ORIGINAL ARTICLE

Influence of years engaged in agriculture and number of pregnancies and deliveries on mortality of inhabitants of the Jinzu River basin area, Japan

E Kobayashi, Y Okubo, Y Suwazono, T Kido, M Nishijo, H Nakagawa, K Nogawa

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See end of article for authors' affiliations

Correspondence to: Dr E Kobayashi, Department of Occupational and Environmental Medicine, Graduate School of Medicine (A2), Chiba University, 1-8-1 Inohana, Chuohku, Chiba 260–8670, Japan; etuko@med.m.chiba-u.ac.jp

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Background: The occurrence of itai-itai disease is thought to be affected by such factors as pregnancy, lactation, hormonal disorders, aging, and calcium deficiency.
Aims: To study the influence of years engaged in agriculture and number of pregnancies and deliveries on the mortality of inhabitants of the Jinzu River basin area, which has been an endemic region for itai-itai disease.
Methods: From 6667 participants (3181 men, 3486 women; participation rate 93.4%) in the 1967 health survey, 3639 subjects (1591 men, 2048 women) whose years engaged in agriculture were established, and 2559 women/2410 women with a known number of pregnancies/deliveries were selected as the target population. These data were confirmed on the basis of self reported replies confirmed afterwards by interview. The survival survey was conducted for 6127 days from 1 August 1967 to 10 May 1984. Subjects were divided according to three water systems: the Jinzu River, non-Jinzu River, and mixed water system; the influence on mortality of the years engaged in agriculture and the number of pregnancies/deliveries was analysed using a Cox's proportional hazards model according to the water systems.
Results: The mean years engaged in agriculture and mean number of pregnancies/deliveries were not different among the three water systems. Cox's hazard ratios of these parameters to mortality were not statistically significant in the any of the water systems.
Conclusions: Neither the years engaged in agriculture nor the number of pregnancies/deliveries influenced mortality in subjects living not only in the non-Jinzu River basin but also in the Jinzu River basin using a Cox's proportional hazards model.

Cadmium contamination from an upstream mine in the Jinzu River basin of the Toyama Prefecture led to the development of itai-itai disease, representing the most severe stage of chronic Cd intoxication in many of the inhabitants of this region since the second world war.[1] Most itai-itai disease patients are elderly postmenopausal women presenting with renal and bone damage. The Japanese word "itai" means "ouch" or "painful" in English. The pain results from unusual changes in bone: osteomalacia with osteoporosis. In May 1968 the Japanese Ministry of Health and Welfare concluded that itai-itai disease developed from osteomalacia corresponding with renal dysfunction from chronic Cd poisoning, and was affected by factors such as pregnancy, lactation, hormonal disorders, aging, calcium deficiency, and others.[2] In the Jinzu River basin, Nakagawa *et al* reported a higher mortality and lower life span linked to patients with itai-itai disease and subjects with suspected disease compared to controls.[3] However, no studies were undertaken to clarify the relation between mortality and factors such as pregnancy, lactation, hormonal disorders, aging, or calcium deficiency in the general population, nor have such studies been undertaken in the other Cd polluted regions of Japan.

We proposed that the occurrence of itai-itai disease could be affected not only by the number of pregnancies/deliveries in women, but also by hard agricultural labour. In this study we investigated the influence of such factors on the mortality of inhabitants of the Jinzu River basin area.

SUBJECTS AND METHODS

In 1967 and 1968, large scale health examinations were conducted among the entire population aged ≥30 years of the Jinzu River basin, non-Jinzu River basin, and a region receiving a mixed water supply. The non-Jinzu River basin is irrigated by two rivers which are not polluted by Cd. Each water system has been used for field irrigation. Subjects for the present study were selected from the 6667 participants (3181 men, 3486 women; participation rate 93.4%) of the 1967 health survey, which was conducted mainly in the heavily polluted region.[4] Of these, 3639 subjects (1591 men, 2048 women) having worked a known number of years in agriculture, and women having a known number of pregnancies (2559 women) and deliveries (2410 women) were selected as the target population of the present study. These data were confirmed on the basis of self reported replies confirmed afterwards by interview. Figure 1 shows the selection process for the study population. The survival survey was conducted for 6127 days, from 1 August 1967 to 10 May 1984.

The subjects were divided according to three water systems: the Jinzu River, non-Jinzu River, and a mixed water system; the influence on mortality of the years engaged in agriculture and the number of pregnancies/deliveries was analysed using a Cox's proportional hazards model, using subjects' age as of 1 August 1967.

RESULTS

Table 1 shows the standardised mortality ratios (SMRs) and the number of subjects at the start and end of the observation period, number of deaths during this period, mean number of observed person-days, mean years engaged in agriculture and number of pregnancies/deliveries according to the water system and gender. Among the three water systems there were

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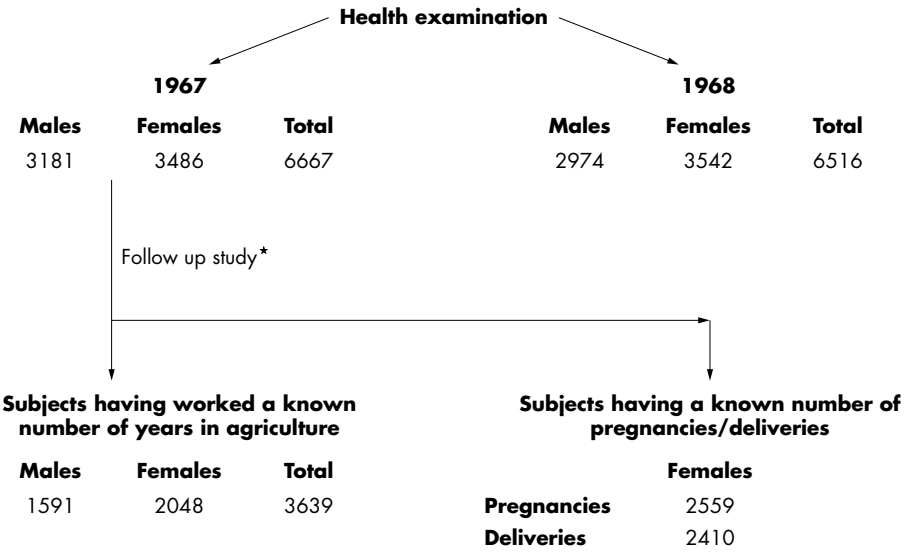

Figure 1 Selection process of the study population. *Follow up study was performed for the subjects who participated in the 1967 health examination.

Table 1 Standardised mortality ratios (SMRs) and inhabitants observed, concerning years engaged in agriculture, number of pregnancies or deliveries, by water system and gender

	SMR		Agriculture		Pregnancy	Delivery
	Males	Females	Males	Females	Females	Females
The other river	0.98	1.06				
No. examined			430	542	690	651
No. examined completely			422	522	659	619
Mean number of observed person-days			5235	5600	5491	5487
No. deaths			125	97	136	129
Mean of age			51.8	48.7		
Mean years engaged in agriculture (y)			31.3	27.4		
Mean number of pregnancies					4.2	
Mean number of deliveries						3.8
Jinzu River + the other	0.76	0.96				
No. examined			164	261	244	220
No. examined completely			164	197	237	214
Mean number of observed person-days			5514	5666	5605	5579
No. deaths			35	30	41	37
Mean of age			50.4	50.1		
Mean years engaged in agriculture (y)			30.4	29.6		
Mean number of pregnancies					4.4	
Mean number of deliveries						4.0
Jinzu River	0.90	1.05				
No. examined			997	1245	1625	1539
No. examined completely			995	1239	1599	1515
Mean number of observed person-days			5328	5513	5501	5491
No. deaths			280	259	336	323
Mean of age			51.7	49.6		
Mean years engaged in agriculture (y)			31.8	28.3		
Mean number of pregnancies					4.3	
Mean number of deliveries						3.9

SMRs were expressed as the ratio of the observed number of deaths and the expected number of deaths. The survival survey was conducted for 6127 days, from 1 August 1967 to 10 May 1984. The expected number of deaths was calculated by multiplying the cumulative observed person-years per decade of age divided according to the water system and sex by the sex specific mortality rates of the general Japanese population in 1976, which was the midpoint of the present observation period.

no differences in mean years engaged in agriculture or mean number of pregnancies/deliveries.

Using a Cox's proportional hazards model we investigated whether trends in years engaging in agriculture could be correlated to mortality. Table 2 shows the results according to the water system and gender. The Cox's hazard ratio for males living in the mixed water system region was statistically significant, while the hazard ratios of the others were not.

Using the same method we analysed the possible influence on mortality of the number of pregnancies/deliveries in women (table 3). The Cox's hazard ratio of number of pregnancies/deliveries was not statistically significant in any of the studied water systems.

DISCUSSION

It is well known that exposure to Cd leads to renal dysfunction, particularly in the renal tubule.[5] The influence of renal dysfunction on mortality was investigated in Cd polluted areas of Japan. Nakagawa *et al* and Nishijo *et al* conducted surveys in the Cd polluted Kakehashi River basin in the Ishikawa

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Table 2 Analysis of length of agriculture, related to mortality, using proportional hazard model of Cox, by water system and sex

	Regression coefficient	SE	Hazard ratio	p
Males				
The other river (n=422)				
Age	8.70×10^{-2}	1.18×10^{-2}	1.09	0.000
Agriculture	9.58×10^{-3}	8.89×10^{-3}	1.01	0.282
Jinzu River + the other (n=164)				
Age	5.56×10^{-2}	2.16×10^{-2}	1.06	0.011
Agriculture	5.11×10^{-2}	1.95×10^{-2}	1.05	0.010
Jinzu River (n=995)				
Age	1.13×10^{-1}	8.18×10^{-3}	1.12	0.000
Agriculture	-5.27×10^{-3}	5.79×10^{-3}	1.00	0.363
Females				
The other river (n=522)				
Age	1.12×10^{-1}	1.29×10^{-2}	1.12	0.000
Agriculture	-9.46×10^{-3}	1.28×10^{-2}	0.99	0.459
Jinzu River + the other (n=197)				
Age	1.53×10^{-1}	3.12×10^{-2}	1.17	0.000
Agriculture	-1.43×10^{-3}	2.58×10^{-2}	1.00	0.956
Jinzu River (n=1239)				
Age	1.12×10^{-1}	8.64×10^{-3}	1.12	0.000
Agriculture	2.38×10^{-3}	7.07×10^{-3}	1.00	0.737

Table 3 Analysis of number of pregnancies or deliveries, correlated to mortality, using proportional hazard model of Cox, by water system

	Regression coefficient	SE	Hazard ratio	p
Pregnancy				
The other river (n=659)				
Age	9.81×10^{-2}	6.66×10^{-3}	1.10	0.000
No. pregnancies	-1.89×10^{-2}	3.42×10^{-2}	0.98	0.582
Jinzu River + the other (n=237)				
Age	1.50×10^{-1}	1.94×10^{-2}	1.16	0.000
No. pregnancies	8.12×10^{-2}	5.35×10^{-2}	1.09	0.131
Jinzu River (n=1599)				
Age	1.09×10^{-1}	5.18×10^{-3}	1.12	0.000
No. pregnancies	2.70×10^{-2}	2.17×10^{-2}	1.03	0.213
Delivery				
The other river (n=619)				
Age	1.07×10^{-1}	7.80×10^{-3}	1.11	0.000
No. deliveries	-3.90×10^{-2}	3.65×10^{-2}	0.96	0.286
Jinzu River + the other (n=214)				
Age	1.51×10^{-1}	2.02×10^{-2}	1.16	0.000
No. deliveries	6.99×10^{-2}	5.75×10^{-2}	1.07	0.225
Jinzu River (n=1515)				
Age	1.08×10^{-1}	5.37×10^{-3}	1.11	0.000
No. deliveries	3.27×10^{-2}	2.34×10^{-2}	1.03	0.163

Prefecture, and Iwata *et al* performed studies in the Cd polluted Kosaka Town in the Akita Prefecture and Tsushima Island in the Nagasaki Prefecture.[6–10] They showed that inhabitants with increased urinary excretion of β_2 microglobulin or retinol binding protein showed high SMRs and Cox's hazard ratios. Moreover Nishijo *et al* showed a dose–response relation between urinary Cd and mortality in a 15 year follow up study of 3119 inhabitants of the Cd polluted Kakehashi River basin.[11] It was clarified that the life span of inhabitants with Cd induced renal dysfunction is shortened. However, studies investigating the influence of other factors on mortality are few, save for the influence of renal dysfunction. In the Jinzu River basin, an association between Cd concentration in rice and mortality was only investigated by Shigematsu[12 13] and Ishihara and colleagues.[14] The results obtained from the two studies were conflicting. We have performed studies of the association between mortality and Cd concentration in rice,[14] total Cd intake,[15 16] and other factors[17 18] in the Cd polluted Jinzu River basin, of which this is one.

Thus far, the most systematic and largest scale health examinations were conducted in 1967 and 1968 around the Jinzu River basin. The target population was composed of inhabitants aged ⩾30 years of rural communities obtaining water from the Jinzu River water system, another river system, and a mixture of the two. The previously mentioned health examinations conducted in 1967 focused mainly on the inhabitants of the heavily polluted region obtaining water from the Jinzu River water system.[4] Results of the urinary findings have already been reported with regard to the 1967 findings.[4] It was shown that in the Jinzu River water system the prevalence of proteinuria, glucosuria, and proteinuria + glucosuria were disproportionately high.[4] Therefore, in this study, we divided the target population according to the water system to clarify the influence of agricultural labour and number of pregnancies/deliveries on mortality of inhabitants of the Jinzu River basin area. Normally, urinary Cd concentration is used as an index of Cd exposure. Since urinary Cd concentrations were measured by a method in which 10–50 ml

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urine were treated with HNO_3/H_2SO_4 and extracted with APDC-MIBK in our laboratory in 1967, we could not measure the Cd concentration in many urine samples.

Shigematsu conducted a 30 year (1948–77) survival survey and investigated the relation between Cd concentrations in unpolished rice and mortality in this region.[12 13] He classified regions into three groups according to Cd concentrations in unpolished rice, and reported that SMRs for heart disease, hypertension, and cardiovascular disease were significantly lower, and SMR for uraemia was significantly increased in the polluted compared to the non-polluted regions in the Jinzu River basin. Nishijo *et al* performed a follow up study for 15 years on 2408 inhabitants living in the Kakehashi River basin in Ishikawa Prefecture,[7] and found that the prognosis of the exposed inhabitants with renal tubular dysfunction was unfavourable, and that the increases in mortality were caused by heart failure and renal disease among the Cd exposed inhabitants. Except for uraemia or renal disease, no specific or common causes of death have been found in either study. Moreover, 83 postmortem examinations were performed on patients with itai-itai disease and subjects with suspected disease, and no specific causes of death were found in the patients. In this study deaths within the target population were investigated via interviews of the families and were confirmed by checking resident cards. As we did not obtain death certificates, the causes of death could not be investigated.

Itai-itai disease developed as a result of Cd contamination from an upstream mine in the Jinzu River basin; 180 of 183 patients with itai-itai disease and 97 of 114 subjects with suspected disease were women (on 28 December 1999). Alternatively, the Jinzu River basin is the best granary of the Toyama Prefecture, and most, if not all of its inhabitants were engaged in hard agricultural labour until roughly 1980. After that time most farmers have used agricultural machines for cultivation of rice in the area. It would be of interest to consider whether factors contributing to development of itai-itai disease might have an impact on the mortality of the general population. Studies investigating whether Cd induced renal injury worsens prognosis of life have been conducted.[6–11] However, until this report there have been no studies undertaken to clarify the relation between other factors such as pregnancy, lactation, hormonal disorders, aging, and calcium deficiency, and mortality. Using a Cox's proportional hazards model we determined that the years engaged in agricultural labour and the number of pregnancies/deliveries had no discernible influence on mortality in subjects living not only outside of the Jinzu River basin but also in the Jinzu River basin. Although the hazard ratio of the years engaged in agricultural labour for males living in the mixed water system region was statistically significant, the hazard ratios of the others were not. We therefore concluded that the years engaged in agricultural labour had no clear infinfluence on mortality. As mentioned above, the Japanese Ministry of Health and Welfare concluded that itai-itai disease developed from chronic Cd poisoning and occurence of the disease was affected by factors such as pregnancy, lactation, calcium deficiency, and others.[2] On the other hand, it was reported that patients with itai-itai disease have a higher mortality and lower life span compared with controls.[3] In this study the years engaged in agricultural labour and the number of pregnancies/deliveries had no discernible influence on mortality. Applying these results to the mortality of itai-itai disease patients, it was thought that high mortality of the patients was mainly caused by effects of Cd poisoning. Specifically, our results agreed in part with the conclusion of Japanese Ministry of Health and Welfare in that itai-itai disease developed from chronic Cd poisoning. However, we could not estimate from our investigation the degree of influence of facters other than Cd exposure on occurence of itai-itai disease. The previous epidemiological investigations reported that factors such as years engaged in agriculture, number of pregnancies/deliveries, nutritional, and economical conditions were not different between homes with and without itai-itai disease.[19]

Authors' affiliations
E Kobayashi, Y Okubo, Y Suwazono, K Nogawa, Department of Occupational and Environmental Medicine, Graduate School of Medicine, Chiba University, Japan
T Kido, Department of Community Health Nursing, Kanazawa University School of Health Sciences, Japan
M Nishijo, H Nakagawa, Department of Public Health, Kanazawa Medical University, Japan

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