

Mortality of inhabitants in an area polluted by cadmium: 15 year follow up

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Abstract

Objective—To assess the influence of environmental exposure to cadmium (Cd) on long term outcome of inhabitants living in an area polluted by Cd.

Methods—A follow up study for 15 years (from 1974-5 to 1991) was carried out on 2408 inhabitants (amounting to 95% of the target population, 1079 men and 1329 women) of the Kakehashi River basin in Ishikawa Prefecture, Japan. These inhabitants had been the subjects of the health impact survey in 1974-5 to evaluate (by measurement of urinary retinol binding protein (RBP)) renal dysfunction induced by Cd. Analysis of mortality was performed by dividing subjects into a urinary RBP positive (≥ 4 mg/l) group and RBP negative (<4 mg/l) group.

Results—After adjustment for age with Cox's proportional hazard model, RBP ≥ 4 mg/l showed a significant relation to mortality in both sexes. At this time, the mortality risk ratio of the RBP positive to negative group was 1.71 in the men and 1.42 in the women. When the SMRs according to causes of deaths in the RBP positive group were compared with those of the RBP negative group or the overall Japanese population increases of SMR for cardiovascular diseases, especially heart failure, and renal diseases were found in both sexes.

Conclusion—These results suggest that the prognosis of the exposed inhabitants with renal tubular dysfunction is unfavourable, and these increases of mortality are due to heart failure and renal diseases.

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Keywords: environmental cadmium; retinol binding protein; mortality

Renal tubular dysfunction is well known as an adverse health effect of environmental cadmium (Cd) exposure, and is characterised by the increased urinary excretion of low molecular weight proteins. Kakehashi River basin in Ishikawa Prefecture has been designated as one of the areas polluted by Cd in Japan.¹ The source of pollution was an upstream copper mine closed in 1971. The Health Authorities of Ishikawa Prefecture conducted a health impact survey in 1974-5 by measuring urinary retinol binding protein (RBP) in morn-

ing urine samples and found a high prevalence of urinary RBP positive (≥ 4 mg/l) subjects among the inhabitants living in the polluted Kakehashi River basin aged >50 years.¹

We followed up the subjects targeted in this 1974-5 health survey for seven years and found that the mortality of the urinary RBP positive group was higher than that of the urinary RBP negative (<4 mg/l) group in men.² We also reported that the mortality of a urinary β_2 -microglobulin positive group was higher than that of a β_2 -microglobulin negative group in both sexes in a nine year follow up study of the subjects in the 1981-2 health impact survey in the same area.³

In the seven year follow up study since the 1974-5 health impact survey, differences in survival rates according to age group and cause of death could not be adequately examined because of small numbers of deaths due to the short observation period. In the follow up study of the remaining subjects of the 1981-2 study, those with severe renal tubular dysfunction may have already died by 1981-2.

Against this background, we conducted a 15 year follow up study of the subjects of the 1974-5 examination, and attempted to determine the long term prognosis of Cd induced renal tubular dysfunction with urinary RBP as an index.

Subjects and methods

In August 1974 and from March to April 1975 the Ishikawa Prefectural Health Authority conducted a two part health impact survey among the inhabitants aged ≥ 50 years in the Cd polluted Kakehashi River basin in Ishikawa Prefecture. A total of 2408 people (1079 men and 1329 women) participated in these surveys, which represented 95.4% of the target population. At the time of the surveys, early morning urinary RBP was measured semiquantitatively by electrophoresis with a cellulose acetate membrane. Table 1 shows the age distribution of the subjects at

Table 1 Prevalence of RBP ≥ 4 mg/l in three age groups

	Men		Women	
	n	RBP ≥ 4 mg/l (%)	n	RBP ≥ 4 mg/l (%)
50-59	483	15 (3.1)	564	10 (1.8)
60-69	365	24 (6.6)	452	30 (6.6)
70-	231	36 (15.6)	313	73 (23.3)
Total	1079	65 (6.0)	1329	113 (8.5)

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Table 2 Analysis of urinary RBP and mortality with Cox's proportional hazard model

Index	Coefficient	SEM	Hazard ratio (95% CI)†	χ^2	P value
Men:					
Age*	1.064	0.055	2.90 (2.60-3.23)	362.82	<0.001
RBP†	0.337	0.155	1.40 (1.04-1.90)	4.76	<0.05
Women:					
Age*	1.173	0.052	3.23 (2.92-3.58)	506.97	<0.001
RBP†	0.466	0.124	1.59 (1.25-2.03)	14.15	<0.001

* Age has been coded as follows: 50-59 = 1, 60-69 = 2, 70-79 = 3, $\geq 80 = 4$; † RBP has been coded as follows: RBP <4 mg/l = 1, RBP ≥ 4 mg/l = 2; ‡ hazard ratio = age ($\times + 10$)/ \times : RBP (≥ 4 / <4).

the time of the health examinations and the prevalence of subjects with ≥ 4 mg/l of RBP. We conducted a follow up survey of the subjects of the 1974-5 health impact survey, from the day of their initial examination until the end of March 1991. The survival (alive or dead) and place of residence (still residing or not in the target area) was determined with the cooperation of the Komatsu Public Health Office and Komatsu Municipal Office. Also, the date and cause of death were investigated from death certificates. Mortality was calculated by the person-years method. The subjects were divided into urinary RBP positive and negative groups, and the data were analysed by Cox's proportional hazard model,⁴ with two variables—age at the time of examination and urinary RBP concentration—to correct for the influence of age when the relation between urinary RBP and mortality was examined, and standardised mortality ratio (SMR) according to cause of death. The SMRs were determined in the RBP positive and negative groups and compared one with the other and with that of the overall Japanese population. Individual causes of death were classified according to the ninth revised International Classification of Diseases. At this time, age distribution and death rate per decade of the overall Japanese population during the observation period were used as standards. For the determination of SMRs,

normal distributions were used when the expected number of deaths was ≥ 30 and approximation equations with Poisson distribution when the expected number of deaths was <30 .⁵ Also, the SMR of the RBP positive and negative groups were compared by the method of Fukutomi *et al.*⁶

Results

Positive urinary RBP showed a significant relation to mortality in both sexes by Cox's proportional hazard model (table 2). At this time, the mortality risk ratio (hazard ratio) of the RBP positive group to the RBP negative group was 1.71 for men and 1.42 for women.

Table 3 shows the SMRs according to causes of death in all men, RBP positive men, and RBP negative men. Although there was no significant difference, the SMR for all causes in all men was lower than that of the overall Japanese population. For all men the SMR for ischaemic heart disease was significantly lower, and SMRs for renal diseases and senility were significantly higher than those of the overall Japanese population. In the men the SMRs of the urinary RBP positive group were higher than those of the overall Japanese population for diabetes mellitus, cardiovascular diseases, respiratory diseases, renal diseases, and senility. These were also significantly higher in the urinary RBP negative group than in the overall Japanese population. Compared with the urinary RBP negative group, SMRs for cardiovascular diseases, respiratory diseases, and renal diseases were significantly higher in the urinary RBP positive group. The greater number of deaths from cardiovascular diseases were due to heart failure, and the SMR of the urinary RBP positive group for heart failure was significantly higher than that of the overall Japanese population or the urinary RBP negative group. A significant increase in SMR for cerebrovascular diseases was not found; however, the SMR for cerebral

Table 3 The causes of deaths among the inhabitants of an area polluted by Cd

Causes of death	ICD No	Men						Women					
		Total		Urinary RBP <4 mg/l		Urinary RBP ≥ 4 μ g/l		Total		Urinary RBP <4 mg/l		Urinary RBP ≥ 4 μ g/l	
		O	SMR	O	SMR	O	SMR	O	SMR	O	SMR	O	SMR
All causes	001-999	469	93.5	420	90.3*	49	134.5***‡	461	101.0	373	98.7	88	156.1***‡‡
Infectious diseases	001-139	12	124.6	12	133.7	0	0	4	68.2	3	15.6	1	154.4
Malignant neoplasms	140-208	109	82.4	104	83.5*	5	64.0	68	80.3+	61	79.5+	7	100.1
Stomach	151	39	95.1	38	98.8	1	39.7	21	87.6	19	87.0	2	93.2
Trachea, bronchus, lung	162	16	60.9*	16	64.7*	0	0	6	64.9	6	70.5	0	0
Diabetes mellitus	250	5	85.1	4	73.0	1	249.3	9	124.4	4	59.9	5	731.5***‡‡‡
Cardiovascular diseases	390-429	90	90.7	76	83.0*	14	182.0***‡	124	116.4	96	103.9	28	197.2***‡‡
Ischaemic heart diseases	410-414	24	63.2*	22	62.5*	2	71.9	28	82.6	25	86.5	3	71.1
Heart failure	428	52	122.5	42	38.1*	10	302.6***‡	86	179.1***	63	155.9*	23	353.0*†
Cerebrovascular diseases	430-438	98	101.4	88	98.9	10	130.0	85	75.1	71	72.4	14	92.6
Cerebral haemorrhage	431-432	22	69.2+	21	71.1	1	44.1	21	68.7	19	65.2*	2	56.0
Cerebral infarction	433,434, 437-7A,B	67	123.2	58	116.6	9	193.5*	55	98.2	45	98.7	10	123.7
Respiratory diseases	460-519	51	104.4	43	95.7	8	206.1*‡	28	82.8	23	78.7	5	108.4
Digestive diseases	520-579	22	116.6	22	124.9	0	0	24	165.8*	22	171.6*	2	120.3
Kidney and urinary diseases	580-599	15	167.0*	11	131.8	4	627.6***‡	17	163.2*	12	134.7	5	432.5***‡
Nephritis and nephrosis	580-589	13	173.2*	9	128.6	4	790.5*	11	140.4	6	85.6	5	621.5***‡
Urinary tract diseases	590-599	2	135.2	2	148.4	0	0.0	6	232.4*	6	259.8*	0	0.0
Senility		26	178.0*	21	162.1*	5	303.0*	67	249.2***	51	238.0***	16	293.5***
Accident and suicide	E800-999	26	135.7+	25	138.7+	1	88.6	20	140.0+	17	131.4	3	221.9

+ P <0.1; * P <0.05; *** P <0.001 significantly greater than the SMR of Japanese general population;

† P <0.05; ‡ P <0.01; ‡‡ P <0.001 significant difference between the SMRs of the two RBP groups. -* P <0.05 significantly less than . . . etc. O = observed.

infarction in the urinary RBP positive group was higher than that of the overall Japanese population, although no significant difference was found between the urinary RBP positive and negative groups. With regard to renal diseases, the SMR for nephritis and nephrosis was significantly higher in the urinary RBP positive than the negative group and the overall Japanese population.

Table 3 also shows the SMRs according to causes of death for women. The SMR for all causes in all women was not different from that of the overall Japanese population, but SMRs for digestive diseases, renal diseases, and senility were significantly higher than those of the overall Japanese population. Although a significant increase in the SMR of all women for cardiovascular diseases was not found, the SMR for heart failure was significantly higher than that of the Japanese general population. In the women, the SMRs of the urinary RBP positive group were higher than those of the overall Japanese population for diabetes mellitus, cardiovascular diseases, diseases of the kidneys and urinary system, and senility, whereas only the SMRs for diseases of the digestive system and senility were significantly higher in the urinary RBP negative group than in the overall Japanese population. The SMRs for diabetes mellitus, cardiovascular diseases, and renal diseases were significantly higher in the urinary RBP positive than the negative group in the women. The SMR for heart failure was higher in both urinary RBP positive and negative groups than in the overall Japanese population, with the increase in the SMR more obvious in the urinary RBP positive group, and the SMR in this group was significantly higher than in the RBP negative group. A significant increase in the SMR of the urinary RBP positive group of women for nephritis and nephrosis was found compared with the RBP negative group and the overall Japanese population.

Discussion

In 1974–5 Ishikawa Prefecture conducted the first health impact survey, measured the RBP concentration in morning urine samples, and found a clear increase in the frequency of abnormally high concentrations.¹ Nogawa *et al* showed a probit regression line between urinary RBP ≥ 4 mg/l and the average Cd concentration in rice for each hamlet, and found a dose-response relation between them.⁷ In 1981–2, the second health impact survey was conducted. Urinary β_2 -microglobulin, and urinary Cd were measured in that survey, and a high prevalence of abnormal values was found.⁸ Ishizaki *et al* also showed a dose response relation between urinary β_2 -microglobulin and urinary Cd in this survey.⁹ In this way, it has been convincingly shown that high prevalence of proximal tubular dysfunction found in the inhabitants of the Kakehashi River basin is attributable to Cd pollution.

In the seven year follow up study of the same subjects investigated here an increased

mortality was found in the urinary RBP positive group only in the men,² whereas in our study in which the observation period was extended to 15 years increased mortalities were found in both sexes in the urinary RBP positive group. These results are similar to those of the report of the 1981–2 Cd health impact survey in which the subjects were followed up for about nine years and in which the prognosis of the urinary β_2 -microglobulin positive group was shown to be unfavourable.³ Also, in a 13–15 year follow up survey of Kosaka town in Akita Prefecture, another region polluted by Cd in Japan, the prognosis of the female inhabitants with positive urinary β_2 -microglobulin was shown to be unfavourable.¹⁰

By contrast, in the reports of Shigematsu *et al* SMRs were significantly lower in towns and villages in the areas polluted by Cd. We conducted a case control study of subjects with itai-itai disease and with suspected disease in the Jinzu River basin, located in Toyama Prefecture, and found high mortalities in both groups.¹³ These discordant results are thought to be due to the fact that Shigematsu *et al* compared a plains area (the polluted area) and a mountainous area (control area), where overall mortalities differ in Japan.

An interesting issue is whether or not the increased mortalities found in areas polluted by Cd are due to increases in mortalities for specific diseases. Of the previously conducted surveys on causes of death in regions in Japan polluted by Cd, that of Shigematsu *et al* found significantly lower SMRs for heart disease, hypertensive diseases, and cerebrovascular diseases in areas polluted by Cd than in control areas.^{11,12} In the polluted Kakehashi River basin in Ishikawa Prefecture studied here, deaths from cardiovascular diseases, especially heart failure, accounted for most of the deaths, with the data on cardiovascular and cerebrovascular diseases differing from those described in the report of Shigematsu *et al*.^{11,12}

Although blood pressure values in the inhabitants of the Kakehashi River basin have not yet been determined, Nogawa and Kawano previously reported that blood pressure was lower in patients with itai-itai disease who live in the Jinzu River basin of Toyama Prefecture than in controls. In our study, no increase was found in the SMRs for hypertensive diseases and cerebral haemorrhage, which are closely associated with hypertension, which indicates that mortalities relating to hypertension may be decreased in this population. On the other hand, in Japan it is customary to ascribe the cause of death to heart failure in cases with no other clear cut cause of death or in those that show a gradual deterioration culminating in death, and this practice may be one factor accounting for the high mortalities for heart failure found in this study.

High morbidities for chronic bronchitis and emphysema,¹⁵ and high mortality for bronchitis¹⁶ have been reported in factory workers exposed to Cd, and in our study, also SMR for respiratory disease was significantly higher

in the men. As the excessive mortality due to respiratory disease found in our study was mainly due to pneumonia and bronchitis and the route of Cd exposure differed from that of factory workers, it is considered that these deaths may not have been due to a direct influence of Cd but rather to a worsening of the general state of health.

In our study we found a high SMR for renal diseases, in particular nephritis and nephrosis, and in the study of Shigematsu *et al* SMR for uraemia was significantly increased.^{11,12} In the Kakehashi River basin targeted in our study, the SMR for diabetes mellitus was also high in the women. Most of the deaths from diabetes occurred early in the observation period when renal dysfunction induced by Cd was not recognised. Renal dysfunction due to Cd is often accompanied by raised urinary glucose. Diabetes may have been mistakenly diagnosed in some of these subjects. Lauwerys *et al* reported frequent deaths from renal disease among inhabitants with a long history of exposure in regions polluted by Cd in Belgium, and Elinder *et al*¹⁸ and Kjellstrom *et al*¹⁹ in a study of mortalities in factory workers exposed to Cd found significantly high values for deaths due to nephritis and nephrosis. These findings suggest that subjects with renal tubular disorder induced by Cd may have advanced renal dysfunction and be at high risk of premature death.

In studies on causes of death in factory workers the impact or lack of impact of Cd on mortality from malignant neoplasms, particularly prostate and lung cancers, has become an issue.^{18,20-22} In our study the number of deaths was small and it was not possible to determine cancer mortalities according to site. A longer follow up period is necessary to evaluate this.

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