



Respiratory Cancer in a Cohort of Copper Smelter Workers: Results from More Than 50 Years of Follow-up

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Several studies have linked inhalation of airborne arsenic with increased risk of respiratory cancer, but few have analyzed the shape of the exposure-response curve. In addition, since inhaled airborne arsenic affects systemic levels of inhaled arsenic, there is concern that inhaled arsenic may be associated with cancers of the skin, bladder, kidney, and liver, which have been linked to ingested arsenic. The authors followed 8,014 white male workers who were employed for 12 months or more prior to 1957 at a Montana copper smelter from January 1, 1938 through December 31, 1989. A total of 4,930 (62%) were deceased, including 446 from respiratory cancer. Significantly increased standardized mortality ratios (SMRs) were found for all causes (SMR = 1.14), all cancers (SMR = 1.13), respiratory cancer (SMR = 1.55), diseases of the nervous system and sense organs (SMR = 1.31), nonmalignant respiratory diseases (SMR = 1.56), emphysema (SMR = 1.73), ill-defined conditions (SMR = 2.26), and external causes (SMR = 1.35). Internal analyses revealed a significant, linear increase in the excess relative risk of respiratory cancer with increasing exposure to inhaled airborne arsenic. The estimate of the excess relative risk per mg/m³-year was 0.21/(mg/m³-year) (95% confidence interval: 0.10, 0.46). No other cause of death was related to inhaled arsenic exposure. *Am J Epidemiol* 2000;151:554-65.

arsenic; dose-response relationship; immunologic; lung neoplasms; occupational diseases

Epidemiologic studies have identified inhalation of airborne arsenic as a cause of lung cancer (1, 2). Arsenic is thought to act principally at a late, or promotional, stage of the carcinogenic process (3, 4). Excess lung cancer risk with increasing exposure to airborne arsenic has been consistently observed in studies of miners (5-11) and smelter workers (7, 12-24). In spite of the many studies, there have been only two detailed analyses of the functional relation between exposure to airborne arsenic and lung cancer risk using data on individual workers (6, 13). Both analyses suggested a concave exposure-response relation (6, 13), as did a limited evaluation of an earlier follow-up of the current study (20). A meta-analysis using published results from several studies supported a concave association for lung cancer and inhaled airborne arsenic exposure (1), although the exposure-response relation was not consistent in every study (25).

While ingestion of arsenic-containing drinking water (26-30), exposure to arsenical pesticides (31-35), and use of arsenic-containing therapeutics (36) have been linked to cancers of the skin, bladder, lung, kidney, and liver, an association between inhaled airborne arsenic and nonrespiratory cancers has not been demonstrated. Such an association is plausible, since inhalation of arsenic-containing dusts elevates levels of systemic arsenic, as demonstrated by the positive correlation of urinary arsenic and inhaled airborne arsenic in smelter workers (37).

In this paper, we report results of a new follow-up of a large cohort study of airborne arsenic-exposed copper smelter workers, including a detailed analysis of the relation between exposure and respiratory cancer mortality and of associations between inhaled arsenic and other causes of death.

MATERIALS AND METHODS

Background

This is the latest in a series of studies of workers at a Montana copper smelter. The initial investigation analyzed the mortality experience of workers employed for 12 months or more prior to 1957, with follow-up from 1938 through 1963 (17). This cohort is referred to as the Lee-Fraumeni cohort. There was an increasing risk of respiratory cancer among workers

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Abbreviations: CI, confidence interval; ERR, excess relative risk; ICD-8, *International Classification of Diseases*, Eighth Revision; SMR, standardized mortality ratio.

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who spent more time in work areas with higher levels of airborne arsenic. Greater mortality from respiratory cancer was also linked to increased exposure to sulphur dioxide, but sulphur dioxide exposure was highly correlated with airborne arsenic exposure, and the effects could not be disentangled. A subsequent investigation assembled workers who were known to be alive in 1964 and followed them through 1977. Again, there was an increasing risk of respiratory cancer with greater inhalation of airborne arsenic exposure, but the association with sulphur dioxide exposure weakened after control for arsenic exposure (20). The original work history data were then supplemented with employment information through 1977, and analyses again confirmed the relation between respiratory cancer and inhaled arsenic exposure (18). In a related analysis, Welch et al. (23) obtained information on smoking for a sample of 1,469 workers from the Lee-Fraumeni cohort and found that smoking did not confound the association between inhaled arsenic exposure and respiratory cancer.

Cohort definition

For this study, we reconstructed the original Lee-Fraumeni cohort. The 8,014 workers in the current analysis differed from the 8,047 workers reported by Lee and Fraumeni (17) because we dropped two subjects identified as females and were unable to locate 31 records. Follow-up started 1 year after initial employment or on January 1, 1938, whichever was later, and continued through December 31, 1989, providing a maximum follow-up of 52 years. Vital status was determined using records from the National Death Index, the Social Security Administration, the Motor Vehicle Administration for Montana and other states, and company records. Causes of death were obtained from death certificates and were coded according to the *International Classification of Diseases*, Eighth Revision (ICD-8) (38). Workers with unknown vital status were assumed to be alive at the end of the study period, except for 81 workers born before 1900, who were assumed to have died of an unknown cause at age 90 years.

Exposure assessment

Estimates of exposure were based on employment records, which provided information on work area, year started, and year ended from the start of employment through September 30, 1977. We did not collect additional work history data for the current investigation; however, there was little loss of exposure information. Among 4,517 workers alive at the beginning of 1978, only 497 workers (11 percent of those alive

and 6 percent of all workers) were employed at the smelter in 1977 (mean age, 55.0 years).

In the 1960s, each work site was ranked on a scale of 1–10 based on its potential for exposure to airborne arsenic and sulphur dioxide. Each work area was classified as a “heavy” (ranks 8–10), “medium” (ranks 4–7), or “light” (ranks 1–3) exposure area for arsenic and for sulphur dioxide. Unspecified or unknown work areas were classified as light-exposure work areas. The link between exposure ranks and airborne arsenic concentration was not known precisely; however, 702 measurements of airborne arsenic, made between 1943 and 1958, were available. These measurements were combined with estimates of workers’ exposure time to create time-weighted average airborne arsenic concentrations of 0.29, 0.58, and 11.3 mg of arsenic per cubic meter (mg/m^3) for areas of light, medium, and heavy arsenic exposure, respectively (39). These values differed from those used by Lee-Feldstein (18) (0.38, 7.03, and 61.99 mg/m^3 for the three levels, respectively), which were not weighted by workers’ exposure times. We created a cumulative exposure index in $\text{mg}/\text{m}^3\text{-year}$, denoted d , as the product of years worked in light (L), medium (M), and heavy (H) exposure areas and the corresponding concentration, i.e., $d = 0.29L + 0.58M + \lambda \times 11.3H$, with $\lambda = 1.0$ (20). Since air filtration masks were available for workers in areas of heavy exposure, particularly in more recent years, a second cumulative exposure index was computed by adjusting the weight for heavy exposure areas to 1.13, i.e., setting λ equal to 0.1. This a priori choice of $\lambda = 0.1$ reflected a maximal reduction of exposure with the use of filtration masks. Although somewhat arbitrary, this value was similar to an empirical, data-derived estimate of λ . Measurement data on sulphur dioxide levels were insufficient to create a quantitative exposure index.

Statistical analysis

We calculated standardized mortality ratios (SMRs) using US population rates as the referent population and the standard Wald confidence intervals (40). We used US mortality rates, rather than state mortality rates, to ensure stability of the rates for rare diseases. For selected cancers, we also computed SMRs based on combined mortality rates from Idaho, Montana, and Wyoming. While SMRs based on the three-state rates were slightly higher, the relation of site-specific SMRs to the SMR for all cancers was similar using the US and the three-state rates. We present only US mortality-based SMRs.

Among the 8,014 workers, 1,616 (20 percent) were under age 30 years, and 1,565 (20 percent) were between aged 30–39 when they stopped working at the smelter. Since there was no information on exposures

TABLE 2. Observed and expected deaths for selected causes and standardized mortality ratios among 8,014 smelter workers, Montana, 1938-1990

Cause (ICD-8* code)	All data			Restricted data†		
	Observed	SMR*	95% CI*	Observed	SMR	95% CI
All causes	5,011‡	1.14	1.11, 1.17	3,125	1.14	1.10, 1.18
All cancers (140-209)	1,010	1.13	1.07, 1.21	599	1.22	1.12, 1.32
Buccal cavity, pharynx (140-149)	26	0.97	0.66, 1.43	15	0.99	0.60, 1.64
Digestive organs and peritoneum (150-159)	250	0.94	0.83, 1.07	153	0.95	0.81, 1.11
Esophagus (150)	17	0.80	0.50, 1.29	9	0.77	0.40, 1.48
Stomach (151)	63	1.16	0.91, 1.49	42	1.10	0.82, 1.49
Liver and biliary tract (155-156)	16	0.82	0.50, 1.33	12	0.94	0.53, 1.65
Pancreas (157)	48	1.02	0.77, 1.36	27	1.04	0.71, 1.51
Respiratory system (160-164)	446	1.55	1.41, 1.70	252	1.83	1.62, 2.07
Larynx (161)	14	1.10	0.65, 1.86	4	0.56	0.21, 1.50
Lung, bronchus, and pleura (162-163)	428	1.58	1.44, 1.74	247	1.91	1.68, 2.16
Skin (172-173)	8	0.53	0.26, 1.06	4	0.51	0.19, 1.37
Prostate (185)	92	1.19	0.97, 1.46	60	1.17	0.91, 1.50
Bladder (188)	37	1.28	0.93, 1.76	27	1.44	0.99, 2.10
Kidney (189)	12	0.57	0.33, 1.01	6	0.55	0.25, 1.23
Hematopoietic and lymphatic cancers (200-209)	52	0.66	0.50, 0.86	31	0.74	0.52, 1.06
Lymphoma (200-201)	11	0.50	0.28, 0.90	6	0.51	0.23, 1.14
Multiple myeloma (203)	5	0.36	0.13, 0.95	2	0.18	0.03, 1.27
Leukemia (204-207)	30	0.88	0.61, 1.26	20	1.06	0.68, 1.64
Other malignant neoplasms	87	0.93	0.75, 1.15	50	1.03	0.78, 1.36
Allergic, endocrine, metabolic, and nutritional diseases (240-279)	68	0.90	0.70, 1.16	34	0.74	0.51, 1.07
Diabetes mellitus (250)	54	0.83	0.63, 1.08	27	0.66	0.45, 0.96
Nervous system and sense organs (320-389)	56	1.31	1.01, 1.70	26	1.08	0.73, 1.58
Circulatory diseases (390-458)	2,378	1.02	0.98, 1.07	1,616	1.09	1.04, 1.15
Arteriosclerosis and CHD* (410-414)	1,574	1.05	0.99, 1.10	1,030	1.15	1.08, 1.22
Vascular lesions of CNS* (430-438)	335	1.03	0.93, 1.15	262	1.12	1.00, 1.27
Nonmalignant respiratory diseases (460-519)	455	1.56	1.42, 2.12	268	1.52	1.35, 1.72
Pneumonia (480-486)	112	1.01	0.84, 1.21	72	0.97	0.77, 1.22
Empysema (492)	93	1.73	1.41, 2.12	53	1.65	1.26, 2.17
Diseases of the digestive system (520-577)	219	1.14	1.00, 1.30	114	1.05	0.88, 1.26
Cirrhosis (571)	102	1.21	1.00, 1.47	36	0.91	0.66, 1.27
Ill-defined conditions and senility (780-799)	97	2.26	1.85, 2.77	60	2.55	1.97, 3.30
External causes (800-998)	416	1.35	1.23, 1.49	210	1.27	1.11, 1.46
Other	213	0.86	0.75, 0.98	130	0.73	0.61, 0.87

* ICD-8, *International Classification of Diseases*, Eighth Revision; SMR, standardized mortality ratio; CI, confidence interval; CHD, coronary heart disease; CNS, central nervous system.

† Data limited to current and former smelter workers last exposed over age 50 years.

‡ In all (restricted) workers, total includes 18 (7) with unknown cause of death and 81 (55) born prior to 1900 and assumed deceased at age 90 years.

Relative risk of respiratory cancer and exposure to airborne arsenic

Results are shown using only the restricted data, which included 252 deaths from respiratory cancer. We first investigated the exposure lag interval, during which inhalation of airborne arsenic was assumed to have no impact on disease outcome. The deviance was similar for all lag intervals between zero and 5 years, and all lag intervals between zero and 10 years were statistically consistent with the data. We set the lag interval to zero for all analyses.

Relative risks for respiratory cancer increased with increasing duration in each arsenic exposure area

(light, medium, and heavy) after adjustment for duration in the other two exposure areas (table 3). For categories of duration 0, 1-4, 5-9, and 10 or more years, relative risks were 1.00, 1.39, 1.30, and 3.01, respectively, for jobs with medium exposure to airborne arsenic and 1.00, 1.11, 1.40, and 3.68, respectively, for jobs with heavy exposure. Relative risks also increased with duration in areas with light exposure to arsenic after adjustment for years in areas with medium and heavy exposure.

A linear excess relative risk model in duration of exposure in each area of arsenic exposure provided good fits to the data after adjustment for duration in the

TABLE 3. Relative risks and 95 percent confidence intervals for respiratory cancer deaths by years of employment in heavy, medium, or light (and unknown) airborne arsenic-exposed work areas, Montana, 1938-1990*

Years exposed	Cases	Person-years	Relative risk	95% CI†	Mean years	Rate × 1,000
<i>Light and unknown airborne arsenic work areas</i>						
1-4	63	39,669	1.00		2.1	1.6
5-14	49	34,197	0.95	0.6, 1.4	9.2	1.4
15-24	39	22,040	1.22	0.8, 1.9	19.4	1.8
25-34	51	15,558	1.86	1.2, 2.9	29.4	3.3
≥ 35	50	9,436	1.98‡	1.3, 3.1	40.5	5.3
Total	252	120,900			13.8	2.1
<i>Medium airborne arsenic work areas</i>						
0	117	67,914	1.00		0.00	1.7
1-4	79	37,232	1.39	1.0, 1.9	1.0	2.1
5-9	12	5,896	1.30	0.7, 2.4	7.0	2.0
≥10	44	9,585	3.01‡	2.0, 4.6	22.5	4.5
Total	252	120,900			5.7§	2.5§
<i>Heavy airborne arsenic work areas</i>						
0	201	103,805	1.00		0.0	2.0
1-4	30	13,211	1.11	0.8, 1.6	0.9	2.3
5-9	4	1,590	1.40	0.5, 3.8	7.3	2.5
≥10	15	2,294	3.68‡	2.1, 6.4	20.7§	6.5§
Total	252	120,900			4.1§	2.9§

* Data limited to current workers and former workers last exposed over age 50 years. All relative risks are adjusted for age, calendar year, work status (current or former), and duration of exposure in the other two exposure categories.

† CI, confidence interval.

‡ Test of trend, adjusted for the other two duration of exposure variables, $p < 0.005$.

§ Computed among exposed.

other two exposure areas (figure 1). Estimates of the excess relative risk per year ((ERR)/year) were 0.04 (95 percent confidence interval (CI): 0.01, 0.08), 0.07 (95 percent CI: 0.04, 0.13), and 0.13 (95 percent CI: 0.05, 0.24) for years in work areas with light, medium, and heavy exposure to arsenic, respectively. Applying a power model to duration in each area of arsenic exposure did not significantly improve fit compared with a linear excess relative risk model. Homogeneity of the three slope parameters was rejected ($p < 0.001$), while homogeneity of the two slope parameters for duration in areas with medium and with heavy exposure to arsenic was not rejected ($p = 0.14$).

Table 4 and figure 2 show increasing relative risks with higher levels of the two cumulative airborne arsenic exposure indices. With $\lambda = 1.0$, the median exposure was 9.7 mg/m³-year, the maximum exposure was 521 mg/m³-year, and linearity in the excess relative risk was rejected. The estimated κ in model 1 was significantly less than one, and $p < 0.001$ for the test of $\kappa = 1$. When work areas with heavy exposure to arsenic were down-weighted by setting $\lambda = 0.1$,

median exposure was 8.5 mg/m³-year, maximum exposure was 52 mg/m³-year, and the relative risks were consistent with a linear excess relative risk model ($p = 0.76$ for test of $\kappa = 1$). For the linear model, the ERR/(mg/m³-year) estimate was 0.21 (95 percent CI: 0.10, 0.46), which was similar to the estimate of 0.18 (95 percent CI: 0.08, 0.41) obtained for $\lambda = 1.0$ and with the data restricted to under 20 mg/m³-year. These results suggested that the curvature in the excess relative risk for the cumulative exposure index with $\lambda = 1.0$ was primarily due to the weight assigned to areas with heavy airborne arsenic exposure. Finally, we estimated both β and λ (which was a factor in the definition of the exposure index). The estimates were 0.20 (95 percent CI: 0.09, 0.45) for β and 0.11 (95 percent CI: 0.06, 0.18) for λ , indicating that our a priori weight of $\lambda = 0.1$ was consistent with the data. Note that the ERR/year estimates for duration of exposure in light, medium, and heavy exposure categories (0.04, 0.07, and 0.13, respectively) had ratios of 1:1.8:3.3, which were very similar to the ratios of 1:2.0:3.9 for the mean airborne arsenic measurements, with $\lambda = 0.1$. This

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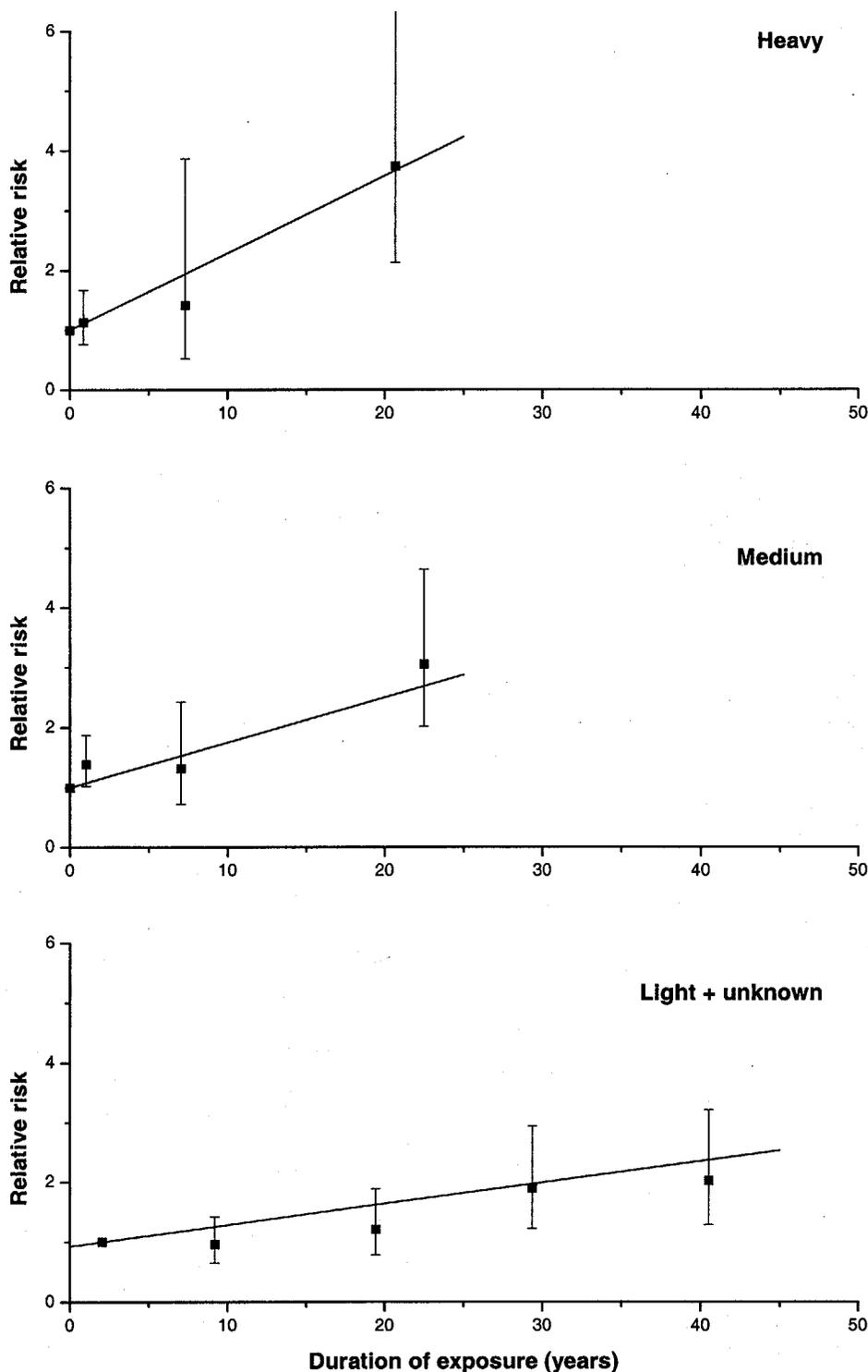


FIGURE 1. Relative risk of respiratory cancer by duration of employment in work areas with light, medium, and heavy exposure to airborne arsenic for current workers and workers aged 50 years or older at last employment in a cohort study of workers at a Montana copper smelter with follow-up from 1938 to 1989.

comparison provided further support for a linear association between inhaled arsenic exposure and respiratory cancer.

We evaluated homogeneity of the linear ERR relation for the cumulative exposure index with $\lambda = 0.1$ for a variety of factors. The $ERR/(mg/m^3\text{-year})$

TABLE 4. Relative risks and 95 percent confidence intervals for respiratory cancer deaths by deciles of cumulative airborne arsenic exposure, Montana, 1938-1990*

Exposure	Weight $\lambda = 0.1$						Weight $\lambda = 1.0$					
	Cases	Person-years	Relative risk	95% CI†	Mean	Rate $\times 1,000$	Cases	Person-years	Relative risk	95% CI†	Mean	Rate $\times 1,000$
I	26	30,130	1.00		1.0	0.9	26	28,098	1.00		0.9	0.9
II	24	28,526	1.10	0.6, 2.0	3.1	0.9	24	26,717	0.99	0.6, 1.8	3.2	0.9
III	25	20,256	1.26	0.7, 2.3	5.8	1.2	25	21,759	1.03	0.6, 1.8	6.4	1.1
IV	26	10,834	1.95	1.1, 3.5	8.0	2.2	26	9,696	2.14	1.2, 3.9	8.7	2.7
V	25	7,093	2.53	1.4, 4.6	9.1	3.6	25	6,106	2.55	1.4, 4.6	9.6	4.1
VI	25	5,971	3.01	1.7, 5.5	10.4	4.3	24	6,253	2.37	1.3, 4.3	11.1	3.8
VII	26	5,709	2.14	1.2, 3.9	11.5	4.0	27	6,446	1.74	1.0, 3.2	12.6	4.2
VIII	25	4,250	2.78	1.5, 5.1	13.0	6.1	25	6,369	3.36	1.9, 6.1	15.8	3.9
IX	25	4,907	3.72	2.0, 6.8	16.7	5.2	25	5,067	2.74	1.5, 5.0	23.2	4.9
X	25	3,194	4.04‡	2.2, 7.4	26.2	7.8	25	4,389	3.96‡	2.2, 7.1	158.4	5.7
Total	252	120,900			6.1	2.1	252	120,900			12.0	2.1

* Cumulative exposure calculated as $0.29 L + 0.58 M + \lambda \times 11.3 H$, where L , M , and H are years worked in areas exposed to light (and unknown), medium, and heavy airborne arsenic, respectively. Multipliers were mean airborne arsenic measurements in mg/m^3 , and λ is a weight for areas of heavy exposure that reflects possible use of protective equipment. Data are limited to current workers and former workers last exposed over age 50 years. All relative risks are adjusted for age, calendar year, and work status (current or former).

† CI, confidence interval.

‡ Test of linear trend, $p < 0.001$.

declined with increasing attained age, time since last exposure, and year of follow-up, but these factors were highly correlated, and analyses could not adequately separate their effects. The ERR/(mg/m^3 -year) did not vary significantly with year first exposed, age first exposed, year of birth, or place of birth.

Respiratory cancer and exposure to airborne arsenic and sulphur dioxide

Table 5 shows relative risks for duration of employment in work areas with heavy and medium arsenic exposure and duration of employment in work areas exposed to heavy and medium sulphur dioxide concentrations adjusted for total duration of employment. Within each sulphur dioxide category, relative risks increased with increasing duration of employment in work areas with heavy and medium arsenic exposure. In contrast, relative risks did not increase with sulphur dioxide exposure within arsenic-exposure categories.

Relative risks of noncancer outcomes and exposure to airborne arsenic

We analyzed relative risks by duration of employment in work areas with light, medium, and heavy arsenic exposure for those causes with statistically elevated SMRs (nonmalignant respiratory diseases, ill-defined conditions and senility, and external causes) among current workers and former workers last exposed at age 50 years and over. In the restricted data, there were 268 deaths from nonmalignant respi-

ratory diseases (ICD-8 codes 460-519). Although the relative risks increased with duration of employment, the gradients of risk were similar for work areas with light (relative risks of 1.00, 1.42, 1.32, and 1.44 for categories 0-4, 5-14, 15-24, and 25 or more years, respectively), medium (relative risks of 1.00, 1.00, and 1.37 for categories 0, 1-4, and >5, respectively), and heavy (relative risks of 1.00, 1.12, and 1.75 for categories of 0, 1-4, and >5 years, respectively) airborne arsenic exposure. The p value for the test of homogeneity was $p = 0.21$, suggesting that the increasing relative risks may have been due to factors other than arsenic exposure. Within the nonmalignant respiratory diseases classification, relative risks for 0, 1-4, and 5 or more years of medium and heavy arsenic exposure were 1.00, 0.84, and 1.04 for pneumonia (ICD-8 codes 480-486; 59 deaths; $p = 0.24$ for test of trend); 1.00, 0.78, and 1.03 for emphysema (ICD-8 code 492; 57 deaths; $p = 0.73$ for test of trend); and 1.00, 1.63, and 3.00 for other respiratory diseases, including chronic obstructive pulmonary disease (ICD-8 code 519; 55 deaths; $p = 0.02$ for test of trend). No other outcome exhibited consistent patterns of higher relative risks with increasing arsenic exposure.

DISCUSSION

In this long-term study of copper smelter workers, we found a linear relation between risk of respiratory cancer and cumulative exposure to airborne arsenic. The linear association with duration of exposure in

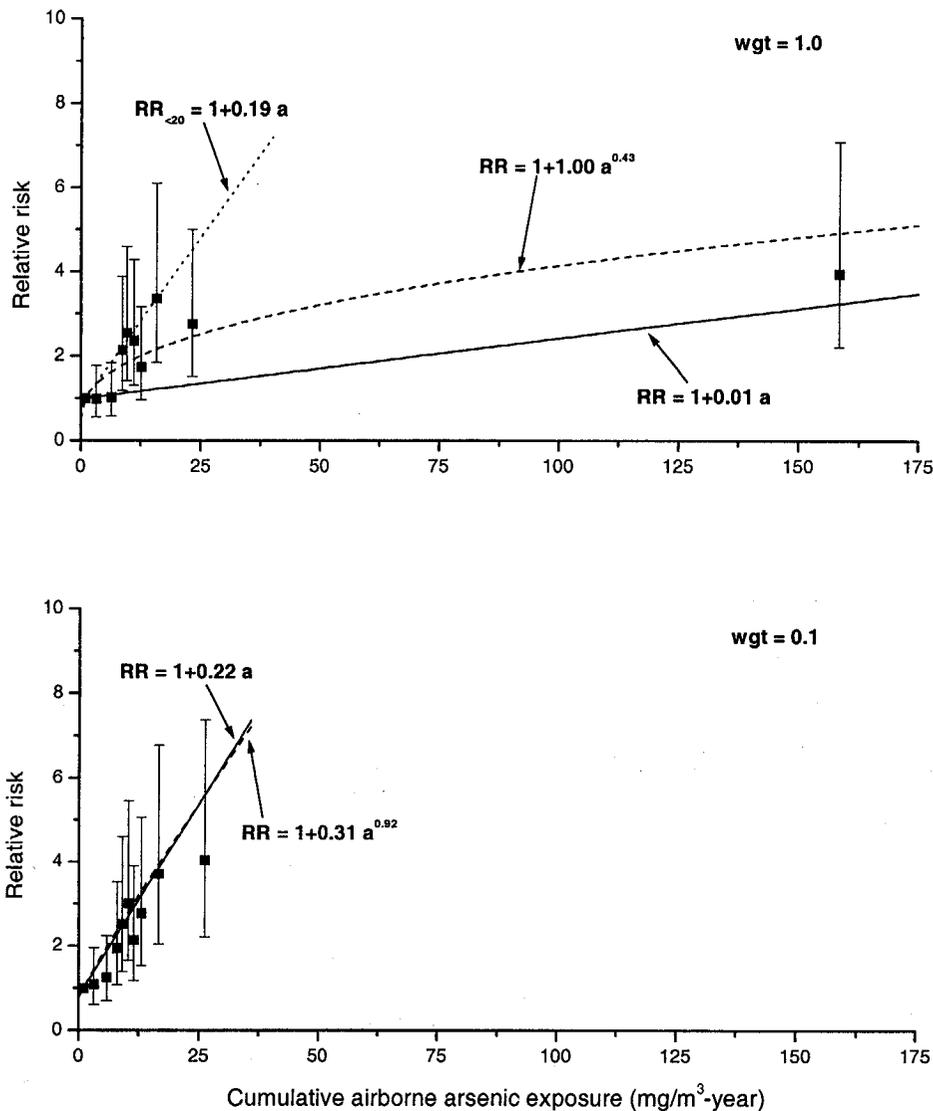


FIGURE 2. Relative risk of respiratory cancer by cumulative airborne arsenic exposure. Wgt, weight given duration in work areas with heavy arsenic exposure in the calculation of cumulative inhaled airborne arsenic exposure. Data from a cohort study of workers at a Montana copper smelter with follow-up from 1938 to 1989.

work areas with light, medium, and heavy exposure to arsenic; the similarity of the ratios of risk estimates for duration of exposure and the mean values of arsenic in air in the three areas; and the linearity of risk with the cumulative arsenic exposure index when duration in work areas with heavy exposure to airborne arsenic was weighted by 0.1 suggest that the concave relation previously reported for these data (1, 20) can be attributed to overweighting the areas with heavy arsenic exposure.

There have been two other detailed analyses of the functional relation of airborne arsenic exposure and respiratory cancer risk using data on individual workers (6, 13). The more detailed of these analyses, using

data from a smelter in Tacoma, Washington, reported a concave relation between lung cancer risk and airborne arsenic exposure, but a linear relation with urinary levels of total arsenic (13, 14). The concave relation with airborne arsenic may represent an artifact of the exposure assessment procedure. Investigators had measurements of airborne arsenic for 11 of 33 departments at the smelter and measurements of urinary arsenic for nearly all workers (14). They computed the arithmetic mean airborne arsenic level, $AM(a_j)$, and the geometric mean urinary arsenic level, $GM(u_j)$, in each of the 11 departments and fitted a power model, $AM(a_j) = \alpha \times GM(u_j)^\beta$, where α and β were unknown parameters and j denoted the j th department. This equation was

TABLE 5. Relative risks and number of respiratory cancer deaths by years of employment in heavy and medium areas of exposure to arsenic and to sulphur dioxide, Montana, 1938-1990†

Years of medium and heavy arsenic exposure	Years of medium and heavy exposure to sulfur dioxide			Total
	0	1-4	≥ 5	
	<i>No.</i>			
0	70	18	8	96
1-4	1	66	11	78
≥5	1	2	73	76
Total	72	86	92	250
	<i>Relative risk‡</i>			
0	1.00	1.25	1.00	1.00
1-4	0.95	1.57	1.42	1.30
≥5	3.39	1.58	1.91	1.79*
Total	1.00	1.21	1.06**	

* *p* value for test of trend = 0.01.

** *p* value for test of trend = 0.31.

† Data are limited to current workers and to former workers last exposed over age 50 years.

‡ All relative risks are adjusted for age, calendar year, work status (current or former), and duration of employment.

then used for each worker to estimate airborne arsenic exposures from urinary arsenic levels.

This approach may have induced bias in the risk estimates. For example, suppose there was a linear relation between airborne arsenic and urinary arsenic for the *i*th individuals in the *j*th department, $a_{ij} = \alpha + \beta \times u_{ij}$; then the induced model at the department level is linear in the arithmetic mean, i.e., $AM(a_{ij}) = \alpha + \beta \times AM(u_{ij})$. In contrast, suppose there was a power relation for individuals, $a_{ij} = \alpha \times u_{ij}^\beta$, then based on a logarithm transformation, the induced model is a power function in the geometric mean, i.e., $GM(a_{ij}) = \alpha \times GM(u_{ij})^\beta$. The regression equation applied to the Tacoma data (14) reflected no obvious antecedent relation between airborne arsenic and urinary arsenic for individuals, and its use may have biased their analysis of risks. This interpretation is supported by data indicating a linear relation between airborne and urinary arsenic (42). For a linear risk model, as in our data, unbiased estimates of the effects of airborne arsenic are obtained using the arithmetic mean (43). For a variable that is approximately log-normally distributed, such as urinary arsenic, the geometric mean underestimates the mean exposure for a department. The convex relation between airborne arsenic and urinary arsenic found by Enterline et al. (14) was probably the consequence of their power model for exposure assessment. For a given urinary arsenic level, the pre-

dicted value overestimated airborne arsenic, thus inducing a concave relation in the regression of SMR on airborne arsenic exposure.

A meta-analysis of published results from six studies concluded that a concave relation existed between respiratory cancer and cumulative airborne arsenic exposure (1). However, this conclusion was strongly influenced by the previous analysis of the Montana data and analysis of the Tacoma data, when, indeed, the exposure-response relations for the individual studies varied substantially in magnitude and shape. The authors proposed several explanations for the non-linearity in the exposure-response: confounding by age, smoking, or other occupational exposure; a non-multiplicative association between airborne arsenic exposure and smoking; a healthy worker survivorship effect; exposure misclassification; or metabolic effects of increased detoxification or decreased potency at higher exposures. While some or all of these factors may have been involved, our analysis found no support for a nonlinear relation.

Inhaled arsenic has been positively correlated with urinary arsenic (13, 42, 44, 45), indicating that respiratory exposure increases systemic levels of arsenic. Since high levels of ingested arsenic in drinking water are linked to high urinary arsenic levels (46-50); to arsenical dermatosis; and to elevated risks of cancers of the skin, bladder, kidney, liver, and lung (26-30, 51), there is concern about a possible relation between inhaled arsenic and cancers at sites other than the lung. Although mortality from skin cancer may have limited relevance in mortality studies, SMR in occupational studies of workers exposed to airborne arsenic were not consistently elevated for any cancer other than respiratory cancer (table 6).

It is unclear why the cancer risk from the inhalation of airborne arsenic in smelter workers is confined to the respiratory tract, whereas the ingestion of arsenic from contaminated drinking water in endemic areas induces a variety of cancers. Using urinary arsenic levels, Bates et al. (51) estimated that heavily exposed Tacoma smelter workers had about half the total arsenic exposure as did Taiwanese who drank water from arsenic-contaminated wells and suggested that the differential cancer risks may reflect variations in cumulative exposure. However, the mean airborne arsenic concentration in our study was 0.36 mg/m³, nearly an order of magnitude higher than that in the Tacoma study (52). Empirical analyses have suggested that inhaled airborne arsenic in mg/m³ results in about a threefold urinary arsenic level in mg/liter (45, 52, 53). Thus, the mean airborne arsenic level in our study was roughly comparable with 1 mg/liter of arsenic in urine. Since 60-75 percent of ingested inorganic arsenic is excreted

TABLE 6. Comparison of standardized mortality ratios for selected causes for several cohort studies of inhaled airborne arsenic, Montana, 1938-1990

Cause	Current, copper smelter		Tacoma, copper smelter (13)		Japan, copper smelter (61)		Sweden, copper smelter (22)		France, gold mines (7)		Yunnan, China, tin mines* (62)	
	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases
All causes	1.1 †	5,011	1.2	1,234	1.0	157	1.2	953	0.8	201	1.1	2,591
All cancers	1.1	1,010	1.4	395	1.9	55	1.4	245	0.9	70	2.4	1,178
Stomach cancer	0.8	17	1.1	18	0.7	10	1.2	88	0.8	4	1.1	32
Liver cancer	0.8	16	0.2	1	1.4	1	1.7	48			1.8	45
Pancreatic cancer	1.0	48	0.9	14	2.7	2						
Respiratory cancer	1.6	446	2.1	188	9.1	29	2.8	79				
Lung cancer	1.6	428	2.1	182	11.9	29	2.9	76	2.1	35	3.1	983
Prostate cancer	1.2	92	1.1	28					0.2	1		
Bladder cancer	1.3	37	0.8	8					0.8	2	0.2	11
Kidney cancer	0.6	12	1.6	11								
Diabetes mellitus	0.8	54	0.9‡	12								
Circulatory diseases	1.0	2,378	0.9‡	412	0.5	7	1.3	488	0.5	43	0.4	47
Nonmalignant respiratory diseases	1.6	455	1.1‡	60					0.5	8		
	Anhui, China, mines (63)		Stokers, Denmark (64)		Arsenic manufacture (65)		Orchardists, males only§ (34)		Arsenic manufacture, males only (32)			
	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases	SMR	No. of cases		
All causes	1.5	814	0.9	366	0.9	214	1.4	336	1.0	197		
All cancers	1.2	278	1.2	136	1.4	64	1.2	—¶	1.2	47		
Stomach cancer	1.3	90							1.7	3		
Liver cancer	1.1	44										
Pancreatic cancer							1.4	—				
Respiratory cancer			1.4	59	2.3	35	0.7	—				
Lung cancer	1.5	60					0.6	—	1.7	23		
Prostate cancer					0.7	2			0.7	1		
Bladder cancer					0.7	1						
Kidney cancer												
Diabetes mellitus			0.8	—								
Circulatory diseases	0.8	142	0.9	166	0.8	96	1.3	—	0.8	82		
Nonmalignant respiratory diseases	3.2	165	1.2	33	1.0	14			1.2	12		

* Using internal analysis, relative risks for high relative to low exposure to airborne arsenic, adjusted for radon progeny exposure.

† Numbers in boldface, statistically significant standardized mortality ratios (SMR).

‡ Values taken from the study by Enterline and Marsh (66).

§ Estimates of the relative hazard from a Cox proportional hazards regression.

¶ —, number of cases not given.

in urine (47), the mean level of inhaled arsenic in our cohort corresponded approximately to long-term ingestion of drinking water with an arsenic level of 1.3-1.7 mg/liter. In endemic areas such as Taiwan, this level of inorganic arsenic in drinking water has been consistently linked to increased risks for cancers of the skin, bladder, kidney, and liver, as well as excess lung cancer mortality (51) that is similar to and possibly exceeds the SMR for respiratory cancer in our study. Moreover, in populations that consumed arsenic-contaminated drinking water, excess risks for lung and liver cancers were substantially lower than risks for bladder, kidney, and skin cancers (51). The reasons for the absence of excess risks of nonrespiratory cancers in smelter workers are uncertain, but it seems likely that the carcinogenic mechanisms associated with inhaled arsenic differ from those related to ingested arsenic (46, 47).

Elevated levels of arsenic in drinking water have also been associated with an increased risk of diabetes mellitus (54, 55) and with peripheral vascular and car-

diovascular disease, but not with cerebrovascular disease (56-58). In contrast, results from occupational studies, including our study, have shown inconsistent associations of inhaled arsenic with diabetes mellitus or circulatory diseases (table 6).

The excess risk of respiratory cancer and chronic obstructive pulmonary disease in our study raises the possibility that use of cigarettes played a role in our results. Although information on smoking was not available, it is noteworthy that mortality from other smoking-related cancers was not excessive. In a sample of 1,469 workers from the original Lee-Fraumeni cohort, there was a higher proportion of smokers compared with US white males. However, the proportion of cigarette smokers did not vary significantly by extent of exposure to airborne arsenic (23, 59), indicating that it was unlikely that smoking confounded the assessment of lung cancer risk with arsenic exposure (60).

The mechanisms of arsenic-induced cancer are unclear, with limited evidence of carcinogenic effects in

experimental animal studies. Using data from the Lee-Fraumeni cohort, Brown and Chu (3) reported a declining risk of respiratory cancer after cessation of employment, suggesting that airborne arsenic acts at a later stage of carcinogenesis, perhaps as a tumor promoter, but they could not rule out an early-stage effect (3). Similar findings were noted in an analysis of the Tacoma data (4). Our updated analysis of the Lee-Fraumeni cohort found a decreasing relative risk with time since last exposure among former workers, a pattern consistent with a late-stage carcinogen or tumor promoter (60).

We found that, using the cumulative exposure index, the ERR/(mg/m³-year) for respiratory cancer declined with calendar year of follow-up. This time trend was not likely due to changes in smoking habits, since cigarette smoking did not appear to be a confounder. Measurements of arsenic in air were available only for the years 1943-1958, and the exposure assessment implicitly assumed that arsenic levels for the light, medium and heavy categories were constant over time. Available monitoring data and anecdotal information indicated that airborne arsenic levels declined over time in work areas with heavy and medium exposures, with lesser reductions of airborne arsenic in work areas with light exposure. These variations in exposure probably accounted at least partly for the significant downward trend in the relative risk for respiratory cancer by year of follow-up. In support of this conclusion, we found that the trend in the relative risks with duration of exposure declined with follow-up for medium and heavy, but not for light, arsenic exposures.

Finally, the risk of respiratory cancer in our updated analysis was found to be linearly related to the cumulative arsenic exposure index with $\lambda = 0.1$. Using this model, adjusting for age, calendar year, current or former employment status, and foreign birth, and assuming a similar effect of airborne arsenic exposure in smokers and nonsmokers, we estimate that the attributable risks for respiratory cancer from inhaled arsenic were 0.60 overall, 0.66 for current workers, and 0.58 for former workers last exposed at age 50 years and older.

In summary, our updated analysis of the Lee-Fraumeni cohort of smelter workers revealed a linear relation between risk of respiratory cancer and cumulative exposure to airborne arsenic. Further, there was no evidence that inhaled arsenic increased mortality from other causes, with the possible exception of chronic obstructive pulmonary disease.

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