Korean J Gastroenterol Vol. 71 No. 6, 338-348
https://doi.org/10.4166/kjg.2018.71.6.338
pISSN 1598-9992 eISSN 2233-6869

ORIGINAL ARTICLE

소화기암 가족력이 소화기암 발생에 미치는 위험 평가

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Gastrointestinal cancer risk in patients with a family history of gastrointestinal cancer

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Background/Aims: This study was performed to evaluate the relationship between family history of gastrointestinal (GI) cancers and incidence of any GI cancer in the Korean population.
Methods: Between January 2015 and July 2016, 711 GI cancer patients and 849 controls in 16 hospitals in Korea were enrolled. Personal medical histories, life styles, and family history of GI cancers were collected via questionnaire.
Results: There was a significant difference in the incidence of family history of GI cancer between GI cancer patients and controls (p=0.002). Patients with family history of GI cancer tended to be diagnosed as GI cancer at younger age than those without family history (p=0.016). The family members of GI cancer patients who were diagnosed before 50 years of age were more frequently diagnosed as GI cancer before the age of 50 years (p=0.017). After adjusting for major confounding factors, age (adjusted odds ratio [AOR] 1.065, 95% confidence interval [CI]; 1.053-1.076), male gender (AOR 2.270, 95% CI; 1.618-3.184), smoking (AOR 1.570, 95% CI; 1.130-2.182), and sibling's history of GI cancer (AOR 1.973, 95% CI; 1.246-3.126) remained independently associated with GI cancers.
Conclusions: GI cancer patients tended to have a first relative with a history of concordant GI cancer. Personal factors (old age and male) and lifestyle (smoking) contribute to the development of GI cancer, independently. Individuals with high risk for GI cancers may be advised to undergo screening at an earlier age. **(Korean J Gastroenterol 2018;71:338-348)**

Key Words: Gastrointestinal neoplasm; Medical history taking; Risk factors

Received February 4, 2018. **Revised** March 27, 2018. **Accepted** April 13, 2018.

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Financial support: This research was supported by Policy Research Program funded by Korean Society of gastrointestinal cancer.
Conflict of interest: None.

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INTRODUCTION

Previous studies have consistently suggested that family history of gastrointestinal (GI) cancer is an important risk factor for the concordant type of GI cancer. The risk of esophageal cancer (EsoCa) is about 7 times higher in subjects with first-degree relatives (FDR) with history of EsoCa,[1] and individuals with family history of gastric cancer (GC) have three times higher risk of developing GC than those without such history.[2] Furthermore, the risk of colorectal cancer (CRC) is 2-6 times higher, depending on the number of affected family members and ages at CRC onset.[3] Independent of hepatitis B virus (HBV) and hepatitis C virus, family history of hepatocellular carcinoma (HCC) was shown to be associated with four times the greater risk of HCC, and this risk was significantly increased by up to 62 times in those with two or more affected family members.[4] On the other hand, familial pancreatic cancer (PC) is only observed in a minority (10%) of PC cases, but a sibling history of PC increases the risk by more than 5-fold.[5]

Only a few studies have reported the relationship of different GI cancers within family members.[6] Different types of GI cancer can occur within family members since several risk factors, including smoking and alcohol, are common to most GI cancers, and genetic mutations may be observed in different GI cancers. Recent studies revealed that GI cancer survivors have an increased risk of different types of GI cancer.[7-9] If GI cancers share common carcinogenesis, family history of GI cancer may also be an important risk factor for the various types of GI cancers.

Therefore, we conducted this study to assess the risks factors for GI cancer in subjects with family history of GI cancer, and to determine how individual cancers are related to family histories in the Korean population.

SUBJECTS AND METHODS

1. Study population

The study was performed as a multi-center study by the Korean Society of Gastrointestinal Cancer, involving 16 medical institutions and hospitals; CHA Bundang Medical Center, Chonnam National University Hospital, Chungbuk National University Hospital, Dongguk University Ilsan Medical Center, Gangnam Severance Hospital, Konyang University Hospital, Korea Cancer Center Hospital, Korea University Medical Center, Kosin University Gospel Hospital, National Medical Center, Myongji Hospital, Severance Hospital, Soonchunhyang University Hospital, and Wonkwang University Sanbon Hospital. Patients who were admitted to a tertiary hospital for benign or malignant disease, between January 2015 and July 2016, were considered eligible for the study. Included patients were ≥18 years of age, and all underwent an interview on health behaviors and family history. Subjects were 711 individuals who had previously been diagnosed with GI cancer on one occasion, and 849 controls, who were admitted for a benign condition. All participants provided written consent, and the study was approved by the institutional review of boards of the participating institutions.

2. Questionnaire

Participants were interviewed using a structured ques-

Table 1. Demographics of the Study Subjects

	Controls (n=849)	GI cancer patients (n=711)	p-value
Age (years)	53.06±15.64	64.87±10.64	<0.001
Sex			
Male	392 (46.2%)	503 (70.7%)	<0.001
Female	457 (53.8%)	208 (29.3%)	
BMI (kg/m^2)	23.18±3.44	22.77±3.24	0.015
Marital status			
Never married	163 (19.2%)	35 (4.9%)	<0.001
Ever married	686 (80.8%)	676 (95.1%)	
Life style			
Alcohol consumption			
Less than 1/week	567 (66.9%)	463 (65.8%)	0.582
More than 1/week	281 (33.1%)	241 (34.2%)	
Smoking			
Never-smoker	532 (62.7%)	269 (37.9%)	<0.001
Current or Ex-smoker	316 (37.3%)	440 (62.1%)	
Physical activity			
More than 1/week	456 (53.8%)	385 (54.2%)	0.434
Less than 1/week	392 (46.2%)	325 (45.8%)	
Diet habit			
Salty diet	353 (41.6%)	311 (43.8%)	0.376
Meat rich diet	363 (42.8%)	315 (44.4%)	0.523
Vegetable poor diet	224 (26.4%)	210 (29.6%)	0.165
Medical history			
Hypertension	209 (24.6%)	259 (36.4%)	<0.001
Diabetes mellitus	100 (11.8%)	141 (19.8%)	<0.001
Chronic liver disease	133 (15.7%)	123 (17.3%)	0.386
B-viral	50 (5.9%)	68 (9.6%)	0.006
C-viral	13 (1.5%)	17 (2.4%)	0.218
Fatty liver	26 (3.1%)	13 (1.8%)	0.12
Alcoholic hepatitis	42 (4.9%)	24 (3.4%)	0.125

GI, gastrointestinal; BMI, body mass index; B-viral, viral hepatitis B; C-viral, viral hepatitis C.

tionnaire, designed by the writers to classify individuals according to their risk for GI cancer. It contains items about demographic characteristics, lifestyle habits (smoking, alcohol consumption, and physical activity), dietary habits (salty food, meat-rich food, and vegetable-rich food), and personal medical history (hypertension, diabetes mellitus, and liver disease). Questions on family history included numbers of siblings and children, marital status, and history of familial GI cancer. In this study, only the family histories of cancer in first-degree relatives were considered. The questionnaire was modified in English and showed as a supplement Table 1.

3. Statistical analysis

Continuous variables are reported as means±standard deviations and group comparisons were performed using Wilcoxon's rank sum test (or Student's t test). Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. To identify independent factors associated with development of GI cancer, explanatory items were selected by univariate analysis, and subsequently subjected to multivariate logistic regression analysis. Adjusted odds ratios (AOR) were calculated to measure degrees of associations, and Hosmer-Lemeshow goodness-of-fit analysis was used to calibrate multivariate logistic regression. For subgroup analysis, GI cancer patients were subdivided into an esophago-gastric cancer (EG ca) group, a CRC group, a HCC group, or a pancreatobiliary cancer (PB ca) group. Patients in these groups were compared with controls to identify risk factors. p-values of <0.05 were considered significant, and all statistical tests were 2-sided. The analysis was performed using SPSS ver. 18.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

The pooled study population included 849 controls and 711 GI cancer patients; characteristics are provided in Table 1. The mean age of GI cancer patients (64.87±10.64 years) was older than that of controls (53.06±15.64 years, p<0.001), and there was a significant difference in sex distribution between two groups (p<0.001). GI cancer patients were more likely to be thinner, married and smokers (p<0.05). Controls and GI cancer patients did not differ with regard to alcohol consumption, physical activity, or diet habits. Hypertension and diabetes were more frequent in GI cancer patients (p<0.05).

Table 2 presents a summary of the family histories of GI cancer in controls and GI cancer patients. Having a family member with history of GI cancer increased the risk (odds ratio [OR] 1.444, 95% confidence interval [CI]; 1.148-1.816) of GI cancer. OR for GI cancer was 2.642 (95% CI; 1.880-3.714) and 5.429 (95% CI; 1.169-25.211) in patients with sibling and child with GI cancer, respectively. However, parental histories of GI cancer were similar in patients (14.3%) and controls (17.0%, p=0.159). No difference was observed between patients and controls with respect to family history of early diagnosed GI cancer (18.1% vs. 12.8%, p=0.156) or whether more than one family member had been diagnosed with GI

Table 2. Distributions of GI Cancer Patients and Controls According to a Family History of GI Cancer

	Controls (n=849)	GI cancer patients (n=711)	p-value	Odds ratio	95% CI
A family history of GI cancer	187 (22.0%)	206 (29.0%)	0.002	1.444	1.148-1.816
Parent	144 (17.0%)	102 (14.3%)	0.159	0.82	0.622-1.080
Sibling	55 (6.5%)	110 (15.5%)	<0.001	2.642	1.880-3.714
Child	2 (0.2%)	9 (1.3%)	0.031	5.429	1.169-25.211
Diagnosed age of family members					
<50 years old	23 (12.8%)	36 (18.1%)	0.156	0.663	0.376-1.170
≥50 years old	157 (87.2%)	163 (81.9%)			
Number of affected family members					
One or none	830 (97.8%)	684 (96.2%)	0.073	1.724	0.951-3.128
Two or more	19 (2.2%)	27 (3.8%)			
Types of GI cancer of family members					
Esophagogastric cancer	93 (11.0%)	122 (17.2%)	<0.01	1.684	1.259-2.251
Colorectal cancer	42 (4.9%)	38 (5.3%)	0.723	1.085	0.691-1.702
Hepatocellular carcinoma	41 (4.8%)	47 (6.6%)	0.13	1.395	0.906-2.147
Pancreatobiliary cancer	25 (2.9%)	17 (2.4%)	0.502	0.807	0.432-1.507

GI, gastrointestinal; CI, confidence interval.

cancer (3.8% vs. 2.2%, p=0.073). In family members, EG ca was the most frequent GI cancer (13.8% of the study subjects) followed by CRC (5.1% of the study subjects).

In order to identify the difference of personal and familial factors by the age of GI cancer diagnosis, we divided patients into two groups; patients diagnosed at <50 years were assigned to Group I, and those diagnosed at ≥50 years to Group II. Four GI cancer patients were excluded from this sub-group analysis because age at GI cancer diagnosis was not recorded in the questionnaire. These two groups were then compared with respect to demographics, life styles, and family histories of GI cancer (Table 3). There were 62 patients (8.8%) in group I, and 645 patients (91.2%) in group II. No difference of sex distribution was observed between the two groups. Patients in group I were more likely to be unmarried and HBV carriers, and more likely to consume alcohol and eat

Table 3. Demographics and Family Histories of GI Cancer Patients Aged < or ≥50 Years at Diagnosis

	Group I[a] (n=62)	Group II[b] (n=645)	p-value
Personal factors			
Diagnosed age (years)	43.84±4.90	65.3±9.3	<0.001
Sex			
Male	40 (64.5%)	460 (71.3%)	0.261
Female	22 (35.5%)	185 (28.7%)	
BMI (kg/m^2)	22.81±3.20	22.76±3.24	0.908
Marital status			
Never married	16 (25.8%)	19 (2.9%)	<0.001
Ever married	46 (74.2%)	626 (97.1%)	
Lifestyle			
Frequent alcohol consumption[c]	32 (52.5%)	207 (32.4%)	0.002
Current or Ex-smoker	37 (59.7%)	399 (62.1%)	0.713
Low physical activity[d]	25 (40.3%)	297 (46.1%)	0.382
Dietary habits			
Salty diet	17 (27.4%)	292 (45.3%)	0.007
Meat rich diet	33 (53.2%)	280 (43.5%)	0.14
Vegetable poor diet	15 (24.6%)	193 (30.0%)	0.379
Medical history			
Hypertension	4 (6.5%)	252 (39.1%)	<0.001
Diabetes mellitus	3 (4.8%)	136 (21.1%)	0.002
Chronic liver disease	13 (21.0%)	110 (17.1%)	0.603
B-viral	11 (17.7%)	57 (8.8%)	0.023
C-viral	2 (3.2%)	15 (2.3%)	0.655
Fatty liver	0 (0%)	13 (2.0%)	0.618
Alcoholic hepatitis	1 (1.6%)	23 (3.6%)	0.714
Familial factors			
Family History of GI cancer	21 (33.9%)	183 (28.4%)	0.361
Parental	16 (25.8%)	86 (13.3%)	0.008
Sibling	5 (8.1%)	103 (16.0%)	0.098
Child	0 (0.0%)	9 (1.4%)	>0.999
Diagnosed age of family members			
<50 years old	8 (38.1%)	28 (15.9%)	0.017
≥50 years old	13 (61.9%)	148 (84.1%)	
Number of affected family member			
One or none	59 (95.2%)	621 (96.3%)	0.724
Two or more	3 (4.8%)	24 (3.7%)	
Types of GI cancer of family members			
Esophagogastric cancer	12 (19.4%)	108 (16.7%)	0.274
Colorectal cancer	5 (8.1%)	33 (5.1%)	0.368
Hepatocellular carcinoma	5 (8.1%)	42 (6.5%)	0.594
Pancreatobiliary cancer	2 (3.2%)	15 (2.3%)	0.655

GI, gastrointestinal; BMI, body mass index.
[a]Group I contained GI cancer patients diagnosed at <50 years old; [b]Group II contained GI cancer patients diagnosed at ≥50 years old; [c]Frequent alcohol consumption means alcohol consumption more than one per week; [d]Low physical activity means physical activity less than one per week.

meat-rich diet (p<0.05). Family histories of GI cancer were not different between the two groups, but twice as many patients (38.1%) in group I had a family member who had diagnosed as GI cancer at younger than 50 years of age (group II, 15.9%, p=0.017). Notably, a higher incidence of parental GI cancer was observed in group I (25.8% vs. 13.3%, p=0.008).

The results of multivariate analysis for the risk of GI cancer are summarized in Table 4. When variables found to be significant by univariate analysis were subjected to multiple logistic regression analysis, only four showed significance. Specifically, the risk of GI cancer was positively associated with age (AOR 1.065, 95% CI; 1.053-1.076), male gender (AOR 2.270, 95% CI; 1.618-3.184), smoking (AOR 1.570, 95% CI; 1.130-2.182), and diagnosis of GI cancer in a sibling (AOR 1.973, 95% CI; 1.246-3.126). After adjusting for significant factors, family history of GI cancer, marital status, hypertension, and diabetes were not found to be related to an increase in the risk of GI cancer.

For subgroup analysis, GI cancer patients were classified according to cancer sites as EG ca, CRC, HCC, and PB ca, and compared with controls (Table 5). EG ca was the most common GI cancer in the present study (311 patients, 43.7%), followed by CRC (188 patients, 26.4%), and PB ca (130 patients, 18.3%). Seven patients had double primary GI cancer.

In the EG ca group (n=311), patients were more likely to be older, married, male, consume alcohol, smoke, and consume salty foods than the controls (p<0.05). Two or more family members with a history of GI cancer tended to be associated with the risk of EG ca (AOR 2.214, 95% CI; 1.111-4.413). Subjects with sibling (AOR 2.898, 95% CI; 1.935-4.342) or child (AOR 5.518, 95% CI; 1.006-30.277) with GI cancer had significantly higher risk of EG cancer, while parental GI cancer history was not significantly related to EG ca (AOR 0.916, 95% CI; 0.643-1.304).

Age, male, marital status, and smoking showed significant associations with CRC patients than with controls, but dietary habits, physical activity, and alcohol drinking did not show any association. The GI cancer history of the sibling's is significantly higher in CRC patients than in the controls (AOR 2.421, 95% CI; 1.482-3.955).

In the HCC group (n=89), 27 HCC patients (30.3%) had more family members with a history of GI cancer compared with the controls (22.8%, p=0.77). HCC patients (22.5%) showed a significantly positive family history of HCC (AOR 5.712, 95% CI; 3.172-10.288). The incidences of chronic viral hepatitis (HBV and hepatitis C virus carrier) and alcoholic hepatitis were significantly increased in this group.

In the PB group (n=130), history of GI cancer in a child was the only aspect of family history found to be associated with PB ca (AOR 10.004, 95% CI; 1.655-60.453). History of PB ca among family members was not significantly higher in the PB ca group (4.6%) than in the controls (2.9%) (AOR 1.595, 95% CI; 0.641-3.965). However, the presence of one type of GI cancer did not show a significant association with the discordant types of GI cancer in a family.

Table 4. Independent Risk Factors Associated with GI Cancer as Determined by Multivariate Analysis

	p-value	AOR	95% CI
Age	<0.001	1.065	1.053-1.076
Sex (male)	<0.001	2.270	1.618-3.184
Ever-smoker	0.007	1.570	1.130-2.182
GI cancer history of sibling	0.004	1.973	1.246-3.126
Hypertension	0.396	1.119	0.863-1.453
Diabetes	0.378	1.153	0.841-1.580
Ever-married	0.203	1.342	0.853-2.114
GI cancer history of children	0.176	3.072	0.604-15.623
GI cancer history of family	0.665	1.075	0.774-1.494

Four factors (family history of GI cancer, marital status, hypertension, and diabetes) did not show any significance.
GI, gastrointestinal; AOR, adjusted odds ratio; CI, confidence interval.

DISCUSSION

In this study, patients with GI cancer tended to have FDR with a history of GI cancer, but this association was usually observed for concordant GI cancer types. Even in the case of PB cancer, no significant association was observed between patients and a family history of PB cancer. GI cancer of siblings was most closely related to the development of GI cancer. We can presume this phenomenon to be the result of limited medical record access for parents, and the patients' children were too young to have developed GI cancer in time of the survey. Nonetheless, our findings indicate that research on familial history of GI cancer over multiple generations is mandatory.

Increased risk of GI cancer in subjects with affected family members may be due to shared genetic susceptibility.[10] Tumors arise as a consequence of the accumulation of mutations as well as deregulations of genes involved in signaling

Table 5. The Family History and the Risk of Each Type of GI Cancer

	Control (n=849)	EG ca (n=311)			CRC (n=188)			HCC (n=89)			PB ca (n=130)		
			AOR	95% CI		AOR	95% CI		AOR	95% CI		AOR	95% CI
Personal factors													
Age (years)	53.06±15.64	64.55±10.29	1.062	1.050-1.074	64.11±11.10	1.056	1.043-1.069	63.18±10.38	1.05	1.032-1.067	67.96±10.40	1.082	1.064-1.10
Sex Male	392 (46.2%)	237 (76.2%)	3.734	2.783-5.009	130 (69.1%)	2.613	1.864-3.662	68 (76.4%)	3.775	2.272-6.271	74 (56.9%)	1.541	1.062-2.236
Female	457 (53.8%)	74 (23.8%)			58 (30.9%)			21 (23.6%)			56 (43.1%)		
BMI (kg/m^2)	23.18±3.44	22.78±3.2	0.965	0.927-1.003	23.39±3.12	1.018	0.972-1.066	23.12±3.55	0.995	0.933-1.060	21.50±3.00	0.85	0.799-0.905
Marital status													
Ever married	686 (80.8%)	300 (96.5%)	6.48	3.467-12.112	182 (96.8%)	7.207	3.140-16.545	78 (87.6%)	1.685	0.876-3.240	123 (94.6%)	4.175	1.913-9.112
Never married	163 (19.2%)	11 (3.5%)			6 (3.2%)			11 (12.4%)			7 (5.4%)		
Lifestyle													
Frequent alcohol[a] consumption	281 (33.1%)	124 (40.1%)	1.361	1.042-1.778	67 (36.6%)	1.175	0.844-1.635	29 (32.6%)	0.986	0.622-1.564	23 (17.7%)	0.45	0.284-0.714
Current or Ex-smoker	316 (37.3%)	201 (64.8%)	3.105	2.366-4.073	121 (64.7%)	3.086	2.218-4.296	61 (68.5%)	3.668	2.296-5.860	62 (47.7%)	1.535	1.059-2.225
Low physical activity[b]	392 (46.2%)	140 (45.0%)	0.931	0.757-1.144	76 (40.6%)	0.796	0.577-1.099	37 (41.6%)	0.829	0.536-1.281	75 (57.7%)	1.586	1.092-2.304
Diet habit													
Salty diet	353 (41.6%)	154 (49.5%)	1.378	1.062-1.789	86 (46.0%)	1.196	0.870-1.645	30 (33.7%)	0.714	0.451-1.132	43 (33.1%)	0.694	0.470-1.026
Meat rich diet	363 (42.8%)	147 (47.3%)	1.2	0.925-1.558	79 (42.2%)	0.979	0.711-1.349	40 (44.9%)	1.093	0.704-1.696	51 (39.2%)	0.864	0.593-1.261
Vegetable poor diet	224 (26.4%)	88 (28.3%)	1.098	0.821-1.467	49 (26.2%)	0.988	0.689-1.415	28 (31.8%)	1.298	0.808-2.085	45 (34.6%)	1.472	0.995-2.180
Medical history													
Hypertension	209 (24.6%)	123 (39.5%)	1.978	1.503-2.602	63 (33.5%)	1.526	1.088-2.141	19 (21.3%)	0.828	0.488-1.403	55 (42.3%)	2.207	1.512-3.221
Diabetes mellitus	100 (11.8%)	50 (16.1%)	1.435	0.994-2.072	31 (16.5%)	1.479	0.954-2.292	25 (28.1%)	2.926	1.762-4.859	37 (28.5%)	2.98	1.930-4.601
Chronic liver disease	133 (15.7%)	29 (9.3%)	0.554	0.362-0.847	19 (10.1%)	0.605	0.364-1.007	64 (71.9%)	13.782	8.376-22.675	12 (9.2%)	0.547	0.294-1.020
B-viral	50 (5.9%)	10 (3.2%)	0.531	0.266-1.060	6 (3.2%)	0.527	0.222-1.247	45 (50.6%)	16.343	9.870-27.061	7 (5.4%)	0.909	0.403-2.051
C-viral	13 (1.5%)	4 (1.3%)	0.838	0.271-2.589	0 (0%)	-	-	12 (13.5%)	10.022	4.420-22.723	1 (0.8%)	0.499	0.065-3.843
Fatty liver	26 (3.1%)	4 (1.3%)	0.412	0.143-1.191	7 (3.7%)	1.224	0.523-2.864	0 (0%)	-	-	2 (1.5%)	0.495	0.116-2.109
Alcoholic hepatitis	42 (4.9%)	11 (3.5%)	0.705	0.358-1.386	3 (1.6%)	0.312	0.096-1.016	9 (10.1%)	2.162	1.015-4.602	2 (1.5%)	0.3	0.072-1.255
Familial factors													
Family History of GI cancer	187 (22.0%)	96 (30.9%)	1.581	1.183-2.113	58 (30.9%)	1.579	1.114-2.240	27 (30.3%)	1.542	0.954-2.492	27 (20.8%)	0.928	0.589-1.461
Parental	144 (17.0%)	49 (15.8%)	0.916	0.643-1.304	31 (16.5%)	0.967	0.632-1.478	9 (10.1%)	0.551	0.270-1.123	14 (10.8%)	0.591	0.330-1.058
Sibling	55 (6.5%)	52 (16.7%)	2.898	1.935-4.342	27 (14.4%)	2.421	1.482-3.955	20 (22.5%)	4.184	2.372-7.383	12 (9.2%)	1.468	0.764-2.823
Child	2 (0.2%)	4 (1.3%)	5.518	1.006-30.277	1 (0.5%)	2.265	0.204-25.106	1 (1.1%)	4.812	0.432-53.607	3 (2.3%)	10.004	1.655-60.453

Table 5. Continued

	Control (n=849)	EG ca (n=311)		CRC (n=188)		HCC (n=89)		PB ca (n=130)	
		AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Age of diagnosis, affected family member									
<50 years old	23 (12.8%)	16 (17.2%)	0.705	0.352-1.411	8 (14.3%)	0.879	0.369-2.092	10 (37.0%)	0.238	0.100-0.567	2 (8.0%)	1.685	0.372-7.624
≥50 years old	157 (87.2%)	77 (82.8%)			48 (85.7%)			17 (63.0%)			23 (92.0%)		
Number of affected family member													
Two or more	19 (2.2%)	15 (4.8%)	2.214	1.111-4.413	5 (2.7%)	1.194	0.440-3.238	4 (4.5%)	2.056	0.684-6.182	3 (2.3%)	1.032	0.301-3.537
One or none	830 (97.8%)	296 (95.2%)			183 (97.3%)			85 (95.5%)			127 (97.7%)		
Type of GI cancer of family member													
EG ca	93 (11.0%)	70 (22.5%)	2.361	1.677-3.325	28 (14.9%)	1.423	0.902-2.244	7 (7.9%)	0.694	0.311-1.546	19 (14.6%)	1.391	0.817-2.369
CRC	42 (4.9%)	14 (4.5%)	0.906	0.488-1.683	21 (11.2%)	2.416	1.394-4.187	1 (1.1%)	0.218	0.030-1.606	2 (1.5%)	0.3	0.072-1.255
HCC	41 (4.8%)	10 (3.2%)	0.655	0.324-1.324	14 (7.4%)	1.586	0.846-2.973	20 (22.5%)	5.712	3.172-10.288	3 (2.3%)	0.466	0.142-1.526
PB ca	25 (2.9%)	6 (1.9%)	0.648	0.263-1.596	3 (1.6%)	0.534	0.160-1.789	2 (2.2%)	0.758	0.176-3.253	6 (4.6%)	1.595	0.641-3.965

GI, gastrointestinal; EG ca, esophagogastric cancer; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PB ca, pancreatobiliary cancer; OR, odds ratio; CI, confidential interval; BMI, body mass index; B-viral, viral hepatitis B; C-viral, viral hepatitis C.

[a]Frequent alcohol consumption means alcohol consumption more than once per week; [b]Low physical activity means physical activity less than once per week.

pathways that regulate cell fate, survival, and genome maintenance.[11] In a previous study, approximately 10% of GC appeared to have a family history of GC, and only half of these cases were associated with inherited cancer predisposition syndromes.[12] However, many GC patients without inherited cancer syndromes also have a genetic defect, and the Cancer Genome Atlas project identified that 25 genes are frequently mutated in GC.[13] In addition to GC, CRC is a well-researched GI cancer about the genetic susceptibility and genetic defect of cancer development. Inherited cancer syndromes, including Lynch syndrome, familial adenomatous polyposis, MUTYH- associated polyposis, and certain hamartomatous polyposis conditions are high risk for CRC. In addition, one-third of CRC patients have increased familial risk, likely related to inheritance, and a number of less penetrant but possibly more frequently susceptibility genes have been identified for this level of inheritance.[14] The risk of PC has been reported to be increased by the presence of hereditary syndromes, including Lynch Syndrome (8.6-fold),[15] familial adenomatous polyposis (4.46-fold),[16] hereditary pancreatitis (53-fold),[17] Peutz- Jeghers syndrome (132-fold),[18] P16-Leiden mutation (47.8-fold),[19] and Familial pancreatic cancer (32-fold).[20] However, the vast majority of PC cases appear to be sporadic. In fact, only 5-10% of PC are explained by familial genetic mutations.[21-23] A genetic defect can cause various GI cancers in individuals under different environments and lifestyles. Even though we were unable to investigate the genetic abnormalities in this study, more research for genetic association of different GI cancers within a family is strongly needed.

Other factors contributing the development of GI cancer in family are lifestyle and environmental factors. Family members not only share genetic defects, but also similar environmental factors, such as dietary, smoking, alcohol drinking, and physical habits. Wu et al. [24] reported that family history of EsoCa and similar lifestyles act synergistically in a population-based case-control study in China. Up to 3-fold higher risk was observed in individuals with a relative of EsoCa when they have lifestyle risk factors, such as smoking, alcohol, high-sodium diet, consuming very hot foods, and fast-eating speed.[24] Some gene variants associated with CRC development also showed different effects depending on environmental factors, such as intake of vitamin D, calcium, and selenium, as well as smoking habit.[14] These observations in-

dicate that a comprehensive lifestyle intervention in these high-risk populations may reduce the incidence of GI cancers. However, in this study, alcohol consumption and dietary habit did not increase the risk of GI cancer. Only smoking was closely related to all kinds of GI cancer. The reason may be that the questions for evaluating alcohol consumption, exercise activity, and dietary habit were not objective or quantitative.

GI cancer under 50 years of age may be more closely associated with genetic predisposition than environmental factors or aging. As aforementioned, even in the absence of hereditary cancer syndrome, family members may share predisposing genetic defects, and be at increased risk of GI cancer if a family member was a victim of early onset GI cancer. Unfortunately, we encountered such associations in this study. If parents had been diagnosed with GI cancer before the age of 50, patients also tended to be diagnosed with GI cancer under the age of 50 years (Table 3). A previous Swedish study suggested that there is a strong association with family history when the proband was affected prior to the age of 60 years in most cancer sites.[6] In a previous Korean study, the incidence of having a FDR with history of GC was higher among patients in their fifth and sixth decades (OR 4.00), but lower among those aged over 60 years (OR 1.81).[2] In another Korean study, the mean age of GC diagnosis was significantly younger in patients with paternal history of GC compared with those without family history (54.4±10.4 years old vs. 58.1±12.0 years old, p<0.001).[25] Individuals with a positive family history of CRC in their fourth and fifth decades were found to have higher relative risks than age-matched controls with the same positive family history, but with a later onset.[26] The risk of CRC was greater in relatives when index patients developed CRC before the age of 45 years (OR 3.87),[3] or the age of 60 years (hazard ratio 2.11).[27] For this reason, the American Cancer Society recommends that patients with a FDR diagnosed CRC less than 60 years should start CRC screening 10 years earlier than the general population.[28] In the case of HCC, a family history of early onset HCC increased the risk of HCC, by up to 5.7-fold, irrespective of the presence of viral hepatitis,[4] and the mean age at HCC diagnosis is significantly dependent on family history of HCC (52 vs. 57 years; p<0.0001).[29]

In this study, we did not identify any familial relationship among the various types of GI cancers. In a population-based case-control study conducted in China, the risk of EsoCa was increased only by a positive family history of EsoCa, and not by family histories of GC or HCC.[24] In a previous Korean study, both patient groups with family history of CRC and GC exhibited an increased incidence of colonic adenoma (OR 1.63, p=0.007 and OR 1.38, p=0.039), but did not show statistically significant results for CRC (OR 0.72, p=0.648 and OR 1.87, p=648).[30] Thus, although the development of different GI cancers are closely related, the risk of developing cancer at a discordant site is not greater in those with a positive family history.

The cost-effectiveness of intensive screening in high risk patients was demonstrated using the Markov model,[31] and thus, efforts should be made to identify individuals at greater risk of developing specific GI cancers and select candidates for more intensive screening programs. In particular, person with a family history of a specific GI cancer should be recommended for more specialized screening for the concordant GI cancer, and cancer screening should be started earlier in those with family history of early onset GI cancer. Liu et al.[32] suggested that women with maternal cancer history should be screened for malignancy at least by the age of 40 years, especially for breast, lung, and gynecological cancers, and that men with maternal cancer history should start cancer screening when they are 45 years of age with a focus on lung and digestive system cancers. To achieve this, recording family history is essential; however, it is an issue that most people are not aware of detailed medical histories of their family members, and doctors tend to not consider history taking seriously.[33] In fact, genetic counseling is performed on only one fourth of CRC patients in America,[34] and hardly at all in our country.

This study has several limitations that warrant consideration. First, because data were obtained using a self-reporting questionnaire, the reliability of family histories of GI cancer is debatable. In a recent systematic review, it was concluded self-reported family histories of cancers appeared to be fairly accurate.[35] However, some people confuse hepatic metastasis with HCC, and the dispersal of family members, variable health care service qualities, and poor memory undoubtedly reduce data accuracy. Moreover, accuracies pertaining to memories may depend on cancer type and severity.[36] People has a tendency to remember family history of pancreatic cancer more correctly than those of other can-

cers (GC and HCC). Second, this study may have selection bias. We included subjects who were admitted to hospitals, and thus, they may have been more aware of their own and their family's health status. We did not select patients and control subjects matched one to one. Therefore, several demographic characteristics showed a difference between the two groups. To adjust for sex and age bias, subgroup analysis was necessary; however, our population size was too small to perform any sub-analyses. Third, the number of subjects was too small for it to be sub-divided, which may hinder the generalizability of our results. Moreover, even though the pathophysiology and clinical course are different, we classified esophageal cancer and gastric cancer into one group because esophageal cancer patients were too small to be categorized separately. Therefore, a large-scale, case-controlled study is needed to obtain more information through generations. We suggest that family history of cancer be included in the Korean National Cancer Survey, and that if a family has an increased incidence of GI cancer, genetic studies is encouraged.

In conclusion, our results showed that GI cancer develops more frequently in individuals with a family history of concordant GI cancer. More intensive screening for EG cancer, CRC, and HCC is recommended for individuals with FDR with the concordant type of GI cancer.

ACKNOWLEDGEMENT

We would especially like to thank all gastroenterologists (Sung Pyo Hong, Eun Sun Kim, Younjoo Kim, Dae Seong Myung, Dong Kee Jang, Seun Ja Park) as well as all participants from each hospital who voluntarily participated in this survey.

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Questionnaire

Study Title: Risk Assessment of Gastrointestinal Cancers in Patients with a Family History of Gastrointestinal Cancer: A Nationwide Multi-Center Study in Korea

Case Number :

DEMOGRAPHICS			
Age	Years old	Sex	1. Male 2. Female
Height	Cm	Weight	kg
Marital status	1. Never married 2. Married	3. Divorced 4. Bereaved	
Number of family members		Number of Children	
LIFE STYLES			
Drinking	1. Less than once per week	2. More than twice per week	
Smoking	1. Never smoker	2. Current smoker	3. Ex-smoker
Exercise	1. Less than once per week	2. More than twice per week	
DIET HABIT			
Salty food	1. Preferred	2. Not preferred	
Meat	1. Preferred	2. Not preferred	
Vegetable	1. Preferred	2. Not preferred	
PERSONAL MEDICAL HISTORY			
Hypertension	1. Yes 2. No	Diabetes	1. Yes 2. No
Chronic liver disease	1. Chronic B-viral hepatitis 3. Steatohepatitis	2. Chronic C-viral hepatitis 4. Alcoholic hepatitis	
Cancer	1. Yes 2. No		
Medication	1. Antihypertensive 4. Cholesterol drug	2. Antidiabetic drug 5. Aspirin	3. Insulin

♣ Personal cancer history (This table can be added as needed)

Types of cancer	1. Gastric cancer 5. Pancreatic cancer 9. Head and neck cancer 13. Cervical cancer 17. Kidney cancer	2. Esophageal cancer 6. Bile duct cancer 10. Lung cancer 14. Endometrial cancer 18. Lymphoma	3. Colorectal cancer 7. Gallbladder cancer 11. Breast cancer 15. Prostate cancer 19. Leukemia	4. Liver cancer 8. Thyroid cancer 12. Ovarian cancer 16. Bladder cancer
Age of cancer diagnosis	Years old			
Cancer stage	1. Stage I	2. Stage II	3. Stage III	4. Stage IV 5. Not known

■ Family history of cancer (This table can be added as needed)

Family members	1. Father 5. Son	2.Mother 6. Daughter	3. Brother	4. Sister
Types of cancer	1. Gastric cancer 5. Pancreatic cancer 9. Head and neck cancer 13. Cervical cancer 17. Kidney cancer	2. Esophageal cancer 6. Bile duct cancer 10. Lung cancer 14. Endometrial cancer 18. Lymphoma	3. Colorectal cancer 7. Gallbladder cancer 11. Breast cancer 15. Prostate cancer 19. Leukemia	4. Liver cancer 8. Thyroid cancer 12. Ovarian cancer 16. Bladder cancer
Age of cancer diagnosis	Years old			