Scand J Work Environ Health 1993;19(1):90-94
Issue date: 1993

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/8159982

Print ISSN: 0355-3140 Electronic ISSN: 1795-990X

Scand J Work Environ Health 1993;19 suppl 1:90—4

Lung cancer in smelter workers — interactions of metals as indicated by tissue levels

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GERHARDSSON L, NORDBERG GF. Lung cancer in smelter workers — interactions of metals as indicated by tissue levels. *Scand J Work Environ Health* 1993;19 suppl 1:90—4. The concentrations of the elements antimony, arsenic, cadmium, chromium, cobalt, lanthanum, lead, selenium, and zinc were determined in lung tissue of 85 deceased smelter workers by neutron activation analysis and atomic absorption spectrophotometry. The concentrations of all of these elements, except zinc, were significantly higher among the workers as compared with rural referents. Workers who died from lung cancer (N = 7) had the lowest lung selenium content relative to other metals, both compared with workers with other diseases and with rural (N = 15) and urban (N = 10) referents. The low lung tissue levels may have influenced the development of lung cancer. The highest lung cadmium concentrations were observed in the lung cancer group, in which, however, smokers and ex-smokers were overrepresented. The observations make it likely that the excess lung cancer risk in this smelter environment is multifactorial in character, involving interactions between both carcinogenic and anticarcinogenic factors.

Key terms: antimony, arsenic, biological half-time, cadmium, chromium, cobalt, lanthanum, lead, lung cancer, lung tissue, selenium, smelter workers, zinc.

In the early 1930s, the disease pattern among smelter workers at the Boliden Mineral Company was dominated by bronchitis, tracheitis, ulcers, laryngitis, perforations of the nasal septum, rhinitis, and dermatitis. In 1951, Lundgren et al (1), in an extensive medical study of 1459 workers, defined a disease at the smelter which they called "Morbus Rönnskär." This disease was characterized by chronic rhino-pharyngeo-tracheo-bronchitis with atrophy of the mucous membranes in the respiratory passages and secretions of thick mucus, emphysema, and impaired pulmonary function. Arsenic trioxide and sulfur dioxide were supposed to be the most important etiologic factors.

Between 1932 and 1948, workers took sick leave because of arsenic dermatitis on a total of 1462 occasions. In 1951, the Company's occupational health physician, Holmqvist (2), analyzed the skin changes, which were either of the eczematous type with erythema, swelling, and papules or vesicles, or of the follicular type with erythema and follicular swelling or follicular pustules.

The first lung cancer cases were reported by the same occupational health physician in the 1960s. In a case-referent study in 1978, Axelson et al (3) found a fivefold increase in lung cancer as compared with the rate among the general population. In a cohort study in 1980, Wall (4) reported a threefold increase in lung cancer as compared with that of the general population and a fivefold increase as compared with that of local populations.

Dust sampling at fixed sampling stations has been carried out since the early 1940s and gradually extended. In the late 1940s, arsenic concentrations ranged from 0.35 to 1.5 mg · m^{-3} at the roasters but decreased to <0.1 mg · m^{-3} in the 1970s. Corresponding sulfur dioxide levels ranged from 70 to 560 (mean 220) mg · m^{-3}. The sulfur dioxide levels in 1945 were approximately 20 times higher than during the period 1958—1964. Airborne lead levels sometimes exceeded 1 mg · m^{-3} at the lead plant in the 1940s.

Environmental monitoring at the smelter has shown that the workers are particularly exposed to high lead levels at the roasters and copper smelting furnace and in the converter hall and the lead plant. There is massive exposure to arsenic at the roasters, the copper smelting furnace, and electrostatic precipitators and in the arsenic plant. Selenium was a major air pollutant at both the precious-metal plant and the selenium plant. Exposure to sulfur dioxide was particularly high at the roasters and the copper smelting furnace and in the sulfuric acid plant.

Determinations of antimony, cadmium, and zinc gave no clear picture of exposure. The levels seem to have been below or up to the occupational exposure limits in force at the time.

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Materials and methods

Lung tissue concentrations of antimony, arsenic, cadmium, chromium, cobalt, lanthanum, lead, selenium, and zinc were determined in 85 deceased male smelter workers and compared with those of 15 rural and 10 urban referents. One reference group was randomly selected from a rural area with living conditions similar to those of the workers but at a distance of about 50 km from the smelter so that the exposure from it could be neglected. The other group was taken from a densely populated urban area, namely, the city of Stockholm (800 km from the smelter), with elevated levels of air pollutants.

The collection of material was started in the late 1970s. Consecutive autopsies of workers and rural referents selected irrespective of diagnosis were undertaken at the County Hospital, Skellefteå, by a single technician. The autopsies of the urban referents were all performed at the State Institute of Forensic Medicine, Stockholm.

Samples of about 2 g of wet weight were taken from the lower part of the upper lobe of the right lung. Quartz instruments were used to avoid contamination. The samples were transferred to quartz ampules and freeze-dried. Before irradiation, the ampules were flame sealed.

The time of employment and the occupations at the smelter were obtained from the Company, and smoking history was collected by means of questionnaires completed by the workers' relatives, supplemented by telephone interviews.

The analytical laboratories available for this study all had a high reputation and were well equipped for scientific work. As the study extended over several years, it was not possible to use only a single laboratory. Zinc and lead were determined by atomic absorption spectrophotometry, and all of the other elements by neutron activation analysis. A detailed description of the analytical techniques used has been given elsewhere (5).

A precision of ±10% was estimated for all of the measurements by atomic absorption spectrophotometry and neutron activation analysis in this investigation. All of the laboratories involved had their own quality-control programs. The accuracy differed somewhat between the metals, but the results were within the required ranges for certified reference materials (5).

Computer tests confirmed that none of the nine metals in the study had a Gaussian distribution, the skewness remaining even after logarithmic transformation. Nonparametric statistical methods were therefore applied, such as the Kruskal-Wallis one-way analysis of variance and Mann Whitney's U-test.

The workers were subdivided into the following six groups according to the diagnoses in the autopsy protocols: (i) lung cancer (N = 7), (ii) gastrointestinal cancer (N = 11), (iii) other cancers (N = 8), (iv) cardiovascular diseases (N = 46), (v) cerebrovascular diseases (N = 8), and (vi) other causes (N = 5).

Results

No significant differences were found in the mean age between the different groups of the smelter workers and the referents (range 66—71 years). The duration of exposure (range 26—32 years) and length of retirement (range 6—11 years) did not differ significantly between the different groups of workers.

About 50% of the workers died from cardiovascular diseases and about one-third from malignancies (8—9% from lung cancer and 13—14% from gastrointestinal cancer). Deaths from cardiovascular diseases predominated in the two reference groups, accounting for 75% in the rural group and 100% in the urban group.

The lung tissue concentrations of antimony, arsenic, cadmium, chromium, cobalt, lanthanum, lead, and selenium were significantly higher for all of the workers as compared with the corresponding concentrations of the rural reference group ($P \leq 0.027$) (table 1). Compared with the urban reference group, the smelter workers had significantly higher lung tissue concentrations of antimony, arsenic, and lead ($P \leq 0.001$). The highest ratio, about 11-fold, was found for antimony in smelter workers when they were compared with unexposed referents (6). A six-fold increase was seen for arsenic.

The lung tissue levels of cadmium were significantly higher in the lung cancer group than in the other groups of workers and rural referents (7). The lung tissue concentrations of selenium in the lung cancer group were significantly lower than those in the lungs of workers who died from cardiovascular diseases ($P < 0.04$), and numerically lower than those in the other groups (8). For the other metals covered by the study, no significant differences were seen between the different groups of smelter workers. However, several of the lung cancer cases also had high lung tissue concentrations of antimony, arsenic, cadmium, lanthanum, and lead; in fact, the highest concentrations of these elements were found in these cases.

Among the workers, the lung tissue concentrations of certain metals (eg, antimony and cobalt) did not decline with time after the exposure had ended. This finding indicates that these metals have a long biological half-time (6, 9).

The ratios between the lung tissue concentrations of the metals studied and the selenium concentrations were used for comparisons between the groups (table 2). A high ratio corresponded to a low content of selenium relative to the concentrations of the other metals and indicated a low protective potential of selenium. The ratios between the lung tissue concentrations of antimony, arsenic, cadmium, lanthanum, lead, chromium, and cobalt and that of selenium were all numerically greater in the lung cancer cases. The ratios for the first five metals were significantly high-

Table 1. Median values of metals in lung tissues of smelter workers and referents. Zinc values in parts per million (mg · kg wet weight^{-1}); all other values in parts per billion (µg · kg wet weight^{-1}).[a]

Group	Element								
	Antimony	Arsenic	Cadmium	Chromium	Cobalt	Lantharum	Lead	Selenium	Zinc
Lung cancer (N = 7)	450	40	390	330	15	6.5	320	71	13.7
Gastrointestinal cancer (N = 11)	376	51	76	470	23	8.4	140	123	11.6
Other cancers (N = 8)	480	49	63	650	21	12.8	197	175	10.6
Cardiovascular diseases (N = 46)	181	34	246	400	16	11.0	141	159	10.9
Cerebrovascular diseases (N = 8)	355	40	114	455	16	8.4	151	142	12.0
Other causes (N = 5)	100	29	108	400	15	6.2	130	215	10.0
All smelter workers (N = 85)	280	38	162	410	16	10.1	140	151	11.5
Rural referents (N = 15)	32	7	39	110	7	5.0	55	110	10.2
Urban referents (N = 10)	19	5	79	199	11	10.0	39	136	12.2

[a] For the statistically significant differences between the various groups, see the text.

Table 2. Median values of element ratios in lung tissues of smelter workers and referents.

Group	Antimony : selenium	Arsenic : selenium	Cadmium : selenium	Chromium : selenium	Cobalt : selenium	Lantharum : selenium	Lead : selenium
Lung cancer	4.53	0.87	8.09	5.15	0.21	0.21	2.28
Gastrointestinal cancer	3.27	0.38	0.76	4.09	0.20	0.07	1.10
Other cancers	2.43	0.26	0.51	3.20	0.09	0.07	0.79
Cardiovascular diseases	1.06	0.19	1.40	1.66	0.10	0.06	0.81
Cerebrovascular diseases	1.92	0.25	0.85	4.82	0.11	0.04	0.83
Other causes	0.47	0.12	0.61	1.86	0.08	0.03	0.56
All smelter workers	1.59	0.23	1.30	2.41	0.10	0.07	0.83
Rural referents	0.29	0.05	0.34	0.88	0.05	0.05	0.58
Urban referents	0.20	0.04	0.70	1.65	0.09	0.08	0.25

er ($P<0.05$) in 27 of 35 comparisons between the lung cancer group and all other groups of smelter workers and referents, corresponding to a low protective potential for selenium (8).

The lung tissue concentrations of the metals did not differ significantly between the smokers, exsmokers and nonsmokers among the workers, with the exception of that of cadmium, which was significantly elevated among the smokers ($P<0.001$) (7).

Discussion

The studied metals are present in the form of sulfides and oxides in the airborne dust at the Rönnskär smelter. These compounds have a low solubility in water. The solubility in the mucous secretion of the respiratory tract, pH around 7.3—7.4, and further down in the alveolar regions of the lungs may be of the same magnitude. These poorly soluble compounds can be expected to have a long residence time in the lungs.

The lung cancer group had the lowest lung selenium concentrations relative to the concentrations of other metals, as compared both with workers dying from other causes and with the two reference groups. The two lowest lung selenium concentrations of all were found in the lung cancer group. Our findings are thus in agreement with those of several animal experiments which showed an anticarcinogenic effect for selenium (10, 11).

Decreased age-specific cancer death rates have been reported from geographic areas with high selenium levels in blood and forage crops (12, 13). A protective effect of selenium has also been suggested in several epidemiologic studies (14, 15), while others have failed to find such an effect.

Low selenium levels may be due to low total intake or increased excretion or to a combination of both. Individual differences in lung elimination may contribute to low selenium levels. A retrospective evaluation of the work histories of the seven workers who died from lung cancer showed that at least five of them had worked at worksites where selenium

was processed or passed through on its way to the selenium plant. Thus a low selenium intake would not be expected.

It is not clear whether lung selenium levels play a causal or pathogenetic role in the development of lung cancer or whether they are a result of the disease. Workers who died from gastrointestinal and other malignancies had approximately the same selenium levels as those found in workers dying from other diseases. These groups must have had at least the same difficulties in consuming food and drink as the lung cancer patients during their final months.

Significantly higher lung cadmium levels were noted in the lung cancer group as compared with the other groups. Smoking frequency was higher in this group, and smoking is a source of cadmium.

It is conceivable that the statistically significant increase in the lung tissue levels of arsenic and chromium among the lung cancer cases contributed to the development of the disease. It is of interest that, in a recent epidemiologic study of arsenic at the smelter, there was an increased risk (standardized mortality ratio 271—1137) of lung cancer which was correlated with the inhaled cumulative arsenic dose. A dose-response relationship was observed only for high arsenic exposures, 15—>100 mg · years^{-1} · m^{-3}, while there was an increased standardized mortality ratio (271—360) which was unrelated to exposure at exposures varying from <0.25 to 15 mg · years^{-1} · m^{-3} (16). It can be speculated that the increased risk found at low exposure levels may be due to metals other than arsenic. In this context, antimony, cadmium, cobalt, and lead, which are suspected carcinogens, may be of interest.

Cobalt is also considered to be an etiologic agent in the development of hard-metal pneumoconiosis (17). Furthermore, antimony exposure may give rise to a picture resembling pneumoconiosis on lung radiographs (18). Long-term inhalation of animals exposed to mixtures of lanthanides high in fluorides may lead to emphysema and chemical bronchitis (19). Concomitant exposure to these metals may further reduce the protective potential of the lung, while interactions can occur which may increase the lung toxicity of the metals concerned. Zinc, which was not increased in the lung tissue of the exposed workers, may also interact with the other metals, eg, by counteracting some of the toxic effects of cadmium.

Lead concentrations in bone, which are an indicator of long-term lead exposure in humans, can be useful in examining possible relationships between lead exposure and cancer. Studies of such concentrations have recently been performed at the smelter (20, 21).

The calculation of correlation coefficients failed to throw any further light on the relationships. The limited population size, varying exposure times, and differences in the duration of retirement among the workers, as well as interindividual differences in metabolism, make evaluation difficult. Furthermore, most of the workers had worked at several different worksites, with varying metal concentrations in the air, over the years.

As would be expected, the tissue concentrations of the metals increased with age and exposure time up to pensionable age among the workers. Thereafter a slow decline with time was seen in the tissue concentrations of the metals in the lung. There was some variation in the pattern as a consequence of some of the factors already discussed.

A multivariate discriminant analysis was also undertaken, but it yielded no further information. No specific pattern was apparent for the lung tissue concentrations when the workers were subdivided according to their main worksite. However, as mentioned earlier, the exposure was mixed. Forty-eight percent of the workers had been working at one to three worksites during their period of employment, 38% at four to six worksites, 11% at seven to nine worksites, and 3% at 10 or more worksites.

Concluding remarks

The results of this study support the view that the cause of lung cancer among smelter workers is multifactorial in character. The high frequency of smoking in the lung cancer group probably played the major role, but high levels of antimony, arsenic, cadmium, chromium, and several other metals may also have contributed to varying extents. Comparatively low levels of selenium indicate reduced protection against the disease. The smelter workers were also exposed to gases such as sulfur dioxide, which are powerful irritants. Some air pollutants are of organic origin (eg, polycyclic hydrocarbons such as benzo[a]pyrene). Of the interactions that may occur, some may increase the carcinogenic risks.

In this retrospective study a long latency period for the development of lung cancer was demonstrated. Cancer cases diagnosed after retirement were not normally covered by any system of occupational health services. This study shows the need both for systematic health surveillance during the workers' active years and for follow-up after retirement.

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