average Arsenic Exposure, $\mu\text{g/L}$	Synergy Index*	Etiologic Fraction (95% CI)
Participants Who Smoked < 25 Pack-Years		
10-699	2.51	0.49 (-0.06 to 1.04)
≥ 700	1.91	0.40 (-0.31 to 1.11)
Participants Who Smoked ≥ 25 Pack-Years		
10-699	1.62	0.32 (-0.11 to 0.75)
≥ 700	2.52	0.55 (0.21 to 0.89)†

Abbreviation: CI, confidence interval.

*Based on relative risks that were adjusted for age, sex, study cohort, years of schooling, and habitual alcohol consumption.

†The 95% CI did not include 0.

eastern study area. The misclassification of exposure due to detection limits should be minimal. In addition, the 3 study groups were compatible in their occupations, ethnic backgrounds, lifestyles, and dietary patterns. Although there were differences in age, cigarette smoking, habitual alcohol consumption, and years of schooling, these factors were adjusted in the regression analyses. To avoid any residual confounding of unknown factors among groups, a variable of study group was included in the analyses. A great effort was made to control for potential confounding factors, such as age, sex, education levels, and habitual alcohol consumption and status of cigarette smoking by adding them to the model. Since the arsenic exposure was estimated not only by water concentration but also by the duration of living in one specific village, the potential effects of immigration and emigration should be minimal. All lung cancer cases were pathologically confirmed, and the cancer registration rate was estimated to be as high as 98% during 1996 to 1999. Even if we might miss some cancer cases in earlier follow-up years, there was no reason to believe that the few missing cases would relate to the arsenic exposure and cigarette smoking in a selective way. Furthermore, the distribution of histologic types of lung cancers were similar to those of the whole country, with squamous cell carcinomas (45%) as

the most common and adenocarcinomas (22%) the next most common.

The arsenic exposure was unknown for 31% of study participants in the southwestern cohort and 15% in the northeastern cohort. Because all these study participants were exposed to arsenic to some extent, their RR of developing lung cancer lay between the lowest and highest exposure levels. The exclusion of this group from the analyses did not alter the study outcome, and they were not included in analyses of dose-response trend and effect modification.

For the southwestern cohort, most residents started drinking artesian well water in the 1910s, and the tap water system was first introduced in the 1960s.² Most residents in Lanyang Basin had been drinking water from shallow wells since the 1940s, and the tap water system was not implemented in this area until the late 1990s.⁴ Although the arsenic concentration in well water might change over time, it was reported that after rechecking the same well water 2 years after the survey, the concentrations were stable in the endemic areas.¹⁵ However, there was no information on the long-term stability of arsenic concentration in the well water. In addition, the measurement of arsenic exposure was based on only 1 large-scale survey in the southwestern and northeastern endemic areas, so there might be some misclassification of arsenic exposure. Nevertheless, this misclassification was considered nondifferential, and the observed asso-

ciations between lung cancer and ingested arsenic could be underestimated. The information on cigarette smoking was obtained only once at recruitment, and it was possible that some of the study participants might have changed their smoking status, which would lead to underestimation of lung cancer risk associated with cigarette smoking.

In this analysis, we confirm our earlier finding of an increased risk of lung cancer associated with increasing levels of arsenic exposure via drinking water. In addition, we found a significant dose-response trend in the finer categories. Although this study is an extension of the previous findings, the results are relevant and of general medical interest. Furthermore, this effect was found to be stronger among those who smoked cigarettes, and the risk could be as high as more than 10-fold.

Our study provides evidence of a synergistic relationship between cigarette smoking and ingested arsenic on the risk of lung cancer. The reductions in cigarette smoking would likely reduce the lung cancer risk accompanied by exposure to arsenic, and similarly, reductions in arsenic exposure would reduce the lung cancer risk among cigarette smokers. Appropriate public health interventions, such as cigarette smoking cessation programs and reduction in arsenic concentration of drinking water, are warranted. Furthermore, it is essential to take cigarette smoking into consideration in the risk assessment and the de-

termination of the maximal contamination level of arsenic in drinking water.

Author Contributions: Dr C.-J. Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: C.-L. Chen, Chiou, Hsueh, C.-J. Chen.

Acquisition of data: C.-L. Chen, Hsu, Hsueh, S.-Y. Chen, Wu, C.-J. Chen.

Analysis and interpretation of data: C.-L. Chen, S.-Y. Chen, Wu, C.-J. Chen.

Drafting of the manuscript: C.-L. Chen.

Critical revision of the manuscript for important intellectual content: C.-L. Chen, Hsu, Chiou, Hsueh, S.-Y. Chen, Wu, C.-J. Chen.

Statistical analysis: C.-L. Chen, Hsu, S.-Y. Chen, Wu.

Obtained funding: C.-J. Chen.

Administrative, technical, or material support: Chiou, Hsueh, C.-J. Chen.

Study supervision: Hsueh, C.-J. Chen.

The Blackfoot Disease Study Group: Graduate Institute of Epidemiology, College of Public Health (Chien-Jen Chen, ScD, Chi-Ling Chen, PhD, Lin-I Hsu, PhD, Wei-Liang Shih, MS, Yi-Hsiang Hsu, MS, Chia-Yen Chen, BS, Yu-Chin Cheng, BS, and Li-Hua Wang, BS) and Graduate Institute of Medical Technology, College of Medicine (Cheng-Yeh Lee, MS), National Taiwan University, Taipei; School of Public Health, Taipei Medical University, Taipei, Taiwan (Hung-Yi Chiou, PhD, Yu-Mei Hsueh, PhD, Meel-Maan Wu, PhD, Iuan-Hong Wang, MS, Yu-Chun Lin, MS); Division of Biostatistics and Bioinformatics, National Health Research Institute, Taipei, Taiwan (Shu-Yuan Chen, PhD); Division of Environmental Health and Occupational Medicine, National Health Research Institute, Kaohsiung, Taiwan (Wei-Lin Chou, MS); Department of Cardiology, Cardinal Tien Hospital, Fu-Jen Catholic University, Taipei, Taiwan (Chih-Hao Wang, MD, PhD); Department of Dermatology, National Taiwan University Hospital, Taipei (Mei-Ping Tseng, MS).

Funding/Support: This study was supported by grants NSC83-0412-B002-231, NSC91-2320-B002-075, NSC92-2320-B002-136, and NSC92-2320-B002-135 from the National Science Council and DOH85-HR-503PL from Department of Health, Executive Yuan, Taiwan. **Role of the Sponsors:** The National Science Council and Department of Health, Executive Yuan, Taiwan, were not involved in the design and conduct of the study, in the collection, management, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

REFERENCES

1. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man: Some Metals and Metalloid Compounds*, Volume 23. Lyon, France: International Agency for Research on Cancer; 1980:139-141.
2. Inter-Organization Programme for the Sound Management of Chemicals, World Health Organization. *Arsenic and Arsenic Compounds*. 2nd ed. Geneva, Switzerland: Inter-Organization Programme for the Sound Management of Chemicals, World Health Organization; 2001.
3. Tseng WP, Chen WY, Sung JL, Chen JS. A clinical study of blackfoot disease in Taiwan: an endemic peripheral vascular disease. In: *Memoirs, College of Medicine, National Taiwan University, Volume 7*. Taipei: National Taiwan University College of Medicine; 1961:1-18.
4. Chiou HY, Huang WI, Su CL, et al. Dose-response

- relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke*. 1997;28:1717-1723.
5. Boyle P, Malsonneuve P. Lung cancer and tobacco smoking. *Lung Cancer*. 1995;12:167-181.
6. Hertz-Picciotto I, Smith AH, Holtzman D, Lipsett M, Alexeeff G. Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. *Epidemiology*. 1992;3:23-31.
7. Chen KP, Wu HY, Wu TC. Epidemiologic studies on blackfoot disease in Taiwan, 3: physicochemical characteristics of drinking water in endemic blackfoot disease area. In: *Memoirs, College of Medicine, National Taiwan University, Volume 8*. Taipei: National Taiwan University College of Medicine; 1962:115-129.
8. Blackwell RQ. Estimation total arsenic ingested by residents in the endemic blackfoot area. *J Formosan Med Assoc*. 1961;60:1143-1144.
9. Lai MS, Hsueh YM, Chen CJ, et al. Ingested inor-

- ganic arsenic and prevalence of diabetes mellitus. *Am J Epidemiol*. 1994;139:484-492.
10. Kuo TL. Arsenic content of artesian well water in endemic area of chronic arsenic poisoning. *Rep Inst Pathol Natl Taiwan Univ*. 1964;20:7-13.
11. Natelson S. *Microtechniques of Clinical Chemistry for the Routine Laboratory*. 2nd ed. Springfield, Ill: Charles C Thomas; 1961:113-119.
12. MacCarthy P, Klusman RW, Rice JA. Water analysis. *Anal Chem*. 1987;59:308R-337R.
13. Walker AM. Proportion of disease attributable to the combined effect of two factors. *Int J Epidemiol*. 1981;10:81-85.
14. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*. 1992;3:452-456.
15. Lo MC, Hsen YC, Lin BK. *The Second Report on the Investigation of Arsenic Content in the Underground Water in Taiwan Province*. Taichung: Taiwan Provincial Institute of Environmental Sanitation; 1977.