

Mortality and Cancer Morbidity among Cadmium-Exposed Workers

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Preliminary data are reported from a study of 269 cadmium-nickel battery factory workers and 94 cadmium-copper alloy factory workers. The target group comprises all workers with more than 5 years exposure to cadmium at any time since the factories started production. An internal reference group of 328 alloy factory workers without cadmium exposure was also studied.

The expected number of deaths and cancers was calculated with the "life-table" method by using national average incidence rates for men in different age groups and at different calendar years.

It was found that among the workers in the battery factory who started work before 1948 there was an increased general mortality in the 1950's mainly due to respiratory disease. The same group had an increased renal disease mortality. There was no increase in general cancer mortality or in general cancer incidence. The risk ratio for nasopharyngeal cancer incidence was 10 (two cases), which was statistically significant. For some other sites like prostate, lung and colon-rectum the risk ratios were also greater than 1 but not statistically significant.

In the alloy factory there was a tendency for an increased mortality in prostatic cancer (four cases). After correction for the "healthy worker effect" using the reference group, the risk ratio for prostatic cancer deaths was calculated as 2.4, but this was not statistically significant. The findings in this study support the earlier reports of an association between human cadmium exposure and increased risk for prostatic cancer.

Introduction

Follow-up studies of workers with excessive cadmium exposure have found several cases that died of emphysema (1-6). Apart from the calculations by Friberg and Kjellström in the review by Friberg et al., (7) no quantitative estimates of excess mortality among cadmium workers have been published.

Cancer is of particular interest when discussing the long-term prognosis after cadmium exposure. Data are accumulating from both animals and humans linking cancer and cadmium exposure. Since Haddow et al. (8, 9) showed that subcutaneous injections of large doses of cadmium compounds in rats could cause sarcomata at the site of injection, a number of studies of rats and mice have confirmed

this finding (10-17). These tumors may metastasize (14). The doses necessary to induce cancer have usually been so large that testicular damage also occurred (18). In some studies tumors were also found in the testes (10, 11, 17).

No conclusive data have been published regarding cadmium induction of cancer in human beings. In 1965 Potts (19) noticed that an unusually high proportion of a group of cadmium battery workers had died of cancer. The numbers were small and no reference group was studied. Kipling and Waterhouse (20) reported that among 248 workers with a minimum of one year's exposure to cadmium oxide the expected number of prostatic cancers was 0.58, and 4 were observed. The expected number was calculated based on the rates in the Birmingham regional cancer register. A similar type of study was performed on 272 cadmium smelter workers in the USA (21). The average cancer mortality rates for the whole of USA was used to calculate expected numbers. For all cancers the SMR was 154 ($p < 0.05$) and for respiratory cancer SMR was 235 ($p < 0.05$). The highest SMR was found for prostatic

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cancer (SMR = 347, $p < 0.05$), (1.15 cases expected, 4 cases observed). This would support the finding by Kipling and Waterhouse. However, a long-term injection study of rats (22) could not show any tumors in the prostate.

The objective of this study was to measure the cause-specific mortality and incidence of cancer in two groups of Swedish workers exposed to cadmium and compare these data with reference data.

Materials and Methods

The target groups comprised all workers with a 5 years or longer exposure to cadmium in two Swedish factories. One of the factories was the cadmium-nickel battery factory which has been studied several times since 1950 (23-25). The workers have been exposed to cadmium oxide dust and nickel hydroxide dust. Before 1947 the cadmium exposure levels were on an average above 1 mg Cd/m³ in air (23). In the 1950's the levels were approximately 200 µg Cd/m³, and between 1962 and 1974 they were about 50 µg Cd/m³ (25). Since then they have decreased further, and most of the workers are now exposed to levels below 5 µg Cd/m³ (26). According to measurements in the 1950's (23) and in the early 1970's (25), the nickel hydroxide exposure levels have been at least the same as the cadmium exposure levels and often up to 10 times as high.

The other factory is a copper-cadmium alloy smelter in which the workers at the furnace have been exposed to cadmium oxide fumes. The production of copper-cadmium alloys started in the 1930's, but reliable measurements of the cadmium exposure via air was first carried out in the middle of the 1960's. The cadmium concentrations were then in the range 100-400 µg Cd/m³ (27). In 1971, local exhaust equipment was installed in the furnace area, and since then the average exposure level has been about 50 µg Cd/m³. It should be pointed out that in this factory the workers were exposed to cadmium oxide fumes and in the other factory to a mixture of cadmium oxide and nickel hydroxide dust.

An internal reference group was used in the alloy factory, comprising all other workers in the same factory who had been employed for at least 5 years and never exposed to cadmium in the factory. These workers were involved in the production of copper and brass tubes as well as various aluminum products.

From company records, lists of all workers who belonged to the target groups were produced. The data include name, birth date (if available), most recently known address, sex, death date (if avail-

able), and exposure and employment experience in this particular company. In the battery factory such records were kept for all years after 1945, and the target group could thus only include those workers who were employed in the factory in 1945 or who started working after that date. In the alloy factory the records went as far back as 1940, which means that the target group was limited to those workers who were employed in 1940 or who started working after that. The lists were sent to the local county offices, where birth dates were checked and the personal number was added to the list. Each Swede has a personal number of 10 digits incorporating the birthdate (year, month, day), the birth place, the birth order, and the sex. In those cases where no birth dates had been found in the company records these could be found in the county offices in most cases. For most of the cases that had died the death date was also recorded from the county office record. The county office could also tell us whether this person was still living in the same county; in those cases where the person had moved outside the county, a further check with the next county to which he moved was carried out. In a few cases the personal numbers could not be found in the county office and a check was carried out with the local parish office (which in Sweden is similar to the office of the registrar of births, deaths, and marriages), and usually it was found that in these cases the person had moved long ago to another county. Further follow-ups were carried out, and eventually complete data about birth and death dates were collected, except for the few workers who had moved abroad. For the cases that had died we asked the parish office to send us a copy of the death record where the cause of death is recorded.

The above procedure has been completed at this stage for the majority of exposed workers. However all data have not yet been collected for approximately 20% of the reference group. The results in this report are based only on those workers for which we have complete information.

Based on the information collected, a list was made of the workers who were alive in 1959 when the Swedish National Cancer Register started. The list of workers in the battery factory has been compared manually with all records for the years 1959-1975 in the Swedish Cancer Register in order to find all new cases of cancer in this group. The procedure will be carried out in the same way for the workers in the alloy factory.

The "life-table" method was used for the calculation of expected number of deaths and new cases of cancer in the target groups. Of the subjects 95% were males, and in order to simplify the calculations the women were excluded from this preliminary

analysis. The national average cause-specific and age-specific death rates and cancer incidence rates were used to calculate the expected number of deaths and cancers in different groups within the target group. This information was received from published reports from the Swedish National Bureau of Statistics. For the group in the battery factory the calculation of expected cases was based on each individual's year of birth, whereas for the alloy factory the calculation was based on groups born in different decades. A calculation based on individual birth years will also be carried out for the alloy factory workers in the final analysis of these data.

The expected and observed numbers were used to calculate risk ratios. It was assumed that the observed numbers of cases followed Poisson distributions with the expected numbers as the modes. The Poisson distributions were used for significance testing.

Results

Battery Factory

There were 269 workers in this exposed group. They were born between 1874 and 1952. Nine of them started working before 1920, 34 started in the 20's, 40 started in the 30's, 103 started in the 40's, 40 started in the 50's and 43 started in the 60's. There was a total of 43 deaths between 1949 and 1975, and 15 new cases of cancers between 1959 and 1975. Eight of the deaths were caused by cancer. There were 19 deaths by cardiovascular diseases, 8 by respiratory diseases, 5 by kidney diseases, and 3 by other diseases.

Calculations of expected and observed deaths based on groups with different years of start of work, different time since first exposure, different duration of exposure, or different calendar years for the death, mostly show lower observed numbers than expected numbers. For instance, for the whole group of workers with exposure duration between 5 and 14 years, the cumulative expected number of deaths between 1945 and 1975 was 20, and the cumulative observed number was only 15. For those with cadmium exposure duration between 15 and 24 years the cumulative numbers were 14 expected and 9 observed. For those with exposure durations between 25 and 34 years, the expected number was 16 and the observed 9, and for those with exposure duration of 35 to 51 years, there was 17 expected cases and only 10 observed. On the other hand, when certain small groups are looked at, the number of total deaths tends to be higher, especially in the 1950's. For these that started work

between 1913 and 1929 there were four observed deaths in 1950 and 1954 as compared to 2.22 expected deaths ($p \leq 0.18$); for those starting in 1930-39, there were two deaths in the same period as compared to an expected 0.49 deaths ($p \leq 0.08$). Further, the group of 19 workers with the highest exposure level and worst clinical condition studied by Friberg (23) had a much greater mortality experience in the 1950's than expected (Fig. 1).

In order to take into consideration the great changes in exposure level that has occurred in the battery factory during the years, the workers were divided into those who started work in 1947 or before, 1948 to 1961, and 1962 and after. For the first group with the highest exposure levels, there was generally a higher total number of expected deaths than the observed number (Fig. 2), except for the 1950's where the "bump" indicates that an overmortality occurred. In most of the time periods, 1945 to 1974, the numbers of cancer and cardiovascular disease deaths are lower than the expected (Fig. 2). However, both for respiratory and kidney disease deaths the observed number are often much higher than the expected numbers. In Figure 3 the mortality risk ratio based on the cumulative observed and expected numbers of respiratory and kidney disease deaths have been plotted. It is seen that the ratios are often much higher than 1. For almost all years the ratios are statistically significantly greater than 1.

For those workers who started work in 1948 to 1961 there was one respiratory death in 1960 as compared to 0.057 expected respiratory disease deaths at that time and there was one kidney disease death in 1970 as compared to 0.057 expected kidney deaths at that time.

The total number of observed and expected new cases of cancer is depicted in Figure 4. For those workers who started after 1961 no cases of cancer were found up to 1975. There was an indication that the workers who started in 1948 to 1961 had almost

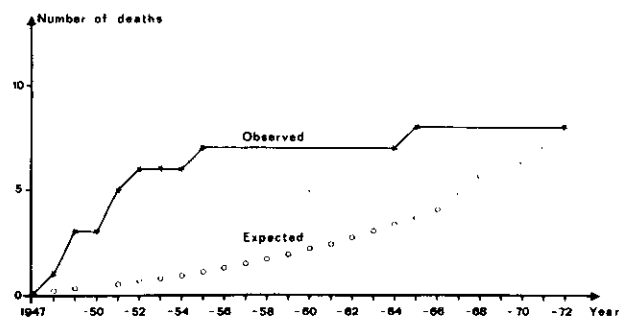


FIGURE 1. Cumulative expected and observed mortality in the group of 19 workers with the highest exposure and worst clinical condition studied by Friberg in 1946 (23).

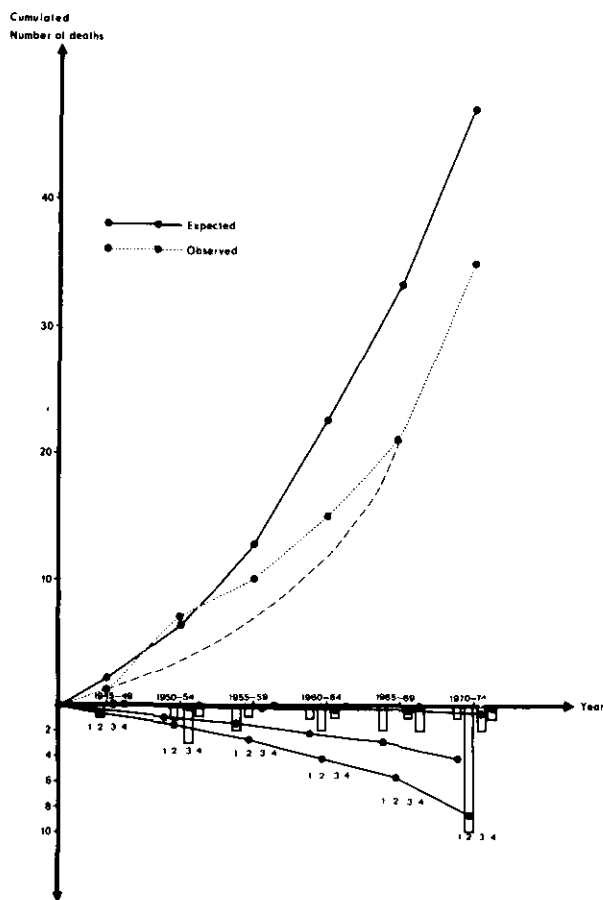


FIGURE 2. Cumulative expected and observed mortality in the group of battery factory workers starting work 1913-1947. The dashed line indicates the possible progression of the curve without the "over-mortality" in the 1950's. The bars at the bottom of the figure indicate observed deaths and the curves indicate expected deaths of cancer (1), cardiovascular disease (2), respiratory disease (3) and kidney disease (4).

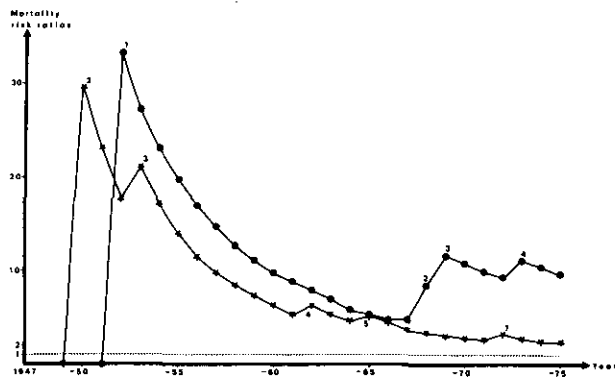


FIGURE 3. Risk ratios (based on cumulative mortality) for (★) respiratory and (●) kidney disease deaths in the group of battery factory workers that started working 1913-1947. The numbers beside the curves indicate the observed number of deaths.

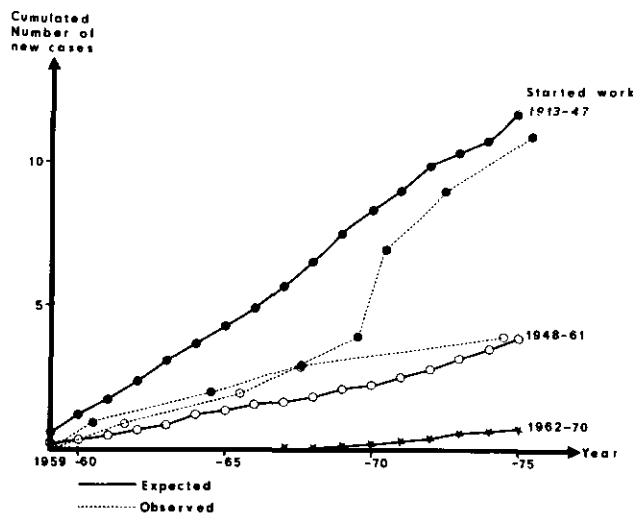


FIGURE 4. Cumulative number of new cases of cancer in the group of battery factory workers stratified according to time of start of cadmium exposure.

twice the expected cancer incidence in the middle of the 1960's, but this increase was not statistically significant. The cumulative expected and observed number of incident cases of cancer in those that were alive in 1959 (started work 1913-1970) at seven different sites is shown in Table 1. Those workers who died during the period 1959-1975 have been excluded from the calculation from the year of death. There were no cases of kidney or pancreas cancer among these workers. There was a tendency for an increased incidence of prostatic, lung and colorectal cancer among these workers, but these risk ratios were not statistically significantly higher than 1. For nasopharyngeal cancer, however, the risk ratio of 10 was statistically significant ($p \leq 0.05$). In the group of other cancers, the observed number tended to be lower than the expected, and the total incidence of cancer was more or less the same in this group as had been expected from the national average.

Table 1. Expected and observed new cases of cancer in 1959-1975 in the whole group of battery factory workers ($n = 228$).^a

| Site | Cancer cases | | Risk ratios |
|----------------|--------------|----------|-------------------|
| | Expected | Observed | |
| Prostate | 1.2 | 2 | 1.67 |
| Lung | 1.35 | 2 | 1.48 |
| Kidney | 0.87 | 0 | 0 |
| Bladder | 1.07 | 1 | 0.93 |
| Colon + rectum | 2.25 | 5 | 2.22 |
| Pancreas | 0.60 | 0 | 0 |
| Nasopharynx | 0.20 | 2 | 10.0 ^b |
| Other | 9.81 | 3 | 0.31 |
| All sites | 16.4 | 15 | 0.91 |

^a "Life-table" method using the Swedish National Cancer Register.

^b Statistically significantly greater than 1.

Both the prostatic cancers occurred in the group that started work before 1948, and for that group the risk ratio of cumulative number of cases between 1959 and 1975 was 2.3 ($p \leq 0.25$). Also all the five colorectal cancers occurred in this group, and the risk ratio for that particular group was 3.1 ($p \leq 0.05$). One nasopharyngeal cancer occurred in the group that started before 1948 and one occurred in the group 1948 to 1961.

Because of the way that data on incident cases of cancer has been collected, there may have been cancers occurring in the 1950's that have not been picked up. A calculation of the number of years since start of exposure when the cancer cases occur may therefore be biased. However, from our data it can be calculated that the first case of prostatic cancer occurred 26 years after start of exposure and for the lung cancer, the colorectal cancer, the nasopharyngeal cancer, and other cancers, the equivalent latency times were 25, 13, 10, and 15 years.

Alloy Factory

For this factory only a preliminary calculation of prostatic cancer mortality has been carried out. More detailed calculations will be made when all the data for the target groups are known. It is unlikely, however, that the "missing" persons would have a different mortality experience than those included here.

In both the exposed and reference groups there were four observed cases of prostatic cancer deaths (Table 2), but the expected number differed. The lower than expected mortality in the reference group would constitute the "healthy worker effect" (28). The p values denote the probability that the true risk ratios are 1.

The healthy worker effect can be corrected for by dividing the risk ratio for the exposed group by the ratio for the reference group or by adjusting the expected number in the exposed group (2.69) to $0.62 \times 2.69 = 1.67$. If it is assumed that the same healthy worker effect applies to the prostatic cancer inci-

dence of the battery factory workers their risk ratio would be 2.7 (1.67/0.62).

Discussion

In view of the well known effects of inhaled cadmium on the lungs and the kidneys (7, 23), it is not surprising that there was an increased mortality in respiratory and renal disease. The over-mortality was most pronounced in the group with the highest cadmium oxide dust exposure, but due to the limited number of workers studied a detailed dose-response relationship could not be evaluated. When the healthy worker effect is accounted for (Fig. 2), it is clear that heavy cadmium exposure can decrease the life expectancy. This was most clearly shown in the group of 19 workers with the highest exposure (Fig. 1).

The cancer incidence data in this study correspond very well with earlier studies (19, 20), of cadmium-exposed battery factory workers. Also in those studies there was no increase in total cancer incidence but at the same time there was a tendency for an increase of prostatic cancer incidence. The risk ratio in one of the studies (20) was similar to our finding, but no quantitative comparisons of risk ratios between studies can easily be made, because the risk ratio may be a function of age, exposure intensity, exposure duration and latency times.

Kolonel (29) claims that there is a significant association of renal cancer with exposure to cadmium. Among the battery factory workers in our study no renal cancers were found. The cadmium exposure estimates in Kolonel's study were not based on individual direct measurements of cadmium exposure but on circumstantial data like past occupation (e.g. electroplating, alloy-making, welding, manufacture of storage batteries), diet history, and smoking habits. The calculated estimates of mean daily dietary cadmium intake in different groups (including reference groups) varied between 122 and 137 μg , which is 5 to 6 times the estimates based on direct measurement (31).

Also, in the cadmium alloy factory group we found a tendency for an increased prostatic cancer mortality. Lemen et al. (21) reported an increase in prostatic cancer mortality in a cadmium smelter. It is unlikely that all these observations of increased prostatic cancer incidence or mortality among cadmium exposed workers in different exposure situations are purely coincidental. Further epidemiological studies of this relationship as well as studies of possible mechanisms for cadmium carcinogenicity are needed.

The high risk ratio for nasopharyngeal cancer among the battery workers is another observation

Table 2. Cumulative expected and observed number of prostatic cancer deaths in 1940-1975 among alloy factory workers.

| | Prostatic cancer deaths | | Risk ratios | p |
|-------------------------------|-------------------------|----------|-------------------|------|
| | Expected | Observed | | |
| Exposed group ($n = 94$) | 2.69 | 4 | 1.49 | 0.29 |
| Reference group ($n = 328$) | 6.42 | 4 | 0.62 ^a | 0.23 |

^a "Healthy worker effect," corrected risk ratio = $1.49/0.62 = 2.4$ ($p = 0.087$).

that merits further study. Large amounts of cadmium particles may be deposited in the nose when the exposure level is high. The retired workers from the battery factory have told us how their noses used to be completely blocked up with dust from the factory (in the 1940's) and that it used to take several days in fresh air before all the dust was out. Anosmia used to be considered a symptom of cadmium poisoning (7) and this could also be related to the very high exposure levels.

As early as 1932, Grenfell and Samuel (31) reported an unusually high occurrence of cancer in the nasal cavity among nickel smelter workers. This has since been confirmed in other studies (32). The workers in the Swedish battery factory have been exposed to higher levels of nickel hydroxide dust than cadmium oxide dust. There is a possible connection between the exposure to the nickel compound and the high risk of nasopharyngeal cancer. Many of the earlier studies of nickel exposure and cancer (32) have also shown an increased risk of lung cancer. The relatively low risk ratio for lung cancer in our study renders the data inconclusive as to the effects of nickel compounds. Differences in smoking habits between groups in different studies may influence the lung cancer risk ratio considerably.

This study is continuing, and it is expected that a more detailed analysis of all data will be published within a year.

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