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Recent Results of Health Examinations on the General Population in Cadmium-Polluted and Control Areas in Japan

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Health examinations by a revised method aimed at detecting renal tubular dysfunctions more effectively were conducted on the general population aged 50 years and over in cadmium-polluted areas (1826 persons) and control areas (1611 persons) in four prefectures in Japan in 1976. Although detailed analysis of the data is not yet completed, some of the results obtained are described here.

The prevalence of glucosuria and low molecular weight proteinuria, frequency of decreased %TRP, and cadmium concentrations in urine are higher in the cadmium-polluted areas than in the controls. Clinically diagnosed cases with tubular dysfunctions seem to follow the same trend as above, though these cases are very few in number and they are limited to the advanced age group.

When cadmium concentration in rice is taken as an index, a dose-response relationship is not necessarily explicit in the observations by prefecture. However, suggestive data are obtained in the observation by district in one cadmium-polluted area.

Designation of Cadmium-Polluted Areas

Health problems due to cadmium pollution in Japan originated from an episode of so-called Itai-itai (Ouch-ouch) disease, which broke out in a rural area in north-central Japan mainly after World War II. The disease was defined as osteomalacia with tubular changes in the kidney and various degrees of osteoporosis, affecting women over 40 years of age who were multiparous and had lived in the area for more than 30 years (*1*).

Systematic studies on Itai-itai disease launched in 1962 disclosed that the disease was attributable to the pollution of water by Cd originating from the effluents of mining plants (*2, 3*). Consequently, the Japanese Government initiated a nationwide survey on Cd pollution throughout the country since 1969. The screening procedure of the survey is illustrated in Figure 1.

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Cd in the environment of the suspected areas was first checked by a preliminary investigation. If Cd concentrations in drainage, drinking water, and rice exceeded the criteria (0.1, 0.01, and 0.4 ppm, respectively), a detailed investigation was performed on water, soil, mud, rice, and vegetables. When the existence of Cd pollution in the area was confirmed by these investigations, the daily Cd intake per capita among the adult population and Cd concentration in urine of not less than 30 adult persons were measured.

A daily Cd intake per capita of 0.3 mg or more and an average Cd concentration in urine of 9 μg/l. or more were the criteria adopted by the Government in designating an area as an "area requiring observation for environmental pollution by Cd." In case of ambient air, 0.1 $\mu g/m^3$ was the criterion adopted. In the designated area, both sexes, 30 years of age and over, of the general population in the area were subjected to health examinations consisting of two steps of screenings.

Seven areas, with a total of about 40,000 population, were thus designated as those requiring observation during 1969–1971. However, more areas were later found to be polluted with Cd, though they were not so designated by the Government.

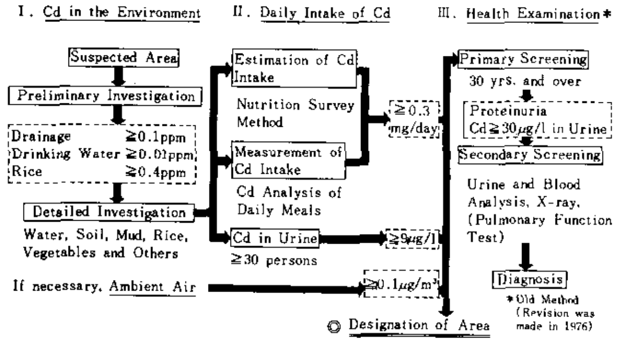

FIGURE 1. Procedure of surveillance for Cd pollution.

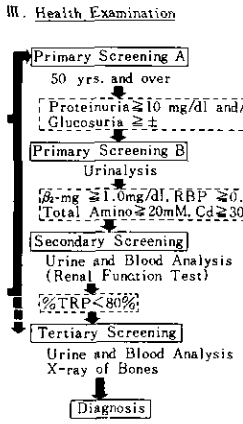

FIGURE 2. Revised method of health examination.

Revised Method of Health Examinations

The health examinations mentioned above which were primarily intended to detect Itai-itai disease and chronic Cd poisoning have been conducted in these designated and other polluted areas according to the standardized method provided by the Environment Agency. However, no definite cases of the disease have been found up to the present in these areas. On the other hand, there have been signs that frequency of tubular dysfunctions and urinary concentration of Cd in the polluted areas are generally higher than in the control areas (*4*). It has therefore been desired that the method of health examinations be revised so as to detect tubular dysfunctions more effectively.

Since immunological tests for detection of low molecular weight proteins in the urine have recently become popular in Japan, our Environment Agency has revised the method of health examinations by adopting these tests in 1976. According to the revised method shown in Figure 2, the age limit of the subjects for primary screening was changed from 30 years to over 50 years and the primary screening itself divided into two steps, A and B. The semiquantitative method of Kingsbury-Clark (*5*) was adopted in primary screening A for testing urinary proteins instead of the qualitative method previously employed. Those subjects showing proteinuria and/or glucosuria in the primary screening A were subjected to primary screening B, in which semiquantitative immunological tests are done.

Secondary screening is performed on those with positive β_2-microglobulin ($\geqslant$ 1.0 mg/dl), retinol binding protein (RBP) (0.4 mg/dl or more), total amino acid (20*mM* or more) and/or Cd (30 μg/l. or more) in urine in the primary screening B. Those showing less than 80% tubular reabsorption of phosphorus (%TRP) calculated from the results of urine and blood analysis in the secondary screening are examined in detail in a tertiary screening. Final diagnosis is made based on the findings obtained from the tertiary screening.

Results of Health Examinations by Revised Method

The health examinations by the revised method were conducted in four prefectures (Akita, Gunma, Ishikawa, and Nagasaki) in 1976 and in two prefectures (Fukushima and Hyogo) in 1977, but this paper deals with the results obtained in 1976. The sex and age distributions of the subjects examined in these four prefectures were not strictly comparable for the Cd-polluted and the control areas as shown in Figure 3. This fact should be taken into consideration in judging the data of overall age groups.

The results of health examinations performed in the four prefectures are summarized in Table 1. The number of the subjects undergoing primary screening A were between 300 and 600 in the polluted areas and between 200 and 500 in the control areas. It is obvious that determination of low molecular weight proteins in urine in primary screening B are likely to be more sensitive than proteinuria in primary screening A in indicating statistically significant differences between the Cd-polluted and the control areas. Glucosuria is also more sensitive than proteinuria in the same sense.

Cd concentrations in urine are definitely higher in the Cd-polluted areas than in the controls. Significant differences in the frequencies of decreased %TRP and tubular dysfunctions are seen between the Cd-polluted and the control areas in two of the four prefectures. Although Cd concentrations in rice are shown in the bottom of Table 1, they do not necessarily correlate with the results of the health examinations.

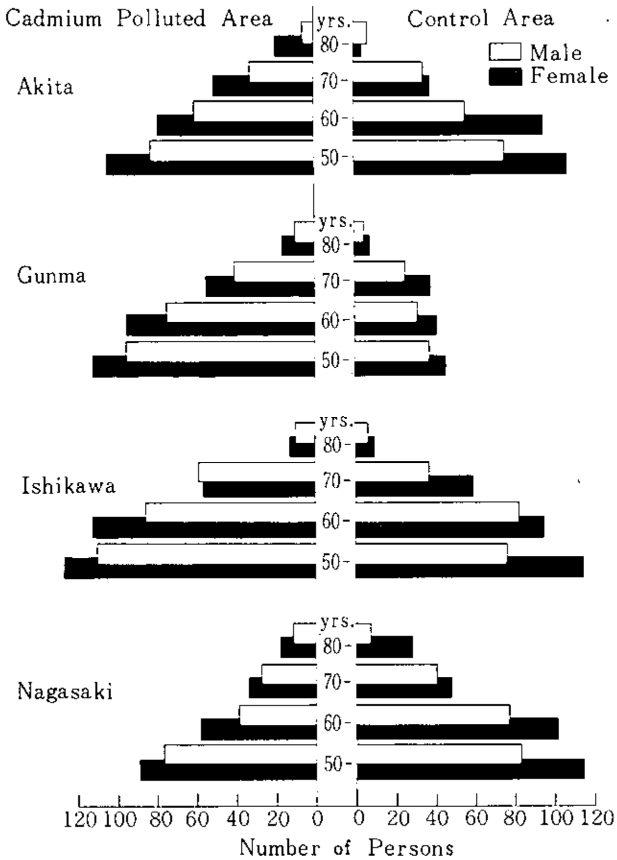

FIGURE 3. Sex and age composition of the area studied by the revised method (four prefectures, 1976).

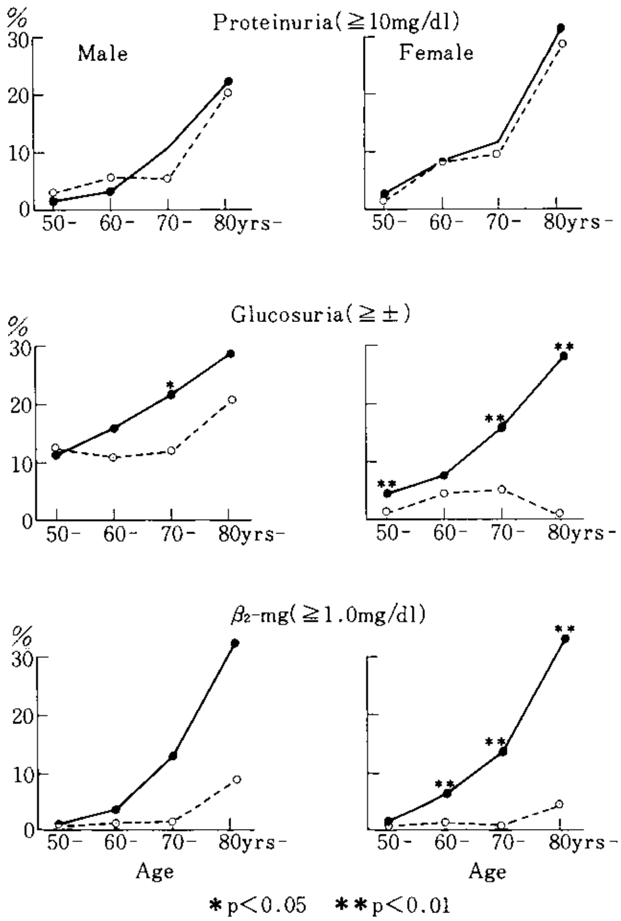

FIGURE 4. Results of urine tests by sex and age in (——) cadmium-polluted and (--) control areas. Four prefectures, 1976.

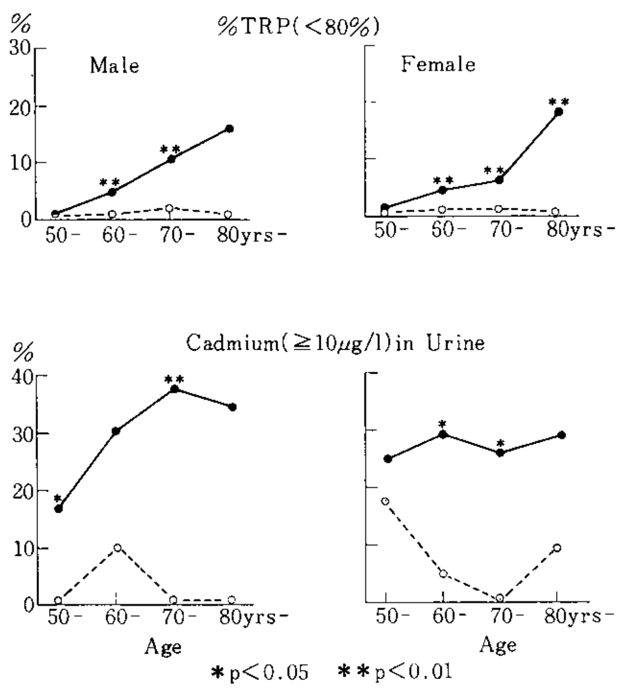

FIGURE 5. Results of %TRP and cadmium in urine by sex and age in (——) cadmium-polluted and (--) control areas. Four prefectures, 1976.

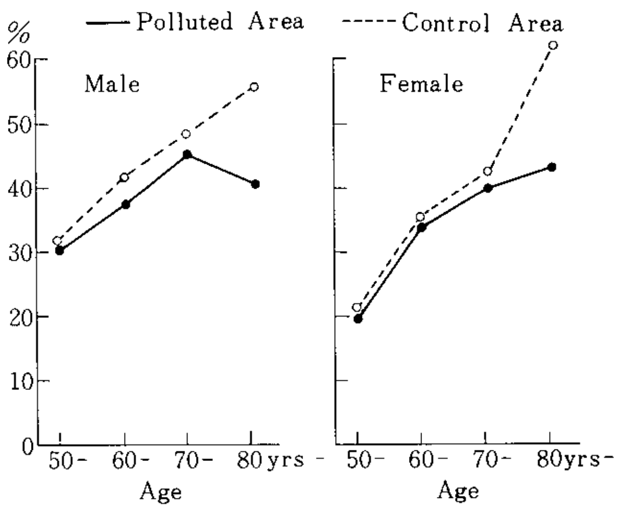

FIGURE 6. Prevalence of hypertension (systolic ≥ 160 mm Hg and/or diastolic ≥ 95 mm Hg) by sex and age in (——) cadmium-polluted and (--) control areas. Four prefectures, 1976.

Table 1. Results of urine tests by revised method in polluted (P) and control (N) areas of four prefectures.[a]

	Akita[b]			Gunma[b]			Ishikawa[b]			Nagasaki[b]		
	P	N	Significance (p)	P	N	Significance (p)	P	N	Significance (p)	P	N	Significance (p)
Primary screening (A)												
No. examined	427	426		500	221		566	470		333	494	
Proteinuria (≥ 10 mg/dl), %	4.4	4.7		2.0	1.8		4.9	3.0		11.4	9.3	
Glucosuria (≥ paper ±), %	11.7	5.1	< 0.01	8.2	7.2		15.0	8.9	< 0.01	11.4	4.0	< 0.01
Concurrent proteinuria glucosuria	2.3	0.5	< 0.05	1.0	0		2.5	0.9		4.2	0	< 0.01
Primary screening (B)												
No. examined	59	44		46	20		99	52		62	66	
β_2-MG	45.8	9	< 0.01	8.7	10.0		59.6	11.5	< 0.01	38.7	7.6	< 0.01
(≥ 1.0 mg/dl), %	(6.3)	(0)	< 0.01	(0.8)	(0.9)		(10.4)	(1.3)	< 0.01	(7.2)	(1.0)	< 0.01
RBP	52.5	2.3	< 0.01	2.2	10.0		57.6	13.5	< 0.01			
(≥ 0.4 mg/dl), %	(7.3)	(0.2)	< 0.01	(0.2)	(0.9)		(10.1)	(1.5)	< 0.01			
Lysozyme				28.3	30.0					19.4	0	< 0.01
(≥ 0.2 mg/dl), %[c]				(2.6)	(2.7)					(3.6)	(0)	< 0.01
Total amino	0	0		8.7	25.0		6.1	3.8		0	4.5	
acid (≥20 mM), %				(0.8)	(2.3)		(1.1)	(0.4)		(0)	(0.6)	
Cd in urine	6.6	4.1	< 0.01	6.8	2.8	< 0.01	9.8	5.2	< 0.01	8.2	5.0	< 0.01
(≥ 30 µg/l.), µg/l.												
Secondary screening												
No. examined	25	1		17	8		54	7		26	6	
%TRP (< 80%), %	24.0	0		52.9	25.0		74.1	14.3	< 0.01	92.3	50.0	< 0.01
	(1.7)	(0)		(1.8)	(1.1)		(8.6)	(0.3)	< 0.01	(7.8)	(0.8)	<0.01
Diagnosis, tubular dysfunction	1.8	0		0.2	0.5		5.2	0	< 0.01	6.0	0	< 0.01
Cd concentration in rice (average), ppm	0.58	0.07		0.62	< 0.10		0.44	< 0.3		0.53	< 0.10	

[a] Subjects were members of both sexes over 50 years of age.
[b] Value in parentheses show percentage compared to results of primary screening A. (The percentage is adjusted by response rate for primary screening B or secondary screening.)
[c] Optionally tested.

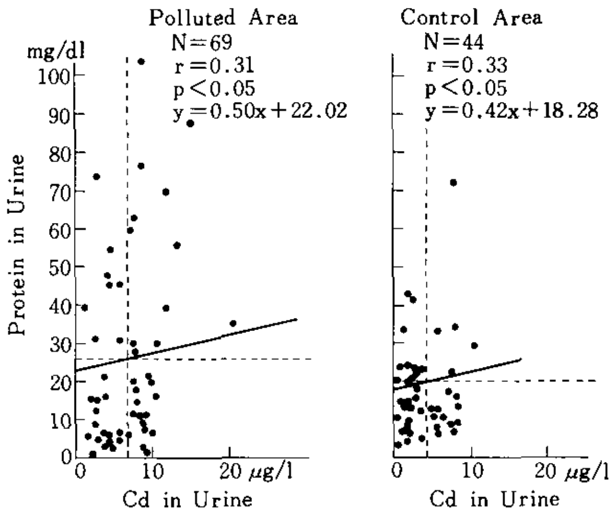

FIGURE 7. Cadmium and protein in urine. Akita Prefecture, 1976.

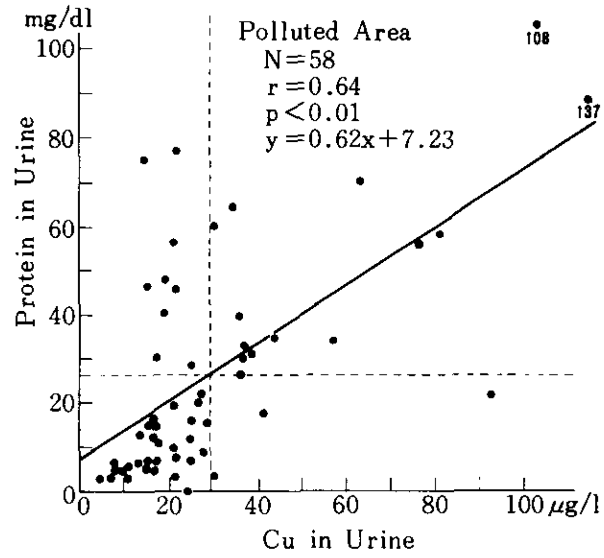

FIGURE 8. Copper and protein in urine. Akita Prefecture, 1976.

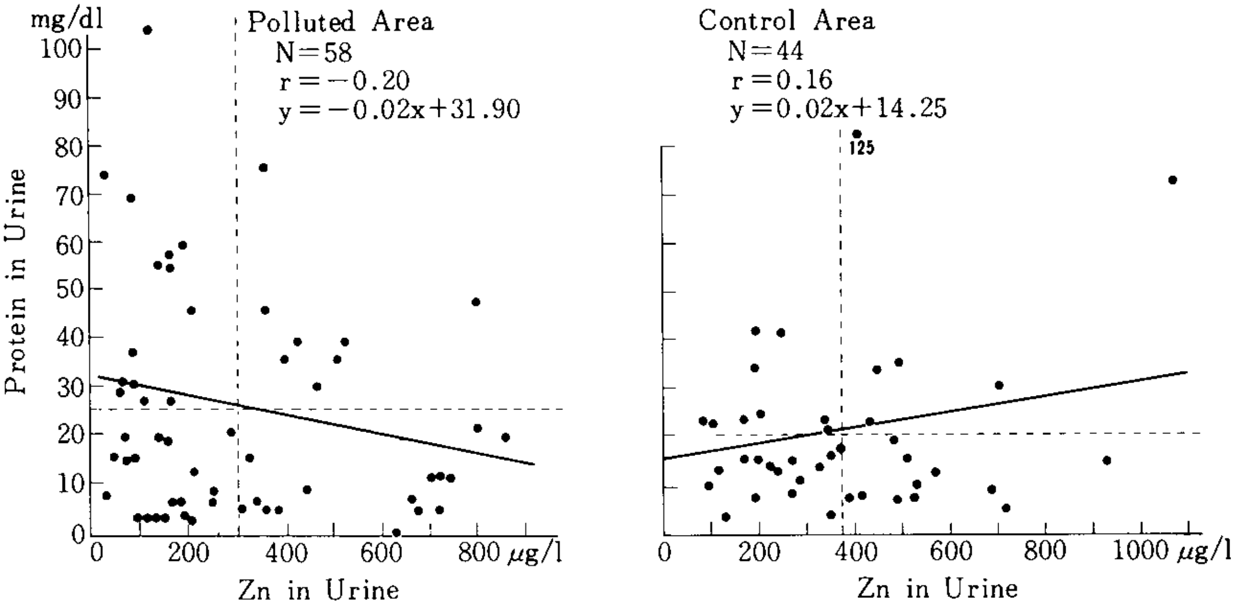

FIGURE 9. Zinc and protein in urine. Akita Prefecture, 1976.

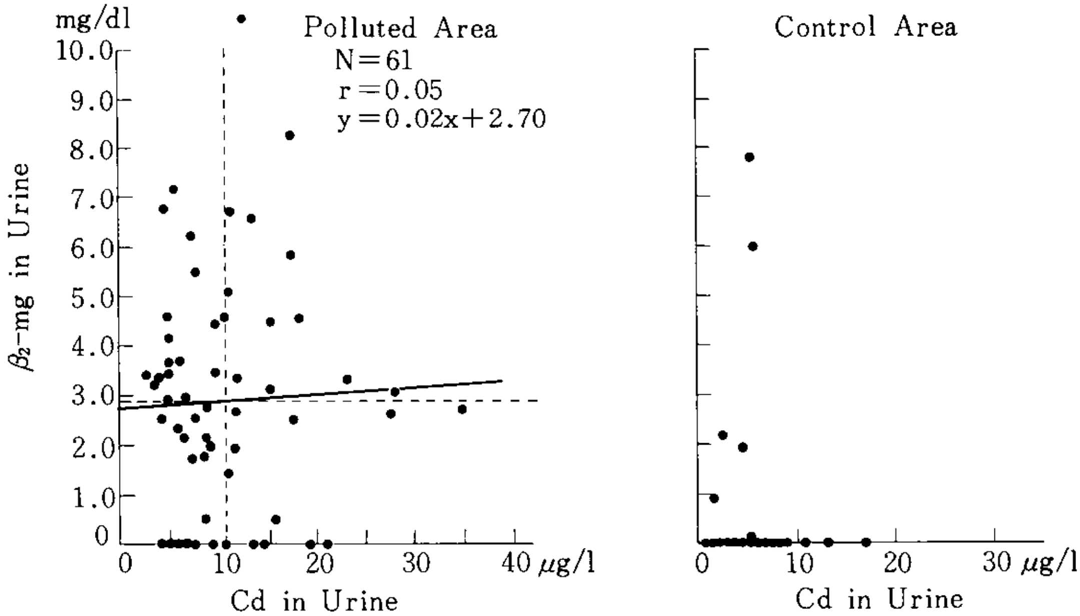

FIGURE 10. Cadmium and β_2-MG in urine, Ishikawa Prefecture, 1976.

The results of health examinations by sex and age in the Cd-polluted and the control areas in the four prefectures are illustrated in Figures 4–6. No statistically significant differences are seen in the frequency of proteinuria by sex and age between the Cd-polluted and the control areas (Fig. 4), but the frequencies of glucosuria, β_2-microglobulinuria (Fig. 4), decreased %TRP and urinary Cd concentrations (Fig. 5) show distinct differences between the two areas, particularly in the older age groups of both sexes. Prevalence of hypertension (Fig. 6) seems to be rather higher, though statistically not significant, in the control areas than in the Cd-polluted areas as already found in other Cd polluted areas in Japan (*6, 7*).

Correlations between Cd, copper, or zinc, and protein in urine in Akita Prefecture are shown in Figures 7–9. Cd in urine is significantly correlated with protein in urine both in the polluted and the control areas (Fig. 7). Copper in urine seems to be

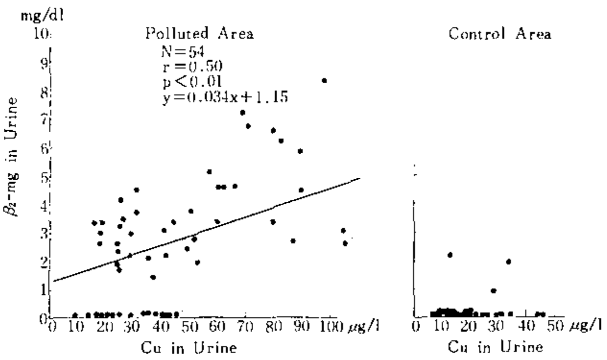

FIGURE 11. Copper and β_2-MG in urine, Ishikawa Prefecture, 1976.

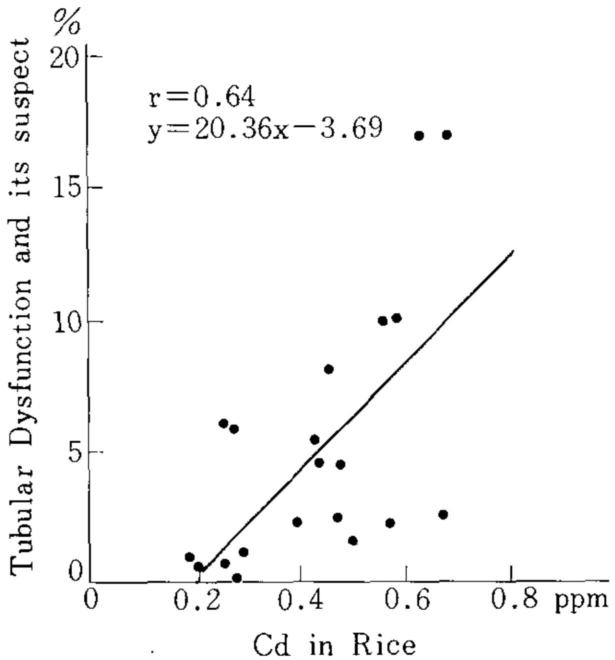

FIGURE 12. Cadmium concentration in rice and frequency of tubular dysfunction and suspected tubular dysfunction among the general population 50 years of age and older in a cadmium-polluted area. Ishikawa Prefecture, 1975.

better correlated with protein in urine than Cd in the polluted area, but not in the control area (Fig. 8). Zinc in urine is not correlated with protein in either area (Fig. 9).

Correlations between Cd or copper and β_2-microglobulin in urine are also found for the data from Ishikawa Prefecture as illustrated in Figures 10 and 11. Although no significant correlation is seen between Cd and β_2-microglobulin in urine, copper in urine is again better correlated with β_2-microglobulin than Cd in the polluted area.

Figure 12 shows the correlation between Cd concentration in rice and frequency of tubular dysfunction or its suspects observed in 20 districts in one Cd polluted area in Ishikawa Prefecture. The correlation was not clear in Table 1 in which observation was made by prefecture, but this figure is suggestive of existence of dose-response relationship between Cd in rice and health effects.

Summary

Health examinations by the revised method aimed at detecting renal tubular dysfunctions were conducted more effectively on the general population 50 years of age and over in the cadmium-polluted and the control areas in four prefectures in 1976. Although detailed analysis of the data is not yet complete, some of the results obtained are described here.

The prevalence of glucosuria and low molecular weight proteinuria, frequency of decreased %TRP, and cadmium concentrations in urine are higher in the cadmium-polluted areas than in the control areas. Clinically diagnosed cases with tubular dysfunctions seem to follow the same trend, though these cases are very few in number and they are limited to the advanced age group.

When cadmium concentration in rice is taken as an index of "dose," a dose-response relationship is not necessarily explicit in the observations by prefecture. However, suggestive data are obtained in the observation by district in one cadmium-polluted area. Further studies are needed in this respect.

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