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The Absence of Correlation between Na in Diet Duplicates and Stomach Cancer Mortality in Japan

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IKEDA, M., NAKATSUKA, H. and WATANABE, T. *The Absence of Correlation between Na in Diet Duplicates and Stomach Cancer Mortality in Japan.* Tohoku J. exp. Med., 1988, **155** (3), 285-294 —— The 24-hr diet duplicates were collected from 488 nonsmoking and nondrinking women at the ages of 30-59 years in 33 regions in Japan in winters, 1977-1981. The daily intake of Na, K, Cl and Na/K ratio for each individual were obtained by the chemical analysis of the duplicates, from which the regional means were calculated and subjected to regression analysis with 1969-1978 regional mortality for stomach cancer (SC), cerebrovascular disease (CVD) and liver cirrhosis for the middle-aged, 1969-1978 regional standardized mortality ratios (SMRs) for cancers of 9 sistes and 9 other diseases (including SC and CVD), and 1978-1982 regional SMRs for SC, uterine cancer and CVD. No significant correlation was observed between intake of Na, K, Cl or Na/K and SC mortality or SMR, in contrast to a significant correlation of CVD mortality and SMR with Na intake (and to a lesser extent with K and Cl intake). Correlation of other cancers with Na was generally insignificant except for pancreatic cancer and possibly breast cancer. Thus, it was concluded that the correlation of daily Na intake with stomach cancer mortality is weaker, if present, than that with cerebrovascular disease mortality. ———— diet duplicate; Japan; mortality; sodium; stomach cancer

Although the possibility has been discussed for many years [for a review, see Joossens and Geboers (1981)] that salt (sodium chloride) is a common etiologic factor of both hypertension and stomach cancer, the diseases of major causes of death in Japan (Statistics and Information Department 1983), the answer for the question whether or not the risk of stomach cancer is higher for those who take salty food items than who do not still remains controversial. Most of the preceding work on the relation of salt and stomach cancer rely the information on salt

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intake habit upon the statement of the examinees such as frequency of salty food intake per day (Haenszel et al. 1972; Correa et al. 1985; Risch et al. 1985; Tajima and Tominaga 1985), and the actual daily amount of salt either ingested or excreted was measured only occasionally (Bernstein and Henderson 1985; Montes et al. 1985).

In the present study, 24-hr diet duplicates were collected in winters, 1977-1981 from farming women in various parts of Japan, and the possible relationship of daily intakes of sodium (Na), potassium (K), chlorine (Cl) and the Na/K ratio with stomach cancer mortality of the regions was examined. A positive correlation of salt intake with cerebrovascular disease mortality in a within-a-country study has been published (Ikeda et al. 1986).

Materials and Methods

Na, K, Cl and Na/K ratio in 24-hr duplicates of diet

The study regions, where 4 or more nonsmoking and nondrinking women at the ages of 30-59 years volunteered for diet examination, were selected for the present study from the 49 regions previously reported (Ikeda et al. 1986). The regions thus selected totaled 33 with 488 participating women. The geographic locations of the study regions are depicted in Fig. 1. The strategy of diet collection was previously described in detail (Watanabe et al. 1985; Ikeda et al. 1986): in brief, the three meals along with any snacks and drinks as were

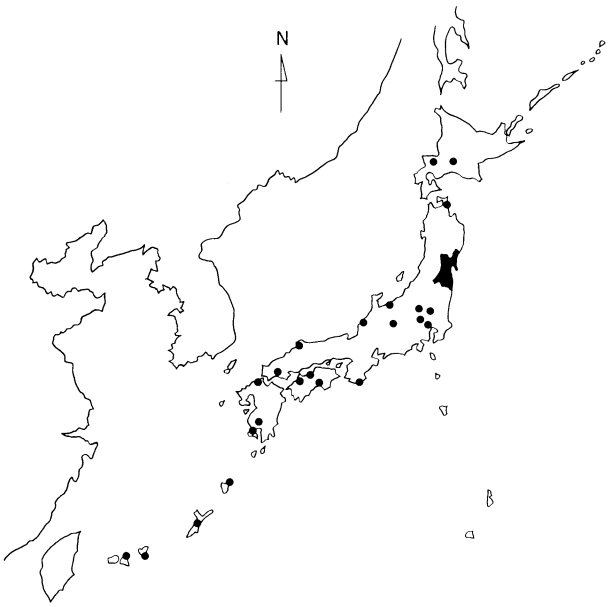

Fig. 1. Geographical distribution of the study regions.
Dots (23 in total) in the figure indicate the region where ≥ 4 nonsmoking and nondrinking 30-59 year-old women offered 24-hr duplicates of diet. The shaded area shows Miyagi prefecture in which 10 additional study regions scattered.

taken were reserved in acid-washed plastic containers during the winters (excluding social occasions) in 1977-1981, and analyzed for Na and K by atomic absorption spectrophotometry after wet-ashing and for Cl with a coulometric clinical chloride counter with the homogenate of the each diet duplicate sample (Ikeda et al. 1986). The Na, K, Na/K and Cl data are cited from a previous publication (Ikeda et al. 1986).

Regional mortality data

The data on mortality and standardized mortality ratio (SMR) by city, town and village in Japan are cited from 3 Ministry of Health and Welfare-sponsored publications. Two types of data were available. One publication reports on the mortality due to stomach cancer, cerebrovascular disease (CVD) and liver cirrhosis for the middle-aged in 1969-1978 (Research Committee on Geographical Distribution of Adult Diseases 1984). Remaining two report on SMR for various diseases including stomach cancer (SC); the first one on SMRs for cancers of 10 sites including the stomach and SMRs for other 9 diseases in 1969-1978 (Research Committee on Geographical Distribution of Adult Diseases 1982), and the second one on SMRs for SC, uterine cancer and CVD in 1978-1982 (Department of Senior Health 1984). In the former two publications, the study period was limited to 1973-1978 for Okinawa prefecture. As the dietary data were obtained from women, the mortality and SMR data for women were cited.

Statistical analyses

As dietary intake of the three electrolytes as well as the Na/K ratio distributed normally (Ikeda et al. 1986), arithmetic mean values ($n \geq 4$) were taken for Na, K, Cl and Na/K as the values to represent the intake in each region. Regression analyses were conducted utilizing a package program supplied by NEC Corporation (Tokyo) for an ACOS 1000 system in the Tohoku University Computer Center.

Results

In Table 1 are summarized the results of regression analyses between the electrolyte contents in the diet duplicates and the 1969-1978 SMRs for cancers of 9 sites and for 9 other diseases including CVD and ischemic heart disease (Research Committee on Geographical Distribution of Adult Diseases 1982). In addition, the results with 1978-1982 SMRs (Department of Senior Health 1984) are shown in parentheses.

It was observed that the correlation with intake of Na, K and Cl as well as Na/K ratio was statistically insignificant ($p > 0.05$) in most cancers with two exceptions of pancreatic cancer and breast cancer, for which the correlation with Na was significant ($p < 0.01$ for pancreatic cancer and $p < 0.05$ for breast cancer). Namely, the correlation coefficients (r) for stomach cancer SMR with electrolytes were statistically insignificant with $p > 0.05$ in all cases examined both for the periods of 1969-1978 and 1978-1982. Correlation was also insignificant with cancers of other sites in the digestive tract, i.e., the esophagus, the colon and the rectum.

Making a sharp contrast, cerebrovascular disease SMR was significantly correlated with the intake of Na, K and Cl both in 1969-1978 and in 1978-1982 in confirmation with the previous observation (Ikeda et al. 1986). Among CVD, cerebral hemorrhage correlated with Na intake, and subarachnoidal hemorrhage

TABLE 1. *Correlation coefficients between standardized mortality ratio and dietary Na, K, Cl or Na/K*

Disease (ICD No.)	Na	K	Cl	Na/K
Cancer				
Esophageal cancer (150)	−0.0319	0.2865	−0.0250	−0.3231
Stomach cancer (151)	0.2775 (0.2739)	0.1879 (0.3059)	0.3147 (0.3255)	0.1055 (0.0333)
Colon cancer (153)	0.1198	0.1246	0.0710	−0.0078
Rectal cancer (154)	0.1651	0.1321	0.1863	0.0268
Liver cancer (155 & 197.8)	−0.2381	−0.2861	−0.1911	−0.0913
Pancreatic cancer (157)	0.4532**	0.2765	0.4028*	0.3058
Lung cancer (162)	−0.0613	−0.0135	−0.0439	−0.0318
Breast cancer (174)	0.3571*	0.2651	0.3383	0.2336
Uterine cancer (180-182)	−0.1108 (−0.2138)	−0.2492 (−0.2246)	−0.0833 (−0.2157)	0.1101 (0.0292)
Other diseases				
Hypertensive heart disease (400.1, 400.9, 402 & 404)	0.1661	0.2972	0.2167	−0.0403
Ischemic heart disease (410-414)	0.4439**	0.4850**	0.4777**	0.0775
Cerebrovascular disease (430-438)	0.4541** (0.5539)**	0.4074* (0.3744)*	0.4039* (0.5011)**	0.2157 (0.3169)
Subarachnoidal hemorrhage (430)	0.3138	0.3704*	0.3519*	0.0035
Cerebral hemorrhage (431)	0.3693*	0.1801	0.3087	0.2943
Cerebral infarction (432-434 & 438.4)	0.3191	0.2914	0.2640	0.1452
Diabetes mellitus (250)	0.0832	−0.0023	0.1111	0.1658
Liver cirrhosis (571)	−0.3072	−0.1222	−0.2611	−0.2381
Tuberculosis (010-019)	−0.1572	−0.1317	−0.1434	−0.1037

The values are correlation coefficients with SMR for 1969-1978 (for 1978-1982 in parentheses). The statistical significance is shown with **for $p<0.01$, and *for $p<0.05$.

TABLE 2. *Correlation coefficients between mortality and dietary Na, K, Cl or Na/K*

Disease (ICD No.)	Na	K	Cl	Na/K
Stomach cancer (151)	0.1355 (0.2412)	0.0383 (0.1765)	0.1243 (0.2912)	0.1108 (0.0773)
Cerebrovascular disease (430-438)	0.3675* (0.3810)*	0.1365 (0.3640)*	0.3001 (0.3434)	0.4175* (0.1685)
Liver cirrhosis (571)	−0.2107 (−0.2098)	−0.0199 (−0.0984)	−0.1552 (−0.1793)	−0.1818 (−0.2320)

Correlation coefficients together with) are shown. The values are correlation coefficients for mortality at 40-64 years of age and that for ≥65 years in parentheses. The statistical significance is indicated with *for $p<0.05$.

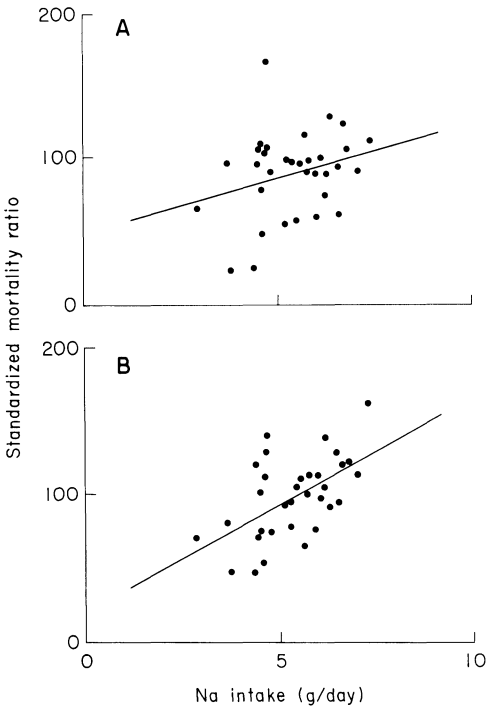

Fig. 2 Relationship of Na intake with standardized mortality ratio for (A) stomach cancer and (B) cerebrovascular disease.
The line in the figure is a calculated regression line represented by
$Y=7.50X+48.5$ ($r=0.274$, $p>0.05$, $n=33$) for stomach cancer,
and $Y=14.7X+18.6$ ($r=0.554$, $p<0.01$, $n=33$) for cerebrovascular disease, where X is Na intake of 30-59 year-old nonsmoking and nondrinking women in 1977-1981, and Y is the standardized mortality ratio for either stomach cancer or cerebrovascular disease for women in 1978-1982.

with K and Cl but at a lower level of significance. Ischemic heart disease SMR also showed significant correlation ($p<0.01$) with intake of the 3 electrolytes studied. SMRs for diabetes mellitus, liver cirrhosis and tuberculosis did not correlate with intake of Na, K nor Cl as expected. The contrast between stomach cancer (with no statistical significance, i.e., $p>0.05$) and CVD ($p<0.01$) is graphically shown in Fig. 2, taking the 1978-1982 SMR and Na intake as examples.

The mortality data of the middle-aged people (in two age groups of 40-64 years and $\geq$65 years) were available only for stomach cancer, CVD and liver cirrhosis (Research Committee on Geographical Distribution of Adult Diseases 1984), and subjected to regression analyses (Table 2). In confirmation of the findings with SMRs, the CVD mortality was significantly related with Na intake both in 40-64 years and $\geq$65 years, and possibly with K and Na/K (K in $\geq$65 years only, and Na/K in 40-64 years only), whereas stomach cancer mortality was

not related with either Na, K nor Na/K at both age ranges studied as was the case of liver cirrhosis.

Discussion

Since the early day discussion (e.g., Sato et al. 1959; Hirayama 1968) on possible association of salty food intake and stomach cancer, and especially after the proposal by Joossens and Geboers (1981) of an idea that salt is an etiologic factor common to hypertension and stomach cancer, a number of reports in the favor of (e.g., Kolonel et al. 1981; Nagai et al. 1982; Correa et al. 1983; Tuyns 1983; Tuomilehto et al. 1984; Bernstein and Henderson 1985; Montes et al. 1985) or against (e.g., Whelton and Goldblatt 1982; Kono et al. 1983) the hypothesis have been published. Regarding the possible relationship on salt and stomach cancer, the proposal of the hypothesis by Joossens and Geboers (1981) is in principle based on the observation that there is a significant relationship between dietary salt intake and stomach cancer incidence when compared multinationally and that reduction in salt intake is paralleled by a decrease in the stomach cancer incidence in many countries.

In recent studies, parallelism in the reduction of salt intake with that of stomach cancer incidence was also observed in Finland (Tuomilehto et al. 1984), whereas Kono et al. (1983) pointed out that the mortality for stomach cancer and stroke in Japan have been declined since 1960's, well before the beginning of reduction in salt consumption. Kolonel et al. (1981) compared food habits and stomach cancer incidence among Hawaii Japanese and Caucasians and found that consumption of rice, pickled vegetables and dried/salted fish has a positive relationship with the cancer incidence. Tuyns (1983) found that a greater proportion of patients with esophageal, stomach or colon cancer liked salted food than expected. Similarly, Correa et al. (1983) made a set of nutritional survey in Columbian villages with different stomach cancer risks using the interview method of Koopman et al. (1981) and suggested that excessive salt intake and reduced potassium intake are associated with a high risk of stomach cancer.

Nagai et al. (1982) made statistical analyses of 1974-1976 national nutritional survey and 1969-1974 SMRs in Japan and observed that the consumption of pickled vegetables and dried/salted fish positively correlated with the incidence of cancers of the esophagus and stomach. In accordance with these findings, Montes et al. (1985) and Bernstein and Henderson (1985) reported higher Na/creatinine ratio in the urine of those who live in the area with higher stomach cancer risk. Kono et al. (1983), however, found a strong correlation of salt intake only with stroke mortality but none with stomach cancer mortality when they examined age- and sex-adjusted mortality rates of these diseases in 1974-1976 and the results of 1966-1970 national nutritional survey. Furthermore, Whelton and Goldblatt (1982) observed no evidence of a greater concordance between stomach cancer and hypertension or CVD than between pancreatic cancer and the two

diseases, which suggests no casual link between the stomach cancer and hypertension/CVD.

One factor worthy of attention is the fact that in most studies the amount of salt considered to be taken is an estimate based on, e.g., interview of the subjects (Kolonel et al. 1981 ; Correa et al. 1983) or otherwise (Nagai et al. 1981 ; Kono et al. 1983) and seldomly measured, even as the amount excreted into urine (Bernstein and Henderson 1985 ; Montes et al. 1985). The efforts were made in the present study to collect 24-hour duplicates of common day diet from various parts of Japan for analyses of Na, K and Cl, as subjective judgement of frequent intake of salty food does not necessarily mean high salt intake. As a typical example from Japanese-style diet, it is often experienced that a small piece (e.g., 45 g) of roasted salted salmon [NaCl content ca. 8.2% (Resources Council 1982)] gives a strong taste of salt while 300 ml of *miso* soup [soup made of fermented soya bean paste, containing 1.2 g of NaCl/100 ml (Sasaki and Kikuchi 1980)] does not taste very salty, although both contains almost the same amount (3.6 g) of salt. It should also be added that chemical analyses were made in a single laboratory to rule out any inter-laboratory differences.

The results were compared with the mortality and SMR data for the same village, town or city. Worthy of noting is that the diet duplicates were collected from nonsmoking-nondrinking women to exclude the factors which might modify the taste as far as possible. It is known that the two social habits increase the incidence of stomach cancer (Hirayama 1975 ; Hoey et al. 1981). Male cases were not studied because the number of nonsmoking and nondrinking men available was very limited (Watanabe et al. 1985). The age range of 30–59 years was selected as the electrolyte intake was almost constant in 30's to 50's among the women studied (Ikeda et al. 1986).

One major drawback in the present study is the reverse relation in time between the diet duplicate collection and mortality/SMR observation. As the mortality/SMR values were calculated based on the observation in 1969–1978 and 1978–1982, it can not reflect the effects of electrolyte intakes in around 1980 when the diet survey was made, unless the dietary habits had been unchanged for preceding decades of years. Such problem can be solved only by a follow-up of mortality/SMR in the nearest future.

The number of diet duplicates collected in each study region was not large due to technical difficulties inherent to this type of study, and thus possigility remains that the samples analyzed might not be the very representative of the local dietary custom. It is possible to argue that each duplicate was collected only on one particular day, and therefore the electrolyte contents would be subject to day-to-day variation in eating although social occasions were carefully excluded. In a preceding study on dietary cadmium intake (in which the diet duplicates of the present study were utilized) and blood cadmium levels, however, a significant correlation was observed between the cadmium in diet and cadmium in

blood when the means were taken as the representative of the regional values, suggesting that the day-to-day difference in diet could be eliminated by pooling of the data (Watanabe et al. 1985) as in the present study. It was also found (Ikeda et al. 1986) that winter-summer difference in salt intake is small and essentially insignificant; summer intake is 95-105% of that in winter in Na, K and Cl in both sexes. Accordingly, the present measure of dietary salt intake can be considered valid and reliable.

Thus, the observation that a significant correlation exists between dietary Na intake and cerebrovascular disease SMR (Table 1) and also CVD mortality of the middle-aged women (Table 2) indicates that the present regression analysis has enough power to detect the correlation between the salt intake and CVD, and reversely, the failure to detect any correlation between salt and stomach cancer suggests the correlation is either absent or weaker than that of CVD within a population of Japan. The significant correlation of cerebrovascular disease SMR with K and Cl (Table 1) can be explained with the fact that dietary intake of Na closely correlates with that of K and Cl ($r=0.6883$ for K and 0.9732 for Cl; $p<0.01$, $n=488$ for both).

Of particular interest is the similarity in the observation that a closer correlation with salt-eating habits tends to be detected with inter-country comparison rather than with intra-population studies both in the epidemiology of hypertension/CVD (e.g., Tobian 1979; Wilhelmsen and Svärdsudd 1982) and stomach cancer (e.g., Joossens and Geboers 1981). It is true that the power of statistical analysis is a function of the width of variation range in the parameters. It is also possible to expect, however, that any possible confounding factors (i.e., factors other than salt intake that is measured or estimated) would vary less within a population than between countries. The reason for the gap between inter-national and intra-population studies remains yet to be studied.

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