Kidney Cancer Mortality

Fifty-year Latency Patterns Related to Arsenic Exposure

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Background: Arsenic in drinking water is associated with kidney cancer. Beginning in 1958, a region of Chile experienced a rapid onset of high arsenic exposure in drinking water, followed by sharp declines when water treatment plants were installed in 1971.

Methods: For the years 1950–1970, we obtained mortality data from death certificates for an exposed region and an unexposed region in Chile. We obtained computerized mortality data for all of Chile for 1971–2000.

Results: Kidney cancer risks for the exposed region compared with the unexposed started to increase about 10 years after high arsenic exposures began in 1958. The peak kidney cancer mortality rate ratio (RR) was 3.4 (95% confidence interval = 2.2–5.1) for men in 1981–1985, with subsequent declines to 1.6 (1.2–2.1) by 1996–2000. Mortality RRs among women were 2.9 (1.8–4.7) in 1981–1985 but remained high longer than for men, increasing further to a RR of 4.4 (3.0–6.4) in 1991–1995. Early-life exposure resulted in an increased RR of 7.1 (3.1–14) for young adults aged 30–39 years, born just before or during the high exposure period.

Conclusions: This study shows a latency pattern of increased mortality from kidney cancer, continuing for at least 25 years after the high exposures began to decline. Early life exposure resulted in markedly higher kidney cancer mortality in young adults.

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Kidney cancer risks have been found to increase with exposure to arsenic in drinking water in Taiwan,[1–8] Argentina,[9] Japan,[10] Finland,[11] and Chile.[12] However, relative risk estimates for kidney cancer are generally lower than those for urinary bladder cancer, and no studies had reported dose-response relationships on the basis of individual exposure assessment. Evidence for causation has been regarded by the International Agency for Research on Cancer (IARC) as insufficient to classify kidney cancer among the cancers caused by arsenic in drinking water.[13]

Region II in the north of Chile (Fig. 1), with a population of 477,000 in 2000, provides a valuable opportunity to investigate the long-term health effects of arsenic. It is one of the driest places on earth, and almost all drinking water in this region is supplied by a few large municipal water sources. Arsenic concentrations have been documented for the past 50 years. This is in contrast to other countries with high arsenic exposures, such as Argentina, Bangladesh, China, India, Taiwan, and the United States, where high arsenic exposures come primarily from wells. Assessing exposure in these other areas is extremely difficult because of the large number of wells, the high variability in arsenic concentrations from well to well, and the general lack of historical arsenic measurements.

The second important aspect of the arsenic exposure scenario in Region II is that the region experienced a rapid onset of very high arsenic exposure in the late 1950s when rivers contaminated with arsenic began to be used for drinking water. Exposure was greatly reduced starting in 1971, when installation of water treatment plants began.[12] More than half of the population in this region lives in Antofagasta and Mejillones (current population: 318,000)—cities that were exposed to levels of arsenic greater than 850 μg/L for a 13-year period (1958–1970) (Table 1).[12]

We recently reported lung cancer, bladder cancer and circulatory disease mortality in Region II from 1950 to 2000.[14,15] Mortality rates from lung and bladder cancers started to increase about 10 years after the high exposures to arsenic in drinking water commenced and did not peak until about 20 years after exposures began to decrease.[14] In contrast, mortality rates from acute myocardial infarction started to increase at the same time that high exposures began and

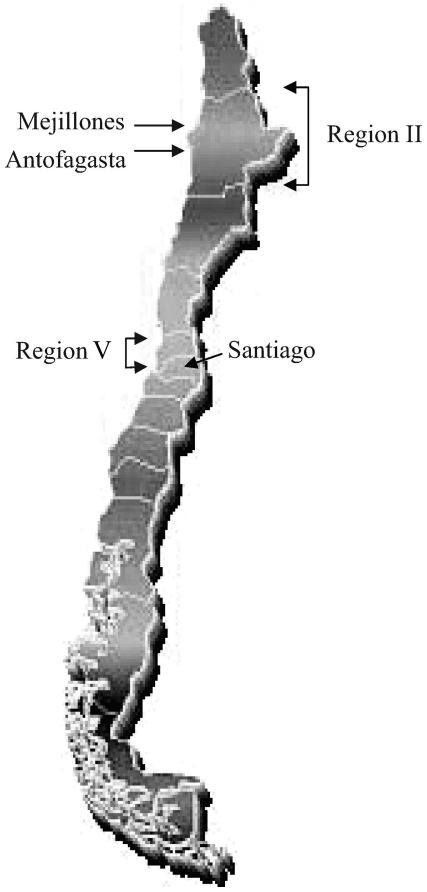

FIGURE 1. Map of Chile showing the exposed Region II and unexposed comparison, Region V.

decreased about 10 years after exposures were reduced.[15] The purpose of the present analysis is to investigate kidney cancer mortality in Region II before, during, and after the period of very high arsenic exposure. We also assess the impact of early life exposure to arsenic, in light of our previous findings of increased mortality from lung cancer, bronchiectasis, and acute myocardial infarction in young adults who had in utero and early childhood exposure to arsenic,[15,16] and increased childhood liver cancer mortality.[17]

METHODS

Exposure Data and Comparison Population

Details concerning the arsenic concentrations in water in Region II have been reported previously.[12,18,19] The concentration of arsenic in drinking water for the cities of Antofagasta and Mejillones (which shared the same water source) increased in 1958 from about 90 μg/L to an average of 870 μg/L (Table 1). With the introduction of a water treatment plant in 1971, Antofagasta's water arsenic concentration dropped to about 110 μg/L, and further reductions occurred with further improvements in treatment.

We selected Region V of Chile as a comparison population.[15–17] The major city of this region (Valparaíso) has had water concentrations close to 1 μg/L.[19] To ensure that Region V was an appropriate choice, preliminary investigations were conducted to compare per capita income, smoking rates, and death certification in Regions II and V.[20–22]

Mortality Data Collection

For years 1950–1970, all death certificates for Region II and Region V were photographed and coded by trained nosologists according to the International Classification of Diseases, Ninth Revision (ICD-9). Death certificates from both regions were intermingled, and nosologists were kept unaware as to the region from which death certificates came. After 1970, death certificates in Chile were coded in the capital Santiago, following the same rules regardless of the region of origin. Computerized mortality data first became available in Chile in 1971. These data were obtained from the Chilean National Institute of Statistics and from the Ministry of Health. The Tenth Revision (ICD-10) codes had been used for 1999 and 2000. For our analysis, all the ICD-10 codes were translated to ICD-9 codes.

Annual estimates of the population living in Regions II and V stratified by age and sex for the period 1950–2000 were obtained from the National Institute of Statistics.

Statistical Analysis

We estimated rate ratios (RRs) for kidney cancer mortality (ICD-9 code 189, ICD-10 codes C64–C66, C68) for Region II compared with Region V from 1950 to 2000, using Poisson regression (SAS version 9.2, SAS Institute, Inc, Cary, NC). To examine trends in kidney cancer mortality RRs, for each year in the study period we estimated the RR for that year combined with the 4 years before and the 4 years after it, thus smoothing short-term fluctuations.

A separate analysis evaluated the impact of early life arsenic exposure on risk of kidney cancer mortality later in life. We defined 2 major birth cohorts: those born during the high-exposure period, who would have experienced exposure in utero, as well as in early childhood, and those born in 1950–1957, just before the high exposure period, who would have experienced high exposure during childhood but not in utero. We focused on the mortality in young adults aged 30–39 years, because those born in the high exposure period 1958–1970 were over 30 years old by the year 2000. For the years 1989–2000, deaths and population estimates were available for 2 major cities in Region II (Antofagasta and Mejillones), which had the highest arsenic exposure. We compared mortality rates in Antofagasta and Mejillones with the rest of Chile using standardized mortality ratios (SMRs). We tested for differences between men and women, and between those born in 1950–1957 and 1958–1970, using Poisson regression interaction terms. There was little difference between sexes ($P = 0.75$) or between those born in

TABLE 1. Arsenic Concentrations (μg/L) in Drinking Water for the Major Cities and Towns in Region II, Chile, From 1950 to 1994, by 5-year Intervals, and Population-weighted Averages Using 1991 Census Numbers[a]

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 (6134)	90	870	870	870	260	110	80	60	40
Calama (100,283)	120	120	120	120	240	230	110	80	40
Chuquicamata[b] (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 (7620)	60	60	60	60	60	60	60	60	60
San Pedro[c] (3070)	600	600	600	600	600	600	600	600	600
Average (390,340)	123	569	568	568	272	176	94	71	43

[a]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.
[b]Data were supplied by Codelco Chile.
[c]Data for Rio Vilama, a major water source for the town.

TABLE 2. Age-adjusted Rate Ratios for Kidney Cancer Mortality for Men and Women Aged 30 Years and Above in Region II (Exposed) Compared With Region V (Unexposed), Chile, 1950–2000

	Men No. Deaths (Mortality Rates per 100,000)			Women No. Deaths (Mortality Rates per 100,000)		
Years	Region II	Region V	RR (95% CI)	Region II	Region V	RR (95% CI)
1950–1954	4 (2)	19 (3)	0.69 (0.23–2.02)	2 (1)	8 (1)	1.27 (0.27–6.00)
1955–1959	9 (4)	22 (3)	1.43 (0.66–3.10)	2 (1)	31 (4)	0.30 (0.07–1.25)
1960–1964	7 (3)	29 (4)	0.91 (0.40–2.08)	7 (4)	21 (3)	1.66 (0.71–3.91)
1965–1969	12 (5)	19 (2)	2.51 (1.22–5.17)	3 (1)	20 (2)	0.76 (0.23–2.57)
1970–1974	15 (6)	45 (5)	1.45 (0.81–2.60)	13 (6)	18 (2)	3.70 (1.81–7.56)
1975–1980[a]	19 (7)	41 (4)	2.13 (1.24–3.68)	9 (3)	26 (2)	1.71 (0.80–3.65)
1981–1985	39 (12)	51 (4)	3.37 (2.21–5.11)	25 (8)	44 (3)	2.89 (1.77–4.72)
1986–1990	63 (17)	102 (8)	2.81 (2.05–3.85)	41 (11)	65 (4)	3.23 (2.18–4.78)
1991–1995	50 (11)	126 (8)	1.78 (1.28–2.47)	49 (11)	57 (3)	4.37 (2.98–6.41)
1996–2000	66 (12)	175 (10)	1.61 (1.21–2.14)	47 (9)	101 (5)	2.32 (1.64–3.28)

[a]Excluding 1976 data that were not available.

1950–1957 and those born in 1958–1970 ($P = 0.73$). We therefore pooled these 2 birth periods, and also present early life exposure results with the sexes combined.

RESULTS

Table 2 presents the mortality rates for kidney cancer in Region II and Region V in 1950–2000. The kidney cancer mortality rates in both regions increased rapidly throughout this period. Table 2 also presents the age-adjusted mortality rate ratios for kidney cancer in Region II compared with Region V from 1950 through 2000. Kidney cancer mortality rate ratios for Region II compared with Region V started to increase about 10 years after high arsenic exposures began in 1958, with an RR of 2.5 (95% confidence interval (CI) = 1.2–5.2) among men for the 5-year period centered in 1967, and an RR of 3.7 (1.8–7.6) for women for the 5-year period centered in 1972. The peak kidney cancer mortality rate ratio was 3.4 (2.2–5.1) for men in 1981–1985, with subsequent declines to 1.6 (1.2–2.1) in 1996–2000. Mortality RRs among women reached 2.9 (1.8–4.7) in 1981–1985 but remained high longer than for men, with an RR of 4.4 (3.0–6.4) in 1991–1995; then the mortality rate ratio declined to 2.3 (1.6–3.3) in 1996–2000. Figure 2 presents the time pattern using 9-year mortality rate ratio estimates.

Table 3 shows SMRs comparing Antofagasta and Mejillones (the 2 major cities in Region II) with the rest of Chile. For young adults aged 30–39 years, born in 1950–1970, who had early life exposure, the SMR was 7.1 (3.1–14). This increased risk is most unlikely to be due to chance ($P < 0.001$).

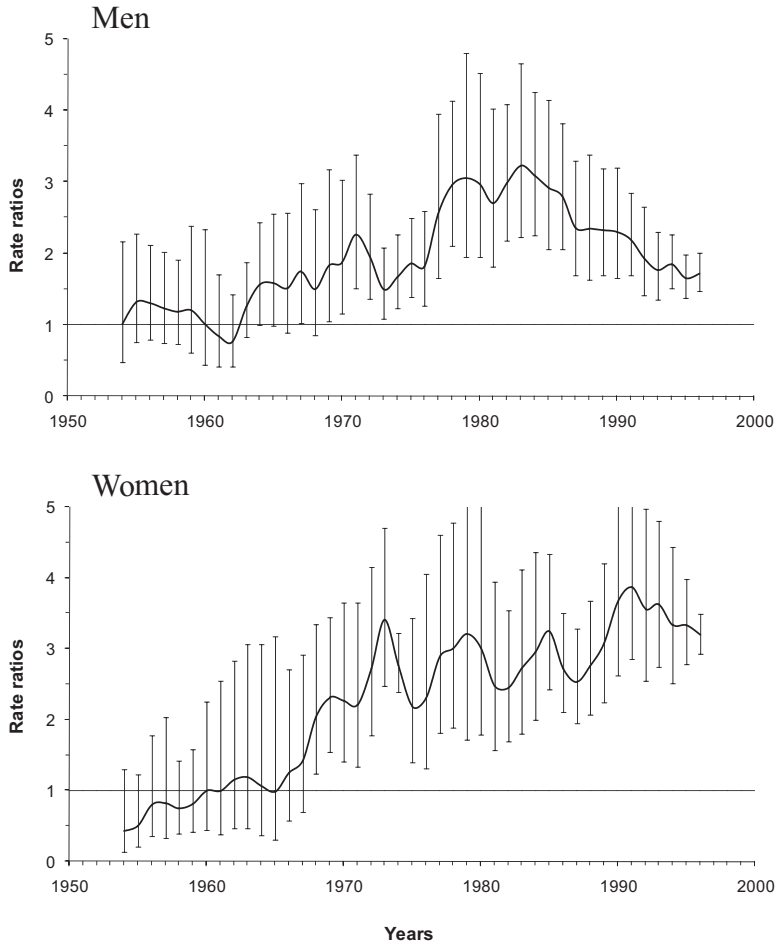

FIGURE 2. Age-adjusted rate ratios and 95% confidence intervals for kidney cancer mortality for men and women aged 30 years and above, Region II (exposed) compared with Region V (unexposed), Chile, 1950–2000. Each point represents an estimate for 9 years and is plotted at the midpoint of the 9-year period, starting with the estimate for 1950–1958, which is plotted at the year 1954.

TABLE 3. Standardized Mortality Ratios[a] for Kidney Cancer Mortality Among Young Adults in Antofagasta and Mejillones[b] Aged 30–39 Years Who Were Born During and Just Before the High-Exposure Period, and for Ages 40 and Above Who Were Born Before 1950 and Would Not Have Had Early Life Exposure

Age (Years)	Birth Cohort	No. Observed Deaths	No. Expected Deaths	SMR (95% CI)
Men				
30–39	1950–1970	4	0.71	5.63 (1.52–14.4)
40+	Before 1950	103	38	2.68 (2.19–3.26)
Women				
30–39	1950–1970	4	0.42	9.52 (2.56–24.4)
40+	Before 1950	84	21	3.91 (3.12–4.84)
Total				
30–39	1950–1970	8	1.13	7.08 (3.05–14.0)
40+	Before 1950	187	60	3.12 (2.69–3.61)

[a]Standardized mortality ratios with expected mortality estimated from the rest of Chile excluding Region II.

[b]Antofagasta and Mejillones used the same water source, containing about 870 μg/L of arsenic, during the period 1958–1970.

DISCUSSION

This 50-year mortality study shows a marked increase in deaths from kidney cancer in both Region II and Region V over the time period of the study. The mortality rate ratio estimates show a latency pattern of increases in Region II above those in Region V in relation to the period of high arsenic exposure. A long latency was apparent, with increased kidney cancer mortality rate ratios continuing for at least 25 years after the high exposure levels began to decline. The latency patterns are consistent with a causal interpretation and strengthen the epidemiologic evidence that arsenic in water causes increased rates of kidney cancer mortality. Adding to this evidence is the similar latency pattern for lung and bladder cancer, both related to arsenic exposure.[14,15] This is the first study on kidney cancer to show an increase in rate ratios after exposure begins. The reductions in relative risk seen following reductions in exposure have also been reported in Taiwan.[8]

Mortality rates of kidney cancer have been reported to be increasing in some countries.[23–26] In the United States, kidney cancer mortality increased from 1.5 per 100,000 deaths in 1983 to 6.5 per 100,000 deaths in 2002.[25] The

reasons for these increases are not clear. The rising incidence of kidney cancer may be largely attributable to an increased ability to detect small renal masses, but this does not explain the marked increase in mortality.[24] As seen in Table 2, kidney cancer mortality greatly increased in the 50-year period of the study, and this increase suggests caution in interpreting the findings. Differences in time patterns of the upward trends could result in variations in RRs between the 2 Regions. Nevertheless, rate ratios increasing about 10 years after high exposure began are consistent with arsenic effects.

The findings of increased mortality rate ratios in young adults who had early life exposure are based on small numbers, but the standardized mortality rate ratios are high, with a 7-fold increased mortality for those born before or during the high exposure period (Table 3). We have previously reported increased mortality in young adults following early-life exposure to arsenic for lung cancer, bronchiectasis,[16] and myocardial infarction.[15] Biologic plausibility for the cancer findings can be found in arsenic experiments conducted on pregnant mice showing increased tumors in offspring.[27,28]

A limitation of our study is the lack of individual exposure data.[29] However, we do not believe that ecologic bias is a problem in our study. Essentially everyone living in Region II was exposed to arsenic at high concentrations, while those in Region V and the rest of Chile were not. This exposure contrast is markedly different from that of most ecologic studies in which it is unclear whether the individuals who get disease are those who were actually exposed. Here we can state that there were increased rates of kidney cancer in the place where virtually everyone was exposed to high concentrations of arsenic in drinking water (Region II) compared with the place where all drinking water sources contained low arsenic concentrations (Region V). Some people who died in Region II may have recently migrated from another part of Chile where they were not exposed, and some from Region II may have migrated in the opposite direction. However, the effect of such migration would be to dilute exposure contrasts and would reduce, rather than cause, the positive associations. From 1965 to 2000, annual internal migration among regions was only 0.6%, compared with 1.2% in Argentina, 3.1% in the United Kingdom, and 6.6% in United States.[30] Although our ecologic study lacks individual data on exposure, the only likely ecologic bias would be a small bias toward the null due to migration.

This study is limited to data from death certificates, most of which are completed by physicians (90% in Region II and 95% in Region V).[22] We did not have death certificate information regarding types of kidney cancer; in particular, we cannot differentiate renal cell carcinoma from transitional cell cancer of the renal pelvis. It is possible that arsenic would have greater impact on transitional cell cancers than on renal cell cancers.[31,32]

Our study also did not have individual data on confounding factors, but it is nevertheless unlikely that our findings are due to confounding. For confounding factors to explain the observed rise and fall in kidney cancer mortality rate ratios, they would have to have a similar relation in time to the rise and fall in arsenic concentrations. In addition, confounding is unlikely to explain the magnitude of mortality rate ratios observed, which increased to more than 3-fold for both men and women. The major population risk factors for kidney cancer are smoking and obesity[33,34]; the relative risks reported for these factors are generally quite low. Relative risk estimates for smoking are usually between 1.5 and 2.[33] We have previously reported that there is little difference in smoking rates between Region II and Region V.[21] Regarding obesity, limited data are available on regional differences in Chile. Mean body mass index (BMI) values by region were reported in the 2003 national health survey involving over 3000 randomly selected adults throughout Chile. BMI levels were higher in Region II (mean = 27.6 kg/cm^2 [95% CI = 26.5–28.7 kg/cm^2]) than in Region V (26.8 kg/cm^2 [26.1–27.5 kg/cm^2]) or the country as a whole (26.8 kg/cm^2 [26.6–27.1 kg/cm^2]).[35] These differences are small and could not have accounted for the relative risks we identified in this study.

In conclusion, the latency patterns of kidney cancer mortality increase in Region II are consistent with arsenic being the causal factor. Given the magnitude of the increased mortality rate ratios, it is unlikely that the differences are due to confounding. Finally, our evidence suggests early life exposure to inorganic arsenic results in markedly increased kidney cancer mortality in young adults.

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