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# Histological types of lung cancer among smelter workers exposed to arsenic

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ABSTRACT The histological distribution of lung cancer was investigated in 93 men who had worked at a Swedish smelter with high levels of arsenic. A comparison was made with a group of 136 patients with lung cancer from the county where the smelter was located. Company records provided information on occupational exposure and data on smoking habits were obtained from a next of kin of each subject. No pronounced differences in the histological types of lung carcinomas between smelter workers and the reference group could be seen for smokers. Some analyses indicated an increased proportion of adenocarcinomas among the smelter workers, which confirmed earlier data, but these findings were difficult to interpret. Cases among smelter workers who had never smoked showed a histological distribution resembling that in smokers, indicating that the work environment at the smelter and smoking had a similar influence on the risk for different types of lung cancer.

Environmental exposures may be associated with specific histological types of lung cancer. Tobacco smoking primarily induces epidermoid carcinomas and small cell carcinomas of the oat cell type, although increased relative risks are generally also found for other histological types.[1–5] Small cell carcinomas seem to predominate among uranium miners, especially in the younger age groups.[6,7] No conclusive evidence is available on associations between other agents and a single type of carcinoma of the lung.[8]

The distribution of histological types of lung cancer in smelter workers exposed to arsenic has been described in a few studies. Newman *et al* found a predominance of poorly differentiated epidermoid carcinomas among 25 cases of bronchogenic carcinoma at a United States copper smelter.[9] On the other hand, Wicks *et al* saw an increased proportion of adenocarcinomas among 42 men with lung cancer at another United States smelter.[10] A preliminary study of 18 cases of lung cancer at a Swedish smelter yielded inconclusive results.[11] No detailed analysis of lung cancer histology in relation to specific exposures at the smelters was attempted in any of the studies.

Inorganic arsenic compounds can induce pulmonary tumours in hamsters, mice, and rats.[12–15] Adenomatous tumours have generally been produced (adenomas and adenocarcinomas) but it is not known if this histological pattern can be generalised to man. The aim of the present study was to investigate the histological types of lung cancer among workers at a Swedish copper smelter. A comparison was also made with the histological distribution among other cases of lung cancer from the same area.

## Material and methods

The study group consisted of two parts, one, the first, from a cohort of 3958 male workers employed for at least three months before 1967 at the Rönnskärsverken copper smelter since the start of operations in 1928.[16] A total of 96 men who had died from carcinoma of the bronchus, lung, or pleura in the cohort were identified up to the end of 1981 in the National Cancer Registry. This registry was established in 1958 and is of high quality for most diagnoses.[17] Three more cases in the cohort were identified up to the end of 1984 in the Regional Cancer Registry at Umeå University.

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Table 1 *Age, year of diagnosis, and diagnostic material as well as smoking for cases of lung cancer among smelter workers and in a reference group. (Values in parentheses represent percentages)*

| | *Smelter workers* | *Reference group* |
|---|---|---|
| No of cases | 93 | 136 |
| Mean age at diagnosis | 64·8 ± 0·9* | 68·0 ± 0·8 |
| Mean year of diagnosis | 1972·5 ± 0·6 | 1971·1 ± 0·4 |
| Diagnostic material: | | |
| Necropsy | 33 (35·5) | 69 (50·7) |
| Large biopsy | 8 (8·6) | 5 (3·7) |
| Small biopsy | 25 (26·9) | 23 (16·9) |
| Necropsy and biopsy | 17 (18·3) | 25 (18·4) |
| Cytology | 10 (10·8) | 14 (10·3) |
| Smoking: | | |
| Never smoker | 10 (10·8) | 18 (13·2) |
| Former smoker | 25 (26·9) | 40 (29·4) |
| Cigarettes | 8 | 10 |
| Pipe | 9 | 14 |
| Cigarettes and pipe | 8 | 16 |
| Smoker | 58 (62·4) | 78 (57·3) |
| Cigarettes | 21 | 24 |
| Pipe | 15 | 18 |
| Cigarettes and pipe | 22 | 36 |
| Mean tobacco consumption among ever smokers (g/day)† | 13·5 ± 1·1 | 18·3 ± 1.4 |

*± Values represent 1 standard error.
†Based on 79 of the smelter workers and 105 reference cases among former smoker and smokers. Daily tobacco consumption computed by adding cigarettes (assuming 1 g of tobacco per cigarette) and pipe tobacco.

The second part of the study group was also obtained from the National Cancer Registry and consisted of men who had died between 1961 and 1979 from carcinoma of the bronchus, lung, or pleura in the municipality where the smelter was located.[18] After excluding men employed at the Rönnskärsverken smelter, 143 cases remained and these constituted the reference group for the smelter workers.

The diagnostic material for all cases was reviewed by one of us (FB). This included examination of histological slides, cytology, and other relevant material. A classification of the tumours was performed according to the World Health Organisation.[19] Both the review and classification were done "blind," without knowledge of whether the individuals from whom the specimens were obtained had worked at the smelter or not. The sources of diagnostic material were classified as necropsy, large biopsy, small biopsy, or cytology. A large biopsy consisted of a large portion of the tumour, usually obtained by lobectomy. Small biopsies consisted of material from bronchogenic biopsies, regional lymph nodes, or distant metastases.

The work environment at the smelter is complex, with several different departments and exposures. High levels of arsenic or sulphur dioxide, or both, are found in some departments. Among the pulmonary carcinogens at the smelter, chromium, nickel, and polyaromatic hydrocarbons should also be mentioned. The exposure assessment for the smelter workers in this study was based on estimations by a safety engineer of exposure levels in each department during different periods.[20] These data were used together with the company records, which contained detailed information on the time spent in various workplaces at the smelter by each worker.

Information on smoking habits was obtained from questionnaires completed by a next of kin of each subject. Earlier studies have shown that smoking data obtained in this way are of high quality.[21 22] Subjects who had never smoked "daily or almost daily" were classified as never smokers.

The comparison of fractions in different groups was made with chi square or Fisher tests; means were compared with conventional *t* tests. All p values correspond to two sided tests.

## Results

The diagnostic material was insufficient or could not be retrieved for four (4·0%) of the cases and seven (4·9%) of the referents. Two of the smelter workers had secondary lung tumours and were also excluded. The subsequent analysis thus includes 93 cases among the smelter workers and 136 in the reference group.

Table 1 shows some characteristics of the cases of lung cancer in the smelter worker and reference groups. There are no major differences between the groups with regard to age at diagnosis and year of diagnosis. There is, however, a lower proportion of cases among the smelter workers with the tissue specimen from necropsy, including those with both necropsy and biopsy specimens ($p = 0·02$). No difference in histological type between necropsy and biopsy were seen for those 42 cases with specimens from both sources (not shown in table). The proportions of smokers and former smokers are similar in smelter workers and the reference group, and it is noteworthy that pipe smoking is almost as common as cigarette smoking in both groups. The mean daily tobacco consumption was lower among the smelter workers for smokers and former smokers taken together ($p = 0·01$). These two smoking categories are combined in the further analyses.

Table 2 shows the histological distribution of lung cancer among never smokers and smokers. In this and the following tables some of the WHO categories are not presented separately. Among never smokers there is a higher proportion of "smoking related" carcinomas—epidermoid and small cell carcinomas—in the smelter workers than in the reference group ($p = 0·05$). Six of the 10 cases among the smelter workers had worked at the roasters or in the arsenic departments, or both. There are no pronounced

Table 2 *Types of lung cancer in smelter workers and in a reference group. (Values in parentheses represent percentages)*

| | *Smelter workers* | | *Reference group* | |
|---|---|---|---|---|
| | *Never smokers* | *Smokers* | *Never smokers* | *Smokers* |
| No of cases | 10 | 83 | 18 | 118 |
| Mean age at diagnosis | 66·9 | 64·6 | 70·3 | 67·7 |
| Epidermoid carcinoma: | | | | |
| Well differentiated | 5 | 17 | 3 | 34 |
| Poorly differentiated | 1 (60·0) | 13 (41·0) | 2 (27·8) | 19 (49·1) |
| Unspecified* | | 4 | | 5 |
| Small cell carcinoma: | | | | |
| Oat cell | 2 | 11 | | 20 |
| Other types | 1 (30·0) | 15 (32·5) | 4 (22·2) | 19 (33·1) |
| Unspecified* | | 1 | | |
| Adenocarcinoma: | | | | |
| Acinar type | 1 | 7 | 1 | 6 |
| Other types | (10·0) | 3 (14·5) | 4 (33·3) | 1 (9·3) |
| Unspecified* | | 2 | 1 | 4 |
| Large cell carcinoma | — | 6 (7·2) | 2 (11·1) | 6 (5·1) |
| Other types | — | 4 (4·8) | 1 (5·6) | 4 (3·4) |

*Diagnostic material consists of cytology.

Table 3 *Histological distribution of lung carcinoma and source of tissue specimen for smokers among smelter workers and in a reference group.* (Values in parentheses represent percentages)*

| | *Smelter workers* | | *Reference group* | |
|---|---|---|---|---|
| | *Biopsy* | *Necropsy* | *Biopsy* | *Necropsy* |
| No of cases | 29 | 44 | 26 | 79 |
| Mean age at diagnosis | 66·0 | 63·8 | 62·0 | 69·8 |
| Epidermoid carcinoma: | | | | |
| Well differentiated | 8 | 9 | 6 | 26 |
| Poorly differentiated | 7 (51·7) | 5 (31·8) | 9 (57·7) | 10 (45·6) |
| Small cell carcinoma: | | | | |
| Oat cell | 2 | 8 | | 20 |
| Other types | 4 (20·7) | 11 (43·2) | 7 (26·9) | 12 (40·5) |
| Adenocarcinoma: | | | | |
| Acinar type | 2 | 5 | 1 | 5 |
| Other types | (6·9) | 3 (18·2) | 1 (7·7) | (6·3) |
| Large cell carcinoma | 5 (17·2) | 1 (2·3) | 1 (3·9) | 3 (3·8) |
| Other types | 1 (3·4) | 2 (4·6) | 1 (3·9) | 3 (3·8) |

*Subjects for whom the diagnostic material consists of cytology have been excluded.

Table 4 *Types of lung cancer for smokers among smelter workers in different exposure categories. (Values in parentheses represent percentages)*

| | *Never roaster or arsenic department* | *Roaster or arsenic department < 5 years* | *Roaster or arsenic department ≥ 5 years* |
|---|---|---|---|
| No of cases | 46 | 20 | 17 |
| Mean age at diagnosis | 63·8 | 63·8 | 67·5 |
| Epidermoid carcinoma: | | | |
| Well differentiated | 11 | 4 | 2 |
| Poorly differentiated | 5 (41·3) | 4 (45·0) | 4 (35·3) |
| Unspecified* | 3 | 1 | |
| Small cell carcinoma: | | | |
| Oat cell | 6 | 2 | 3 |
| Other types | 6 (28·3) | 7 (45·0) | 2 (29·4) |
| Unspecified* | 1 | | |
| Adenocarcinoma: | | | |
| Acinar type | 4 | 1 | 2 |
| Other types | 2 (15·2) | 1 (10·0) | (17·7) |
| Unspecified* | 1 | | 1 |
| Large cell carcinoma | 4 (8·7) | | 2 (11·8) |
| Other types | 3 (6·5) | | 1 (5·9) |

*Diagnostic material consists of cytology.

differences in the histological distribution for smokers between the smelter workers and the reference group.

In view of the differences in the source of the diagnostic material between smelter workers and the reference group (see table 1) a separate analysis of biopsy and necropsy specimens was performed and the results are shown in table 3. Subjects with specimens from both necropsy and biopsy have been put in the necropsy category. Only smokers are included in the analysis. No major differences between the groups are seen for the biopsy specimens. On the other hand, there is an increased proportion of adenocarcinomas among the smelter workers for the necropsy specimens ($p = 0{\cdot}04$). The interpretation of the findings is complicated by age differences between the groups.

Table 4 shows the distribution of histological types of lung cancer in different exposure groups among smelter workers who smoked. The analysis is based on estimated exposure to arsenic, which was highest among roaster workers and workers in the arsenic departments. No consistent differences in the histological picture may be seen between the exposure groups. There is, however, a tendency towards a higher number of poorly differentiated epidermoid carcinomas with increasing arsenic exposure. Several other exposure categories among the smelter workers have been analysed but no consistent patterns in the histological distribution could be detected.

## Discussion

The histological distribution of lung cancer among smokers did not differ greatly between the smelter workers and the reference group. This also applied to different exposure groups among the smelter workers. Some results were similar to those in previous studies of smelter workers, such as an increased fraction of adenocarcinomas and poorly differentiated epidermoid carcinomas[9 10] but these data were difficult to interpret. There is an overall increase in the risk of lung cancer among smokers at the Rönnskärsverken smelter,[18] which in the absence of pronounced differences in the histological distribution implies that the risk is increased for all types. A direct comparison of absolute or relative risks for different histological types in smelter workers and the reference group was not possible because the population bases were not known in detail—for example, with regard to smoking habits.

There was a lower tobacco consumption among the cases of lung cancer who smoked at the smelter than in the reference group, which confirms earlier data.[18] No valid analysis of cumulative tobacco consumption was possible because of insufficient information on age at start of smoking. A lower than expected tobacco consumption in the cases of lung cancer among the smelter workers who smoked may be interpreted as an influence of the occupational environment.

The cases of lung cancer among never smoking smelter workers showed a histological distribution similar to that in smokers. This probably reflects the exposure to carcinogenic agents at the smelter, which influence the risk of different histological types in the same way as smoking. Most of the cases of lung cancer who never smoked had worked in the roasting or arsenic departments, or both, where the exposure to inorganic arsenic is high. It would be interesting to see an analysis of the histological distribution of lung cancer among non-smokers in other occupational groups with substantial exposure to carcinogenic agents.

The source of tissue specimens differed between the smelter workers and the reference group but the reason for this is not clear. Hospital care in Sweden is strictly area based, which means that the diagnostic material in both groups to a large extent originated from the same hospitals. As a rule there are differences in the histological distribution of lung cancer between specimens obtained from biopsy and from necropsy.[8] Epidermoid carcinomas are usually more common in materials based on biopsies (see table 3). On the other hand, the histological type probably also influences the source of specimen. For example, epidermoid carcinomas may more often be operated on. It is thus not evident that a standardisation would be done in the analysis for source of diagnostic material. A similar line of reasoning may be valid also for age at diagnosis.

It may be concluded that the work environment at the smelter did not seem to result in major changes in the histological distribution of lung cancer in smokers. Smelter workers who had never smoked had a histological distribution resembling the one in smokers, indicating that the work environment and smoking influence the risk for different types of lung cancer in a similar way.

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