

# Cancer mortality of cadmium workers

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**ABSTRACT** Several epidemiological studies of workers exposed to cadmium indicate an increased risk of lung and prostatic cancer. The increase is statistically significant in some of the studies but the SMR is greater than 100 in almost all. A cohort study of the mortality among 522 Swedish workers exposed to cadmium for at least one year in a nickel-cadmium battery plant support the earlier findings. The SMR for lung and prostatic cancer increased with increasing dose and latency but did not obtain statistical significance. A combination of all the available data from the most recent follow up of causes of death among cadmium workers in six different cohorts shows 28 cases of prostatic cancer (SMR = 162) and 195 cases of lung cancer (SMR = 121). This new analysis suggests that long term, high level exposure to cadmium is associated with an increased risk of cancer. The role of concomitant exposure to nickel needs further study.

It is well known that exposure to cadmium in the general and occupational environment may induce kidney damage but its possible carcinogenicity is more controversial.<sup>1</sup> In 1965 Potts observed an unusually high mortality from prostatic cancer (three cases out of eight deaths),<sup>2</sup> which was later epidemiologically confirmed in a retrospective follow up study using cancer register data.<sup>3</sup> There were four observed prostatic cancer cases versus 0.58 expected in a group of 248 workers from a battery plant. The report by Lemen *et al* of a statistically significant increase of lung and prostatic cancer mortality among cadmium smelter workers created a considerable interest in the question of cadmium carcinogenicity,<sup>4</sup> and several epidemiological studies were undertaken in subsequent years. Animal data had shown that cadmium injections could induce sarcomas at the injection site and Leydig cell tumours in the testicles.<sup>5</sup> Based on the available human and animal data in 1976, IARC concluded that occupational exposure to cadmium in some form, possibly the oxide, increased the risk of prostatic cancer,<sup>5</sup> and one study suggested an increased risk of lung cancer.<sup>4</sup>

A report in the *Lancet*, however, presents mainly negative data with regard to cancer mortality and cadmium exposure.<sup>1</sup> In 6995 men born before 1940 and exposed to cadmium for more than one year be-

tween 1942 and 1970 no excess of prostatic cancer was found and there was only a "marginal" excess of lung cancer, but this was unrelated to exposure levels. Only 199 of the men, however, had consistently experienced high cadmium exposure.<sup>6</sup>

We have updated the mortality of a Swedish cohort of battery workers exposed to cadmium and nickel and have considered different latent periods from the first exposure which has not been done in most previous studies.

## Study group and methods

The target group comprised all 545 men who had been exposed to cadmium for at least one year between 1940 and 1980 in a Swedish cadmium-nickel battery factory and who had not died before 1951. The levels of cadmium oxide dust in the air had been about 1 mg Cd/m<sup>3</sup> before 1947, about 0.3 mg Cd/m<sup>3</sup> in 1947-62, about 0.05 mg Cd/m<sup>3</sup> in 1962-74,<sup>7</sup> and about 0.02 mg Cd/m<sup>3</sup> since 1975.<sup>8</sup> The nickel hydroxide exposure levels were usually 2-10 times higher than those for cadmium oxide.<sup>7</sup> Identifying data were received from the factory occupational health service. Vital status was checked through parish death register and national insurance records. Underlying causes of death were ascertained from death certificates.

The expected numbers of deaths up to age 80 in 1951-83 were calculated from person-years at risk and

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the five year class, sex, and calendar year specific mortality rates in the whole Swedish population. Data on cause of death at age 80 and above were not included as diagnosis was considered to be less valid at this high age. Statistical significance was tested using the Poisson distribution when the expected number of cases were less than five and  $\chi^2$  test when the expected number was five or more.

The exposure, target population, and methods have been described in more detail in earlier reports with shorter follow up.<sup>9-11</sup>

### Results from the Swedish cohort

Of the 545 men in the cohort, 17 had emigrated, three could not be traced, and three had died before 1951. The expected and observed numbers of deaths in the remaining group of 522 men (table 1) shows a low mortality from all causes (SMR = 92), which agrees with the commonly reported "healthy worker effect" frequently seen in comparisons with expected numbers calculated from national populations.<sup>12</sup>

In addition to the 133 deaths before age 80, 14 deaths occurred after age 79, giving an overall cumulative mortality of 28% in the cohort.

In the cohort as a whole (n = 522) the observed numbers of deaths for most diseases were similar to the expected numbers (table 1). The most common cause of death was cardiovascular disease (SMR = 91) and the second most common was cancer (SMR = 115). The excess cancer mortality is not statistically significant and neither is the excess in any other site. In the previous report six died from lung cancer,<sup>11</sup> but during the subsequent three years another two cases were recorded. There were no additional deaths from prostatic cancer. Three cases were diagnosed as nephritis and nephrosis compared with an expected number of 1.0 (SMR = 300). Scrutinising the death certificates showed that the fourth case of renal disease (table 1) should more correctly be included in this group.<sup>10</sup>

Table 1 Observed numbers of death before age 80 (1951-83) and SMR\*

| ICD No  | Cause of death                    | All workers<br>(n = 522) |        |
|---------|-----------------------------------|--------------------------|--------|
|         |                                   | Obs                      | SMR    |
| 1-999   | All causes                        | 133                      | 92     |
| 140-209 | Cancers (all sites):              | 39                       | 115    |
| 147     | Nasopharynx                       | 1                        | > 1000 |
| 150-151 | Oesophagus stomach                | 4                        | 77     |
| 152-154 | Intestines                        | 8                        | 195    |
| 157     | Pancreas                          | 3                        | 130    |
| 162     | Lung                              | 8                        | 133    |
| 185     | Prostate                          | 4                        | 108    |
| 188     | Bladder                           | 2                        | 182    |
| 390-459 | Diseases of circulatory system    | 63                       | 91     |
| 460-519 | Diseases of respiratory system:   | 6                        | 95     |
| 490-493 | Obstructive respiratory diseases  | 3                        | 111    |
| 520-577 | Diseases of digestive system      | 5                        | 79     |
| 580-607 | Diseases of genitourinary system: | 4                        | 148    |
| 581-584 | Nephritis and nephrosis           | 3                        | 300    |
| 800-999 | Violent and accidental death      | 12                       | 94     |

\*SMR, standardised mortality ratio, is calculated as the ratio between observed number of deaths and the expected number, calculated from the general Swedish population.

Latent periods of 10 or 20 years and a minimum of five years of exposure were incorporated into the calculations of the SMR for the cancers that had an SMR greater than 100 in table 1. With the exception of nasopharyngeal cancer, only those with two or more observed cases are included. Data on nasopharyngeal cancer are given because this form of cancer was known to be associated with exposure to nickel.<sup>13,14</sup> For lung, prostate, and bladder cancer and nephritis or nephrosis the SMR was increased (table 2) but only the excess deaths from nephritis and nephrosis were statistically significant.

The exposure to cadmium in the battery plant was considerably higher before 1963.<sup>7,8</sup> The subgroup of workers with a 20 year latent period would all have been exposed before that year. Thus the mortality in this subgroup is of particular interest in order to elucidate the possible carcinogenic effects from high exposure to cadmium (table 2).

Table 2 Observed numbers of death from certain diagnoses before age 80 (1951-83) and SMR†, with different requirements on exposure times and time lapse since the first exposure

| ICD No  | Cause of death          | All workers<br>(n = 522) |     | Workers with at<br>least 5 years<br>of exposure<br>10 years latency<br>(n = 340) |      | Workers with at<br>least 5 years<br>of exposure<br>20 years latency<br>(n = 295) |      |
|---------|-------------------------|--------------------------|-----|--|------|--|------|
|         |                         | Obs                      | SMR | Obs  | SMR  | Obs  | SMR  |
|         |                         |                          |     |  |      |  |      |
| 152-154 | Cancer of intestines    | 8                        | 195 | 6  | 182  | 4  | 148  |
| 157     | Cancer of pancreas      | 3                        | 130 | 2  | 105  | 1  | 67   |
| 162     | Cancer of lung          | 8                        | 133 | 8  | 163  | 7  | 175  |
| 185     | Cancer of prostate      | 4                        | 108 | 4  | 125  | 4  | 148  |
| 188     | Cancer of bladder       | 2                        | 181 | 2  | 222  | 2  | 250  |
| 581-584 | Nephritis and nephrosis | 3                        | 300 | 3  | 375* | 3  | 600* |

\*p < 0.05.

†SMR is calculated as the ratio between observed number of deaths and the expected number, calculated from the general Swedish population.

### Summary of available data on lung and prostatic cancer among cadmium workers

Thirteen reports besides this study of cancer among cadmium workers in the United Kingdom, United States, and Sweden have been published.<sup>1-4,6,9,10,15-20</sup> A summary of the data on prostatic cancer (table 3) shows SMRs in the range 0 to 667 with a median of 167; in only four reports did the SMR reach statistical significance. Several of the studies mixed "high exposed" workers with others who had "median" or "low" exposure. For instance, in the study of 6995 workers reported in the *Lancet*<sup>1</sup> only 199 workers belonged to the high exposure group<sup>6</sup> and a recent study of the prevalence of proteinuria among the workers in the medium or low exposure groups showed that none had cadmium induced proteinuria.<sup>21</sup> In such cases the exposure will tend to be diluted and an increased mortality difficult to identify.

By contrast, 46% of the cadmium workers employed before 1962 (and still employed in 1974) in the Swedish cohort had cadmium induced proteinuria (beta-2-microglobulin higher than 97.5-percentile in reference group).<sup>7</sup> Only 9% of those employed after 1962 had such proteinuria. It may be that most of the

workers in the study by Armstrong and Kazantzis<sup>1</sup> had insufficient exposure to cadmium to induce the cadmium associated cancers.

Several recent reports (table 3) include data updating earlier studies. If the latest follow up data for the six examined groups are combined we find that 17.2 prostatic cancers were expected and 28 were observed (SMR = 162,  $p = 0.02$  two tailed).

The data on lung cancer mortality (table 4) show a similar pattern and the same criticism with regard to the dilution of the exposed group may be applied. The reported SMRs vary between 81 and 235 with a median of 131. In three reports the SMRs reach statistical significance. The combined data for the most recent observation on five populations is; 161.4 expected lung cancer deaths and 195 observed (SMR = 121,  $p = 0.008$  two tailed).

### General discussion

When all the available data on lung and prostatic cancer among cadmium workers are compiled (tables 3 and 4) there is a clear impression of an increased incidence of these cancers among cadmium workers compared with the expected figures from the general

Table 3 Summary of mortality and incidence data for cancer of the prostate reported in studies of cadmium workers

| Study population | Type of industry                   | First study |         |        | Second study |         |        | Third study |         |                | Fourth study |         |       |
|------------------|------------------------------------|-------------|---------|--------|--------------|---------|--------|-------------|---------|----------------|--------------|---------|-------|
|                  |                                    | SMR         | Obs/Exp | Ref    | SMR          | Obs/Exp | Ref    | SMR         | Obs/Exp | Ref            | SMR          | Obs/Exp | Ref   |
| 1                | Ni-Cd battery plant in UK          | 667**       | 4/0.6   | (3)    | 117          | 7/6.0   | (17)   | 235         | 4/1.7   | (6)†           | 400**        | 8/2.0   | (20)‡ |
| 2                | Cd-smelter in USA                  | 444*        | 4/0.9   | (4)§   | 136          | 3/2.2   | (19)   |             |         |                |              |         |       |
| 3                | Ni-Cd battery plant of Sweden      | 167         | 2/1.2   | (9)    | 167          | 4/2.4   | (10)¶  | 148         | 4/2.7   | (this study)†† |              |         |       |
| 4                | Cd-Cu alloy plant in Sweden        | 148         | 4/2.7   | (9)    |              |         |        |             |         |                |              |         |       |
| 5                | Cd-Cu alloy plant in UK            | 66          | 1/1.5   | (15)†  | 267*         | 8/3.0   | (16)‡‡ | 191         | 9/4.7   | (6)†           |              |         |       |
| 6                | 17 different plants using Cd in UK | 0           | 0/2.9   | (1,6)† |              |         |        |             |         |                |              |         |       |

\*Significant at  $p < 0.05$ ; \*\*Significant at  $p < 0.01$ .

†High or medium exposure.

‡Incidence, high exposure.

§20 years of latency.

||Incidence.

¶High exposure, 10 years latency.

‡‡ $\geq 5$  years of high exposure, 20 years latency.

‡‡Vicinity workers.

Table 4 Summary of mortality data for lung cancer reported in studies of cadmium workers

| Study population | Type of industry                   | First study |         |        | Second study |         |       | Third study |         |              | Fourth study |         |      |
|------------------|------------------------------------|-------------|---------|--------|--------------|---------|-------|-------------|---------|--------------|--------------|---------|------|
|                  |                                    | SMR         | Obs/Exp | Ref    | SMR          | Obs/Exp | Ref   | SMR         | Obs/Exp | Ref          | SMR          | Obs/Exp | Ref  |
| 1                | Ni-Cd battery plant in UK          | 114         | 5/4.4   | (3)    | 121          | 77/63.4 | (17)  | 131         | 26/19.9 | (6)†         | 127*         | 89/70.2 | (18) |
| 2                | Cd-smelter in USA                  | 235*        | 12/5.1  | (4)    | 164*         | 20/12.2 | (19)  |             |         |              |              |         |      |
| 3                | Ni-Cd battery plant of Sweden      | 143         | 2/1.4   | (9)‡   | 158          | 6/3.8   | (10)§ | 175         | 7/4.0   | (this study) |              |         |      |
| 5                | Cd-Cu alloy plant in UK            | 81          | 10/12.4 | (15)†  | 138          | 36/26.1 | (16)¶ | 101         | 47/46.4 | (6)†         |              |         |      |
| 6                | 17 different plants using Cd in UK | 112         | 32/28.6 | (1,6)† |              |         |       |             |         |              |              |         |      |

\*Significant at  $p < 0.05$ .

†High or medium exposure.

‡Incidence.

§High exposure, 10 years latency.

|| $\geq 5$  years of high exposure, 20 years latency.

¶Vicinity workers.

population. If the latest data from each examined group are added together the SMR for lung and prostatic cancer are 121 and 142 respectively. These data are similar to those found in our study (table 1) when time of first exposure was not considered. With increasing latent period the SMRs progressively increased in the Swedish cohort (table 2). This is similar to the experience of occupational cancer mortality after, for instance, exposure to asbestos<sup>22</sup> and to soot.<sup>23</sup> The lack of a significant excess mortality from cancer in some of the earlier reports may be due not only to the small size of the high exposure population but also to the fact that time from first exposure was not taken into account.

Seven deaths from lung cancer in the Swedish cohort occurred among 295 men who had experienced at least five years exposure to cadmium and were employed before 1963, and had thus been exposed to about 0.3 mg Cd/m<sup>3</sup> or more for at least a part of their exposure period. This is similar to what Thun *et al* reported in their recent follow up on cancer mortality of cadmium production workers in the United States.<sup>19</sup> They found a significant exposure response relation between the cumulative exposure to cadmium and the incidence of lung cancer.<sup>19</sup> Among cadmium production workers who had experienced at least two years of exposure to cadmium in air concentrations in the order of 0.1 to 1 mg/m<sup>3</sup> the SMR for lung cancer was about 200. On the other hand, the new follow up on United States cadmium production workers provides no new evidence of an excess in prostatic cancer.<sup>19</sup> It should be pointed out in this context that a recent study of rats found a dose related increase of lung cancer incidence at cadmium chloride levels below 0.1 mg Cd/m<sup>3</sup>.<sup>24</sup>

The workers in the Swedish factory were exposed to nickel hydroxide as well as to cadmium oxide. The one death due to nasopharyngeal cancer (table 1) raises the suspicion of an effect of nickel as well as of cadmium. Nickel exposure may also have contributed to the excess in lung cancers seen in the British battery plant.<sup>18</sup> The possibility of exposure to asbestos is another problem, although there are no indications that asbestos has been used to any large extent in the Swedish factory.

Differences in smoking habits between the examined and reference populations may easily bias the results of epidemiological studies, particularly with regard to lung cancer. There is no evidence to indicate that Swedish cadmium workers smoke more than the general Swedish population. In 1981 52% of the currently employed workers in the Swedish battery plant were smokers, 11% were former smokers, and 37% had never smoked.<sup>10</sup> These percentages are similar to the smoking habits of the general Swedish population. Axelsson has shown that differences in smoking habits

between a study population and the general population usually do not produce SMR values higher than 140.<sup>25</sup>

Our interpretation is that the accumulating data on the mortality of cadmium workers with high exposure levels in the past (above 0.3 mg Cd/m<sup>3</sup>) support an association between lung cancer and cancer of the prostate and the exposure to cadmium. Further epidemiological studies are needed to examine the influence of associated exposures, in particular that of nickel hydroxide.

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- <sup>2</sup> Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;**294**:687-90.
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