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ORIGINAL ARTICLE

Retrospective Study

Individual having a parent with early-onset gastric cancer may need screening at younger age

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Abstract

AIM: To evaluate whether individuals with gastric cancer (GC) are diagnosed earlier if they have first-degree relatives with GC.

METHODS: A total of 4282 patients diagnosed with GC at National Cancer Center Hospital from 2002 to 2012 were enrolled in this retrospective study. We classified the patients according to presence or absence of first-degree family history of GC and compared age at diagnosis and clinicopathologic characteristics. In addition, we further classified patients according to specific family member with GC (father, mother, sibling, or offspring) and compared age at GC diagnosis among these patient groups. Baseline characteristics were obtained from a prospectively collected database. Information about the family member's age at GC diagnosis was obtained by questionnaire.

RESULTS: A total of 924 patients (21.6%) had a first-degree family history of GC. The mean age at GC diagnosis in patients having paternal history of GC was 54.4 ± 10.4 years and was significantly younger than in those without a first-degree family history (58.1 ± 12.0 years, $P < 0.001$). However, this finding was not observed in patients who had an affected mother (57.2 ± 10.0 years) or sibling (62.2 ± 9.8 years). Among patients with family member having early-onset GC (< 50 years old), mean age at diagnosis was 47.7 ± 10.3 years for those with an affected father, 48.6 ± 10.4 years for those with an affected mother, and 57.4 ± 11.5 years for those with an affected sibling. Thus, patients with a parent diagnosed before 50 years of age developed GC 10.4 or 9.5 years earlier than individuals without a family history of GC (both $P <$

0.001).

CONCLUSION: Early-onset GC before age of 50 was associated with parental history of early-onset of GC. Individual having such family history need to start screening earlier.

Key words: Gastric cancer; Family history; Family member; Age at diagnosis; Screening

Core tip: A family history of cancer is associated with earlier age of onset of several cancers, but not clear in gastric cancer (GC). We found that individuals with a paternal history of GC tended to diagnosis at younger age than those patients without family history, also individuals with a parent diagnosed before 50 years of age developed GC about 10 years earlier than those patients without family history. The finding that patients with a parental history of GC, especially those who had parents with early-onset GC, diagnosed at younger age supports the need for early screening in these individuals.

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INTRODUCTION

A family history of cancer increases the risk of several cancers[1-3]. In addition, the earlier a family member diagnosed to have a colorectal cancer, breast cancer, ovarian cancer, prostate, and thyroid cancer, the higher the risk of developing cancer for others in the family. A family history of cancer is also associated with earlier age of onset for colorectal cancer, breast cancer, ovarian cancer, prostate cancer, and thyroid cancer[4-7]. Taken together, these studies suggest that individuals with a family history of colorectal, breast, or ovarian cancer, especially with earlier age of onset, should undergo screening earlier than the normal population[2,6,8-10] and may require surgery[11] or chemoprevention[12] to reduce their cancer risk.

Family history is also an important risk factor for gastric cancer (GC). Studies have shown that individuals with a family history of GC have a higher risk of developing GC than controls (OR = 1.3-8.5)[13-19], and early diagnosis is associated with a higher GC risk for other family members[20]. However, the relationship between family history and age at GC onset/diagnosis is unclear. Therefore, in this study we compared age at diagnosis in patients with or without a first-degree family history of GC to determine whether patients with a family history of GC are diagnosed earlier.

MATERIALS AND METHODS

Patients

For this retrospective study we identified 5413 patients with GC at the National Cancer Center Hospital in South Korea using a prospectively collected database. For all patients the diagnosis of gastric adenocarcinoma was confirmed by histology from October 2002 to December 2012.

We excluded 1131 patients who were inadequately evaluated for cancer stage, Lauren's classification, family history, or age at diagnosis. Our final study population consisted of 4282 patients (Figure 1). The study protocol was approved by the Institutional Review Board of the National Cancer Center, South Korea (NCCNCS-13-820).

We classified the 4282 patients according to presence or absence of first-degree family history of GC and compared age at diagnosis and clinicopathologic characteristics. In addition, we further classified patients according to specific family member with GC (father, mother, sibling, or offspring) and compared age at GC diagnosis among these patient groups.

Classification of patients according to first-degree family member

Because we wanted to evaluate the influence of paternal and maternal history separately, we excluded patients with a family history of both parents developing GC (n = 18). We defined patients with a paternal history (n = 349, 37.8%) as those whose father only was affected (n = 315) or both father and sibling (but not mother) were affected (n = 34) (Figure 2). Similarly, we defined patients with a maternal history (n = 229, 24.8%) as those whose mother only was affected (n = 203) or both mother and sibling (but not father) were affected (n = 26). We defined patients with a sibling history as those whose sibling (but not parents) was affected (n = 319, 34.5%). Of the 16 patients who had offspring with GC, those who also had other affected family members were classified into the paternal, maternal, or sibling history group. The remaining nine patients had offspring only with GC; because of its small size, this subgroup was excluded from analysis.

Definition of clinicopathologic variables

Age at diagnosis and clinicopathologic characteristics were compared between patients with or without a first-degree family history. Among the clinicopathologic variables, current *Helicobacter pylori* (*H. pylori*) infection was defined by positive histology or rapid urease test (RUT) results, whereas past *H. pylori* infection was defined by positive serology but negative

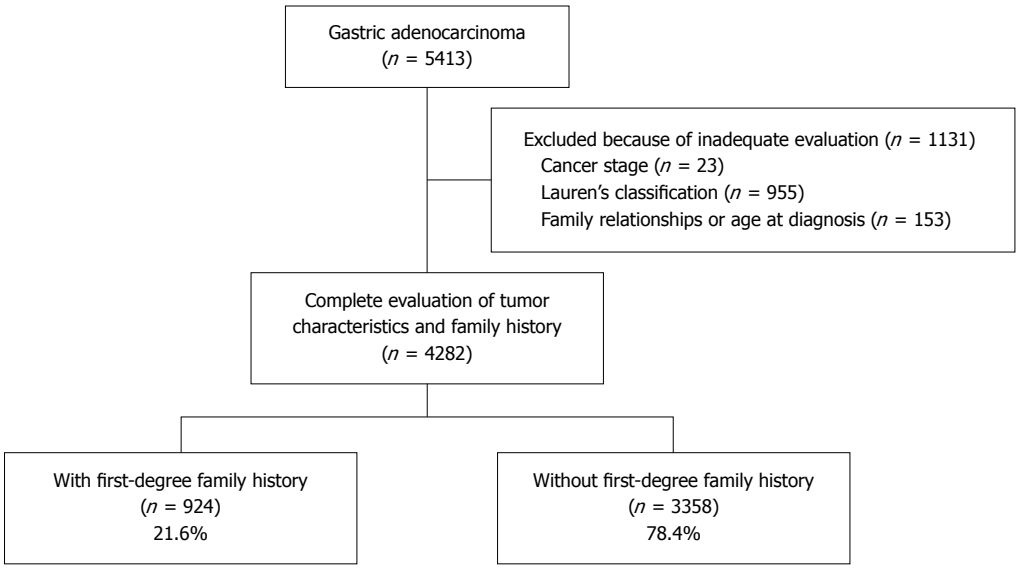

Figure 1 Flow diagram for classification of patients with gastric cancer based on the presence or absence of a first-degree family history.

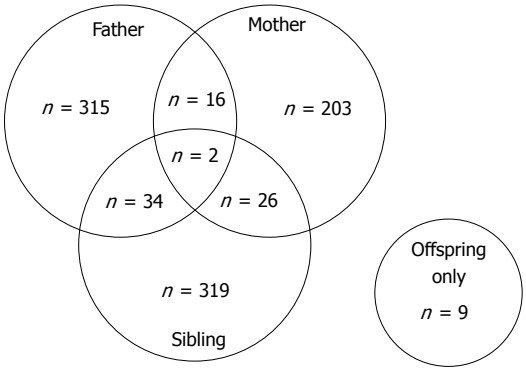

Figure 2 Classification of patients with gastric cancer according to affected first-degree family members.

histology and RUT results. Negative *H. pylori* infection was defined by negative results for all three tests (histology, RUT, and serology).

Cancer was staged according to the TNM classification on the basis of final pathology, abdominal computed tomography, or endoscopic ultrasonography findings. TNM classification was performed according to the 7th edition of the American Joint Committee on Cancer 7th cancer staging manual[21].

Statistical analysis

χ^2 tests were performed to compare categorical variables and evaluate the relationship between *H. pylori* infection status and cancer stage. Independent t-tests were performed to assess significant differences between the means of two unrelated groups. One-way analysis of variance (ANOVA) was performed to compare the means of three unrelated groups. A post-hoc test was done using Tukey's honestly significant difference (HSD) test. Analyses were performed with the STATA version 10.0 (Stata Corp, College Station, TX, United States). $P < 0.05$ was considered significant. The statistical methods of this study were reviewed by Jungnam Joo from Cancer Biostatistics Branch, Nation Cancer Center, South Korea.

RESULTS

Age at diagnosis and clinicopathologic characteristics according to the presence of first-degree family history of GC

Figure 1 shows the flow diagram of patient inclusion and classification. Age at diagnosis and clinicopathologic characteristics of both groups are summarized in Table 1. Patients with a family history had smaller lesions and more intestinal-type cancers than the patients without a family history. However, overall mean age, proportion of male patients, *H. pylori* infection status, and cancer stage did not differ significantly between groups.

Age at diagnosis of gastric cancer according to affected family member

Among patients with a first-degree family history of GC, age at diagnosis was evaluated according to the affected family member (Table 2). The mean age at diagnosis was 54.4 ± 10.4 for patients with a paternal history, 57.2 ± 10.0 years for patients with a maternal history, and 62.2 ± 9.8 years for patients with a sibling history ($P < 0.001$, one-way ANOVA), and each pair of means differed significantly ($P < 0.05$, Tukey's HSD test). Patients with a paternal history were younger at the time of diagnosis than those without a family history. However, age at diagnosis for patients with a maternal history did not differ significantly from that of those without a family history, and patients with a sibling history were older at diagnosis than those without a family history.

Table 1 Clinicopathologic characteristics of patients with or without a first-degree family history of gastric cancer *n* (%)

	Total (4282)	With first-degree family history	Without first-degree family history	
		n = 924 (21.6%)	*n* = 3358 (78.4%)	*P* value
Age at diagnosis, yr (mean ± SD)	58.0 ± 11.8	58.0 ± 10.7	58.1 ± 12.0	0.897[1]
Male	2886 (67.4)	620 (67.1)	2266 (67.5)	0.827[1]
Female	1396 (32.6)	304 (32.9)	1092 (32.5)	
Tumor diameter (mean ± SD)	4.0 ± 2.7	3.8 ± 2.6	4.2 ± 2.8	0.004[1]
Lauren's classification				< 0.001[2]
Intestinal	2251 (52.6)	544 (58.9)	1707 (50.8)	
Diffuse	1642 (38.3)	300 (32.5)	1342 (40.0)	
Mixed	389 (9.1)	80 (8.6)	309 (9.2)	
H. pylori infection status				0.174[2]
Current	2851 (66.6)	612 (66.2)	2239 (66.7)	
Past	622 (14.5)	114 (12.3)	508 (15.1)	
Negative	536 (12.5)	119 (12.9)	417 (12.4)	
Not available	273 (6.4)	79 (8.5)	194 (5.8)	
GC stage				0.081[2]
Stage 1	3009 (70.3)	679 (73.5)	2330 (69.4)	
Stage 2	568 (13.3)	114 (12.3)	454 (13.5)	
Stage 3	476 (11.1)	92 (10.0)	384 (11.4)	
Stage 4	229 (5.3)	39 (4.2)	190 (5.7)	

[1]Independent *t*-test; [2]χ^2 test. SD: Standard deviation; GC: Gastric cancer; *H. pylori*: *Helicobacter pylori*.

Table 2 Age at diagnosis and clincopathologic characteristics of patients with gastric cancer according to affected first-degree family member *n* (%)

	Father	Mother	Sibling	*P* value		
	n = 349 (37.8%)	*n* = 229 (24.8%)	*n* = 319 (34.5%)	Father *vs* mother	Father *vs* sibling	Mother *vs* sibling
Age at diagnosis, yr (mean ± SD)	54.4 ± 10.4	57.2 ± 10.0	62.2 ± 9.8	0.002[1]	< 0.001[1]	< 0.001[1]
Male	252 (72.2)	137 (59.8)	213 (66.8)	0.002[2]	0.127[2]	0.095[2]
Female	97 (27.8)	92 (40.2)	106 (33.2)			
Tumor diameter (mean ± SD)	3.9 ± 2.8	3.9 ± 2.4	3.8 ± 2.4	0.988[1]	0.661[1]	0.661[1]
Lauren's classification				0.764[2]	0.003[2]	0.021[2]
Intestinal	191 (54.7)	132 (57.6)	205 (64.3)			
Diffuse	130 (37.3)	81 (35.4)	80 (25.1)			
Mixed	28 (8.0)	16 (7.0)	34 (10.7)			
H. pylori infection status				0.530[2]	0.519[2]	0.827[2]
Current	241 (69.1)	150 (65.5)	206 (64.6)			
Past	43 (12.3)	25 (10.9)	42 (13.2)			
Negative	37 (10.6)	32 (14.0)	45 (14.1)			
Not available	28 (8.0)	22 (9.6)	26 (8.2)			
Gastric cancer stage				0.193[2]	0.746[2]	0.186[2]
Stage 1	254 (72.8)	166 (72.5)	235 (73.7)			
Stage 2	41 (11.7)	28 (12.2)	43 (13.5)			
Stage 3	35 (10.0)	30 (13.1)	27 (8.5)			
Stage 4	19 (5.4)	5 (2.2)	14 (4.4)			

[1]Independent *t*-test; [2]χ^2 test. *H. pylori*: *Helicobacter pylori*.

Clinicopathologic characteristics of GC according to affected family member

Among patients with a first-degree family history of GC, clinicopathologic characteristics were evaluated according to the affected family member (Table 2). The proportion of males was higher among patients who had a paternal history compared with those who had a maternal history. Intestinal-type GC was more common among patients with a sibling history compared with those who had a paternal history or maternal history. However, mean tumor size, *H. pylori* infection status, and cancer stage did not differ significantly among groups.

Age at diagnosis of patients who had a first-degree family member with early-onset GC

Age at diagnosis of patients who had a first-degree family member diagnosed with early-onset GC (diagnosed before the age of 50) was compared with the age at diagnosis of patients without a first-degree family history (58.1 ± 12.0) (Table 3). We found that the age at diagnosis of patients who had a father with early-onset GC or mother with early-onset GC was younger than that of patients without a family history (both $P < 0.001$).

Table 3 Age at diagnosis of patient with first-degree family member diagnosed gastric cancer before and after 50 years old

Family member diagnosed before 50 yr old (n = 172)		Family member diagnosed after 50 yr old (n = 752)	*P* value
Father	47.7 ± 10.3 (n = 39)	55.3 ± 10.1 (n = 310)	< 0.001[1]
Mother	48.6 ± 10.4 (n = 24)	58.2 ± 9.5 (n = 205)	< 0.001[1]
Sibling	57.4 ± 11.5 (n = 100)	64.3 ± 8.1 (n = 219)	< 0.001[1]
Total	54.6 ± 10.5	58.8 ± 10.2	< 0.001[1]

[1]Independent *t*-test. Data are presented as mean ± SD.

Table 4 Age at diagnosis of patients with a first-degree family member diagnosed with gastric cancer before 50 years of age and patients without a first-degree family history *n* (%)

Patient's age at diagnosis, (yr)	Patients with family member diagnosed before 50 yr of age			Patients without a first-degree family history
	Father n = 39	Mother n = 24	Sibling n = 100	n = 3358
< 40	10 (25.6)	5 (20.8)	7 (7.0)	239 (7.1)
40-49	13 (33.3)	8 (33.3)	19 (19.0)	610 (18.2)
50-59	10 (25.6)	6 (25.0)	31 (31.0)	854 (25.4)
⩾ 60	6 (15.4)	5 (20.8)	43 (43.0)	1655 (49.3)
P-value[1]	< 0.001	0.004	0.573	

[1]Compared with patients without first-degree family history, χ^2 test.

However, the age at diagnosis of patients who had a sibling with early-onset GC was not significantly different from that of patients without a family history.

Age at diagnosis of patients with a first-degree family member diagnosed before or after 50 years of age

Among patients with a first-degree family history of GC, age at diagnosis was evaluated according to the affected family member's age at diagnosis (Table 3). Patients who had a family member with early-onset GC were also younger on average at the time of diagnosis compared with patients whose family member had later-onset GC (P < 0.001). Similar results were obtained when evaluating age at diagnosis according to GC diagnosis (< 50 years *vs* > 50 years) of the father, mother, or sibling (all P < 0.001).

We also found that patients whose fathers had later-onset GC were younger at the time of diagnosis than patients without a first-degree family history. However, age at diagnosis of patients whose mothers had later-onset GC did not differ significantly from that of patients without a first-degree family history, and patients whose siblings had later onset GC were older at the time of diagnosis.

Age at diagnosis of patients who had a first-degree family member with early-onset GC vs those without a first-degree family history

We then classified patients according to age at diagnosis (10-year intervals) and compared age at diagnosis between patients who had a first-degree family member with early-onset GC and patients without a first-degree family history of GC (Table 4). The proportion of patients who were younger than 50 years at the time of diagnosis was higher among those who had a father or mother with early-onset GC compared with those without a family history. However, the age at diagnosis of patients who had a sibling with early-onset GC was similar to that of patients without a family history.

DISCUSSION

In this study, we evaluated whether patients with GC who had a first-degree family history of the disease were younger at the time of diagnosis. We found that patients with a paternal history of GC were 3.7 years younger on average at diagnosis than patients without a family history. Patients whose fathers had early-onset GC (diagnosed before 50 years of age) were 10.4 years younger at diagnosis than patients without a family history, and those whose mothers had early-onset GC were 9.5 years younger. We also found that patients whose fathers had later-onset GC were 2.8 younger at diagnosis than patients without a family history, although age at diagnosis of patients with mothers or siblings with later-onset GC was similar to that of patients without a family history.

There are several hypotheses for the relationship between parent history of GC and age at diagnosis. The sharing of environmental risk factors is one possible explanation. The family is the core unit of *H. pylori* transmission, and *H. pylori* is more prevalent among family members of patients with GC. In addition, similar dietary patterns such as high sodium consumption may explain the increased risk of GC in individuals with a family history of the disease[22,23]. Although these factors could increase the risk of GC among the family members, their relationship with early onset of the disease remains unclear. In addition, genes that control the inflammatory response may also contribute to gastric cancer development. In particular, polymorphisms in genes encoding the cytokines interleukin-1β, interleukin-10, and tumor necrosis factor-α have been reported to increase the risk of gastric adenocarcinoma in family members of patients with GC, possibly by inducing hypochlorhydria and atrophic gastritis in response to *H. pylori* infection[24,25].

In diffuse type gastric cancer, 1%-3% of cases with familial clustering meet the criteria for hereditary diffuse gastric cancer caused by CDH1 germline mutations, which appears to increase the risk of early-onset GC[26-28]. We were unable to evaluate tumor histology of the family members because of the retrospective nature of our study; however, hereditary diffuse gastric cancer appears to be uncommon in South Korea[29]. In our study only 13 patients (1.4%) of those with a family history of GC had three or more

affected family members.

In our study, patients with a paternal history of GC developed the disease earlier than patients with other affected first-degree family members. In a study of colorectal cancer, Lindor *et al*[30] explained that preferential inactivation of the maternal X chromosome could unmask the X-linked allele inherited from the father that predisposes the daughter to develop cancer at a younger age. Alternatively, individuals with a family history of cancer may be younger at the time of diagnosis because they are likely to undergo screening earlier than the general population. For example, Claus *et al*[10] reported that women with a family history of breast cancer may be offered more intensive surveillance. Kang *et al*[31] compared GC screening rates, smoking rates, and dietary patterns (*e.g.*, sodium, vitamin, and fiber consumption) between individuals with or without a family history of GC and found that although lifestyle factors (*e.g.*, smoking, diet) did not differ between two groups, those with a family history of GC may undergo screening at a younger age.

In older patients, intestinal-type GC is more common than diffuse GC[32,33]. In addition, patients with a family history of GC were more likely to have intestinal-type GC than patients without a family history[34]. This relationship between histologic type and age at diagnosis is consistent with our finding that patients with a sibling history of GC, who were older at the time of diagnosis than patients without a first-degree family history, were more likely to develop intestinal-type GC than diffuse or mixed type GCs (Table 2). Alternatively, patients with a sibling history may develop intestinal-type GC because of lifestyle factors such as *H. pylori* infection or diet.

Studies of colorectal cancer[2,35], breast cancer[10,35], prostate cancer[35], and lung cancer[35], have found that these cancers develop at a younger age in the offspring of patients with early-onset cancer. These findings were supported by Hemminki *et al*[1], who also reported that age at diagnosis of colon, rectal, uterine, or ovarian cancers in a parent was associated with age at cancer diagnosis in their offspring. Our study also showed that patients who had a parent with early-onset GC were younger at the time of diagnosis than patients without a first-degree family history. In fact, diagnosis before the age of 40 occurred in more than 20% of patients with a parental history of early-onset GC but in only 7.1% of patients without a family history of GC (Table 4). Therefore, we recommend that patients who have a parent with early-onset GC begin surveillance for GC before the age of 40.

Our study has several limitations. First, we obtained information about the age at diagnosis of first-degree family members using a questionnaire, without direct confirmation. Although these answers rely on the patient's memory, family relationships in South Korea are typically close, and age at the time of cancer diagnosis in a family member was usually clearly remembered. Second, we didn't evaluate genetic factors that could be responsible for characteristics of GC.

The finding that patients with a parent history of GC, especially those who had parents with early-onset GC diagnosed before age of 50, were younger at the time of diagnosis supports the need for earlier screening in these individuals, beginning preferably before the age of 40.

COMMENTS

Background

A family history of cancer is associated with earlier age of onset for several cancers, but the association is not clear in gastric cancer (GC).

Research frontiers

This is the first study to evaluate whether individuals with GC are diagnosed earlier if they have first-degree relatives with GC.

Innovations and breakthroughs

The authors classified patients according to presence or absence of first-degree family history of GC and compared age at diagnosis. In addition, we classified patients according to specific family member with GC (father, mother, sibling, or offspring) and compared age at GC diagnosis among these patient groups.

Applications

The finding supports the need for earlier GC screening before the age of 40 in individuals with a parent history of GC, especially those who had a parent with early-onset GC diagnosed before age of 50.

Terminology

The authors defined patients with a first-degree family history of GC as those with specific family member with GC (father, mother, sibling, or offspring). The authors also defined patients having parents with early-onset GC as those whose father or mother was affected before age of 50.

Peer-review

This study compared age at diagnosis in patients with or without a first-degree family history of GC. The mean age at GC diagnosis in patients having paternal history of GC was significantly younger than in those without a first-degree family history (54.4 *vs* 58.1), and patients with a parent diagnosed before 50 years of age developed GC about 10 years earlier than individuals without a family history of GC.

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