Lung Cancer and Arsenic Concentrations in Drinking Water in Chile

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Cities in northern Chile had arsenic concentrations of 860 μg/liter in drinking water in the period 1958–1970. Concentrations have since been reduced to 40 μg/liter. We investigated the relation between lung cancer and arsenic in drinking water in northern Chile in a case-control study involving patients diagnosed with lung cancer between 1994 and 1996 and frequency-matched hospital controls. The study identified 152 lung cancer cases and 419 controls. Participants were interviewed regarding drinking water sources, cigarette smoking, and other variables. Logistic regression analysis revealed a clear trend in lung cancer odds ratios and 95% confidence intervals (CIs) with increasing concentration of arsenic in drinking water, as follows: 1, 1.6 (95% CI = 0.5–5.3), 3.9 (95% CI = 1.2–12.3), 5.2 (95% CI = 2.3–11.7), and 8.9 (95% CI = 4.0–19.6), for arsenic concentrations ranging from less than 10 μg/liter to a 65-year average concentration of 200–400 μg/liter. There was evidence of synergy between cigarette smoking and ingestion of arsenic in drinking water; the odds ratio for lung cancer was 32.0 (95% CI = 7.2–198.0) among smokers exposed to more than 200 μg/liter of arsenic in drinking water (lifetime average) compared with nonsmokers exposed to less than 50 μg/liter. This study provides strong evidence that ingestion of inorganic arsenic is associated with human lung cancer. (Epidemiology 2000;11:673–679)

Keywords: arsenic, lung cancer, water pollutants, smoking, synergy, case-control study, environmental epidemiology.

Humans are exposed to organic and inorganic arsenic through environmental and occupational sources. Lung cancer is known to be caused by occupational exposure to arsenic via inhalation.[1] The main occupational exposures occur in workers who are engaged in smelting and refining copper, gold, and lead ores; in producing agricultural pesticides; in using arsenic as pigments and dyes; and in manufacturing glass, semiconductors, and various pharmaceutical substances from which there may be high exposure to airborne arsenic.[1] The most extensive human exposure to inorganic arsenic, however, results from naturally occurring inorganic arsenic in drinking water, long known to be a cause of skin cancer. Surprising evidence, originating from studies in Taiwan, indicated that the ingestion of inorganic arsenic also increases mortality from cancer originating in various internal sites, including lung.[2–9] Further evidence of a link between the ingestion of inorganic arsenic and increased lung cancer risks was found in a small cohort study in Japan involving residents using well water contaminated with inorganic arsenic[10] and in large population studies in Cordoba, Argentina,[11] and northern Chile.[12,13] The purpose of the present study was to investigate inorganic arsenic and lung cancer in northern Chile in a case-control study, with individual assessment of exposure based on arsenic concentrations in water sources piped to households. It is the first large, population-based lung cancer case-control study concerning arsenic in drinking water. A preliminary research report of work in progress on this study was presented at a scientific meeting in Brazil[14] and included some of the results we present more fully in this paper.

Subjects and Methods

The study area included regions I, II, and III in northern Chile. Details on the study area and methods are described more fully elsewhere.[14] Briefly, the population in region II experienced high exposure to inorganic arsenic in past years from natural contamination of drinking water originating in the Andes mountains, whereas water sources in regions I and III contained relatively little arsenic (Table 1).

Identification of Lung Cancer Cases

Nurses were recruited for the study and trained in interviewing techniques in each major city of northern Chile: Arica and Iquique in region I; Antofagasta in region II, and Copiapó in region III. They identified lung cancer and bladder cancer cases in the public hospitals, where the large majority (80–90%) of cancer patients are ad-

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TABLE 1. Average Arsenic Concentration in Drinking Water in the Three Study Area Regions in Northern Chile (1930–1994)

Region	City or Town	Population >18 Years of Age*	Average Arsenic Concentration (μg/Liter) Years					
			1930–1957	1958–1970	1971–1977	1978–1979	1980–1987	1988–1994
I	Arica	109,508	10	10	10	10	10	10
	Putre	2,240	1	1	1	1	1	1
	Iquique	97,825	60	60	60	60	60	60
	Huara	1,340	30	30	30	30	30	30
	Pica	1,761	10	10	10	10	10	10
	Pozo Almonte	3,857	40	40	40	40	40	40
II	Tocopilla	15,964	250	250	636	110	110	40
	María Elena	8,440	250	250	636	110	110	39
	Calama	74,030	150	150	287	110	110	40
	San Pedro	1,757	600	600	600	600	600	600
	Antofagst	149,186	90	860	110	110	70	40
	Mejillons	4,086	90	860	110	110	70	37
	Taltal	6,869	60	60	60	60	60	60
III	Chañaral	8,631	15	15	15	15	15	15
	Diego de Almagro	17,236	1	1	1	1	1	1
	Copiapó	64,532	15	15	15	15	15	15
	Caldera	7,568	15	15	15	15	15	15
	Tierra Amarilla	7,319	15	15	15	15	15	15
	Vallenar	29,347	1	1	1	1	1	1
	Freirina	3,114	1	1	1	1	1	1
	Huasco	4,828	1	1	1	1	1	1
	A. Carmen	3,169	1	1	1	1	1	1

* Population numbers were obtained from the 1992 census.

mitted. In this paper we report the results for the lung cancer cases only. Eligible cases were all those admitted to public hospitals with lung cancer in the study region between November 1994 and July 1996, in whom lung cancer was pathologically confirmed and first diagnosis was either during the current hospital admission or no more than 1 year before the current admission. There were two public hospitals in region I, three public hospitals in region II, and three public hospitals in region III. Most cancer patients, however, were referred from the smaller public hospitals to the main public hospitals of Antofagasta, Iquique, Arica, and Copiapó. The interviewers went daily to the admissions department and the pathology laboratories of these main hospitals to identify patients diagnosed with lung cancer. The smaller public hospitals were visited approximately once a month. The majority of patients, about 70%, were interviewed while still in the hospital. The remaining 30% were visited and interviewed in their homes after discharge.

Selection of Controls

The methods we used for selection of controls for this study were complicated and unusual for several reasons. We used hospital controls because selection of a random sample representative of the general population would have been prohibitively expensive. Selection of random samples from the general population is difficult in itself in Chile, and locating selected participants would be expensive in the study area, which includes scattered small populations in remote areas. Using hospital controls meant that most controls could be identified and interviewed in the few major hospitals in the study area. Only 20% of controls had to be interviewed in their homes after discharge.

To avoid the problem of matching on exposure instead of matching on hospital, we defined all patients admitted to any public hospital in the whole study area as eligible controls. We identified the number of patients admitted to each hospital in 1991 and created a frequency distribution of admissions by hospital. Our goal was to obtain the same frequency distribution in our control group. We created an ordered listing for control selection with each hospital repeated on the list the number of times required to create the target frequency distribution.

For each index case with lung cancer, we selected two controls. The hospital to be the source for each control was identified as above. The first control was randomly selected from among patients who were admitted to the chosen hospital with a cancer not known or suspected to be related to arsenic, within a month of the admission of the index case to their hospital, and who were within 4 years of age of the index case. We excluded as controls patients admitted with cancer of the liver, skin, kidney, bladder, or prostate, as each site has been found to be related to arsenic in some studies.

We selected a second control group in the same manner as the cancer control group but from among patients admitted to the next hospital on the list with a diagnosis other than cancer and also excluding from consideration those admitted with cardiovascular, skin, or neurologic diseases.[15] These diseases were excluded because of evidence that arsenic may increase the risks of some conditions within each of these disease groups.

At the same time, we also selected controls for a concurrent bladder cancer study in a manner identical to that described for the lung cancer cases. We pooled

these controls with those selected for the lung cancer cases to increase the study power.

In view of the complexity of control group selection, we made several validity checks, as follows. (1) We compared key results for the cancer and noncancer control groups separately before pooling. (2) We compared key results for the combined control group with those selected for the lung cancer patients alone before combining the two control groups. (3) We compared the achieved hospital distribution of the controls with the target distribution. (4) We compared the actual distribution of the controls by county of residence at the time of diagnosis with that which would be predicted for a random sample from the general population based on the 1992 census given the age distribution of the controls. Regions I, II, and III have ten, nine, and nine counties within them, respectively. (5) We also used this predicted county distribution for the controls in the final validity check on the basis of the critical criterion that the exposure of controls should be representative of the exposure of the source population in which cases occurred. We grouped counties in the study area into five exposure levels on the basis of average arsenic concentrations in water supplies during the period 1958–1970. We then compared the control group distribution in these counties at the time of the study with that expected for a random population sample based on the 1992 census. In this way, we could examine indirectly the representativeness of the control group, with regard to general population exposure to arsenic in water, to investigate potential bias created by the complex control group selection methods used in this study.

Participant Interviews

The nurse interviewer read a letter of consent to all study subjects, explaining the method of the study and the general aim. The nurse then administered a structured questionnaire, including information related to socioeconomic status (SES), lifetime residential history, occupation, and smoking. The focus in the occupational interview was to identify work with potential arsenic exposure in copper smelting.

Exposure Assessment

Almost 100% of urban households are served by city water systems, and the large majority of the population in this desert region receives water from town or city supplies. In the 1992 census, the population coverage by public water systems in the main cities was as follows: region 1, Arica 92% and Iquique 94%; region 2, Antofagasta 90% and Calama 93%; and region 3, Copiapó 86% and Vallenar 84%. These cities represent 88%, 83%, and 59% of the households in the respective regions. The coverage is lower in the small towns of each region: region 1, 64–80%; region 2, 76–89%; and region 3, 67–91%. Since 1950, water companies have been required to carry out detailed chemical tests of the water, including measuring arsenic levels, at least once a year. We collected data on arsenic concentrations from 1950 through 1994. Table 1 presents average arsenic concentration in drinking water from 1930 through 1994 for the study area in northern Chile including regions I, II, and III. Water arsenic concentrations have been rounded, taking into account knowledge concerning when changes in water sources occurred. Concentrations in earlier years, 1930–1957, were estimated on the basis of measurements in the 1950s. Using lifetime residential histories, we assigned to each participant the average water arsenic concentration for the county in which he or she resided for each year. We calculated average arsenic water concentrations from 1930 to the present. In addition, we calculated the average arsenic water concentrations for the counties of residence for 1958–1970, when some of the highest exposures occurred.

The population-weighted average arsenic concentration for region II in these years was 578 μg/liter, much higher than the population-weighted average of 212 μg/liter for the second highest concentration period, which was from 1971 through 1977.

Statistical Methods

We evaluated lifetime (1930 to the present) average arsenic exposure as a categorical variable with five exposure strata. We also examined peak exposures on the basis of the average water concentration for each participant in 1958–1970, stratified into seven categories. We used the lowest exposure categories as reference to calculate odds ratios (ORs). We conducted unconditional regression analyses using StataCorp statistical software (release 4.0, 1995; College Station, TX) adjusting for age, sex, SES, smoking, and working in a copper smelter. Age was treated as both a continuous and a categorical variable. The results were similar, and we have presented the findings using categorical variables for six age strata. We included smoking as a continuous variable (average packs of cigarettes smoked per year) in logistic regression analyses and assessed synergy in a stratified analysis of smokers and nonsmokers (ever/never smoked at least 100 cigarettes total in lifetime). We estimated an SES score that took into account monthly income, years of school, occupation, and house commodities. We entered SES as a continuous variable and also stratified SES into three levels: low, medium, and high. We reviewed occupational histories for copper smelting or refining as potential exposure to inhaled arsenic. We included an indicator variable for this exposure in the logistic regression analyses and also the number of years worked in this occupation. We first conducted analyses with cancer and noncancer controls separately. We conducted the main analyses using an overall combined control group, including cancer and noncancer controls, and also the controls selected for the bladder cancer patients in a concurrent case-control study with identical control selection methods. We examined synergy between arsenic and smoking in stratified analyses involving never-smokers and ever-smokers analyzed separately.

We conducted unconditional logistic regression analyses that included the matching variables sex and age as

TABLE 2. Expected Number of Controls by Hospital in the Study Area Based on 1992 Discharges from Each Major Hospital in Northern Chile

Hospital	Eligible Noncancer Discharges	Noncancer Controls Expected	Noncancer Controls Selected	Eligible Cancer Discharges	Cancer Controls Expected	Cancer Controls Selected	Total Controls Expected	Total Controls Selected	Selected/ Expected Controls
Arica	13,137	68	44	288	38	24	106	68	0.6
Iquique	10,578	55	42	175	23	26	78	68	0.9
Antfgst	16,138	84	124	717	94	98	178	222	1.2
Copiapó	8,776	45	42	92	12	19	57	61	1.1
Total	48,629	252	252	1,273	167	167	419	419	

TABLE 3. Selected Characteristics and Exposures among Lung Cancer Cases and Controls

	Cases	Total Controls	Cancer Controls	Noncancer Controls	Controls for Lung Cancer Cases	Control for Bladder Cancer Cases
Numbers	151	419	167	252	237	182
Percentage male	72%	61%	52%	67%	64%	57%
Average age	61	64	64	64	61	68
Percentage ever smoked	80	55	56	53	55	55
Average packs of cigarettes (lifetime)	142	63	67	61	64	62
SES score	74	73	70	75	76	69
Worked in copper smelting	7	5	4	6	4	6
Average As water concentration (μ/liter)						
1930–1996	171	109	103	114	106	114
1958–1970	464	280	250	301	265	300

SES = socioeconomic status.

TABLE 4. Assessment of Control Group Representativeness of Source Population Exposure Based on Residential Location in 1992, and Concentration of Arsenic in Drinking Water for That Town or City in the Period 1958–1970

Arsenic Water Concentration 1958–1970, μg/Liter	Population over 18 Years of Age	Control Numbers Expected	Control Numbers Selected	Ratio of Selected to Expected Controls
0–49	264,450	179	152	0.8
50–99	104,694	70	88	1.3
100–399	98,434	66	33	0.5
400 and over	155,029	104	146	1.4
Totals	622,607	419	419	

indicator variables, with one for sex and six for age strata.

Results

Participation of Lung Cancer Cases

During the 20 months of enrollment, 217 subjects were newly diagnosed with lung cancer in the hospital. Of these subjects, 151 (70%) agreed to participate and were interviewed. There were few refusals among cases and controls (less than 5%). The main reasons for nonparticipation were that the patient was not at the hospital when we attempted to contact him or her, the patient had moved from home and could not be located, and the patient was too sick to complete the questionnaire.

Validation of Control Group

We included a total of 419 controls into the analysis phase of the study, 167 cancer controls and 252 noncancer controls. There were fewer cancer controls because of difficulties finding sufficient subjects meeting age- and sex-matching criteria, particularly among men. A series of validation checks was undertaken for the controls. We compared the achieved control group distribution between hospitals with the target distribution based on admissions in 1991 (Table 2). We found major discrepancies. The main differences between the observed and expected control distributions resulted from the main hospitals of Arica and Antofagasta. The former provided fewer controls and the latter provided more controls than expected. One explanation for these differences may be variation in the capability of the field workers to recruit study subjects. In Antofagasta we had hired two field workers, which may explain the increased recruitment of controls. Because of the discrepancy, we investigated various parameters relating to control group validity.

Table 3 presents some basic information for cases and controls and compares characteristics and exposures of the total combined control group with those of the cancer and noncancer controls, those controls directly

selected for lung cancer patients, and those selected for the bladder cancer cases. The combined control group had been exposed to an average arsenic concentration of 109 μg/liter in drinking water between 1930 and 1994 and an average of 280 μg/liter for the peak exposure period 1958–1970. Because the differences in exposure for the various control sources were small, we present results from major analyses using the overall combined control group.

The overall criterion for assessing control group validity in a case-control study is that the control group should provide an unbiased estimate of the exposure distribution of the general population in which the cases occurred. This distribution was assessed indirectly using the 1992 census. Table 4 presents the results based on water arsenic concentration in the period 1958–1970 that are already presented in Table 1. Population numbers in 1992 were used to estimate an expected distribution for 419 randomly selected controls (column 3 of Table 4). This distribution was then compared with the actual distribution of the selected controls (column 4). The final column shows the ratio of the selected numbers of controls to that expected. The baseline exposure category (0–49 μg/liter) is reasonably represented (selected controls to expected ratio of 0.8). The high exposure category is overrepresented, however, owing to overselection of controls from Antofagasta (Table 2), the only location with water concentration above 400 μg/liter in the period 1958–1970 (Table 1). The impact of this bias would be to underestimate ORs for the highest arsenic exposure. The next-to-highest arsenic exposure category, 100–300 μg/liter, however, appears to be markedly underrepresented, which would lead to overestimation of ORs. This assessment is indirect. In data analysis, the actual residential location of cases and controls was used throughout to determine arsenic water concentrations, rather than just residential location at the time of the study. Nevertheless, the likely direction of bias is apparent, with underestimation of ORs in the highest exposure levels and overestimation of ORs at the lower water concentrations. At relatively low concentrations of 50–99 μg/liter, the ORs may be underestimated. The extent of bias is also dependent on ascertainment of cases. Although case ascertainment was thorough, it is possible that some underascertainment would have occurred in the same cities in which controls were underselected.

Table 5 presents findings based on average drinking water concentration from 1930 (or year of birth if the subject was born later) through 1994 using all controls pooled and compares results of analyses conducted with different control groups. The fourth column presents ORs using the pooled controls and adjustment by sex and age, and the fifth column also includes adjustment for smoking, SES, and working in copper smelting. Clear trends in ORs are apparent. The remaining columns of the table show that similar results are obtained if cancer controls are used alone, noncancer controls are used

TABLE 5. Number of Cases and Controls, Odds Ratio Estimates,* and 95% CI for Lung Cancer by Exposure to Arsenic in Drinking Water: Average Concentration during 1930–1994

Average Water Arsenic Concentration (μg/Liter)	Cases N = 151	Controls Combined Control Group N = 419	OR Age- and Sex-Adjusted		OR Full Model						Controls Frequency Matched to Lung Cancer (N = 237 Controls)	95% CI
			(N = 419 Controls)	95% CI	Total (N = 419 Controls)	95% CI	Cancer Controls (N = 167 Controls)	95% CI	Noncancer Controls (N = 252 Controls)	95% CI		
0–10†	9	104	1		1		1		1		1	
10–29	5	39	1.5	0.4–4.6	1.6	0.5–5.3	1.5	0.4–5.7	1.5	0.4–5.4	1.1	0.3–3.9
30–49	8	23	4.0	1.4–12.1	3.9	1.2–12.3	5.4	1.4–21.6	3.6	1.0–12.5	3.5	1.0–11.8
50–199	50	124	4.6	2.2–10.0	5.2	2.3–11.7	4.2	1.8–10.0	6.4	2.7–15.5	3.9	1.7–9.1
200–400	79	129	8.0	3.8–17.0	8.9	4.0–19.6	9.5	4.0–22.6	8.5	3.6–20.2	7.7	3.3–17.8

* Estimates compare results of analyses conducted with different control groups adjusting for age and sex only, and for age, sex, cumulative lifetime cigarette smoking, years of work in copper smelting, and socioeconomic status.
† Referent category.

TABLE 6. Number of Cases and Controls, Odds Ratio Estimates for Lung Cancer, Adjusted for Age, Sex, Cumulative Lifetime Cigarette Smoking, Working in Copper Smelting, and Socioeconomic Status (SES), According to Exposure to Arsenic in Drinking Water: Average Concentration during Peak Years of Exposure, 1958–1970

	Cases	Controls	OR Age-/Sex-Adjusted	95% CI	OR Full Model	95% CI
Average Arsenic Exposure (μg/Liter)						
0–10	11	92	1		1	
10–29	3	62	0.4	0.1–0.5	0.3	0.1–1.2
30–59	4	19	0.0	0.6–7.2	1.8	0.5–6.9
60–89	22	51	0.1	1.8–9.2	4.1	1.8–9.6
90–199	13	36	0.8	1.1–7.0	2.7	1.0–7.1
200–399	23	44	0.4	2.0–10.0	4.7	2.0–11.0
400–699	11	12	0.9	2.4–19.8	5.7	1.9–16.9
700–999	64	103	0.3	3.1–12.8	7.1	3.4–14.8
Male *vs* Female			0.7	1.1–2.7	1.1	0.6–1.8
Ever *vs* never smoked					4.3	2.6–7.3
SES medium *vs* low					1.3	0.7–2.5
SES high *vs* low					2.3	0.5–12.1
Ever/never worked in copper smelting					1.7	0.7–4.4

TABLE 7. Interaction of Exposure to Arsenic and Smoking on Relative Risk of Lung Cancer

1930–1994 Average Arsenic in Drinking Water (μg/Liter)	Never Smoked				Ever Smoked			
	Cases 30	Controls 189	OR	95% CI	Cases 121	Controls 230	OR	95% CI
≤49	2	63	1*		20	103	6.1	1.31–39.2
50–199	11	59	5.9	1.2–40.2	39	66	18.6	4.13–116.4
≥200	17	67	8.0	1.7–52.3	62	61	32.0	7.22–198.0

* Referent category.

alone, or if the matched controls selected directly for the lung cancer patients are used alone (excluding the additional controls derived from the bladder cancer study).

Table 6 presents findings based on the period of peak exposure in Antofagasta, 1958–1970. All controls have been included. A clear trend is again apparent. In the full-model logistic regression analysis, we found an OR of 4.3 [95% confidence interval (CI) = 2.6–7.3] for lung cancer associated with smoking, a 70% increase in relative risk associated with copper smelting, and apparently slightly higher relative risks associated with higher SES.

Table 7 presents results for nonsmokers and smokers of cigarettes. Similar results were obtained after adjusting for age and sex. Our findings demonstrate a positive trend in relative risk of lung cancer with exposure to increasing concentration of arsenic in drinking water among nonsmokers as well as a greater-than-additive effect for these exposures combined. The OR for smokers in the highest arsenic-exposure category (32.0) is much greater than that expected (13.1 = 8.0 + 6.1 – 1) on the basis of the OR for nonsmokers in the highest arsenic-exposure category (8.0) and the OR for smokers in the lowest arsenic-exposure category (6.1).

Finally, Figure 1 presents the time-window pattern of exposure of cases and controls. Cases had higher exposures than controls, especially in the period 1955–1975. Thus, the markedly increased relative risks of lung cancer found in this study relate to exposures that predominately occurred 20–40 years before cancer diagnosis.

Discussion

This is the first study based on a large population exposed to arsenic in drinking water conducted to document the relation between this exposure and lung cancer risks and to evaluate synergy with other exposures. The relative risk estimate among the most highly exposed (OR = 8.9; 95% CI = 4.0–19.6) is consistent with that from a small cohort study in Japan that reported eight cases of lung cancer in people who had been drinking water containing even higher concentrations of inorganic arsenic (more than 1,000 μg/liter, actual level not

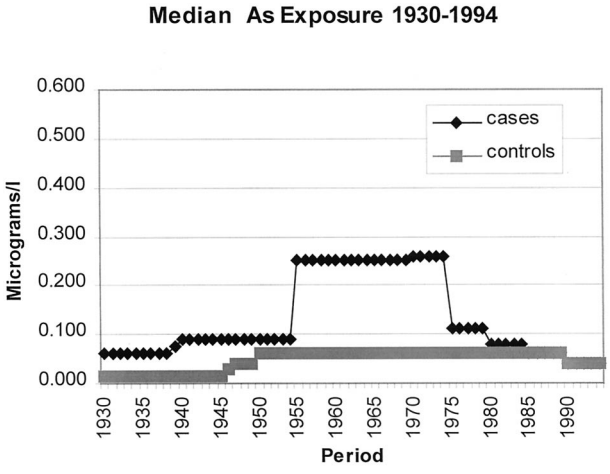

FIGURE 1. Median arsenic exposure, 1930–1994.

specified) with 0.51 expected cases (standardized morbidity ratio = 15.7; 95% CI = 7.4–31.0).[10] The relative risk estimates reported here are also consistent with the overall population standardized mortality ratios for lung cancer in region II of Chile of 3.8 for men (95% CI = 3.5–4.1) and 3.1 for women (95% CI = 2.7–3.7)[13] using all of Chile, excluding region II, as the referent population. When coupled with lung cancer findings related to arsenic exposure in Taiwan[2–9] and Argentina,[11] the overall evidence is sufficient to conclude that ingestion of inorganic arsenic increases the risk of lung cancer.

The main weakness of the study concerns control selection. The use of hospital controls with matching by hospital, as is usually done, would have effectively matched on exposure, because arsenic concentrations in water supplies vary by city and geographic location throughout the study area. For example, if an Antofagasta hospital patient were selected as a control for a lung cancer patient also admitted to an Antofagasta hospital, the likelihood is that both patients would have been drinking from the same water supply and would have had similar exposure to the very high arsenic levels in Antofagasta water supplies in past years. It is clear, however, that the control selection criteria were not fully adhered to and that relatively more controls were chosen from the highly exposed city of Antofagasta than from the lower-exposure cities of Arica and Iquique (Table 2). Nevertheless, the direction of this bias is clear in that it would result in underestimation of risks for the highest exposures (Table 4). Thus, the control selection problem does not affect causal inference in that, if anything, correcting for this bias would only add to the evidence of increased lung cancer risks associated with arsenic in drinking water. In addition, evaluation of analyses using various control groups shown in Table 3 shows little difference in effect estimates according to average exposure. This stability in control group exposure, and the contrast with exposure among cases, supports the validity of the study findings.

The shape of the dose-response relation between ingested arsenic and lung cancer risk is important when considering population cancer risks and drinking water standards. The only previous study with any dose-response information based on knowledge of individual exposure was the cohort study in Japan.[10] This study only included three dose-exposure categories, and the number of subjects was small at all dose categories, especially the two lowest (no cases reported for <50 μg/liter, and just one case for 50–990 μg/liter). Hence, the present study is the first to provide potentially useful dose-response data. Clear trends in dose response are apparent when concentrations are averaged over 1930–1994 (Table 5) and also when the peak exposure period 1958–1970 is considered (Table 6). The dose-response information in both tables is consistent with supralinearity, which has previously been explored in the context of lung cancer risks from inhaled arsenic.[16,17] We note that the apparently low OR associated with smoking alone is due the fact that the majority of smokers in a survey of two major cities in region II smoked fewer than ten cigarettes per day.[13] In our case-control study, even among patients with lung cancer, the average number of cigarettes smoked per day was only 13.3.

Published evidence concerning synergy between ingested arsenic and smoking in causing lung cancer is limited. A meta-analysis of studies of inhalation of inorganic arsenic and cigarette smoking supports a synergistic effect of the two exposures.[15] On the basis of small numbers, synergy between arsenic ingestion and smoking was suggested in the Japanese cohort study.[10] Even in the present study with more than ten times the number of lung cancer cases as in the Tsuda study, confidence limits are broad. The findings, however, support a synergistic action between the two exposures.

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