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Family History-related Risk of Gastric Cancer in Japan: A Hospital-based Case-Control Study

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In Japan, there have been a few reports on the familiar factors of gastric cancer (GC) and on the GC risk related to family history (FH) at other cancer sites. We analyzed the association between GC occurrence and a positive FH of cancer of the stomach and of other sites in a hospital-based case-control study. The subjects included cases histologically confirmed as incident cancer of the stomach (n=136; 86 male and 50 female patients) and sex and age (± 1 year)-matched controls. GC risk was high when a subject had a parental history of GC [Mantel-Haenszel odds ratio adjusted for sex and age (OR)=2.3; 95% confidence interval (95%CI):1.1–5.0]. GC risk was almost unity for a cancer FH of any other cancer site, even among closer relatives, suggesting little or no contribution to GC occurrence. The familial occurrence of GC found in this study suggests the existence of a genetic susceptibility to cancer of the stomach. Further, females tended to show higher GC risks than males, when reporting an affected mother (OR=6.0; 95%CI:1.1–31.4 and OR=1.4; 95%CI:0.4–4.8, respectively), whereas males showed a slightly higher risk than females when reporting an affected father (OR=2.4; 95%CI:0.8–7.5 and OR=2.3; 95%CI:0.4–15.6, respectively). This suggests a possible gender difference in how environmental factors influence GC occurrence. The development of gastric tumors seems to be due to a complex and unknown interaction between environmental and genetic factors.

Key words: Gastric cancer — Odds ratio — Familiar aggregation — Case-control study — Gender difference

Previous studies have shown an increase in gastric cancer (GC) associated with family history (FH) in Italy[1–3] and several other countries.[4,5] Although familial factors have been considered important in GC susceptibility, there have been few reports on familial factors of GC in Japan.[6–8] There have also been few reports concerning the risk of FH of cancers at sites other than the stomach.[7] Because various cancers share some common risk factors, GC risk for positive FH of other cancers may improve our understanding of the carcinogenesis of GC.

With these background considerations in mind, we analyzed the association between GC occurrence and a positive FH of cancer of the stomach and of other sites in a hospital-based case-control study of GC in Japan.

MATERIALS AND METHODS

Subjects The subjects in this analysis were younger than 75 years old and had histologically confirmed incident cancer of the stomach ($n=136$; 86 male and 50 female patients). They were admitted to Ishikawa Prefectural Central Hospital. Their median age was 57 years.

Controls The control group comprised 136 patients younger than 75 years with histologically confirmed non-neoplastic disorders, admitted to Ishikawa Prefectural Central Hospital. They were matched in sex and age (± 1 year) to the subjects with GC. The residences of almost all subjects and controls lay within the city where the hospital was located. The median age was 57 years. In the controls, gastric ulcer was most common (21%), followed by cholecystlithiasis (19%), enterocolitis (14%), gastritis (13%) and other digestive diseases, such as pancreatitis, hepatitis and duodenal ulcer.

Data collection Patients with GC were usually interviewed at the time of endoscopy or during hospitalization for surgery or other medical investigations. The main causes of morbidity and mortality of 1st to 3rd degree relatives (parents, offspring, siblings, grandparents, aunts and uncles) were employed for the analysis. The diagnosis of cancer was based on familial reports or medical reports on previous hospitalization.

Analysis Adjusted odds ratio for the association between GC risk and FH and its 95% confidence intervals were calculated by Mantel-Haenszel summary estimates, organizing the data stratified by sex and age groups (<60, $60\leq$) into 4 strata.

In order to clarify the difference in GC risk between close and distant relatives, we classified by type as follows: 1st degree relatives, 2nd or 3rd degree relatives, siblings and parents. Further, we considered the FH data of cancer not only of the stomach, but also at other cancer sites.

Table I. Distribution of Subjects with Gastric Cancer (GC) and Controls According to Family History (FH) of GC

GC FH	No. of cases	No. of controls	OR[a] (CI)[b]
1st to 3rd degree relatives			
negative	108	118	1.0
positive	28	18	1.7
	(20.6)	(13.2)	(0.9–3.3)
Male[c]			
negative	69	71	1.0
positive	17	15	1.2
	(19.8)	(17.4)	(0.6–2.5)
Female[c]			
negative	39	47	1.0
positive	11	3	4.5
	(22.0)	(6.0)	(1.3–15.2)
2nd or 3rd degree relatives			
negative	127	127	1.0
positive	9	9	1.0
	(6.6)	(6.6)	(0.4–2.5)
1st degree relatives[d]			
negative	115	126	1.0
positive	21	10	2.3
	(15.4)	(7.4)	(1.1–5.0)
Parental history			
negative	115	126	1.0
positive	21	10	2.3
	(15.4)	(7.4)	(1.1–5.0)
Sibling history			
negative	129	129	1.0
positive	7	7	1.0
	(5.1)	(5.1)	(0.4–2.8)
Total	136	136	

a) Mantel-Haenszel estimate adjusted for sex and age.
b) 95% confidence interval.
c) Any 1st to 3rd degree relatives.
d) Risk for 1st degree relatives is the same as for parental GC due to the absence of any subject reporting offspring with GC.

Table II. Distribution of Subjects and Controls According to Sex and a Parental History of Gastric Cancer (GC)

	Parents with GC				
	None	Father	Mother	Either[c]	Total
Cases					
Male	72	9	5	14	86
	(83.7)	(10.5)	(5.8)	(16.3)	(100.0)
Female	43	2	5	7	50
	(86.0)	(4.0)	(10.0)	(14.0)	(100.0)
Total	115	11	10	21	136
	(84.6)	(8.1)	(7.4)	(15.4)	(100.0)
Controls					
Male	78	4	4	8	86
	(90.7)	(4.7)	(4.7)	(9.3)	(100.0)
Female	48	1	1	2	50
	(96.0)	(2.0)	(2.0)	(4.0)	(100.0)
Total	126	5	5	10	136
	(92.6)	(3.7)	(3.7)	(7.4)	(100.0)
OR[a]					
Male	1.0	2.4	1.4	1.9	
		(0.8–7.5)[b]	(0.4–4.8)	(0.8–4.6)	
Female	1.0	2.3	6.0	4.2	
		(0.4–15.6)	(1.1–31.4)	(1.0–17.4)	
Total	1.0	2.4	1.9	2.3	
		(0.9–6.4)	(0.7–4.9)	(1.1–5.0)	

a) Mantel-Haenszel estimate adjusted for sex and age.
b) 95% confidence interval. *c*) Either father or mother.

RESULTS

The distribution of GC subjects and the controls according to GC FH is given in Table I. GC risk increased over twofold for subjects reporting a parent with GC. GC risk was almost unity for subjects reporting a sibling with GC and for those reporting 2nd or 3rd degree relatives.

When considered separately, females tended to show higher GC risks than males when reporting a GC in 1st to 3rd degree relatives [Mantel-Haenszel odds ratio (OR) =4.5; 95% confidence interval (95%CI):1.3–15.2 and OR=1.2; 95%CI:0.6–2.5, respectively], especially when a parent was affected (OR=4.2; 95%CI:1.0–17.4 and OR=1.9; 95%CI:0.8–4.6, respectively) (Table II). The higher risk of females with parental GC was derived from the excess risk when reporting an affected mother (OR=6.0; 95%CI:1.1–31.4) as compared with an affected father (OR=2.3; 95%CI:0.4–15.6). Unlike females, male subjects showed a lower risk of GC occurrence when reporting an affected mother (OR=1.4; 95%CI: 0.4–4.8) than an affected father (OR=2.4; 95%CI:0.8–7.5), although neither was significant.

Table III shows the distribution of cases and controls according to FH of cancers except for GC. The GC risk was almost unity for subjects reporting any relative with other cancers, except when female subjects reported maternal cancers other than GC (OR=5.7; 95%CI:1.1–30.9) (Table IV).

DISCUSSION

In this study, GC risk was found to be high when a subject reported a parental history of GC. However, the risk did not significantly increase for subjects who reported GC among distant relatives such as 2nd or 3rd degree relatives. In addition, GC risk was almost unity for a cancer FH of any other cancer site, even among closer relatives.

A prospective study conducted in Japan by Kato *et al.*[6] revealed that a positive FH of GC within parents and siblings significantly increased the risk of death from stomach cancer (relative risk=2.01, 95%CI:1.12–3.63). An earlier investigation by La Vecchia *et al.*,[1] in a hospital-based case-control study, showed that relative

Table III. Distribution of Subjects with Gastric Cancer and Controls According to Family History (FH) of Other Cancers

FH of other cancers	No. of cases	No. of controls	OR[a] (CI)[b]
1st to 3rd degree relatives			
negative	102	101	1.0
positive	34	35	1.0
	(25.0)	(25.7)	(0.6–1.7)
Male[c]			
negative	65	61	1.0
positive	21	24	0.8
	(24.4)	(28.2)	(0.4–1.6)
Female[c]			
negative	37	39	1.0
positive	13	11	1.3
	(26.0)	(22.0)	(0.5–3.1)
2nd or 3rd degree relatives			
negative	120	118	1.0
positive	16	18	0.9
	(11.8)	(13.2)	(0.4–1.8)
1st degree relatives			
negative	114	112	1.0
positive	22	24	0.9
	(16.2)	(17.6)	(0.5–1.7)
Parental history			
negative	114	117	1.0
positive	22	19	1.2
	(16.2)	(14.0)	(0.6–2.3)
Sibling history			
negative	125	121	1.0
positive	11	15	0.7
	(8.1)	(11.0)	(0.3–1.6)
Total	136	136	

a) Mantel-Haenszel estimate adjusted for sex and age.
b) 95% confidence interval.
c) Any 1st to 3rd degree relatives.

Table IV. Distribution of Subjects with Gastric Cancer (GC) and Controls According to Sex and Parental History of Other Cancers

	Parents with cancers other than GC				
	None	Father	Mother	Either[c]	Total
Cases					
Male	73	9	7	13	86
	(84.9)	(10.5)	(8.1)	(15.1)	(100.0)
Female	41	4	5	9	50
	(82.0)	(8.0)	(10.0)	(18.0)	(100.0)
Total	114	13	12	22	136
	(83.8)	(9.6)	(8.8)	(16.2)	(100.0)
Controls					
Male	71	9	8	15	86
	(82.6)	(10.5)	(9.3)	(17.4)	(100.0)
Female	46	3	1	4	50
	(92.0)	(6.0)	(2.0)	(8.0)	(100.0)
Total	117	12	9	19	136
	(86.0)	(8.8)	(6.6)	(14.0)	(100.0)
OR[a]					
Male	1.0	1.0	0.8	0.8	
		(0.4–2.5)[b]	(0.3–2.3)	(0.4–1.9)	
Female	1.0	1.5	5.7	2.6	
		(0.4–6.1)	(1.1–30.9)	(0.3–8.3)	
Total	1.0	1.1	1.4	1.2	
		(0.5–2.4)	(0.6–3.3)	(0.6–2.3)	

a) Mantel-Haenszel estimate adjusted for sex and age.
b) 95% confidence interval. *c*) Either father or mother.

risk of GC for a subject having a parent with GC was 2.5 and the corresponding 95%CI was 1.7–3.6. Zanghieri *et al.*[2] studied a 2-year extract of a population-based cancer registry and observed the excess occurrence of parental GC in subject families; they estimated the risk as 1.61 (the 95%CI was not calculated), although this was not statistically significant. Palli *et al.*[3] found a significant association between GC occurrence and history of GC in a parent in a population-based case-control study and estimated the risk as 1.7, 95%CI:1.3–2.2. Taken together with our estimate, the GC risk for a positive FH seems to be increased about 2 times compared with that for a negative FH.

La Vecchia *et al.*[1] also found that the risk of stomach cancer was almost unity for a cancer FH of a number of other cancer sites (including esophagus, intestines, liver, pancreas, gall bladder and lung) among 1st degree relatives. Their report is consistent with ours, although we could not analyze each of the other cancer sites individually, because of the small number of occurrences. These findings indicate that a positive cancer FH of other cancer sites makes little or no contribution to GC occurrence.

We realize that the analysis used in this study makes no distinction between genetic and environmental factors shared by family members. However, previous researchers have suggested that genetic factors might be of importance in the pathogenesis of gastric tumors. The main findings can be summarized as follows: (1) The risk of GC among close relatives is higher than that expected in the general population.[9–11] (2) Some of the most common precancerous lesions of the stomach, such as pernicious anemia and severe atrophic gastritis, seem to be genetically determined.[12, 13] (3) GC is more frequent among members with Lynch II syndrome ("cancer family syndrome") than in the general population[14] and "gastric cancer families."[15] (4) The almost simultaneous occurrence of gastric cancer in two monozygotic twins.[16] Taken together with these findings, the familial occurrence of GC noted in this study suggests genetic susceptibility to cancer of the stomach.

We also observed that familial risk of GC was higher in females, and was especially high in those reporting a parental GC. This is consistent with the observation by Palli *et al.*[3] Gender differences concerning the risk might

be explained partly by the reporting of FH by women being generally more reliable. Since a subject is probably more affected by the death or disease of parents than of other relatives, gender difference in the risk was considered unlikely to be due to differences in reporting only.

Considering that there is no difference in the ability of the mother and father to genetically influence offspring, the excess risk for females with maternal GC should be mainly derived from environmental factors. Lifestyle may contribute to this, since maternal dietary practices strongly affect the dietary habits and nutrition of offspring. If this is so, it remains unclear why male subjects did not show the same trend as female subjects. There may be a gender difference in how certain environmental factors are involved in GC occurrence. Generally, when males marry, the influence of maternal dietary habit and nutrition stops. Unlike males, females continued to be influenced by their mothers even after marriage. This may explain the gender difference in GC risk.

In this study, females were also found to show excess GC risk when reporting a maternal FH of cancers at other cancer sites. Various tumors are thought to share some common risk factors with GC and it is possible that some play a role in producing gender differences in GC risk.

One of the limitations of this study is that the information was mainly based on self-reporting or familiar reports. Therefore, we can not exclude the possible effect of recall bias on the elevation of the relative risk for GC patients with positive FH of cancers.

Another weak point of the present study is the small sample size of study subjects. The results obtained from the present study should be confirmed with a larger sample size in the future.

As in many common diseases, the development of gastric tumors seems to be due to complex and largely unknown interactions between environmental and genetic factors. In order to understand better the mechanism of familial aggregation of GC risk, further study of familial GC, including biological markers, will be needed.

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