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*Original Article*

# Increased Urinary β2-microglobulin and Mortality Rate by Cause of Death in a Cadmium-polluted Area

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## Abstract

**To clarify the effect of environmental cadmium (Cd) exposure on the life prognosis of inhabitants living in a Cd-polluted area, the standardized mortality ratio (SMR) according to cause of death in urinary β2-microglobulin (β2-MG)-positive subjects (≥1000 μg/gCr) was compared to that of the Japanese general population and β2-MG-negative subjects (< 1000 μg/gCr).**

**The SMR for all causes of death of both sexes was higher than that of the Japanese general population and β2-MG-negative subjects. Among women, the SMR for malignant neoplasms was higher than that of β2-MG-negative subjects. For cardiovascular disease and cerebrovascular disease, especially heart failure and cerebral infarction, SMRs were significantly higher in both sexes. The SMR for renal diseases was significantly high in the men and tended to be high in the women.**

**These results suggest that the prognosis of urinary β2-MG-positive subjects with Cd-induced renal tubular dysfunction is unfavorable, with higher mortality rates due to renal diseases, cerebral infarction and heart failure contributing to this. Although the increase of the mortality rate was slight, Cd might affect cancer mortality in women.**

Key words: Cadmium pollution, Mortality, Urinary β2-microglobulin, Cause of death, Follow-up study

## Introduction

The kidney is one of the target organs affected by chronic cadmium (Cd) poisoning, and proximal renal tubular dysfunction frequently develops in inhabitants of areas environmentally polluted by Cd as well as in industrial workers exposed to Cd[1,2].

Regarding the relation between Cd exposure and mortality, Shigematsu et al.[3,4] reported lower standard mortality ratios (SMRs) in inhabitants of Cd-polluted areas as compared with the inhabitants of non-polluted areas, with the SMR becoming lower the higher the degree of pollution. In contrast, we reported a high mortality in patients with itai-itai-desease characterized by severe renal tubular dysfunction and osteomalacia living in the Jinzu River basin of Toyama Prefecture, Japan, as compared to a control group matched for place of residence, sex and age[5,6]. We followed up the inhabitants of the Cd-polluted Kakehashi River basin in Ishikawa Prefecture in Japan twice and reported that the mortality rate of subjects with Cd-induced renal dysfunction was high[7-10]. Specificity, the subjects of the health impact survey conducted in 1974-5 excreting ≥ 4 mg/l of retinol-binding-protein (RBP) into the urine and followed up after periods of 7 and 15 years showed a higher mortality rate as compared to the group excreting less than 4 mg/l. In addition, the subjects of the second health impact survey conducted in 1981-2 excreting ≥1000 μg/g creatinine (Cr) of β2-microglobulin (β2-MG) into the urine and followed up after a 9-year period showed a higher mortality rate than the subjects excreting less than 1000 μg/gCr, with the mortality rate becoming higher as the amount of β2-MG excreted increased.

Thus, it has become clear that Cd exposure adversely affects subsequent mortality, although it is not yet well understood in what way Cd exposure affects individual causes of death. In regard to the causes of death in a Cd-polluted area, we reported

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there to be high mortality owing to heart failure, which means a gradual deterioration culminating in death and renal diseases in the urinary RBP-positive subjects[7, 10]. However, because the method used to measure RBP was semi-quantitative and the number of subjects who were urinary RBP-positive was small, it was not possible to investigate the relationship between cause of death and Cd exposure in detail, especially cancer mortality and Cd exposure. In the present study, we calculated SMR according to cause of death based on a follow-up study of 3,178 subjects examined in the 1981-2 health impact survey with detailed investigation into the effect of Cd on cause of death.

## Materials and Methods

In 1981-2 a study to clarify the impact of Cd exposure on health was conducted among 3,492 inhabitants of the Cd-polluted Kakehashi River basin in Ishikawa Prefecture aged 50 or more years from whom early morning urine samples were collected and the amount of β2-MG excreted measured[11]. β2-MG was measured with an RIA method, and this value corrected according to the creatinine (Cr) level (measured according to Jaffe's method).

**Table 1 The number of subjects and person years observed**

| | Total | Men | Women |
|---|---|---|---|
| The number of subjects examined | 3178 | 1424 | 1754 |
| β2-MG(+) subjects (%) | 534 (16.8) | 205 (14.3) | 329 (18.8) |
| Total person-years of observation | 25227.0 | 11130.5 | 14096.5 |
| Mean observed years per person | 7.9 | 7.8 | 8.0 |

β2-MG/Cr (μg/gCr) was used as an index of renal tubular dysfunction. Of the subjects, 3,178 were followed from the time of the health examination until the end of March 1991, and their mortality status was determined. The person-years (PY) method was used to calculate mortality rates. The total observed person-years amounted to 25,227, with a mean value per subject of 7.9 years. The number of subjects who died during the observation period was 575 (18.1% of the total), and 59 (1.9%) moved outside of the target area and were lost to follow-up (Table 1). Individual causes of death were ascertained from the death certificates. Causes of death were classified according to the 9th Revised International Classification of Diseases.

Based on the results of the 1981-2 health examination, the subjects were divided into a β2-MG-positive group (urinary β2-MG excretion ≥ 1000 μg/gCr) and β2-MG-negative group (< 1000 μg/gCr), and SMR according to cause of death in each group was calculated. At this time, as a reference, the mortality rates according to decade of the general Japanese population during the observation period were used. For the determination of SMR, normal distribution was used when the expected number of deaths was ≥ 30 and Poisson distribution when it was < 30 [12]. In addition, the SMRs of the β2-MG-positive and negative subjects were compared using the method of Fukutomi et al.[13].

## Results

The SMRs according to cause of death for the men and women are shown in Tables 2 and 3, respectively. The SMRs for all causes of death in the β2-MG-positive subjects were 129.5 for men and 146.0 for women, with these values both being sig-

**Table 2 The causes of death among the male inhabitants of the Cd polluted area**

| | ICD code | β2-MG(-) | | β2-MG(+) | |
|---|---|---|---|---|---|
| | | Obs. | SMR | Obs. | SMR |
| All causes | 001-999 | 197 | 78.0 -*** | 99 | 129.5 *&& |
| Infectious diseases | 001-139 | 5 | 115.4 | 2 | 176.1 |
| Malignant neoplasms | 140-208 | 56 | 71.3 -* | 16 | 91.1 |
| Esophagus | 150 | 1 | 27.0 | 1 | 135.8 |
| Stomach | 151 | 13 | 64.9 -+ | 5 | 109.3 |
| Colon, Rectum | 153, 154 | 8 | 108.8 | 1 | 58.6 |
| Liver | 155 | 4 | 39.9 -* | 1 | 58.3 |
| Pancreas | 157 | 3 | 67.1 | 0 | 0 |
| Lung | 162 | 12 | 71.6 | 6 | 153.8 |
| Diabetes mellitus | 250 | 1 | 35.4 | 1 | 139.9 |
| Cardiovascular diseases | 390-429 | 33 | 66.1 -** | 23 | 133.1 |
| Ischemic heart diseases | 410-414 | 11 | 62.2 -+ | 2 | 37.0 -+ |
| Heart failure | 428 | 19 | 77.0 | 19 | 207.7 **& |
| Cerebrovascular diseases | 430-438 | 34 | 85.6 | 21 | 157.0 *& |
| Cerebral hemorrhage | 431-432 | 8 | 72.0 | 4 | 142.4 |
| Cerebral infarction | 433, 434, 437.7A, B | 22 | 102.3 | 17 | 208.8 **& |
| Diseases of the respiratory system | 460-519 | 24 | 76.5 | 10 | 82.1 |
| Diseases of the digestive system | 520-579 | 12 | 95.3 | 7 | 226.6 |
| Diseases of kidney and urinary system | 580-599 | 4 | 73.2 | 5 | 257.1 *& |
| Nephritis and nephrosis | 580-589 | 4 | 83.4 | 5 | 304.3 *& |
| Senility | | 7 | 155.8 | 6 | 176.9 |
| Accident and suicide | E800-999 | 15 | 130.2 | 5 | 211.7 + |

β2-MG(-): β2-MG < 1000 μg/gCr β2-MG(+): β2-MG ≥ 1000 μg/gCr
+ P < 0.1, *P < 0.05, **P < 0.01, ***P < 0.001: Significant difference in comparison with SMR of Japanese general population
& P < 0.05, && P < 0.01: Significant difference in comparison with SMR of β2-MG(-) group.

**Table 3 The causes of death among the female inhabitants of the Cd polluted area**

| | ICD code | β2-MG(-) | | β2-MG(+) | |
|---|---|---|---|---|---|
| | | Obs. | SMR | Obs. | SMR |
| All causes | 001-999 | 142 | 77.2 -** | 136 | 146.0 ***&& |
| Infectious diseases | 001-139 | 2 | 82.6 | 1 | 97.5 |
| Malignant neoplasms | 140-208 | 25 | 54.7 -** | 18 | 117.1 & |
| Esophagus | 150 | 0 | 0 | 3 | 1028.9 **&& |
| Stomach | 151 | 6 | 59.6 | 4 | 111.4 |
| Colon, Rectum | 153, 154 | 3 | 52.4 | 3 | 149.3 |
| Liver | 155 | 0 | 0 | 0 | 0 |
| Pancreas | 157 | 4 | 126.3 | 0 | 0 |
| Lung | 162 | 3 | 57.2 | 2 | 107.5 |
| Breast | 174 | 1 | 42.7 | 2 | 430.3 +& |
| Uterus | 179, 180, 182 | 0 | 0 | 0 | 0 |
| Diabetes mellitus | 250 | 1 | 33.9 | 2 | 164.7 |
| Cardiovascular diseases | 390-429 | 37 | 86.4 | 39 | 157.6 **& |
| Ischemic heart diseases | 410-414 | 10 | 77.8 | 6 | 87.1 |
| Heart failure | 428 | 24 | 109.1 | 32 | 239.8 ***&& |
| Cerebrovascular diseases | 430-438 | 28 | 107.6 | 34 | 221.6 ***&& |
| Cerebral hemorrhage | 431-432 | 9 | 99.4 | 3 | 74.34 |
| Cerebral infarction | 433, 434, 437.7A, B | 14 | 77.1 | 21 | 184.7 **& |
| Diseases of the respiratory system | 460-519 | 10 | 58.8 -* | 11 | 105.8 |
| Diseases of the digestive system | 520-579 | 11 | 127.1 | 9 | 220.4 * |
| Diseases of kidney and urinary system | 580-599 | 6 | 121.4 | 4 | 152.0 |
| Nephritis and nephrosis | 580-589 | 2 | 48.0 | 3 | 139.2 |
| Diseses of the urinary tract | 590-599 | 4 | 536.0 ** | 1 | 217.6 |
| Senility | | 10 | 151.1 | 18 | 273.5 |
| Accident and suicide | E800-999 | 7 | 103.0 | 3 | 122.2 |

β2-MG(-): β2-MG < 1000 μg/gCr β2-MG(+): β2-MG ≥ 1000 μg/gCr
+ P < 0.1, *P < 0.05, **P < 0.01, ***P < 0.001: Significant difference in comparison with SMR of Japanese general population
& P < 0.05, && P < 0.01: Significant difference in comparison with SMR of β2-MG(-) group.

nificantly higher than those of the general Japanese population and the β2-MG-negative subjects.

The SMRs for cardiovascular diseases in the β2-MG-positive subjects were 133.1 for men and 157.6 for women, the value for women being significantly higher than those of the general Japanese population and the β2-MG-negative subjects. However, for β2-MG-positive subjects of both sexes the SMR for ischemic heart disease was low, with a significant increase in deaths due to heart failure seen. The SMRs for cerebrovascular diseases in the β2-MG-positive subjects were 157.0 for men and 221.6 for women, these values being significantly higher than those of the Japanese general population and the β2-MG-negative subjects. In particular, the SMR for cerebral infarction was high in the β2-MG-positive subjects of both sexes, compared to those of the general Japanese population and the β2-MG-negative subjects.

The SMR for diseases of the digestive system in the β2-MG-positive subjects showed high values in both sexes (men: 226.6, women: 220.4). In the women this value was significantly higher than that of the Japanese general population, but the difference between β2-MG-positive subjects and negative subjects was not significant. Moreover, no individual disease of the digestive system showed a particularly increased mortality rate.

The SMR for diseases of the kidney and urinary system showed high values in both sexes (men: 257.1, women: 152.0). The value in the men was significantly higher than those of the Japanese general population and the β2-MG-negative subjects, and it also, tended to be higher, although not significantly so, in the women.

In the β2-MG-positive subjects the SMR for malignant neoplasms was not high in the men (91.1), but at 117.1 in the women was significantly higher than that of the β2-MG-negative subjects. Looking at mortality due to malignant neoplasms according to site, among the β2-MG-positive women esophageal cancer accounted for 3 deaths, with the SMR for this disease being significantly higher than those of the general Japanese population and the β2-MG-negative subjects. In addition, the SMR for breast cancer in the β2-MG-positive subjects was significantly high as compared to the β2-MG-negative subjects.

## Discussion

Adverse health effects of environmental Cd pollution have been reported in many regions in Japan [2], a notable example being itai-itai disease in the Jinzu River basin located in Toyama Prefecture [14]. The Kakehasi River basin in Ishikawa Prefecture has also been designated an Cd-polluted area [2]. The source of pollution in this case was upstream mine, which was closed in 1971. Two health impact surveys were conducted in 1974-5 [15] and 1981-2 [11] to clarify the presence/absence of a high prevalence of renal tubular dysfunction. As an index of renal tubular dysfunction, urinary RBP was measured in the former survey and β2-MG in the latter, and in both surveys the positive rate of urinary low molecular weight protein, was demonstrably increased compared to those of inhabitants living in control areas. Based on the

results of these surveys, Nogawa et al.[16] demonstrated probite regression lines between the average rice Cd concentration in each hamlet and the urinary RBP-positive rate, and an S-shaped dose-resoponse relationship was identified[16]. Ishizaki et al.[17] and Nogawa et al.[18] also clarified the relationship between urinary β2-MG-positive rates and urinary Cd concentrations or rice Cd concentrations. These findings showed that high rate of low molecular weight protein excretors in the Cd-polluted area is attributable to Cd environmental pollution. In addition, we followed up the subjects of these 2 health impact surveys, and demonstrated that the mortality rates of the subjects with high excretion of urinary RBP or β2-MG are higher, than those of both subjects with normal excretion of urinary RBP and β2-MG, and the Japanese general population[7-10]. Moreover, mortality rates increased in proportion to increases in the amount of urinary β2-MG excreted[8].

An interesting issue is whether these increased mortality rates in subjects with renal tubular dysfunction are due to an increase in mortality from a specific disease. In the 15-year follow-up study of the subjects of 1974-5 survey, causes of death were investigated and it was reported that the increases of mortality were mainly due to heart failure and renal diseases, and no increase of mortality for all malignant neoplasms was found[10]. However, because of the small number of RBP-positive subjects, we could not analyze the effect of Cd exposure on causes of death, particularly on the mortality rate for malignant neoplasms.

The relation between Cd exposure and malignant neoplasms has been discussed mainly in studies of industrial workers. Previous studies have documented excessive deaths from prostate and lung cancer in Cd-exposed factory workers[19-23]. Ades and Kazantzis[23] reported that the increase of the risk of lung cancer death is significant after adjusting confounding factors, smoking and exposure of other toxic substances. In the present study, however, no difference of mortality from lung cancer was found for either sex, and no case of prostatic cancer was observed in urinary β2-MG-positive men. It has also been reported that a history of exposure to Cd is frequently present in renal cancer patients[24], but there was no case of renal cancer in urinary β2-MG-positive subjects of either sex. In the women, the SMR for all malignant neoplasms of urinary β2-MG-positive subjects was higher than that of urinary β2-MG-negative subjects, and the mortality rates for esophageal and breast cancer were high in the present study. However, the deaths due to these cancers were too few to decide the relation to Cd exposure.

The report by Shigematu et al. of SMRs of inhabitants living in the Cd-polluted Jinzu River basin was the only report to show cancer mortality of different organs in women exposed to Cd, but they did not find a significant excess of death from either esophagial or breast cancer. A longer follow-up period is necessary to evaluate this issue exactly more precisely.

In the present study, the largest number of deaths was due to cardiovascular diseases, particularly heart failure. The SMRs for cardiovascular diseases and hypertensive diseases were reported to be significantly higher in the inhabitants of the Cd-polluted village of Shiphan in England who were studied in a 40-year follow-up survey[25]. However, no increase in either the SMR for hypertensive diseases or in the high prevalence of hypertension was noted in the inhabitants living in the Kakehashi River basin. Also the SMR for cerebrovascular diseases, especially cerebral infarction, showed high values in this study. Shigematu et al.[4] reported that in the Cd-polluted Jinzu River basin in Toyama Prefecture SMRs for hypertensive diseases and cerebrovascular diseases were lower in both sexes than those of the control area. However, most of the deaths from cerebrovascular diseases observed by Shigematu et al. were suspected to be deaths arising from cerebral hemorrhage whose association with hypertension is thought to be strong. In this study also, no increase in the SMR for cerebral hemorrhage was observed. Kjellstrom et al.[26] and Elinder et al.[20] did not find increased mortality rates for cerebrovascular and cardiovascular diseases in Swedish battery factory workers. Therefore, the increases of mortality from heart failure and cerebral infarction may be partly explained by the fact that in Japan it is customary to ascribe the cause of death to cardiac failure or cerebral arteriosclerosis (cerebral infarction) on the death certificate in cases in which no other clear cause of death is apparent or those showing a gradual deterioration culminating in death.

However, in the women an excess of deaths from diseases of the digestive system was found in this study, the difference of SMR between β2-MG-positive subjects and negative subjects was not significant and individual diseases contributing to this increase of mortality were not detected. There are few reports that show the effect of Cd on the mortality of diseases of the digestive system in orally exposed subjects.

Death rates due to renal diseases have been reported to be high in women living in a Cd-polluted area in Belgium[27]. Mortality due to renal diseases has also been reported to be high in industrial workers exposed to Cd[20, 26, 28]. In this study as well, high mortality rates for nephritis/nephrosis in the urinary β2-MG-positive subjects were high in the men, and also, although not significantly so, tended to be higher in the women. In the 15-year follow up study[10] since the 1974-5 health impact survey, SMR for renal diseases was significantly higher in both sexes, because the subjects of the study included cases with more severe renal dysfunction.

The above results suggest that the prognosis of urinary β2-MG-positive subjects with Cd-induced renal tubular dysfunction is unfavorable, with higher mortality rates due to nephritis / nephrosis, cerebral infarction and heart failure contributing to this. In women, there may exist a relation between mortality due to cancer of specific organs and Cd exposure.

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