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Cancer Epidemiology, Biomarkers & Prevention

Research Article

Increased Lung and Bladder Cancer Incidence in Adults after *In Utero* and Early-Life Arsenic Exposure

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Abstract

Background: From 1958 to 1970, >100,000 people in northern Chile were exposed to a well-documented, distinct period of high drinking water arsenic concentrations. We previously reported ecological evidence suggesting that early-life exposure in this population resulted in increased mortality in adults from several outcomes, including lung and bladder cancer.

Methods: We have now completed the first study ever assessing incident cancer cases after early-life arsenic exposure, and the first study on this topic with individual participant exposure and confounding factor data. Subjects included 221 lung and 160 bladder cancer cases diagnosed in northern Chile from 2007 to 2010, and 508 age and gender-matched controls.

Results: ORs adjusted for age, sex, and smoking in those only exposed in early life to arsenic water concentrations of ≤110, 110 to 800, and >800 μg/L were 1.00, 1.88 [95% confidence interval (CI), 0.96–3.71], and 5.24 (3.05–9.00; $P_{trend} < 0.001$) for lung cancer, and 1.00, 2.94 (1.29–6.70), and 8.11 (4.31–15.25; $P_{trend} < 0.001$) for bladder cancer. ORs were lower in those not exposed until adulthood. The highest category (>800 μg/L) involved exposures that started 49 to 52 years before, and ended 37 to 40 years before the cancer cases were diagnosed.

Conclusion: Lung and bladder cancer incidence in adults was markedly increased following exposure to arsenic in early life, even up to 40 years after high exposures ceased. Such findings have not been identified before for any environmental exposure, and suggest that humans are extraordinarily susceptible to early-life arsenic exposure.

Impact: Policies aimed at reducing early-life exposure may help reduce the long-term risks of arsenic-related disease. *Cancer Epidemiol Biomarkers Prev; 23(8); 1529–38. ©2014 AACR.*

Introduction

Children and fetuses may be particularly susceptible to environmental carcinogens (1), but to date the evidence for this is mostly indirect or based on animal studies with inconsistent results (2). Few human data are available, especially for common exposures, such as arsenic, or common cancers such as lung and bladder cancer. Most human data suggesting that early-life events may cause adult cancer involve exposures that are rare (e.g., atomic bomb radiation or diethylstilbestrol) or difficult to assess historically (e.g., secondhand tobacco smoke; refs. 3–5). This paucity of research has important public health implications, because almost all current environmental regulations are based on animal or occupational studies where exposures occurred in adults (6). The failure to incorporate effects from exposures in young children and fetuses ("early-life"), not only for arsenic but for any harmful agent, could lead to standards that are not sufficiently protective.

Millions of people worldwide are exposed to naturally occurring arsenic in their drinking water (7), and ingested arsenic is an established cause of lung, bladder, and skin cancer (8). The major problem in studying the long-term carcinogenic impacts of early-life exposure to arsenic, or

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Table 1. Historical concentrations of arsenic in drinking water (μg/L) in northern Chile by year

			Average arsenic concentration (μg/L) Years						
Region	City or town	Population[a]	1930–57	1958–70	1971–77	1978–79	1980–87	1988–2005	2005+
I	Arica	168,594	10	10	10	10	10	10	9
	Putre	1,799	1	1	1	1	1	1	1
	Iquique	196,941	60	60	60	60	60	60	10
	Huara	2,365	30	30	30	30	30	30	30
	Pica	5,622	10	10	10	10	10	10	10
	Pozo Almonte	9,855	40	40	40	40	40	40	40
II	Tocopilla	21,827	250	250	636	110	110	40	10
	Maria Elena	6,852	250	250	636	110	110	39	39
	Calama	125,946	150	150	287	110	110	40	38
	San Pedro	4,522	600	600	600	600	600	600	600
	Antofagasta	270,184	90	860	110	110	70	40	10
	Mejillones	7,660	90	860	110	110	70	37	10
	Taltal	10,101	60	60	60	60	60	60	60
	Recent migrants	82,312	<10	<10	<10	<10	<10	<10	<10

[a]Population data are based on the 2002 Chile census (13).

any chemical agent, is the difficulty in following study subjects and their exposure patterns beginning in early life and into those ages where adult cancer risks are high, usually a period of 50 years or more. Accurate exposure data over this many years are rarely available. However, a unique scenario in Region II of northern Chile offers a rare opportunity to investigate the long-term effects of arsenic with good data on past exposure. In the late 1950s, river water from the nearby Andes Mountains containing high concentrations of naturally occurring arsenic was diverted to the largest city in the area (Antofagasta) to supply drinking water (9). This resulted in a 13-year period (1958–70) during which >100,000 people were exposed to arsenic concentrations >800 μg/L. Treatment plants installed since 1970 reduced concentrations to <10 μg/L today (Table 1). Several other cities in this area had arsenic water concentrations between 110 μg/L and 800 μg/L, and these also declined at about the same time. Another set of cities has continuously had arsenic water concentrations at much lower levels. Region II lies in the Atacama Desert, the driest inhabited place on earth. There are very few water sources and essentially everyone lives in one of the cities and drinks water from one of the few large public water supplies in each city. In addition, historical records of arsenic concentrations are available for all cities in this area, including Antofagasta, with records dating back >40 years. Consequently, retrospective assessments of lifetime arsenic exposure can be estimated in this area with good accuracy simply by knowing the cities in which a person lived.

The scenario in Region II, with its well-documented exposure, occurring 4 to 5 decades ago (i.e., with an appropriate latency), good records on exposure, large numbers of people exposed, and a distinct rise and decline in exposure is incredibly rare in epidemiology and provides a rare opportunity to examine the long-term cancer risks of a common *in utero* or childhood exposure.

Previously, we reported that arsenic-related ORs of lung, bladder, and kidney cancer were high in this area, but analyses of early-life exposure were not reported (10, 11). We have also reported ecologic findings linking early-life arsenic to high lung and bladder cancer mortality, but data on cancer incidence or individual data on exposure, migration, and smoking were not available (12). Here, we report the first findings ever to link an early-life environmental chemical exposure to high risks of adult cancer incidence and the first study on this topic with individual data on life-long exposure and potential confounders.

Materials and Methods

Participants

The study area comprised two neighboring regions (Regions I and II) in northern Chile with a population of about one million people (Table 1; ref. 13). Study design details are reported elsewhere (11). Briefly, lung and bladder cancer cases were ascertained from all pathologists, hospitals, and radiologists in the area and included people who: (i) had primary lung or bladder cancer first diagnosed between October 2007 and December 2010; (ii) lived in the study area at the time of diagnosis; (iii) were >25 years old when diagnosed; and (iv) were able to provide interview data or had a close relative who could. Seventy-two percent were histologically confirmed, with the remaining diagnoses based on radiologic (CT) and physician's clinical findings. Controls without lung, bladder, or kidney cancer were randomly selected from the 2007–2009 Chilean Electoral Registry for the study area,

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frequency matched to cases by gender and 5-year age group. Our analyses showed that the Electoral Registry contained >95% of people over the age of 50 years compared with the national census.

Interviews

After obtaining informed consent, participants were interviewed in person using a standardized questionnaire. For deceased subjects, we interviewed the nearest relative ("proxy"). Participants were asked to provide all residences lived at and all jobs held for ≥6 months. This included the residence the parents lived at when the child was born, and thus included *in utero* exposure. Questions about tobacco covered age when smoking began, periods quit, total years smoked, cigarettes smoked per day, and secondhand smoke exposure. Subjects were asked about their typical drinking water intake currently and in the past, but these data had small impacts on classifying exposure in this study so were not used here. Other questions asked about race, occupational exposures, and height and weight (e.g., body mass index; BMI) currently, 20 and 40 years ago.

Arsenic exposure

For each subject, each residence was linked to an arsenic water concentration measurement for that city or town for the relevant time period so that an arsenic concentration could be assigned to each year of each subject's life. Details on the arsenic water measurements are provided elsewhere (14, 15). Most records were obtained from municipal water companies, who supply essentially all water in the study area and are required to perform chemical testing at least yearly. Additional measurements were collected from government agencies, research studies, and other sources (9, 16–20). Arsenic measurements were also available for all large cities in Chile outside the study area, and these were also linked to residences. Arsenic water concentrations were available for >95% of all residences for both cases and controls. Residences for which water records were not available were in areas not known to have high arsenic levels so were assigned a value of zero. Bottled water and water filtered with reverse osmosis were also assigned a value of zero but were rarely used until recently. Cumulative (μg/L-years) and average exposures were calculated as the sum and mean, respectively, of subject's yearly arsenic concentrations.

Statistical analyses

Cancer ORs were calculated using unconditional logistic regression. Variables entered into logistic regression models included sex, age (year), and smoking (three categories of average cigarettes per day while smoking: 0, 1–9, >10). Additional models included mining work (yes or no), obesity (recent BMI ±30 kg/m^2), socioeconomic status (SES) scores (lower vs. upper two tertiles), or self-reported exposure to a known carcinogen at work, including asbestos, silica, or arsenic (yes or no). SES scores were based on self-reports of 12 items, including ownership of household appliances, car, computer, and domestic help (one point for each household item and two points each for a car or domestic help). Local researchers advised that these items are a better way to assess SES in this area than education or income. Adjusting for smoking pack-years or 10-year age categories had little impact on results.

To assess the impacts of early-life exposure, cancer ORs were calculated for subjects who were exposed to arsenic water concentrations of 111 to 800 μg/L or >800 μg/L at birth or as children ≤age of 15 years but not exposed >110 μg/L as adults (≥25 years old), using subjects who were never exposed >110 μg/L at any time as the reference. Category cutoff points were based on the distribution of arsenic water concentrations in the major cities: Arica and Iquique, ≤110 μg/L; Calama and Tocopilla, 111 to 800 μg/L; and Antofagasta and Mejillones, >800 μg/L (Table 1). Setting the lower cutoff point at 10 or 60 μg/L greatly reduced sample sizes because several of the higher exposure cities had arsenic water concentrations near 110 μg/L for a few years after their higher exposures ended. Defining adults as ≥age of 16 years did not substantially change ORs but resulted in smaller sample sizes because many children who were highly exposed at the age of 15 years were also highly exposed for a few years after. Because most of the highest exposures in Region II did not begin until 1958, all subjects exposed to water concentrations >800 μg/L as children were ages 70 years or under during our study, so these analyses were restricted to subjects ≤70 years old.

ORs were also calculated for subjects exposed to arsenic water concentrations of 111 to 800 μg/L or >800 μg/L as adults (≥age 20) but not before ("adult-only exposure"), using subjects who were never exposed >110 μg/L at any time as the reference. All subjects exposed to arsenic water concentrations >800 μg/L only as adults were ≥60 years old, so these analyses were restricted to subjects ≥ age of 60 years.

In most analyses, arsenic exposure was based on the highest known arsenic water concentration to which the subject was exposed during the relevant ages, although cumulative exposure was also assessed. This was entered as a continuous variable and ORs are presented for a cumulative exposure of 10 mg/L-years, roughly the level associated with living in Antofagasta for the 13-year high exposure period. Dose–response trends were assessed using the Cochrane-Armitage test for linear trend, and analyses were done in SAS version 9.2 (SAS Institute Inc.).

Results

Overall, 370 lung and 289 bladder cancer cases were ascertained. Of these, 46 lung and 23 bladder cancer cases were ineligible based on age and residential criteria. Of the remaining, four lung (1.2%) and 12 (4.5 percent) bladder cancer cases could not be located, moved outside the study area, or provided insufficient residential information. Of the remaining, 14 lung (4.4%) and 22 (8.7%) bladder cancer

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Table 2. Demographic characteristics of subjects never highly exposed or only exposed *in utero* or as children

	Controls	Bladder cancer cases		Lung cancer cases	
	N (%)	*N* (%)	OR[a] (95% CI)	*N* (%)	OR[a] (95% CI)
Total	286 (100)	90 (100)		139 (100)	
Sex					
Female	101 (35.3)	16 (17.8)		40 (28.8)	
Male	185 (64.7)	74 (82.2)		99 (72.2)	
Age, y					
≥60	128 (44.8)	31 (34.4)		61 (43.9)	
50–59	112 (39.2)	36 (40.0)		64 (46.0)	
<50	46 (16.1)	23 (25.6)		14 (10.1)	
Smoking: daily average					
Never	91 (31.8)	20 (22.2)	1.00 (Ref.)	26 (18.7)	1.00 (Ref.)
0–9 cigs/d	126 (44.1)	29 (32.2)	1.05 (0.56–1.97)	29 (20.9)	0.81 (0.44–1.46)
≥10 cigs/d	69 (24.1)	41 (45.6)	2.70 (1.46–5.02)	84 (60.4)	4.26 (2.48–7.31)
Mining work					
No	239 (83.6)	73 (81.1)	1.00 (Ref.)	116 (83.4)	1.00 (Ref.)
Yes	47 (16.4)	17 (18.9)	1.18 (0.64–2.19)	23 (16.6)	1.01 (0.58–1.74)
BMI >30 kg/m^2[b]					
No	278 (97.2)	85 (94.4)	1.00 (Ref.)	132 (95.0)	1.00 (Ref.)
Yes	8 (2.8)	5 (5.6)	2.04 (0.65–6.41)	7 (5.0)	1.84 (0.65–5.19)
SES (tertiles)					
High	103 (36.0)	38 (42.2)	1.00 (Ref.)	42 (30.2)	1.00 (Ref.)
Medium	112 (39.2)	20 (22.2)	0.48 (0.26–0.89)	53 (38.1)	1.16 (0.71–1.88)
Low	71 (24.8)	32 (35.6)	1.22 (0.70–2.17)	44 (31.7)	1.52 (0.90–2.56)
	Mean (SD)	**Mean (SD)**	***P***	**Mean (SD)**	***P***
Drinking water arsenic exposure[c]					
Maximum (μg/L)	207.5 (294.5)	506.7 (387.0)	<0.001	431.9 (384.8)	<0.001
Cumulative (mg/L-y)	3.48 (4.12)	7.45 (5.56)	<0.001	6.91 (5.58)	<0.001
Average (μg/L)	66.8 (78.6)	147.9 (106.3)	<0.001	130.1 (104.9)	<0.001
Drinking water intake (L/d)[c]					
Current	1.66 (1.00)	2.01 (1.28)	0.003	1.87 (0.88)	0.002
20 y ago	1.89 (1.25)	2.04 (1.21)	0.003	1.98 (0.83)	0.002
Municipal (%)[d]	89.6 (19.4)	93.6 (12.3)	0.32	91.1 (0.17)	0.89
Residences[c]					
Average number	3.2 (2.0)	2.8 (1.9)	0.04	2.9 (1.8)	0.10
Average length, y	25.8 (16.3)	30.2 (18.4)	0.12	29.1 (17.6)	0.09
In study area (%)[e]	77.7 (28.6)	82.0 (29.3)	0.32	87.0 (23.5)	0.89

Abbreviations: cigs, cigarettes; Ref, reference.

[a]Unadjusted OR comparing bladder or lung cancer cases with controls. ORs are not reported for age and sex because subjects were frequency matched on these factors.

[b]BMI 20 years before cancer diagnosis (cases) or subject ascertainment (controls).

[c]Mean, SDs, and *P* values comparing bladder or lung cancer cases with controls.

[d]Percentage of all drinking water supplied by municipal sources (versus bottled, private well, or other source). Includes sources for residences outside the study area.

[e]Percentage total person-time in Regions I and II in northern Chile.

cases or their next-of-kin declined participation. The large majority of cases were interviewed within 4 to 5 months of diagnosis, and 39.6% and 17.7% of lung and bladder cancer cases had died before interview so proxy interviews were performed. Among 872 initially selected controls with viable addresses, 78 (8.9%) no longer lived at the address and could not be located, were ineligible due to illness, or gave insufficient information. Of the remaining

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Table 3. Demographic characteristics of subjects never highly exposed or only exposed as adults

	Controls	Bladder cancer cases		Lung cancer cases	
	N (%)	*N* (%)	OR[a] (95% CI)	*N* (%)	OR[a] (95% CI)
Total	332	84		115	
Sex					
Female	105 (31.6)	24 (28.6)		38 (33.0)	
Male	227 (68.4)	60 (71.4)		77 (67.0)	
Age, y					
>80	51 (15.4)	18 (21.4)		20 (17.4)	
70–80	157 (47.3)	40 (47.6)		53 (46.1)	
<70	124 (37.3)	26 (31.0)		42 (36.5)	
Smoking: highest daily average					
Never	140 (42.2)	25 (29.8)	1.00 (Ref.)	28 (24.3)	1.00 (Ref.)
0–9 cigs/d	110 (38.2)	27 (35.7)	1.37 (0.76–2.50)	16 (20.9)	0.73 (0.37–1.41)
≥10 cigs/d	82 (19.6)	32 (34.5)	2.19 (1.21–3.94)	71 (54.8)	4.33 (2.59–7.25)
Mining work					
No	273 (82.2)	64 (76.2)	1.00 (Ref.)	93 (80.9)	1.00 (Ref.)
Yes	59 (17.8)	20 (23.8)	1.45 (0.81–2.57)	22 (19.1)	1.09 (0.64–1.88)
BMI >30 kg/m^2[b]					
No	311 (93.7)	78 (92.9)	1.00 (Ref)	106 (92.2)	1.00 (Ref)
Yes	21 (6.3)	6 (7.1)	1.14 (0.44–2.92)	9 (7.8)	1.26 (0.56–2.83)
SES (tertiles)					
High	88 (26.5)	27 (32.1)	1.00 (Ref)	20 (17.4)	1.00 (Ref.)
Medium	100 (30.1)	26 (31.0)	0.85 (0.46–1.56)	31 (27.0)	1.36 (0.73–2.56)
Low	144 (43.4)	31 (36.9)	0.70 (0.39–1.25)	64 (55.6)	1.96 (1.11–3.45)
	Mean (SD)	**Mean (SD)**	***P***	**Mean (SD)**	***P***
Drinking water arsenic exposure[c]					
Maximum (μg/L)	237.7 (323.7)	490.1 (387.2)	<0.001	275.9 (346.7)	0.50
Cumulative (mg)	4.18 (4.79)	7.67 (6.29)	<0.001	4.54 (5.03)	0.52
Average (μg/L)	58.8 (64.5)	105.7 (83.1)	<0.001	64.9 (70.3)	0.51
Drinking water intake (L/d)[c]					
Current	1.63 (0.80)	1.98 (0.80)	<0.001	1.68 (0.57)	0.08
20 y ago	1.86 (1.18)	1.92 (1.15)	<0.001	1.81 (0.78)	0.08
Municipal (%)[d]	89.6 (18.6)	92.6 (16.5)	0.48	85.8 (23.0)	0.16
Residences[c]					
Average number	3.7 (2.1)	3.2 (1.9)	0.07	3.8 (2.1)	0.70
Average length (y)	28.5 (20.0)	35.2 (24.5)	0.04	28.0 (19.4)	0.73
In study area (%)[e]	74.8 (26.1)	78.7 (23.1)	0.48	75.4 (27.9)	0.16

Abbreviations: cigs, cigarettes; Ref, reference.

[a]Unadjusted OR comparing bladder or lung cancer cases with controls. ORs are not reported for age and sex because subjects were frequency matched on these factors.

[b]BMI 20 years before cancer diagnosis (cases) or subject ascertainment (controls).

[c]Mean, SDs, and *P* values comparing bladder or lung cancer cases with controls.

[d]Percentage of all drinking water supplied by municipal sources (vs. bottled, private well, or other source). Includes sources for residences outside the study area.

[e]Percentage total person-time in Regions I and II in northern Chile.

794, 154 (19.4%) declined to participate. An additional 72 bladder, 85 lung cancer cases, and 132 controls were exposed >110 μg/L both in early life and as adults and were excluded. Demographic variables were similar in these subjects compared with the included subjects, although these excluded subjects were older (median age 69 vs. 65 in included subjects, $P < 0.001$) and had higher overall arsenic exposures (Supplementary Table S1). Potential controls who did not participate were younger (63.7 vs. 66.0 years, respectively) and more likely male

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Table 4. Lung and bladder cancer ORs in subjects only exposed *in utero* and as children and in subjects only exposed as adults

			Unadjusted		Adjusted[a]	
Arsenic	**Controls**	**Cases**	**OR (95% CI)**	**P_{trend}**	**OR (95% CI)**	**P_{trend}**
Lung cancer						
Exposed only *in utero* or as children[b]						
≤110 μg/L	201	59	1.00 (Ref.)		1.00 (Ref.)	
111–800 μg/L	41	20	1.66 (0.90–3.05)		1.88 (0.96–3.71)	
>800 μg/L	44	60	4.65 (2.86–7.55)	<0.001	5.24 (3.05–9.00)	<0.001
Exposed only as adults[c]						
≤110 μg/L	226	74	1.00 (Ref.)		1.00 (Ref.)	
111–800 μg/L	41	13	0.97 (0.49–1.91)		0.95 (0.46–1.97)	
>800 μg/L	65	28	1.32 (0.79–2.20)	0.34	1.32 (0.75–2.34)	0.35
Bladder cancer						
Exposed only *in utero* or as children[b]						
≤110 μg/L	201	29	1.00 (Ref.)		1.00 (Ref.)	
111–800 μg/L	41	13	2.19 (1.05–4.58)		2.94 (1.29–6.70)	
>800 μg/L	44	48	7.56 (4.30–13.30)	<0.001	8.11 (4.31–15.25)	<0.001
Exposed only as adults[c]						
≤110 μg/L	226	30	1.00 (Ref.)		1.00 (Ref.)	
111–800 μg/L	41	12	2.20 (1.04–4.66)		2.21 (1.03–4.74)	
>800 μg/L	65	42	4.87 (2.83–8.38)	<0.001	4.71 (2.61–8.48)	<0.001

Abbreviation: Ref, reference.

[a]Adjusted for age, sex, and smoking.

[b]Average arsenic water concentrations in the three exposure categories were 49.6, 254.6, and 860 μg/L.

[c]Average arsenic water concentrations in the three exposure categories were 45.8, 313.2, and 860 μg/L.

(72.5 vs. 67.3%) than those who did, but inclusion rates were similar among the major exposure areas: 75.5% in Antofagasta, 71.3% in Iquique and Calama, and 74.5% in Arica. The participating control's cities of residence at the time of ascertainment were similar to the population distribution of the 2002 Chile census (Supplementary Table S2).

Sociodemographic characteristics are shown for those with early-life (Table 2) and adult-only exposure (Table 3). Cases and controls were similar for most variables, although both bladder and lung cancer cases were more likely to be heavy smokers than controls. Cancer ORs were not elevated for those smoking <10 cigarettes per day although the median cigarettes smoked per day while smoking in this group was low (3.0 cigs/day) and the majority were former smokers (60.7%). Cases also had higher average, cumulative, and maximum arsenic exposures.

Lung cancer ORs in those only exposed in early life for arsenic water concentrations of ≤110, 111 to 800, and >800 μg/L were 1.00, 1.88 (95% CI, 0.96–3.71), and 5.24 (3.05–9.00; Table 4). Corresponding ORs for adult-only exposure were 1.00, 0.95 (0.46–1.97), and 1.32 (0.75–2.34). Bladder cancer ORs in those only exposed in early life for these same arsenic water concentrations were 1.00, 2.94 (1.29–6.70), and 8.11 (4.31–15.25). Corresponding bladder cancer ORs for adult-only exposure were 1.00, 2.21 (1.03–4.74), and 4.71 (2.61–8.48). ORs for early-life exposure were similar when other age categorizations were used (Supplementary Table S3).

ORs for early-life exposure were similar in males, in nonproxy subjects, and in analyses adjusted for occupational exposures, SES, and obesity (Fig. 1). ORs in females were slightly lower but the differences compared with males were not statistically significant. Lung cancer ORs in those ages 60 to 70 years who were exposed only in early life were 1.00, 3.58 (95% CI, 1.06–12.1), and 5.17 (2.14–12.5; $P_{trend} < 0.001$) for arsenic water concentrations of ≤110, 111 to 800, and >800 μg/L (not in tables). Corresponding bladder cancer ORs for this age group were 1.00, 2.72 (0.47–15.7), and 8.01 (2.88–22.2).

Figure 2 shows the lung and bladder cancer ORs comparing subjects exposed >800 μg/L with subjects exposed ≤110 μg/L at each individual age of exposure, ignoring exposures at any other age. For both cancers, ORs are highest for earlier ages of exposure. Lung and bladder cancer ORs adjusted for age, sex, and smoking for each 10 mg/L-year increase in cumulative exposure in those highly exposed in early life but not as adults were 4.49 (2.84–7.11) and 5.21 (3.11–8.73), respectively. Corresponding ORs in those with adult-only exposure were 1.20 (0.74–1.94) and 3.23 (2.02–5.18).

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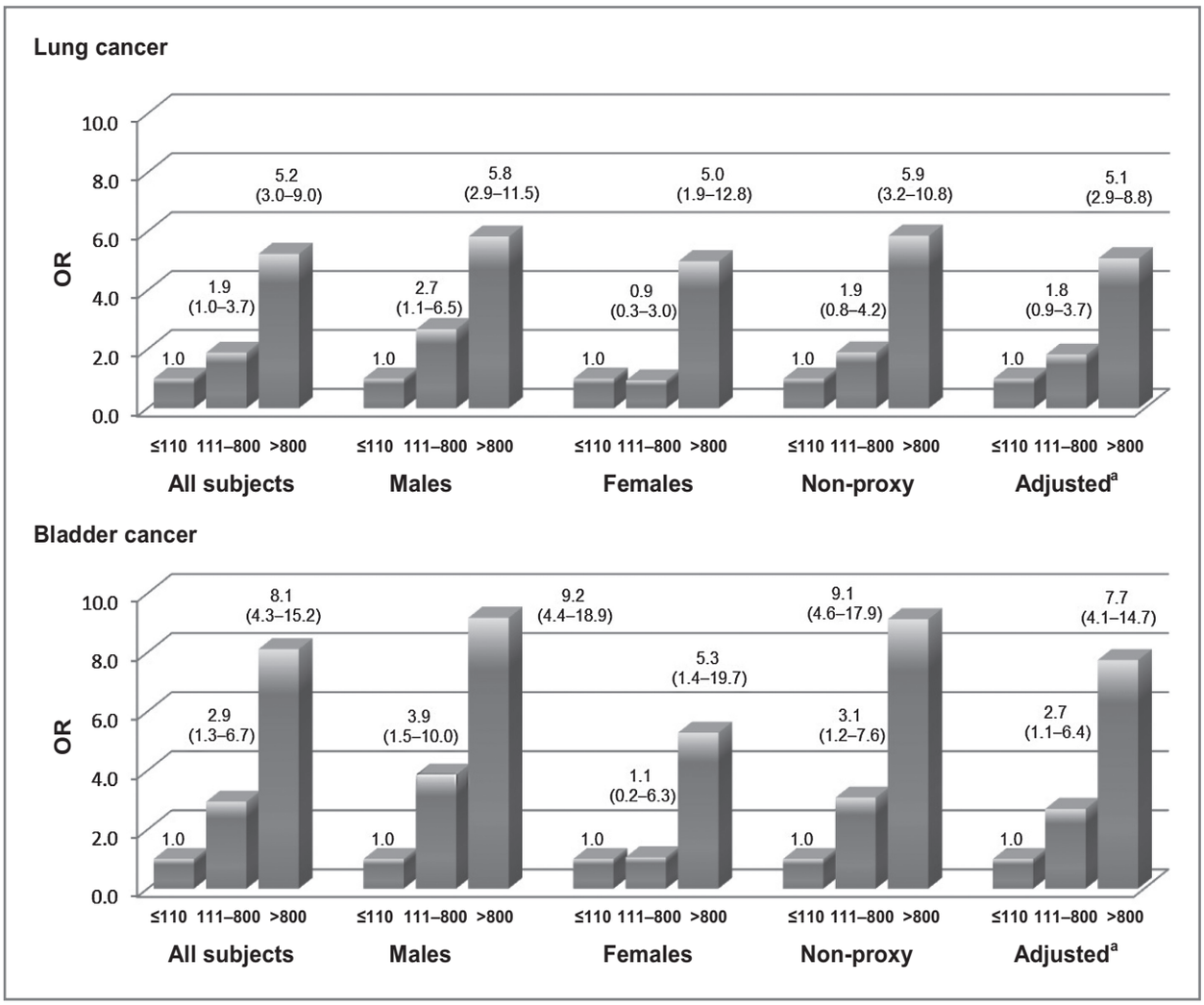

Figure 1. Cancer ORs for *in utero* and childhood exposure by categories of arsenic concentrations (μg/L) in males, females, nonproxy subjects, and in additionally adjusted analyses. [a]Adjusted for age, sex, smoking, mining work, occupational carcinogen exposure, SES, and obesity.

Discussion

These findings provide rare human evidence that an early-life environmental exposure can be associated with very high risks of cancer in adults. The presence of dose–response relationships and low *P* values suggest that these findings are unlikely due to chance. The particularly novel aspect of this study is the unique exposure situation in northern Chile which allowed us to assess early-life exposure impacts of over a period of >50 years with accurate data on past exposure, and this is the first analytic study ever to link an early-life or *in utero* environmental chemical exposure to high risks of cancer for such a long period after the exposures occurred.

Other research supports the plausibility of our findings. Ingested arsenic is an established cause of bladder and lung cancer (8), and is known to cross the placenta (21). Studies of low birth weight, smoking, lung infections, and air pollution all provide evidence that early-life events can lead to lung damage manifested later in life (22–24). Our studies in Chile have linked early-life arsenic exposure to respiratory symptoms, lung function decrements, and mortality from lung cancer, bladder cancer, and bronchiectasis (12, 25, 26). In rodents, although arsenic-caused tumors are difficult to induce when arsenic is given in adulthood (27), prenatal exposures have been shown to induce adult tumors much more readily (28).

There are several reasons why *in utero* or childhood exposures may confer high cancer risks. The fetal and early childhood periods are times of rapid organogenesis and cell proliferation, which may allow for mutagenic, epigenetic, or other permanent carcinogenic alterations. These are also periods when metabolism, detoxification, and excretion pathways are undeveloped, and when intake of air and water (and the contaminants in them) are higher on a body weight basis (1). In laboratory experiments, gestational arsenic exposure has been linked

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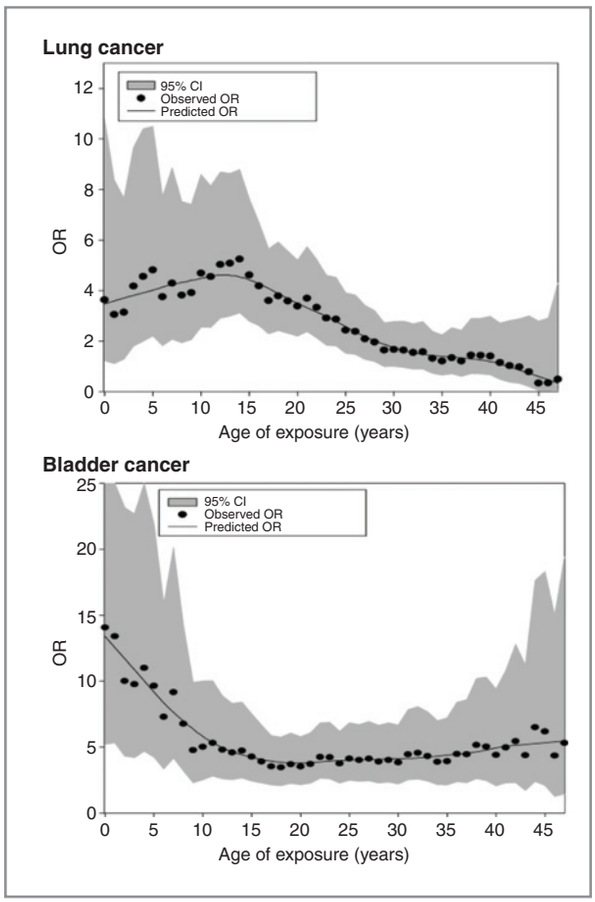

Figure 2. Cancer ORs comparing subjects exposed >800 μg/L with subjects exposed ≤110 μg/L by age of exposure. For example, the lung cancer OR comparing those exposed >800 μg/L at the age of 10 years with those exposed ≤110 μg/L at the age of 10 years is 4.7 (95% CI, 2.6–8.6). ORs are adjusted for age, sex, and smoking.

to overexpression of estrogen receptor and EGF genes (29), carcinogenic changes in stem cells (30), and increased tumorigenicity of other agents (28). Arsenic has been linked to epigenetic effects such as altered DNA methylation, histone modification, and miRNA expression, and these might also increase long-term cancer risks (31). These later findings may be especially relevant to *in utero* exposures because the embryonic period is a time of significant reprogramming of DNA methylation (32, 33).

Early-life exposure has been unequivocally linked to adult cancer in human studies for only a few other agents: asbestos, high-dose radiation, and diethylstilbestrol (34). However, these exposures are rare and their relevance to lower chronic exposures is uncertain (35). In our study, the large majority of exposures >100 μg/L ended around 1970, so latency patterns were the same in those with childhood and adult-only exposures. We found higher ORs in those with early-life exposure compared with those exposed only as adults. However, because subjects in the latter group were older, the relative impacts of earlier versus later-life exposure on absolute risks cannot be determined from these data. It could be hypothesized that early-life arsenic exposure is only increasing cancer in younger age groups where absolute risks are low. However, we found that lung cancer ORs for early-life exposures were high in adults ages 60 to 70 years. Because these are the ages where lung cancer is most common in Chile, early-life exposure likely had a major impact on absolute risks in this study area. Consistent associations between lung cancer and adult exposure were not seen in this study, although a small increase in risk or the role of chance cannot be ruled out. Further evaluations involving larger sample sizes and a broader number of years of case ascertainment may help elucidate the risks from adult-only exposure.

Exposure misclassification could have resulted from missing exposure data; inaccurate recall of residential history, water sources, or water consumption; or arsenic from nondrinking water sources. Because exposure was assessed similarly in cases and controls, most of these were likely nondifferential and biased ORs toward the null. And, because exposure was primarily based on the cities in which the subjects lived, and errors in recalling this information are likely minimal, the impact of recall errors are probably small. Proxy interviews were more common among cases than controls. However, previous research has shown that proxy respondents can provide reasonably accurate residential histories (36). In addition, the fact that results were similar when proxy subjects were excluded suggests that including these subjects caused little bias. Arsenic may come from food, occupations, or dust from mine tailings. However, adjustments for arsenic or other carcinogen exposure at work had little effect (Fig. 1), and analyses done in Regions I and II have shown that arsenic exposures from food or mine tailings are small compared with the intake associated with consuming water with arsenic concentrations of 110 to 850 μg/L (37, 38). Errors in identifying cases may have occurred but cases were ascertained using the same procedures throughout the study area, and hospital cancer committees and death certificates were used to locate missed cases. Confounding is also possible but unlikely, given the fact that findings changed little with adjustments.

Overall, we found evidence that lung and bladder cancer incidence in adults was markedly increased following exposure to arsenic in early life up to 40 years after high exposures ceased, providing evidence that humans are extraordinarily susceptible to lifelong effects from early-life arsenic exposure. In Chile and elsewhere, many of the highest exposures have ended, but our results suggest that high cancer risks from early-life exposures are likely to continue decades after the exposures are stopped. Public awareness campaigns aimed at reducing important coexposures might help reduce arsenic-related mortality in these areas (39). Also, routine screening with low-dose lung CT has been shown to reduce mortality in heavy smokers (40), raising the possibility that this may also be effective in people with past arsenic exposure.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Steinmaus, C. Ferreccio, J. Acevedo, Y. Yuan, J. Liaw, J. Garcia, L.E. Moore, S.G. Perez, A.H. Smith
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Study supervision: C. Steinmaus, C. Ferreccio, J. Acevedo

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