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LUNG CANCER MORTALITY AMONG MEN LIVING NEAR AN ARSENIC-EMITTING SMELTER[1]

GÖRAN PERSHAGEN

Pershagen, G. (National Institute of Environmental Medicine and Dept. of Environmental Hygiene, Karolinska Institute, S-10401 Stockholm, Sweden). Lung cancer mortality among men living near an arsenic-emitting smelter. *Am J Epidemiol* 1985;122:684–94.

Etiologic factors for lung cancer were studied by the case-control technique among 636 men, including 212 with pulmonary carcinoma, who had died between 1961 and 1979 in a county in northern Sweden. Data on smoking habits, occupation, and residence were obtained from a next of kin to each study subject. Validation against data from other sources indicated that the exposure information was of high quality. A relative risk of 2.0 for lung cancer was seen among men who had lived within approximately 20 km from a large copper smelter. The increased risk, which is statistically significant ($p < 0.05$), could not be explained by smoking habits or occupational background. Smelter workers and miners had relative risks for lung cancer of 3.0 and 4.1, respectively. No firm conclusions can be drawn on the cause of excess lung cancer risk in the smelter area, but it seems plausible that the very substantial emissions to air from the smelter, especially of arsenic, may have played a role.

air pollution; arsenic; lung neoplasms; metallurgy; mining

Exposure to inorganic arsenic compounds can increase the risk of lung cancer among smelter workers and workers engaged in the production and use of arsenic-containing pesticides (1–7). The data often show positive dose-response relationships. A recent study on experimental animals confirms the pulmonary carcinogenicity of inorganic arsenic (8).

Some investigations on populations living near copper smelters and other point emission sources of arsenic to air have revealed moderate increases in lung cancer mortality (9–12). Other studies have failed to detect an effect in such situations (13, 14). No detailed exposure data were given in the studies, which makes it difficult to evaluate the findings. Furthermore, there was no adequate control of possibly important confounding factors, e.g., smoking habits and various occupational exposures.

A major arsenic-producing smelter is located in northern Sweden. Several studies have shown severe health effects among workers, e.g., a high prevalence of occupational dermatitis and chronic pulmonary disease as well as an increased mortality from cardiovascular disease and lung cancer (15–18). Inorganic arsenic is probably of etiologic importance for most of these effects. Although the emissions from the smelter have been substantial during sev-

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From the National Institute of Environmental Medicine and Department of Environmental Hygiene, Karolinska Institute, S-10401 Stockholm, Sweden.

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eral decades, a pilot study on cause-specific mortality in the area near the smelter showed no effects other than an increased mortality from lung cancer among men (19). The excess mortality was no longer statistically significant when the smelter workers were excluded, although a tendency remained. Only a crude picture of the effects among subjects not employed at the smelter was given in this study, and no information was available on smoking habits or other exposures of importance for lung cancer.

The purpose of this investigation was to study etiologic factors for lung cancer among men living near the Swedish smelter, in particular those effects related to community exposure. The study design made it possible to control for various confounders in the assessment of risks associated with different exposure factors as well as to evaluate interactions between these factors.

Materials and methods

Study area

The Rönnskärsverken smelter is located at the tip of a peninsula on the Gulf of Bothnia in northern Sweden (figure 1). Operations were started in 1930. Ores with a high content of arsenic have been used in the production of copper, lead, zinc, and other metals. The smelter has been one of the major producers of arsenic products in the world for several decades (20).

The smelter operations have resulted in substantial emissions of various metals and of sulfur dioxide. During the period 1930–1950, the yearly arsenic emissions to air amounted to several hundred tons (19). In recent years, the emissions of arsenic to air have decreased to less than 50 tons a year (20). Other metals which have been emitted to air in large amounts include copper, lead, and zinc.

Measurements of metal concentrations in suspended dust have been made at several stations up to 7 km from the smelter since the late 1960s. The ambient air levels of arsenic and lead were mostly below 0.5 $\mu g/m^3$ as a monthly average; however, a few values exceeded 1 $\mu g/m^3$. No measurement data are available for the time periods when the smelter emissions were highest.

Analyses of metals in soil and plants show that dust fallout primarily takes place within 10–20 km from the smelter (21). With this information and the prevailing wind directions (north-south), two parishes near the smelter were chosen as the exposed area. The remaining part of the county to which these parishes belong constituted the reference area. Both the exposed and reference areas are sparsely populated with scattered villages, but they also contain some urban districts (figure 1). From the 1975 national census, it may be estimated that about 70–80 per cent of the population in the two areas live in villages and towns.

Source of subjects

The study was performed according to the case-control (case-referent) technique with a methodology similar to the one used by Pershagen (5). The cases constituted men who had died between 1961 and 1979 in the study area, i.e., the county containing both the exposed and reference areas, with a diagnosis of carcinoma of the bronchus, lung, or pleura. A total of 215 cases were identified from the National Register on Causes of Death. This register contains information from the death certificate and is of high validity for most diagnoses (22). An additional six cases were identified from a regional cancer register. These men had died from causes other than their pulmonary carcinoma. Of the 221 cases identified, 172 (77.8 per cent) were histologically confirmed and 20 (9.1 per cent) cytologically confirmed, while in 29 (13.1 per cent), the diagnosis was based on clinical and radiologic evidence.

Deceased controls were chosen in order to obtain comparable exposure information by questionnaire for cases and controls (see below). Controls were extracted from the

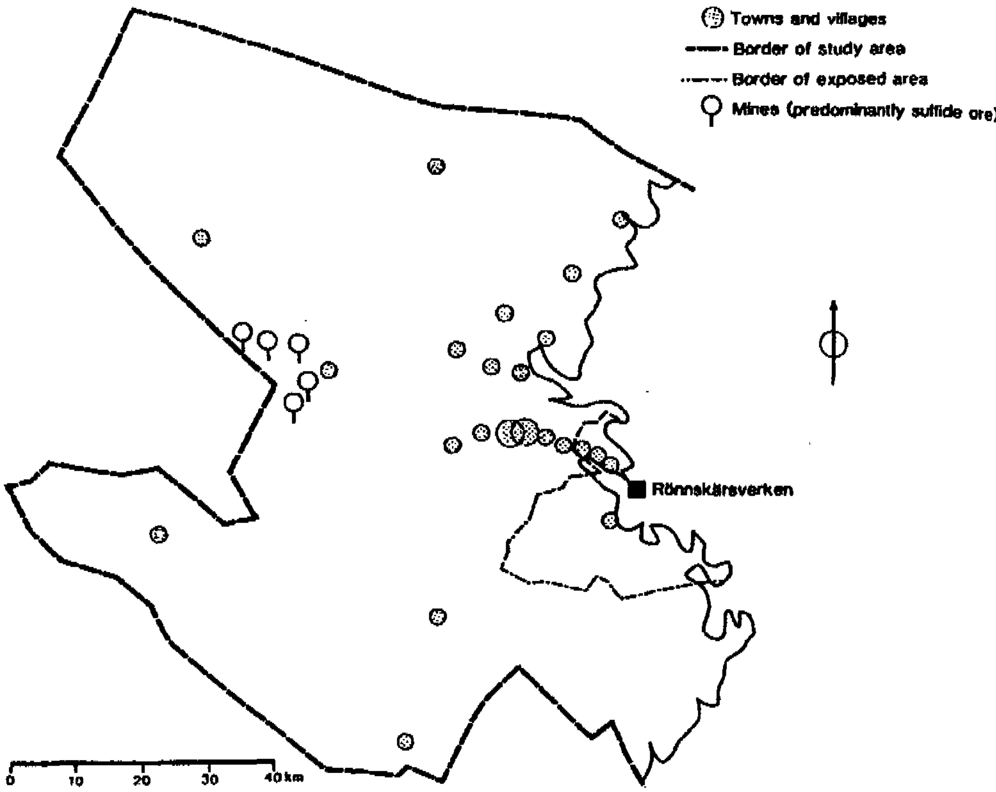


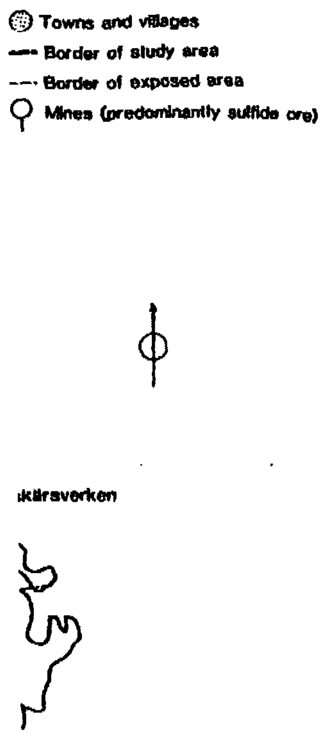
FIGURE 1. Map of the Rönnskärsverken smelter and the exposed area as well as mines, towns, and villages in the study area.

National Register on Causes of Death among men who had died in the study area during the same time period as the cases but without a diagnosis of carcinoma of the bronchus, lung, or pleura. Two controls were randomly chosen for each case among those who were born the same year as a case.

Source of exposure information

Information on occupation, smoking habits, and home addresses during the whole life span of each case and control was obtained by a questionnaire mailed in 1982 to a next of kin. Additional information was gathered by telephone interview, e.g., when questionnaire answers were incomplete. A similar methodology has been shown to provide data of high quality (23, 24). The questionnaire information on home addresses and employment at the Rönnskärsverken smelter was validated by comparison with data from parish registers and company records, respectively.

It was possible to obtain questionnaire information for 212 (96 per cent) of the 221 cases and for 386 (91 per cent) of their 424 matched controls. Those controls for whom questionnaire data could not be obtained were replaced by new controls, selected according to the original criteria. A detailed comparison of age, cause of death, and parish at time of death (from the death certificate) did not reveal any differences between controls who were replaced and new controls. Thus, questionnaire information was available for a total of 212 cases and 424 matched controls. This constituted the study group.



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For subjects other than workers at the Rönnskärsverken smelter, the "main occupation" according to the questionnaire answers has been used in the analysis. The duration of the main occupation was at least five years for all such subjects. Employees at the Rönnskärsverken smelter were classified as smelter workers irrespective of the duration of employment, using questionnaire as well as company record data.

Subjects who had lived in either of two parishes close to the Rönnskärsverken smelter (figure 1), and who were not miners or smelter employees, were classified as exposed. It was not possible to obtain data from parish registers for one of these parishes until 1961, and consequently the classification is based on questionnaire information only.

The questionnaire information on smoking habits included age at start of smoking, daily consumption of cigarettes and/or pipe tobacco, and age at which the subject stopped smoking (when applicable). Subjects who had never smoked as well as those who had stopped at least 15 years before time of death were classified as nonsmokers and the remainder as smokers.

Statistical methods

The data analyses were performed according to the methods described by Mantel and Haenszel (25) and Miettinen (26). Interactions between exposure factors have been evaluated with the method suggested by Walker (27). The correlation coefficient within the matched triplets of cases and controls was low, i.e., less than 0.1, for the exposure categories used to assess community exposure effects. This shows that year of birth was of no significant importance as a confounding factor, and thus the matching was abandoned in further analyses.

RESULTS

Tables 1 and 2 compare the questionnaire data on employment at the Rönnskärsverken smelter and residence in one of the parishes near the smelter with similar information from company records and parish registers, respectively. The questionnaire data on smelter employment had a sensitivity of 92 per cent and a specificity of 99 per cent. There was no difference in the sensitivity or specificity between cases and controls (not shown). In the following analyses, all 121 subjects who were reported as employees at the Rönnskärsverken smelter in the questionnaires and/or company records were classified as such. There were strong indications that the six men who were reported as Rönnskär employees in the questionnaires, but who were not found in the company records, had actually worked at the smelter on a contract basis.

The questionnaire data on residence in one of the parishes near the smelter had a

TABLE 1

Comparison of data on employment at the Rönnskärsverken smelter: questionnaire vs. company records

Questionnaire*	Company records: Employed at smelter, Yes	Company records: Employed at smelter, No	Company records: Total
Employed at smelter			
Yes	106	6	112
No	9	515	524
Total	115	521	636

* Sensitivity: 106/115 = 0.92; specificity: 515/521 = 0.99.

TABLE 2

Comparison of data on residence in a parish in the exposed area: questionnaire vs. parish registers

Questionnaire*	Parish registers: Residence in parish, Yes	Parish registers: Residence in parish, No	Parish registers: Total
Residence in parish			
Yes	48	10	58
No	9	517	526
Total	57	527	584

* Sensitivity: 48/57 = 0.84; specificity: 517/527 = 0.98.

TABLE 3

Distribution of smoking habits, residence in the exposed area, and mining and smelter work among cases and controls

Age (years) and subjects	Nonsmokers				Smokers			
	Reference area*	Exposed area*	Miners	Smelter workers	Reference area*	Exposed area*	Miners	Smelter workers
36–65								
Cases	1	0	0	3	34	9	5	24
Controls	43	8	3	13	59	8	3	18
66–75								
Cases	5	2	3	5	36	18	4	24
Controls	63	10	1	10	56	12	1	14
76–95								
Cases	5	2	0	2	15	11	0	4
Controls	47	7	0	1	33	10	1	3
Total								
Cases	11	4	3	10	85	38	9	52
Controls	153	25	4	24	148	30	5	35
Relative risk†	(1)	2.3‡	10.4‡	8.4	8.3	17.5	35.2‡	26.2
95% confidence interval§		0.7–7.6	2.7–40.2	3.2–21.9	4.5–15.4	8.9–34.4	12.2–102.0	12.7–53.9
Relative risk among smokers†					(1)	2.2	3.1‡	2.5
95% confidence interval§						1.3–3.9	1.1–9.3	1.5–4.2

* Miners and smelter workers excluded.
† Computed by the Mantel-Haenszel method (25).
‡ Aggregation of strata with zero cases or controls.
§ Estimated according to Miettinen (26).

sensitivity and specificity of 84 and 98 per cent, respectively (table 2). The comparison has been limited to those men for whom a complete lifetime residence history could be obtained from the parish registers. No meaningful analysis of residence data could be performed for the other parish in the exposed area (see "Source of exposure information").

Table 3 shows the distribution of smoking habits, residence in the exposed area, and mining and smelter work among cases and controls. The smelter workers and miners are analyzed separately, and these two categories are not included in the table among the residents in the exposed and reference areas. There is a relative risk of about 2 for lung cancer among both nonsmokers and smokers in the exposed area in comparison with nonsmokers and smokers in the reference area. Only the excess risk among smokers is statistically significant (the lower limit of the 95 per cent confidence interval exceeds 1.0). The relative risks for miners and smelter employees are increased both among nonsmokers and smokers. There is close to a multiplicative interaction between residence in the exposed area and smoking, with a relative risk for lung cancer of 17.5 among smokers in the exposed area. This interaction significantly exceeds an additive effect between the two factors upon statistical testing ($p < 0.05$).

There are differences in the occupational distribution between subjects in the exposed and reference areas. Figure 2 shows the occupational distribution among con-

d smelter work

kers	
Miners	Smelter workers
5	24
3	18
4	24
1	14
0	4
1	3
9	52
5	35
35.2‡	26.2
12.2–102.0	12.7–53.9
3.1‡	2.5
1.1–9.3	1.5–4.2

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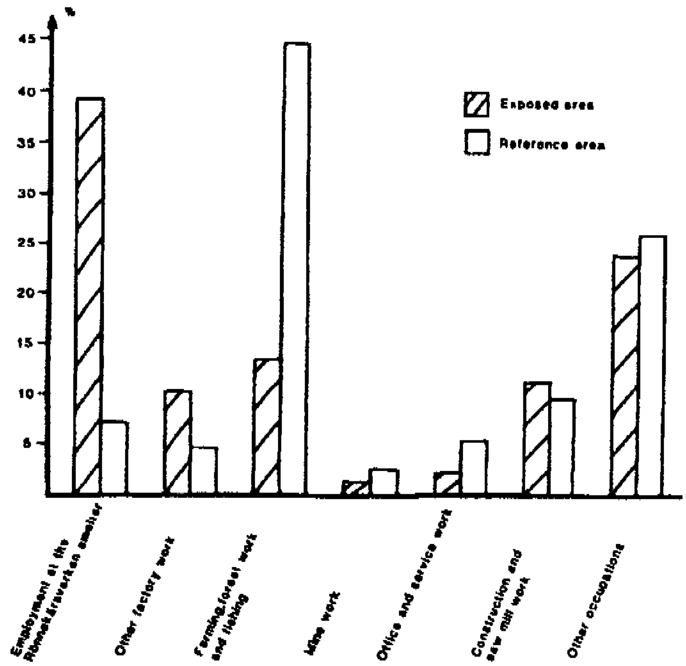

FIGURE 2. Occupational distribution among controls in the exposed and reference areas.

TABLE 4

Age- and smoking-standardized relative risks associated with residence in the exposed area near the smelter, as well as with mining and smelter work

Exposure group	Relative risk*	95% confidence interval†
Residence in exposed area‡	2.0§	1.2–3.4
Miners	4.1§	1.7–9.7
Smelter workers	3.0	2.0–4.7

* Computed by the Mantel-Haenszel method (25).

† Estimated according to Miettinen (26).

‡ Standardization for occupational groups as in figure 2 in addition to standardization for age and smoking habits. Miners and smelter workers excluded.

§ Aggregation of strata with zero cases or controls.

trols in the two areas. This can be expected to reflect the situation in the population from which the cases originate. The fraction of smelter workers is higher in the exposed area than in the reference area (38.2 and 7.0 per cent, respectively). The opposite is seen for farmers, forest workers, and fishermen, who are more common in the reference area (44.8 per cent) than in the exposed area (13.5 per cent). No other pronounced differences are obvious between the areas. Taken as a whole, the data indicate that occupational distribution should be considered when comparing lung cancer risks in the two areas.

Table 4 shows age- and smoking-standardized relative risks for lung cancer associated with residence in the exposed area as well as for miners and smelter workers. The relative risk for residence in the exposed area is also standardized for occupation according to figure 2. Men in the exposed area have a relative risk of 2.0 for lung cancer (95 per cent confidence interval 1.2–3.4) in comparison with those who had never lived in the area. There were tendencies toward increased lung cancer risks within all occupational groups in the exposed area (not shown). Table 4 shows that the relative risks for lung cancer are increased both for miners and smelter workers (4.1 and 3.0, respectively).

TABLE 5

Tobacco consumption among smokers in the exposed and reference areas as well as for miners and smelter workers

Exposure group and subjects	No. of subjects	Tobacco consumption (g/day)*	
		Mean	Standard deviation
Reference area			
Cases	75	16.0†	11.7
Controls	110	11.6	9.2
Exposed area			
Cases	34	13.9	10.0
Controls	29	12.3	7.1
Miners and smelter workers			
Cases	52	12.3	10.1
Controls	36	12.6	9.8

* Computed by adding cigarettes (assuming 1 g of tobacco/cigarette) and pipe tobacco.

† Higher than in controls ($p < 0.05$).

TABLE 6

Housing characteristics for controls in the exposed and reference areas as well as for miners and smelter workers

Exposure group	No. of subjects	Type of house for 25 years or more (%)			
		Wooden	Material other than wood	One or two stories with basement	Three or more stories
Reference area	279	86.4	4.3	13.3	2.9
Exposed area	51	82.4	5.9	5.9	3.9
Miners and smelter workers	64	82.8	4.7	31.3*	4.7

* Higher than in the other exposure groups ($p < 0.05$).

Table 5 gives the average daily tobacco consumption among smokers in the exposed and reference areas as well as in a combined group of miners and smelter workers. It was possible to obtain detailed information on use of cigarettes and pipe tobacco for 84 per cent of the smokers, and these are included in the table. There is a higher tobacco consumption among cases than among controls in the exposed ($p > 0.05$) and reference ($p < 0.05$) areas. The average daily tobacco consumption among smokers in the study group is about 13 g, including both cigarettes and pipe tobacco. There is a tendency toward a higher daily tobacco consumption among cases in the reference area than in the other groups, while a reverse situation is seen among controls. No meaningful analysis was possible of cumulative tobacco consumption because of insufficient information on age at start of smoking.

Table 6 shows some housing characteristics for controls which are of importance for the indoor levels of radon and radon daughters (28). Relevant data for time periods longer than 25 years could be obtained in 90 per cent of the subjects. About 80–85 per cent of the subjects in all exposure groups had lived in wooden houses for 25 years or more. Similarly, no pronounced differences between the groups are seen either for living in houses of material other than wood or with at least three stories. A higher fraction of miners and smelter workers had lived in one- or two-story houses with a basement than the subjects in the reference and exposed areas ($p < 0.05$). The relative risks for lung cancer associated with residence in the exposed area were increased in all the types of houses (not shown).

DISCUSSION

This study was initiated as a result of the findings in a pilot study by Pershagen et al. (19) which indicated a relative risk for lung cancer of 1.7 among men living near the Rönnskärsverken smelter who had not been employed at the smelter. The present study shows that the excess risk also remained after standardization for age, smoking habits, and occupation. Furthermore, it could not be explained by differences in tobacco consumption among smokers or in housing characteristics which may be of importance for the exposure to radon and radon daughters. Although the control of these potential confounding factors was crude in some instances, it is unlikely that they explain the excess risk.

Subjects who at any time had been residents of two parishes near the smelter were regarded as exposed. Analyses have also been performed with restrictions regarding the duration of residence in these parishes. As a rule, higher lung cancer risks were indicated in subjects with longer residence in the exposed area, but the results were inconclusive because of small numbers. The residence classification was based on data from the questionnaires only. A comparison with data from parish registers showed that the questionnaire information was of high quality, at least with regard to specificity. It should be pointed out that poor precision in the exposure classification, without other influences on validity, would lead to an underestimation of any risks.

No firm conclusions can be reached on the cause of the increased lung cancer risks in the exposed area, but it is not unlikely that the smelter emissions may have been of importance. The emissions to air from the smelter contain a number of carcinogenic agents, with quantitative domination by inorganic arsenic. The excess lung cancer risk in the exposed area is close to the risk increase in low exposure groups of two recently published studies on arsenic-exposed smelter workers (7, 29). In view of the limited exposure data from the smelter, it is difficult to estimate dose-response relationships and to make comparisons with the occupational data. Furthermore, if lung cancer risk is related to the smelter emissions, it is difficult to determine the responsible agent or agents.

It is noteworthy that the point estimate for the relative risk of lung cancer is not very different between residents of the exposed area (2.0) and smelter workers (3.0). It should be kept in mind, however, that in order to be certain that the comparison between residents in the exposed and reference areas was not confounded by occupational exposure at the Rönnskärsverken smelter, the smelter worker category also included workers with very low exposures, e.g., office workers and workers with only a few months of employment. Furthermore, the selection of deceased controls may have resulted in a biased estimate of the relative risk if the exposures under study affected the mortality of common causes of death. In view of the observations of an increased mortality from cardiovascular disease among smelter workers (18), some underestimation of the relative risk would be expected in this group. On the other hand, it is unlikely that the selection of deceased controls had any effect on the comparison of lung cancer risks between the exposed and reference areas (5).

Lung cancer risks were higher among smokers than among nonsmokers in all occupational groups. There was also a higher average daily tobacco consumption in the reference area among cases who smoked than among controls who smoked, and a similar tendency was seen in the exposed area. This is to be expected if there is a positive dose-response relationship between smoking and lung cancer. The lack of a higher tobacco consumption in cases than in controls among miners and smelter workers may partly be explained by important influences of other factors on the occurrence of lung cancer in these groups.

A number of epidemiologic studies have shown an increased lung cancer incidence in air-polluted areas, e.g., in urban environments (30). Differences in smoking habits partly explain these results, but an excess risk often remains after standardization for this factor. Some studies indicate a synergism with regard to lung cancer between smoking and community exposure to air pollutants (31, 32). In the present study, there is an interaction between smoking and residence in the exposed area, which significantly exceeds an additive effect. Exposure to air pollutants may have been of importance for the increased lung cancer risks in the exposed area and could also have contributed to the interactions with smoking.

Women were not included in the present study for several reasons, one of which is the technical difficulty in obtaining valid exposure information from a next of kin. The average life expectancy was more than five years longer for females than for males during the time period at issue, which made it easier to obtain information from the spouse for males who were deceased than for females who were deceased. A crude analysis of lung cancer mortality from 1961 to 1974 among females in the Rönnskär area did not reveal any clear effects; however, this was based on five cases only and on a lack of data on smoking habits (5, 19). A low number of female lung cancer cases is expected because smoking used to be much less common among women than among men. This would also make any interactions with smoking less common among women than among men. At present, no meaningful evaluation is possible on community exposure effects among women in the smelter area.

Exposure to inorganic arsenic is of importance for the increased lung cancer risks at the Rönnskärsverken smelter (5, 17, 18). A recent study among workers at this smelter indicates that there is a multiplicative interaction between arsenic exposure and smoking in relationship to lung cancer (33). In the present investigation, there was no clear interaction between smelter work and smoking in excess of an additive effect, which indicates that the interaction with smoking is not pronounced among smelter workers without arsenic exposure. This may explain the conflicting results of other studies on smoking interactions in copper smelter workers (6, 34, 35), in which some of the authors did not separately analyze the workers with heavy arsenic exposure.

There was also no interaction between mining and smoking beyond an additive effect upon statistical testing. Earlier studies on miners have given conflicting results. Multiplicative (36, 37), additive (38), and even preventive (39) effects of smoking have been reported. These inconsistencies can probably be explained to some extent by differences in the mining environments. The mines in the study area are of the sulfide ore type, where exposure to arsenic and radon may give rise to increased lung cancer risks. An investigation on workers from one of these mines indicated that lung cancer risk was relatively higher among nonsmokers than among smokers (40), which is consistent with the findings in the present study.

Swedish studies have indicated an increased risk of lung cancer associated with living in rural one-family houses made of material other than wood and/or with a basement in comparison with living in rural wooden houses without a basement (41, 42). This may be related to exposure to radon emanating from the building material and the ground. An effort was made to classify the dwellings of the subjects in the present study with regard to characteristics of importance for the indoor radon and radon daughter levels. No apparent differences in housing characteristics were found between subjects in the exposed and reference areas. Information in the questionnaires was not detailed enough for detecting houses made of highly radioactive aerated concrete, but according to the local public health board, this building material was not more common in the exposed than in the reference area. No systematic measurements have yet been made on ground leakage of radon in the two areas.

In conclusion, the results show that men living in the vicinity of a large copper smelter have an increased risk of lung cancer. The excess risk also remains after standardization for smoking habits and occupational background. It is plausible that the very substantial air emissions from the smelter, e.g., of arsenic, may have played a role. No firm conclusions can be drawn, especially in view of the inadequate exposure data. A continued follow-up of lung cancer incidence in the area near the

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e in the area near the smelter is desirable. If there is a causal link to the smelter emissions, the excess risk should diminish because of the major emission reductions performed in recent years.

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