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Mortality Study of Inhabitants in a Cadmium-Polluted Area

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In Japan there are several areas of environmental pollution of cadmium (Cd) including the Jinzu River basin. Itai-itai disease has affected inhbitants in polluted areas of Toyama Prefecture within this area (Tsuchiya 1978). However, few long-term follow-up studies of inhabitants in polluted areas have been conducted to examine the effect of Cd-induced disorders on survival. The Kakehashi River basin in Ishikawa Prefecture suffered from the Cd pollution caused by Ogoya Mine (closed in 1971) located upstream. In epidemiological surveys conducted by Ishikawa Prefecture in 1974 and 1975 (Ishikawa Prefecture 1976), Cd-induced disorders were found in terms of excretion of 4 mg/l or more retinol binding protein (RBP) in 206 (7.7 %) of 2,691 inhabitants aged over 50, accounting for 96 % of the total population in 23 Cd-polluted communities. The purpose of the present study is to clarify the health risk due to environmental pollution with Cd on the basis of follow-up inhabitants in the Kakehashi River basin in Ishikawa Prefecture between 1974 and 1982.

MATERIALS AND METHODS

Of the 23 communities selected for the health survey in 1974–75, a similar survey was conducted in 20 in 1981 and 1982. The subjects of the present study were all inhabitants more than 50 years of age in the 20 communities who received the health examination in 1974 or 1975. Inhabitants in the 1974–75 survey who were not found in the 1981–82 survey were followed-up by the cooperation of Komatsu Health Center to confirm whether they had moved out of the community or had died. For those who died, the dates and causes of death were confirmed by death records. For those who

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Table 1. Inhabitants of cadmium-polluted areas who were examined and observed

	Total	Male	Female
Number of persons examined	2,414	1,078	1,336
Persons with urine RBP	185[a] (7.7)[b]	72[a] (6.7)[b]	113[a] (8.5)[b]
Total person-years of observation	15,274.25	6,734.5	8,539.75
Mean observation years per person	6.3	6.2	6.4

a: Number of persons b: percent

moved, the dates of movement were also investigated. Of the total population of 2,537 inhabitants (1,138 males and 1,399 females) in the 20 communities, 2,414 participated in the 1974-75 health survey (the rate of examinees, 95 %; 1,078 males and 1,366 females). During the follow-up period from 8 years (4 communities) between 1974 and 1982 at the longest to 6 years between 1975 and 1981 (2 communities) at shortest, 403 inhabitants (209 males and 194 females) died, and 74 (28 and 46, respectively) moved out of the communities, 24 of whom were found to be alive or dead.

The groups with positive and negative urine RBP (4 mg/l or more) in the 1974-75 health survey were compared with respect to the overall mortality rate and the mortality rate according to the cause of death. Since the follow-up period varied from 6 to 8 years according to the community, the person-years method was employed for calculation of mortality rates. The total person-years of observation was 15,274.25, and the mean follow-up period per person was 6.3 years (Table 1). In the positive RBP group there was a large number of aged inhabitants; because of definite differences in age composition between this group and the negative RBP group, it was difficult to make a direct comparison of mortality rates. We therefore used the age composition of the negative RBP group as a basis for calculating observed/expected risk ratios (observed deaths / expected deaths) of the positive RBP group. Poisson distribution was used to test comparison of risk ratios. Causes of death were classified according to the Nineth Corrected International Classification of Diseases.

RESULTS AND DISCUSSION

The kidney is important target organ for Cd, and low-molecular-weight proteinuria, such as retinol

binding proteinuria and β2-microglobulinuria, is an indicator representing the earliest Cd-induced disturbance of this organ (Piscater 1966; Hansn et al 1977; Kjellstrom et al 1977). The urine β2-microglobulin concentration is reported to be closely associated with creatinine clearance and %TRP (Nogawa et al 1980; Nogawa 1984), and an increase of low-molecular-weight proteins in urine indicates functional abnormality of the kidney, particularly the uriniferous tubule. The determination of urine RBP (Fukushima 1975) employed in the present study is less accurate than that of β2-microglobulin. However, the latter method was not commonly used in the 1974-75 period, and the urine RBP level was determined in the health survey on inhabitants in Cd-polluted areas in the Kakehasi River basin by Ishikawa Prefecture.

On the other hand, since retinol binding proteinuria is associated with nephropathy and other diseases due to various causes, the environmental pollution with Cd may not be the sole reason for the high incidence of positive urine RBP among the inhabitants. The Cd concentration in the rice produced in polluted areas and those in the blood and urine are used as indicators for Cd exposure, and the urine Cd level is believed to reveal long-standing exposure to Cd (Lauwery et al 1976; Hassler et al 1983; Bernald et al 1980). Using the same subjects as these in our survey, Nogawa et al (1978) detected close relationships between the mean Cd concentration in the rice produced in each community and the positive urine RBP rate, and between the urine Cd concentration and the positive urine RBP rate. They observed a probit regression line between the urine Cd concentration and the positive urine RBP rate, which showed a sigmoid dose-response relationship. Ishizaki (1985) have reported similar findings using the positive urine β2-microglobulin rate in the same Cd-polluted areas. These reports clarified that the high positive urine RBP rate among the inhabitants in the Kakehashi River basin was due to the environmental pollution with Cd.

Of the 2,414 examinees of the 1974-75 health survey, urine RBP was positive in 185 (72 males and 113 females), of whom 76 (41.1 %; 34 males and 42 females) died during the follow-up period. Urine RBP was negative in 2,229 inhabitants (1,006 males and 1,223 females), 327 of whom died (14.7 %; 175 males and 152 females). The overall mortality rate in the positive RBP group was about 2.8 times that of the negative group. By sex, the male mortality rates for both the positive and negative RBP groups were high, and the ratio of deaths with positive to negative RBP was 2.7 : 1 for males and 3.0 : 1 for females. The mortality rate per 1,000 person-years was higher in

Table 2. Mortality rates (per 1,000 person-years) by sex and age group

		Inhabitants without urine RBP		Inhabitants with urine RBP	
		Number of deaths	Mortality rate	Number of deaths	Mortality rate
Male	Total	175	27.46	34	93.86
	50-59	14	6.90	1	18.96
	60-69	53	19.95	4	36.95
	70-79	66	46.69	15	107.53**
	80-89	35	137.80	12	197.53
	90-	7	400.00	2	2000.00
Female	Total	152	19.20	42	67.44
	50-59	4	1.62	0	0
	60-69	34	10.36	1	6.12
	70-79	45	27.08	19	82.07**
	80-89	61	128.90	18	102.13
	90-	8	310.68	4	266.67

RBP: retinol binding protein
** significant difference ($P<0.01$) compared with inhabitants without urine RBP

the positive RBP group (77.2) than in the negative RBP group (22.9). By sex, the mortality rate for males with positive urine RBP was 93.9 per 1,000 person-years, and that with negative urine RBP, 27.5, and those for females were 67.4 and 19.2, respectively. Thus, the mortality rates for inhabitants with positive urine RBP were higher, both male and female, than those for the negative RBP group. Table 2 shows the mortality rates per 1,000 person-years according to the age group. In the males, with the exception of those over the age of 90, the positive RBP group showed higher mortality rates than those of the negative RBP group, with the diffrerence being significant in the 70 to 79-year old group ($P < 0.01$). This tendency was not observed in the females with the exception of a significant excess mortality rate in the 70 to 79-year-old group with positive urine RBP ($P < 0.01$).

In the positive RBP group, the observed/expeected risk ratio, which was calculated to correct the difference in the age composition between the positive and negative RBP groups, was 1.91 for the males and 1.19 for the females, with a siginificantly excess number of deaths among the males with positive urine RBP ($P < 0.001$). Table 3 shows the observed/expected risk ratio in the positive RBP group according to the cause

Table 3. Expected and observed cases of specific causes of death in the inhabitants with retinol binding proteinuria

	ICD code	Cases of specific causes Observed	Expected	risk ratio
Male				
All causes	001-999	34	17.81	1.91***
Malignant neoplasms	140-208	4	4.16	0.96
Cardiovascular diseases	393-398 410-414 420-429	8	2.92	2.73
Cerebrovascular diseases	430-448	7	4.74	1.48
Respiratory diseases	460-519	5	1.30	3.85*
Nephritis, Renal insufficiency	580-589	4	0.14	28.69***
Diabetes	250	1	0.24	4.18
Other diseases		5	4.17	1.20
Females				
All causes	001-999	42	35.40	1.19
Malignant neoplasms	140-208	4	3.02	1.32
Cardiovascular diseases	393-398 410-414 420-429	12	8.82	1.36
Cerebrovascula diseases	430-448	6	7.38	0.81
respiratory diseases	460-519	2	1.61	1.24
Nephritis, Renal insufficiency	580-589	2	0.57	3.59
Diabetes	250	3	0.50	6.00**
Other diseases		13	13.64	0.95

* significant difference ($P<0.05$) compared with inhabitants without retinol binding protrinuria
** significant difference ($P<0.01$)
***significant difference ($P<0.001$)

of death. The male ratios for nephritis-renal insufficiency (ICD code 580-589), diabetes (250), respiratory diseases (460-519) and cardiovascular diseases (393-398, 410-414, 420-429) were 28.69, 4.18, 3.85, and 2.73 respectively, and the female risk ratios for diabetes and nephritis-renal insufficiency were 6.00 and 3.59, respectively. The positive RBP group showed a large number of deaths, and this tendency was statistically significant for nephritis-renal insufficiency (male; $P < 0.001$), respiratory

diseases (males; $P < 0.05$) and diabetes (female; $P < 0.01$). However, the observed/expected risk ratio for malignant neoplasms (140-208) was 0.96 for males and 1.32 for females, and that for cerebrovascular diseases (430-448), 1.48 and 0.81, respectively. The mortality rates for these categories were similar in the positive RBP group and negative RBP group. Nephropathy due to Cd is a disturbance of the uriniferous tubules, accompanied by proteinuria and glucosuria. Since most of subjects with positive urine sugar were treated as diabetics in the surveyed area, it is possible that the deaths due to diabetes include those due to Cd-induced nephropathy.

The influence of health disorders due to the environmental pollution with Cd on survival has been reported on the basis of analysis of the mortality distribution in Cd-polluted areas (Shigematsu et al 1980 and 1982; Ono et al 1985). They observed that the standardized death ratios and corrected mortality rates of the inhabitants in the polluted areas were similar to those in the non-polluted areas used as a control, or lower in the Jinzu River basin where Itai-itai disease occured. We have already pointed out that there were problems in selecting subjects in their studies (Kawano et al 1986). It is important to find the natural course of disease, i.e., onset and recovery or death, in examing the incidence of disease (death) and its influences by long-term follow-up of population. The 15-year follow-up of control inhabitants of the same age living in the area where patients with Itai-itai disease lived, revealed that mortality rate in the patient group was significantly higher with shorter survival periods, compared with the control group (Kawano et al 1986). These findings support those of the present study.

In conclusion, it is obvious that the health risk due to the exposure to Cd has some adverse effects on survival, for which renal disorder was greatly responsible. At this moment, the difference in mortality rate may increase if the effect of Cd exposure, to which the group with negative urine RBP is also subject, is taken into account.

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