suitable multiple regression models with several independent variables, demonstrating that Cd exposure at a level insufficient to induce renal dysfunction had no effect on BMD or urinary Ca excretion. In short, Cd would not induce bone mineral loss without renal dysfunction.

This result conflicts with those of the OSCAR study in Sweden (Alfvén et al., 2000) and the CadmiBel study in Belgium (Staessen et al., 1999), which proposed that low-dose Cd exposure would increase the risk of osteoporosis. This discrepancy may be partly due to differences among the investigated populations, including subject numbers, ethnic characteristics, or exposure routes: The European studies analyzed around 300–500 Caucasian women exposed to Cd mainly via inhalation, while our current study consisted of more than 1200 dietary-Cd-exposed Japanese women. But much more important must be the difference in Cd exposure levels: mean Cd-U of the investigated subjects in the European studies and our study were about 0.5 and 3.5 μg/g cr., respectively (incidentally, Cd-U levels of patients with Itai-itai disease were around 20 μg/g; cr. Kasuya et al., 1992b). It is unthinkable that the people with much lower Cd exposure are more at risk of osteoporosis, even if the difference in the race or exposure routes is taken into consideration.

This inconsistency must be derived from the misinterpretation of statistics, since careful inspection could not detect any essential differences between the results. In the OSCAR study, the negative correlation between Cd-U and BMD indicated by multiple regression analysis was actually not statistically significant as judged by the 95% CI, but age and weight were significantly correlated with BMD, corresponding to our result. On the other hand, the multiple regression analysis in the CadmiBel study showed a "statistically significant" relationship between BMD and urinary Cd excretion, but it probably had no "practical significance" because of the large number. For example, in our multiple regression models on Ca-U (Table 7), Cd-B and Cd-U showed statistical significance ($P<0.05$) despite very low PCC (<0.1), indicating that significance test with the large number of degrees of freedom would produce a false positive (Armitage and Berry, 1994; Horiguchi et al., 2004). In such cases, comparison of the SPRC between variables should take precedence over P values to judge the "practical significance". Therefore, the reasonable interpretation of their analysis result would be "the contributions of age and body size were much larger than Cd exposure," which reconciles to ours. There is another study reporting that Cd-U was correlated with BMD in the general Japanese female population (Honda et al., 2003), but the authors also judged the significance only by statistical P values despite the large number of degrees of freedom. Therefore, the results of the multiple regression analysis in this study were actually almost the same as ours, too; age and menstrual status were the most important factors, followed by weight, and Cd-U was the least important. In short, age and body weight are always the most important contributors to BMD in the general population without high Cd pollution.

Our study also demonstrated that urinary Ca excretion was primarily affected by renal tubular function, not by Cd exposure, among women without Cd-induced renal tubular dysfunction. This means that Ca excretion is independent of Cd but dependent on renal function. Therefore, Cd exposure at even higher levels sufficient to induce renal dysfunction would increase Ca excretion primarily due to the deterioration of renal tubular reabsorption (Aoshima et al., 1993). This result further supports our contention that bone mineral loss occurs after Cd-induced renal injury severely progresses. This conflicts with the CadmiBel study again, which suggested that calciuria would be a sensitive renal tubular biomarker for a low degree of Cd exposure in the general population (Buchet et al., 1990). However, their multiple regression models did not include renal tubular function as an independent variable.

The classical explanation that Cd-induced bone injury is a secondary effect of renal dysfunction still seems to be the most reasonable. Therefore, urinary low molecular weight proteins should be still the most sensitive and significant indicators to detect the adverse effects of Cd in the general population. The prospective study of this population will provide additional useful information for risk management of environmental exposure to Cd.

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