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Mortality of cadmium-exposed workers

A five-year update

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KAZANTZIS G, LAM T-H, SULLIVAN KR. Mortality of cadmium-exposed workers: A five-year update. *Scand J Work Environ Health* 14 (1988) 220—223. A cohort mortality study of cadmium-exposed workers initially followed to the end of 1979 has been updated for a further five years. The update has confirmed the findings of the original study with a significant excess risk from bronchitis related to intensity of exposure, although over the five-year period the excess mortality was no longer significant, a finding suggesting that the risk from bronchitis may now be declining in this cohort. In contrast, there is now a stronger indication of an excess risk from lung cancer related to intensity of exposure, significant for both the total and the five-year periods. There was again no increased risk from prostatic cancer, and from this and other studies it appears unlikely that cadmium, in the concentrations encountered in this and other recent studies, acts as a prostatic carcinogen. As in the initial study, there was no significant excess risk from hypertensive disease, nor any suggestion of an increased risk from cerebrovascular or renal disease.

Key terms: bronchitis, lung cancer, prostate cancer, stomach cancer.

The International Register of Potentially Toxic Chemicals (IRPTC) of the United Nations Environment Programme (UNEP) includes cadmium in its listing of environmentally dangerous chemical substances and processes of global significance (11). Atmospheric emissions of cadmium from man-made sources are considered in the IRPTC to exceed those of natural origin by one order of magnitude. Cigarette smokers were observed to be potentially at risk because of the high absorption of cadmium from tobacco smoke. Certain compounds of cadmium have been shown to give rise to cancer in animal studies (5), but the role of cadmium as a human carcinogen remains uncertain. The International Agency for Research on Cancer (IARC) in 1982 considered the evidence for the carcinogenicity of cadmium to be sufficient in animals, but limited in humans (3). Their classification of cadmium at that time as a 2B carcinogen was proposed for reclassification to category 2A in 1987.

The study of groups with occupational exposure is of particular value in elucidating adverse effects, as not only is exposure likely to have been greater in the occupational than in the general environment, but also absorption is markedly more effective following the inhalation of cadmium oxide fume and cadmium-containing dusts than after the ingestion of cadmium in food or water. A cohort of almost 7 000 male workers born before 1940 and exposed to cadmium for more than one year between 1942 and 1970 was initially followed with regard to mortality experience to the end of 1979 (1, 4). A statistically significant excess of deaths recorded as bronchitis was related to both intensity and duration of exposure, predominantly in the small group of men with heavy past exposure to cadmium. There were marginally more deaths from lung cancer than expected, but the excess was not related to exposure levels. No excess of deaths due to prostatic cancer, cerebrovascular disease, or renal diseases and no significant excess due to emphysema or hypertensive disease were observed. This cohort study has now been updated for a further five years to include all deaths to the end of 1984.

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Material and methods

Details of the methods used for the cohort analysis have been given earlier (1) and are briefly summarized here. Deaths were coded by underlying and other causes according to the eighth revision of the International Classification of Diseases (ICD) (13). Expected numbers were calculated from mortality rates for the population of England and Wales corrected to the eighth revision ICD codes, and regional variation in mortality was taken into account by the use of the cause-specific standardized mortality ratio (SMR) for standard regions published by the Office of Population Censuses and Surveys for the period 1969—1973. The ratios of observed to expected deaths (SMR values) were calculated, in five-year age and calendar strata, with the use of the Oxford Man-year Program devised

Table 1. Cause-specific mortality in relation to cadmium exposure (1943—1984). (O = observed cases, E = expected cases, SMR = standardized mortality ratio, 95 % CI = confidence interval)

Disease (ICD)	Exposure to cadmium															
	Ever high				Ever medium				Always low				Total			
	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI	O	E	SMR	95 % CI
All causes	60	56.3	107	80—133	319	328.2	97	87—108	2 088	2 119.0	99	94—103	2 467	2 504.3	99	95—102
All neoplasms (140—239)	22	14.7	150	94—227	86	84.8	101	80—123	579	523.5	111	102—120	687	623.1	110	102—118
Lung cancer (162)	12	6.2	194	100—339	41	34.0	121	84—158	224	200.7	112	97—126	277	240.9	115	101—129
Stomach cancer (151)	3	1.6	189	39—553	12	9.1	131	68—230	83	59.8	139	109—169	98	70.6	139	111—166
Prostate cancer (185)	—	0.6	0	0—615	—	4.0	0	0—92	30	28.6	105	71—150	30	33.2	90	61—129
Hypertensive diseases (400—404)	1	0.8	124	3—692	8	4.8	168	72—331	40	35.7	112	77—147	49	41.3	119	85—152
Cerebrovascular diseases (430—438)	2	4.8	42	5—151	23	29.0	79	50—119	153	196.5	78	66—90	178	230.3	77	66—89
Bronchitis (490—491)	13	3.4	382	203—654	25	17.1	146	94—215	140	114.3	123	102—143	178	134.9	132	113—151
Emphysema (492)	—	0.2	0	0—185	—	1.3	0	0—284	16	9.2	174	99—282	16	10.8	149	85—241
Nephritis and nephrosis (580—584)	1	0.4	258	7—1 437	1	2.2	45	1—248	14	16.2	86	47—145	16	18.9	85	49—138

by J Peto in 1980, the 95 % confidence interval (95 % CI) of the SMR being used to indicate statistical significance.

In addition to the seven disease categories for which there was some a priori reason to believe that a relationship to cadmium exposure might exist, stomach cancer was now included for detailed analysis because an excess mortality had been observed in a reanalysis of the 1979 data (6). Thus eight categories, together with "all causes" and "all neoplasms," have been included in the present report. Deaths occurring in these 10 categories have been followed to the age of 85 years. For a further 32 disease categories a screening procedure has been used with a censoring age of 75 years.

Jobs were again classified according to the level of past cadmium exposure into the three groups high, medium and low, and the years at risk were divided on the basis of these categories into the three groups "ever high" for a minimum period of one year, "ever medium" for a minimum period of one year, and "always low." For those workers who were still employed after 1979, their employment status between 1980—1984 was updated.

Rescrutiny of the initial study population identified a small number of erroneous entries, which reduced the number of workers included in the SMR analysis from 6 995 to 6 958 for the five-year period. The mean duration of exposure to cadmium was 12 years, and the mean interval from first exposure to the end of follow-up was 29 years. The distribution of the workers in the five principal industries involved was as in the initial study. By the end of 1984, 2 523 (36 % of the study population) had died; 4 184 (60 %) were known to be alive; 184 (3 %) had emigrated; and 67 (1 %) could not be traced. The reported tabulations refer to 2 467 decedents below the age of 85 years. The five years 1980—1984 gave an extra 21 857 person-years to the study with a total now of 173 961 person-years for the period 1943—1984.

Results

Cause-specific mortality in relation to cadmium exposure for the total study period is shown in table 1. With the additional five years of follow-up, all-cause mortality remained virtually unchanged. All-cause mortality increased with length of follow-up, being significantly lower than expected for those followed for less than 10 years (SMR 79, 95 % CI 68—90) and significantly higher than expected for those followed for more than 30 years (SMR 139, 95 % CI 104—174), a finding in keeping with the commonly observed "healthy worker effect."

Over the five-year period there were 26 deaths coded as bronchitis or chronic bronchitis, this level indicating a nonsignificant excess (SMR 132, 95 % CI 86—194) which was not related to intensity of exposure. However over the total study period the excess mortality from bronchitis was highly significant (SMR 132, 95 % CI 113—151), particularly in the small high-exposure group (SMR 382, 95 % CI 203— 654). There was a small but significant number of deaths from emphysema over the five-year period, all from the low-exposure group (SMR 277, 95 % CI 102—603) which, for the total study period, approached a significant level, again all in the low-exposure group (SMR 174, 95 % CI 99—282).

Mortality from all neoplastic disorders was significantly raised for both the five-year and the total study period (SMR 124, 95 % CI 106—142 and SMR 110, 95 % CI 102—118, respectively), attributed mainly to an increase in lung and stomach cancer mortality. The SMR for prostatic cancer had fallen from 99 in the 1979 cohort to 90 in the total study period, with 30 observed deaths in the low-exposure group and again no deaths in the medium- or high-exposure categories.

The five-year update contributed 75 additional cases of lung cancer, now giving a significant excess mortal-

ity both for the five-year period (SMR 134, 95 % CI 103—164) and the total study period (SMR 115, 95 % CI 101—129), an increasing SMR with intensity of exposure occurring in both the five-year and the total study periods (SMR 359, 95 % CI 131—780, and SMR 194, 95 % CI 100—339, respectively, for the high-exposure group). However a statistical test for trend was not significant. The increased lung cancer risk occurred mainly for those employed before 1940, rising with length of employment and also with length of follow-up. In an examination of lung cancer mortality in relation to type of industry, the copper cadmium alloy plants included in the study showed an excess mortality in the five-year update (SMR 231, 95 % CI 115—413). However the pattern of mortality was determined largely by long employment in a primary production plant, starting before 1940, but with only low or medium exposure to cadmium.

There were 22 deaths from stomach cancer over the five-year period (SMR 179, 95 % CI 112—271) with 98 deaths over the total study period (SMR 139, 95 % CI 111—166), seen mainly in the low-exposure category for men employed less then 10 years.

A small, nonsignificant excess mortality was observed for the category nephritis and nephrosis in the five-year update, but not for the total study period. There was no excess mortality from hypertensive disease in the five-year period, with a small, nonsignificant excess for the total study period. The SMR for cerebrovascular disease was significantly lower than expected in both the five-year and the total study period. Screening for the other 32 disease categories showed a significantly low SMR for diseases of the circulatory system (ICD 390—458) with an SMR of 83 (95 % CI 73—94) for the five-year period and an SMR of 89 (95 % CI 84—94) for the total study period. Within this broad category, ischemic heart disease (ICD 410—414) gave SMR values of 87 (95 % CI 74—100) for the five-year period and 92 (95 % CI 85—98) for the total study period.

Discussion

The five-year update of the 1979 cohort study confirmed and strengthened the findings of the original study with a marked excess mortality from diseases coded as bronchitis or chronic bronchitis, which showed a strong relationship to both intensity and duration of exposure. As in the initial study, there were no deaths coded as emphysema in the high- or medium-exposure groups, but now with a significant excess mortality in the low-exposure group. It is difficult to interpret these emphysema deaths in relation to cadmium exposure, as emphysema tends to be under-reported as an underlying cause of death in Great Britain.

With regard to cancer of the prostate, there were again no deaths in the small high-exposure or larger medium-exposure groups. These findings support the conclusion reached by Doll (2), in reviewing the evidence following the initial study (1), that cadmium should now cease to be regarded as a prostatic carcinogen. The Environmental Protection Agency in the United States has also concluded, from a review of existing studies, that there is insufficient evidence of a risk of prostatic cancer from exposure to cadmium oxide dust and fume (12).

Since the initial study, an unequivocal dose-related increase in the incidence of primary carcinoma of the lung has been shown in rats following the prolonged inhalation of a cadmium chloride aerosol (9). An update of a cohort study on American smeltery workers with heavy past exposure to cadmium oxide has shown an excess lung cancer mortality related to cumulative exposure to cadmium, but with certain assumptions having been made with regard to exposure to arsenic and cigarette smoke (10). However nickel cadmium battery workers exposed to cadmium oxide dust have shown no clear evidence of an increased lung cancer risk (8). In the initial cohort study, a significant excess of lung cancer deaths was shown only for men employed more than 10 years in the always low-exposure category, and it was considered unlikely that this excess could have been related to cadmium exposure. There is now a stronger indication of an excess risk from lung cancer, with a significant excess mortality in the cohort as a whole, and also in the small, high-exposure group. The increased risk was the most marked for men who were first exposed before 1940, with long exposure, and who have a long period of follow-up. However the majority of lung cancer deaths were from a large nonferrous smeltery which provided over 60 % of the total study population, but with only low or medium exposure to cadmium. In a subsequent case-referent study in the smeltery, the excess lung cancer mortality was found to be related to length of employment in the smeltery, but not to cumulative exposure to cadmium (results of Ades & Kazantzis awaiting publication). A working group on the carcinogenicity of cadmium (14) found the epidemiologic data on lung cancer difficult to interpret because of confounding from multiple occupational exposures including other putative carcinogens and because of the difficulty with the absence of smoking histories in assessing the contribution from cigarette smoking. A further case-referent study of lung cancer in workers with heavy past exposure to cadmium, taking account of concomitant exposures, is in progress.

In the initial study decedents were included below the age of 85 years for those causes believed a priori to be related to cadmium exposure and below the age of 75 years in a screening procedure adopted for other causes. An increased mortality from stomach cancer was identified in the 1979 cohort after a reanalysis in which a censoring age of 85 years was taken instead of 75 years. This increased stomach cancer mortality has been confirmed in the current update. In the five-

year period 22 additional cases of stomach cancer have been identified, giving a significantly raised SMR of 179 for the five years and an SMR of 139 for the total period of study. In contrast to lung cancer, however, no relationship has been identified with intensity or duration of exposure, the excess risk occurring in the low-exposure group and among men with less than 10 years' employment making it unlikely that cadmium could have been responsible.

With regard to other diseases of interest, the small excess mortality from hypertensive disease, which was not statistically significant in the initial study, has remained virtually unchanged, and similarly there has been no change in the mortality pattern in the category nephritis and nephrosis, which showed a nonsignificant deficit. However, as in the initial study, deaths from cerebrovascular disease were significantly lower than expected. While this finding is likely to be due to chance, it should be noted that a low mortality from cerebrovascular disease had previously been observed for cadmium-polluted areas in Japan (7). Furthermore, in a screening for 32 other causes of death, a deficit has also been found for diseases of the circulatory system and, within this category, for deaths from ischemic heart disease. While the overall pattern does not show cadmium to be a risk factor for the cardiovascular system, these observations of a possible reduced risk require further study.

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References

1. Armstrong BG, Kazantzis G. The mortality of cadmium workers. Lancet 1 (1983) 1424—1427.
2. Doll R. Occupational cancer: A hazard for epidemiologists. Int J Epidemiol 14 (1985) 22—31.
3. International Agency for Research on Cancer. Chemicals, industrial processes and industries associated with cancer in humans, volumes 1 to 29. Lyon 1982. (IARC monographs on the evaluation of carcinogenic risk of chemicals to humans, supplement 4).
4. Kazantzis G, Armstrong BG. A mortality study of cadmium workers in the United Kingdom. Scand J Work Environ Health 8 (1982): suppl 1, 157—160.
5. Kazantzis G, Lilly LJ. Mutagenic and carcinogenic effects of metals. In: Friberg L, Nordberg GF, Vouk V, ed. Handbook on the toxicology of metals. Elsevier, Amsterdam 1986, pp 319—389.
6. Lam TH, Sullivan KR, Kazantzis G. Further observations on the mortality of cadmium exposed workers: Progress report. International Lead Zinc Research Organization. New York, NY 1985.
7. Shigematsu I, Kitamura S, Takeuchi J, Minow M, Nagai M, Usui T, Fukushima M. A retrospective mortality study on cadmium-exposed populations in Japan. In: Cadmium Association. Cadmium 81: Edited proceedings, third international cadmium conference, Miami. London 1982, pp 115— 118.
8. Sorahan T. Mortality from lung cancer among a cohort of nickel cadmium battery workers: 1946—84. Br J Ind Med 44 (1987) 803—809.
9. Takenaka S, Oldiges M, Konig H, Hochrainer D, Oberdorster G. Carcinogenicity of cadmium aerosols in Wistar rats. J Natl Cancer Inst 70 (1983) 367—373.
10. Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of US cadmium production workers — An update. J Natl Cancer Inst 740 (1985) 325—333.
11. United Nations Environment Programme. List of environmentally dangerous chemical substances and processes of global significance: Report of the executive director of UNEP to the 12th session of its governing council (IRPTC). Geneva 1984.
12. United States Environmental Protection Agency. Updated mutagenicity and carcinogenicity assessment of cadmium (final report). Washington, DC 1985.
13. World Health Organization. Manual of the international statistical classification of disease, injuries and causes of death. World Health Organization, Geneva 1967.
14. ———. Carcinogenicity of cadmium. Lancet 2 (1986) 931.

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