Jpn. J. Cancer Res. (Gann), 79, 1067–1074; October, 1988

A Case-Control Study of Gastric Cancer and Diet in Northern Kyushu, Japan

Suminori KONO,[*1,*5] Masato IKEDA,[*2] Shinkan TOKUDOME[*3] and Masanori KURATSUNE[*4]
[*1]*Department of Public Health, School of Medicine, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-01,* [*2]*University of Occupational and Environmental Health-Japan, Yahatanishi-ku, Kitakyushu 807,* [*3]*Saga Medical School, Saga 840-01 and* [*4]*Nakamura-gakuen College, Fukuoka 814*

A case-control study of gastric cancer was done in a rural area of northern Kyushu, Japan, in relation to dietary habits especially focusing on the relationship with the consumption of broiled fish. The study was based upon 139 cases of newly diagnosed gastric cancer at a single institution, 2,574 hospital controls and 278 controls sampled randomly from the residents of the study area (with sex and year of birth matched). No association was observed between the consumption of broiled fish and gastric cancer risk whether three types of broiled fish (raw fish, dried fish and salted fish) were analyzed separately or as a single category. However, consistently in the comparisons with both sets of controls, the risk of gastric cancer was inversely related with the consumption of fruits and positively associated with cigarette smoking. A decreased risk of gastric cancer was also noted among those with high consumption of green tea (10 or more cups per day).

Key words: Gastric cancer — Diet — Case-control study

Although gastric cancer has declined in most industrialized countries in the past decades, Japan is still among the countries showing the highest mortality rate in the world.[1,2] Environmental, especially dietary, factors have been implicated as being causally associated, but the etiology of this cancer is essentially unknown.[1,2] In connection with the discovery of strong mutagenicity of pyrolysis products of proteins and amino acids,[3–5] it has been suggested that the consumption of broiled fish may be related to gastric cancer in Japan. Our analysis of atomic bomb survivors suggested a positive relationship between deaths from gastric cancer and frequent intake of broiled fish.[6] Since eating broiled fish is a traditional dietary habit in Japan, the issue of gastric cancer and broiled fish is a matter of importance. Taking account of known methodological drawbacks of case-control studies,[7,8] we conducted a case-control study of gastric cancer in a rural area of northern Kyushu, Japan, to investigate further the relationship between the consumption of broiled fish and the risk of gastric cancer.

Previous epidemiological studies of gastric cancer have reported positive or negative associations with various foods.[9–13] Among these, of particular interest are an inverse relationship with the consumption of fresh vegetables and fruits and a positive association with salty food intake.[14] Experimental evidence also suggests an etiological implication of these associations. Fresh vegetables and fruits are rich in vitamin C, and the latter may impede gastric carcinogenesis by inhibiting the formation of nitroso compounds which are highly carcinogenic.[15] It has been demonstrated that salt has an enhancing effect on the occurrence of glandular stomach cancer in rats, possibly by disturbing the gastric mucous barrier.[16] A second aim of this study was to examine whether these previously reported associations could be replicated.

Materials and Methods

A small provincial city, Karatsu City, and nine neighboring towns/villages in Saga Prefecture, Japan, were selected as a study area to utilize the information accrued at the Karatsu Stomach Institute, which operates as a referral center for the diagnosis of gastrointestinal diseases in this area. About two-thirds of the patients of the Institute are referred by general practitioners and one-third through cancer screening programs in the study area.

Cases were those who were newly diagnosed as having gastric cancer at the Institute and who were

[*5] To whom correspondence should be addressed.

then residents of the study area. Two sets of controls were recruited; the so-called hospital controls and general population controls. During the period from 1979 to 1982, subjects aged 20–75 years who visited the Institute for the first time were interviewed before diagnostic procedures for the present study. Results of radiological and endoscopic examinations and histology reports were presented to us 1–2 months later. A total of 139 incident cases of gastric cancer were identified among 4,729 subjects interviewed, and 122 (88%) were histologically confirmed, while the remaining 17 cases were diagnosed by endoscopy (three of them were confirmed to have had gastric cancer at surgery). Subjects aged 25–75 years who were found to be free of gastrointestinal diseases were selected as hospital controls (2,574 subjects). Diagnostic procedures of these controls included barium study of the stomach (2,196), gastroendoscopy (308 including 10 on whom biopsy was done) and large bowel examinations (70).

Two general population controls were selected for each case, matching sex and year of birth by two-stage stratified random sampling. A 10% sample of residents was first drawn by stratifying sex, year of birth and residence (10 municipalities) from the computerized file of residents as of January 1979. When cases were identified, controls were randomly selected from this 10% sample list throughout the study period.

Patients of the Institute were interviewed by a nurse and two clerks of the Institute, and general population controls were interviewed at home by public health nurses of the Karatsu Public Health Center using the same questionnaire. Interviews by public health nurses were supervised by two chief public health nurses. These chief nurses and the three staff of the Institute were trained and instructed regarding the administration of questionnaires. Particular caution was exercised in adhering to guidelines of the questionnaires. There was virtually no refusal in the interviews, except for one patient of the Institute and one person selected as a general population control.

The questionnaire was designed to obtain information regarding occupation (current job and major lifetime job) and dietary habits as well as smoking habit. All questions about diet were precoded, and the subjects were queried regarding the average frequency of consumption of food items (see Table I) in the year preceding the interview or before a change of dietary habit if the change had occurred in the past one year. In the cases of mandarin oranges, bran-paste pickles and pickled green vegetables, the frequency of consumption at high season was asked, because consumption of such foods varies greatly depending upon the season in the study area. For most of the food items, there were 5 categories of frequency of consumption: more than once/day, almost daily, 1–3 times/week, 1–3 times/month and none (or almost none). For rice and green tea, the daily amount of consumption was asked, with four categories as possible responses.

Table I. Agreement of Consumption Frequencies[a] Assessed by the Two Groups of Interviewers (48 Pairs)

Food item	Intraclass correlation coefficient	Signed rank test (P-value)
Rice	0.57	NS[b]
Bread	0.49	NS
Miso (bean paste) soup	0.77	NS
Sashimi (sliced raw fish)	0.56	<0.05
Fish cooked with soy-sauce	0.34	<0.05
Broiled fish		
Raw fish	0.33	NS
Dried fish	0.35	<0.05
Salted fish	0.20	NS
Grilled meat	0.34	NS
Steak/hamburger steak	0.30	NS
Raw vegetables	0.24	<0.01
Green yellow vegetables	-0.07	NS
Bran-paste pickles	0.41	NS
Pickled green vegetables	0.61	<0.10
Pickled radish	0.10	NS
Salty foods	0.23	NS
Milk	0.80	<0.05
Mandarin oranges	0.51	NS
Fruits; others	0.44	NS
Green tea	0.66	NS
Sake	0.80	NS
Shouchu	0.84	NS
Beer	0.70	NS
Whisky/brandy	0.79	NS

a) Based on the three-level categorization as used in case-control comparisons.
b) NS: not significant at the 10% level.

In analysis, the frequency of consumption of each food item was divided into three levels so as to include as equal a number as possible in each level. Frequency of broiled fish combined was calculated simply by summing the scores of weekly frequency for the three types of broiled fish (5, 2, 0.5 and 0 for the categories of daily, 1–3 times/week, 1–3 times/month and none, respectively).

Since the interviews of general population controls were conducted by public health nurses, the uniformity of interviews between the group of public health nurses and the Institute staff was tested at the end of the study period. The last 48

consecutive controls from the general population were reinterviewed by either of the three staff of the Institute 0.5–8 months later. The degree of agreement was assessed by intraclass correlation coefficient and signed-rank test[17] using the same categories of consumption frequency as used in the case-control comparison. As shown in Table I, there were food items on which comparability was not acceptable. The comparison with general population controls was, therefore, restricted to items showing a good agreement (arbitrarily, intraclass correlation coefficient >0.4 and no significant difference at the 10% level in the signed-rank test). Intraclass correlations for smoking and job (lifetime) categories were 0.92 and 0.93, respectively.

Unconditional logistic regression analysis was used for the comparison between cases and hospital controls, always including terms for sex and age (5 classes), and conditional logistic regression was used for the comparison with general population controls.[18] Relative risk for each level was the antilogarithm of the regression coefficient of the corresponding indicator variable, and 95% confidence interval was similarly calculated from the regression coefficient and its standard error. Scores of 0–2 were given to the three levels of consumption frequency in assessing the trend. Statistical significance of relative risk and trend was tested by using the standardized regression coefficient. All the statistical analyses were performed using the Statistical Analysis System.[19, 20]

Results

Table II shows the distribution of cases and the two sets of controls according to age class and job category. Since nearly 10% of the subjects reported having no current job, the major lifetime job was analyzed here. Sex- and age-adjusted relative risk of gastric cancer for the professional and administrative class and that of the clerical and sales class with blue-collar and housewife as the baseline were 0.4 (P=0.04) and 0.8 (P=0.39), respectively, in the comparison with hospital controls. The corresponding figures in the comparison with general population controls were 1.1 (P=0.84) and 0.7 (P=0.34), respectively. Cigarette smoking was associated with the risk of gastric cancer as shown in Table III, although the relation was not statistically significant in the comparison with the general population.

Table IV summarizes the comparison between cases and hospital controls for the frequency of consumption of each food item and of total broiled fish. There was no relationship between the risk of gastric cancer and the consumption of broiled fish whether broiled fish were examined separately or as a single category. Consumption of mandarin oranges and other fruits was inversely related with gastric cancer risk although the trend marginally failed to reach the significance level. Neither pickles nor salty foods were associated with the risk of gastric cancer. Results from the restricted comparison with general population controls were by-and-large consistent with those of the comparison with hospital controls as given in Table V. The relationship with mandarin oranges was less striking, but the decreased risk at high consumption of

Table II. Distribution of Cases and Controls by Age and Occupation

Category	Cases		Hospital controls		General population controls	
	Male	Female	Male	Female	Male	Female
Age class						
25–34	3	1	274	154	5	2
35–44	2	3	285	314	5	6
45–54	14	18	275	393	25	34
55–64	28	25	204	330	56	53
65–75	27	18	133	212	57	35
Occupation						
Professional/ administrative	6	1	158	105	11	1
Clerical/sales	16	3	255	207	30	18
Blue-collar	52	47	758	797	107	85
Housewife	—	14	—	294	—	26

Table III. Relative Risks of Gastric Cancer (and Numbers of Cases/Controls) According to Smoking Habit

Sex	Never smoked	Smoked[a]		χ^2 for trend
		Low	High	
Comparison with hospital controls[b]				
Male	1.0 (12/261)	1.2 (29/718)	1.9 (33/192)	4.07*
Female	1.0 (49/1238)	2.5* (15/153)	1.4 (1/12)	6.41*
Both	1.0 (61/1499)	1.7* (44/871)	2.5* (34/204)	9.44*
Comparison with general population controls[c]				
Male	1.0 (12/32)	1.1 (29/68)	1.8 (33/48)	2.69
Female	1.0 (49/101)	1.1 (15/27)	1.0 (1/2)	0.10
Both	1.0 (61/133)	1.1 (44/95)	1.8 (34/50)	2.52

a) Smoked at least one cigarette/day for 6 months or more. Those who smoked ≧20 cigarettes/day and for ≧30 years were classified into the high level.
b) Based on unconditional logistic regression including terms for age-class (and sex for combined analysis).
c) Based on conditional logistic regression.
* $P<0.05$ (two-sided).

Table IV. Relative Risks of Gastric Cancer (and Numbers of Cases/Controls) According to Frequencies of Consumption of Food Items and Combined Foods: Comparison with Hospital Controls[a]

Food	Frequency of consumption			χ^2 for trend
	Low	Intermediate	High	
Rice[b]	1.0 (46/882)	1.2 (86/1461)	0.7 (7/231)	0.03
Bread[c]	1.0 (106/1841)	1.4 (23/388)	0.6 (10/345)	0.92
Miso (bean paste) soup[c]	1.0 (13/171)	0.6 (28/597)	0.6 (98/1806)	1.19
Fish				
Sashimi (sliced raw fish)[e]	1.0 (46/809)	0.8 (62/1264)	0.9 (31/501)	0.24
Fish cooked with soy-sauce[e]	1.0 (18/387)	0.7 (64/1533)	1.1 (57/654)	1.85
Broiled fish, combined	1.0 (47/837)	0.9 (41/795)	1.0 (51/942)	0.01
Raw fish[d]	1.0 (42/551)	0.8 (37/812)	0.7 (60/1211)	2.31
Dried fish[d]	1.0 (47/689)	0.9 (42/946)	0.9 (50/939)	0.05
Salted fish[d]	1.0 (66/1006)	0.9 (34/852)	1.0 (39/716)	0.00
Grilled meat[d]	1.0 (72/910)	0.7 (39/1148)	0.9 (28/516)	0.59
Steak/hamburger steak[d]	1.0 (94/1218)	0.6* (27/976)	0.9 (18/380)	2.22
Raw vegetables[c]	1.0 (12/191)	1.1 (50/800)	0.8 (77/1583)	1.74
Green yellow vegetables[c]	1.0 (5/145)	1.6 (49/790)	1.3 (85/1639)	0.46
Bran-paste pickles[c]	1.0 (66/1254)	0.9 (37/749)	1.0 (36/571)	0.01
Pickled green vegetables[c]	1.0 (26/610)	1.1 (51/976)	1.1 (62/988)	0.04
Pickled radish[c]	1.0 (74/1321)	0.9 (45/956)	1.1 (20/297)	0.01
Salty foods[c]	1.0 (79/1380)	0.8 (33/778)	1.4 (27/416)	0.82
Milk[c]	1.0 (57/1060)	1.3 (36/582)	1.0 (46/932)	0.03
Mandarin oranges[c]	1.0 (34/476)	0.7 (53/977)	0.6* (52/1121)	3.78
Fruits; others[c]	1.0 (34/536)	1.0 (79/1245)	0.6 (26/793)	3.38
Green tea[f]	1.0 (74/1382)	1.1 (57/937)	0.6 (8/255)	0.89

a) Based on unconditional logistic regression including terms for sex and age class.
b) Low, none or 1–3 bowls/day; intermediate, 4–6 bowls; high, ≧7 bowls.
c) Low, none or 1–3 times/month; intermediate, 1–3 times/week; high, once/day or more.
d) Low, none; intermediate, 1–3 times/month; high, 1–3 times/week or more.
e) Low, 1–3 times/week or less; intermediate, once/day; high, ≧2 times/day.
f) Low, none or 1–4 cups/day; intermediate, 5–9 cups; high, ≧10 cups.
* $P<0.05$ (two-sided).

Table V. Relative Risks of Gastric Cancer (and Numbers of Cases/Controls) According to Frequencies of Consumption of Selected Foods: Comparison with General Population Controls[a]

Food	Frequency of consumption[b]			χ^2 for trend
	Low	Intermediate	High	
Rice	1.0 (46/103)	1.3 (86/157)	0.9 (7/18)	0.20
Bread	1.0 (106/210)	1.4 (23/32)	0.5 (10/36)	0.88
Miso soup	1.0 (13/14)	0.5 (28/62)	0.5 (98/202)	1.13
Bran-paste pickles	1.0 (66/157)	1.3 (37/68)	1.6 (36/53)	3.45
Mandarin oranges	1.0 (34/58)	0.9 (53/101)	0.7 (52/119)	1.24
Fruits; others	1.0 (34/60)	1.1 (79/127)	0.5* (26/91)	4.84*
Green tea	1.0 (74/143)	1.2 (57/92)	0.4* (8/43)	2.38

a) Based on conditional logistic regression.
b) See the footnote in Table IV for frequency category.
* $P<0.05$ (two-sided).

Table VI. Relative Risks (RR), 95% Confidence Intervals (95% CI) and *P*-values for Smoking and Selected Food Items in Multiple Logistic Regressions

Factor (Category)	Comparison with hospital control[a]		Comparison with general population control[b]	
	RR (95% CI)	*P*-value	RR (95% CI)	*P*-value
Smoking (Ever vs. never)	1.8 (1.1–2.9)	0.01	1.3 (0.8–2.2)	0.27
Mandarin oranges (daily vs. less)	0.8 (0.5–1.2)	0.22	1.0 (0.6–1.7)	0.95
Fruits; others (daily vs. less)	0.7 (0.4–1.0)	0.08	0.5 (0.3–0.8)	0.008
Green tea (≧10 cups/day vs. less)	0.5 (0.3–1.1)	0.10	0.3 (0.1–0.7)	0.007

a) Based on unconditional logistic regression including terms for sex and age class as well as 4 variables listed.
b) Based on conditional logistic regression including 4 variables listed.

green tea (≧10 cups/day) was more prominent. None of the four alcoholic beverages showed any association with gastric cancer risk in terms of consumption frequency in the comparison with either hospital controls or general population controls. The results presented in Tables IV and V were little influenced by adjustment for occupational class.

The net association of gastric cancer risk with smoking and consumptions of mandarin oranges, other fruits, and green tea was examined in multiple logistic regression with these variables dichotomously categorized. As shown in Table VI, the consumption of mandarin oranges was not independently related to gastric cancer risk, and the association with cigarette smoking was not substantial in the comparison with general population controls.

Discussion

The present study was able to overcome some of the known disadvantages of case-control studies. Controls from two sources were drawn from the same catchment area, and interviews were done before diagnostic procedures for both cases and hospital controls to minimize recall bias due to cognition of disease status. There are, however, problems to be acknowledged before discussing the present findings.

The present study, like other case-control studies, related recent dietary habits to the risk of gastric cancer. It has been claimed that diet as assessed by the current habits may have no bearing on the development of gastric cancer with a latent period of decades.[7,8] Yet

measuring diet in the distant past is recognized to be extremely difficult. Recent studies indicated that the diet as recalled from the distant past was biased by the current dietary habits.[21, 22] Although we had no definite knowledge of the extent to which the current diet reflected the past one, we assumed that residents in the study area, particularly the elderly, had rather stable dietary habits. Controls from the general population were interviewed by public health nurses while cases and hospital controls were interviewed by the Institute staff. Despite precautionary measures, it was found that administration of the questionnaire differed between the two groups. Comparison with the general population controls was, therefore, inevitably restricted to only a limited number of food items which were judged to be comparable. Nevertheless, consistent findings in comparisons with controls from two different sources would provide stronger evidence. The agreement test was designed to check the comparability in interviewing between cases and general population controls, but poor agreement may also indicate inherent imprecisions of the dietary method itself. This is particularly probable in assessing collectively the consumption of foods such as vegetables and meat.

The present study failed to show an association between gastric cancer and the consumption of broiled fish. An earlier case-control study had examined the relationship with charcoal-broiled fish in Japan but failed to demonstrate an association.[23] A recent case-control study, again in Japan, also showed no relation between gastric cancer and broiled fish intake.[24] Yet the cohort study of atomic bomb survivors observed a weak association between broiled fish intake and gastric cancer mortality.[6] Sex- and age-adjusted relative risk was estimated as 1.7 ($P < 0.05$) for those eating broiled fish twice or more per week as compared with those with less frequent consumption.[6] In these studies, as in the present study, intake of broiled fish was assessed in terms of consumption frequency although the categorization was slightly different. A weak association might not be detected if the measurement suffers from imprecision. Because dietary inquiry is necessarily retrospective in a case-control study, the findings of a cohort study may be regarded as more reliable than those of a case-control study. However, it should be noted that the cohort study of atomic bomb survivors had some weak points which made the observed association less convincing. In that study, intake of dried fish was not related to gastric cancer risk, though dried fish is usually broiled before serving, and the dose-response relationship was not examined in detail.[6] Reanalysis of this cohort, based on a larger number of deaths, particularly to search for a dose-response relation, is needed to consolidate the association with broiled fish intake at least in this population. It is relevant to mention that animal experiments have not thus far demonstrated gastric carcinogenicity of mutagenic compounds of the pyrolysates.

Regarding the two other issues of *a priori* interest, namely, whether the risk of gastric cancer is inversely related to the consumption of fresh vegetables/fruits and whether the risk is positively associated with salt intake, the present study was able to reproduce the former association but not the latter. The inverse relationship with fresh vegetables/fruits is the most consistent finding of previous studies on gastric cancer and diet, while epidemiologic evidence for the salt hypothesis is still limited.[1, 2] Evidence for a protective effect of fresh vegetables/fruits has been further accumulated by recent case-control studies in different countries.[25–27] If vitamin C is responsible for the protective effect of fresh vegetables and fruits, the decreased risk of gastric cancer among those consuming a large amount of green tea can also be explained, since green tea is rich in vitamin C, and 10 cups of green tea is roughly estimated to contain 40–50 mg of vitamin C. This amount corresponds to as much as one-third of the daily intake of the average Japanese. Previous studies on green tea did not assess in detail the relation between the amount of green tea and gastric cancer risk. One case-control study reported that relative risk was 0.67 of those drinking 4 cups or more per day as compared with those with less frequent consumption, but the difference was without statistical significance.[24]

A positive association was observed regarding cigarette smoking in the present study. As reviewed in the report of the U.S. Surgeon

General,[28] previous case-control and prospective studies have observed an association between cigarette smoking and gastric cancer. Nevertheless, the case for causality of the association has been weakened because a dose-response relationship has not been consistently observed and the risk increment owing to smoking is generally small.[2,28] The present findings may add further evidence for a causal association between cigarette smoking and gastric cancer.

Acknowledgments

The authors acknowledge the cooperation of the Karatsu Stomach Institute and the Karatsu Public Health Center. We are especially grateful to Ms. T. Uchiyama, Ms. K. Tanaka and Ms. K. Ohba of the Institute and Ms. Y. Kinoshita and Ms. T. Katabuchi of the Public Health Center for interviewing the study subjects. This study was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan.

(Received July 7, 1988/Accepted Aug. 26, 1988)

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