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# Marked Increase in Bladder and Lung Cancer Mortality in a Region of Northern Chile Due to Arsenic in Drinking Water

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Studies in Taiwan and Argentina suggest that ingestion of inorganic arsenic from drinking water results in increased risks of internal cancers, particularly bladder and lung cancer. The authors investigated cancer mortality in a population of around 400,000 people in a region of Northern Chile (Region II) exposed to high arsenic levels in drinking water in past years. Arsenic concentrations from 1950 to the present were obtained. Population-weighted average arsenic levels reached 570 μg/liter between 1955 to 1969, and decreased to less than 100 μg/liter by 1980. Standardized mortality ratios (SMRs) were calculated for the years 1989 to 1993. Increased mortality was found for bladder, lung, kidney, and skin cancer. Bladder cancer mortality was markedly elevated (men, SMR = 6.0 (95% confidence interval (CI) 4.8–7.4); women, SMR = 8.2 (95% CI 6.3–10.5)) as was lung cancer mortality (men, SMR = 3.8 (95% CI 3.5–4.1); women, SMR = 3.1 (95% CI 2.7–3.7)). Smoking survey data and mortality rates from chronic obstructive pulmonary disease provided evidence that smoking did not contribute to the increased mortality from these cancers. The findings provide additional evidence that ingestion of inorganic arsenic in drinking water is indeed a cause of bladder and lung cancer. It was estimated that arsenic might account for 7% of all deaths among those aged 30 years and over. If so, the impact of arsenic on the population mortality in Region II of Chile is greater than that reported anywhere to date from environmental exposure to a carcinogen in a major population. *Am J Epidemiol* 1998; 147:660–9.

arsenic; bladder neoplasms; lung neoplasms; mortality

Chronic ingestion of inorganic arsenic is an established cause of various skin effects including keratoses, hyperpigmentation, and skin cancer (1). More recently, studies in Taiwan (2–9) have raised the possibility that ingestion of arsenic in drinking water was also a cause of several internal cancers including bladder, kidney, liver, and lung cancer. Extremely large relative risks can be estimated from the ecologic mortality study in Taiwan, the greatest being for bladder cancer. At the highest level of exposure, around 800 μg/liter, relative risk estimates for bladder cancer mortality were 28.7 for men and 65.4 for women (4, 10). A subsequent study in an arsenic-exposed region of Argentina also found increased bladder cancer mortality. The bladder cancer relative risks for the highest exposed areas were 2.1 for men and 1.8 for women when compared with the rest of the country (11). These relative risk estimates are much lower than those in Taiwan, but arsenic water levels were lower in Argentina, and it was estimated that only about 20 percent of the population had been exposed.

Limited additional evidence that ingestion of inorganic arsenic might cause internal cancers can be derived from two small cohort studies. One involved patients who had been prescribed Fowler's solution which contains 1 percent potassium arsenite. A threefold increased risk of bladder cancer mortality was reported based on five cases (12). The second cohort study involved 141 arsenic-poisoned patients in a mining town in Japan who had been exposed to arsenic due to contamination of their drinking water, in addition to occupational exposures experienced by some of them (13). Two urinary tract cancers were reported in patients who also had Bowen's disease, whereas the expected number for those cancers was only 0.26. Seven lung cancer deaths were reported, and a dose-response analysis showed lung cancer mortality ratios increasing up to 16.4 for the highest exposure category (8). However, both these cohort studies suffer from problems due to small numbers, and the second study involved inhalation as well as ingestion pathways of exposure.

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Abbreviations: CI, confidence interval; COPD, chronic obtructive pulmonary disease; RR, relative risk; SMR, standardized mortality ratio.

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The purpose of this paper is to present the results of a mortality study in Region II of Chile (figure 1). (A region in Chile is the equivalent of a province, and the regions are numbered sequentially from north to south, beginning with Region I.) Rivers that originate in the Andes mountains and that contain arsenic from natural geologic sources have been used to supply water to cities and towns throughout the region. Consequently, Region II has experienced high levels of arsenic in drinking water in past years (14, 15). Cases of arsenic-caused skin lesions were first reported in the 1970s (16). Investigators in Chile have previously reported that there might be an increased incidence and mortality from several cancers in this region (17, 18). The present study was in part stimulated by these earlier findings. However, both this study and our earlier study in Argentina had clear a priori hypotheses based on our review of the literature completed in 1990 in which we stated that, "studies strongly suggest that ingested inorganic arsenic causes cancer of the bladder, kidney, lung and liver, and possibly other sites. However, confirmatory studies are needed" (8). Because of the high arsenic water levels in past years, a stable population with widespread exposure to arsenic in drinking water, and good sources of mortality data, Region II was an ideal population in which to search for further evidence that ingestion of arsenic might cause increased mortality from these internal cancers.


**FIGURE 1.** Map of Chile identifying Region II.

## MATERIALS AND METHODS

Mortality data for persons aged 30 years and over were assembled for Region II from the Departamento de Informacion de Servicio de Salud de Antofagasta for the years 1989–1993 for the following causes of death: bladder, kidney, liver, lung and non-melanoma skin cancers, chronic obstructive pulmonary disease, and for all other causes of death combined. Causes of death had been coded according to the 9th Revision of the *International Classification of Diseases* (ICD-9). ICD-9 code 173 was used in this study to identify non-melanoma skin cancer deaths. Chronic obstructive pulmonary disease (COPD) deaths were identified using ICD-9 codes 490 to 496, but excluding 493. The few deaths in Region II where the place of usual residence reported on the death certificate was outside the region were excluded.

Standardized mortality ratios were estimated for Region II as follows. Census data were used to calculate the person-years at risk in Region II during 1989–1993 by 10-year age groups, for men and women separately. National mortality data were obtained for 1991, the midpoint of the study period, and age- and sex-specific mortality rates were calculated for each cause of death of interest for the rest of Chile excluding Region II. The expected number of deaths was then calculated for Region II by multiplying the rest of Chile 1991 age- and sex-specific mortality rates by the person-years at risk for residents in Region II for the period 1989–1993. Standardized mortality ratios were estimated by dividing observed deaths by expected deaths. Statistical tests of significance were based on the Poisson distribution, and 95 percent confidence intervals were calculated using exact methods (19).

Data on arsenic water concentrations in Region II from 1950 to 1994 were obtained from the Empresa Servicios Sanitarios de Antofagasta, Servicio de Salud de Antofagasta, and Codelco, Chile. Large numbers of measurements were available for drinking water in the two largest cities, Antofagasta and Calama, where many arsenic analyses have been conducted each year since the 1960s. Data from smaller towns were much more limited. In some instances, only recent measurements of water levels were available, but historical information on water sources existed which could be used to identify likely water arsenic concentrations in past years. In view of the non-systematic water sampling conducted throughout the region, and because of the need to make informed judgments based on his-

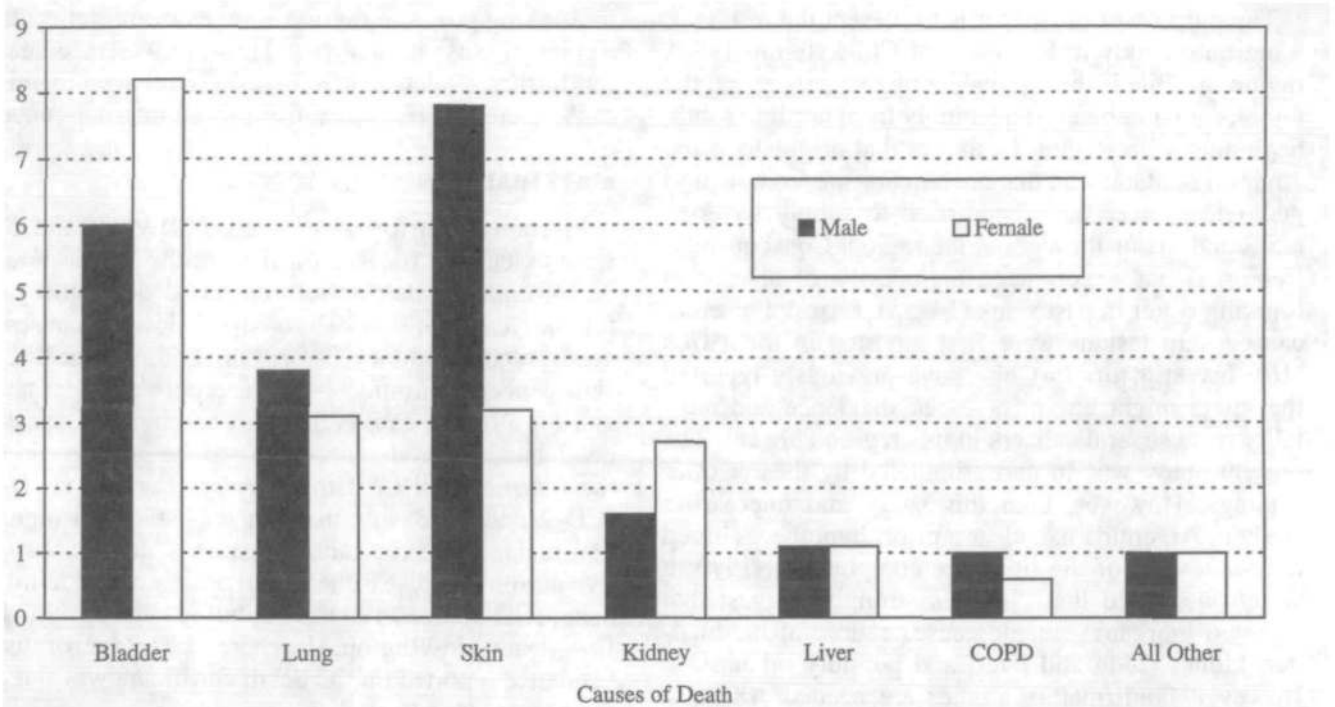


**FIGURE 2.** Male and female standardized mortality ratios (SMRs) for bladder, lung, skin, kidney, and liver cancer, chronic obstructive pulmonary disease, and all other causes of death in Region II, Chile, 1989–1993.

torical information on water sources used in various towns over the years, we asked knowledgeable personnel from the Laboratorio del Ambiente in Antofagasta to help determine past arsenic concentrations in drinking water. The classification of water arsenic levels was done by chemists at this laboratory who have been measuring the arsenic concentration of Region II waters for many years. Approximate average levels of arsenic in drinking water were estimated for all towns and cities in the region by 5-year intervals from 1950 to 1994, rounded to the nearest 10 μg/liter. We then calculated population weighted averages to give a rough indication of likely average arsenic water concentrations for the total population.

Limited smoking information was available for the two largest cities of the region, Antofagasta and Calama, from a national survey conducted in 1990 using a geographically stratified random sample based on the 1982 census (20). Participants were asked if they smoked cigarettes in the previous month, and, if so, the average number of cigarettes they smoked per day.

## RESULTS

Results are presented for population exposure data (table 1), population mortality (tables 2 and 3 and figure 2), attributable risk (table 4), and for cigarette smoking (table 5).

### Population exposure

Around 440,000 people currently live in Region II of Chile. The data on measurements of arsenic in drinking water collected for this study show that drinking water containing high levels of arsenic had been present throughout the region since the 1950s (table 1). The largest city in the region is Antofagasta (1991 population 219,310). The city's water in the early 1950s contained about 90 μg/liter of arsenic, but in 1957 a water supply system was introduced involving the rivers of Toconce and Holajar which contained 800 and 1,300 μg/liter of arsenic, respectively (21). As a result, the average arsenic level in Antofagasta's drinking water rose to 870 μg/liter. In 1970, the arsenic levels decreased when the treatment plant Salar del Carmen commenced operations. Water from the treatment plant averaged 260 μg/liter at first, but improvements made to the plant during the 1970s and 1980s gradually reduced arsenic levels to about 40 μg/liter by the 1990s (table 1).

The nearby town of Mejillones is supplied with water from Antofagasta, and, therefore, has the same arsenic levels in its drinking water (table 1). The second largest city in the region is Calama (1991 population 100,283). Arsenic levels in this city's drinking water supply averaged around 120 μg/liter in the 1950s and 1960s (table 1). Due to changing water

**TABLE 1. Arsenic concentration (μg/liter) in drinking water for major cities and towns in Region II, from 1950 to 1994, by 5-year intervals, and population weighted averages using 1991 census numbers***

| City or town (1991 population) | 1950–1954 | 1955–1959 | 1960–1964 | 1965–1969 | 1970–1974 | 1975–1979 | 1980–1984 | 1985–1989 | 1990–1994 |
|---|---|---|---|---|---|---|---|---|---|
| Antofagasta (219,310) | 90 | 870 | 870 | 870 | 260 | 110 | 80 | 60 | 40 |
| Mejillones (6,134) | 90 | 870 | 870 | 870 | 260 | 110 | 80 | 60 | 40 |
| Calama (100,283) | 120 | 120 | 120 | 120 | 240 | 230 | 110 | 80 | 40 |
| Chuquicamata† (17,414) | 250 | 150 | 130 | 130 | 130 | 110 | 80 | 60 | 10 |
| Tocopilla (21,039) | 250 | 250 | 250 | 250 | 520 | 460 | 110 | 80 | 40 |
| Maria Elena (15,470) | 250 | 250 | 250 | 250 | 520 | 460 | 110 | 80 | 40 |
| Taltal (7,620) | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| San Pedro‡ (3,070) | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 |
| Average (390,340) | 123 | 569 | 568 | 568 | 272 | 176 | 94 | 71 | 43 |

* Except where indicated, the average water levels were obtained from Empresa Servicios Sanitarios de Antofagasta for 1950–1967 and Servicio de Salud Antofagasta for 1968–1994.
† Data were supplied by Codelco Chile.
‡ Data for Rio Vilama, a major water source for the town.

sources, the levels increased to 240 μg/liter in the 1970s. An arsenic removal plant reduced these levels to around 100 μg/liter in the 1980s, with improvements further reducing the levels to around 40 μg/liter currently.

Arsenic levels are also given in table 1 for the smaller population centers. Except for Taltal, all population centers had water supplies containing more than 100 μg/liter in the 1950s, 1960s, and 1970s. However, by the end of the 1980s, all major water supplies contained less than 100 μg/liter of arsenic, except for the small remote town of San Pedro where use of drinking water containing 600 μg/liter continues to the present. The populations listed in table 1 include about 90 percent of the total population of 440,000 in Region II. We therefore calculated population-weighted average water arsenic levels for each 5-year period using the data in table 1 to get an approximate estimate of the average drinking water arsenic levels consumed by inhabitants of the whole region. The averages, which are shown at the bottom of table 1, increased from a little more than 100 μg/liter in the early 1950s, to around 570 μg/liter from 1955 up to 1969. Average levels since then have gradually decreased to less than 100 μg/liter by 1980, and to about 40 μg/liter by 1990.

In contrast to Region II, there are no major populations exposed to arsenic in drinking water in the rest of Chile. A nationwide survey involving 2,000 urinary samples found average arsenic levels to be about 14 μg/liter (22). This information suggests there were no significant exposures to arsenic at that time from either water or food. The same is likely to be true for earlier years since, except for Region II, there have been no major water supply changes in the country in response to arsenic levels.

## Population mortality

Tables 2 and 3 present the mortality data for Region II, with expected numbers of deaths calculated using mortality rates from the rest of Chile for 1991. Table 2 shows that the overall bladder cancer mortality rate among men was six times that of the rest of Chile (standardized mortality ratio (SMR) = 6.0, 95 percent confidence interval (CI) 4.8–7.4, $p < 0.001$). There was also a marked increase in lung cancer mortality (SMR = 3.8, 95 percent CI 3.5–4.1, $p < 0.001$) and skin cancer (SMR = 7.7, 95 percent CI 4.7–11.9, $p < 0.001$). A smaller increase in mortality was found for kidney cancer (SMR = 1.6, 95 percent CI 1.1–2.1, $p = 0.012$), but there was no increase in mortality from liver cancer (SMR = 1.1, 95 percent CI 0.8–1.5, $p = 0.392$). No overall increase in deaths from COPD was detected (SMR = 1.0, 95 percent CI 0.8–1.1, $p = 0.926$). For all other deaths combined, the mortality rate in Region II was almost identical to that for the rest of Chile (SMR = 1.0, 95 percent CI 0.99–1.05, $p = 0.146$).

Table 3 presents findings for women, which were generally similar to those for men. Markedly increased standardized mortality ratios were found for bladder cancer (SMR = 8.2, 95 percent CI 6.3–10.5, $p < 0.001$), kidney cancer (SMR = 2.7, 95 percent CI 1.9–3.8, $p < 0.001$), lung cancer (SMR = 3.1, 95 percent CI 2.7–3.7, $p < 0.001$), and skin cancer (SMR = 3.2, 95 percent CI 1.3–6.6, $p = 0.016$). No increased mortality from liver cancer (SMR = 1.1, 95 percent CI 0.8–1.5, $p = 0.377$) nor from all other causes of death (SMR = 1.0, 95 percent CI 0.97–1.03, $p = 0.979$) was detected. In contrast to men, the overall mortality rates for COPD among women were actually lower in Region II than in the rest of the

**TABLE 2. Age-specific observed and expected deaths and standardized mortality ratios (SMR) for men aged 30 years and over in Region II of Chile, 1989–1993**

| Category | Age group (years) | | | | | | | SMR | 95% CI* | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | ≥80 | Total | | | |
| Person-years at risk | | | | | | | | | | |
| Region II (1989–1993) | 162,291 | 117,585 | 72,374 | 45,384 | 17,995 | 4,969 | 420,598 | | | |
| Rest of Chile (1991) | 980,004 | 667,729 | 442,652 | 294,145 | 147,247 | 51,575 | 2,583,532 | | | |
| Bladder cancer | | | | | | | | | | |
| Observed deaths | 1 | 6 | 15 | 30 | 29 | 12 | 93 | | | |
| Expected deaths | 0 | 0.9 | 1.8 | 4.6 | 5.1 | 3.1 | 15.5 | | | |
| Observed/expected | – | 6.7 | 8.3 | 6.5 | 5.7 | 3.9 | | 6.0 | 4.8–7.4 | <0.001 |
| Kidney cancer | | | | | | | | | | |
| Observed deaths | 1 | 1 | 8 | 16 | 9 | 4 | 39 | | | |
| Expected deaths | 0.7 | 2.8 | 4.7 | 10.0 | 5.0 | 1.7 | 25.0 | | | |
| Observed/expected | 1.4 | 0.3 | 1.7 | 1.6 | 1.8 | 2.4 | | 1.6 | 1.1–2.1 | 0.012 |
| Liver cancer | | | | | | | | | | |
| Observed deaths | 2 | 4 | 6 | 20 | 11 | 5 | 48 | | | |
| Expected deaths | 1.3 | 3.6 | 7.8 | 14.5 | 9.7 | 5.1 | 42 | | | |
| Observed/expected | 1.5 | 1.1 | 0.8 | 1.4 | 1.1 | 1.0 | | 1.1 | 0.8–1.5 | 0.392 |
| Lung cancer | | | | | | | | | | |
| Observed deaths | 14 | 48 | 142 | 177 | 129 | 34 | 544 | | | |
| Expected deaths | 1.2 | 8.1 | 28.5 | 61.8 | 32.1 | 12.0 | 143.2 | | | |
| Observed/expected | 11.7 | 5.9 | 4.9 | 2.9 | 4.0 | 2.8 | | 3.8 | 3.5–4.1 | <0.001 |
| Skin cancer | | | | | | | | | | |
| Observed deaths | 0 | 1 | 3 | 7 | 3 | 6 | 20 | | | |
| Expected deaths | 0 | 0.2 | 0 | 0.7 | 0.8 | 0.9 | 2.6 | | | |
| Observed/expected | 0 | 5.0 | – | 10.0 | 3.8 | 6.7 | | 7.7 | 4.7–11.9 | <0.001 |
| Chronic obstructive pulmonary disease | | | | | | | | | | |
| Observed deaths | 4 | 4 | 18 | 34 | 34 | 30 | 124 | | | |
| Expected deaths | 0.8 | 2.8 | 9.6 | 33.1 | 45.5 | 32.9 | 124.7 | | | |
| Observed/expected | 5.0 | 1.4 | 1.9 | 1.0 | 0.7 | 0.9 | | 1.0 | 0.8–1.1 | 0.926 |
| All other deaths | | | | | | | | | | |
| Observed deaths | 339 | 381 | 682 | 1,063 | 1,111 | 820 | 4,396 | | | |
| Expected deaths | 363 | 485.6 | 694.2 | 1,044.7 | 1,022.9 | 689.6 | 4,299.9 | | | |
| Observed/expected | 0.9 | 0.8 | 1.0 | 1.0 | 1.1 | 1.2 | | 1.0 | 0.99–1.05 | 0.146 |

* CI, confidence interval.

country (SMR = 0.6, 95 percent CI 0.4–0.7, $p < 0.001$).

Tables 2 and 3 show age-specific data as well as the overall standardized mortality ratios. The mortality ratios (observed/expected deaths) for bladder, kidney, liver, and skin cancers, and all other deaths combined, are not related to age in either sex. However, lung cancer mortality ratios are particularly high in younger men aged 30–39 years (SMR = 11.7, 95 percent CI 6.4–19.6, $p < 0.001$). In addition, a decreasing trend by age in COPD deaths is apparent, with higher rates among younger men, particularly those aged 30–39 years.

The age-specific findings for women presented in table 3 parallel those for men. The highest mortality ratios were found for lung cancer among women aged 30–49 years and for COPD among women aged 30–39 years.

## Population attributable risk

Estimation of the population attributable risk, or the proportion of all deaths which might be attributable to arsenic, is given in table 4. Among men, 93 bladder cancer deaths were observed with 15.5 expected. Hence, the excess number of bladder cancer deaths attributable to arsenic was about 77.5. If bladder, kidney, lung, and skin cancers are added, the estimate of the excess cancer deaths for the region is 509.7. In total, 5,264 deaths from all causes were observed in Region II among men for ages 30 years and above between 1989 and 1993. If arsenic was indeed the cause of the excess cancer deaths, then 509.7 deaths, or 9.7 percent, were attributable to arsenic (table 4).

For women, the excess number of lung, bladder, kidney, and skin cancer deaths totaled 191.6. Between 1989 and 1993, a total of 3,833 deaths from all causes were observed among women aged 30 years and above in Region II. Dividing the excess cancer deaths by total deaths gives 0.049, suggesting that 4.9 percent of the cancer deaths among women were attributable to arsenic (table 4).

## Smoking

Table 5 presents smoking data which includes all ages, but unfortunately the data were not available for men and women separately. As demonstrated in the table, there is no evidence to suggest a higher smoking prevalence in the two major cities, Antofagasta and Calama, which include nearly 80 percent of the total population of Region II. The proportion of those who

**TABLE 3. Age-specific observed and expected deaths and standardized mortality ratios (SMR) for women aged 30 years and over in Region II of Chile, 1989–1993**

| Category | Age group (years) | | | | | | | SMR | 95% CI* | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | ≥80 | Total | | | |
| Person-years at risk | | | | | | | | | | |
| Region II (1989–1993) | 150,930 | 111,174 | 73,144 | 51,755 | 26,068 | 9,988 | 423,059 | | | |
| Rest of Chile (1991) | 986,889 | 697,759 | 493,554 | 365,846 | 216,065 | 91,468 | 2,851,581 | | | |
| Bladder cancer | | | | | | | | | | |
| Observed deaths | 1 | 1 | 10 | 18 | 22 | 12 | 64 | | | |
| Expected deaths | 0 | 0 | 0.7 | 1.0 | 3.5 | 2.6 | 7.8 | | | |
| Observed/expected | – | – | 14.3 | 18.0 | 6.3 | 4.6 | | 8.2 | 6.3–10.5 | <0.001 |
| Kidney cancer | | | | | | | | | | |
| Observed deaths | 3 | 1 | 4 | 11 | 11 | 4 | 34 | | | |
| Expected deaths | 0.1 | 1.5 | 1.9 | 3.8 | 4.3 | 0.8 | 12.4 | | | |
| Observed/expected | 30 | 0.7 | 2.1 | 2.9 | 2.6 | 5 | | 2.7 | 1.9–3.8 | <0.001 |
| Liver cancer | | | | | | | | | | |
| Observed deaths | 1 | 2 | 6 | 11 | 7 | 10 | 37 | | | |
| Expected deaths | 0.4 | 1.9 | 6.2 | 11.1 | 9.3 | 5.9 | 34.8 | | | |
| Observed/expected | 2.5 | 1.0 | 0.9 | 1.0 | 0.8 | 1.7 | | 1.1 | 0.8–1.5 | 0.377 |
| Lung cancer | | | | | | | | | | |
| Observed deaths | 5 | 23 | 21 | 41 | 47 | 17 | 154 | | | |
| Expected deaths | 1.2 | 3.0 | 8.0 | 16.0 | 13.3 | 7.5 | 49.0 | | | |
| Observed/expected | 4.2 | 7.7 | 2.6 | 2.6 | 3.5 | 2.3 | | 3.1 | 2.7–3.7 | <0.001 |
| Skin cancer | | | | | | | | | | |
| Observed deaths | 0 | 0 | 1 | 3 | 0 | 3 | 7 | | | |
| Expected deaths | 0 | 0 | 0.3 | 0.3 | 0.2 | 1.4 | 2.2 | | | |
| Observed/expected | 0 | 0 | 3.3 | 10 | 0 | 2.1 | | 3.2 | 1.3–6.6 | 0.016 |
| Chronic obstructive pulmonary disease | | | | | | | | | | |
| Observed deaths | 6 | 1 | 6 | 7 | 16 | 13 | 49 | | | |
| Expected deaths | 0.1 | 1.9 | 6.2 | 16.4 | 29 | 35.2 | 88.7 | | | |
| Observed/expected | 60.0 | 0.5 | 1.0 | 0.4 | 0.6 | 0.4 | | 0.6 | 0.4–0.7 | <0.001 |
| All other deaths | | | | | | | | | | |
| Observed deaths | 166 | 264 | 335 | 649 | 923 | 1,151 | 3,488 | | | |
| Expected deaths | 134.4 | 255 | 380.9 | 665.1 | 917.4 | 1,133.4 | 3,486.1 | | | |
| Observed/expected | 1.2 | 1.0 | 0.9 | 1.0 | 1.0 | 1.0 | | 1.0 | 0.97–1.03 | 0.979 |

* CI, confidence interval.

smoked cigarettes was estimated to be 22.1/100 persons in Region II versus 24.3/100 persons in the rest of Chile. The proportion of persons who smoked more than a pack a day was actually lower in Antofagasta (0.8 percent) and Calama (1.1 percent) than in the rest of the country (1.5 percent).

## DISCUSSION

Ecologic studies have often been criticized because of potential biases (23). The main problems of ecologic studies arise when relative risks at the individual level are small, and when the prevalence of exposure is low. However, exposure to arsenic in drinking water has been widespread in Region II, as shown in table 1. Furthermore, the standardized mortality ratios found for bladder and lung cancer are remarkably high and cannot be attributed to problems of the ecologic study design.

The highest water concentrations of arsenic occurred between 1955 and 1970 when the population weighted average was around 570 μg/liter (table 1). Mortality has been assessed from 1989–1993. Thus, the shortest latency from first exposure to these high levels of arsenic in drinking water would be about 20 years, and the longest latency would be 38 years. However, average arsenic concentrations in excess of 100 μg/liter continued up to 1980, and mortality may have increased well before 1989. Therefore, boundaries cannot be put on latency based on this study. In a cohort study in England (12), a threefold increased risk of bladder cancer mortality was observed after treatment with Fowler's solution (potassium arsenite). There were five bladder cancer deaths, three of which occurred within 10 years of first exposure and two which occurred more than 20 years later (12). This study supports a wide range of latencies. The only other study with latency information for internal cancers was conducted in Taiwan, and only indirect latency information is available from it. In a cohort study that identified internal cancers (9), the highest risk estimates (lung cancer, relative risk (RR) = 4.6; bladder cancer, RR = 5.1) involved subjects with more than 30 years of exposure. The main exposures in Argentina also occurred many years before the findings of increased bladder cancer mortality (11). Considered overall, the latency from arsenic exposure in drinking water to increased internal cancer mortality appears to be long.

We do not know of data concerning the accuracy of death certificates in Chile, but there is no reason to suggest that it would vary by region. Hospitals are accessible in all cities and cancers are diagnosed with

**TABLE 4. Calculations of excess deaths and population attributable risks (PAR) for bladder, kidney, lung, and skin cancer mortality in men and women aged 30 years and over in Region II of Chile, 1989–1993**

| Sex and type of cancer | Observed deaths | Expected deaths | Excess deaths | PAR (%) | 95% CI* |
|---|---|---|---|---|---|
| Men | | | | | |
| Bladder cancer | 93 | 15.5 | 77.5 | | |
| Kidney cancer | 39 | 25.0 | 14.0 | | |
| Lung cancer | 544 | 143.2 | 400.8 | | |
| Skin cancer | 20 | 2.6 | 17.4 | | |
| Total excess deaths from these cancers | | | 509.7 | | |
| Total deaths from all causes | | | 5,264 | | |
| Population attributable risk | | | | 9.7 | 7.2–12.1 |
| Women | | | | | |
| Bladder cancer | 64 | 7.8 | 56.2 | | |
| Kidney cancer | 34 | 12.4 | 21.6 | | |
| Lung cancer | 154 | 49.0 | 105.0 | | |
| Skin cancer | 7 | 2.2 | 4.8 | | |
| Total excess deaths from these cancers | | | 191.6 | | |
| Total deaths from all causes | | | 3,833 | | |
| Population attributable risk | | | | 4.9 | 1.9–7.6 |

* CI, confidence interval.

**TABLE 5. Smoking habits among men and women in the two major cities in Region II in 1990 compared with data for the rest of Chile***

| Category | Nonsmoker | | Smoking habits (cigarettes/day) | | | | | | | | Smoking habits unknown | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Occasional | | 1–9 | | 10–19 | | ≥20 | | | | | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| Antofagasta | 163,500 | 76.4 | 13,223 | 6.2 | 27,445 | 12.8 | 7,845 | 3.7 | 1,800 | 0.8 | 270 | 0.1 | 214,083 | 100 |
| Calama | 92,214 | 80.4 | 8,268 | 7.2 | 10,944 | 9.5 | 1,788 | 1.6 | 1,233 | 1.1 | 222 | 0.2 | 114,669 | 100 |
| Rest of Chile | 5,443,466 | 75.1 | 581,686 | 8.0 | 837,878 | 11.6 | 228,617 | 3.2 | 109,421 | 1.5 | 46,215 | 0.6 | 7,247,283 | 100 |

* Data were obtained from the Ministerio de Planificacion y Coordinacion Nacional Republica de Chile IIIa, Encuesta CASEN.

biopsies in most cases. More than 99 percent of death certificates in Region II are completed by physicians, as was indicated by a survey in 1995. The corresponding proportion for the rest of Chile was 97 percent. In the period covered in this study, 1989–1993, the association of arsenic with internal cancers was not widely known in Region II, nor elsewhere. Therefore, diagnostic bias cannot explain the findings.

Skin cancer mortality data do not provide a reliable indicator of underlying non-melanoma skin cancer incidence. Nevertheless, both here and in arsenic-exposed regions of Taiwan, skin cancer mortality was clearly elevated.

A major strength of this study is that it was undertaken with the clear a priori hypotheses that increased risks would be found for bladder, kidney, lung, liver and skin cancer, based largely on findings in Taiwan and partly supported by findings in Argentina. It was also hypothesized a priori that the highest standardized mortality ratios would be found for bladder cancer. Increased risks were found for four of the five cancers of interest. However, it was surprising that increased risks were not found for liver cancer (SMR = 1.1 for both men and women). This result raises the possibility that the arsenic association found in Taiwan could be due to synergistic effects with other risk factors such as aflatoxin or hepatitis B.

While smoking is an established cause of cancers of the lung, bladder, and kidney, confounding due to smoking can be dismissed as the reason for the increased mortality from these cancers in Region II. There are three reasons for this. First, recent smoking data from Region II, although limited, do not support higher smoking rates than in the rest of Chile (table 5). Second, no increase was found for mortality from COPD, which is strongly related to cigarette smoking (tables 2 and 3). Indeed, COPD mortality among women in Region II was lower than for the rest of the country (table 3). Third, the extent of increased risks are much too large to attribute to cigarette smoking. Studies in various populations have shown that the relative risk of bladder cancer for smokers compared with non-

smokers are generally in the range of 2 to 4 (24). On this basis alone, smoking can be dismissed as the reason for the bladder cancer standardized mortality ratios of 8.2 for women and 6.0 for men. Although the standardized mortality ratios for kidney cancer of 2.7 for women and 1.6 for men in Region II are smaller, smoking could not be the explanation because it is not strongly related to this cancer (25).

Smokers have increased mortality from lung cancer with relative risks of the order of 10 when compared with nonsmokers. On the surface, it might seem that the standardized mortality ratios of 3.1 for women and 3.8 for men in Region II could be due to smoking. However, this is not the case because smoking also occurs in the comparison population, the rest of Chile. In fact, it is extremely unlikely that confounding due to smoking could result in total population lung cancer relative risks greater than 2 (26).

While smoking can be rejected as producing overall confounding in this study, there remains the surprising finding of very high relative risks for COPD deaths for both men and women in the age range 30–39 years. Four deaths were reported among men with 0.8 expected (table 2), and six deaths among women with 0.1 expected (table 3). These ten individuals who died from COPD would have been young children at the time of the peak water arsenic levels in the period 1955 to 1970. One possibility is that their arsenic exposures as children contributed to their early deaths from COPD. Support for this hypothesis comes from two other studies in Chile (14, 27). In one study (27), the results of five autopsies were reported for children who died in 1968 and 1969 in Antofagasta, and who had evidence of arsenic poisoning including skin lesions. Lung tissue was examined in four of the five with abnormalities being found in each of them, in two cases including interstitial fibrosis (27). In 1976, a survey which included 144 school children in Antofagasta with skin pigmentation due to arsenic reported a history of bronchopulmonary disease 2.5 times more often in these children (15.9 percent) than in children with normal skin (6.2 percent) (14). More recently, evidence of chronic respiratory disease in arsenic-exposed patients has been found in a survey of over 7,000 people in an area in West Bengal, India, with arsenic in drinking water (28). Among 156 cases with skin lesions due to arsenic, most of whom were under age 40 years, 57 percent were found to have symptoms of respiratory disease. Lung function tests carried out on 17 patients showed evidence of restrictive disease in 16 of them, either alone (9 patients), or in combination with evidence of obstructive disease (6 patients). Further confirmation is needed, but the evidence to date suggests that arsenic may have specific pulmonary effects in children contributing to increased COPD mortality in young adulthood.

Occupational exposures to arsenic, especially in mining and refining of copper, would be expected to contribute to some increase in lung cancer risk. However, occupational exposures mainly involve men, so the fact that similar results were found for both men and women supports the hypothesis that arsenic in drinking water is the predominant source of exposure that produces the cancer mortality findings.

The arsenic attributable mortality in Region II is 9.7 percent (7.2–12.1) for men and 4.9 percent (1.9–7.6) for women, leading to an average of 7.3 percent of all deaths among persons aged 30 years and over. These attributable risks are very high. Although high relative risks between 7 and 10 were found for mesothelioma and asbestosis in a population near asbestos mining in South Africa (29), the total numbers and size of the population involved were much smaller than in Region II of Chile. Aflatoxin may produce high risks of primary liver cancer, but the effect is usually in conjunction with hepatitis B and is confined to a single cancer (30). The total attributable mortality risks associated with arsenic in Region II are much higher than those so far observed in these and other populations exposed to environmental carcinogens. Indeed, arsenic attributable cancer mortality in Region II of Chile exceeds that estimated for cigarette smoking in developing countries as a whole (31).

Dose-response relations are not identifiable from this mortality study because individual exposure data are lacking. Whether or not risks of internal cancers are also increased at lower levels of exposure than in Region II is of considerable public health importance (10). The drinking water standard is 50 μg/liter of arsenic in many countries, a level only about ten times lower than was present in Region II in past years (table 1). One study (32) has raised the possibility that there might be effects at even lower arsenic concentrations. It has been postulated that arsenic might only exert effects when capacity for detoxification of arsenic by methylation is exceeded at high levels of exposure. However, in a previous study in Region II (33, 34), we found non-methylated arsenic in the urine of participants in only slightly higher proportions in highly exposed persons (600 μg/liter in water) compared with persons with low arsenic exposure (15 μg/liter in water). Therefore, there is no reason to believe that methylation will protect against arsenic carcinogenicity at low exposure levels. Furthermore, although no good animal models exist for arsenic and cancer, the two bioassays that have found positive results have found carcinogenic effects for methylated arsenic (35, 36).

In conclusion, markedly increased cancer risks have been found in this study in Chile to be associated with arsenic in drinking water. High priority should be given to studies at lower levels of exposure such as those associated with 50 μg/liter, the drinking water standard for much of the world.

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