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Influence of a Positive Family History on the Clinical Course of Inflammatory Bowel Disease

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Abstract

Background and aims: Previous studies on the difference in phenotypes and disease course between familial and sporadic inflammatory bowel disease (IBD) have been controversial, although family history is considered to increase the risk of developing IBD.
Methods: The influence of family history on phenotype and disease course of IBD was analysed in 2805 Korean patients with Crohn's disease (CD) and 3266 with ulcerative colitis (UC). Familial IBD was defined as the existence of one or more first-, second- and/or third-degree relatives affected with CD or UC.
Results: A positive family history of IBD was noted in 191 patients with CD (6.8%) and 212 patients with UC (6.5%). In the patients with CD, the probability of anti-TNF use was higher in the familial cases than in the sporadic cases (56.3 vs 43.4%, respectively, at 10 years, *p* = 0.019). When analysed after excluding patients who had undergone intestinal resection within 1 year of diagnosis, the cumulative probability of intestinal resection was higher in the familial cases than in the sporadic cases (55.0 vs 32.2%, respectively, at 10 years; *p* = 0.007). In multivariate analysis, family history was an independent risk factor for the time to first intestinal resection in patients with CD (hazard ratio: 1.61, 95% confidence interval: 1.13–2.29; *p* = 0.009). In patients with UC, younger age at diagnosis and more females were observed in the familial cases (*p* < 0.001).
Conclusions: The present study suggests the possibility of a more aggressive clinical course of CD in familial compared with sporadic cases.

Key Words: Crohn's disease; ulcerative colitis; familial history

1. Introduction

Inflammatory bowel disease (IBD), which is represented by Crohn's disease (CD) and ulcerative colitis (UC), is an idiopathic, chronic inflammatory bowel disorder. Although the etiology of IBD is not fully understood, its pathogenesis is suggested to be a complex interaction between genetic, environmental, immunologic, and microbiologic factors.[1,2] In these interactions, IBD is widely accepted as a disharmonized immune response against intestinal antigens in genetically susceptible individuals under the influence of several environmental factors.[1–6] Recently, genome-wide association studies

have revealed 163 loci associated with IBD, which contribute to the phenotype of CD and UC and are also implicated in other immune-mediated disorders.[7] In addition, environmental factors such as diet and smoking are thought to play key roles in IBD pathogenesis, and among the suggested environmental factors, gut microbiota have emerged as a potent etiology in IBD.[8,9]

Sharing susceptible genes and environmental factors, familial aggregation in IBD has been well documented in the literature. The rate of family history in CD and UC has been reported to be approximately between 2% and 15%, and the rate in patients with CD is usually higher than that in patients with UC.[8,10–12] The increased risk of CD and UC in first-degree relatives of affected IBD patients has been consistently reported.[10,13–15] However, the magnitude of the positive rate and of the increased risk of developing IBD among relatives varies greatly among studies, which have typically focused on first-degree relatives, rather than second- and third-degree relatives.[8,10,12,15–17] In addition, regarding clinical phenotypes and disease course, the difference between sporadic and familial IBD has remained unclear. Some studies have reported that disease onset was earlier and disease extent was greater in familial IBD cases, whereas other studies have not shown any significant differences in phenotypes between familial and sporadic IBD cases.[8,11,18] Moreover, difference in disease course between the two groups has rarely been reported in the literature.[10,12,19,20]

The aim of our present study was to evaluate the influence of a positive family history on the phenotypes and disease course of IBD in a single hospital-based large cohort in South Korea. The basic characteristics between familial and sporadic IBD patients were compared, and the differences in medication use and surgical rate between familial and sporadic patients were analysed.

2. Methods

2.1. Study population

A total of 6106 patients with CD or UC who visited the Asan Medical Center, a tertiary university hospital in Seoul, South Korea, between June 1989 and April 2015 were enrolled in the present study. The diagnosis of CD and UC was based on conventional clinical, radiologic, endoscopic, and histopathologic criteria.[17,21–23] Patients included in the study had been diagnosed with CD and UC as far back as 1981 and 1977, respectively. Patients who were referred simply for a second opinion or diagnosed with other types of IBD (indeterminate colitis or intestinal Behcet's disease) were excluded from the analysis.

2.2. Study design and treatment policy

From the Asan IBD registry, which has been prospectively maintained since 1997, detailed demographic and clinical information were retrieved and analysed. Information regarding the registry has previously been described in detail.[21,22] The data obtained from the registry included follow-up period, sex, date of birth, date of symptom onset, date of diagnosis, smoking status, family history of IBD, disease location and extent, disease behaviour, perianal fistula, use and start date of medication, and information on surgical treatment related to IBD. Information on the dose and duration of medication was collected from electronic medical records. In addition to a routine update at each visit for changes in clinical status, such as development of complications or requirement of new medications, clinical information that may be altered during the follow-up but is easily overlooked by clinicians, such as family history and smoking status, was updated at least annually. Whenever information was missing from the registry, we reviewed medical records or interviewed

patients to obtain it. Detailed information on relatives affected with IBD (including the number of affected relatives, degree of kinship, type of IBD, date of diagnosis, hospital of IBD diagnosis, and disease status of each member) were also collected. If necessary, the medical records of other hospitals where the diagnosis of IBD was made were requested, and family history was verified.

Our treatment strategies for CD and UC have been previously described in detail[21,22,24,25] and are based on a step-up approach, with the addition of more potent therapies when patients become unresponsive or unable to tolerate first-line therapy, similar to that of Western countries.[21,22] Thiopurines (azathioprine/6-mercaptopurine) were less frequently used in the 1990s, and anti-TNF agents were approved for CD and UC treatments in Korea in 2000 and 2007, respectively.[21,22] Thus, the use of medications and the need for surgical treatment were analysed in patients diagnosed with CD or UC since 2000. Other immunosuppressants such as methotrexate and cyclosporine have very rarely been prescribed in Korea. The early use of thiopurines or anti-TNF agents was defined as initiation within the first year of diagnosis and at least 6 months before the first intestinal resection.[22,26,27] The Ethics committee of Asan Medical Center approved the study protocol, and written informed consent was obtained from all of the patients.

2.3. Disease definitions

Disease phenotypes were classified according to the Montreal classification.[28,29] Briefly, in CD, disease location was categorized as ileal disease (L1), colonic disease (L2), or ileocolonic disease (L3). Disease behaviour was categorized as nonstricturing and nonpenetrating (B1), stricturing (B2), or penetrating (B3). In UC, the extent of disease was categorized as proctitis (E1), left-sided colitis (E2), or extensive colitis (E3).[21,25]

Familial cases were defined as patients with one or more first-, second-, and/or third-degree relatives affected with CD or UC. Sporadic cases were defined as patients without any relatives affected with IBD. Patients only with relatives affected with intestinal Behcet's disease, with fourth- or higher degree relatives affected with IBD, and with relatives whose IBD diagnosis was not confirmed were excluded from the analysis. For the analysis of concordance rate for the type of IBD, the members of each family were grouped in as many consanguineous pairs as possible. When the IBD type was matched in a pair, the pair was counted as concordant.[4]

2.4. Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR), and categorical variables were expressed as number and percentage (%). The Mann–Whitney *U* test was used to compare continuous variables between groups, and the chi-square or Fisher's exact test was used to compare categorical variables. The cumulative probabilities of the use of thiopurines/anti-TNF agents or first intestinal resection were calculated using the Kaplan–Meier method. The log-rank test was used to compare the cumulative probabilities between groups. A Cox proportional hazards model was used to assess predictors of the cumulative probability of first intestinal resection and to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Variables with *p* values <0.2 in the univariate analysis were included in the multivariate analysis. The proportional hazards assumptions were tested using scaled Schoenfeld residuals. There were no violations of the proportional hazards assumptions for any of the variables included in the Cox model. The analyses were performed using the IBM SPSS version 21.0 for Windows (IBM Co., Armonk, NY) and R statistical software version 3.1.2. *p* < 0.05 was considered to indicate significance.

3. Results

3.1. Family history

A total of 6071 patients were included in the analysis, consisting of 2805 (46.2%) patients with CD and 3266 (53.8%) patients with UC. A positive family history was noted in 403 (6.6%) patients: 191 (6.8%) of the 2805 CD patients and 212 (6.5%) of the 3266 UC patients. The proportions of IBD patients with first-, second-, and third-degree relatives affected were 74.2%, 15.1%, and 10.7%, respectively (Table 1). The proportion of familial cases among all of the prevalent cases in each 3-year period increased over the study period between 1989 and 2015 in both CD and UC patients: from 0% and 1.2%, respectively, in 1989–1991 to 6.5% and 6.3%, respectively, in 2013–2015 (see Supplementary Figure 1). All the familial cases were in 249 families, and of these, 142 families had two or more affected members included in the registry. When the concordance rate for the IBD types was calculated, 244 of 295 pairs (82.7%) were matched by type: 105 pairs were matched for CD and 139 pairs for UC.

3.2. Baseline characteristics

The baseline demographic data for each of CD and UC are presented in Table 1, and the baseline clinical characteristics comparing sporadic and familial cases in patients with CD and UC are summarized in Tables 2 and 3. In patients with CD, there were no significant differences between sporadic and familial cases in terms of gender, age at diagnosis, duration from symptom onset to diagnosis, smoking status at diagnosis, disease location and behaviour at diagnosis, and perianal fistula at diagnosis (Table 2). In patients with UC, the median age at symptom onset (30 years vs 34 years) and at diagnosis (31 years vs 36 years) were significantly lower in familial cases than in sporadic cases (both $p < 0.001$; Table 3). The proportion of male patients was also significantly lower in familial cases than in sporadic cases (47.6% vs 55.2%, $p < 0.05$), especially in familial cases with first-degree relatives affected (44.8%, $p < 0.01$). Smoking status and disease extent at diagnosis did not differ between familial and sporadic groups.

3.3. Medication use

Among the 2486 patients diagnosed with CD since 2000, thiopurines (azathioprine/6-mercaptopurine) and anti-TNF agents were administered in 2142 patients (86.2%) and 720 patients (29.0%), respectively (Table 2). The use of thiopurines did not differ between sporadic and familial cases (86.0% vs 88.5%). However, anti-TNF agents were more frequently used in familial cases compared with sporadic cases (36.4% vs 28.4%, $p < 0.05$; Table 2). When the cumulative probability of medication use was assessed in patients with CD (Figure 1A and 1B), the probability of anti-TNF use, but not of thiopurine use, was significantly higher in familial than in sporadic cases ($p = 0.019$). The cumulative probabilities of anti-TNF treatment at 1, 5, and 10 years from diagnosis were 10.8%, 30.5%, and 56.3%, respectively, in familial cases, whereas they were 6.7%, 22.3%, and 43.4%, respectively, in sporadic cases.

Among the 2549 patients diagnosed with UC since 2000, thiopurines and anti-TNF agents were administered in 605 (23.7%) and 241 (9.5%) patients, respectively (Table 3). There was no significant difference in the use of thiopurines and anti-TNF agents between sporadic and familial cases. The cumulative probabilities of thiopurine and anti-TNF treatment also did not significantly differ between the two groups (Figure 1C and 1D).

3.4. Surgery

Among the 2486 CD patients, a total of 751 patients (30.2%) underwent intestinal resection during the follow-up period. The rate of intestinal resection was higher in familial CD cases (34.5%) than in sporadic CD cases (29.9%), although the difference was not statistically significant (Table 2). The cumulative probability of intestinal resection was not significantly different between sporadic and familial cases ($p = 0.083$; Figure 2A). The cumulative probabilities at 1, 5, and 10 years from diagnosis were 13.0%, 28.4%, and 60.8%, respectively, in familial cases, whereas they were 14.3%, 25.9%, and 41.9%, respectively, in sporadic cases. However, when reanalysed in 2137 CD patients after excluding 327 sporadic (14.1%) and 22 familial cases (13.3%) who underwent intestinal resection within 1 year of diagnosis, the cumulative probability of intestinal resection was significantly higher in familial cases than in sporadic cases ($p = 0.007$; Figure 2B). The 5- and 10-year cumulative probabilities of intestinal resection were 16.4% and 55.0%, respectively, in familial cases, whereas they were 13.5% and 32.2%, respectively, in sporadic cases. Among the 2549 UC patients, a total of 137 patients (5.4%) underwent colectomy during the follow-up period. The cumulative probability of colectomy was not different between sporadic and familial cases (Figure 2C). This result did not change even after excluding 48 sporadic (2.0%) and 2 familial cases (1.3%) that underwent colectomy within 1 year of diagnosis (Figure 2D).

Table 1. Baseline demographic data in the study patients with Crohn's disease (CD) and ulcerative colitis (UC).

	CD patients	UC patients	p value
No. of patients	2805	3266	
Male, n (%)	2030 (72.4%)	1786 (54.7%)	<0.001
Age at symptom onset, years[a]	20 (16–26)	34 (24–45)	<0.001
Age at diagnosis, years[a]	22 (18–29)	36 (26–47)	<0.001
Duration from onset to diagnosis, months[a]	12 (3–37)	3 (1–10)	<0.001
Duration of follow-up, months[a]	78 (35–129)	82 (36–148)	<0.001
Smoking status at diagnosis			<0.001
Never, n (%)	1802 (65.3%)	1886 (60.1%)	
Ex, n (%)	173 (6.3%)	698 (22.3%)	
Current, n (%)	785 (28.4%)	553 (17.6%)	
Familial cases, n (%)	191 (6.8%)	212 (6.5%)	
1st degree, n (%)	134 (4.8%)	165 (5.1%)	
2nd degree, n (%)	28 (1.0%)	33 (1.0%)	
3rd degree, n (%)	29 (1.0%)	14 (0.4%)	

[a]Median (IQR, interquartile range).

Table 2. Clinical characteristics of sporadic and familial Crohn's disease (CD).

	Sporadic CD	Familial CD			p value[a,b,c]
		All	1st degree	2nd + 3rd degree	
No. of patients	2614	191	134	57	
Male , *n* (%)	1895 (72.5%)	135 (70.7%)	91 (67.9%)	44 (77.2%)	
Age at symptom onset, years[d]	20 (16–26)	19 (16–25)	20 (16–27)	19 (16–24)	
Age at diagnosis, years[d]	22 (18–29)	21 (18–29)	21 (18–30)	21 (18–27)	
Duration from onset to diagnosis, months[d]	12 (4–37)	10 (3–35)	9.5 (3–34)	12 (4–36)	
Duration of follow-up, months[d]	78 (35–129)	78 (41–135)	80.5 (43–127)	64 (37–138)	
Smoking status at diagnosis					
Never, *n* (%)	1667 (64.9%)	135 (71.1%)	96 (72.2%)	39 (68.4%)	
Ex, *n* (%)	164 (6.4%)	9 (4.7%)	8 (6.0%)	1 (1.8%)	
Current, *n* (%)	739 (28.8%)	46 (24.2%)	29 (21.8%)	17 (29.8%)	
Disease location at diagnosis					
L1, *n* (%)	628 (24.6%	51 (27.1%)	32 (24.4%)	19 (33.3%)	
L2, *n* (%)	192 (7.5%)	12 (6.4%)	11 (8.4%)	1 (1.8%)	
L3, *n* (%)	1735 (67.9%)	125 (66.5%)	88 (67.2%)	37 (64.9%)	
Disease behaviour at diagnosis					
B1, *n* (%)	1996 (77.6%)	156 (81.7%)	115 (85.8%)	41 (71.9%)	
B2, *n* (%)	265 (10.3%)	18 (9.4%)	12 (9.0%)	6 (10.5%)	
B3, *n* (%)	310 (12.1%)	17 (8.9%)	7 (5.2%)	10 (17.5%)	
Perianal fistula at diagnosis, *n* (%)	1108 (44.0%)	75 (40.3%)	49 (37.7%)	26 (46.4%)	
Ever use of medication[e]					
Azathioprine/6-MP, *n* (%)	1996 (86.0%)	146 (88.5%)	98 (86.7%)	48 (92.3%)	
Anti-TNF agents, *n* (%)	660 (28.4%)	60 (36.4%)	41 (36.3%)	19 (36.5%)	<0.05[a]
Intestinal resection[e], *n* (%)	694 (29.9%)	57 (34.5%)	38 (33.6%)	19 (36.5%)	

[a]Familial (all) vs sporadic; [b]familial (1st degree) vs sporadic; [c]familial (2nd + 3rd degree) vs sporadic; [d]median (IQR, interquartile range); [e]in 2486 patients diagnosed with CD since 2000.

Table 3. Clinical characteristics of sporadic and familial ulcerative colitis (UC).

	Sporadic UC	Familial UC			p value[a,b,c]
		All	1st degree	2nd + 3rd degree	
No. of patients	3054	212	165	47	
Male, *n* (%)	1685 (55.2%)	101 (47.6%)	74 (44.8%)	27 (57.4%)	<0.05[a], <0.01[b]
Age at symptom onset[d], years[d]	34 (24–46)	30 (22–41)	30 (22–41)	31 (20.5–41.5)	< 0.001[a], <0.005[b]
Age at diagnosis[d]	36 (26–47)	31 (23–43)	31 (23–43)	31 (21.5–42.5)	< 0.001[a], <0.005[b] <0.05[c]
Duration from onset to diagnosis, months[d]	3 (1–10)	3 (1–12)	4 (1–12.5)	3 (0.5–5.5)	<0.05[b]
Duration of follow-up, months[d]	81 (35–145)	108.5 (58.5–186.5)	120 (63–192)	95 (45.5–165)	<0.001[a], <0.001[b]
Smoking status at diagnosis					
Never	1748 (59.7%)	138 (66.7%)	109 (67.7%)	29 (63.0%)	
Ex	665 (22.7%)	33 (15.9%)	25 (15.5%)	8 (17.4%)	
Current	517 (17.6%)	36 (17.4%)	27 (16.8%)	9 (19.6%)	
Disease extent at diagnosis					
E1	1281 (46.3%)	88 (47.1%)	69 (48.3%)	19 (43.2%)	
E2	809 (29.3%)	56 (29.9%)	43 (30.1%)	13 (29.5%)	
E3	675 (24.4%)	43 (23.0%)	31 (21.7%)	12 (27.3%)	
Ever use of medication[e]					
Azathioprine/6-MP	565 (23.5%)	40 (26.8%)	31 (27.4%)	9 (25.0%)	
Anti-TNF agents	221 (9.2%)	20 (13.4%)	15 (13.3%)	5 (13.9%)	
Colectomy[e]	132 (5.5%)	5 (3.4%)	4 (3.5%)	1 (2.8%)	

[a]Familial (all) vs sporadic; [b]familial (1st degree) vs sporadic; [c]familial (2nd + 3rd degree) vs sporadic; [d]median (IQR, interquartile range); [e]in 2549 patients diagnosed with UC since 2000.

To further evaluate the relationship between family history and intestinal resection in CD, multivariate Cox regression analysis was performed in the 2137 CD patients (Table 4). The potential confounding factors were age at diagnosis, sex, smoking status, disease location at diagnosis, disease behaviour at diagnosis, and early use of thiopurines and anti-TNF agents. Of these, five factors with *p* values <0.2 in the univariate analysis were included in the Cox regression model. The multivariate analysis showed that family history was an independent risk factor for the time to first intestinal resection (HR: 1.61, 95% CI: 1.13–2.29; *p* = 0.009). Other independent risk
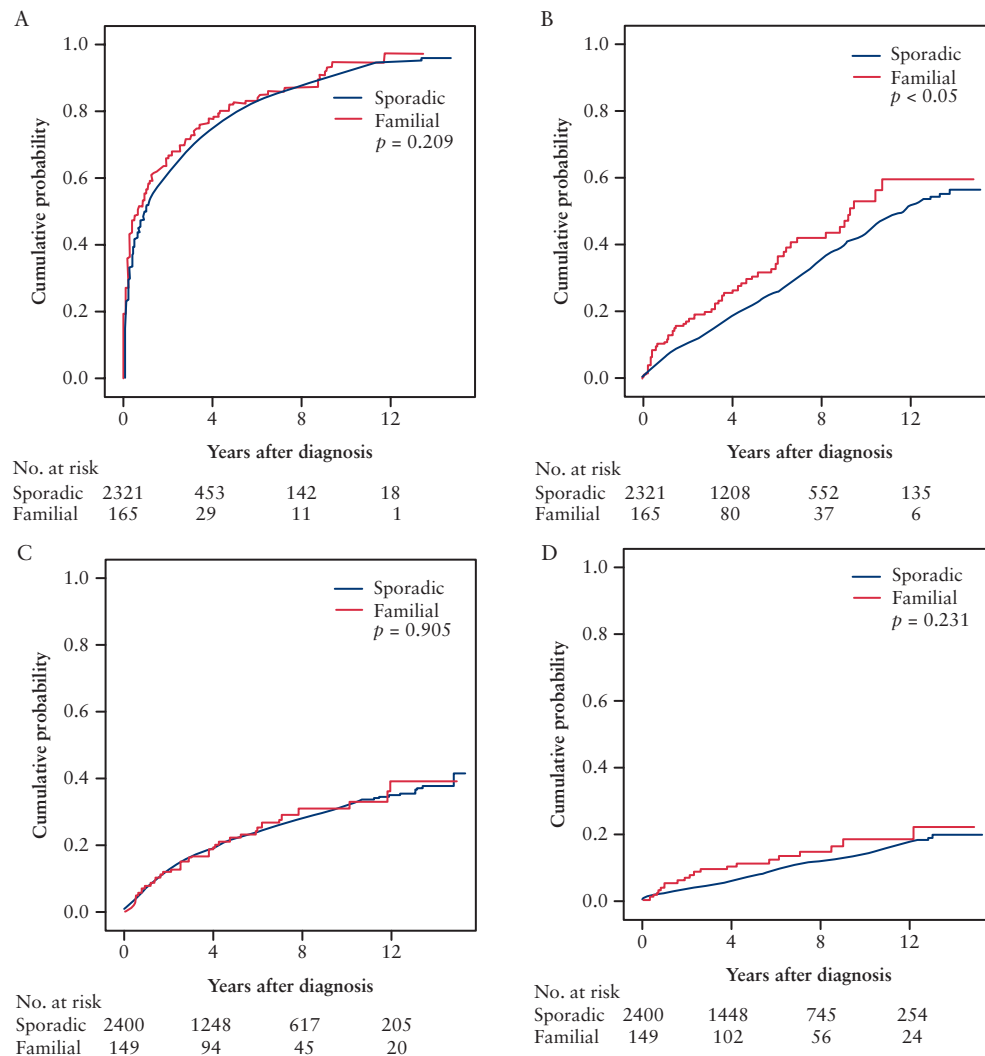
Figure 1. Cumulative probability of medication use in sporadic and familial cases in 2486 patients with Crohn's disease (CD) and 2549 patients with ulcerative colitis (UC) who were first diagnosed in or later than the year 2000: (A) Thiopurine use in CD; (B) anti-TNF use in CD (familial vs sporadic, $p = 0.019$); (C) thiopurine use in UC; (D) anti-TNF use in UC.

factors were disease location at diagnosis (L3, HR: 3.29, 95% CI: 1.80–6.01; L1, HR: 3.74, 95% CI: 2.00–7.01; $p < 0.001$), disease behaviour at diagnosis (B2, HR: 1.96, 95% CI: 1.42–2.70; B3, HR: 2.99, 95% CI: 2.12–4.22; $p < 0.001$), and early use of thiopurines (HR: 0.80, 95% CI: 0.64–0.99; $p = 0.043$).

## 4. Discussion

We investigated the influence of a positive family history on the baseline characteristics and disease course in a large well-defined cohort of Korean patients with CD and UC. In patients with CD, the rates of anti-TNF use and intestinal resection were significantly higher in familial cases than in sporadic cases. In patients with UC, younger age at diagnosis and a higher proportion of female patients were observed in familial cases. Because the use of medications, such as thiopurines and anti-TNF agents, and the need for surgery are regarded as markers for an aggressive disease course, our results suggest that CD, but not UC, may have a more aggressive clinical course in familial cases.

In terms of anti-TNF use, the higher rate in familial CD cases does not necessarily mean that familial CD cases have a more aggressive disease course than do sporadic cases, because patients with

family members affected by this disease may be more concerned about their disease and therefore be more likely to adopt a more aggressive approach earlier in the disease course. Nevertheless, the higher rate of anti-TNF use in familial CD cases in our present study was coupled with a higher rate of intestinal resection. The results were thought to suggest the possibility of a more aggressive disease in these patients.

In the initial analysis regarding intestinal resection, the cumulative probability did not appear to be significantly different in sporadic and familial CD cases. However, when reanalysed after excluding patients who underwent intestinal resection within 1 year of diagnosis, the cumulative probability of intestinal resection was significantly higher in familial CD cases. A significant difference was evident in the mid- and late-period of the Kaplan–Meier curve, from which it was inferred that the presence of a family history in CD patients may influence the need for surgical treatment during the course of the disease rather than at diagnosis. To appropriately evaluate the influence of medication on disease course, the duration of medication use before surgery needs to be of sufficient time. Therefore, patients who underwent surgery at diagnosis or within 1 year of diagnosis were excluded in previous reports.[22,26,30] In
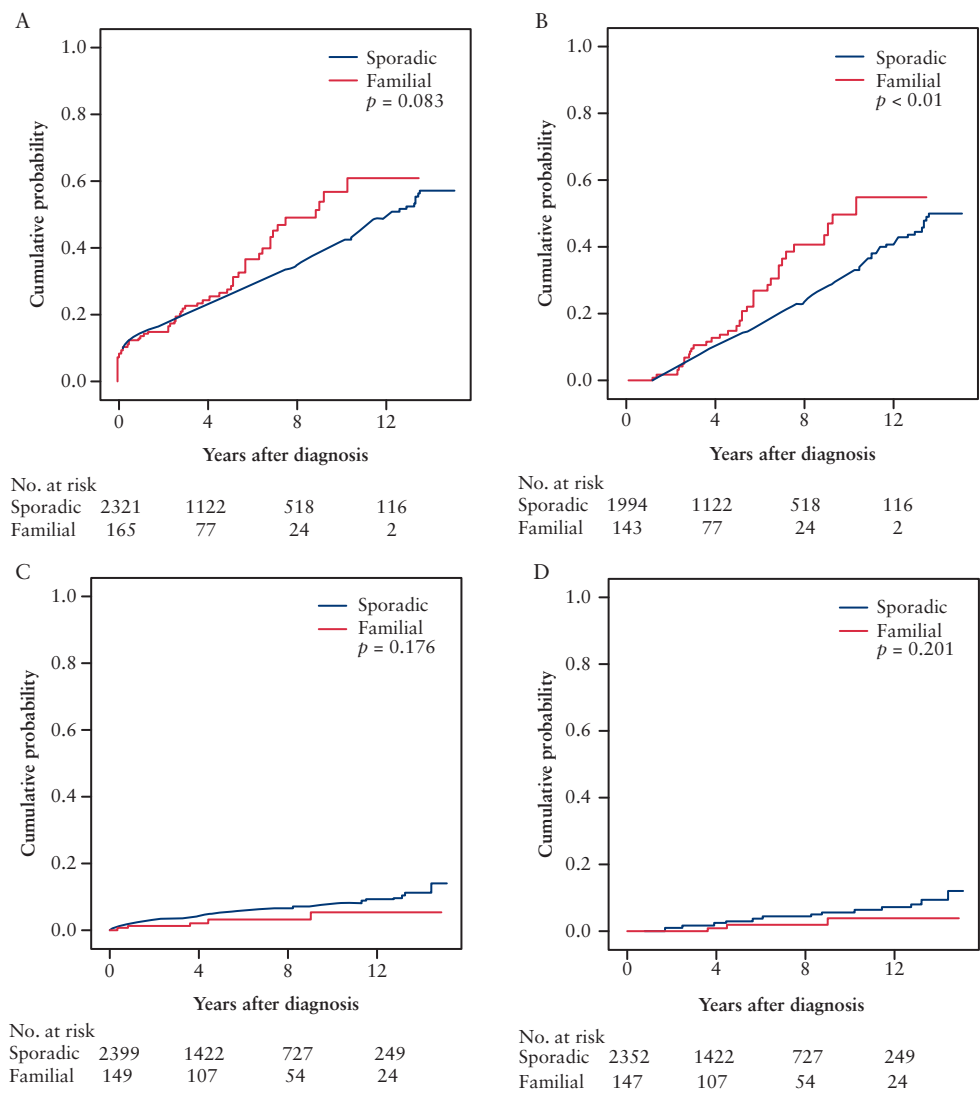
Figure 2. Cumulative probability of surgery in sporadic and familial cases in patients with Crohn's disease (CD) and ulcerative colitis (UC) who were first diagnosed in or later than the year 2000: (A) Intestinal resection in 2486 CD patients; (B) intestinal resection in 2137 CD patients (after excluding cases with intestinal resection within 1 year of diagnosis) (familial vs sporadic, *p* = 0.007); (C) colectomy in 2549 UC patients; (D) colectomy in 2499 UC patients (after excluding cases with colectomy within 1 year of diagnosis).

addition, in our previous work we found that the frequency of complicated behaviour and perianal fistula at diagnosis has been increasing recently[22]; we suggested that this temporal change was due to selective referral of patients with more severe disease. Therefore, it may be necessary to exclude patients who have undergone surgery at diagnosis or very early during the disease course to avoid the referral bias. For these reasons, patients who had undergone intestinal resection within 1 year of diagnosis were excluded from our analysis of risk factors for intestinal resection. In the multivariate analysis, a positive family history proved to be an independent risk factor for intestinal resection (HR: 1.61, 95% CI: 1.13–2.29). These results are in accordance with those from a recent population-based cohort study in Denmark. That study showed that patients with familial CD had a significantly higher risk of major surgery than sporadic CD cases after 2 years of disease duration (HR: 1.62, 95% CI: 1.26–2.07), and the difference in the cumulative incidence of surgery between sporadic and familial CD cases seemed to be apparent 4 or 5 years after diagnosis.[20] This Danish study supports our suggestion that family history influences intestinal resection in CD patients

over the course of the disease rather than at diagnosis. Since age at symptom onset and diagnosis was similar in familial and sporadic CD cases, it is unlikely that early detection of disease would reduce the time to surgery.

To the best of our knowledge, our present study is the first to evaluate the influence of family history on the long-term clinical course of both CD and UC in a large cohort of non-Caucasian patients. Unlike our study, most previous studies failed to show a positive association between a family history and the need for intestinal resection in CD patients.[10–12,19,20,31–34] Whether there are any differences in disease course between familial and sporadic cases of IBD has been investigated in studies of various designs, including single-centre studies,[32–34] multicentre studies,[11,19] population-based studies,[12,20] and a meta-analysis.[31] Of these, only a population-based study using the national registries of Denmark[20] and a multicentre study in a United States paediatric population[19] have demonstrated that familial IBD cases have an increased need for surgery and/or medication. A Norwegian population-based cohort study showed a higher relapse rate in familial UC cases, but

Table 4. Factors associated with intestinal resection in Crohn's disease.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Sex						
Male	Reference			Not included		
Female	1.05	0.85–1.30	0.651			
Age at diagnosis						
17–40	Reference			Not included		
<17	0.95	0.72–1.24	0.700			
>40	1.15	0.73–1.83	0.546			
Smoking status at diagnosis						
Never	Reference			Reference		
Ex	1.23	0.81–1.87	0.339	1.21	0.79–1.85	0.391
Current	1.28	1.03–1.59	0.028	1.14	0.91–1.43	0.256
Disease location at diagnosis						
L2	Reference			Reference		
L3	3.32	1.82–6.07	<0.001	3.29	1.80–6.01	<0.001
L1	4.58	2.46–8.54	<0.001	3.74	2.00–7.01	<0.001
Disease behaviour at diagnosis						
B1	Reference			Reference		
B2	2.03	1.48–2.77	<0.001	1.96	1.42–2.70	<0.001
B3	2.96	2.13–4.13	<0.001	2.99	2.12–4.22	<0.001
Early use of thiopurines						
No	Reference			Reference		
Yes	0.86	0.70–1.07	0.175	0.80	0.64–0.99	0.043
Early use of anti-TNF agents						
No	Reference			Reference		
Yes	1.36	0.89–2.10	0.159	1.40	0.88–2.23	0.160
Familial history						
Sporadic	Reference			Reference		
Familial	1.61	1.14–2.28	0.007	1.61	1.13–2.29	0.009

HR, hazard ratio; CI, confidence interval.

no difference was observed in the need for surgery or medication.[12] The causes of there being varied results across the previous studies are not clear. Nevertheless, the main limitation of those previous studies was their limited power to detect relevant differences between sporadic and familial cases. Most single-centre studies to date have included only a small number of patients. Although multicentre or population-based studies have the advantage of including larger number of patients, they also have the potential disadvantage of inhomogeneous data. The criteria for medication use and performing surgery may also be differ somewhat between different hospitals. Among the studies regarding the influence of family history on the clinical course of IBD, our current study is the third largest to date, with 6071 patients, following a Danish population-based study of 27 886 patients[20] and a Spanish multicentre study of 11 983 patients.[11] Our current study is the largest single-centre study yet performed.[32–34] Therefore, although our study was limited in terms of the generalizability of the results, which is an issue intrinsic to any single-centre study, it has higher statistical power than other small-scale studies, and it also has the advantage of containing homogenous and high-quality data.

In accordance with previous studies,[11,18,31,32] we found that age at diagnosis of UC in familial cases was younger than that in sporadic cases. Young age at diagnosis has been considered one of the clinical predictors for a more aggressive disease course.[35] In contrast with the situation in CD, however, we did not find any differences in the clinical course of UC between familial and sporadic cases, even though the number of UC patients included in our analysis was higher than that of CD patients. There are a few possible explanations for this

difference. First, there is a possibility that the much less infrequent need for surgery and/or medication use in our UC patients compared with our CD patients resulted in insufficient statistical power to detect relevant differences between sporadic and familial cases.[21,22] Second, since the influence of genetics on disease development is lower in UC than in CD, its influence on clinical course may also be lower.[3,8,36] In fact, little is known about the functional implications of genetic factors, although 163 loci associated with IBD have been identified in recent genetic studies.[7,37] However, we believe that the results cannot preclude a genetic influence on disease course. Third, considering that the median age at diagnosis was 36 years in UC and 22 years in CD, it is likely that family members with UC lived apart and in different environments at the time of diagnosis, whereas family members with CD may more often have lived together in shared environments. This difference may lead to a more varied clinical course in familial UC cases than in familial CD cases. In this respect, it is notable that the only study to report a positive correlation between a family history and clinical course of UC was conducted in paediatric-onset UC patients.[19] Fourth, patient awareness about UC disease in familial cases may reduce the age at symptom onset and diagnosis. Even mild symptoms, such as low-grade diarrhoea or intermittent haematochezia, could bring such patients to the clinic. In case of CD, although the reason behind the similar ages at diagnosis between familial and sporadic cases was not clear, it seems to be due to the fact that patients with CD are diagnosed at a much earlier age due to unwillingness to visit the clinic with nonspecific gastrointestinal symptoms in young patients and the lower incidence of CD compared with UC in Korea.[23]

The proportion of male patients was significantly lower in our familial UC cases (47.6%) than in our sporadic UC cases (55.2%), especially in the familial cases with affected first-degree relatives (44.8%). However, the male-to-female ratio in familial and sporadic UC is variable in the literature, even in Western multicentre and population-based studies.[11,12]

In addition to the presence of a family history, location at diagnosis, behaviour at diagnosis, and early use of thiopurines were found to be independent risk factors for intestinal resection in CD, in agreement with the previous reports.[22,26] Early use of anti-TNF agents did not have any impact on surgery in our analysis, possibly because of the strict regulation of anti-TNF use by the national health insurance system in Korea.

The results of the present study showing the possibility of a more aggressive course in familial CD have several clinical and research implications. When a patient visits an IBD clinic, aggressive treatment such as early use of thiopurines or anti-TNF should be considered in patients with a family history more than it would be in sporadic cases, and especially in those of the former with other risk factors related to complications. In addition, the results of medication use and resection rate in patients with CD may indicate a reduced response to thiopurines and anti-TNF drugs in familial CD cases sharing genetic and environmental factors. Therefore, research on drug concentrations/autoantibodies, lifestyles, and even patient behaviour in familial cases will be needed.

As we suggested earlier, there were several limitations to our present study. First, our analysis was performed at a single tertiary referral centre, which limits our ability to generalize our findings. Second, the prevalence rate of IBD is rapidly increasing in Korea,[23] and so is the frequency of family history of IBD (Supplementary Figure 1). In our epidemiological study, the mean annual incidence rates of CD and UC increased from 0.05 and 0.34 per 100 000 inhabitants, respectively, in 1986–1990 to 1.34 and 3.08 per 100 000 inhabitants, respectively, in 2001–2005.[23] It seems likely that the increasing frequency of familial cases over the study period was largely influenced by the increasing prevalence of IBD. It is uncertain whether the results obtained from this dynamic setting can be applied to patients in Western countries, where the rates of IBD and of cases with a family history are rather more stable.

In conclusion, our single referral centre–based cohort study suggests the possibility of a more aggressive clinical course in familial CD cases than in sporadic CD cases. However, additional population-based studies are needed to assess the true influence of family history on Korean CD; this will also provide insight into whether the effects in patients in the East differ from those in the West.[12,20]

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Conflict of Interest

Suk-Kyun Yang received a research grant from Janssen Korea Ltd, but this grant was not related to the topic of the current study. The remaining authors have no competing interests to declare.

Author Contributions

SKY, SWH, and SHP designed the study; MSK, WSK, JML, HSL, YSY, and CSY collected and interpreted the data; SWH and SHP performed the statistical analysis; DHY, KJK, BDY, JSB, SJM, and JHK cared for the patients and critically reviewed the manuscript; SWH drafted the manuscript; SKY and CSY contributed to data interpretation and critically reviewed and revised the manuscript; and SKY is the guarantor of the article and approved the final manuscript. All of the authors read and approved the final manuscript.

Supplementary Data

Supplementary data to this article can be found at *ECCO-JCC* online.

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