ORIGINAL ARTICLE

Gut and Liver, Vol. 14, No. 1, January 2020, pp. 79-88

The Influence of Family History on Stage and Survival of Gastric Cancer According to the *TGFB1* C-509T Polymorphism in Korea

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Background/Aims: The survival rate of gastric cancer (GC) is known to be higher in patients with a family history (FH) of GC. There is an association between a polymorphism in the transforming growth factor-β1 (*TGFB1*) gene and the risk of GC in patients with first-degree relatives with GC. This study was performed to investigate whether a FH affects GC outcomes according to the *TGFB1* C-509T polymorphism. **Methods:** *TGFB1* was genotyped by the polymerase chain reaction-restriction fragment length polymorphism method in 1,143 GC patients, including 216 patients (18.9%) with first-degree relatives with GC. **Results:** The proportion of stage I-II GCs was significantly higher in patients with a FH than in those without a FH of GC (83.8 vs 74.9%, p=0.005). The association between a FH of GC and stage I-II GC was not significant in subgroups divided based on the *TGFB1* C-509T polymorphism and sex. A FH did not affect the overall survival rate of GC in patient with all stages and each stage. The overall survival rates were not significantly different between patients with the CC and CT/TT genotypes of the *TGFB1*-509 polymorphism. **Conclusions:** Patient with a FH of GC had lower cancer stage (I-II) at diagnosis than those without a FH of GC, but there was no significant difference in overall survival between the patients with and without a FH of GC. A FH did not influence the tumor stage or overall survival in patients stratified by the presence of the *TGFB1* C-509T polymorphism. **(Gut Liver 2020;14:79-88)**

Key Words: Transforming growth factor beta1; Polymorphism; Gastric cancer; Family medical history; Sex

INTRODUCTION

Despite the decreasing incidence and mortality of gastric cancer (GC) in recent decades worldwide, GC ranks as the fifth most common cancer in incidence and the third most common cause of death from cancer worldwide.[1] Gastric carcinogenesis is a multistep and a multifactorial process in which *Helicobacter pylori* infection plays a pivotal role,[2] and complex interactions between genetic and environmental factors are involved. Smoking, high consumption of salted and nitrated food, low socioeconomic status and heavy alcohol consumption are known to be independent risk factors for GC.[3,4] Genetic alternations, such as mutations, single nucleotide polymorphisms, and DNA methylation, are associated with the development of GC.[5]

A family history (FH) of GC is also a strong risk factor for GC.[6] Most GCs are sporadic, and approximately 10% of GC shows familial clustering; however, only approximately 1% to 3% of GCs comes from inherited GC predisposition syndromes, such as hereditary diffuse gastric carcinoma and familial adenomatous polyposis.[7] The risk of GC in people with a FH is approximately 3-fold higher than in those without a FH.[6] There are a limited number of studies on the association of a FH with the survival of GC patients.[8-11] A meta-analysis of five studies reported the beneficial effects of a FH on the survival of GC.[12] It is not clear why a FH of GC affects patient survival. People with a FH tend to undertake health screenings early and frequently,[13] and they usually show good health-related behaviors, such as nonsmoking, nonalcoholic drinking, and consistent exercise. In addition, genetic differences, such as microsatellite instability,[8] in FHs may be associated with a good prognosis.

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Received on October 18, 2018. Revised on February 26, 2019. Accepted on March 23, 2019. Published online January 7, 2020.
pISSN 1976-2283 eISSN 2005-1212 https://doi.org/10.5009/gnl18471
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Transforming growth factor-beta (TGF-β) is known to have a dual role of inhibiting and promoting carcinogenesis; TGF-β suppresses the proliferation of normal epithelial and low-invasive cancer cells but enhances the proliferation of highly invasive cancer cells by stimulating angiogenesis and suppressing the immune response. The *TGFB1* C-509T polymorphism, which is in the promoter region of the *TGFB1*, has been found to directly influence its gene expression and is most commonly studied in elucidating its association with the risk of various cancers.[14] For GC, it can be concluded that the *TGFB1*-509T allele is susceptible for GC, although there is inconsistency among studies.[15-18] Our research group have reported that the CT genotype in the *TGFB1*-509 polymorphism was associated with an increased risk in the development of GC (odds ratio [OR], 1.35; 95% confidence interval [CI], 1.07 to 1.71), especially for intestinal-type GC (OR, 1.43; 95% CI, 1.08 to 1.90).[16] In addition, we reported a study of 123 GC patients with a FH and 639 age- and sex-matched control GC patients without a FH; in that study, we found that intestinal-type GC patients with a FH spent their youth in rural areas more frequently (OR, 2.0; 95% CI, 1.0 to 3.9), and had fewer *TGFB1*-509T (OR, 0.5; 95% CI, 0.3 to 0.9) than GC patients without a FH.[19] Ebert *et al*.[20] reported increased TGF-β1 expressions in the gastric mucosa of patients with GC and their first-degree relatives (FDRs) compared with healthy controls. From these results, it is suggested that both genetic polymorphisms and environmental factors affect the carcinogenesis of intestinal-type GC in patients with a FH. Furthermore, we assumed that the CC genotype in *TGFB1*-509 polymorphism might be involved in a better prognosis in patients with a FH of GC.

The incidence rate of GC was generally 2- to 3- folds higher in males than females,[1] and the disparity in the survival between sexes has not been fully evaluated. A recent Korean study showed that female GC patients were significantly younger and associated with signet ring cell carcinoma compared with male patients, and had a significantly poorer overall survival, especially among young patients (aged ≤45 years) with advanced GC.[21] It was concluded that female is a significantly poorer prognostic factor among young patients with signet ring cell carcinoma. Our previous research demonstrated that the effect of obesity on GC showed a sex difference; that is, obesity was related to an increased risk of early GC and well- or moderately differentiated adenocarcinoma in males but not in females.[22] Gastric carcinogenesis appears to differ according to sex. This difference has been explained by environmental factors, including *H. pylori* infection, smoking, and dietary patterns, and hormones such as estrogen.[13,23]

On the basis of these published findings and the distinct roles of TGF-β1, our hypothesis is that a FH of GC would affect the TNM stage of GC, and this influence might be associated with the CC genotype of *TGFB1*-509 polymorphism. To prove this hypothesis, the aim of this study was to investigate the effect of a FH on the TNM stage and overall survival according to the *TGFB1* C-509T polymorphism.

MATERIALS AND METHODS

1. Patients

Between January 2006 and March 2017, 1,228 patients diagnosed with GC by endoscopic examinations were enrolled at the Seoul National University Bundang Hospital, South Korea. All patients were ethnically Koreans. Eighty-five patients were excluded if they met more than one of the following criteria: (1) not GC on final endoscopic or surgical pathology; (2) carcinoma *in situ* on final endoscopic or surgical pathology; (3) incomplete medical records; (4) *TGFB1* genotyping not measured. Eventually, 1,143 GC patients were included. This study protocol was approved by the Ethics Committee at the Seoul National University Bundang Hospital (IRB number: B-1805/471-306).

The gastric mucosa from endoscopic biopsy specimens were examined for histological evaluation, determination of the *H. pylori* infection status and *TGFB1* genotyping. The informed consent was provided to all patients, and they were asked to complete a questionnaire under the supervision of a trained interviewer. The questionnaire included questions regarding age, sex, smoking and drinking habits, history of *H. pylori* eradication, and FH of GC. A "positive family history" was defined as having any FDRs (parent, sibling, or offspring) diagnosed with GC. Clinicopathological data, including final pathological reports and results of computed tomography, were collected using the electronic medical chart system. GCs were staged using the 7th edition of the TNM staging system of the American Joint Committee on Cancer (2010) based on final pathologic examination. Clinical outcomes, such as recurrence or death, were obtained from medical records until the date of death, loss-to-follow-up or March 2017 (end date of the study). The causes of death were ascertained based on medical records and death certificates. Some data on date and causes of death were collected from the Ministry of Public Administration and Security and the National Statistical Office. Overall survival was calculated only in patients who underwent endoscopic and surgical resections with a curative intention and was defined as the time from diagnosis to death resulting from any cause.

2. *H. pylori* infection status

The *H. pylori* infection status was determined by histologic examination with rapid urease test (CLOtest; Delta West, Bentley, Australia), the Giemsa staining and culture.[16] If all the results of these tests were negative, ^{13}C-urea breath test (UBiTkit; Otsuka Pharmaceutical, Tokyo, Japan) and serum immunoglobulin G antibody for *H. pylori* detected by an enzyme-linked immunosorbent assay (Genedia *H. pylori* ELISA; Green Cross Medical Science Corp., Eumseong, Korea) were performed. Negative *H. pylori* infection was defined when all above clinical

tests for *H. pylori* were negative and patients did not have a history of prior *H. pylori* eradication.

3. *TGFB1* genotyping

Genomic DNA was extracted from gastric antral mucosa by proteinase K digestion and phenol/chloroform extraction. The purified DNA was used to determine the genotypes of *TGFB1*-509 using a modified method of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR primers were as followed: 5'-GTA TGG GGT CGC AGG GTG TT-3' (forward) and 5'-CAG ATG CGC TGT GGC TTT GC-3' (reverse). The DNA was initially denatured at 95°C for 5 minutes, followed by 40 cycles of 30 seconds at 95°C, 30 seconds at 62°C, and 30 seconds at 72°C, and the PCR was finished by a final extension cycle at 72°C for 10 minutes. The overnight digestion of the PCR products was performed at 37°C with restriction enzyme, Bsu36I (add bovine serum albumin) for *TGFB1*-509 genotypes (New England BioLabs, Beverly, MA, USA). The DNA fragments were separated on a vertical 2.5% agarose gel and stained with ethidium bromide at 120 V for 45 minutes. The laboratory personnel were blinded to group status.

4. Statistical analysis

Comparisons of demographic and clinicopathologic variables were performed using the Student t-test or chi-square test (Fisher exact test) for continuous variables and categorical variables, respectively. Separate analyses were performed depending on having a FH (with and without a FH) in total, male and female groups. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Multivariate analyses for survival were performed using the Cox proportional hazard model. All analyses were performed using SPSS for Windows, version 22 (IBM Corp., Armonk, NY, USA). The p-values of <0.05 were considered statistically significant.

RESULTS

1. Clinicopathologic characteristics of patients with GC according to a FH

Among the 1,143 patients with GC, 216 (18.9%) had a FH of GC. Table 1 demonstrates the clinicopathologic characteristics of patients. The female proportion was 32.4% (370/1,143). There were no significant differences in age, sex, smoking and drinking, body mass index, blood type, and *H. pylori* infection status between patients with and without a FH in total, male and female groups. The age at diagnosis of GC was not significantly different between patients with and without a FH in all groups. Intestinal-type GCs were not significantly more frequent in patients with a FH than in those without a FH, and there were no statistically significant differences in differentiation, tumor depth and nodal metastasis between patients with and without a FH. In the total patient group, the proportion of distant metastasis was significantly lower in patients with a FH than without a FH (6.5% vs 11.5%, p=0.029). In the total and male groups, the proportion of stage I-II tumors was higher in patients with a FH compared to patients without a FH (total group, 83.8% vs 74.9%, p=0.005; male group, 83.9% vs 75.3%, p=0.026; female group, 86.3% vs 73.9%, p=0.096).

2. Association between a FH of GC and the *TGFB1* C-509T polymorphism

The genotype frequency of *TGFB1*-509 was not significantly different between patients with and without a FH in the total, male and female groups (Table 1). When CT and TT genotypes were combined because those were assumed to have a dominant allele effect, the frequency of T-carriers was also not significantly different between patients with and without a FH of GC (total group, 70.8% vs 85.5%, p=0.092; male group, 73.2% vs 76.0%, p=0.475; female group, 65.7% vs 74.6%, p=0.137). No significant associations between polymorphism and the tumor stage in GC patients according to sex and a FH were observed (Table 2).

3. Overall survival of GC according to a FH and the *TGFB1* C-509T polymorphism

During the follow-up period, 304 patients (26.6%) died, and 39 patients (3.4%) had recurrence of GC. The mean follow-up period was 86.28±46.02 months (range, 12 to 180 months). In the female group, death was significantly lower in patients with a FH than in those without a FH, though the number of deaths was small (13.4% vs 26.4%, p=0.025). A total of 1,030 GC patients underwent endoscopic or surgical resection with a curative intention.

The overall survival rates for GC patients were compared according to a FH and *TGFB1* C-509T polymorphism in total, male and female groups. In the female group, the overall survival rate was better in GC patients with a FH than in those without a FH, but there was no significant difference (p=0.051). In total and male groups, the overall survival rate was not significantly different between patients with and without a FH (total group, p=0.596; male group, p=0.457). The overall survival rates were not significantly different between CC and CT/TT genotypes of *TGFB1*-509 in total, male, and female groups (total group, p=0.341; male group, p=0.204 , and female group, p=0.769).

Next, the overall survival rates were compared in each stage of GC. Fig. 1 shows the overall survival curves according to GC stage in patients with and without a FH. There was no significant difference in the overall survival rates between patients with and without a FH in all stages and each stage (Fig. 2). The overall survival rates were not significantly different between CC and CT/TT genotypes of *TGFB1*-509 in all stages, stage I-II and stage III-IV (Fig. 3). Finally, in subgroup analysis according to a FH and stage of GC, the differences in the overall survival rates were not significant between CC and CT/TT genotypes in

Table 1. Clinicopathologic Characteristics of Patients Stratified by Sex and Family History of Gastric Cancer in First-Degree Relatives

	Total			Male			Female		
	FH (+) (n=216)	FH (–) (n=927)	p-value	FH (+) (n=149)	FH (–) (n=624)	p-value	FH (+) (n=67)	FH (–) (n=303)	p-value
Age, yr	60.42±10.36	60.04±12.42	0.642	60.93±10.12	60.83±11.41	0.914	59.27±10.87	58.41±14.18	0.581
<40	8 (3.7)	53 (5.7)	0.440	3 (2.0)	19 (3.0)	0.763	5 (7.5)	34 (11.2)	0.592
≥40&<60	89 (41.2)	358 (38.6)		60 (40.3)	241 (38.6)		29 (43.3)	117 (38.6)	
≥60	119 (55.1)	516 (55.7)		86 (57.7)	364 (58.3)		33 (49.3)	152 (50.2)	
Sex			0.637						
Male	149 (67.3)	624 (69.0)							
Female	67 (32.7)	303 (31.0)							
Smoking*			0.620			0.507			0.383
Current/ex-smoker	133 (61.9)	568 (63.7)		126 (84.6)	526 (86.7)		7 (10.6)	42 (14.7)	
Nonsmoker	82 (38.1)	324 (36.3)		23 (15.4)	81 (13.3)		59 (89.4)	243 (85.3)	
Drinking*			0.984			0.776			0.548
Drinker	152 (70.7)	630 (70.6)		125 (83.9)	500 (82.9)		27 (40.9)	130 (45.0)	
Nondrinker	63 (29.3)	262 (29.4)		24 (16.1)	103 (17.1)		39 (59.1)	159 (55.0)	
BMI, kg/m^2*	23.37±3.21	23.11±3.13	0.283	23.49±2.88	23.21±2.94	0.305	23.11±3.85	22.90±3.49	0.667
<23	87 (42.6)	380 (45.4)	0.631	53 (38.1)	234 (41.5)	0.635	34 (52.3)	146 (53.5)	0.967
≥23&<25	63 (30.9)	231 (27.6)		48 (34.5)	172 (30.5)		15 (23.1)	59 (21.6)	
≥25	54 (26.5)	226 (27.0)		38 (27.3)	158 (28.0)		16 (24.6)	68 (24.9)	
Blood type			0.659			0.450			0.723
B blood	46 (21.3)	185 (20.0)		34 (22.8)	125 (20.0)		12 (17.9)	60 (19.8)	
Non-B blood	170 (78.7.3)	742 (80.0)		115 (77.2)	499 (80.0)		55 (82.1)	243 (80.2)	
H. pylori infection			0.281			0.832			0.086
Positive	187 (86.6)	775 (83.6)		125 (83.9)	519 (83.2)		62 (92.5)	256 (84.5)	
Negative	29 (13.4))	152 (16.4)		24 (16.1)	105 (16.8)		5 (7.5)	47 (15.5)	
Lauren histotype			0.409			0.744			0.409
Intestinal	132 (61.1)	538 (58.0)		100 (67.1)	410 (65.7)		32 (47.8)	128 (42.2)	
Diffuse or mixed	84 (38.9)	389 (42)		49 (32.9)	214 (34.3)		35 (52.2)	175 (57.8)	
Differentiation			0.448			0.635			0.598
Differentiated†	128 (59.3)	523 (56.4)		96 (64.4)	389 (62.3)		32 (47.8)	134 (44.2)	
Undifferentiated‡	88 (40.7)	404 (43.6)		53 (35.6)	235 (37.7)		35 (52.2)	169 (55.8)	
Depth of invasion*			0.284			0.468			0.412
pT1-T2	167 (79.1)	643 (75.6)		114 (79.2)	435 (76.3)		53 (79.1)	208 (74.3)	
pT3-T4	44 (20.9)	207 (24.4)		30 (20.8)	135 (23.7)		14 (20.9)	72 (25.7)	
Lymph node metastasis*			0.197			0.213			0.633
pN0	117 (68.8)	425 (63.5)		78 (69.6)	280 (63.3)		39 (67.2)	145 (63.9)	
pN1-N3	53 (31.2)	244 (36.5)		34 (30.4)	162 (36.7)		19 (32.8)	82 (36.1)	
Distant metastasis			0.029			0.096			0.140
Absent	202 (93.5)	820 (88.5)		138 (92.6)	548 (87.8)		64 (95.5)	272 (89.8)	
Present	14 (6.5)	107 (11.5)		11 (7.4)	76 (12.2)		3 (4.5)	31 (10.2)	
TNM stage									
I&II	181 (83.8)	694 (74.9)	0.005	125 (83.9)	470 (75.3)	0.026	56 (83.6)	224 (73.9)	0.096
III&IV	35 (16.2)	233 (25.1)		24 (16.1)	154 (24.7)		11 (16.4)	79 (26.1)	

Table 1. Continued

	Total			Male			Female		
	FH (+) (n=216)	FH (–) (n=927)	p-value	FH (+) (n=149)	FH (–) (n=624)	p-value	FH (+) (n=67)	FH (–) (n=303)	p-value
TGFB1 C-509T polymorphism			0.256			0.633			0.274
CC	63 (29.2)	227 (24.5)		40 (26.8)	150 (24.0)		23 (34.3)	77 (25.4)	
CT	104 (48.1)	500 (53.9)		76 (51.0)	345 (55.3)		28 (41.8)	155 (51.2)	
TT	49 (22.7)	200 (21.6)		33 (22.1)	129 (20.7)		16 (23.9)	71 (23.4)	
Resection			-			-			-
Endoscopic	56 (25.9)	215 (23.2)		43 (28.8)	155 (24.8)		13 (19.4)	60 (19.8)	
Surgical	148 (68.5)	611 (65.9)		97 (65.1)	400 (64.1)		51 (76.1)	219 (72.2)	
No	12 (5.6)	101 (10.9)		9 (6.1)	69 (11.1)		3 (4.5)	32 (8.0)	
Follow-up period, mo	88.96±43.52	85.66±48.58		83.64±44.44	85.73±46.54	0.618	100.79±39.24	85.5±46.75	0.006
Death	50 (23.1)	254 (27.4)	0.203	41 (27.5)	174 (27.9)	0.928	9 (13.4)	80 (26.4)	0.025
Recurrence	9 (4.2)	30 (3.2)	0.498	6 (4.0)	24 (3.8)	0.918	3 (4.5)	6 (2.0)	0.211

Data are presented as mean±SD or number (%).
FH, family history; BMI, body mass index; *H. pylori*, *Helicobacter pylori*; pT, tumor depth; pN, lymph node metastasis.
*Patients with incomplete records were excluded; †Includes well- or moderately differentiated adenocarcinoma; ‡Includes poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, papillary adenocarcinoma, mucinous adenocarcinoma, adenosquamous carcinoma and undifferentiated adenocarcinoma.

Table 2 Comparison of TNM Stages of Gastric Cancer Stratified by a FH and the Presence of the *TGFB1* C509T Polymorphism

	Total				Male				Female			
	FH (+)		FH (–)		FH (+)		FH (–)		FH (+)		FH (–)	
	CC	CC/TT	CC	CC/TT	CC	CC/TT	CC	CC/TT	CC	CC/TT	CC	CC/TT
Stage I&II	49 (77.8)	132 (86.3)	170 (74.9)	524 (74.9)	30 (75.0)	95 (87.2)	113 (75.3)	357 (75.3)	19 (82.6)	37 (84.1)	57 (74.0)	167 (73.9)
Stage III&IV	14 (22.2)	21 (13.7)	57 (25.1)	57 (25.1)	10 (25.0)	14 (12.8)	37 (24.7)	117 (24.7)	4 (17.4)	7 (15.9)	20 (26.0)	59 (26.1)
p-value	0.123		0.992		0.074		0.997		0.876		0.982	

Data are presented as number (%).
FH, family history.

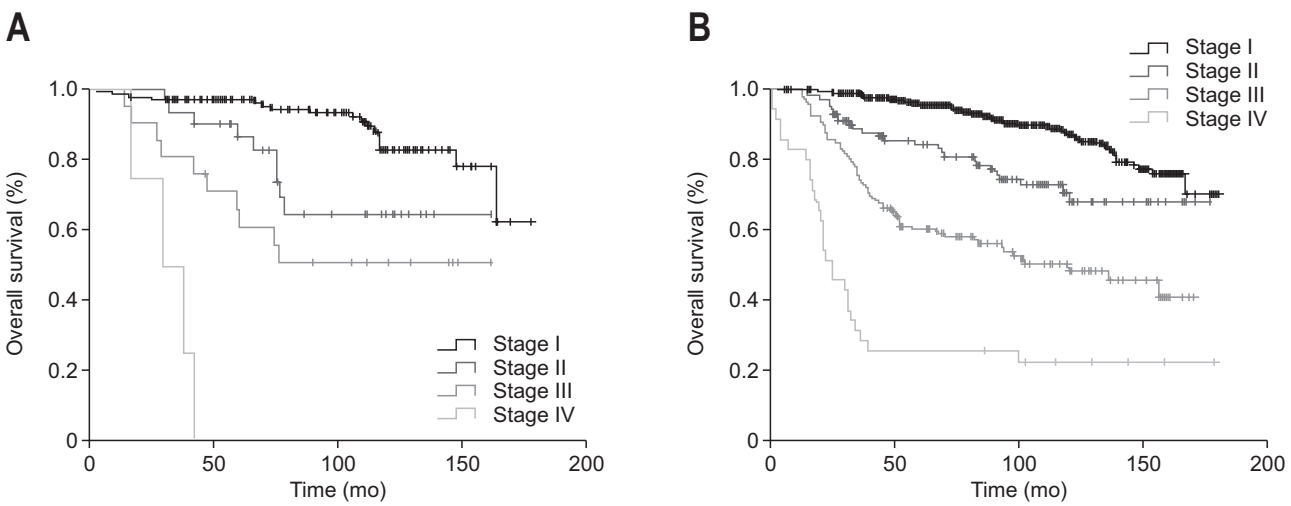

Fig. 1. The overall survival curves according to the stage of gastric cancer in patients with (A) and without a family history of gastric cancer (B).

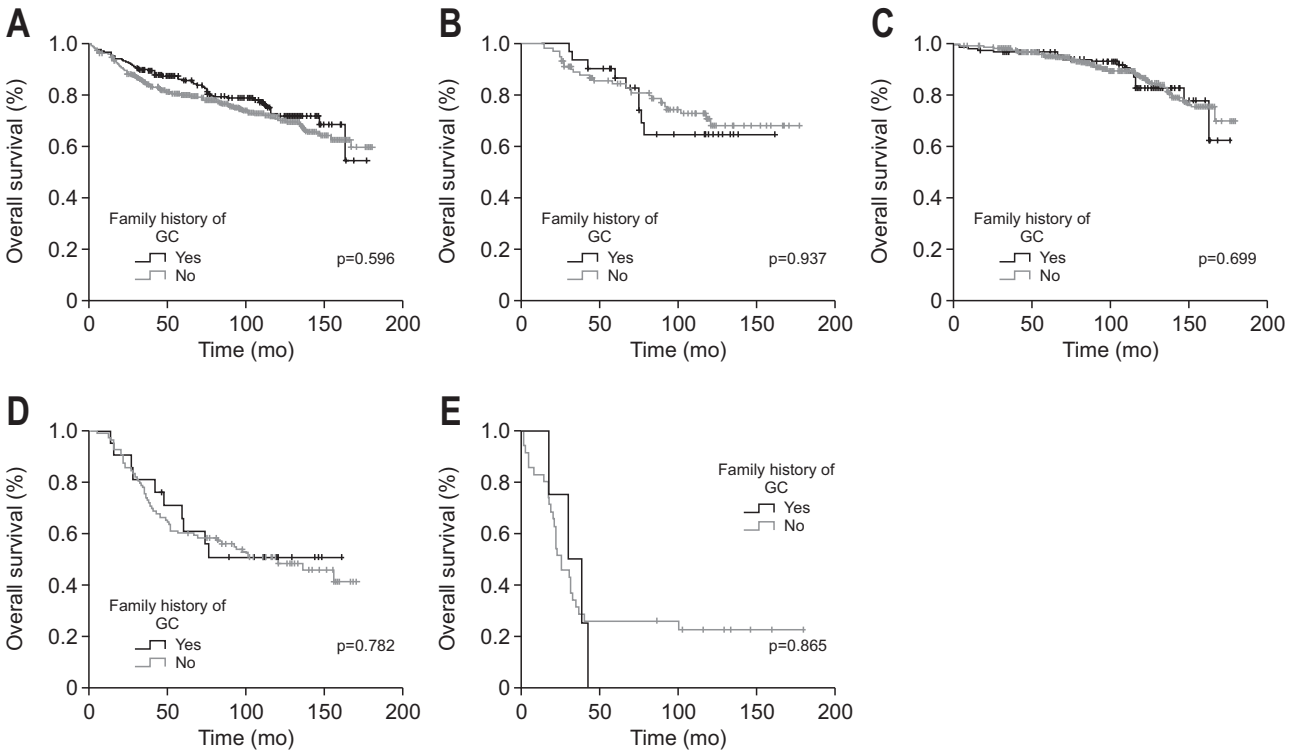

Fig. 2. Comparison of overall survival between patients with and without a family history of gastric cancer (GC) with all stages (A), stage I (B), stages II (C), stage III (D), and stage IV (E).

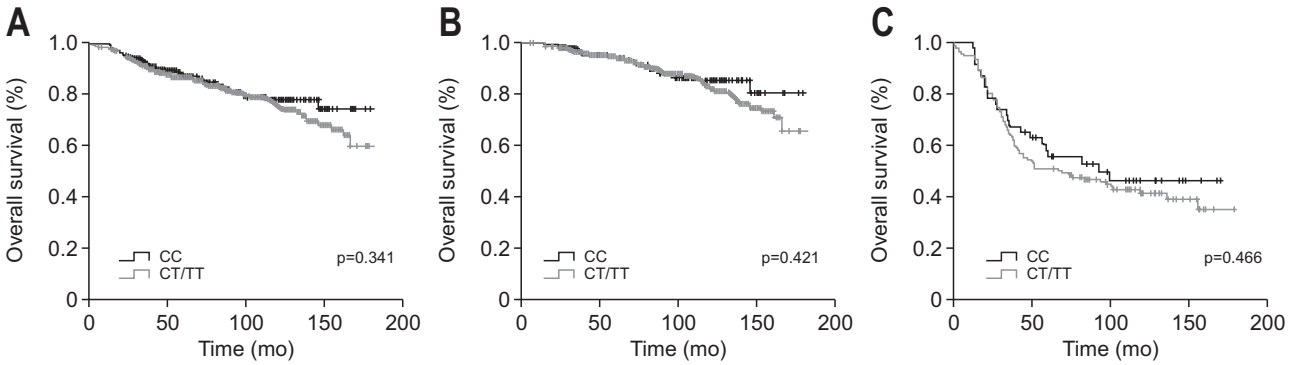

Fig. 3. Comparison of overall survival in patients with the CC and CT/TT genotypes of the *TGFB1*-509 polymorphism in all stages of gastric cancer (A), stages I-II (B), and stages III-IV (C).

patients with and without a FH (Fig. 4).

Multivariate analyses using Cox proportional hazards model to investigate whether FH of GC and genotypes *TGFB1*-509 polymorphism affected the overall survival revealed that age, T stage, N stage, M stage, and *H. pylori* infection were independent prognostic factors for overall survival. However, FH of GC and CC genotype were not independent risk factors for overall survival (p=0.708 and p=0.728, respectively) (Table 3).

DISCUSSION

We found that patients with a FH had more stage I-II GCs than those without a FH in total and male patient groups; however, except for tumor stage, there were no significant differences in the other characteristics between the patients with and without a FH. The overall survival rates of GC were not significantly different between patients with and without a FH. The association between a FH and stage I-II GC was not significant according to the *TGFB1* C-509T polymorphism. Regarding the *TGFB1* C-509T polymorphism, tumor stage and overall survival were not different between CT/TT and CC genotypes according to sex and a FH. In addition, FH of GC and CC genotype were not independent risk factors for overall survival.

Previous studies have shown conflicting results on the as-

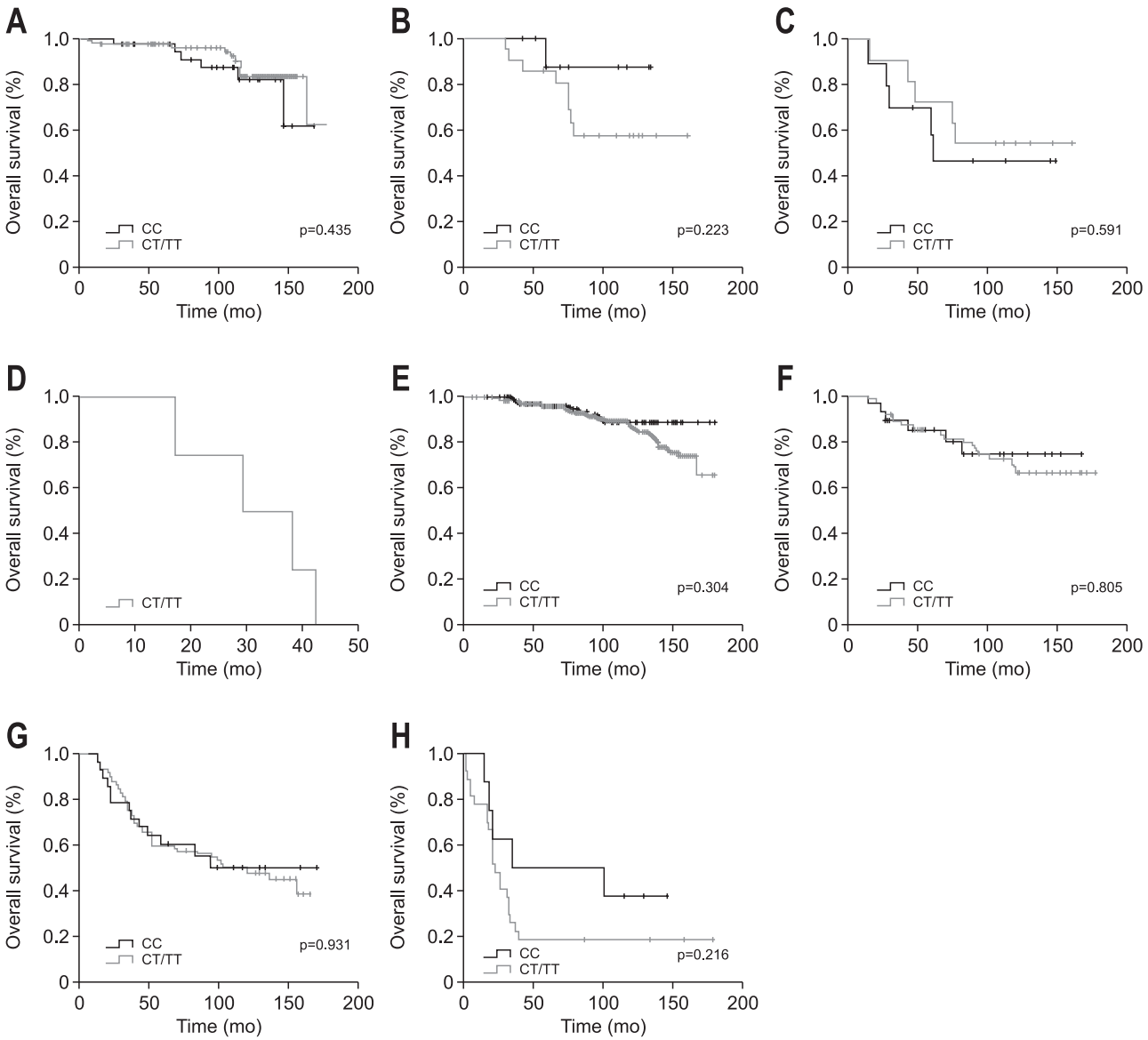

Fig. 4. Comparison of overall survival in patients stratified by family history of gastric cancer and genotypes of *TGFB1*-509 polymorphism. The overall survival curves of patients with a family history of gastric cancer are shown for those with stage I (A), stage II (B), stage III (C), and stage IV (D). The overall survival curves of patients without a family history of gastric cancer are shown for those with stage I (E), stage II (F), stage III (G), and stage IV (H).

sociation of a FH with GC survival.[8-10,24,25] A Korean study of 1,273 patients with GC showed that a FH was associated with a reduced risk of recurrence and death in patients with stage III-IV GC but was limited by the small number of patients in the stage III-IV group (only 48 patients with a FH) and the inclusion of 51 patients with second-degree relatives of GC.[8] By contrast, a recent large Korean study with 2,736 patients reported that the disease-specific survival rate was not significantly different between patients with and without a FH in all stages, but this study also included first- or second-degree relatives with GC.[25] The strength of the present study is that it is the largest study to investigate the clinicopathological features and survival of patients with only FDRs of GC.

In the present study, patients with a FH were not younger, and patients with a FH did not have a better survival though they had a less advanced tumor stage. In particular, the distant metastasis rate in GC patients with a FH was significantly lower than in those without a FH, and this result might be associated with an earlier diagnosis in patients with a FH due to early and frequent health screening. Korean and Italian studies reported that intestinal-type GCs were more frequent in patients with a FH than in patients without a FH,[8,9] which might explain the favorable prognosis of GC patients with a FH. However, our study showed that the proportion of intestinal type GC was not significantly different between patients with and without a FH. The overall survival rates in the female patient group with a FH

Table 3. Multivariate Analysis of Overall Survival of Patients with Gastric Cancer Using a Cox Proportional Hazards Regression Model

Variable	Hazard ratio	95% CI	p-value
Age	1.045	1.031–1.059	0.000
Sex (male vs female)	1.168	0.726–1.880	0.523
Smoking (current/ex-smoker vs nonsmoker)	0.829	0.523–1.313	0.424
Drinking (drinker vs nondrinker)	1.044	0.734–1.486	0.810
Body mass index (≥25 kg/m^2 vs <25 kg/m^2)	0.836	0.578–1.209	0.340
Family history of gastric cancer (positive vs negative)	0.952	0.641–1.415	0.808
H. pylori infection (positive vs negative)	0.648	0.452–0.928	0.018
Lauren histiocyte (diffuse/mixed vs intestinal)	1.115	0.809–1.537	0.504
T stage (T3-T4 vs T1-T2)	2.196	1.498–3.220	0.000
N stage (N1-N3 vs N0)	2.354	1.609–3.444	0.000
M stage (M1 vs M0)	4.025	2.511–6.452	0.000
TGFB1 C-509T polymorphism (CC vs CT+TT)	1.066	0.744–1.527	0.728

CI, confidence interval; *H. pylori*; *Helicobacter pylori*.

tended to be better than those without a FH without significant differences. The number of deaths in the female group was only nine (13.4%). The small number of female patients might be insufficient to prove significance, and the effects of a FH might be significant in a study with a large number of patients.

The molecular pathogenesis associated with GC in patients with a FH of GC has not to be elucidated yet. We hypothesize that genetic differences, such as the *TGFB1* polymorphism, might be associated with the prognosis of GC in patients with a FH. Disappointingly, the overall survival was not significantly different according to the *TGFB1* C-509T polymorphism. Additionally, the association between a FH and stage I-II GC was not significant according to this polymorphism and sex. Many studies have concluded that T allele carriers of the *TGFB1* C-509T polymorphism have an increased risk of GC development.[15-18] The possibility of using *TGFB1* polymorphisms as predictive biomarkers has been studied in other types of cancer. The T allele carriers of the *TGFB1* C-509T polymorphism had a lower 5-year disease-free survival rate in breast cancer,[26] and the TT genotype of the *TGFB1*-509 polymorphism was found to be associated with an increased risk of aggressive prostate cancer[27] and shorter median survival in colorectal cancer.[28] There have been a few studies on the relationship between the *TGFB1* polymorphism and the prognosis of GC. A Chinese case control study reported an association between the C-509T polymorphisms and an increased risk for stage III-IV GC.[29] Some studies reported that increased TGF-β1 expression was associated with poor prognosis of GC.[30,31] In another study, significantly favorable overall survival was demonstrated in the patients with elevated serum TGF-β1 concentrations.[32] However, these studies were conducted on a small sample size, thus may have been insufficient to lead to significant conclusions. To the best of our knowledge, this is the first study to elucidate the association between the *TGFB1* C-509T polymorphism and GC survival. Multiple causative factors involved in the progression of GC and various polymorphisms affect TGF-β1 production.[33] The functional significance of many *TGFB1* polymorphisms remains unclear, and further larger studies are needed to justify such polymorphisms as prognostic biomarkers.

Gastric carcinogenesis might be different according to sex. Male dominance of GC has been well known,[23] and our group previously reported that the effect of obesity on GC was different between sexes.[22] The known environmental risk factors between males and females did not explain this difference enough, and a possible role of sex hormones was suggested. Estrogen acts through estrogen receptors (ERs) that have genomic and nongenomic effects. Genomic effects appear through estrogen responsive elements located at the promotor of target genes, and it affects transcription factors such as AP-1 and Sp-1.[34] Nongenomic effects are mediated through protein-kinase cascades.[34] There has been much evidence on a protective role of estrogen in GC,[13] which might be mediated through ERα and ERβ,[35,36] and some studies have suggested prognostic importance of ERβ in GC.[37,38] The roles of estrogen in colorectal cancers were elucidated more clearly, and ERβ prevents the tumorigenesis of colorectum by regulating mismatch repair gene expression and inducing apoptosis while suppressing the proliferation and inflammatory response.[34,39] From these results, all analyses were conducted according to sex; however, there were no significant differences between sexes.

In the present study, the mean age at diagnosis of GC in patients with a FH was similar to that in patients without a FH (60.42±10.36 years vs 60.04±12.42 years), but this age gap between with and without a FH of GC was not much different compared to other studies.[8,40] The National Cancer Center in Korea reported that the mean age at diagnosis of GC in patients with a FH was even higher than that for sporadic cancer (57.1 years vs 58.1 years). Fang *et al*.[40] showed that patients with a

FH had a better survival rate as they were younger (65.4 years vs 54.1 years) and had a less advanced tumor stage and that a FH had no direct effect on GC survival; however, the familial GC patients in that study were enrolled on the basis of the strict definition. A lack of awareness of the extent to which GC is familial might exist. The term "familial" often is used as a meaning of only a positive FH, while "hereditary" indicates alterations in specific genes, and a gene defect can be determined in only 1% to 3% of cases. There is a possibility that those with inherited GC might be included into general GC with a FH, but this possibility accounts for a very small percentage of familial clustering.

A major limitation of the present study was that a FH of GC was self-reported. However, self-reporting of having a FH with respect to cancer is reasonably accurate, especially for FDRs.[41] Therefore, any information bias would not likely be significant. The questionnaire covering FH of GC was given to each subject on the day of admission before any definite diagnosis, but it was not given at every visit; thus, there might be subjects who have affected family members with GC after enrollment. In addition, we could not include the data on age at initial endoscopy and intervals of endoscopic screening, which might be different according to a FH.

In conclusion, patients with a FH had lower cancer stage (I-II) at diagnosis than those without a FH. However, no survival differences between the patients with and without a FH were observed. The *TGFB1* C-509T polymorphism did not influence the tumor stage and survival. The influence of a FH on the tumor stage and overall survival was not significant according to the *TGFB1* C-509T polymorphism. Although this result was negative, further studies in larger cohorts are needed to clarify the exact role of a FH in GC prognosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by the Seoul National University Bundang Hospital Research fund (grant number: 13-2018-002) and by the National Research Foundation (NRF) of Korea grant for the Global Core Research Center (GCRC) funded by the Korea government (MSIP) (number: 2011-0030001).

AUTHOR CONTRIBUTIONS

Study concept and design: N.K. Data acquisition: M.K. Data analysis and interpretation: H.J.K. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: H.J.K. Statistical analysis: J.B.L. Obtained funding: N.K., S.W. Administrative, technical, or material support; study supervision: N.K.

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