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BRIEF ARTICLES

Comparison of patients by family history with gastric and non-gastric cancer

Xue-Fu Zhou, Yu-Long He, Wu Song, Jian-Jun Peng, Chang-Hua Zhang, Wen Li, Hui Wu

Xue-Fu Zhou, Yu-Long He, Wu Song, Jian-Jun Peng, Chang-Hua Zhang, Wen Li, Hui Wu, Department of Gastrointestinal Surgery, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China
Author contributions: Zhou XF and He YL contributed equally to this work; Zhou XF, He YL, Song W, Peng JJ and Zhang CH designed the research; Zhou XF, Song W, Peng JJ and Zhang CH performed the research; Zhou XF, He YL, Li W and Wu H analyzed data; Zhou XF and He YL wrote the paper.
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Correspondence to: Yu-Long He, Professor, Department of Gastrointestinal Surgery, the First Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China. ylh@medmail.com.cn
Telephone: +86-20-87755766 Fax: +86-20-87331059
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Abstract

AIM: To compare the gastric cancer (GC) patients by their family history with gastric and non-GC.

METHODS: Positive family histories within second-degree relatives and clinicopathological features were obtained for 256 patients.

RESULTS: Of the 256 probands, 112 (76 male, 36 female) were incorporated into familial GC (FGC) group: at least two GC members; 144 (98 male, 46 female) were included in the non-FGC group (relatives only affected with non-GCs). Of 399 tumors in relatives (181 from FGC against 212 from non-FGC), GC was the most frequent, followed by esophageal, hepatocellular, and colorectal cancer. Nasopharyngeal cancer was next to lung cancer but prior to breast and urogenital cancers. Most affected members aggregated within first-degree relatives (FGC: 66 siblings, 48 fathers, 31 mothers, four offspring; non-FGC: 56 fathers, 55 siblings, 43 mothers, and 15 offspring). The ratio of males to females in affected first-degree relatives was usually higher in male probands. Paternal history of GC was a slight risk for GC in males (OR = 1.19, 95% CI: 0.53-2.69), while risk of GC by maternal history of non-GCs was increased in females (OR = 0.46, 95% CI: 0.22-0.97). Diffuse-GC was the major histological type in all subgroups. Difference in tumor sites between the two groups was derived from an excess of upper sites in non-FGC female probands.

CONCLUSION: Distribution of associated non-GCs in a family history of GC may vary with geographic areas. GC may have different genetic and/or environmental etiology in different families, and a certain subtype may be inherited in a female-influenced fashion.

Key words: Gastric cancer; Family history; Familial gastric cancer; Familial predisposition; Female-influenced fashion

Peer reviewer: Toru Hiyama, MD, PhD, Health Service Center, Hiroshima University, 1-7-1 Kagamiyama, Higashihiroshima 739-8521, Japan

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INTRODUCTION

It has long been recognized that approximately 10% of gastric cancer (GC) patients present with some kinds of familial aggregation[1]. Family history of GC has previously been studied in many regions, including eastern Asian[2-9], North American[10-12], northern European[13-15], and Mediterranean countries[16-21]. A much higher incidence of familial GC (FGC) was reported from Mediterranean countries[19], while a relatively low occurrence was noted in northern European countries[14]. Some studies, although not all, showed that a family history of GC might be considered a stronger risk factor for women[2,3], or that risk of GC might be higher for subjects with an affected sibling rather than a parent[13,15,16,21]. The risk of GC associated with family history for non-GC has been found with different cancers in different studies[5,10,15,21]. In addition, the histological type of FGC was pronounced for "intestinal" and/or "diffuse" cancers in different studies[13,16]. An unusual form, the hereditary diffuse GC, which is a typical case of FGC caused by a truncation

germline mutation of CDH1, has never been found in eastern Asia[8]. Therefore, a number of features of FGC, including incidence, clinicopathological characteristics, family member risk and etiology, are still in debate.

Previous studies have indicated that familial predisposition to GC may have different genetic and/or environmental correlations in different populations. Although GC is one of the most common cancers in China, few data about its family history are available. Thus, to provide further data on the issue, we designed a proband-based case-control study to explore the traits related to family history of GC in south China.

MATERIALS AND METHODS

The data were obtained from three hospitals in Guangdong Province in south China: the First Affiliated Hospital of Sun Yat-Sen University, the First Affiliated Hospital of Guangdong Pharmaceutic University, and the People's Hospital of Meizhou city. A total of 2260 patients with histologically demonstrated GC admitted between 2000 and 2007 were enrolled in this study. A patient with positive oncologic family history records during his hospitalization or the follow-up was identified as a proband. Features of a proband, including gender, age of onset, and site and histological type of tumor, were taken into account. In addition, the oncologic family history of a proband consisting of data on gastric and/or non-GCs in the relatives was evaluated.

The oncologic family history of each proband was obtained using structured interviews carried out either in person or by telephone. The interviews were always conducted by the same two medical clinicians. After a brief explanation of the purpose of the study, verbal consent was requested before starting the questionnaire. The patient or the closest relative, usually a wife, husband or child, was asked to report the family history. Since an accurate history of third-degree relatives of a proband was relatively hard to obtain, we focused on the first to second-degree relatives, asking about the total number of family members, whether anyone had been diagnosed with cancer, the type of the cancer, and the age of onset.

In this study, according to present recognition[1], a positive family history was defined as a history of cancer within second-degree relatives, while FGC was referred to the presence of at least two GC family members, but also included relatives with history of non-GC. A clear positive family history was obtained for 256 of the total patients. The 256 probands were divided into two groups: a FGC group; and a non-FGC group (patients with relatives affected with non-GCs only), then each group was sorted again according to gender. Tumor location of a proband was identified by three sub-types: upper, medium, and lower site. Histological typing, usually made according to WHO classification, was converted to a Lauren classification. Chi-square test and risk estimate (OR) were used to evaluate the statistical significance. A P value less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS 13.0 software.

RESULTS

Of the 256 probands, 112 subjects (76 male, 36 female) reported a family history of GC (it also included relatives with histories of non-GC) and were incorporated into the FGC group; 144 subjects (98 male, 46 female) reported only a family history for non-GC and were included in the non-FGC group. Mean age of probands in FGC and non-FGC were 56.7 years (range 20-87 years) and 55.4 years (range 28-77 years), and the proportions of young patients (no more than 45 years) were 18.8% (21/112) and 20.1% (29/144), respectively ($\chi^2 = 0.08$, $P > 0.05$).

Table 1 shows the overall ranking of associated tumors within second-degree relatives of the 256 probands. A total of 399 neoplastic diseases were reported, 182 from FGC compared with 217 from non-FGC. GC was by far the predominant tumor in affected relatives of FGC (154 GCs against 28 non-GCs) as well as in the overall affected relatives of both groups. Of the non-GCs from affected relatives, esophageal cancer was the most frequent, hepatocellular cancer was the second, and colorectal cancer was the third. The "Canton tumor", a nasopharyngeal cancer (NPC) that has been rarely reported in previous studies, was the fifth, after lung cancer, but prior to breast and urogenital cancers.

Table 2 presents the distribution and number of affected family relatives of the 256 probands. Most affected members aggregated within the first-degree relatives. Among the total 318 (195 male, 123 female) affected first-degree relatives, males were more predominant in members affected with GCs (90 male *versus* 39 female) than in those with non-GCs (105 male *versus* 84 female) ($\chi^2 = 6.53$, $P < 0.05$). In general, among the first-degree relatives, siblings were the most frequently affected relatives, fathers were the next, and mothers were the third. This sequence was repeated among the relatives of FGC (siblings 66, fathers 48, mothers 31), but affected fathers were the most frequent in non-FGC (fathers 56, siblings 55, mothers 43). The ratio of males to females in affected first-degree relatives was usually higher in male than in female probands, and showed a decreasing trend in the four subgroups (Table 3).

Table 4 shows the OR, as estimators of relative risks, together with the corresponding 95% CI for reported parental history of cancers when male and female probands were compared. Paternal history of GC showed a slightly higher risk for males than for females, although there was no statistical significance (OR = 1.19, 95% CI: 0.53-2.69). In contrast, maternal history seemed to affect both genders to the same degree (OR = 0.93, 95% CI: 0.37-2.35). GC risk by paternal history of non-GC was almost the same for both genders (OR = 0.99, 95% CI: 0.48-2.02), but maternal history was less likely to be a risk factor for males, but was a risk factor for females (OR = 0.46, 95% CI: 0.22-0.97). Table 5 exhibits 14 probands whose parents were both affected. Five pairs of affected parents who reported at least one

Table 1 Ranking of associated tumors in family relatives of 256 probands

Associated tumors	FGC (n = 112)		Non-FGC (n = 144)		No. of associated tumors	Percentage
	Male proband[1] (n = 76)	Female proband (n = 36)	Male proband[2] (n = 98)	Female proband[3] (n = 46)		
Stomach	108	46			154	38.6
Esophagus	7	1	43	22	73	18.3
Liver	2	1	17	18	38	9.5
Colorectum	1		23	10	34	8.5
Lung	4	2	10	9	25	6.3
Nasopharynx			14	3	17	4.3
Breast	3		5	5	13	3.3
Urogenital organ		1	4	7	12	3.0
Larynx			5	1	6	1.5
Pancreas			3	1	4	1.0
Others[4]	4	2	12	5	23	5.8
Total	129	53	136	81	399	100

[1]One proband associated with lung cancer; [2]One proband associated with colorectal cancer; another nasopharyngeal cancer. One relative (father) associated with both lung and colorectal cancer; [3]One proband associated with breast cancer; another endometrial cancer; [4]Other malignant tumors including brain tumors, leukemia, lymphoma, oral cancer, and thyroid cancer.

Table 2 Distribution and number of affected relatives of 256 probands

Affected relatives	FGC (n = 112)				Non-FGC (n = 144)		No. of affected relatives	Percentage
	Male proband (n = 76)		Female proband (n = 36)		Male proband (n = 98)	Female proband (n = 46)		
	GC	Non-GC	GC	Non-GC	Non-GC	Non-GC		
Father	31	3	14		38	18	104	26.5
Mother	17	5	9		24	19	74	18.8
Brother	34	4	10	2	23	7	80	20.4
Sister	7	2	5	2	16	9	41	10.4
Son	1				3	7	11	2.8
Daughter	1	1		1	2	3	8	2.0
Second-degree	17	5	8	2	27	16	75	19.1
Total	108	20	46	7	133	79	393	100

Table 3 Ratio of male to female in affected first-degree relatives in four subgroups

Gender of affected relatives	FGC (n = 112)		Non-FGC (n = 144)	
	Male proband (n = 76)	Female proband (n = 36)	Male proband (n = 98)	Female proband (n = 46)
Male	73	26	64	32
Female	33	17	42	31
Total	106	43	106	63
Ratio of male to female	2.21	1.53	1.52	1.03

$\chi^2_{trend} = 5.03$, $P < 0.05$.

suffering from GC had five affected sons only, while nine pairs of parents both suffering from non-GCs had five affected daughters and four affected sons.

Table 6 displays the histological types of the 256 probands. According to Lauren classification, diffuse GC was the major histological type in all subgroups. The frequency of the intestinal type was lower in the FGC than in the non-FGC group, but no statistical difference was found between them. Table 7 shows the distribution of tumor sites of the 256 probands. The lower site was the most frequent tumor location in FGC probands, in contrast to upper sites in non-FGC probands ($\chi^2 = 10.69$, $P < 0.05$). The statistical difference in tumor sites between the two groups was derived from an excess of upper sites presenting in non-FGC female probands (male subgroups: $\chi^2 = 4.99$, $P > 0.05$; female subgroups: $\chi^2 = 9.67$, $P < 0.05$).

DISCUSSION

In the present study of family history of GC in south China, we compared the association between the family history with GCs and non-GCs, and the risk of GC between male and female probands by parental oncologic history. Our study confirmed that overall ranking of associated non-GCs in relatives was different from that reported in other studies to some degree, and that the ratio of males to females in affected first-degree relatives was usually higher in male than in female probands. We also found that the risk of GC was increased in females

Table 4 Relative risk of GC by comparing male with female probands from their paternal or maternal history of cancers

Affected parents	FGC[1] (*n* = 108)		OR (95% CI)	Non-FGC (*n* = 144)		OR (95% CI)
	Male proband (*n* = 72)	Female proband (*n* = 36)		Male proband (*n* = 98)	Female proband (*n* = 46)	
Father	31	14	1.19 (0.53-2.69)	38	18	0.99 (0.48-2.02)
Mother	17	9	0.93 (0.37-2.35)	24	19	0.46 (0.22-0.97)

[1]Deletion of four male probands with parental history of non-GCs.

Table 5 Comparison of 14 probands with both affected parents

Serial number	Father	Mother	Proband	Adenocarcinoma of proband
1	GC	GC	Son	Poorly
2	GC	BC	Son	Poorly
3	GC	EMC	Son	Poorly
4	GC	EC	Son	Poorly
5	HC	GC	Son	Poorly
6	HC	EC	Daughter	Moderately
7	EC	EC	Son	Moderately
8	EC	EC	Daughter	Moderately
9	CRC	EC	Son	Poorly
10	CRC	BC	Daughter	Poorly
11	LC	CRC	Son	Poorly
12	LC	LC	Daughter	Mucinous
13	NPC	PC	Son	Poorly
14	NPC	HC	Daughter	Signet-ring cell

BC: Breast cancer; CRC: Colorectal cancer; EC: Esophageal cancer; EMC: Endometrial cancer; GC: Gastric cancer; HC: Hepatocellular cancer; LC: Lung cancer liver; NPC: Nasopharyngeal cancer; PC: Pancreatic cancer; Moderately: Moderately differentiated adenocarcinoma; Poorly: Poorly differentiated adenocarcinoma; Mucinous: Mucinous adenocarcinoma; Signet-ring cell: Signet-ring cell carcinoma.

when a maternal history of non-GC was present. On the other hand, the risk for GC in males was only slightly (not significantly) increased if a paternal history of GC was present. Moreover, a trend toward upper tumor sites was observed only in females with a family history of non-GC.

Associated tumor categories and their frequencies of family history of GC have been reported previously. Recent studies were consistent with the higher predisposition to gastric than to any of the non-GCs in family members[2,19]. The frequency of GC among all affected relatives was also highest in our study. However, the frequency of non-GC in family members differed from the results in other reports. For example, colorectal, lung, and uterine cancers were the highest in ranking in a Japanese report[9], while colorectal, breast, and lung cancer were prevalent in an Italian report[20], lung/larynx cancer, gastrointestinal cancer, and leukemia/lymphoma were most frequent in a study from Turkey[18], and colorectal and lung cancer were most common in a report from Taiwan[6]. In general, the overall ranking of associated non-GCs in family histories of GC varied from region to region, but the preceding tumors were usually the most frequent ones occurring in that general population.

Eastern Guangdong is one of the regions with the highest incidence of esophageal cancer in China. Guangdong is also one of the regions with the highest incidence of hepatitis B, and HBV-related hepatic cancer is one of the most common tumors in this region. Therefore, esophageal and hepatic cancers, which are usually frequent in general population, are more common in Guangdong. This may be interpreted as that esophageal and hepatic cancers were the two most frequently associated non-GCs among the relatives in our study. Moreover, Guangdong is the region with the highest incidence of NPC in the world. NPC, rare in other general populations, is quite common among Cantonese. This may explain why NPC was much more frequently reported in our study in contrast to other studies, but was less frequently encountered with the most common tumors (usually common both in local residents and in the general population) within our study groups. From this, we can infer that the overall rankings of associated non-GCs in family history of GC may be correlated to the categories of common cancers in the general population, but also show their own regional incidences. This suggests that GC probably shares similar genetic and/or environmental etiologic pathways with other common tumors.

The risk of GC by family oncologic history has been debated in different studies. Although no normal control was included as part of this study, we assumed that siblings being the most frequently affected relatives might support the idea that the risk of GC was higher for subjects with an affected sibling rather than an affected parent[13,15,16,21]. It may be also debated if the risk of GC has no association with family history of any cancer other than GC, because our data showed a very high proportion of relatives affected with esophageal cancers, and esophageal cancer usually shares very similar geographic distribution with gastric cardia cancer in China[22].

Gender-influenced familial predisposition to GC has also been investigated previously[2,3]. Although our study was not a population-based case-control study, the results reconciled a number of points raised in a Japanese study[2]. The findings of this study indicated that risk of GC by paternal history of GC seemed to be a slight risk for males compared with females, while the increment in the risk for GC was prominent in females when they reported a maternal history of non-GCs. However, we did not find a higher risk for females when they reported a maternal history of GCs, which had been described in the previous study[2].

Besides gender-related familial risk of GC, a gender difference was also found in affected first-degree

Table 6 Distribution of tumor histological types (converting the WHO to the Lauren classification) of 256 probands

Lauren classification	WHO classification	FGC (n = 112)		Non-FGC (n = 144)	
		Male proband (n = 76)	Female proband (n = 36)	Male proband (n = 98)	Female proband (n = 46)
Intestinal type	Well	3		2	
	Moderately	19	6	39	12
	Mucinous	5	3	5	3
	Total	27	9	46	15
Diffuse type	Poorly	44	24	39	25
	Signet-ring cell	3	2	11	6
	Undifferentiated	2	1	2	
	Total	49	27	52	31

Well: Well differentiated adenocarcinoma; Undifferentiated: Undifferentiated carcinoma; No statistical differences of histological types were found between any two subgroups, although ratio of intestinal to diffuse types was lower in FGC than in Non-FGC (36/76 = 0.47 from FGC against 61/83 = 0.73 from non-FGC).

Table 7 Distribution of anatomical sites of tumors in 256 probands

Tumor site	FGC (n = 112)		Non-FGC (n = 144)	
	Male proband (n = 76)	Female proband (n = 36)	Male proband (n = 98)	Female proband (n = 46)
Upper	22	5	42	16
	27		58	
Medium	20	7	27	15
	27		42	
Lower	34	24	29	15
	58		44	
χ^2, P value	$\chi^2 = 10.69$, $P < 0.05$			

Difference of tumor sites between two male subgroups: $\chi^2 = 4.99$, $P > 0.05$; two female subgroups: $\chi^2 = 9.67$, $P < 0.05$.

relatives in different families in our study. The ratio of males to females in the affected first-degree relatives was usually higher in FGC than in non-FGC. This may be attributed to the male predominance in GC development. However, the ratio of the affected relatives was usually higher in male than in female probands in both groups. This may also indicate that gender influences the familial predisposition to GC in a certain way. Moreover, gender variations still existed in the affected offspring when both parents suffered from different cancers. Affected daughters were not found in families in which at least one of the two affected parents had GC, but were more frequent in families in which both affected parents suffered from non-GCs. These differences in GC risk by gender and family oncologic history imply that familial predisposition to GC may have a compound genetic and/or environmental correlation in different families.

Lauren's classification system classifies GC under two major histological variants: an intestinal type, likely to be related to environmental factors, and the diffuse type, more likely to have a primary genetic etiology. Our data show that the diffuse type was the more common histological form in all subgroups. However, the frequency of histological type of GC with oncologic family history varied with different studies. Japanese studies[4,7] reported that the undifferentiated histological type was dominant in FGC, and there was a predisposition to the intestinal type when both parents suffered from GCs while to the diffuse type when both parents suffered from non-GCs. The dominance of the intestinal type and the diffuse type was reported in Italy and Poland, respectively[13,16,20]. These variations indicate that familial predisposition to GC may be a multifactor disease.

Many studies have verified that environmental factors may play a more important role than do host genetics in GC development. The prevalence of *Helicobacter pylori* infection has been regarded as an important risk factor for familial aggregation of GC, and may be a strong risk factor for distal, rather than for proximal, GC[23,24]. However, this could not be fully interpreted for the familial predisposition to GC in south China, because of a higher proportion of diffuse GC in all subgroups and no statistical difference of tumor site between the two male subgroups. Some studies have found no appreciable interactions between family history of GC and environmental factors, such as lifestyles[25]. Our investigation detected a pedigree with a father and two brothers affected with GCs, but one of the brothers, suffering from GC at the age of 62 years, had been adopted by another family in his childhood. This suggests that FGC may be predominantly the diffuse type and may be accounted by factors other than just environmental exposures.

Furthermore, a Japanese study[26] reported that an increment of an upper tumor was observed only in patients with a maternal history of GC, but our study displayed the same increment only in females with family histories of non-GC. Our result might be partially influenced by a higher incidence of esophageal cancer among the family members suffering from non-GCs, because the higher prevalence of upper tumors may be due to the higher prevalence of esophageal tumors in this region which is usually associated with a high incidence of gastric cardia cancer. Site-specific risk for female GC that was linked to a family history of non-GC, as well as site-specific risk for GC linked to a maternal history of GC from a Japanese study, provides further evidence that a type of familial susceptibility to GC, to some extent, may be dominated in a female-influenced way.

Some explanations should be provided for the data demonstrated in this study. We focused the discussion primarily on the data of first-degree relatives, because reports of family history will always be clearer in those we know better (i.e. first-degree relatives) and will be less clear as we extend to second and third degree relatives. Therefore, the data of first-degree relatives may introduce fewer inherent biases. The percentage of positive oncologic family histories and incidences of FGC (11.2% and 4.9%) are much lower than those cited in the literatures. It is possible that our data may not show substantial percentages because some patients were unwilling to tell their family history, but this limitation was unlikely to contribute substantially to the differences we observed. Genetic factors may in fact be more important in a young GC development, and therefore may be likely associated with familial susceptibility in a young patient[27,28]. However, the percentages of young patients among the total patients (20.0%) and the 256 probands (19.5%) had no statistical difference, and both were higher than 10% in GC population cited in literatures[28]. These data indicated that the proportion of young patients in the GC population was higher in south China, but an association between young individuals and the inheritance of GC in a cancer family was not found. Therefore, the etiology and the terms used to describe familial tendency of a young GC patient should be reconsidered.

In conclusion, the overall ranking of associated non-GCs in the family history of GC may vary with geographic areas. Familial predisposition to GC may be related to compound genetic and/or environmental etiologies; and a certain subtype of GC may be inherited in a female-influenced fashion.

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COMMENTS

Background

Gastric cancer (GC) is a major clinical challenge because of its frequency, poor prognosis and limited treatment options. The etiology of GC is still uncertain, but its familial aggregation in a variable but significant proportion of cases suggests the importance of genetic predisposition. The risk of developing GC is greater in relatives of patients with oncological family history than in relatives of sporadic cancer. Previous studies have indicated that familial predisposition to GC may have different genetic and/or environmental correlations in different populations. Although GC is prevalent in China, scanty information about its family history is available.

Research frontiers

Familial predisposition to GC may be partly due to the fact that relatives tend to be exposed to the same environmental risk factors, but also to inheritable susceptibility. In this field, the research hotspot is how to identify risk relatives, and risk factors (including different prevalence of various susceptibility genes, and the impact of various environmental factors) in a family with disease.

Innovations and breakthroughs

Studies on family history of GC, the association of familial risk of GC with the age of onset GC, with family member gender, or with family history of non-GCs, usually yielded contrasting results. This study believed that the overall ranking of associated non-GCs in the family history of GC may depend on geographical variations; familial predisposition to GC may be related to compound genetic and/or local environmental factors; and a certain subtype of GC may be inherited in a female-influenced fashion.

Applications

The data presented in this article represents important data about familial predisposition to GC with a high prevalence. This will add to the available body of knowledge about GC inheritance and aid in future research into this important disease.

Terminology

Familial GC (FGC) is simply designated as a cancer family with at least two GC members, also including those affected with non-GCs. Among the cases of FGC, several situations can be identified according to the histopathologic type of GC and the number of affected relatives, which encompasses specific syndromes/diseases as follows: hereditary diffuse GC, familial diffuse GC, and familial intestinal GC.

Peer review

Zhou *et al* designed a proband-based study to provide further data on factors of familial predisposition to GC. This paper is interesting and written well.

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