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A Case-Control Study of Single and Multiple Stomach Cancers in Saitama Prefecture, Japan

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A case-control study of stomach cancer was done in Saitama Prefecture, Japan, in relation to dietary, smoking, and drinking habits. The study was based on two sets of cases (216 male single and 35 male multiple stomach cancer cases newly diagnosed and of adenocarcinoma type), and 483 male controls derived from residents of Saitama Prefecture. Dietary habits were investigated for the intake of 12 separate foods and 12 food groups by means of a food frequency questionnaire, including individual taste preferences. Among the single stomach cancer series, dose-response relationships were observed for 7 dietary items (preference for salty foods, miso soup, boiled fish, pickled vegetables, nuts, raw vegetables, and seaweed) in the multiple logistic regession analysis. As for the multiple stomach cancer case series, dose-response relationships were observed for 3 dietary items (miso soup, fruits, and seaweed) in the multiple logistic regression analysis. Cigarette smoking and alcohol use were not significantly related to the risk of either single or multiple stomach cancer.

Key words: Alcohol — Case-control study — Diet — Stomach cancer, single — Stomach cancer, multiple

Stomach cancer is the most common cancer in Japan, though mortality from this cancer has gradually decreased over the past decades, possibly following the westernization of this country.[1,2] Diet has been a main focus in the epidemiology of stomach cancer, and it has been suggested that diets high in salt and low in raw vegetables and fruits increase the risk of stomach cancer.[3,4] Recent publications have suggested that cigarette smoking may be related to the risk of stomach cancer,[5–12] though the epidemiological evidence is not conclusive.[4]

The association between dietary habits and stomach cancer should be made much clearer by a study on single and multiple stomach cancers, because it can be hypothesized that patients with multiple stomach cancer might have been more highly exposed to risk factors. We therefore conducted a case-control study of single and multiple stomach cancers in Saitama Prefecture, Japan, in relation to diet, cigarettes, and alcohol use.

MATERIALS AND METHODS

Seven provincial cities and 2 towns in the vicinity of the Saitama Cancer Center Hospital were selected as a study area.

Cases and controls For the purpose of case-control studies of several cancers, we have consecutively surveyed the lifestyles of patients admitted to the Saitama Cancer Center Hospital from August 1984 to July 1990. A total of 5,075 inpatients was interviewed before diagnostic procedures at Saitama Cancer Center Hospital by the authors and two colleagues. The histological examination revealed 328 single stomach cancer inpatients (230 males and 98 females), as reported in our previous paper,[13] and 32 multiple stomach cancer inpatients (27 males and 5 females) in the study area.

To recruit general population controls, letters requesting participation in the lifestyle survey were mailed to 4,052 residents who were randomly selected from the electoral registry in the study area with stratification of age and sex. Of the 4,052, a total of 1,113 (27.5%) volunteered to participate in the lifestyle survey. After arranging an interview by telephone, they were interviewed at their homes from July 1986 to December 1990 by the same staff who interviewed inpatients. Unfavorable results at the initial contact were: refusal 937, no response 1,959, and not known at the listed address 43. Of the 1,113, we excluded 150 subjects who had not lived in Saitama Prefecture for ten years or more and/or who were on a long-term special diet for medical reasons. The remaining 963 subjects (483 males and 480 females) formed a general population control pool.

Subjects for analysis For multiple stomach cancer, female patients were excluded because of the small number (5 cases), and so were 2 male patients who had not lived in Saitama Prefecture for ten years or more and/or who were on a long-term special diet for medical reasons. Ten male multiple stomach cancer patients, who lived in the vicinity of the study area, were combined.

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Table I. Distribution of Cases and Controls by Age

Age	Single stomach cancer cases	Multiple stomach cancer cases	Control
–54	78	8	189
55–64	65	14	132
65+	73	13	162
Total	216	35	483

For the sake of balance, we also excluded female single stomach cancer patients. Of the 230 male single stomach cancer patients, we further excluded 14 patients for the same reasons as in the multiple stomach cancer series. A total of 216 male single and 35 male multiple stomach cancer patients and 483 male controls from the general population control pool were identified (Table I)

Lifestyle questionnaire Interviews with the inpatients were done before diagnostic procedures at the Hospital. They were requested to give lifestyle information related to the period before the onset of symptoms of the disease that had led to the current hospital admission.

Questions on dietary habits included the frequency of intake of 12 food items (rice, miso soup, green tea, coffee, black tea, broiled fish, boiled fish, broiled meat, pickled vegetables, nuts, smoked food/bacon/ham and raw vegetables) and of 12 food groups (bread, noodle, potato, soybean products (except miso soup), fruits, green-yellow vegetables, white vegetables, seaweed, fish/shellfish (all types), meat, egg, and dairy products). Six consumption frequency categories were prepared for most dietary items. We also asked about invividuals' preferences for salty foods, sweet foods, spicy foods, and hot non-alcoholic beverages (including tea, coffee, and miso soup).

Consumption of cigarettes and alcoholic beverages was ascertained so as to calculate the total amounts of cigarettes and ethanol consumed over the subject's lifetime.

Data processing The frequency of consumption for each food item was divided into three levels in order to include as equal a number as possible in each level. Unconditional logistic regression analysis was used for the comparison between cases and controls.[14]

The relative risk and its 95% confidence interval were calculated based on the regression coefficient and its standard error for an indicator term corresponding to a level of independent variable. Trend of association was assessed by a logistic regression model assigning scores to the levels of the independent variable. Statistical significance (two-sided) was determined based on the ratio of the regression coefficient to its standard error. The statistical analyses were performed by using the Statistical Analysis System.[15]

RESULTS

Among the dietary associations with single stomach cancer risk, 14 food items showed statistically significant trends (Table II). Preference for salty foods and the consumption of rice, miso soup, boiled fish, and pickled vegetables were positively related to a risk of single stomach cancer. An inverse relation was observed for the consumption of coffee, nuts, raw vegetables, potato, soybean products fruits, green-yellow vegetables, white vegetables, and seaweed.

Among the dietary associations with multiple stomach cancer risk, 5 food items demonstrated statistically significant trends (Table III). Miso soup was consumed more frequently among cases than among controls, and nuts, fruits, seaweed, and fish/shellfish were consumed less often by cases than by controls. There was no clear trend between the risk of multiple stomach cancer and the consumption of the remaining 23 dietary items.

There was no material association between single and multiple stomach cancer risk and any of the indices of cigarette smoking and alcohol consumption (Tables IV and V).

To examine the independent association between single stomach cancer risk and various dietary habits, smoking habits and 14 items of dietary habits, which had a statistically significant trend in Table II, were simultaneously included in a multiple logistic regression model. As shown in Table VI, preference for salty foods and consumption of such foods as miso soup, boiled fish, pickled vegetables, nuts, raw vegetables, and seaweed were independently related. As for multiple stomach cancer, smoking habits and 5 items of dietary habits, which had a statistically significant trend in Table III, were simultaneously evaluated in the same model. Consumption of miso soup, fruits, and seaweed were independently related (Table VI). After adjustment for dietary items, cigarette smoking was found to be not significant as a risk factor of either single or multiple stomach cancer. In brief, for single stomach cancer, relative risks calculated with respect to never-smokers as the reference, were 1.0 (95% CI=0.5 to 1.8) for ex-smokers and 1.1 (95% CI=0.6 to 2.0) for current smokers, and the corresponding values were 0.6 (95% CI=0.2 to 2.2) and 0.7 (95% CI=0.2 to 2.3), respectively, for multiple stomach cancer.

DISCUSSION

A possible shortcoming of the present study may lie in the selection bias in recruiting general population controls, because less than 30% of control candidates participated in this study. We cannot fully evaluate the degree of their deviation from the whole general popula-

Table II. Relative Risks[a] of Single Stomach Cancer by Dietary Items in Food Frequency History Questionnaire

Food item	Frequency of consumption			Trend
	Low	Intermediate	High	*P*-value
Preference for				
salty foods[b]	1.0	1.6 (1.0–2.4)	2.6 (1.7–3.9)	0.00
sweet foods[b]	1.0	1.1 (0.7–1.6)	1.2 (0.8–1.8)	0.36
spicy foods[b]	1.0	1.1 (0.7–1.6)	1.1 (0.7–1.8)	0.68
hot beverages[b]	1.0	1.0 (0.6–1.6)	1.2 (0.8–1.9)	0.28
12 individual food items				
Rice[c]	1.0	1.6 (1.1–2.3)	2.4 (1.3–4.4)	0.00
Miso soup[d]	1.0	1.3 (0.9–1.9)	2.3 (1.5–3.7)	0.00
Green tea[e]	1.0	1.2 (0.8–1.7)	0.9 (0.6–1.3)	0.65
Coffee[f]	1.0	0.7 (0.5–1.0)	0.7 (0.4–1.0)	0.04
Black tea[g]	1.0	1.3 (0.9–2.0)	1.1 (0.7–1.7)	0.40
Broiled fish[h]	1.0	0.9 (0.6–1.3)	0.8 (0.4–1.3)	0.31
Boiled fish[h]	1.0	1.3 (0.9–1.8)	1.9 (1.0–3.7)	0.04
Broiled meat[i]	1.0	1.4 (0.8–2.3)	1.1 (0.6–2.0)	0.97
Pickled vegetables[j]	1.0	1.5 (0.9–2.4)	1.9 (1.2–3.0)	0.01
Nuts[k]	1.0	0.6 (0.4–0.9)	0.5 (0.3–0.8)	0.00
Smoked food/bacon/ham[i]	1.0	1.3 (0.8–2.0)	1.1 (0.7–1.8)	0.73
Raw vegetables[l]	1.0	0.7 (0.4–1.1)	0.4 (0.3–0.6)	0.00
12 food groups				
Bread[m]	1.0	1.0 (0.6–1.4)	0.9 (0.6–1.4)	0.71
Noodle[m]	1.0	1.3 (0.9–1.9)	1.2 (0.8–2.0)	0.32
Potato[m]	1.0	0.8 (0.6–1.2)	0.4 (0.2–0.9)	0.03
Soybeam products[n] (except miso soup)	1.0	0.6 (0.4–0.8)	0.6 (0.3–0.9)	0.00
Fruits[m]	1.0	0.8 (0.5–1.3)	0.6 (0.3–0.9)	0.00
Green-yellow vegetables[n]	1.0	0.5 (0.3–0.7)	0.5 (0.3–0.7)	0.00
White vegetable[o]	1.0	0.8 (0.5–1.1)	0.6 (0.4–0.8)	0.01
Seaweed[m]	1.0	0.5 (0.3–0.8)	0.4 (0.2–0.7)	0.00
Fish/shellfish[n] (in all types)	1.0	0.7 (0.5–1.0)	0.9 (0.5–1.4)	0.19
Meat[m]	1.0	1.4 (0.8–2.5)	1.1 (0.7–2.0)	0.85
Egg[m]	1.0	1.1 (0.7–2.0)	1.0 (0.6–1.7)	0.74
Dairy products[m]	1.0	0.7 (0.5–1.2)	0.9 (0.6–1.3)	0.68

a) Based on unconditional logistic regression; adjustment for age (see Table I) and smoking status. *b*) Low, no; intermediate, moderate; high, yes. *c*) Low, ≤3 bowls/day; intermediate, 4–5/day; high, ≥6/day. *d*) Low, ≤1 cup/day; intermediate, 2/day; high, ≥3/day. *e*) Low, ≤4 cups/day; intermediate, 5–7/day; high, ≥8/day. *f*) Low, ≤1 cup/wk; intermediate, 2–9/wk; high, ≥10/wk. *g*) Low, none; intermediate, ≤1 cup/wk; high, ≥2/wk. *h*) Low, ≤1/wk; intermediate, 2–3/wk; high, ≥4/wk. *i*) Low, none; intermediate, ≤1/wk; high, ≥2/wk. *j*) Low, ≤5/wk; intermediate, 6–13/wk; high, ≥14/wk. *k*) Low, none; intermediate, ≤2/mth; high, ≥3/mth. *l*) Low, ≤1/wk; intermediate, 2–5/wk; high, ≥6/wk. *m*) Low, ≤1/wk; intermediate, 2–4/wk; high ≥5/wk. *n*) Low, ≤4/wk; intermediate, 5–7/wk; high ≥8/wk. *o*) Low, ≤7/wk; intermediate, 8–14/wk; high ≥15/wk.

tion as to risk factors of stomach cancer. Nevertheless, it should be mentioned that smoking status in our general population controls did not differ from that in the general population in Japan; there was no significant difference ($P=0.82$ in males) in the percentage of current smokers between the general population in Japan (about 59% in males aged 20 years or more in the period from 1986 to 1990)[16] and our general population controls (about 53%).

In the present study, cigarette smoking was not associated with the risk of stomach cancer before (Table IV) or after adjusting for dietary factors. The lack of such an association was also consistently observed throughout the two stomach cancer series. Cigarette smoking may be

Table III. Relative Risks of Multiple Stomach Cancer by Dietary Items in Food Frequency History Questionnaire

Food item	Frequency of consumption			Trend *P*-value
	Low	Intermediate	High	
Preference for				
salty foods	1.0	1.5 (0.6–3.6)	1.5 (0.6–3.8)	0.38
sweet foods	1.0	1.6 (0.6–3.7)	1.2 (0.5–2.9)	0.77
spicy foods	1.0	0.8 (0.4–1.8)	0.3 (0.1–1.3)	0.12
hot beverages	1.0	1.3 (0.4–3.7)	1.1 (0.4–3.3)	0.90
12 individual food items				
Rice	1.0	1.3 (0.6–2.9)	2.4 (0.7–7.5)	0.15
Miso soup	1.0	1.6 (0.7–3.5)	3.4 (1.4–8.3)	0.01
Green tea	1.0	1.5 (0.6–3.5)	1.6 (0.7–3.9)	0.30
Coffee	1.0	1.2 (0.5–2.8)	1.6 (0.7–3.9)	0.27
Black tea	1.0	0.9 (0.4–2.1)	1.6 (0.7–4.1)	0.43
Broiled fish	1.0	0.6 (0.3–1.2)	0.5 (0.1–1.7)	0.13
Boiled fish	1.0	1.9 (0.9–3.9)	0.7 (0.1–5.4)	0.29
Broiled meat	1.0	3.7 (0.9–16.1)	1.4 (0.2–8.0)	0.90
Pickled vegetables	1.0	0.7 (0.3–2.0)	0.9 (0.4–2.1)	0.92
Nuts	1.0	0.3 (0.1–0.8)	0.3 (0.1–0.7)	0.01
Smoked food/bacon/ham	1.0	1.6 (0.6–3.9)	0.6 (0.2–1.9)	0.36
Raw vegetables	1.0	0.4 (0.2–1.1)	0.4 (0.2–1.0)	0.11
12 food groups				
Bread	1.0	1.1 (0.5–2.5)	1.0 (0.4–2.4)	0.98
Noodle	1.0	2.0 (0.9–4.6)	1.0 (0.3–3.4)	0.68
Potato	1.0	0.6 (0.3–1.3)	0.6 (0.2–2.2)	0.22
Soybean products (except miso soup)	1.0	0.8 (0.4–1.7)	0.5 (0.2–1.7)	0.28
Fruits	1.0	0.3 (0.1–0.9)	0.2 (0.1–0.6)	0.00
Green-yellow vegetables	1.0	0.5 (0.2–1.0)	0.4 (0.2–1.1)	0.06
White vegetables	1.0	1.1 (0.4–2.5)	1.4 (0.6–3.2)	0.47
Seaweed	1.0	0.1 (0.1–0.4)	0.2 (0.1–0.4)	0.00
Fish/shellfish (in all types)	1.0	0.6 (0.3–1.3)	0.2 (0.0–1.2)	0.03
Meat	1.0	0.8 (0.3–1.9)	0.5 (0.2–1.4)	0.15
Egg	1.0	0.3 (0.1–0.9)	0.5 (0.2–1.1)	0.26
Dairy products	1.0	0.7 (0.3–1.9)	0.7 (0.3–1.5)	0.35

Categories of frequency of consumption are the same as in Table II.

etiologically related to stomach cancer, but it is unlikely to play an important role in the development of stomach cancer by itself.

A decreased risk of stomach cancer was associated with the consumption of fresh vegetables and fruits, this being consistent with previous studies.[5, 7–9, 11, 17–20] Our analyses showed a highly significant *P* value for fruits (Tables II and III). The relative risk for multiple stomach cancer was smaller than that for single stomach cancer. Consumption of raw vegetables and green-yellow vegetables also significantly reduced the risk of single stomach cancer. This protective effect may be due to the existence of such anticarcinogens as vitamins A and C in vegetables and fruits.[3]

We also found a clear inverse relation to seaweed and nuts (Tables II and III). Seaweed may thus be another dietary factor inversely associated with stomach cancer, possibly due to the anti-cancer effect of vitamin C, as in the cases of raw vegetables and fruits.[21] As for nuts, we can not readily explain this observation. Individuals who prefer nuts may share a common characteristic that decreases their risk, for example, they may have good teeth with adequate chewing ability. More precise investigations are needed.

As shown in Table III, the consumption of fish/shellfish reduced the risk of multiple stomach cancer. Fish/shellfish is a food rich in selenium.[22] Recently, evidence has been presented supporting the hypothesis that de-

Table IV. Relative Risks and 95% Confidence Intervals for Stomach Cancer Due to Cigarette Smoking[a)]

History	No. of cases/ controls	Relative risk (95% CI)	Trend *P*-value
On single stomach cancer			
Cigarette smoking			—
Never	24/71	1.0	
Ex	57/155	1.1 (0.6–1.8)	
Current	135/257	1.5 (0.9–2.6)	
Cigarette years			0.40
Nonsmoker	24/71	1.0	
≤800	124/265	1.4 (0.8–2.3)	
>800	68/143	1.3 (0.8–2.4)	
On multiple stomach cancer			
Cigarette smoking			—
Never	4/71	1.0	
Ex	9/155	0.9 (0.3–3.0)	
Current	22/257	1.4 (0.5–4.3)	
Cigarette years			0.61
Nonsmoker	4/71	1.0	
≤800	16/265	1.1 (0.3–3.3)	
>800	13/143	1.3 (0.4–4.2)	

a) Adjustment for age.

Table V. Relative Risks and 95% Confidence Intervals for Stomach Cancer Due to Alcohol Intake[a)]

History	No. of cases/ controls	Relative risk (95% CI)	Trend *P*-value
On single stomach cancer			
Alcohol drinking			—
Never	33/74	1.0	
Past	11/25	1.0 (0.4–2.2)	
Occasional	48/108	1.0 (0.6–1.7)	
Daily	124/276	1.0 (0.6–1.6)	
Total alcohol consumption (ml/lifetime)			0.56
Nondrinker	33/74	1.0	
<500,000	79/187	0.9 (0.6–1.6)	
≥500,000	69/133	1.1 (0.7–1.9)	
On multiple stomach cancer			
Alcohol drinking			—
Never	3/74	1.0	
Past	5/25	4.7 (1.0–21.6)	
Occasional	11/108	2.6 (0.7–9.6)	
Daily	16/276	1.4 (0.4–5.2)	
Total alcohol consumption (ml/lifetime)			0.15
Nondrinker	3/74	1.0	
<500,000	11/187	1.7 (0.4–6.4)	
≥500,000	14/133	2.5 (0.7–9.3)	

a) Adjustment for age and smoking status.

Table VI. Relative Risks, 95% Cofidence Intervals and *P*-Values for Food Items in a Multiple Logistic Regression Model

Food item	Frequency of consumption			Trend *P*-value
	Low	Intermediate	High	
On single stomach cancer				
Preference for salty foods	1.0	1.3 (0.8–2.1)	2.0 (1.2–3.2)	0.00
Rice	1.0	1.3 (0.9–1.9)	1.6 (0.8–3.1)	0.11
Miso soup	1.0	1.3 (0.9–2.0)	1.9 (1.1–3.3)	0.01
Coffee	1.0	0.9 (0.5–1.3)	0.9 (0.6–1.4)	0.58
Boiled fish	1.0	1.5 (1.0–2.2)	1.8 (0.9–3.9)	0.02
Pickled vegetables	1.0	1.7 (1.0–3.0)	1.8 (1.1–3.1)	0.05
Nuts	1.0	0.6 (0.4–1.0)	0.5 (0.3–0.8)	0.01
Raw vegetables	1.0	0.7 (0.4–1.1)	0.6 (0.3–1.0)	0.04
Potato	1.0	1.3 (0.9–1.9)	0.7 (0.3–1.5)	0.99
Soybean products (except miso soup)	1.0	0.7 (0.5–1.1)	0.7 (0.4–1.2)	0.13
Fruits	1.0	0.9 (0.5–1.6)	0.8 (0.5–1.3)	0.34
Green-yellow vegetables	1.0	0.7 (0.4–1.0)	0.8 (0.4–1.4)	0.30
White vegetables	1.0	0.9 (0.6–1.4)	0.7 (0.4–1.1)	0.15
Seaweed	1.0	0.6 (0.4–1.2)	0.5 (0.3–0.9)	0.03
On multiple stomach cancer				
Miso soup	1.0	2.4 (1.0–5.9)	5.5 (2.0–15.2)	0.00
Nuts	1.0	0.4 (0.2–1.0)	0.4 (0.1–1.1)	0.07
Fruits	1.0	0.4 (0.1–1.3)	0.4 (0.1–0.9)	0.05
Seaweed	1.0	0.2 (0.1–0.4)	0.1 (0.1–0.4)	0.00
Fish/shellfish (in all types)	1.0	0.8 (0.3–1.7)	0.1 (0.0–1.2)	0.07

Categories of frequency of consumption are the same as in Table II.

creased selenium status is associated with an increased risk of cancer.[23, 24] A study showed that the impact of selenium deficiency may be significant for gastrointestinal cancers.[25] It would be premature to conclude, however, that consumption of fish/shellfish is protective against stomach cancer, since a dose-response relationship was not observed for single stomach cancer (Table II).

A large-scale prospective study in Japan reported that miso soup (soybean paste soup) was inversely related to stomach cancer risk.[6] On the other hand, a significantly positive correlation was found between age-adjusted mortality rate of stomach cancer and average amount of salt excretion in 24-h urine.[26] Another experiment also showed an enhancing effect of dietary salt on gastric cancer in rats.[27] In our study, consumption of miso soup was consistently positively related to both single and multiple stomach cancer. The relative risk for multiple stomach cancer was larger than that for single stomach cancer; multiple stomach cancer patients consumed more miso soup than single stomach cancer patients. Residents in Saitama often consume miso which contains about 1.9 g of salt per bowl.[21] An excess intake of salt from miso soup may cancel out a possible protective effect of soybean products.

The findings obtained by the multiple logistic regression analysis (Table VI) were somewhat unclear. Miso soup and seaweed were common risk factors for single and multiple stomach cancer, but fruits and raw vegetables were not common. However, the associations with these dietary items were consistent over the two cancer series in both univariate and multivariate analyses, with or without statistical significance.

In spite of the small numbers of multiple stomach cancer patients, a dose-reponse relationship was observed in several dietary factors, and the relative risks for multiple stomach cancer tended to be larger among risk-enhancing factors and smaller among risk-reducing factors than those for single stomach cancer (Table VI). Further, associations with most dietary items were consistent between the two cancer series, that is, no one specific dietary item was related to multiple stomach cancer alone. This lack of specific dietary items might be due to small numbers of multiple cancer, but these findings seem to support the view that patients with multiple stomach cancer were more highly exposed to risk factors and/or less exposed to preventive ones in their lifestyles. The findings obtained from male subjects should also be applicable to females because previous studies have found almost no sex difference.[3, 4]

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