Relationship of Urinary Sodium and Potassium and of Urinary Sodium/Creatinine, Potassium/Creatinine and Sodium/Potassium Ratios to Stomach Cancer and Cerebrovascular Disease Mortalities in Japanese Women

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Joossens and Geboers (1981, 1987) proposed the hypothesis that salt is a common etiologic factor for both cerebrovascular disease (CVD) and stomach cancer (SC) mortality. Although salt has been identified as a factor that predispose to SC (Joossens et al. 1981; Correa 1985), little is known on the etiology of SC. High blood pressure is known to be a risk factor of CVD (Katsuki and Hirota 1966; Kannel et al. 1970); however, the cause of hypertension is still in dispute. The age-adjusted death rates of these two diseases, both major causes of
death in Japan, have been decreasing since the mid-nineteen sixties. Japanese traditionally had a very high salt intake with an average of 240–470 mmol/day (14–27 g/day) in the late fifties (Sasaki 1964). The salt intake has recently dropped to 170–330 mmol/day (10–19 g/day) (Ikeda et al. 1986).

A number of reports (Kolonel et al. 1981; Nagai et al. 1982; Tuyns 1988; Buiatti et al. 1989; Coggon et al. 1989) in favor of the hypothesis presented by Joossens and Geboers (1981, 1987) have been published. However, correlation studies in Japan (Kono et al. 1983; Ikeda et al. 1988) have indicated that mortality rates and standardized mortality ratios (SMRs) of SC hardly correlated with salt intake. In contrast, the mortality rates and SMRs of CVD significantly correlated with salt intake.

In the present study, the daily amount of salt excreted in the urine was collected from middle-aged women from various regions in Japan to assess the validity of Joossens's hypothesis.

**SUBJECTS AND METHODS**

The data on the Na, K, and Na/creatinine (Cr), K/Cr, and Na/K ratios in urine are cited from previous publications (Takemori et al. 1988, 1989). Briefly, a prefectural seat, and a city and two towns or villages were randomly selected from each prefecture in Japan. Thus a total of 169 municipalities were studied (88 urban cities and 81 rural towns or villages) (Fig. 1). Subjects were female residents of these municipalities with ages between 40 to 69, who participated health examinations conducted by the municipalities. Fifty subjects were selected from each municipality. The filter paper sampling technique for urine (Takemori 1980) was used to collect urine samples from March to December in 1985. The details of collection and analyses have been described previously (Takemori et al. 1988). The Na/Cr (mmol/g), K/Cr (mmol/g), and Na/K (mmol/mmol) ratios were calculated on the basis of the concentration of Na, K and Cr in the spot urine. Twenty-four-hour urinary Na and K excretions were estimated on the basis of the concentrations of Na, K and Cr in the spot urine by the predictive equations presented by Kawasaki et al. (1985, 1986) for Na and by Hirata et al. (1985) for K.

The individual SMRs for the 169 municipalities during the period of 1979–1988 were kindly provided from the authors of a report (Anzai et al. 1990). Thus, Pearson's correlation coefficients between the variables including SMRs for the diseases of interest and average urinary Na, K, Na/Cr, K/Cr, and Na/K obtained from each municipality were calculated.

**RESULTS**

Table 1 shows Pearson's correlation coefficients between the electrolytes and the SMRs for all causes of death, cancer of all sites, SC, ischemic heart disease, CVD, cerebral hemorrhage or cerebral infarction. It was observed that the SMR levels for all causes of death, cancer of all sites, SC or ischemic heart disease did not correlate significantly with the urinary electrolytes or ratios. Fig. 2 shows that these was no significant correlation between urinary Na and SC SMR levels. On the other hand, the SMR levels for CVD, cerebral hemorrhage, and cerebral infarction correlated significantly with Na, Na/Cr, and Na/K (except that there
was no correlation with cerebral infarction) (Table 1). Fig. 3 shows the correlation between urinary Na and CVD SMR levels.

Table 2 shows the correlation between the SMR levels of several causes of death. SC and ischemic heart disease significantly correlated with CVD and cerebral infarction.

Table 3 shows the correlation between the urinary electrolytes and their ratios. Strong correlations were observed among them.

**DISCUSSION**

In the present study, the data on Na, K, Na/Cr, K/Cr and Na/K in urine are cited from previous studies (Takemori et al. 1988, 1989). Subjects and the method of collecting urine sample and the relevant particulars including the season of urine collection and the reasons of limiting the subjects to female were discussed in the previous studies. The correlation between urinary salts and blood pressure was also discussed previously.
TABLE 1. Pearson’s correlation coefficients between the female standardized mortality ratio from 1979 to 1988 and Na, K, \( \text{Ka}/\text{Cr}, \text{K}/\text{Cr}, \) and Na/K in the urine of middle-aged female adults (40–69 years old) in 169 municipalities in Japan\(^a\)

<table>
<thead>
<tr>
<th>Causes of death (ICD detailed list code)</th>
<th>Na</th>
<th>K</th>
<th>Na/Cr(^b)</th>
<th>K/Cr</th>
<th>Na/K</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes of death</td>
<td>0.110</td>
<td>0.025</td>
<td>0.060</td>
<td>0.012</td>
<td>0.040</td>
</tr>
<tr>
<td>Cancer of all sites (140–208)</td>
<td>0.010</td>
<td>0.062</td>
<td>-0.044</td>
<td>0.049</td>
<td>-0.092</td>
</tr>
<tr>
<td>Stomach cancer (151)</td>
<td>0.018</td>
<td>0.089</td>
<td>0.006</td>
<td>0.087</td>
<td>-0.079</td>
</tr>
<tr>
<td>Ischemic heart disease (410–414)</td>
<td>0.082</td>
<td>0.071</td>
<td>0.048</td>
<td>0.063</td>
<td>-0.019</td>
</tr>
<tr>
<td>Cerebrovascular disease (430–438)</td>
<td>0.334**</td>
<td>0.078</td>
<td>0.277**</td>
<td>0.067</td>
<td>0.222**</td>
</tr>
<tr>
<td>Cerebral hemorrhage (431, 432)</td>
<td>0.253**</td>
<td>-0.056</td>
<td>0.197*</td>
<td>-0.063</td>
<td>0.264**</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>0.255**</td>
<td>0.103</td>
<td>0.198*</td>
<td>0.093</td>
<td>0.132</td>
</tr>
</tbody>
</table>

\(^a\)ICD-9 international detailed list code is used for SMR for 1979–1988.
\(^b\)Cr, creatinine
\(* p<0.05, \text{**} p<0.01."

Fig. 2. Relationship between urinary Na and stomach cancer SMR levels.
Symbols represent the regions (shown in Fig. 1) in which each municipality is located: *, Hokkaido; o, Tohoku-I; □, Tohoku-II; +, Kanto-I, ×; Kanto-II; ■, Hokuriku; △, Tohkai; ★, Kinki-I; ◦, Kinki-II; ▽, Chugoku; ▼, Shikoku; •, North Kyushu; ♦, South Kyushu.
The hypothesis proposed by Joossens and Geboers (1981, 1987) was based on the strong correlation between CVD and SC mortality observed both within a country and among countries, and on the decrease in CVD and SC mortality after wide spread use of refrigerators which made it possible to preserve food without using salt.

Hypertension is an important risk factor for CVDs (Katsuki and Hirota 1966;
The mean sodium intake and blood pressure levels have been found to be correlated in the general population (Gleibermann 1973; Simpson 1985). Some within-population studies on Oriental populations (Kesteloot et al. 1980, 1987; Takemori et al. 1989) have reported that sodium intake is correlated positively with blood pressure. On the other hand, an inverse relation (McCarron et al. 1984) or no relation (Karvonen and Punsar 1977; Staessen et al. 1981) between sodium intake and blood pressure have also been reported.

Case-control studies of SC and diet through questionnaires (Haenszel et al. 1972; You et al. 1988; Buiatti et al. 1989; Coggon et al. 1989) have indicated that a high intake of salt, pickled vegetables, dried/salted fish, and a low intake of raw vegetables, fresh fruits and citrus fruits are associated with the development of SC. In the study on the taste for salt (Tuyns 1988), among people who systematically added salt to their food, high relative risks for SC, colon cancer and rectal cancer were observed. Studies on the relationship between diet and the incidence or SMRs of SC (Kolonel et al. 1981; Nagai et al. 1982) have indicated positive associations of SC with the consumption of rice, pickled vegetables, and dried or salted fish, and negative associations with the intake of vitamin C and tofu (soybean curd). Hirayama (1984) summarized the characteristics of both the descriptive and analytic epidemiology of SC in Japan; dietary changes, especially the reduced intake of salted food are considered to be the major reasons behind the recent decline in mortality; the daily intake of green-yellow vegetables, soybean paste soup and milk is also considered to be a risk-reducing factor.

An etiologic model to explain the mechanisms of gastric carcinogenesis has been proposed and updated by Correa (1975, 1985). Irritants such as dietary salt, alcohol and cigarette smoking which can damage the gastric mucosa have been proposed as facilitators of gastric carcinogenesis.

As described above, there are many studies implicating salt in the etiology of SC. Kono et al. (1983) and Ikeda et al. (1988), however, found that the mortality rate of SC showed no correlation with salt (or Na) intake in several regions in Japan, while the mortality rate or SMR levels of CVD was strongly correlated

\begin{table}
\centering
\caption{Pearson's correlation coefficients between the urinary Na, K, Na/Cr, K/Cr or Na/K in middle-aged female adults (40-69 years old) in 169 municipalities in Japan}
\begin{tabular}{cccc}
\hline
 & Na & Na/Cr & K/Cr & Na/K \\
\hline
Na & 0.396** & 0.951** & 0.390** & 0.619** \\
K & 0.337** & 0.981** & -0.378** & \\
Na/Cr & & 0.329** & 0.705** & \\
K/Cr & & & -0.400** & \\
\hline
\end{tabular}
\footnotesize{aCr, creatinine.} \\
\footnotesize{**p < 0.01.}
\end{table}
with salt (or Na) intake. The same results were obtained in this study (Table 1). In the studies that showed a positive correlation with SC, information on salt intake was obtained from questionnaires on the usual frequency of consumption of particular food items or on the use of salt. On the other hand, in the studies where no correlation was found, the salt intake was calculated on the basis of the actual daily amount of salt either ingested (Kono et al. 1983; Ikeda et al. 1988) or excreted (in our study). In reviewing the etiology of SC, Mirvish (1983) described that animal experiments suggest that SC may be correlated with the extent of gastric exposure to hypertonic salt solutions, whereas CVDs might be more closely correlated with total salt consumption. Sakata and Moriyama (1990) showed that the average Japanese consumption of salt in 1950 (21.7 g/day) was nearly double the consumption of 11.7 g/day in 1990, and that miso (soybean paste) and tsukemono (vegetables preserved in salt), which are Japanese traditional salty foods, seem to no longer be the major source of Na intake for the average Japanese, since Japanese people now have a tendency to get Na from a variety of foods. Hirohata et al. (1991) found a linear correlation for SC SMR levels with salt intake from highly salted foods such as salted fish, pickled vegetables (preserved for long periods), salted fish-eggs or salted fish guts (siokara). The fact that Japanese salt intake from traditionally highly salted foods has decreased gradually and that salt is now consumed through various foods may partly explain why there is no relation between the actual daily amount of either ingested or excreted salt and the SC SMR levels. In the research on the correlation between salt and SC, as described above, it is necessary to investigate the salt index; the hypertonic salt intake originate from highly salted foods, or the total salt intake measured by a 24-hr diet duplicate collection or a 24-hr urine collection.

Kamiyama and Michioka (1983) compared the mutagenicity of diets in different regions. The patterns of the mutagen-positive food group such as broiled meat, grilled fish and salted fish guts were approximately equal in Akita (located in Tohoku and facing the Japan Sea), Iwate (located in Tohoku and facing the Pacific Ocean) and Kagoshima (located in South Kyushu and facing the Pacific Ocean) in Japan, while mutagen-negative food groups such as fresh vegetables, fresh western vegetables and potatoes, decreased in Kagoshima, Iwate and Akita (in this order). The SC mortality also increased in the same order (Kamiyama 1988). In Fig. 2, the municipalities located in Tohoku-I (facing the Japan Sea) and Hokuriku district, had high SC SMR levels, whereas the municipalities located in Tohoku-II (facing the Pacific Ocean) had lower SMR levels (except a few municipalities) about equal to the SMR for municipalities in South Kyushu. This pattern was similar to the pattern of mutagen-positive and mutagen-negative food groups described by Kamiyama (1988). In Fig. 3, on the other hand, the municipalities located in Tohoku-I and Tohoku-II had higher CVD SMR levels and higher urinary Na excretion.
In this study, no factors other than salt intake were taken into account. This may be the reason why the correlations between urinary Na excretion and SMR levels for blood pressure-related diseases such as CVD were significant, while those correlation coefficients were relatively small. Furthermore, this may also explain why there is no correlation between urinary Na excretion and female SMR levels for SC. Social class, the consumption of dietary fiber, raw vegetables, fresh fruit, alcohol, and cigarette smoking are known to be related to both SC and CVD. The introduction of a model of multifactorial causation, taking account of both risk factors and risk reducing factors (Hirayama 1984) such as mutagen-positive diet and mutagen-negative diet as described by Kamiyama and Michioka (1983), may explain these results.

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References

Relation of Na to Stomach Cancer and Stroke


