

# Risk of mortality, cancer incidence, and stroke in a population potentially exposed to cadmium

Paul Elliott, Richard Arnold, Samantha Cockings, Naomi Eaton, Lars Järup, Jennifer Jones, Mike Quinn, Michael Rosato, Iain Thornton, Mireille Toledano, Emma Tristan, Jon Wakefield

## Abstract

**Objectives**—To follow up mortality and cancer incidence in a cohort potentially exposed to cadmium and to perform a geographical (ecological) analysis to further assess the health effects of potential exposure to cadmium.

**Methods**—The English village of Shipham has very high concentrations of cadmium in the soil. A previous cohort study of residents of Shipham in 1939 showed overall mortality below that expected, but a 40% excess of mortality from stroke. This study extends the follow up of the cohort for mortality to 1997, and includes an analysis of cancer incidence from 1971 to 1992, and a geographical study of mortality and cancer incidence. Standardised mortality and incidence ratios (SMRs and SIRs) were estimated with regional reference rates. Comparisons were made with the nearby village of Hutton.

**Results**—All cause cohort mortality was lower than expected in both villages, although there was excess cancer incidence in both Shipham (SIR 167, 95% confidence interval (95% CI) 106 to 250) and Hutton (SIR 167, 95% CI 105 to 253). There was an excess of mortality from hypertension, cerebrovascular disease, and nephritis and nephrosis, of borderline significance, in Shipham (SMR 128, 95% CI 99 to 162). In the geographical study, all cause mortality in Shipham was also lower than expected (SMR 84, 95% CI 71 to 100). There was an excess in genitourinary cancers in both Shipham (SIR 160, 95% CI 107 to 239) and Hutton (SIR 153, 95% CI 122 to 192).

**Conclusion**—No clear evidence of health effects from possible exposure to cadmium in Shipham was found despite the extremely high concentrations of cadmium in the soil.

(Occup Environ Med 2000;57:94-97)

Keywords: cadmium; mortality; cancer incidence

Land in the village of Shipham, Somerset, was mined for zinc from the 17th to the 19th century. The large quantities of cadmium (an impurity in the zinc carbonate) brought to the surface now contaminate the soil throughout the village. In the late 1970s, a national geochemical survey found unusually high concentrations of cadmium and other toxic metals in the soil.<sup>1</sup>

It is well known that exposure to cadmium causes kidney injury.<sup>2,3</sup> High exposure to cadmium was the cause of the severe itai-itai (ouch-ouch) skeletal disease in Japan, where cadmium contaminated rice was ingested by the local population.<sup>4,5</sup> Data from animal experiments have indicated that cadmium may play a part in the aetiology of cardiovascular disease, but the association in humans has been weak and inconclusive.<sup>2,3</sup> Cadmium has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC).<sup>6</sup> The IARC noted, however, that there were several constraints influencing the evaluation, which to a large extent was based on animal experiments, where the animals predominantly were exposed to inhaled or injected cadmium. The epidemiological evidence originates from occupationally exposed workers, with sparse historical data on exposure to cadmium, rarely accounting for confounding factors—for example, smoking). By contrast, a recent review concluded that there was only weak evidence for cadmium as a human carcinogen, in particular after oral exposure.<sup>7</sup>

The findings in the geochemical survey gave rise to a detailed investigation, where extremely high concentrations of cadmium were found, ranging up to 360 µg/g in surface garden soils,<sup>8</sup> much higher than those found in the polluted area in Japan, where the itai-itai disease occurred. Background concentrations in the United Kingdom for cadmium in soil are typically <1 µg/g. The concentrations of cadmium in soil in contaminated areas in Japan were in the order of 3 µg/g. There was therefore concern that the health of the residents of Shipham was at risk.<sup>9</sup> The average dietary intake of cadmium was found to be double (30 µg/day) that of the average United Kingdom concentration (14 µg/day),<sup>10</sup> but no measurable effects on the health of the population of Shipham could be detected.<sup>11</sup> No comparable data were available for Hutton.

A cohort mortality study of Shipham from 1939 to 1979 found that all cause mortality was similar to a neighbouring village (Hutton) outside the mining area, although conditions associated with cadmium toxicity, such as hypertensive, cerebrovascular, and genitourinary disease had apparently higher risk among the residents of Shipham, with a significant excess of cerebrovascular mortality (standardised mortality ratio (SMR) 140, p<0.05).<sup>12</sup>

The present study extends the follow up of mortality in the previous cohort by 18 years to 1997 and examines cancer incidence among

Small Area Health  
Statistics Unit,  
Imperial College  
School of Medicine,  
Norfolk Place, London  
W2 1PG, UK  
P Elliott  
R Arnold  
S Cockings  
N Eaton  
L Järup  
M Toledano  
J Wakefield

Environmental  
Geochemistry  
Research Group, TH  
Huxley School of the  
Environment, Earth  
Sciences and  
Engineering, Imperial  
College, London, UK  
I Thornton  
E Tristan

Office for National  
Statistics,  
1 Drummond Gate,  
London SW1V 2QQ,  
UK  
J Jones  
M Quinn  
M Rosato

Correspondence to:  
Dr Lars Järup, Department  
of Epidemiology and Public  
Health, Imperial College  
School of Medicine, Norfolk  
Place, London W2 1PG, UK

Accepted 27 September 1999

Table 1 Follow up of 1939 study cohort (SMRs for selected end points for residents (men and women combined) of Shipham ( $n=351$ ) and Hutton ( $n=260$ ), with reference rates estimated for the South West Region, 1946–58, and the South West Health Region, 1959–97)

Cause	Shipham			Hutton		
	Observed	SMR	95% CI	Observed	SMR	95% CI
All causes of death	254	90	79 to 101	185	90	78 to 104
Malignant neoplasms	42	81	59 to 110	33	88	61 to 124
Gastrointestinal cancers	11	56	28 to 100	11	77	39 to 138
Lung cancer	14	146	80 to 246	4	58	16 to 148
Breast cancer (female only)	5	88	29 to 205	1	24	1 to 131
Genitourinary cancer	8	88	38 to 172	11	167	83 to 298
Prostate cancer	1	41	4 to 229	2	124	15 to 447
Ovarian cancer	3	158	33 to 462	4	284	77 to 727
Kidney/bladder cancer	2	81	10 to 294	2	113	14 to 408
Other genitourinary cancer	2	92	11 to 331	3	191	39 to 558
Other malignant neoplasms (males)	2	58	5 to 162	2	83	10 to 301
Other malignant neoplasms (females)	2	45	5 to 162	4	119	32 to 304
Circulatory diseases, and nephritis and nephrosis	159	101	85 to 117	106	93	76 to 112
Hypertension, cerebrovascular disease, and nephritis and nephrosis	68	128	99 to 162	31	81	55 to 116
Other circulatory diseases	91	86	69 to 106	75	97	79 to 122
Respiratory diseases	18	53	32 to 84	19	79	47 to 123

the cohorts in Shipham and Hutton, from 1971 to 1992. To further assess potential health effects in the population currently living in Shipham, a geographical (ecological) study was also carried out.

## Methods

### COHORT STUDY

The original study cohorts were defined as the resident 1939 populations of Shipham and Hutton, totalling 504 and 414 study subjects respectively.<sup>12</sup> Our follow up analysis included subjects from the original 1939 cohort who were subsequently followed up until 1997. The same exclusion criteria as in the initial cohort study were applied. People who had died before 1946, children who had died before the age of 10, and wartime evacuees were excluded. The mortality analyses thus include a total of 351 residents of Shipham and 260 Hutton residents. Cancer incidence was assessed from 1971 to 1992. Deaths and cancer registrations were traced at the National Health Service Central Register in Southport.

The study period spanned almost 60 years, and five changes in international classification of disease (ICD) coding. Some end points therefore had to be grouped. The groupings used in the present study vary slightly from those used in the earlier cohort study, in which deaths had been coded up to the eighth revision of the ICD (ICD-8), whereas here deaths from 1979 were coded to ICD-9.

For cancer incidence, cases between 1946 and 1971, before the establishment of the national cancer registration system, were excluded, leaving 199 residents of Shipham and 149 Hutton residents available for these analyses.

Data for England and Wales were used to estimate age, sex, cause, and period specific mortality in 5 year age groups for the South West Region from 1939 to 1958. Data for the South West Health Region were available thereafter. For both mortality and cancer incidence, site specific regional rates were used to calculate the expected number of cases. The SMRs and cancer incidence ratios (SIRs) were

then computed, along with 95% confidence intervals (95% CIs).

### GEOGRAPHICAL STUDY

The study populations were the 1991 census wards of Shipham and Hutton. Mortality (1981–92) and cancer incidence (1974–89) were assessed. The postcode of residence was used to identify cases from the national cancer and mortality databases, held by the United Kingdom Small Area Health Statistics Unit (SAHSU). Death certificates and individual case notes (where applicable) of all cases of genitourinary cancer in Shipham were requested. Approval was obtained from each of the relevant local research ethics committees.

Population data were obtained from the “estimating with confidence” population estimates of the published 1991 census counts.<sup>13</sup>

As in the cohort study, expected rates were calculated for each end point with age, sex, and cause specific rates from the South West Region. Adjustment for socioeconomic deprivation was made with Carstairs’ score.<sup>14</sup> The SMRs and SIRs were computed along with 95% CIs.

## Results

### COHORT STUDY

A total of 254 deaths (72%) in Shipham and 185 deaths (71%) in Hutton were reported from 1946 to 1997 (table 1). Point estimates of both all cause mortality in Shipham (SMR 90, 95% CI 79 to 101) and in Hutton (SMR 90, 95% CI 78 to 104), and cancer mortality (SMR 81, 95% CI 59 to 110, and SMR 88, 95% CI 61 to 124 respectively) were lower than in the reference region. There was an excess of mortality from hypertension, cerebrovascular disease, and nephritis and nephrosis, of borderline significance, in Shipham (SMR 128, 95% CI 99 to 162).

There was a significant excess in combined cancer incidence both in Shipham and in Hutton (SIR 167, 95% CI 106 to 250 and SIR 167, 95% CI 105 to 253, table 2). In Shipham the excess was significant in women (SIR 200, 95% CI 117 to 231), but not in men (SIR 137, 95% CI 5 to 298).

Table 2 Follow up of the 1939 study cohort, men and women combined (SIRs for selected cancer sites with South West Health Region reference rates, 1971–92)

Cause	Shipham			Hutton		
	Observed	SIR	95% CI	Observed	SIR	95% CI
All malignant neoplasms	23	167	106 to 250	22	167	105 to 253
Gastrointestinal cancers	6	152	56 to 332	6	160	59 to 349
Lung cancer	5	246	80 to 574	3	161	33 to 472
Breast cancer (female only)	5	296	96 to 690	2	133	16 to 481
Genitourinary cancers	3	113	23 to 331	5	199	65 to 465
Prostate cancer	1	148	4 to 824	1	150	4 to 838
Ovarian cancer	1	303	8 to 1689	0	—	—
Bladder or kidney cancer	0	—	—	3	372	77 to 1086
Other genitourinary cancers	1	186	5 to 1034	1	202	5 to 1123
Other malignant neoplasms (males)	0	—	—	2	163	20 to 587
Other malignant neoplasms (females)	4	167	46 to 429	4	174	48 to 446

Table 3 Geographical study, men and women combined (SMR, 1981–92 and SIR, 1974–89 for selected end points in Shipham and Hutton, standardised for age, sex, and Carstairs quintile with the South West Region as the reference population)

Cause (ICD-9)	Shipham			Hutton		
	Observed	SMR	95% CI	Observed	SMR	95% CI
All cause mortality	138	84	71 to 100	498	99	91 to 108
Cerebrovascular mortality	20	87	56 to 135	63	96	75 to 122
Cancer incidence:		SIR			SIR	
All cancers	86	110	89 to 136	330	132	119 to 147
Lung	11	115	64 to 208	43	133	98 to 179
Breast, female	7	73	35 to 152	37	126	91 to 174
Genitourinary tract	24*	160	107 to 239	75	153	122 to 192
Prostate	12*	257	146 to 452	21	132	86 to 202
Ovary	5	257	107 to 618	9	148	77 to 285
Cervix or uterus	3	113	36 to 350	10	119	64 to 222
Bladder	4	112	42 to 298	26	223	152 to 328

\*Includes one case of probable pancreatic cancer, apparently miscoded as prostate cancer. Results without this case are: for genitourinary cancer (n=23), SIR=154 (102–231), and for prostate cancer (n=11), SIR=235 (130–425)

#### GEOGRAPHICAL STUDY

There were 138 deaths (1981–92) and 24 genitourinary cancers reported in the Shipham ward from 1974–89 (table 3). In Hutton, there were 498 deaths and 75 genitourinary cancers. All cause mortality in Shipham was lower than in the rest of the region (SMR 84, 95% CI 71 to 100), whereas in Hutton, it was similar to that in the region as a whole (SMR 99, 95% CI 91 to 108).

In both Shipham and Hutton, there was an excess of genitourinary cancer (SIR 160, 95% CI 107 to 239 and SIR 153, 95% CI 122 to 192, respectively). In Shipham, the excess was predominantly in cancer of the prostate (SIR 257, 95% CI 146 to 452) and ovary (SIR 257, 95% CI 107 to 618). In Hutton, there was excess risk of bladder cancer (SIR 223, 95% CI 152 to 328) and a non-significant excess risk of prostate cancer (SIR 132, 95% CI 86 to 202).

#### Discussion

The results of the cohort analyses showed lower all cause mortality in Shipham than in the South West Region as a whole, similar to the findings in the earlier study.<sup>12</sup> Total cancer mortality was also low, whereas cancer incidence was significantly higher than in the reference region, in both Shipham and the control village of Hutton.

There was an excess mortality from cerebrovascular disease, hypertension, and ne-

phritis and nephrosis (relative risk (RR) 128, 95% CI 99 to 162) among residents of Shipham in the cohort study, but this did not reach conventional levels of significance. Compared with some of the other causes of death, the confidence interval was relatively narrow, being based on 68 deaths. Unfortunately, it has not been possible to separate the diagnoses included from each other due to changes in classification of the ICD over time, so it remains unclear whether any excess risk may be associated with hypertension, cerebrovascular disease, or nephritis and nephrosis. There was no excess cerebrovascular mortality in the geographical analysis. A study among a population environmentally exposed to cadmium in Belgium found no excess cardiovascular mortality,<sup>15</sup> although an excess was recorded in a recent Japanese study among people exposed to cadmium.<sup>16</sup>

Although there was no evidence of an excess risk of incidence or mortality of genitourinary cancers in the cohort study, there was a 50%–60% excess of genitourinary cancer in both villages in the geographical study. In Shipham, there were twofold to threefold risks for cancers of the prostate and ovary, although these findings were based on small numbers of cases (12 and five, respectively). In the control village of Hutton, the excess was largely due to a twofold risk of bladder cancer.

Early findings suggested that cadmium might cause prostate cancer.<sup>17</sup> Later studies have shown only slight<sup>18 19</sup> or no<sup>20 21</sup> increases in risk. The inconsistency of the findings associating exposure to cadmium with risk of prostate cancer is recognised by the IARC in its classification of cadmium as a carcinogen.<sup>6</sup> As noted in the introduction, IARC based its classification largely on experimental animal studies. The results from our geographical study apparently lend weak support to the hypothesis that cadmium may be associated with prostate cancer, although these results are not supported by the findings in the cohort study. The members of the Shipham cohort can be assumed to have had potential exposure to cadmium in the soil over several years. In particular, children growing up in Shipham may have been exposed to cadmium through ingestion of soil (geophagia).

The geographical study covered a period of population growth, including inward migration, and thus residents may have had potential exposure only over a relatively short period. Further investigations showed that eight of the 22 cases of genitourinary cancer with available data had been resident in Shipham for <10 years. It should also be noted that the results are based on small numbers of cases. As several tests of significance were carried out (all of which are reported in the tables), some of the significant results may have occurred by chance alone. Thus, the increased risk of prostate cancer may well be a chance finding, and studies on larger, environmentally exposed, populations are needed to further explore the potential role of orally ingested cadmium in the development of prostate cancer.

The assessment of potential exposure was based on the geographical distribution of cadmium in soil. Limited data exist on the actual exposure to cadmium in the population.<sup>10</sup> Previous data indicate that the cadmium content in the soil is extremely high in Shipham.<sup>8</sup> However, the mean intake of cadmium through the diet was estimated to be 0.2 mg/week,<sup>10</sup>—that is, 30 µg/day—which is much lower than the 200 µg/day recorded in the contaminated areas in Japan.<sup>22</sup>

For comparison, the current provisional tolerable weekly intake (PTWI), suggested by the World Health Organisation (WHO) is 70 µg/day.<sup>7</sup> It is likely that most residents of Shipham would have been only marginally exposed to cadmium, because of its low bioavailability and the ready availability (at least in recent years) of commercially grown fresh produce. Thus the soil content of this toxic metal cannot readily be translated into human health risks. Preferably biomarkers should be used to assess exposure. Cadmium in urine reflects the total body burden<sup>7</sup> and low urinary concentrations thus indicate that exposure has been limited. Low cadmium concentrations were found in blood and urine in a survey of residents of Shipham in 1979,<sup>11</sup> but few of the older residents of Shipham (those with the longest periods of potential exposure) participated in the survey. Biological data (cadmium in blood or urine) were not available for use in the present investigation. Any further study needs to include biomarkers to assess cadmium dose as well as markers of renal and bone damage.

In summary, no clear evidence of health effects from possible exposure to cadmium was found among a population potentially exposed to exceedingly high concentrations of cadmium in the soil. The United States Environmental Protection Agency has demanded that soil contaminated with cadmium should be removed if concentrations exceed 90 ppm (µg/g), as found recently in a Superfund site (National Zinc Company, Oklahoma, EPA ID OKD000829440). This soil concentration is exceeded in many parts of Shipham. Our analyses suggest that the risk to human health is low, at least in an area where evidence of considerable human exposure to cadmium has not been clearly established.

The Small Area Health Statistics Unit is funded by a grant from the Department of Health, Department of the Environment, Transport and The Regions, Health and Safety Executive, Scottish Office Home and Health Department, Welsh Office, and Northern Ireland Department of Health and Social Services.

This work was also supported by an equipment grant from the Wellcome Trust, UK. We thank the Office for National Statistics (formerly the Office of Population Censuses and Surveys) for provision of data. The views expressed in this publication are those of the authors and not necessarily those of the funding departments or of the Office for National Statistics. We thank Mrs Ann Fisher, Manager of the Bristol office of the South and West Cancer Intelligence Unit, for her help in confirming details of cancers diagnosed in Shipham, and Professor Ivan Perry (University of Cork) who helped initiate the study.

- 1 Webb JS, Thornton I, Thompson M, *et al.* *The Wolfson geochemical atlas of England and Wales*. Oxford: Oxford University Press, 1978.
- 2 Friberg L, Elinder CG, Kjellström T, *et al.* *Cadmium and health: a toxicological and epidemiological appraisal*. Boca Raton: Fla CRC Press, 1986:2.
- 3 World Health Organisation. *Cadmium. Environmental health criteria*. Vol 134. Geneva: WHO, 1992:280.
- 4 Hagino N, Kono M. A study on the cause of Itai-itai-disease. *Proceedings of the 17th meeting of the Japanese Society of Clinical Surgeons*. 1955. (In Japanese.)
- 5 Kjellström T. Mechanism and epidemiology of bone effects of cadmium. [review]. *IARC Sci Publ* 1992;2:301–10.
- 6 International Agency for Research on Cancer. Cadmium and cadmium compounds. In: *Beryllium, cadmium, mercury and exposure in the glass manufacturing industry. IARC Monographs on the evaluation of carcinogenic risks to humans*. Lyon: IARC, 1993;58:119–237.
- 7 Järup L, Berglund M, Elinder CG, *et al.* Health effects of cadmium exposure: a review of the literature and a risk estimate. *Scand J Work Environ Health* 1998;24(suppl 1):1–51.
- 8 Thornton I. Content of soils and dust. In: Morgan H, ed. *The Shipham report. An investigation into cadmium contamination and its implications for human health*. *Sci Total Environ* 1988;75:21–39.
- 9 Simms DL, Morgan H. Introduction. In: Morgan H, ed. *The Shipham report. An investigation into cadmium contamination and its implications for human health*. *Sci Total Environ* 1988;75:1–10.
- 10 Morgan H, Smart GA, Sherlock JC. Intakes of metal. In: Morgan H, ed. *The Shipham report. An investigation into cadmium contamination and its implications for human health*. *Sci Total Environ* 1988;75:71–100.
- 11 Strehlow C, Braltrap D. Health Studies. In: Morgan H, ed. *The Shipham report. An investigation into cadmium contamination and its implications for human health*. *Sci Total Environ* 1988;75:101–33.
- 12 Inskip H, Beral V, McDowall M. Mortality of Shipham residents: 40 year follow up. *Lancet* 1982;i:896–9.
- 13 Simpson S, Cossey R, Diamond I. 1991 population estimates for areas smaller than districts. *Popul Trends* 1997;90:31–9.
- 14 Carstairs V, Morris R. Deprivation: explaining differences between mortality between Scotland and England. *BMJ* 1989;299:886–9.
- 15 Staessen JA, Buchet JP, Ginocchio G, *et al.* Public health implications of environmental exposure to cadmium and lead: an overview of epidemiological studies in Belgium. Working groups. *J Cardiovasc Risk* 1996;3:26–41.
- 16 Nishijo M, Nakagawa H, Morikawa Y, *et al.* Mortality of inhabitants in an area polluted by cadmium: 15 year follow up. *Occup Environ Med* 1995;52:181–4.
- 17 Potts CL. Cadmium proteinuria. The health of battery workers exposed to cadmium oxide dust. *Ann Occup Hyg* 1965;8:55–61.
- 18 Armstrong BG, Kazantzis G. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case control study. *Br J Ind Med* 1985;42:540–5.
- 19 Elghany NA, Schumacher MC, Slattery ML, *et al.* Occupation, cadmium exposure, and prostate cancer. *Epidemiology* 1990;1:107–15.
- 20 West DW, Slattery ML, Robison LM, *et al.* Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. *Cancer Causes Control* 1991;2:85–94.
- 21 Rooney C, Beral V, Macconochie N, *et al.* Case-control study of prostatic cancer in employees of the United Kingdom Atomic Energy Authority. *BMJ* 1993;307:1391–7.
- 22 Iwata K, Saito H, Moriyama M, *et al.* Renal tubular function after reduction of environmental cadmium exposure: a 10 year follow up. *Arch Environ Health* 1993;48:157–63.