

Fifty-Year Study of Lung and Bladder Cancer Mortality in Chile Related to Arsenic in Drinking Water

Guillermo Marshall, Catterina Ferreccio, Yan Yuan, Michael N. Bates, Craig Steinmaus, Steve Selvin, Jane Liaw, Allan H. Smith

- Background** Region II of Chile (the second most northerly administrative region) experienced dramatic increases in average arsenic water concentrations beginning in 1958, followed by marked declines in the 1970s when water treatment plants were installed. This history provides a unique opportunity to study time trends in the development of arsenic-related cancers, including lung and bladder cancers.
- Methods** We investigated lung and bladder cancer mortality from 1950 to 2000 for region II compared with region V, where drinking water was not contaminated with arsenic. Mortality data were obtained from 218 174 death certificates for the two regions for 1950–1970 and from mortality data tapes that identified 307 541 deaths in the two regions for 1971–2000. Poisson regression models were used to identify time trends in rate ratios (RRs) of mortality from lung and bladder cancers comparing region II with region V.
- Results** Lung and bladder cancer mortality rate ratios for region II compared with region V started to increase about 10 years after high arsenic exposures commenced and continued to rise until peaking in 1986–1997. The peak lung cancer mortality RRs were 3.61 (95% confidence interval [CI] = 3.13 to 4.16) for men and 3.26 (95% CI = 2.50 to 4.23) for women. The peak bladder cancer RRs were 6.10 (95% CI = 3.97 to 9.39) for men and 13.8 (95% CI = 7.74 to 24.5) for women. Combined lung and bladder cancer mortality rates in region II were highest in the period 1992–1994, with mortality rates of 153 and 50 per 100 000 men and women, respectively, in region II compared with 54 and 19 per 100 000 in region V.
- Conclusions** Such large increases in total population cancer mortality rates have, to our knowledge, not been documented for any other environmental exposure. The long latency pattern is noteworthy, with mortality from lung and bladder cancers continuing to be high until the late 1990s, even though major decreases in arsenic exposure occurred more than 25 years earlier.

J Natl Cancer Inst 2007;99:920–8

Drinking water in region II of Chile is supplied mainly by rivers originating from springs in the Andes mountains that contain inorganic arsenic, some at very high concentrations. Before 1958, the arsenic concentration in the water supply in the main city of region II, Antofagasta, was approximately 90 µg/L (1), nearly twice the drinking water standard in much of the world (50 µg/L) until the recent lowering of the level in some countries (to 10 µg/L in most cases). In 1958, this source was supplemented with water from the Toconce and Holajar rivers, which contain extremely high levels of arsenic (1); as a result, the arsenic concentrations in the water supply of Antofagasta and the nearby city of Mejillones averaged 870 µg/L during 1958–1970. Other cities and towns in the region also had high concentrations of arsenic in their water supplies. Installation of a water treatment plant in Antofagasta in 1971, and later in other cities and towns, led to marked reductions in arsenic concentrations in the water.

The sudden rise and subsequent fall of arsenic concentrations in region II provides a unique opportunity to investigate time trends in arsenic-associated cancer. Also, by contrast to other high-

arsenic areas in the world, where most of the arsenic is obtained from well water and historical exposure reconstruction is difficult, Northern Chile has a very dry climate, and each town and city has just one or two sources of water originating from rivers for which arsenic measurements have been recorded since the 1950s. The arsenic monitoring data for region II water supplies provide

Affiliations of authors: Departamento de Salud Pública, Escuela de Medicina (GM, CF), and Departamento de Estadística, Facultad de Matemáticas (GM), Pontificia Universidad Católica de Chile, Santiago, Chile; Arsenic Health Effects Research Program, School of Public Health, University of California, Berkeley, CA (YY, CS, JL, AHS); School of Public Health, University of California, Berkeley, CA (MNB, SS).

Correspondence to: Allan H. Smith, MD, PhD, Arsenic Health Effects Research Program, School of Public Health, University of California, Berkeley, 140 Warren Hall, MC 7360, Berkeley, CA 94720-7360 (e-mail: ahsmith@berkeley.edu).

See "Notes" following "References."

DOI: 10.1093/jnci/djm004

© The Author 2007. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.

exposure data of a quality far exceeding that of other arsenic-exposed regions of the world, for which past exposures are invariably difficult to ascertain.

Increased mortality from lung and bladder cancers has previously been reported in region II of Chile compared with the rest of the country. These cancers have also been associated with high levels of arsenic in water supplies in Taiwan (2–5) and Argentina (6,7). The results from Chile confirmed that the elevated cancer rates in these other countries were likely to be attributable to arsenic, and in 2002, the Working Group of the International Agency for Research on Cancer classified arsenic in drinking water as a cause of lung and bladder cancers, along with skin cancer (8).

Little is known about the latency period from commencement of increased exposure to arsenic to increased risk of cancer. Some studies have suggested that latency periods may be more than 30 years long (9–14). The relatively sharp peak in water arsenic concentrations in region II of Chile during 1958–1970 allows construction of longitudinal mortality time patterns that can be used to investigate latency periods associated with diseases caused by arsenic exposure, including cancer.

We previously reported marked increases in lung and bladder cancer mortality in the years 1989–1993 in arsenic-exposed region II of Chile compared with the rest of Chile (15). These findings led us to investigate mortality in region II for the 50-year period 1950–2000. In this paper, we present lung and bladder cancer mortality for these years in region II compared with region V, which is otherwise similar to region II but not exposed to arsenic in drinking water. The unique exposure scenario—in a large population with well-documented information on past exposure via drinking water—provides a rare opportunity to investigate the latency effects of a widespread environmental carcinogen, including the latency period between the reduction in exposure to reductions in cancer rates.

Subjects and Methods

Setting

Chile is a long, narrow country that is divided into 15 administrative regions that are numbered from north to south, with region II being the second northernmost (Fig. 1). A single comparison region for region II was chosen because International Classification of Diseases (ICD) coding of death certificates for the whole country for a period of 20 years (from 1950 to 1970, when computerized data were not already available) would have been prohibitively expensive. Because the country varies in characteristics from north to south, in particular in factors related to climate, we wished to select a nearby region for comparison. To increase statistical precision, it was also desirable that the number of people in the referent population be greater than the number in region II. Regions I and III were first considered, but both were rejected because they are adjacent to region II and there was an increased potential for migration between them and because there has been some arsenic exposure in these two regions, although it is minor compared with that in region II (16). Region IV is small, with population numbers similar to those in region II. Region V is located in the northern half of Chile, with a population more than three times larger than that of region II. In 2000, the population of region II was 477 332 and that

CONTEXT AND CAVEATS

Prior knowledge

Arsenic in drinking water is known to cause bladder, lung, and nonmelanoma skin cancer. However, little is known about the latency period.

Study design

Ecologic study comparing lung and bladder mortality for a period of 50 years in two regions of Chile—region II, which experienced a sudden rise and subsequent fall in arsenic levels in the drinking water during that time, and the sociodemographically similar region V, in which arsenic levels remained low.

Contribution

Lung and bladder cancer mortality in region II started to increase about 10 years after water arsenic levels increased and peaked 10–20 years after the levels dropped back down. At the peak, lung cancer mortality was about three times higher in region II than in region V in both men and women; bladder cancer was six times higher in men and 14 times higher in women.

Implications

A clear latency pattern for mortality from lung and bladder cancer after arsenic exposure is evident.

Limitations

This was an ecologic study that did not account for migration and did not have individual data on arsenic exposure or on other risk factors for lung and bladder cancer.

of region V was 1 508 749; the ratio has been similar throughout the study period.

To ensure that region V was an appropriate choice of comparison region, in preliminary work (data not shown) we compared key sociodemographic factors and relevant medical information among region II, region V, and the whole of Chile. Per capita income in region V in 1990 (US \$2053) was similar to that of the country as a whole (US \$2011) (17). Region II had a much higher per capita income (US \$3853), but the difference mainly reflected the presence of the mining industry in region II, which generated large exports but not higher personal income. Data from smoking surveys carried out on random population samples in 1990 and 1992 (18) suggest little in the way of smoking differences between the two regions and the rest of the country, with both years giving similar data. In 1990, 26.6% of surveyed men and 19.3% of surveyed women in Chile said they smoked. The corresponding figures for region II and region V were, respectively, 27.4% and 28.5% for men and 16.6% and 20.2% for women. Finally, we analyzed information concerning death certification by regions in the country, based on a study conducted in 1983 (19). For the whole country, 85.6% of the death certificates in that year were certified by physicians, and region II and region V had similar percentages, with 89.8% and 94.5% physician certification, respectively.

Mortality Data

Mortality data covering the period 1950–2000 for individuals aged 30 years and above were obtained from three different sources. For the period 1950–1970, a period for which electronic mortality data were not available, we obtained death certificates for regions II and V

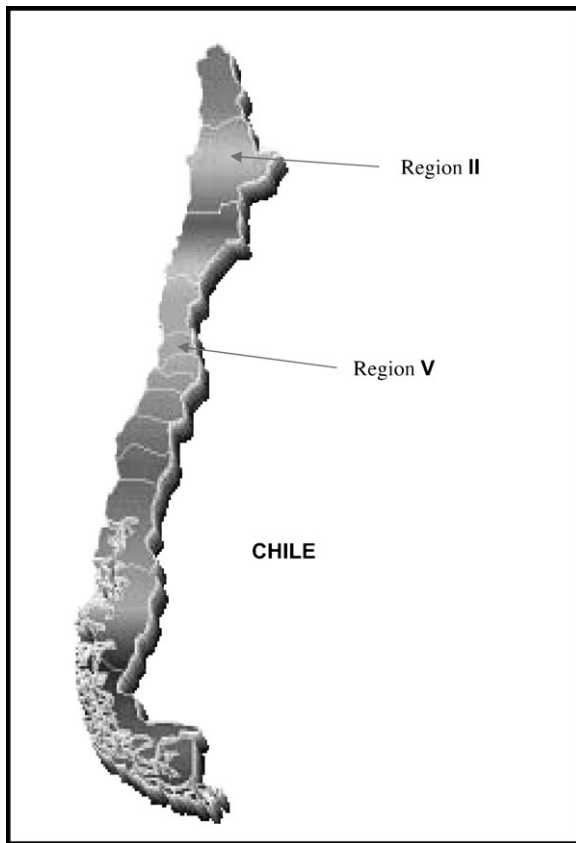


Fig. 1. Map of Chile, showing regions II and V. The country is administratively divided into regions that are numbered from north to south.

from the Chilean Civil Registry and Identification Department. Digital photographs were taken of the 218174 death certificates for regions II and V and they were downloaded to a central computer, after which study nosologists coded the causes of death according to the International Classification of Diseases, 9th Revision (20). The nosologists were given a mixture of death certificates from each region and coded causes of death without knowing from which region the death certificate originated. A separate person entered the data on the region from which the death certificates originated.

For the periods 1971–1975 and 1977–1982, computerized mortality data that included cause of death were obtained from the Chile National Institute of Statistics (Instituto Nacional de Estadísticas) including 52155 deaths for regions II and V for 1971–1975, and 58638 deaths for 1977–1982. However, no mortality data are available for the country for the year 1976. Finally, for the period 1983–2000, mortality data were obtained from the Ministry of Health for all of Chile including 196748 deaths for regions II and V.

Census data were used to calculate the denominators for mortality rates. Chile has had a total population census roughly every 10 years, including 1940, 1952, 1960, 1970, 1982, 1992, and 2002. Census data were obtained for region II, region V, and the rest of Chile from the National Institute of Statistics (Instituto Nacional de Estadísticas) for men and women separately in 10-year age groups. We estimated population counts with a linear interpolation for years between each census.

Data on Arsenic Levels in Drinking Water

Data on water arsenic concentrations for cities and towns in region II from 1950 to 1994 were obtained from a previous study (15), in which approximate average levels of arsenic in sources of drinking water were given for all towns and cities in region II.

Statistical Methods

Lung cancer (ICD code 162) and bladder cancer (ICD code 188) mortality rate ratios for region II compared with region V were estimated using Poisson regression for each 3 years of calendar time between 1950 and 2000, for men and women separately. Because these cancers are rare in persons below age 30 years, the analysis was restricted to those aged 30 years and above. Age adjustment incorporated 10-year age groups starting with ages 30–39 years and continuing to ages 80 years and above. Ten-year age groups were chosen because the census data were available in that form. From 1971 through 2000, it was possible to estimate rate ratios for region II compared with all of the rest of Chile; 95% confidence intervals (CIs) were calculated based on the asymptotic normality of the logarithm of the rate ratio estimate (21).

Poisson regression models were used to smooth the effect of arsenic exposure over time. In these models, the response variable was the number of observed deaths in each age group for each year, for both region II and region V. The model for the expected number of deaths in age group i , region j , and year t can be expressed as

$$\log \mu_{ijt} = \alpha + \text{age}_i + \text{region}_j + \text{year}_t + f(t, \text{region}_j) + \log \text{population}_{ijt},$$

where $f(t, \text{region}_j)$ is a cubic spline representing the interaction between year and region, with region V as reference. The log rate ratio for period t between regions II and V can be represented as

$$\log \text{RR}_t = \text{region}_2 = f(t, \text{region}_2).$$

This model for analyzing time trends was first presented by Hastie and Tibshirani (22) and has subsequently been used with Poisson regression by many authors (23,24). We used spline smoothing with generalized cross-validation to estimate the amount of smoothing. We also plotted mortality rate ratios estimated for each successive 3-year period, along with the smoothed function and its 95% confidence interval, to check that the smoothed function was compatible with the underlying mortality data. Finally, we separated the mortality data into three 20-year birth cohorts chosen in relation to 1958, when the high arsenic exposures commenced, and repeated the Poisson regression analysis for each birth cohort separately. The birth cohorts were chosen to identify childhood exposure (those born in 1938–1957) and two earlier birth cohorts, one having young adult exposure who were born in the period 1918–1937 and the second with older age adult exposure who were born before 1918.

Results

Water arsenic concentrations for towns and cities in region II, and the overall population-weighted averages, are presented in Table 1, which was published previously (15). To place these arsenic concentrations in water into context, the highest

Table 1. Arsenic concentrations ($\mu\text{g/L}$) in drinking water in major cities and towns in region II of Chile and population-weighted averages for all of region II from 1950 to 1994 calculated using 1991 census population numbers*

City or town (population, 1991 census)	1950–1954	1955–1959	1960–1964	1965–1969	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994
	Antofagasta (219310)	90	870	870	870	260	110	80	60
Mejillones (6134)	90	870	870	870	260	110	80	60	40
Calama (100283)	120	120	120	120	240	230	110	80	40
Chuquicamata (17414)	250	150	130	130	130	110	80	60	10
Tocopilla (21039)	250	250	250	250	520	460	110	80	40
María Elena (15470)	250	250	250	250	520	460	110	80	40
Taltal (7620)	60	60	60	60	60	60	60	60	60
San Pedro (3070)	600	600	600	600	600	600	600	600	600
Average for region II	123	569	568	568	272	176	94	71	43

* Data published previously (15).

population-weighted average for region II was $569 \mu\text{g/L}$, a little more than 10 times the $50 \mu\text{g/L}$ level that was, until recently, the drinking water standard in much of the world. Arsenic concentrations in water are low in the rest of Chile, including region V. For example, the water arsenic concentrations in tap water in Valparaíso, the largest city of region V, were in the range of $0.5\text{--}1.1 \mu\text{g/L}$ when sampled in 1998 (25).

We calculated lung cancer mortality rates and mortality rate ratios (RRs) for men and women separately, comparing region II with region V for the period 1950–2000 and comparing region II with the rest of Chile for the period 1971–2000 (Table 2). The peak rate ratio for lung cancer among men was in the period 1992–1994, with an RR estimate of 3.61 (95% CI = 3.13 to 4.16), and the peak rate ratio for lung cancer among

women was in the period 1989–1991, with an RR of 3.26 (95% CI = 2.50 to 4.23). We did a similar analysis for bladder cancer (Table 3). The peak rate ratio for bladder cancer among men was in the period 1986–1988, with an RR of 6.10 (95% CI = 3.97 to 9.39), and the peak rate ratio among women was in the period 1992–1994, with an RR of 13.8 (95% CI = 7.74 to 24.5).

Mortality rates per 100000 persons per year are also given in Table 2 for lung cancer and in Table 3 for bladder cancer. Combined lung and bladder cancer mortality rates in region II were highest in the period 1992–1994, with mortality rates per 100000 persons of 153 for men (lung cancer, $n = 130$, plus bladder cancer, $n = 23$) in region II compared with 54 (lung cancer, $n = 47$, plus bladder cancer, $n = 7$) in region V. The corresponding rates

Table 2. Observed lung cancer deaths and lung cancer mortality rates and rate ratios for men and women aged 30 years and above in region II compared with region V and the rest of Chile, 1950–2000*

Years	Males						Females					
	No. of deaths		Mortality rates (per 100000)		Rate ratio (95% CI) compared with		No. of deaths		Mortality rates (per 100000)		Rate ratio (95% CI) compared with	
	II	V	II	V	V	Rest of Chile†	II	V	II	V	V	Rest of Chile†
1950–1952	22	80	20	24	0.93 (0.59 to 1.46)		2	40	2	11	0.24 (0.0 to 14.64)	
1953–1955	38	103	33	29	1.26 (0.87 to 1.83)		12	43	13	11	1.33 (0.70 to 2.52)	
1956–1958	26	110	21	29	0.83 (0.54 to 1.27)		4	39	4	9	0.49 (0.18 to 1.37)	
1959–1961	35	137	28	33	0.93 (0.64 to 1.34)		13	49	12	11	1.28 (0.69 to 2.35)	
1962–1964	48	154	37	35	1.20 (0.87 to 1.66)		12	54	10	11	1.10 (0.59 to 2.06)	
1965–1967	45	139	34	30	1.33 (0.95 to 1.86)		16	64	13	12	1.28 (0.74 to 2.21)	
1968–1970	102	222	75	44	1.98 (1.57 to 2.51)		18	85	14	15	1.11 (0.67 to 1.84)	
1971–1973	109	312	75	58	1.54 (1.24 to 1.92)	2.46 (2.02 to 2.99)	23	112	16	18	1.08 (0.69 to 1.69)	1.79 (1.18 to 2.72)
1974–1975‡	95	163	92	43	2.59 (2.01 to 3.34)	3.42 (2.77 to 4.22)	14	53	14	12	1.38 (0.76 to 2.48)	1.68 (0.99 to 2.87)
1977–1979	175	268	103	43	2.93 (2.42 to 3.55)	3.46 (2.96 to 4.03)	44	79	26	11	2.89 (2.00 to 4.18)	2.88 (2.12 to 3.91)
1980–1982	238	319	131	48	3.37 (2.85 to 3.98)	3.96 (3.47 to 4.53)	42	111	23	14	1.96 (1.37 to 2.79)	2.23 (1.64 to 3.05)
1983–1985	209	347	104	48	2.72 (2.29 to 3.23)	3.04 (2.64 to 3.51)	40	116	20	14	1.77 (1.23 to 2.53)	1.85 (1.35 to 2.54)
1986–1988	251	338	114	43	3.35 (2.84 to 3.94)	3.74 (3.28 to 4.26)	66	133	30	15	2.52 (1.87 to 3.38)	2.80 (2.18 to 3.59)
1989–1991	315	408	131	49	3.48 (3.00 to 4.03)	4.13 (3.68 to 4.64)	92	142	38	15	3.26 (2.50 to 4.23)	3.41 (2.76 to 4.22)
1992–1994	345	425	130	47	3.61 (3.13 to 4.16)	4.20 (3.76 to 4.70)	91	178	34	17	2.54 (1.97 to 3.27)	2.81 (2.27 to 3.48)
1995–1997	302	534	101	55	2.43 (2.11 to 2.79)	3.27 (2.91 to 3.68)	121	199	42	18	2.97 (2.37 to 3.72)	3.16 (2.62 to 3.80)
1998–2000	345	460	104	44	3.13 (2.72 to 3.60)	3.63 (3.25 to 4.05)	96	222	31	19	2.08 (1.64 to 2.64)	2.26 (1.84 to 2.77)

* CI = confidence interval; R II = region II; R V = region V.

† Mortality data for the rest of Chile were not available in electronic form until 1971.

‡ Omitting 1976, for which data were not available in electronic form.

Table 3. Observed bladder cancer deaths and bladder cancer mortality rates and rate ratios for men and women aged 30 years and above in region II compared with region V and the rest of Chile for the period 1950–2000*

Years	Males						Females					
	No. of deaths		Mortality rates (per 100000)		Rate ratio (95% CI) compared with		No. of deaths		Mortality rates (per 100000)		Rate ratio (95% CI) compared with	
	II	V	II	V	V	Rest of Chile†	II	V	II	V	V	Rest of Chile†
1950–1952	5	14	4	4	1.31 (0.16 to 11.0)		1	7	1	2	0.71 (–)	
1953–1955	4	14	3	4	1.04 (0.34 to 3.16)		2	7	2	2	1.42 (0.29 to 6.83)	
1956–1958	8	13	7	3	2.27 (0.94 to 5.47)		3	6	3	1	2.48 (0.62 to 9.91)	
1959–1961	3	21	2	5	0.53 (0.16 to 1.79)		3	14	3	3	1.07 (0.31 to 3.71)	
1962–1964	5	14	4	3	1.42 (0.51 to 3.96)		6	11	5	2	2.80 (1.03 to 7.57)	
1965–1967	9	26	7	6	1.47 (0.69 to 3.13)		4	11	3	2	1.92 (0.61 to 6.03)	
1968–1970	11	23	8	5	2.13 (1.04 to 4.37)		3	11	2	2	1.47 (0.41 to 5.28)	
1971–1973	9	24	6	4	1.71 (0.80 to 3.69)	3.64 (1.82 to 7.31)	7	11	5	2	3.45 (1.34 to 8.91)	6.80 (3.01 to 15.4)
1974–1975‡	9	7	9	2	5.95 (2.22 to 16.0)	5.00 (2.50 to 10.0)	4	7	4	2	3.09 (0.9 to 10.56)	5.35 (1.90 to 15.1)
1977–1979	17	38	10	6	2.10 (1.19 to 3.72)	2.91 (1.78 to 4.76)	10	10	6	1	5.39 (2.24 to 13.0)	4.71 (2.45 to 9.05)
1980–1982	35	33	19	5	5.04 (3.13 to 8.10)	5.10 (3.59 to 7.26)	22	13	12	2	9.10 (4.59 to 18.1)	6.28 (4.01 to 9.82)
1983–1985	41	34	20	5	5.77 (3.66 to 9.09)	5.42 (3.91 to 7.51)	22	14	11	2	8.41 (4.30 to 16.4)	7.14 (4.54 to 11.2)
1986–1988	47	37	21	5	6.10 (3.97 to 9.39)	5.99 (4.41 to 8.14)	37	27	17	3	7.28 (4.44 to 12.0)	10.4 (7.23 to 14.9)
1989–1991	52	53	22	6	4.73 (3.23 to 6.94)	5.86 (4.38 to 7.84)	35	28	14	3	6.61 (4.02 to 10.9)	8.33 (5.80 to 12.0)
1992–1994	62	60	23	7	4.95 (3.47 to 7.06)	6.63 (5.06 to 8.67)	42	16	16	2	13.8 (7.74 to 24.5)	9.32 (6.67 to 13.0)
1995–1997	56	59	19	6	4.43 (3.07 to 6.38)	5.05 (3.82 to 6.67)	44	30	15	3	7.60 (4.78 to 12.1)	8.45 (6.11 to 11.7)
1998–2000	58	62	18	6	4.27 (2.98 to 6.11)	5.12 (3.89 to 6.73)	50	28	16	2	9.16 (5.76 to 14.5)	8.53 (6.29 to 11.6)

* CI = confidence interval.

† Mortality data for the rest of Chile were not available in electronic form until 1971.

‡ Omitting 1976, for which data were not available in electronic form.

for women in 1992–1994 were 50 in region II (lung cancer, $n = 34$, plus bladder cancer, $n = 16$) compared with 19 in region V (lung cancer, $n = 17$, plus bladder cancer, $n = 2$).

The time patterns of increased mortality from lung and bladder cancers in region II compared with region V are displayed in Fig. 2. Separately estimated mortality rate ratios for each 3-year period fall mostly within the confidence bands of the smoothed Poisson regression functions. Trends of increasing risk are generally apparent between about 1968 (10 years after high exposures commenced) and 1978 (20 years after high exposures commenced). The rate of lung cancer in men in region II was already about twice that in region V by the period 1968–1970 (RR = 1.98, 95% CI = 1.57 to 2.51; Table 2). Among women, the lung cancer RR had reached 2.89 (95% CI = 2.00 to 4.18) by the period 1977–1979. Bladder cancer mortality rate ratios rose even higher than those for lung cancer (Fig. 2). Among men, the RR had reached 5.95 (95% CI = 2.22 to 16.0) in the period 1974–1975, and among women, the RR had reached 3.45 (95% CI = 1.34 to 8.91) in the period 1971–1973 (Table 3).

With the exception of bladder cancer among women, there was evidence that rate ratios had started to decline after peaking around 1990 (Fig. 2). However, the wide confidence bands preclude definitive statements about reductions in rate ratios, especially among women.

The time trends in the rate ratios for three birth cohorts comparing region II with region V are presented in Fig. 3. Lung cancer rate ratios were markedly elevated for the male birth cohort born in 1938–1957, who would have experienced high exposures as young children. By contrast, there was no evident difference in lung cancer rate ratios between the birth cohorts of

women. For bladder cancer, high rate ratios can be seen for each birth cohort. The mortality rate ratio appeared to continue to increase for women born before 1918, but by the year 2000, the data involved a relatively small number of women, all above the age of 80 years.

Discussion

In this study, clear latency patterns between arsenic exposure and lung and bladder cancer mortality can be seen because of the large population exposed (251 976 residents in region II in 1970), accurate data on past exposure, and the precise time pattern of commencement and decline of high exposures. To highlight the size of the study, there were 3406 lung cancer deaths in the exposed population (see Table 2). Latency patterns are usually difficult to obtain for human cancers. The largest study so far published concerning lung cancer and arsenic involved 1525 lung cancer deaths, but that number includes both those exposed to arsenic and those not exposed to arsenic (26). We report here very high rate ratios for both lung cancer (3- to 4-fold) and bladder cancer (6- to 10-fold) following exposure to arsenic in drinking water. Rate ratio estimates of this size for a defined large population living in a region of a country are, we believe, without precedent for any cause of any human cancer. Active cigarette smoking results in higher relative risks for lung cancer among smokers compared with nonsmokers (10- to 20-fold) (27) but lower relative risk estimates for bladder cancer (2- to 4-fold) (28). However, relative risks with active cigarette smoking relate to the subset of a population who are smokers rather than involving a total population within a region of a country, as is the case

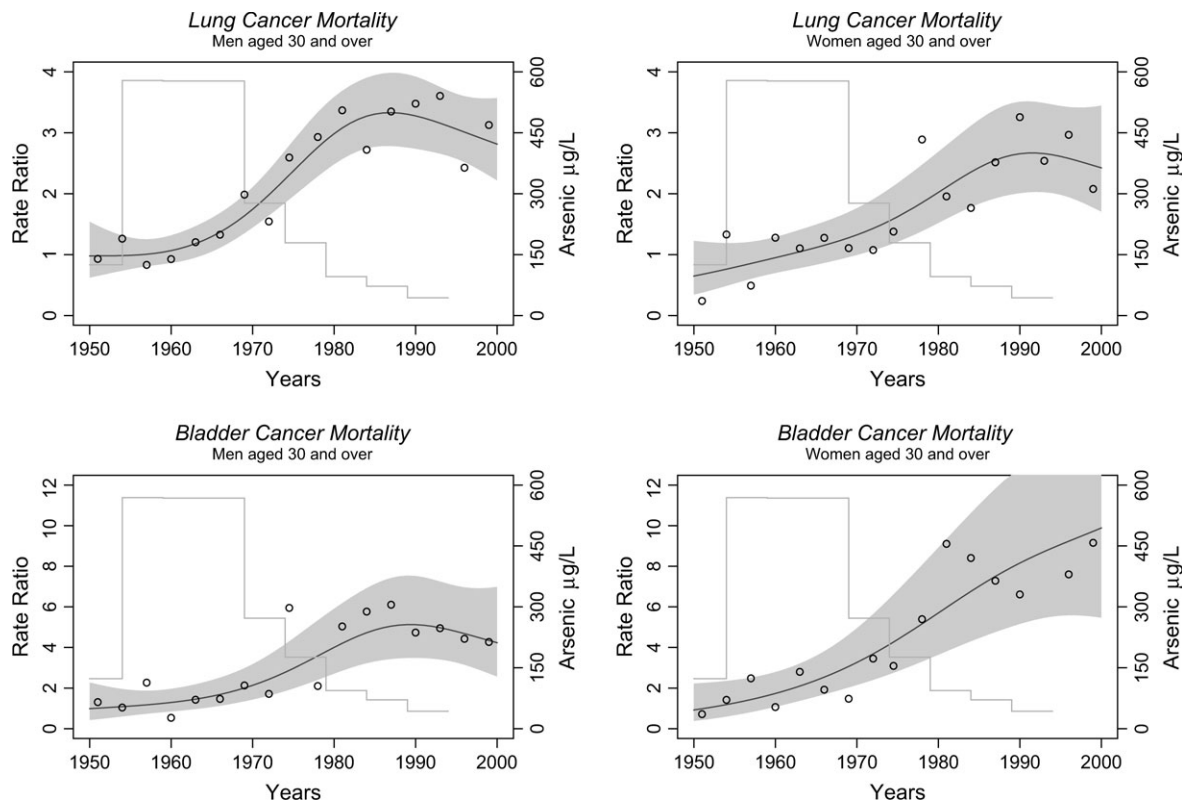


Fig. 2. Lung and bladder cancer mortality rate ratios comparing region II with region V for men and women aged 30 and above, separately, as estimated by Poisson regression with smoothing. The **shading** represents the 95% confidence bands. The **circles** represent the mortality rate ratios plotted at the midpoint of each successive 3-year period. Histograms (**gray lines**) of the population-weighted average arsenic water concentrations for region II, from 1950 to 1994 in 5-year increments, are also presented (vertical axes at right).

with arsenic in water sources in region II of Chile, so the local public health impact of arsenic in water is potentially greater.

The birth cohort analyses show very high lung cancer relative risks for men born in the 20-year period, 1938–1957, just before the very high arsenic exposures commenced, and who would have been exposed as children or adolescents (Fig. 3). We previously reported high lung cancer mortality rates for young adults in the period 1989–2000 in Antofagasta who would have experienced early life exposure to arsenic in water (29). The data presented here include all of region II, span more years, and confirm the earlier findings. We know of no mechanistic explanation for the finding that boys appear to be more susceptible than girls to subsequently developing lung cancer when exposed to arsenic in water as children. We are planning further investigations to assess variation in the impact of exposure at different ages.

A major strength of our study was the ability to assess arsenic exposures with less uncertainty than other studies. In almost all epidemiology studies of arsenic-related cancers that have been carried out to date, a major problem has been retrospective exposure assessment. High arsenic concentrations in drinking water in the rest of the world (including Taiwan, Argentina, Mongolia, Bangladesh, India, Mexico, Thailand, Nepal, and the United States) are found in well water sources, for which there are, at best, limited historical records of arsenic concentrations (30).

Many of the water sources in these populations are small private domestic wells used by only a few people or families. Thus,

assessing exposure in epidemiology studies can involve identifying and measuring arsenic concentrations in water from hundreds of individual wells. There may be considerable variation in arsenic concentration among wells close to each other, and there is often uncertainty about the well from which a person consumed water decades ago. This lack of information leads to major uncertainties in individual and population exposure estimates for long latency outcomes, such as cancer. We have carried out studies involving sampling of well water in Argentina (12), West Bengal (31–35), and California and Nevada (11,36,37), and in each location there have been major problems in locating (for sampling) the wells used by individuals decades ago. Even if the right well is located, there is uncertainty about whether current arsenic levels are representative of the water consumed at the earlier period. In the epidemiology studies from Taiwan, for example, past exposure to arsenic was not determined, other than to note how long individuals drank from the well they were using at the time the studies were conducted. In one recent Taiwan study, for example, only a single measurement was used for each subject, even if subjects had used many different water sources over the course of their lives (14).

Estimating exposures to arsenic in drinking water in Northern Chile is considerably less uncertain than doing so in the places described above. In Northern Chile, wells were not used to obtain water. Until recently, bottled water was also not used. Because of the extreme dryness of the area, all water came from a relatively small number of large municipal water supplies, for which there

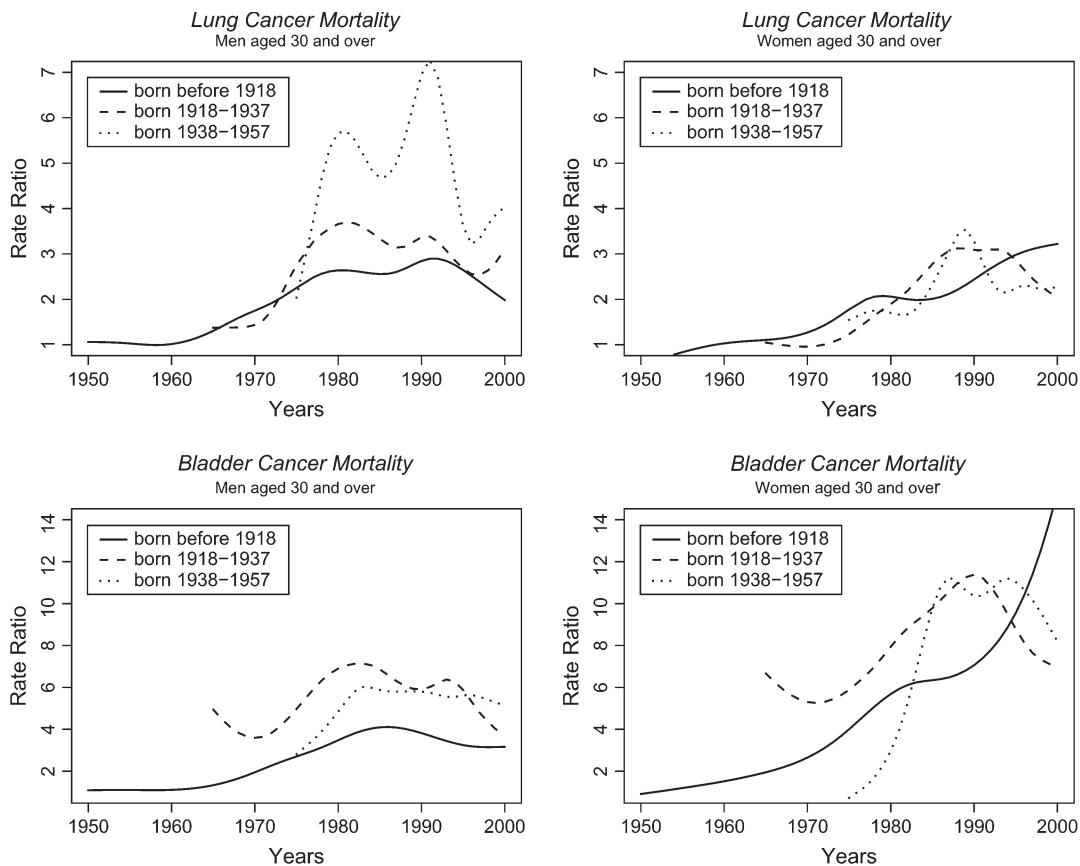


Fig. 3. Lung and bladder cancer mortality rate ratios comparing region II with region V for men and women aged 30 and above, separately, as estimated by Poisson regression with smoothing for three birth cohorts, one born in 1938–1957 before the high exposures commenced in 1958 (**dotted lines**) and two older birth cohorts, one born before 1918 (**solid lines**) and the second born in 1918–1937 (**dashed lines**).

are historical records of water concentrations of arsenic. As a result, simply knowing the town in which a person lived during a particular year accurately establishes the arsenic concentration in the water they drank. However, in this paper, we present mortality findings for the region as a whole, rather than subdividing by city and town, because census and mortality data were not available by city and town of residence for the whole period 1950–2000.

We have previously shown that the elevated cancer rates found in region II are related to arsenic contamination of water supplies and not to some bias or confounding factor, such as smoking (15). While smoking is an established cause of cancers of the lung and bladder, confounding due to smoking can be dismissed as the reason for the increased mortality from these cancers in region II, for three reasons. First, as noted above, the smoking data from region II do not support higher smoking rates than in the rest of Chile. Second, the extent of increased risks is much too large to attribute to cigarette smoking. Studies in various populations have shown that the relative risks of bladder cancer for smokers compared with nonsmokers are generally in the range of 2–4 (28). On this basis alone, smoking can be dismissed as the reason for the bladder cancer mortality ratios shown in Table 3, many of which exceed 5. Smokers do have increased mortality from lung cancer with relative risks of the order of 10–20 when compared with nonsmokers (27), and it might seem that the standardized mortality ratios reaching around 3–4 for men and women in region II could be due

to smoking. However, this is not the case because smoking also occurs in the comparison populations, region V and the rest of Chile. In fact, it is extremely unlikely that confounding due to smoking could result in lung cancer rate ratios greater than 2 (38). Third, the case–control study of lung cancers diagnosed in 1994–1996 in region II of Chile had data on individual smoking for each participant, and although there was strong evidence of increased risks with arsenic exposure, there was no evidence of confounding with smoking (16).

The latency patterns we show here provide further evidence for the causal relationship between arsenic in the water in region II of Chile and increased rates of lung and bladder cancer because increased rates of these cancers temporally followed the increase in arsenic exposure in a plausible manner. Smoking is the most important population cause for both lung cancer and bladder cancer in most of the world. As noted above, the smoking prevalence figures given above show that smoking rates in region II and region V are about the same.

Although confounding from different smoking patterns is not an issue, potential synergy between arsenic and smoking could be important. Other research we have conducted (9–11) suggests that smoking might be a cofactor with arsenic in bladder cancer causation and that smoking and arsenic might be synergistic in increasing the risk of lung cancer (16). Historically, in Chile as elsewhere, males have been more likely to be smokers than females. It is possible that

interaction of arsenic with tobacco results in some of the differences in the mortality trends seen in our study between males and females. However, the mortality rate ratio for bladder cancer rises higher for women than men, which does not support the idea that smoking is a required co-carcinogen for arsenic to cause bladder cancer. If smoking were a required co-carcinogen, then one would expect the impact of arsenic on bladder cancer rates to be greater for men than for women since they smoke more.

The increase in bladder cancer mortality we report in this study could be due in part to increased fatality of tumors related to arsenic and not just to increased incidence alone. Lung cancer is highly fatal, and trends in mortality rates are closely related to incidence rates. However, bladder cancer survival rates are relatively good, and bladder cancer mortality rates therefore reflect a combination of both incidence rates and case fatality rates. Our previous investigation of chromosomal alterations in bladder cancer biopsies, including tumor biopsies from region II of Chile, indicated that tumors from arsenic-exposed patients may behave more aggressively than tumors from unexposed patients (39).

A limitation of this ecologic study is that it could not account for migration in and out of region II. However, because arsenic exposures in region II are much higher than in the rest of Chile and elsewhere, migration in or out would have diluted, not increased, the rate ratios reported in this paper. Patterns of increased mortality are clear, and rate ratios would likely have increased even further if analyses could have been confined to persons with long-term residence in region II. In addition, migration among regions in Chile is relatively low. From 1965 to 2000, annual internal migration between regions was only 0.6%, compared with 1.2% in Argentina, 3.1% in the United Kingdom, and 6.6% in the United States (40). Further limitations include not having individual data on arsenic exposure and not having individual data on other risk factors such as smoking and occupational exposures.

In conclusion, we have found a clear latency pattern for lung and bladder cancer mortality for both men and women that is consistent with the effects of a large increase in population exposure to arsenic starting in 1958. Increased rate ratios became evident close to 10 years after exposure increased, peaked in the years around 1990, and continued to be markedly elevated up to the year 2000. The impact of arsenic in drinking water on this large population is without precedent for environmental causes of human cancer, and it points to the public health priority of ensuring that arsenic concentrations in drinking water are controlled worldwide.

References

- (1) Cornejo-Catalan J. Panorama de arsenicismo en la II region. In: *Primera Jornada Sobre Arsenicismo Laboral y Ambiental II Region*. Antofagasta (Republica de Chile): Ministerio de Salud Antofagasta Departamento de Programas Sobre El Ambiente, y Asociacion Chilena de Seguridad; 1991. p. 15–34.
- (2) Chen CJ, Chuang YC, Lin TM, Wu HY. Malignant neoplasms among residents of a blackfoot disease-endemic area in Taiwan: high-arsenic artesian well water and cancers. *Cancer Res* 1985;45:5895–9.
- (3) Chen CJ, Wang CJ. Ecological correlation between arsenic level in well water and age-adjusted mortality from malignant neoplasms. *Cancer Res* 1990;50:5470–4.
- (4) Chen CJ, Wu MM, Lee SS, Wang JD, Cheng SH, Wu HY. Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. *Arteriosclerosis* 1988;8:452–60.
- (5) Chiou HY, Hsueh YM, Liaw KF, Horng SF, Chiang MH, Pu YS, et al. Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. *Cancer Res* 1995;55:1296–300.
- (6) Hopenhayn-Rich C, Biggs ML, Fuchs A, Bergoglio RM, Tello EE, Nicolli HB, et al. Bladder cancer mortality associated with arsenic in drinking water in Argentina. *Epidemiology* 1996;7:117–24.
- (7) Hopenhayn-Rich C, Biggs ML, Smith AH. Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. *Int J Epidemiol* 1998;27:561–9.
- (8) International Agency for Research on Cancer. Some drinking-water disinfectants and contaminants, including arsenic. Vol 84. Lyon (France): World Health Organization; 2004.
- (9) National Research Council. Arsenic in drinking water: 2001 update. Washington (DC): National Academy Press; 2001.
- (10) Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol* 1995;141:523–30.
- (11) Steinmaus C, Yuan Y, Bates MN, Smith AH. Case-control study of bladder cancer and drinking water arsenic in the Western United States. *Am J Epidemiol* 2003;158:1193–201.
- (12) Bates MN, Rey OA, Biggs ML, Hopenhayn C, Moore LE, Kalman DA, et al. Case-control study of bladder cancer and exposure to arsenic in Argentina. *Am J Epidemiol* 2004;159:381–9.
- (13) Chen CJ, Chuang YC, You SL, Lin TM, Wu HY. A retrospective study on malignant neoplasms of bladder, lung and liver in blackfoot disease endemic area in Taiwan. *Br J Cancer* 1986;53:399–405.
- (14) Chiou HY, Chiou ST, Hsu YH, Chou YL, Tseng CH, Wei ML, et al. Incidence of transitional cell carcinoma and arsenic in drinking water: a follow-up study of 8,102 residents in an arseniasis-endemic area in north-eastern Taiwan. *Am J Epidemiol* 2001;153:411–8.
- (15) Smith AH, Goycolea M, Haque R, Biggs ML. Marked increase in bladder and lung cancer mortality in a region of Northern Chile due to arsenic in drinking water. *Am J Epidemiol* 1998;147:660–9.
- (16) Ferreccio C, Gonzalez CA, Milosavljevic V, Marshall G, Sancha AM, Smith AH. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology* 2000;11:673–9.
- (17) Instituto Nacional de Estadística. Anuario de Demografía 1995. Santiago (Chile): Departamento de Estadísticas, Demográficas y Sociales, Servicio de Registro Civil e Identificación. Ministerio de Salud; 1996.
- (18) La Encuesta de Caracterización Socioeconómica. Ministerio de Planificación y Cooperación Nacional República de Chile. IIIa Encuesta CASEN (Caracterización Socio Económica Nacional). 15th ed. Santiago (Chile); 1992.
- (19) Castillo B, Mardones G. Medical certification of deaths in the health services of Chile. *Rev Med Chil* 1986;114:693–700.
- (20) World Health Organization. Manual of the international statistical classification of diseases, injuries and causes of death, ninth revision. Vol 1. Geneva (Switzerland): World Health Organization; 1977.
- (21) Lachin JM. Biostatistical methods: the assessment of relative risks. New York: John Wiley; 2000. p. 476–8.
- (22) Hastie TJ, Tibshirani T. Generalized additive models. London: Chapman and Hall; 1990.
- (23) Roemer WH, van Wijnen JH. Daily mortality and air pollution along busy streets in Amsterdam, 1987–1998. *Epidemiology* 2001;12:649–53.
- (24) Schwartz J. Air pollution and daily mortality in Birmingham, Alabama. *Am J Epidemiol* 1993;137:1136–47.
- (25) Hopenhayn C, Ferreccio C, Browning SR, Huang B, Peralta C, Gibb H, et al. Arsenic exposure from drinking water and birth weight. *Epidemiology* 2003;14:593–602.
- (26) Chiu HF, Ho SC, Yang CY. Lung cancer mortality reduction after installation of tap-water supply system in an arseniasis-endemic area in South-western Taiwan. *Lung Cancer* 2004;46:265–70.
- (27) Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. *J Natl Cancer Inst* 1993;85:457–64.
- (28) Silverman DT, Hartge P, Morrison AS, Devesa SS. Epidemiology of bladder cancer. *Hematol Oncol Clin North Am* 1992;6:1–30.

- (29) Smith AH, Marshall G, Yuan Y, Ferreccio C, Liaw J, von Ehrenstein O, et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *Environ Health Perspect* 2006;114:1293–6.
- (30) Nordstrom DK. Public health. Worldwide occurrences of arsenic in ground water. *Science* 2002;296:2143–5.
- (31) Mitra SR, Mazumder DN, Basu AR, Block GS, Haque R, Samanta S, et al. Nutritional factors and susceptibility to arsenic-caused skin lesions in West Bengal, India. *Environ Health Perspect* 2004;112:1104–9.
- (32) von Ehrenstein OS, Guha Mazumder DN, Yuan Y, Samanta S, Balmes J, Sil A, et al. Decrements in lung function related to arsenic in drinking water in West Bengal, India. *Am J Epidemiol* 2005;162:533–41.
- (33) Guha Mazumder DN, Steinmaus C, Bhattacharya P, von Ehrenstein OS, Ghosh N, Gotway M, et al. Bronchiectasis in persons with skin lesions resulting from arsenic in drinking water. *Epidemiology* 2005;16:760–5.
- (34) von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, Ghosh N, Yuan Y, Windham G, et al. Pregnancy outcomes, infant mortality and arsenic in drinking water in West Bengal, India. *Am J Epidemiol* 2006; 163:662–9.
- (35) Haque R, Mazumder DN, Samanta S, Ghosh N, Kalman DA, Smith MM, et al. Arsenic in drinking water and skin lesions: dose-response data from West Bengal, India. *Epidemiology* 2003;14:174–82.
- (36) Warner ML, Moore LE, Smith MT, Kalman DA, Fanning E, Smith AH. Increased micronuclei in exfoliated bladder cells of individuals who chronically ingest arsenic-contaminated water in Nevada. *Cancer Epidemiol Biomarkers Prev* 1994;3:583–90.
- (37) Steinmaus CM, Yuan Y, Smith AH. The temporal stability of arsenic concentrations in well water in western Nevada. *Environ Res* 2005; 99:164–8.
- (38) Axelson O. Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health* 1978;4:85–9.
- (39) Moore LE, Smith AH, Eng C, Kalman DA, DeVries S, Bhargava V, et al. Arsenic-related chromosomal alterations in bladder cancer. *J Natl Cancer Inst* 2002;94:1688–96.
- (40) Soto R, Torche A. Spatial inequality, migration, and economic growth in Chile. *Cuad Econ* 2004;41:401–24.

Notes

The authors declare that they have no competing financial interests. This research was supported by the National Institute of Environmental Health Sciences grants, R01 ES10033-03 and P42-ES04705, and the University of California Center for Occupational and Environmental Health. The study sponsors had no role in the experimental design or the collection, analysis, or interpretation of the data or in the writing and submission of the manuscript.

Manuscript received July 10, 2006; revised April 9, 2007; accepted May 4, 2007.