Title
Arsenic, Tobacco Smoke, and Occupation

Journal
Epidemiology, 24(6)

ISSN
1044-3983

Authors
Ferreccio, Catterina
Yuan, Yan
Calle, Jacqueline
et al.

Publication Date
2013-11-01

DOI
10.1097/ede.0b013e31829e3e03

Peer reviewed

Arsenic, Tobacco Smoke, and Occupation

Associations of Multiple Agents with Lung and Bladder Cancer

Catterina Ferreccio,[a] *Yan Yuan,*[b] *Jacqueline Calle,*[a] *Hugo Benítez,*[c] *Roxana L. Parra,*[c] *Johanna Acevedo,*[a] *Allan H. Smith,*[b] *Jane Liaw,*[b] *and Craig Steinmaus*[b]

Background: Millions of people worldwide are exposed to arsenic in drinking water, and many are likely coexposed to other agents that could substantially increase their risks of arsenic-related cancer.

Methods: We performed a case-control study of multiple chemical exposures in 538 lung and bladder cancer cases and 640 controls in northern Chile, an area with formerly high drinking water arsenic concentrations. Detailed information was collected on lifetime arsenic exposure, smoking, secondhand smoke, and other known or suspected carcinogens, including asbestos, silica, and wood dust.

Results: Very high lung and bladder cancer odds ratios (ORs), and evidence of greater than additive effects, were seen in people exposed to arsenic concentrations >335 µg/L and who were tobacco smokers (OR = 16, 95% confidence interval = 6.5–40 for lung cancer; and OR = 23 [8.2–66] for bladder cancer; Rothman Synergy Indices = 4.0 [1.7–9.4] and 2.0 [0.92–4.5], respectively). Evidence of greater than additive effects were also seen in people coexposed to arsenic and secondhand tobacco smoke and several other known or suspected carcinogens, including asbestos, silica, and wood dust.

Conclusions: These findings suggest that people coexposed to arsenic and other known or suspected carcinogens have very high risks of lung or bladder cancer.

(*Epidemiology* 2013;24: 898–905)

Arsenic in drinking water is a well-established cause of lung and bladder cancer, and tens of millions of people worldwide are exposed.[1] Exposure to other agents such as tobacco smoke or occupational carcinogens, like asbestos or silica, could create large subgroups of people in arsenic-exposed areas whose cancer risks are especially high. Numerous public health agencies have called for research and policies that take into account the cumulative effects of multiple agents.[2] To date, however, relatively few regulations and policies have done this, primarily because of lack of data. We used data from a large case-control study in northern Chile to investigate the possible cumulative risks of arsenic, tobacco smoke, and other known or suspected carcinogens.

METHODS

Study Area

The study area consisted of regions I and II in northern Chile, two contiguous regions with a population of 922,579 people.[3] 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) for drinking, leading to a 13-year period (1958–1970) with an average concentration of 860 µg/L in the city's water supply. Installation of a treatment plant reduced this to <10 µg/L today.[4] Other cities in the area offer a wide range of exposure (Table 1). The major occupation in this area was mining of copper and other minerals, and this produced a variety of exposures, including silica, dusts, welding fumes, asbestos, and solvents.

Participant Selection and Interviews

Cases included people who 1) had primary lung or bladder cancer first diagnosed between October 2007 and December 2010; 2) lived in the study area at the time of diagnosis; 3) were over age 25 years when diagnosed; and 4) were able to provide interview data or had a close relative who could. Lung and bladder cancer were selected because lung cancer is the main cause of arsenic-related death,[5] and bladder cancer is associated with higher relative risks than any other arsenic-related cancer.[6] Cases were ascertained from all pathologists, hospitals, and radiologists in the area. Few people leave the study area for medical care because the nearest large medical facilities outside the area are in Santiago, 675 miles away. The large majority of cases were histologically confirmed (98% for bladder cancer and 72% for lung cancer), with the remaining diagnoses based on a combination of radiologic (computed tomography)

Submitted 19 September 2012; accepted 19 March 2013; posted 12 September 2013.

From the [a]Departamento de Salud Pública, Universidad Católica de Chile, Santiago, Chile; [b]Arsenic Research Group, School of Public Health, University of California, Berkeley, CA; and [c]Hospital de Antofagasta, Antofagasta, Chile.

Supported by US National Institute of Environmental Health Sciences grants 5R01ES014032 and P42ES04705.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com). This content is not peer-reviewed or copy-edited; it is the sole responsibility of the author.

Correspondence: Craig Steinmaus, University of California, School of Public Health, 50 University Hall, MC7360, Berkeley, CA 94720–7360. E-mail: craigs@berkeley.edu.

ISSN: 1044-3983/13/2406-0898
DOI: 10.1097/EDE.0b013e31829e3e03

TABLE 1. Historic Arsenic Concentrations in Drinking Water (μg/L) in Northern Chile by Year

			Average Arsenic Concentration (μg/L)						
			Years						
Region	City or Town	Population[a]	1930–1957	1958–1970	1971–1977	1978–1979	1980–1987	1988–1994	1995+
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 Chile census conducted in 2002.[3]

and physician's clinical findings. Cases or their next of kin were usually interviewed within 3–4 months of diagnosis. Controls without lung or bladder cancer who otherwise met the above criteria were randomly selected from the Chilean Electoral Registry, frequency matched to bladder or lung cancer cases separately by sex and 5-year age group.[6] When a case was identified, a control was selected from a list of potential controls comprising a random subsample of the Electoral Registry for the whole study area. The Electoral Registry contained >95% of people over age 50 years when compared with the Chile national census. All participants were interviewed in person using a standard study questionnaire. For deceased subjects, the nearest relative was interviewed. Participants were asked to identify all residences they occupied for 6 months or longer. Questions regarding tobacco exposure covered age when smoking began, periods of quitting, total years smoked, typical number of packs smoked per week, and exposure to secondhand smoke as a child and adult, including the number of people in the house who smoked and the number of hours per week and years exposed. Subjects were also asked about their typical water intake at the time of interview and 20 years before, but these data had little impact on classifying exposure because the range in water arsenic concentrations (over 80-fold) was much greater than the range in water intake. Subjects were also asked whether they had been exposed to other known or suspected carcinogens (Supplementary Table 1, http://links.lww.com/EDE/A701), either at home or work, the jobs or hobbies in which these exposures occurred, and the number of hours per week and years exposed. These chemicals were selected and classified a priori based on lists of known or suspected bladder, lung, or kidney carcinogens (kidney cancer was assessed separately) from the International Agency for Research on Cancer,[7] or recent data suggesting links to cancer.[8–11]

Exposure Assessment

Lifetime arsenic exposure was estimated by linking each subject's residences within the study area to the water arsenic concentration of the water supply of the city or town of each residence, so that an arsenic concentration could be assigned to each year of a subject's life. Arsenic measurements were available from government agencies, research studies, and other sources, covering >97% of all drinking water sources in the area.[12–17] Until recently, few people in this region drank bottled water or used water filters. Arsenic concentrations were also available for all large cities in Chile outside the study area, and these were also linked to residences, although almost all water in Chile outside the study area has arsenic concentrations <10 μg/L.[4] Almost all subjects spent most of their lives either in regions I and II or in one of the other larger cities in Chile, so we were able to assign an arsenic drinking water concentration to >95% of all residences. Several indices of arsenic exposure were developed using the yearly concentrations, including the highest arsenic concentration to which the subject was exposed for any one year; the highest concentration for any contiguous 5, 20, or 40 year period; cumulative exposure in μg/L-years (calculated by summing the yearly concentrations); and average exposure (calculated by taking the average of the yearly exposures). Because the latency period of arsenic-related cancer is several decades,[18] and because Antofagasta had the largest population and highest exposures in the area, some analyses were limited to arsenic exposures before 1971, the year when high exposures in Antofagasta ended. (Limiting exposures to

only those occurring 5, 20, and 40 years before cancer diagnosis or study recruitment produced similar results.) For each arsenic exposure index, subjects were divided into four groups based on quartiles for all subjects. This resulted in arsenic categories similar to the highest arsenic water concentrations in the four major population centers of our study area: Arica, Iquique, Calama, and Antofagasta.

In the assessment of direct (firsthand) smoking, separate analyses compared never-smokers to ever-smokers and never-smokers to heavier smokers (smoking an average of >10 cigarettes per day for ≥6 months, the median among smokers). Analyses of secondhand smoke were limited to never-smokers. Secondhand smoke exposure was classified as yes or no based on whether the subject reported any exposure for at least 6 months, and separate analyses were conducted for childhood and adult exposure. Because there were relatively small numbers of never-smokers, arsenic exposure was divided into only two categories in these analyses.

Exposure to other known or suspected carcinogens was initially classified as yes or no based on any reported exposure. Subjects with proxy interviews were excluded from these analyses. Women were also excluded because very few reported these exposures. We assessed only those agents to which ten or more cases and controls combined reported exposure. Few subjects were exposed to known occupational bladder carcinogens so only lung cancer results are presented.

Statistical Analysis

Interactions between arsenic, tobacco smoke, and the other exposures were evaluated using the Rothman Synergy Index.[19] In brief, relative risks were estimated separately for people who were exposed only to arsenic (RR_A), people exposed only to the second agent (RR_S), and people exposed

TABLE 2. Demographic Characteristics of Controls and Bladder and Lung Cancer Cases, Northern Chile 2007–2010

	Controls		Bladder Cancer Cases				Lung Cancer Cases			
	No.	(%)	No.	(%)	OR[a]	(95% CI)	No.	(%)	OR[a]	(95% CI)
Total	640	(100)	232	(100)			306	(100)		
Sex										
Women	209	(33)	62	(27)	1.00		91	(30)	1.00	
Men	431	(68)	170	(73)	1.33	(0.95–1.86)	215	(70)	1.15	(0.85–1.54)
Race										
Other	195	(31)	35	(15)	1.00		70	(23)	1.00	
European	445	(70)	197	(85)	2.47	(1.67–3.64)	236	(77)	1.48	(1.08–2.02)
Age (years)										
70+	269	(42)	94	(41)	1.00		112	(37)	1.00	
60–69	193	(30)	76	(33)	1.13	(0.79–1.61)	111	(36)	1.38	(1.00–1.90)
50–59	132	(21)	39	(17)	0.85	(0.55–1.30)	69	(23)	1.26	(0.87–1.81)
40–49	39	(6)	23	(10)	1.69	(0.96–2.96)	10	(3)	0.62	(0.30–1.27)
30–39	7	(1)	0	(0)	—[a]		4	(1)	1.37	(0.40–4.76)
Body mass index >30 kg/m^2[b]										
No	612	(96)	216	(93)	1.00		287	(94)	1.00	
Yes	28	(4)	17	(7)	1.72	(0.92–3.20)	19	(6)	1.45	(0.79–2.63)
Smoking										
Never	242	(38)	65	(28)	1.00		59	(20)	1.00	
Ever	398	(62)	167	(72)	1.56	(1.13–2.17)	247	(81)	2.55	(1.85–3.51)
Socioeconomic status (tertiles)										
Low	231	(36)	73	(32)	1.00		126	(41)	1.00	
Medium	203	(32)	66	(28)	1.03	(0.70–1.51)	103	(34)	0.93	(0.67–1.28)
High	206	(32)	93	(40)	1.43	(1.00–2.04)	77	(25)	0.69	(0.49–0.96)
Water arsenic concentrations (μg/L)[c]										
0–59	138	(22)	23	(10)	1.00		48	(16)	1.00	
60–199	193	(30)	27	(12)	0.84	(0.46–1.52)	52	(17)	0.77	(0.49–1.21)
200–799	144	(23)	60	(26)	2.50	(1.48–4.22)	69	(23)	1.38	(0.89–2.13)
≥800	165	(26)	122	(53)	4.44	(2.75–7.15)	137	(45)	2.39	(1.61–3.54)

[a]Unadjusted ORs and 95% CIs comparing bladder or lung cancer cases to controls.
[b]Based on self-reported usual height and weight reported for 20 years before diagnosis (cases) or ascertainment (controls).
[c]Highest single year exposure throughout the subject's entire lifetime from birth to diagnosis (cases) or ascertainment (controls). Categories are based on concentrations in the four largest cities in the study area: Arica, Iquique, Calama, and Antofagasta.
[d]An OR was not calculated because there were no bladder cancer cases in this age group.

TABLE 3. Odds Ratios for Bladder Cancer in Relation to Arsenic Concentrations in Water, by Smoking Status, Northern Chile, 2007–2010

	Arsenic <11 µg/L[a]		Arsenic >335 µg/L[a]		ORs[b] (95% CI) for Arsenic Within Smoking Strata
	Cases/Controls	OR[b] (95% CI)	Cases/Controls	OR[b] (95% CI)	
Never smoker	6/79	1.0	19/34	8.9 (3.0–26)	8.9 (3.0–26)
Smoked >10 cigs/day	14/45	4.1 (1.3–13)	33/18	23 (8.2–66)	6.2 (2.5–15)
OR[b] (95% CI) for smoking within arsenic strata		4.1 (1.3–13)		3.2 (1.3–8.0)	

Measure of interaction on an additive scale: Rothman Synergy Index (95% CI) = 2.0 (0.9–4.5).
Measurement on a multiplicative scale: ratio of ORs (95% CI) = 0.64 (0.17–2.5).
[a]These are the lower and upper quartiles of average lifetime exposure up to 1971, the end of the high exposure period in Antofagasta.
[b]Adjusted for age, sex, socioeconomic status, and secondhand tobacco smoke exposure.

to both (RR_{AS}), using people exposed to neither as the reference. A synergy index (S) was then calculated as: $S = (RR_{AS} - 1) / ([RR_A + RR_S] - 2)$. Using this method, S = 1 in the absence of synergy, and S>1 when biological interactions are greater than additive. Confidence intervals (CIs) for S were estimated using the methods of Hosmer and Lemeshow,[20] and findings are presented as suggested by Knol and VanderWeele.[21]

Lung and bladder cancer odds ratios (ORs) were calculated using unconditional logistic regression. Potential confounding variables entered into regression models included sex, age (10-year age groups), smoking, and tertiles of socioeconomic status (SES) scores. SES scores were based on 12 items including ownership of household appliances, car, computer, and domestic help. Analyses were done in SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The names of 370 persons with lung cancer and 289 persons with bladder cancer were obtained from local pathologists, radiologists, or hospitals. Of these, 46 persons with lung cancer and 23 with bladder cancer were ineligible based on age and residential criteria. Of the remaining, 18 persons with lung cancer (6%) and 34 with bladder cancer (13%) (or their next of kin) could not be located, had moved outside the study area, provided insufficient residential information, or declined participation. Among 872 controls selected from the Electoral Registry with viable addresses, 232 (27%) no longer lived at the address and could not be located, were ineligible because of illness, gave insufficient information, or declined participation. Sex, age, and SES were similar among cases and controls (Table 2). Bladder and lung cancer cases were more likely than controls to be of European descent, smokers, and exposed to higher arsenic concentrations.

Tables 3 and 4 show the lung and bladder cancer ORs for arsenic exposure stratified by smoking status. The bladder cancer OR in heavier smokers in the highest arsenic exposure category (OR = 23, 95% CI = 8.2–66) was substantially higher than that in heavier smokers with low arsenic exposure (OR = 4.1, 95% CI = 1.3–13) or in never-smokers with high arsenic exposure (OR = 8.9, 95% CI = 3.0–26). The synergy index for arsenic and smoking was 2.0 (95% CI = 0.92–4.5). The pattern was similar for lung cancer, although with a higher synergy index (S = 4.0, 95% CI = 1.7–9.4). Dose–response patterns for arsenic in smokers and never-smokers are shown in Supplementary Table 2 (http://links.lww.com/EDE/A701). Similar patterns were seen in analyses of those smoking >20 cigarettes per day, arsenic exposure tertiles, cumulative arsenic exposure (Supplementary Tables 3–7, http://links.lww.com/EDE/A701), or duration or pack-years of smoking (not shown).

Tables 5 and 6 shows the ORs in never-smokers for arsenic exposure stratified by childhood secondhand smoke

TABLE 4. Odds Ratios for Lung Cancer in Relation to Arsenic Concentrations in Water, by Smoking Status, Northern Chile, 2007–2010

	Arsenic <11 µg/L[a]		Arsenic >335 µg/L[a]		ORs[b] (95% CI) for Arsenic Within Smoking Strata
	Cases/Controls	OR[b] (95% CI)	Cases/Controls	OR[b] (95% CI)	
Never smoker	16/79	1.0	18/34	2.0 (0.8–5.0)	2.0 (0.84–5.0)
Smoked >10 cigs/day	28/45	3.8 (1.7–8.5)	46/18	16 (6.5–40)	4.2 (2.0–9.0)
OR[b] (95% CI) for smoking within arsenic strata		3.8 (1.7–8.5)		5.4 (2.1–14)	

Measure of interaction on an additive scale: Rothman Synergy Index (95% CI) = 4.0 (1.7–9.4).
Measurement on a multiplicative scale: ratio of ORs (95% CI) = 1.9 (0.61–5.7).
[a]These are the lower and upper quartiles of average lifetime exposure up to 1971, the end of the high exposure period in Antofagasta.
[b]Adjusted for age, sex, socioeconomic status, and secondhand tobacco smoke exposure.

TABLE 5. Odds Ratios for Bladder Cancer in Relation to Arsenic Concentrations in Water in Never-smokers, by Exposure to Childhood Secondhand Smoke, Northern Chile, 2007–2010

	Arsenic <200 µg/L[a]		Arsenic >200 µg/L[a]		ORs[b] (95% CI) for Arsenic Within Secondhand Smoke Strata
	Cases/Controls	OR[b] (95% CI)	Cases/Controls	OR[b] (95% CI)	
No secondhand smoke exposure	20/131	1.0	24/47	3.4 (1.7–6.9)	3.4 (1.7–6.9)
Secondhand smoke exposed	7/49	0.9 (0.36–2.4)	14/15	7.0 (2.8–17)	6.8 (2.2–21)
ORs[b] (95% CI) for secondhand smoke within arsenic strata		0.9 (0.36–2.4)		1.7 (0.68–4.3)	

Measure of interaction on an additive scale: Rothman Synergy Index (95% CI) = 2.6 (0.77–8.5).
Measurement on a multiplicative scale: ratio of ORs (95% CI) = 2.1 (0.57–7.5).
[a]Average lifetime exposure up to 1971, the end of the high exposure period in Antofagasta.
[b]Adjusted for age, sex, and socioeconomic status.

exposure. The highest ORs were seen for persons exposed to both arsenic and secondhand smoke. Synergy indices were >1.0 for both bladder (S = 2.6, 95% CI = 0.77–8.5) and lung cancer (S = 2.1, 95% CI = 0.25–17). No evidence of interaction was seen between arsenic and adult secondhand smoke exposure (not shown). Among those reporting any secondhand smoke exposure, the median number of hours exposed per day was 4.

Table 7 shows lung cancer ORs in analyses of arsenic and other occupational or environmental exposures. For each of the agents assessed, ORs are presented for three separate groups, using subjects who had low arsenic exposure and who were not exposed to the other agent of interest as the reference group. These three groups (and their corresponding ORs from left to right in Table 7) are 1) subjects who had reported exposure to the other agent but had low arsenic exposure; 2) subjects who did not report exposure to the other agent but had high arsenic exposure; and 3) subjects who had reported exposure to the other agent and had high arsenic exposure. Low and high arsenic exposure in these analyses were defined as the lowest (<11 µg/L) or highest (>335 µg/L) quartiles of average arsenic concentration in water before 1971. Very high ORs (eg, >10) were seen for subjects coexposed to arsenic and several of the other carcinogens assessed. Synergy indices substantially above 1.0 were seen for many of the agents known or suspected to cause lung cancer, including asbestos (S = 2.7), silica (S = 2.0), wood dust (S = 3.1), welding fumes (S = 2.4), soot (S = 2.5), and fiberglass (S = 2.5). The category "any carcinogen" included any of the known or suspected lung carcinogens listed in Table 7 plus beryllium, bis(chloromethyl) ether, chromium, and cadmium. Synergy indices for arsenic and agents not known or suspected to cause lung cancer (such as benzene and solvents) were mostly near 1.0. Categorizing arsenic based on other indices such as cumulative or highest exposure had little effect on results. Results were also essentially unchanged when we limited analyses to histologically confirmed cases, when we incorporated number of smokers in the home or total years of exposure to the secondhand smoke exposure variable, or when we based exposure to carcinogens on number of hours per week and total years. Additional adjustments for body mass index, race, or mining work had little impact on results.

DISCUSSION

Overall, these findings suggest that people exposed to a combination of arsenic in drinking water and some other known or suspected carcinogen, including tobacco smoke, asbestos, silica, and wood dust, have lung and bladder cancer risks that are >10 times higher than those who are unexposed. Synergy indices were substantially greater than 1.0 for several

TABLE 6. Odds Ratios for Lung Cancer in Relation to Arsenic Concentrations in Water in Never-smokers, by Exposure to Childhood Secondhand Smoke, Northern Chile, 2007–2010

	Arsenic <200 µg/L[a]		Arsenic >200 µg/L[a]		ORs[b] (95% CI) for Arsenic Within Secondhand Smoke Strata
	Cases/Controls	OR[b] (95% CI)	Cases/Controls	OR[b] (95% CI)	
No secondhand smoke exposure	26/131	1.0	13/47	1.4 (0.66–3.1)	1.4 (0.66–3.1)
Secondhand smoke exposed	12/49	1.4 (0.64–3.3)	8/15	2.8 (1.0–7.8)	1.9 (0.56–6.2)
ORs[b] (95% CI) for secondhand smoke within arsenic strata		1.4 (0.64–3.3)		1.6 (0.43–5.4)	

Measure of interaction on an additive scale: Rothman Synergy Index (95% CI) = 2.1 (0.25–17).
Measurement on a multiplicative scale: ratio of ORs (95% CI) = 1.5 (0.38–5.8).
[a]Average lifetime exposure up to 1971, the end of the high exposure period in Antofagasta.
[b]Adjusted for age, sex, and socioeconomic status.

TABLE 7. Lung Cancer Odds Ratios in Men in Relation to Exposure to Other Agents, Exposure to High Concentrations of Arsenic in Water, or Both, Using People not Exposed to the Other Agent and with Low Arsenic Concentrations in Water as the Reference Group, Northern Chile, 2007–2010

Other Agent	Unexposed			Exposed			Unexposed			Exposed				
Arsenic[a]	Low Exposure			Low Exposure			High Exposure			High Exposure			Synergy Index	
	N	OR[b]	(95% CI)	N	OR[b]	(95% CI)	N	OR[b]	(95% CI)	N	OR[b]	(95% CI)	S	(95% CI)
Any carcinogen[c,d]	6/66	1.0	Ref	11/69	1.8	(0.57–5.4)	19/35	5.2	(1.8–15)	27/25	12.1	(3.8–38)	2.2	(0.90–5.5)
Asbestos	16/128	1.0	Ref	1/7	1.6	(0.15–18)	40/57	6.0	(2.9–12)	6/3	16	(2.8–95)	2.7	(0.52–14)
Silica	11/101	1.0	Ref	6/34	1.8	(0.56–5.6)	30/45	6.2	(2.6–15)	16/15	13	(3.9–43)	2.0	(0.77–5.2)
Wood dust[d]	9/104	1.0	Ref	8/31	2.5	(0.82–7.8)	34/53	7.6	(3.2–18)	12/7	26	(6.0–120)	3.1	(1.1–9.3)
Welding fumes	12/94	1.0	Ref	5/41	1.0	(0.30–3.2)	33/50	5.6	(2.4–13)	13/10	12	(3.7–38)	2.4	(0.80–7.1)
Coke oven	14/109	1.0	Ref	3/26	0.9	(0.22–3.6)	34/44	6.0	(2.7–13)	12/16	6.6	(2.2–19)	1.1	(0.42–3.1)
Soot	13/113	1.0	Ref	4/22	1.7	(0.44–6.6)	41/56	6.3	(2.9–14)	4/5	16	(2.2–120)	2.5	(0.56–11)
Fiberglass	15/117	1.0	Ref	2/18	1.4	(0.25–7.4)	40/56	6.1	(2.9–13)	4/6	14	(2.6–81)	2.5	(0.56–11)
Benzene	16/131	1.0	Ref	1/4	1.0	(0.08–11)	44/56	6.3	(3.1–13)	2/4	8.7	(0.63–120)	1.5	(0.19–11)
TCE	16/132	1.0	Ref	1/3	2.4	(0.19–30)	43/55	7.3	(3.5–15)	3/5	6.7	(1.1–40)	0.73	(0.11–4.7)
Other solvents	16/129	1.0	Ref	1/6	1.9	(0.16–21)	45/58	6.9	(3.3–14)	1/2	4.2	(0.27–67)	0.48	(0.02–12)
Acrylic	15/130	1.0	Ref	2/5	4.6	(0.65–32)	44/57	7.0	(3.3–15)	2/3	10	(0.94–110)	0.97	(0.11–8.3)
Any solvent[e]	15/126	1.0	Ref	2/9	1.6	(0.26–9.2)	42/53	6.9	(3.3–15)	4/7	7.6	(1.4–41)	1.0	(0.22–4.7)
Vapors	13/119	1.0	Ref	4/16	1.8	(0.47–7.0)	41/57	8.0	(3.6–18)	5/3	15	(2.3–96)	1.8	(0.35–8.9)
Other chemicals	10/113	1.0	Ref	7/22	3.9	(1.1–13)	32/43	8.5	(3.6–20)	14/17	7.7	(2.5–24)	0.64	(0.25–1.7)
Mining	12/102	1.0	Ref	5/33	1.2	(0.34–4.1)	36/43	7.4	(3.2–17)	10/17	6.9	(2.0–24)	0.90	(0.31–2.6)

N indicates number of cases/controls; Ref, reference group; TCE, trichloroethylene.

[a]High arsenic exposure is defined as an average lifetime arsenic concentration in water up to 1971 of >335 µg/L. Low arsenic exposure is defined as an average lifetime arsenic concentration in water up to 1971 of <11 µg/L.

[b]All ORs are adjusted for age, smoking, and socioeconomic status.

[c]Includes any of the known or suspected lung carcinogens listed in this table (asbestos, silica, wood dust, welding fumes, coke oven emissions, soot, and fiberglass) as well as beryllium, bis(chloromethyl) ether, chromium, and cadmium.

[d]Further details on these analyses are shown in Supplementary Tables 8 and 9 (http://links.lww.com/EDE/A701).

[e]Includes benzene, TCE, and any other solvent.

of the coexposures assessed here, suggesting that the combined effects of these multiple carcinogens are greater than additive.

This study has several advantages for studying the health effects of arsenic. First, the study took place in an area with a history of high concentrations of arsenic in drinking water and good data on past exposure. Obtaining accurate data on historical exposures is important because the latency for many carcinogens is several decades or more. Northern Chile is the driest habitable place of earth, and over 97% of all water is obtained from a small number of public water systems that supply each city or town. Historical records of arsenic concentrations are available for all of these systems, with many dating back 40 years or more and showing very stable concentrations over time. Because of this small number of water sources and good historical records, lifetime arsenic exposure can be accurately estimated simply by knowing the cities or towns in which a person has lived.

The second major advantage is that the arsenic exposures were very high (eg, >800 µg/L) and have been linked to high relative risks of lung and bladder cancer.[5,22] Higher relative risks have greater statistical power and are less likely to be because of confounding or bias than relative risks near 1.0.[23] The third advantage of this study is that detailed information was collected on other known or suspected carcinogens including smoking, child and adult secondhand smoke, asbestos, silica, and wood dust. This information allowed us to investigate the combined effects of multiple carcinogenic exposures.

Multiple exposures were assessed in this study, and it is possible that some of these findings could be because of chance or correlations between exposures. Evidence against chance being an explanation include the fact that many of the OR CIs excluded 1.0 and that synergy indices tended to be high for agents already known or suspected to cause lung cancer (eg, asbestos), but not for agents not linked to lung cancer (eg, solvents). Tobacco smoke, asbestos, silica, coke production, and soot are all established causes of lung cancer.[7] Wood dust is an established cause of nasopharyngeal cancer but has also been linked to lung cancer in several studies.[8–11]

Several of the findings presented here are consistent with previous studies. For example, studies have reported evidence of synergistic relationships between arsenic and smoking in lung cancer, including a previous study in northern Chile.[24–26] A recent study in Bangladesh reported evidence of a synergistic relationship between arsenic, smoking, and fertilizer use for premalignant skin lesions.[27] The study reported here is novel in being the first to examine the combined effects of arsenic with secondhand tobacco smoke, asbestos, silica, wood dust, and several other common carcinogenic

exposures. With regard to bladder cancer, previous studies in Argentina and the United States by our research group have reported somewhat higher arsenic-associated bladder cancer relative risks in smokers compared with nonsmokers, but sample sizes were small and arsenic exposures and relative risks were low.[28,29] In contrast, the study reported here is the first to provide fairly good evidence that a synergistic relationship may exist between arsenic and smoking for bladder cancer.

Although the exact mechanisms of the synergistic associations identified here are unknown, several possibilities exist. For example, simultaneous exposures to different agents working by the same pathways could overwhelm repair or detoxification processes that would normally help prevent cancer. Alternatively, early exposure to arsenic could cause permanent biochemical changes that then lead to greater susceptibility to subsequent exposures. In mice, Waalkes et al[30] found that while arsenic exposure had no effect by itself, the number of skin tumors following exposure to 12-*O*-tetradecanoyl phorbol-13-acetate increased by three-fold in mice pretreated with arsenic in the fetal period. Also in mice, Danaee et al[31] found that pretreatment with arsenic increased UV radiation–related mutagenesis in a greater than additive fashion, and that arsenic inhibited the repair of UV-induced DNA damage. Results such as these provide a possible biological basis for the synergistic relationships identified in our study.

An interesting feature of our findings is that arsenic exposures in our study area occur primarily by ingestion whereas the other exposures we evaluated are primarily by inhalation. These interactions are not biologically implausible because some research has shown that ingested arsenic can accumulate in the lung.[32,33] In addition, a previous analysis has shown that the lung cancer risks linked to arsenic are related to its internal dose as measured by urinary arsenic concentrations, and the risks based on internal dose are essentially the same regardless of whether arsenic is inhaled or ingested.[34]

Because exposure information was collected retrospectively, some exposure misclassification is likely. However, exposure was assessed similarly in cases and controls, so some of this misclassification is likely nondifferential, biasing ORs and synergy indices toward the null.[35] Because arsenic exposure in this area can be determined based primarily on the cities or towns in which the subjects lived, and errors in recalling residency information are expected to be minimal, the impact of misclassification of arsenic exposure is likely small. Arsenic levels were not collected for residences outside Chile, but the large majority of subjects spent their whole lives in Chile and none lived in areas outside Chile with known high arsenic concentrations. Arsenic exposure may also come from food or air, although a previous analysis in this area showed that these exposures would make up less than 2% of the total arsenic intake in subjects who lived in Antofagasta during the high exposure period.[36]

With regards to misclassification of smoking status, studies assessing plasma cotinine levels have shown that self-reported smoking status can reliably distinguish smokers from nonsmokers.[37] The validity of self-reported secondhand smoke exposure is less clear. Willemsen et al[38] found that self-reported secondhand smoke exposure correlated reasonably well with air nicotine concentrations in office workers (R = 0.65). In an investigation of 9320 US adults, Max et al[39] identified a positive predictive value of 80% and a negative predictive value of only 64% between self-reported secondhand smoke exposure and serum cotinine, although the cutoff point used to define a positive cotinine level was somewhat low (≥0.05 ng/mL). Overall, some nondifferential misclassification of secondhand smoke (and resulting bias of ORs toward the null) is likely. Differential misclassification could occur if cases tended to recall their past secondhand smoke exposure with greater or less accuracy than controls. The extent of this bias is unknown. But, the fact that bladder and lung cancer ORs for secondhand smoke exposure in people without high arsenic exposure were close to 1.0 (0.91 and 1.3, respectively) suggests that this bias, if present, was not strong.

Exposures to the other agents like asbestos or silica could also have been misclassified. As mentioned above, nondifferential misclassification would most likely bias ORs toward the null. Several studies have shown that most people are able to recall their past occupational exposures with fair to good accuracy, although results vary across studies.[40] In a study of 951 shipyard workers, the prevalence of pleural plaques correlated much better with self-reported asbestos exposure than with expert's estimates based on job titles.[41] A study of drycleaners reported sensitivities and specificities >90% for self-reported trichloroethylene exposure compared with employer reports.[42] Differential misclassification could conceivably occur if cases recall exposures differently than controls, although an in-depth review of this topic concluded that there is little evidence for this.[40] Our finding of higher ORs and synergy indices for those agents known to cause lung cancer (eg, asbestos, silica, soot) compared with those agents not linked to lung cancer (eg, benzene, trichloroethylene), and lack of evidence of synergy between known carcinogens of the lung and the risks of bladder cancer, is further evidence that differential recall did not cause the positive results reported here. Subjects related almost all of these other chemical exposures to their workplaces, and few exposures from hobbies were reported. Because we did not ask about specific hobbies, it is possible that some exposures were missed, although any bias from this was likely nondifferential.

The ORs in this study changed very little with adjustment for smoking, other carcinogens, body mass index, mining work, or SES. Relatively small changes were seen with adjustment for age and sex. Confounding from other factors like diet or radon is possible. However, in order to cause important confounding, a variable must be associated with both the exposure and outcome of interest,[43] and there is no evidence that radon, diet, or other factors are strongly enough related to arsenic exposure in this study area to cause the elevated ORs identified here.

Tens of millions of people are exposed to arsenic worldwide, and many of these people are probably coexposed to at least one of the other agents assessed here. Furthermore, lung and bladder cancer are among the most common cancers worldwide. These factors, combined with the large magnitude of the relative risks identified here, highlight the large numbers of excess cancer cases likely to be related to these combined exposures and the possible benefits of interventions aimed at reducing these exposures.

REFERENCES

1. Ravenscroft P. *Predicting the Global Distribution of Natural Arsenic Contamination of Groundwater. Symposium on Arsenic: The Geography of a Global Problem*. London: Royal Geographical Society; 2007.
2. President's Cancer Panel. *Reducing Environmental Cancer Risk. What We Can Do Now? 2008–2009 Annual Report. U.S. Department of Health and Human Services. National Institutes of Health.* Bethesda, MD: National Cancer Institute; 2009.
3. Instituto Nacional de Estadisticas. *Resultados Generales Censo 2002.* Santiago, Chile: Departmento de Comunicaciones, Departmento de Estadisticas Demografias y Sociales, Servicio de Registro Civil e Identificacion, Ministerio de Salud; 2002.
4. Smith AH, Marshall G, Yuan Y, 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;114:1293–1296.
5. 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;147:660–669.
6. National Research Council. *Arsenic in Drinking Water 2001 Update.* Washington, DC: Subcommittee to Update the 1999 Arsenic in Drinking Water Report, National Research Council; 2001.
7. International Agency for Research on Cancer. *Agents Classified by the IARC Monographs, Volumes 1–105. List of Classifications by Cancer Site.* Lyon: International Agency for Research on Cancer; 2012. Available at: http://monographs.iarc.fr/ENG/Classification/index.php. Accessed 14 November 2012.
8. Wu X, Delclos GL, Annegers JF, et al. A case-control study of wood dust exposure, mutagen sensitivity, and lung cancer risk. *Cancer Epidemiol Biomarkers Prev*. 1995;4:583–588.
9. Bhatti P, Newcomer L, Onstad L, et al. Wood dust exposure and risk of lung cancer. *Occup Environ Med*. 2011;68:599–604.
10. Jayaprakash V, Natarajan KK, Moysich KB, et al. Wood dust exposure and the risk of upper aero-digestive and respiratory cancers in males. *Occup Environ Med*. 2008;65:647–654.
11. Barcenas CH, Delclos GL, El-Zein R, Tortolero-Luna G, Whitehead LW, Spitz MR. Wood dust exposure and the association with lung cancer risk. *Am J Ind Med*. 2005;47:349–357.
12. Borgoño JM, Venturino H, Vicent P. Clinical and epidemiologic study of arsenicism in northern Chile (author's transl). *Rev Med Chil*. 1980;108:1039–1048.
13. Rivara MI, Cebrián M, Corey G, Hernández M, Romieu I. Cancer risk in an arsenic-contaminated area of Chile. *Toxicol Ind Health*. 1997;13:321–338.
14. Zaldívar R. Arsenic contamination of drinking water and foodstuffs causing endemic chronic poisoning. *Beitr Pathol*. 1974;151:384–400.
15. Smith AH, Arroyo AP, Guha-Mazumder DN, et al. Arsenic-induced skin lesions among Atacameno people in Northern Chile despite good nutrition and centuries of exposure. *Environ Health Perspect*. 2000;108:617–620.
16. Sancha AM, O'Ryan R. Managing hazardous pollutants in Chile: arsenic. *Rev Environ Contam Toxicol*. 2008;196:123–146.
17. CONAMA. *Technical Information Sheet: Analysis of Human Exposure to Arsenic in Large Cities (Study No. 21–0022–002).* In: Pino P, ed. Santiago: Comisión Nacional del Medio Ambiente; 2000.
18. Marshall G, Ferreccio C, Yuan Y, et al. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. *J Natl Cancer Inst*. 2007;99:920–928.
19. Rothman KJ. The estimation of synergy or antagonism. *Am J Epidemiol*. 1976;103:506–511.
20. Hosmer DW, Lemeshow S. Confidence interval estimation of interaction. *Epidemiology*. 1992;3:452–456.
21. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41:514–520.
22. Steinmaus CM, Ferreccio C, Romo JA, et al. Drinking water arsenic in northern chile: high cancer risks 40 years after exposure cessation. *Cancer Epidemiol Biomarkers Prev*. 2013;22:623–630.
23. Greenland S. Causation and causal inference. In: Rothman K, Greenland S, eds. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott Raven; 1998:7–28.
24. Ferreccio C, González C, Milosavjlevic V, Marshall G, Sancha AM, Smith AH. Lung cancer and arsenic concentrations in drinking water in Chile. *Epidemiology*. 2000;11:673–679.
25. Chen CL, Hsu LI, Chiou HY, et al.; Blackfoot Disease Study Group. Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. *JAMA*. 2004;292:2984–2990.
26. Hertz-Picciotto I, Smith AH, Holtzman D, Lipsett M, Alexeeff G. Synergism between occupational arsenic exposure and smoking in the induction of lung cancer. *Epidemiology*. 1992;3:23–31.
27. Melkonian S, Argos M, Pierce BL, et al. A prospective study of the synergistic effects of arsenic exposure and smoking, sun exposure, fertilizer use, and pesticide use on risk of premalignant skin lesions in Bangladeshi men. *Am J Epidemiol*. 2011;173:183–191.
28. Bates MN, Rey OA, Biggs ML, et al. Case-control study of bladder cancer and exposure to arsenic in Argentina. *Am J Epidemiol*. 2004;159:381–389.
29. 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;158:1193–1201.
30. Waalkes MP, Liu J, Germolec DR, et al. Arsenic exposure in utero exacerbates skin cancer response in adulthood with contemporaneous distortion of tumor stem cell dynamics. *Cancer Res*. 2008;68:8278–8285.
31. Danaee H, Nelson HH, Liber H, Little JB, Kelsey KT. Low dose exposure to sodium arsenite synergistically interacts with UV radiation to induce mutations and alter DNA repair in human cells. *Mutagenesis*. 2004;19:143–148.
32. Marafante E, Rade J, Sabbioni E, Bertolero F, Foà V. Intracellular interaction and metabolic fate of arsenite in the rabbit. *Clin Toxicol*. 1981;18:1335–1341.
33. Vahter M, Marafante E. Intracellular interaction and metabolic fate of arsenite and arsenate in mice and rabbits. *Chem Biol Interact*. 1983;47:29–44.
34. Smith AH, Ercumen A, Yuan Y, Steinmaus CM. Increased lung cancer risks are similar whether arsenic is ingested or inhaled. *J Expo Sci Environ Epidemiol*. 2009;19:343–348.
35. Rothman K, Greenland S. Precision and validity in epidemiologic studies. In: Rothman K, Greenland S, eds. *Modern Epidemiology*. 2nd ed. Philadelphia, PA: Lippincott Raven; 1998:115–134.
36. Ferreccio C, Sancha AM. Arsenic exposure and its impact on health in Chile. *J Health Popul Nutr*. 2006;24:164–175.
37. Sasaki S, Braimoh TS, Yila TA, Yoshioka E, Kishi R. Self-reported tobacco smoke exposure and plasma cotinine levels during pregnancy–a validation study in Northern Japan. *Sci Total Environ*. 2011;412–413:114–118.
38. Willemsen MC, Brug J, Uges DR, Vos de Wael ML. Validity and reliability of self-reported exposure to environmental tobacco smoke in work offices. *J Occup Environ Med*. 1997;39:1111–1114.
39. Max W, Sung HY, Shi Y. Who is exposed to secondhand smoke? Self-reported and serum cotinine measured exposure in the U.S., 1999-2006. *Int J Environ Res Public Health*. 2009;6:1633–1648.
40. Teschke K, Olshan AF, Daniels JL, et al. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med*. 2002;59:575–593; discussion 594.
41. Järvholm B, Sandén A. Estimating asbestos exposure: a comparison of methods. *J Occup Med*. 1987;29:361–363.
42. Ahlborg GA Jr. Validity of exposure data obtained by questionnaire. Two examples from occupational reproductive studies. *Scand J Work Environ Health*. 1990;16:284–288.
43. Axelson O. Aspects on confounding in occupational health epidemiology. *Scand J Work Environ Health*. 1978;4:85–89.