Jpn. J. Cancer Res. 83, 568–575, June 1992

A Prospective Study of Stomach Cancer among a Rural Japanese Population: A 6-Year Survey

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Stomach cancer mortality was prospectively studied among 9753 Japanese men and women who first responded to a mailed questionnaire in 1985 and were then followed through May 31, 1991. During this follow-up period, 57 stomach cancer deaths were identified. Current smokers had an increased risk of deaths from stomach cancer compared with never smokers (relative risk (RR) = 2.29, 95% confidence interval (CI): 1.15–4.56), but there was no dose-response to amount of cigarettes smoked. Daily alcohol drinkers who consumed 50 ml or more of alcohol per day also had a greater risk than nondrinkers (RR = 3.05, 95% CI: 1.35–6.91). There was no association between stomach cancer mortality and individual food consumption except a positive association with fruit intake. However, frequent use (≥3–4/week) of broiling of meats and traditional style Japanese salad preparation in their cooking procedures were positively associated with stomach cacer mortality. The RR values compared with infrequent use (≤1–2/month) were 2.27 (95% CI: 1-06–4.85) and 3.10 (95% CI: 1.40–6.85), respectively. A positive family history of cancer, especially stomach cancer, significantly increased the risk of stomach cancer deaths (RR = 2.01, 95% CI: 1.12–3.63). The effects of these variables remained after adjustment for other variables.

Key words: Stomach cancer — Cooking method — Smoking — Alcohol — Family history

Stomach cancer is one of the most common cancers worldwide,[1)] and in Japan it is still the leading cancer despite a declining trend.[2)] Because the incidence of stomach cancer varies markedly from place to place and from one generation to the next, it has been hypothesized that its incidence is determined largely by environmental factors.[3)]

Although recent epidemiologic studies have suggested that *Helicobacter pylori* is one of major causes of stomach cancer, its infection is considered to be neither sufficient nor necessary for gastric carcinogenesis.[4)] Diet, which varies markedly with geographical areas, ethnic groups and generations, is also likely to play an important role in the etiology of stomach cancer. Studies have suggested that foods rich in nitrate or nitrite and their derivatives, a high salt diet, a high carbohydrate diet and a diet low in fresh fruits and vegetables increase the risk of stomach cancer, although the findings are not always consistent.[3)] Several researchers have also found that alcohol drinkers and cigarette smokers have a greater risk for stomach cancer than nondrinkers and nonsmokers,[5–14)] but others have not supported this observation, or a dose-response relationship has not been clear.

Host factors have also been suspected to play some role in gastric carcinogenesis. Several studies, though no prospective ones, have reported familial aggregation of stomach cancer,[15, 16)] although they did not separate out genetic from environmental factors.

The inconsistency in the findings of past studies suggests that further studies are necessary to establish etiological factors for stomach cancer. Therefore, to obtain additional evidence on the relationships of diet, alcohol, smoking and family history to stomach cancer risk, we conducted a prospective study among a rural Japanese population which kept a traditional style of Japanese dietary habits, in contrast to urban populations.

MATERIALS AND METHODS

A baseline survey for a population-based cohort study on relationships between various environmental factors and cancer was carried out in 1985 using a mailed self-administered questionnaire. The subjects for this survey included all male inhabitants aged 40 or more and all female inhabitants aged 30 or more of Higashi-kamo county, located in a mountainous area of Aichi prefecture, Japan. A total of 9753 subjects responded (85.9%) to the survey. Through a questionnaire survey, information was collected on family history of cancer within parents and siblings, dietary habits, including consumption frequency of 25 food items, and alcohol drinking habits. The frequency of use of each of the major cooking methods for dinner (all foods) or for meats and fish was also recorded by the person in charge of cooking in a family. Frequency of food consumption and use of each cooking method was originally classified into five categories (never or rarely, 1–2 times/month, 1–2 times/week, 3–4 times/week and daily), then the categories were combined into three groups for analyses. Daily intake of total alcohol was estimated for daily drinkers

based on the amount and average percent of alcohol content for each beverage. These questionnaire data of individuals were also linked with the computerized data from another questionnaire survey conducted in 1983–84 to collect basic information on personal lifestyle (including smoking habits), by using individual identification numbers.

Changes in the resident registration of the study area were continuously checked to identify subjects who moved away. Information on deaths among the study subjects was collected by examination of death certificates. The length of observation period was computed for each subject as the time from the baseline survey to death or moving away, or May 31, 1991. During this follow-up period, 3% (292 subjects) of the original cohort moved out of the study area. Cox's proportional hazards regression model[17] was used to estimate the relative risk (RR) and the 95% confidence interval (CI) for each category of various exposure variables, adjusted for sex (a dummy variable), age at the baseline survey (a continuous variable) and other appropriate variables. A test for trend in the log of the relative hazard was also performed by using Cox models.

RESULTS

During the follow-up period representing 55,284 person-years at risk, a total of 57 stomach cancer deaths (35 males and 22 females) were identified among 9753 study subjects. The mortality markedly increased with age from the 50s in males and from the 60s in females (Table I).

Table II shows relative risk for smoking and drinking habits. Compared with never smokers, past and current smokers had a greater risk of death from stomach cancer. The relative risk for current smokers was statistically significant (2.29, 95% CI: 1.15–4.56). When current smokers were further classified by the number of cigarettes per day, no dose-response relationship was observed (RR was 2.58 for 1–19 cigarettes/day and 1.88 for 20 or more cigarettes/day). Compared with nondrinkers, subjects who consumed 50 ml or more alcohol per day had a statistically significantly increased risk of death from stomach cancer (RR=3.05, 95% CI: 1.35–6.91). When analyzed by sex, the results for males were statistically significant while females showed similar but insignificant trends.

Table III lists relative risks for major food items. No relation was observed except a positive association with fruit intake. Other food items high in salt or nitrite also showed no relation to stomach cancer risk.

Table IV presents relative risks according to cooking methods. The risk of stomach cancer increased with increasing use of traditional style of Japanese salad (P-value for trend=0.002). A similar but insignificant trend was also observed for broiling foods, while broiling of meats was statistically significantly positively associated with stomach cancer risk (P=0.025).

Table I. Age- and Sex-specific Mortality Rates for Gastric Cancer per 100,000 Person-Years

Age	Male	Female	Total
	Rate (No.)	Rate (No.)	Rate (No.)
30–39	—	18.5 (1)	18.5 (1)
40–49	19.8 (1)	35.2 (2)	28.0 (3)
50–59	98.0 (8)	34.4 (3)	65.1 (11)
60–69	199.5 (11)	45.7 (3)	115.9 (14)
70–79	318.7 (10)	233.9 (10)	269.8 (20)
80+	466.8 (5)	176.6 (3)	288.9 (8)
Total	152.7 (35)	68.0 (22)	103.1 (57)

As shown in Table V, subjects who had a family history of any kind of cancer had a statistically significantly increased risk of death from stomach cancer (RR=2.31, 95% CI: 1.37–3.90). When analyzed by type of cancer in families, a family history of stomach cancer was statistically significantly associated with the risk of stomach cancer death (RR=2.01, 95% CI: 1.12–3.63).

When 12 cases who died within one year from the baseline survey were excluded, the results for most of the variables (smoking, drinking, family history of cancer and traditional style Japanese salad) were statistically significant, although some of the associations became statistically insignificant because of the decrease in power. The biggest difference was observed for broiling meats; the RR for 1–2 times/week was 2.08 and that for 3–4 times or more/week was 1.76.

With simultaneous adjustment for the above significant variables, i.e., smoking, drinking, cooking methods and family history of cancer, in multivariate analyses, each of these variables had a significant effect on stomach cancer mortality (Table VI).

DISCUSSION

Although a number of case-control studies have been conducted on the relation between diet and stomach cancer, there have been limited number of prospective studies.[12–14, 18] Prospective studies have an advantage in reducing several kinds of biases associated with data collection and inherit no methodological problems in the selection of a suitable control group. A limitation of the present study was that detailed dietary information, especially quantitative estimates of nutrient and food consumption, were not available. Furthermore, caution

should be exercised in interpreting the results, because a subclinical disease may already have influenced baseline dietary habits among cases who died after a relatively short follow-up period. We should also consider the possibility that the results of the present study based on mortality data reflected prognostic factors of stomach cancer. The statistical significance of some results could be due to chance because of multiple comparisons.

Several earlier cohort studies have observed that cigarette smokers had a greater risk of deaths from stomach cancer than never smokers.[10–14] However, most of the studies did not show a dose-response relationship.[10–13] The results of the present study were consistent with these earlier findings. This suggests that the elevated risk may be independent of the effects of cigarette smoking themselves and that cigarette smokers share a common characteristic that increases their stomach cancer risk. We found in our previous study that current smokers were very different from never smokers in many aspects of their lifestyle.[19] Another possible interpretation is that the larger the amount of cigarettes smoked, the higher the mortality from diseases which are more smoking-specific, such as lung cancer. This may be competitive with stomach cancer deaths.

Although heavy alcohol drinkers ($\geq$50 ml/day) had an elevated risk of stomach cancer in the present study, past studies have yielded equivocal findings on the effect of alcohol consumption. None of the cohort studies of excessive drinkers (alcoholics and brewery workers) found an excess in risk of deaths from stomach cancer.[20–22] Other cohort studies based on general populations did not show a positive association between alcohol intake and stomach cancer risk.[12–14] On the contrary, several case-control studies have found that alcohol drinkers

Table II. Age- and Sex-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer by Smoking and Drinking Habits

Sex	Variables	No. of cases /person-years	Rate[a]	RR	95% CI
Total	Smoking status				
	Never smoker	26/37810.3	68.8	1.00	
	Ex-smoker	6/2553.2	235.0	2.61	0.97–7.00
	Current smoker	25/14194.1	176.1	2.29	1.15–4.56
	Alcohol intake				
	None	26/32417.5	80.2	1.00	
	Occasional	12/10872.6	110.4	1.75	0.84–3.61
	Daily $<$50 ml[b]	7/6593.9	106.2	1.20	0.48–3.00
	$\geq$50 ml	12/5153.7	232.8	3.05	1.35–6.91
Male[c]	Smoking status				
	Never smoker	7/7482.6	93.6	1.00	
	Ex-smoker	5/2360.3	211.8	2.56	0.81–8.12
	Current smoker	23/12795.8	179.7	2.58	1.09–6.10
	Alcohol intake				
	None	8/7007.6	114.2	1.00	
	Occasional	9/5124.2	175.6	2.31	0.88–6.07
	Daily $<$50 ml[b]	6/5616.0	106.8	1.31	0.45–3.81
	$\geq$50 ml	12/5042.1	238.0	3.63	1.44–9.11
Female[c]	Smoking status				
	Never smoker	19/30327.7	62.6	1.00	
	Ex-smoker	1/192.9	518.4	4.87	0.64–36.8
	Current smoker	2/1398.3	143.0	1.69	0.39–7.31
	Alcohol intake				
	None	18/25409.9	70.8	1.00	
	Occasional	3/5748.4	52.2	1.12	0.32–3.90
	Daily	1/1189.0	84.1	1.29	0.17–9.69

a) Per 100,000 person-years.
b) Ethanol content.
c) Only age-adjusted.

Table III. Age- and Sex-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer by Individual Dietary Habits

Dietary habits	No. of cases /person-years	Rate[a]	RR	95% CI
Main cereals at breakfast				
Rice	50/46160.5	108.3	1.00	
Mixed/others	5/5740.2	87.1	1.04	0.41–2.61
Bread	2/3312.6	60.4	0.68	0.17–2.79
Miso soup				
<1 cup/day	10/10627.1	94.1	1.00	
1 cup/day	26/29488.2	88.2	0.88	0.42–1.82
≥ 2 cups/day	18/14969.8	120.2	1.04	0.48–2.25
			$P=0.845$[b]	
Pickles				
$\leq$1–2/week	11/8216.1	133.9	1.00	
3–4/week	5/7920.0	63.1	0.51	0.18–1.48
Daily	33/35608.7	92.7	0.75	0.38–1.49
			$P=0.593$	
Meats				
$\leq$1–2/week	23/23633.8	97.3	1.00	
3–4/week	17/17172.1	99.0	1.25	0.66–2.34
Daily	3/3914.0	76.6	1.08	0.32–3.61
			$P=0.617$	
Fish				
$\leq$1–2/week	18/23948.1	75.2	1.00	
3–4/week	18/14742.5	122.1	1.71	0.89–3.28
Daily	3/3453.0	86.9	1.21	0.36–4.11
			$P=0.263$	
Green-yellow vegetables				
$\leq$1–2/week	11/13519.9	81.4	1.00	
3–4/week	19/18790.2	101.1	1.32	0.63–2.77
Daily	27/22940.3	117.7	1.54	0.77–3.11
			$P=0.225$	
Other vegetables				
$\leq$1–2/week	11/11628.6	94.6	1.00	
3–4/week	10/12671.6	78.9	0.88	0.37–2.07
Daily	36/30841.5	116.7	1.15	0.59–2.27
			$P=0.567$	
Fruits				
$\leq$1–2/week	16/17622.4	90.8	1.00	
3–4/week	15/19357.1	77.5	0.97	0.48–1.96
Daily	26/18271.6	142.3	1.92	1.03–3.59
			$P=0.035$	

a) Per 100,000 person-years.
b) *P*-Value for trend.

had an increased risk of stomach cancer.[5–9] The studies that found an association implicated a variety of sources of alcohol, beer,[6] sake (Japanese rice wine),[5] wine[7] and hard liquors,[8] but a dose-response was rarely found or reported. In our cohort, most of the alcohol intake came from sake. Jedrychowski *et al.*[23] found that drinking a certain type of strong alcoholic beverages before breakfast significantly increased the risk of stomach cancer and speculated that the consumption of strong alcoholic beverages on an empty stomach might lead to damage to the gastric mucosa and consequently enhance penetration of gastric carcinogens, alter their metabolism or

Table IV. Age- and Sex-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer by Cooking Method for Dinner

Cooking methods	No. of cases /person-years	Rate[a]	RR	95% CI
Boiling				
≤1–2/week	8/6961.7	114.9	1.00	
3–4/week	16/16820.8	95.1	0.77	0.33–1.81
Daily	30/29612.6	101.3	0.77	0.35–1.68
			P=0.597[b]	
Broiling				
≤1–2/week	23/27819.0	82.7	1.00	
3–4/week	25/21022.4	118.9	1.47	0.83–2.58
Daily	4/3027.0	132.1	1.70	0.59–4.92
			P=0.147	
Broiled meats[c]				
≤1–2/month	14/18995.9	73.7	1.00	
1–2/week	17/12890.9	131.9	2.00	0.98–4.06
≥3–4/week	13/9280.5	140.1	2.27	1.06–4.85
			P=0.025	
Broiled fish[c]				
≤1–2/month	8/8253.8	96.9	1.00	
1–2/week	24/25787.9	93.1	0.97	0.31–3.01
≥3–4/week	19/17855.0	106.4	1.77	0.59–5.33
			P=0.159	
Deep-frying				
≤1–2/month	7/10768.0	65.0	1.00	
1–2/week	34/29620.4	114.8	1.83	0.81–4.13
≥3–4/week	12/11641.7	103.1	1.71	0.67–4.34
			P=0.299	
Stir-frying				
≤1–2/month	5/6524.8	76.6	1.00	
1–2/week	22/23371.6	94.1	1.30	0.49–3.42
≥3–4/week	24/23139.6	112.6	1.63	0.62–4.28
			P=0.260	
Traditional style Japanese salad				
≤1–2/month	8/13668.6	58.5	1.00	
1–2/week	17/22563.1	75.3	1.31	0.57–3.04
≥3–4/week	26/14174.5	183.4	3.10	1.40–6.85
			P=0.002	

a) Per 100,000 person-years.
b) *P*-Value for trend.
c) Not limited to dinner.

provide a cell-proliferation stimulus leading to promotion of initiated cells. Drinking on empty stomach was also found to be a risk factor for stomach cancer in China.[9] A similar situation may occur in the stomach of heavy drinkers who tend to eat less food. Additionally, carcinogenic substances, such as nitrosamines, are present in some types of alcoholic beverages,[24] and acetaldehyde, a metabolite of ethanol, has carcinogenic potential.[25] Thus, alcohol could be causally associated with stomach cancer risk.

There is a hypothesis that nitroso compounds ingested or formed in the stomach may contribute to gastric carcinogenesis.[26] Correspondingly, possible food sources of these compounds, such as salted-dried fish,[16] cured meats[8] and pickled vegetables,[6] have been positively associated with the risk of stomach cancer in several case-control studies. A high salt diet has also been associated with an increased risk of stomach cancer in past case-control studies.[6,9] Excessive salt intake can injure gastric mucosa and induce gastritis.[27] Similarly, a

Table V. Age- and Sex-adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer According to Family History of Cancer

Type of family history of cancer	No. of cases /person-years	Rate[a]	RR	95% CI
All sites				
No	31/40812.8	76.0	1.00	
Yes	26/14470.9	179.7	2.31	1.37–3.90
Stomach cancer				
No	42/47385.8	88.6	1.00	
Yes	15/7897.8	189.9	2.01	1.12–3.63
Colorectal cancer				
No	51/51477.0	99.1	1.00	
Yes	6/3806.7	157.6	1.53	0.65–3.56
Uterine cancer				
No	48/50676.4	94.4	1.00	
Yes	9/4607.3	195.3	1.97	0.97–4.02

a) Per 100,000 person-years.

Table VI. Relative Risks (RR) and 95% Confidence Intervals (CI) for Gastric Cancer in Multivariate Analyses Including Smoking, Alcohol Intake, Cooking Methods and Family History of Stomach Cancer in Addition to Age and Sex

Variables	RR	95% CI
Smoking status		
Never smoker	1.00	
Ex-smoker	2.62	0.97–7.05
Current smoker	2.18	1.07–4.43
Alcohol intake		
None	1.00	
Occasional	1.77	0.85–3.68
Daily <50 ml[a]	1.16	0.46–2.89
≥ 50 ml	2.75	1.20–6.29
Broiled meats		
$\leq$1–2/mo	1.00	
1–2/wk	1.97	0.97–4.01
$\geq$3–4/wk	2.08	0.97–4.46
	$P=0.044$[b]	
Traditional style Japanese salad		
$\leq$1–2/mo	1.00	
1–2/wk	1.26	0.54–2.92
$\geq$3–4/wk	2.97	1.34–6.59
	$P=0.002$	
Family history of stomach cancer		
No	1.00	
Yes	1.87	1.04–3.38

a) Ethanol content.
b) *P*-Value for trend.

high carbohydrate diet (consumption of various types of starchy foods) has been suspected to contribute to the occurrence of stomach cancer.[5,9] It may act as a physical irritant of the gastric mucosa and a high carbohydrate/low protein diet could also lead to reduction of gastric mucus, thus facilitating carcinogen absorption. However, the present prospective study found no association between stomach cancer risk and individual food items, except fruits. In a rural population, environmental factors to which the population is exposed may rather be homogenous. Likewise, other prospective studies have generally yielded disappointing results.[12–14] One reason for this may be the homogeneity of diet or food availability within a population or within an area. Another possible reason is that such prospective studies were not necessarily designed for evaluation of stomach cancer, so that questionnaires did not cover sufficient foods specifically related to gastric carcinogenesis. Although vitamin C has been demonstrated to inhibit the formation of nitroso compounds in the stomach,[28] our analysis did not support the protective effect of fruit intake, but rather revealed an adverse effect. We do not have any specific explanation of this peculiar association and no detailed information on types of fruits consumed is available.

It has been suggested that cooking practices may alter cancer risk even if the same foods are ingested. Certain carcinogenic substances, such as benzo[*a*]pyrene,[29] and other mutagenic heterocyclic amines called aminoimidazoazaarenes (AIAs),[30] which are now also proven to be mammalian carcinogens, are produced through cooking processes. Feeding experiments of these substances in animals have demonstrated DNA adducts in several pos-

sible target organs, including stomach.[31] Relatively high concentrations of these substances have been detected in meats and fish cooked at a high temperature, i.e., broiled or fried meats and fish.[29, 30] Given uniform cooking methods, red meats, i.e., pork and beef, contain the highest concentrations of AIAs, followed by chicken and then fish.[32] Our finding on cooking methods, that broiling, especially broiling of meats, may increase the risk of stomach cancer, is consistent with this view. Although meat consumption itself was not related to stomach cancer risk, broiling was only the third commonest cooking method of meats in this population, following boiling and stir-frying, suggesting that these findings are not necessarily inconsistent. Past epidemiologic studies also found that frequent consumption of broiled, grilled or barbecued meats increased the risk of several sites of cancer.[33-38] A cohort study in Japan showed that frequent consumption of broiled fish was associated with an increased risk of stomach cancer.[18] Because the baseline survey for this cohort study was conducted in 1968–70 when meat consumption of Japanese was still low, the association with broiled meats may not have been detected. Another important finding on cooking methods in the present study is a positive association between consumption of traditional style Japanese salad and stomach cancer risk. In the preparation procedure, vegetables, fish & shellfish and seaweed are usually boiled, sometimes raw or salted, and then mixed with traditional style Japanese dressing. The procedure itself is not likely to produce much mutagens, but the persistence in traditional style cooking methods in high risk areas may result in a greater risk of developing stomach cancer. Frequent consumption of traditional soups was also associated with an increased risk of stomach cancer in Italy.[16] Since the person in charge of cooking in a family responded to the questionnaire in the present study, information on cooking methods may be more accurate than individual food frequency data. However, we should consider the possibility that all of family members do not necessarily eat all kinds of food cooked.

Familial aggregation of stomach cancer has been observed by several researchers and it has been revealed that family members of a stomach cancer case have around two times the risk of developing the same cancer compared to the general or referent population.[15, 16] To our knowledge, there have been no prospective studies on this association. Our prospective study confirmed an increased risk of stomach cancer associated with a family history, which was independent of other risk factors detected in this analysis. Therefore, some genetic factors may be involved in gastric carcinogenesis, especially when environmental factors to which a population is exposed are homogeneous. Yet we can not exclude confounding from other unknown environmental factors shared by family members. We previously observed a significant site-concordance in cancer history between husbands and wives who have different genetic backgrounds, but share similar home environments for many years.[39]

Although the present study revealed that several environmental and familial factors were associated with stomach cancer risk, no clear association with individual food consumption was observed. Besides, this is still an interim report, so that the evidence from the present study is far from definitive. Further analyses will be required after accumulating a larger number of incident cases.

(Received January 17, 1992/Accepted March 7, 1992)

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