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Family History of Crohn's Disease Is Associated with an Increased Risk for Crohn's Disease of the Pouch

Bo Shen, MD, Feza H. Remzi, MD, Jeffrey P. Hammel, MS, Bret A. Lashner, MD, MPH, Charles L. Bevins, MD, PhD, Ian C. Lavery, MD, Jan Wehkamp, MD, and Victor W. Fazio, MB, MS

Digestive Disease Institute and Lerner Research Institute, Cleveland Clinic, Cleveland, OH

Abstract

Introduction—Crohn's disease (CD) of the pouch can occur in patients with restorative proctocolectomy and ileal pouch-anal anastomosis originally performed for a pre-operative diagnosis of ulcerative colitis (UC). CD of the pouch was often observed in patients with a family history of CD.

Aim—To determine whether the family history of CD increased the risk for CD of the pouch in patients who underwent restorative proctocolectomy.

Methods—A total of 558 eligible patients seen in the Pouchitis Clinic were enrolled, including 116 patients with CD of the pouch and 442 patients with a normal pouch or other pouch disorders. Demographic and clinical variables were included in the study. Multivariable logistic regression analyses were performed.

Results—The adjusted multivariable logistic analyses revealed that the risk for CD of the pouch was increased in patients with a family history of CD with odds ratio (OR) of 3.22 (95% CI 1.56–6.67), or with a first-degree relative with CD (OR=4.18, 95% CI 1.48–11.8), or with a greater number of family members with CD (OR=2.00 per family member, 95% CI 1.19–3.37), adjusting for age, gender, smoking status, duration of IBD, duration of having a pouch, and a pre-op diagnosis of indeterminate colitis or CD. In addition, patients with a younger age and longer duration of having a pouch had a higher risk for CD of the pouch. A diagnosis of CD of the pouch was associated with a poor outcome with a greater than 5-fold estimated increased odds of pouch failure (OR=5.58 and 95% CI, 2.74 – 11.4).

Conclusions—The presence of a family history of CD is associated with an increased risk for CD of the pouch, which in turn has a high risk for pouch failure.

Keywords

Crohn's disease; Inflammatory Bowel Disease; Family History; Ileal Pouch; Pouchitis; Restorative Proctocolectomy; Ulcerative Colitis

INTRODUCTION

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) has become the surgical treatment of choice for the majority of ulcerative colitis (UC) patients with medically-refractory disease or dysplasia, as well as for the majority of patients with familial adenomatous polyposis (FAP).^{1,2,3} This surgical procedure is generally contraindicated in

patients with known Crohn's colitis before or during colectomy. Nonetheless, *de novo* Crohn's disease (CD) of the pouch can develop after IPAA which is performed in patients with a pre-operative diagnosis of UC or indeterminate colitis (IC). The true incidence of CD of the pouch in patients is not known. Reported cumulative frequencies range from 2.7% to 13%.^{4,5,6,7,8,9,10,11} CD of the pouch can be categorized into 3 clinical phenotypes: inflammatory, fibrostenotic, and fistulizing.¹²

The etiology and pathogenesis of post-IPAA CD are unknown. Previous studies have shown that the risk factors for CD of the pouch were a long duration of having a pouch, being an active smoker;¹³ a pre-operative diagnosis of IC, ¹⁴ and seropositive anti-*Saccharomyces cerevisiae* (ASCA)-IgA.¹⁵ It appears that each of the clinical phenotypes of CD of the pouch is associated with different risk factors.¹⁶ A recent study involving 16 patients with CD of the pouch showed that IPAA patients with a pre-operative diagnosis of UC who had a family history of CD had an increased risk for CD of the pouch with a hazard ratio of 8.1.¹⁵ Our hypothesis was that family history of CD in first-degree and/or second-degree relatives was associated with an increased risk for post-operative CD in UC or IC patients who underwent restorative proctocolectomy with IPAA.

PATIENTS AND METHODS

Patients

The Cleveland Clinic Institutional Review Board approved this study, and informed consent was obtained from all patients. A total of 558 consecutive, eligible patients were prospective studied, of whom 116 patients had CD of the pouch. All patients were recruited from our Pouchitis Clinic staffed by an IBD specialist (B.S.) and 3 colorectal surgeons (V.W.F, F.H.R., I.C.L.) from March 2002 to July 2007. The study group consisted of 116 patients with CD of the pouch and the control group had 442 patients with a normal pouch or other pouch disorders.

Diagnostic Criteria

Patients with CD of the pouch were diagnosed based on a combined assessment of symptoms, endoscopy, histology, and radiography using the criteria previously published by our group.^{12,16,17} CD of the pouch belonged to either of the three clinical phenotypes modified for the Vienna Classification¹⁸ and Montreal Classification:¹⁹ inflammatory; fibrostenotic; and fistulizing CD.¹⁷ *Inflammatory CD of the pouch* was defined as ulcerated lesions of the small bowel or afferent limb without diffuse pouchitis (excluding backwash ileitis from backwash pouchitis) these ulcers persisted despite ≥ 4 weeks of antibiotic therapy. *Fibrostenotic CD of the pouch* was defined as the presence of ulcerated strictures in the small bowel, distal ileum, afferent limb, mid-pouch, or pouch inlet with concurrent ulcers or inflammation of the afferent limb. The diagnosis of inflammatory or fibrostenotic CD of the pouch was made after exclusion of regular (more often than weekly) NSAID use at time of the diagnosis. ²⁰ *Fistulizing CD of the pouch* was defined as having a fistula that developed 12 months after the ileostomy takedown in the absence of surgically related local complications such as abscess, leak, anastomotic separation, and sepsis. The lesions included perianal fistulae, pouch-vaginal fistulae, pouch-bladder fistulae, entero- or pouch-cutaneous fistulae. If fistulas that developed less than 12 months after surgery were considered either due to CD or surgery-related complications. For these patients, a diagnosis of CD would be made if they later on developed other features of CD (such as small bowel ulcers or stricture, the presence of granulomas on histology, or symptomatic or radiographic response to a therapy with immunomodulators or biological agents). A great caution was taken for making a diagnosis of Crohn's disease of the pouch, as the diagnosis would carry great psychosocial and medical impact on the patients. We have established a diagnostic

algorithm for CD of the pouch used in Pouchitis Clinic (Figure 1). In our clinical practice, one of the most intriguing challenges has been the distinction between surgery-related fistula/leak vs. fistulizing CD. After an extensive clinical, radiographic, endoscopic, and histologic evaluation was performed and the diagnosis was not conclusive, a diagnostic trial of biological agents was used make the distinction between surgical complications and fistulizing CD.

Diagnosis of normal pouch, pouchitis, cuffitis, and irritable pouch syndrome (IPS) was based on the criteria as previously published by our group.¹³ Backwash ileitis from diffuse pouchitis was defined endoscopic and histologic contiguous inflammation of diffuse pouchitis and distal ileitis at the afferent limb with a widely patent pouch inlet.

Family History of Inflammatory Bowel Disease

The presence of familial CD was used only for those with one or more first-degree (parents, offspring, or siblings of the index patients) or second-degree relatives who had CD. A complete family history of CD was elicited by the treating physician (B. S.) during patients' office visit. If the patients' family members had sought clinical care at the Cleveland Clinic, their electronic medical charts were reviewed and the ICD-9-CM codes were verified.

Inclusion and Exclusion Criteria

In order to qualify for the study, patients with CD of the pouch needed to meet all of the following inclusion criteria: 1) > 15 years old; 2) being able to give consent; 3) being evaluated and followed-up in the Pouchitis Clinic; 4) having underlying IBD; and 5) having a diagnosis of CD of the pouch or other pouch conditions, including healthy pouch, irritable pouch syndrome, pouchitis, and cuffitis.²¹ Exclusion criterion was pouch patients with underlying FAP or colon neoplasm.

Protocol

An outpatient evaluation with a combined assessment of demographic, clinical, endoscopic, histologic, and radiographic data were conducted. The data were entered into our prospectively maintained Pouchitis Database. All patients underwent outpatient pouch endoscopy with biopsy. Segmental evaluation and biopsy of the afferent limb, pouch, and rectal columnar cuff were performed during pouch endoscopy. The endoscopic features of each segment were documented and biopsies were separately labeled. The Pouchitis Disease Activity Index (PDAI) endoscopy scores (range 0–6) were measured to grade inflammation of the afferent limb, pouch, and cuff, respectively. Examination under general anesthesia, retrograde radiographic pouchography, CT enterography, MRI of the pelvis, or small bowel capsule endoscopy were performed if the diagnosis of CD of the pouch was not conclusive by routine clinical, endoscopic, and histologic examination. All patients were followed after IPAA completion and the ileostomy closure for a minimum of 12 months. All patients had undergone IPAA for a minimum of 12 months before assessment.

Definitions of Variables

The definitions of demographic and clinical variables were described as our previous studies.^{12,13,17} “use of immunomodulators” – use of immunomodulators for more than 6 months after the ileostomy take-down for inflammatory conditions of the pouch, concurrent autoimmune disorders, or as post-liver transplant immune suppression; “use of biologics” – any use of infliximab or adalimumab for inflammatory conditions of the pouch (including CD of the pouch or chronic pouchitis) or concurrent autoimmune disorders; “pouch failure” – dysfunctional pouch requiring in pouch resection or a permanent diversion;

“hospitalization” - admission to our institution or outside hospital for at least 24 hours with a primary diagnosis related to disorder(s) of the pouch.

Outcome Measurement

The primary outcome was CD of the pouch. The primary analysis was the assessment of association between the family history of CD or other covariates and CD of the pouch. The secondary outcome was the evaluation of the risk for pouch failure in patients with IPAA.

Statistical Analysis

Univariable and multivariable associations between CD diagnosis and quantitative variables were assessed using Wald P-values from logistic regression models. Logistic regression models were also used to estimate odds ratios (OR) of a CD diagnosis between levels of categorical variables or relative to a specified difference in a quantitative variable. Of primary interest was the association between a diagnosis of CD of the pouch and a family history of CD, where family history was assessed in separate analyses as absent/present, number of first degree relatives with CD, and the total number of family members with CD. OR with 95% confidence intervals (CI) were estimated for each variable in the multivariable models. The odds ratio of pouch failure and 95% confidence interval relative to each metric of family history of CD were also calculated using univariable logistic regression models.

RESULTS

Of 558 patients, 21% had CD of the pouch, 10% had refractory pouchitis, 21% had acute pouchitis, 13% had cuffitis, 19% had IPS or other functional pouch disorders, 6% had surgical complications, and 11% had normal pouches. A total of 116 patients with CD of the pouch were studied who comprised 20.8% of the whole eligible patient population in the Pouchitis Clinic (Figure 2). Granulomas on mucosal biopsies were found in 11 (9.5%) of 116 cases with CD of the pouch. Demographic and clinical data were listed in Table 1. Six patients (1.1%) with a known pre-operative diagnosis of Crohn's colitis underwent restorative proctocolectomy with IPAA, although it was controversial whether Crohn's colitis without evidence of perianal disease or small bowel involvement was an absolute contraindication for IPAA. Detailed family history of IBD was listed in Table 2.

The mean follow-up at the Pouchitis Clinic for all 558 patients was 2.78 ± 1.72 (standard deviation) years. The mean follow-up was 2.80 ± 1.74 and 2.53 ± 1.70 years, for patients with or without CD of the pouch, respectively ($P = 0.72$). During the follow-up period, 11 (2.0%) patients had pouch failure due to surgical complications, including pelvic sepsis and pouch sinuses; 23 patients (4.1%) had failure due to CD of the pouch or chronic antibiotic-refractory pouchitis.

Univariable analyses demonstrated that among 125 patients with a family history of IBD (CD or UC), 28 (22.4%) developed CD of the pouch, while among the 433 patients without family history of CD, there were 88% (20.3%) developed CD of the pouch. ($P = 0.61$). Focusing on family history of CD, a diagnosis of CD of the pouch was found to be more likely for patients with a family history of CD (OR=3.38, 95% CI 1.69–6.75), for patients with a first degree relative with CD (OR=4.56, 95% CI 1.72–12.1), and for a greater number of family members with CD (OR=2.11 per family member, 95% CI 1.27–3.50). The adjusted multivariable results were: patients with a family history of CD (OR=3.22, 95% CI 1.56–6.67), patients with a first degree relative with CD (OR=4.18, 95% CI 1.48–11.8), and a greater number of family members with CD (OR=2.00 per family member, 95% CI 1.19–3.37) (see tables below for details). A diagnosis of CD of the pouch was univariably

associated with a poor outcome with a greater than 5-fold estimated increased odds of pouch failure (OR=5.58 and 95% CI, 2.74 – 11.4).

Family History of CD

Logistic regression analysis revealed that patients with a family history of CD had an increased risk for CD of the pouch with an OR of 3.22 (95% CI 1.56 – 6.67), adjusting for age, gender, smoking status, duration of IBD, duration of pouch, and a pre-op diagnosis of IC or CD (Table 3). In addition, patients with a younger age and longer duration of pouch had a higher risk for CD of the pouch.

Number of First Degree Relatives with CD

To further assess the association between the family history of CD and CD of the pouch, a separate logistic regression analysis of the impact of total number of first-degree relatives with CD on occurrence of CD of the pouch of the index patients was performed. The analysis again showed that patients with a family history of CD had a significantly increased risk for CD of the pouch with an OR of 4.18 (95% CI 1.48 – 11.8), adjusting for age, sex, smoking status, duration of pouch, duration of IBD, and a pre-op diagnosis of IC or CD (Table 4). In addition, patients with a younger age and longer duration of pouch had a higher risk for CD of the pouch.

Total Number of Family Members with CD

A separate logistic regression analysis of the impact of total number of relatives with CD on the occurrence of CD of the pouch was performed. The analysis again revealed that patients with a family history of CD had a significantly increased risk for CD of the pouch with an OR of 2.00 (95% CI 1.19 – 3.37), adjusting for age, gender, smoking status, duration of IBD, duration of pouch, and a pre-op diagnosis of IC or CD (Table 5). In addition, patients with a younger age and longer duration of pouch had a higher risk for CD of the pouch.

DISCUSSION

Patients with a pre-operative or intra-operative diagnosis of UC or IC can develop clinical, endoscopic, radiographic, or histologic features of CD after IPAA. The identification of risk factors for CD of the pouch has been difficult largely because CD of the pouch develops infrequently after IPAA and there are a small number of patients available for meaningful statistical analysis.^{15,22,23} Previous studies have revealed risk factors associated with CD of the pouch, including female gender (in a pediatric population),²⁴ active smoking,¹³ and a longer duration of having a pouch.¹³

Taking advantage of infrastructure and medical and surgical expertise in the Pouchitis Clinic, we were able to enroll 116 patients with a diagnosis of CD of the pouch. Our current studies again showed that a younger age and a long duration of IPAA were associated with a high risk for CD of the pouch. Furthermore, the logistic regression analysis revealed that patients with a family history of CD had a significantly increased risk for CD of the pouch with an OR of 3.22, adjusting for age, gender, smoking status, duration of IBD, duration of having a pouch, and a pre-op diagnosis of IC or CD. A diagnosis of CD of the pouch was associated with a poor outcome with greater than 5-fold estimated increased odds of pouch failure.

The etiology and pathogenesis of CD are complex. Familial studies have been extensively performed in non-pouch CD patients. Multiple lines of evidence indicate that genetic factor play a major role in susceptibility to CD. Studies have shown that family history,^{25,26} Jewish ethnicity,²⁶ the presence of other diseases with recognized genetic susceptibility²⁷

and polymorphisms of CARD15 mutations 26:28:29:30), Wnt-signaling pathway transcription factor Tcf-4,³¹ interleukin-23 receptor³² are the risk factors for CD. In population-based studies, approximately 5% to 10% of all affected individuals with IBD report a positive family history of the disease.^{33:34:35:36:37:38:39:40:41} Previous twin studies suggested that both environmental and genetic factors play in the development of CD.^{42:43:44:45} This notion from the non-pouch patients is supported by our current study on CD of the pouch in which younger age, along with a family history of CD, was shown to be associated with an increased risk for CD of the pouch.

CD of the pouch can occur under the following circumstances: 1) it occurs in a selected group of patients *intentionally* performed for a preoperative diagnosis of Crohn's colitis in the absence of small bowel, penetrating, or perianal disease;⁴⁶ 2) CD is also *inadvertently* found in colectomy specimens of patients with a pre-operative diagnosis of UC or IC;^{5:6:7:8:9:20:46:47} and 3) *de novo* CD of the pouch may develop weeks or years after IPAA and a reassessment of the proctocolectomy specimens may show no evidence of CD.^{7:8} *De novo* CD of the pouch by far is the most common. It is not clear why the probands first presented as UC or IC and why some patients developed CD of the pouch just weeks after the ileostomy take-down, while others had CD of the pouch yearly after the creation of IPAA. We speculate that an altered bowel anatomy with changes in luminal environment in IPAA may reset the "thermostat" for the interaction between the genetic and environmental factors patients with underlying IBD.

There are potential implications of our current study. The presence of a family history of CD in a patient with underlying UC or IC, together with other risk factors may influence the decision on whether IPAA should be performed. In the era of advanced medical therapy, particularly the widely use of biological agents, decisions on continuous medical therapy vs. restorative proctocolectomy with IPAA in patients with steroid-dependent or steroid-refractory UC can be difficult to make. Medical and surgical therapy each has its advantages and disadvantages. In a patient who is at the "cross-road" for medical vs. surgical treatment, a high risk for CD of the pouch may tip the balance favoring continuous medical therapy. Based on the results of this and other previous studies, the young patient with underlying UC who actively smokes and has a family history of CD, may be not ideal candidate for IPAA because of the high risk for CD of the pouch and pouch failure.

There are limitations to our study. First, there might have been referral bias, since all the patients in the current study were seen in the setting of a subspecialty Pouchitis Clinic where patients with a spectrum of pouch disorders were diagnosed and managed by an IBD specialist and colorectal surgeons. The high prevalence (20.8%, 116/558) of CD of the pouch among all pouch patients reflected demographics of the Pouchitis Clinic, which might predispose to a selection bias. In our current study, there were a small number of patients with healthy, normal pouches and only a few of them had a family history of CD. However, we expected that results and conclusions from this study may also be applied to other clinical settings where patients with normal pouches are often seen. We would also expect that the referral bias may have a minimum impact on the association between family history of CD and a diagnosis of CD of the pouch, as in the cohort study, the cases (positive family history) and controls (no family history) had the same opportunity to develop CD (such as similar duration of a pouch and similar rates of cigarette smoking). Second, we might have uncovered more patients with CD of the pouch with a longer follow-up. Third, we did not investigate whether a family history of CD had an impact on each of the 3 phenotypes of CD of the pouch and whether there was a concordance in clinical phenotypes of CD between the proband cases and their affected family members, since it is difficult to verify the diagnosis and clinical features without extensive diagnostic tests. Fourth, the establishment of a positive family history of CD was based on patients' recall when they first visited the

Pouchitis Clinic. There might have been recall bias. If the patients' family members had sought clinical care at the Cleveland Clinic, their electronic medical charts were reviewed and the ICD-9-CM codes were verified. However, it was technically not feasible to verify the diagnosis of CD among all family members, particularly in those who sought medical care at outside institutions. Nonetheless, we believed that a careful clinical interview is more accurate than patients' self reporting or mailed questionnaire-based survey in obtaining family history. Finally, not every possible factor has been investigated in this study or modeled in the multivariable analyses because of the sample size. Immunogenetic profiles of patients with or without a familiar history of CD were not investigated. Laboratory study on markers reported to be associated with CD such as ASCA, and NOD2/CARD15 genetic polymorphisms^{48,49,50} are ongoing in the Pouchitis Clinic.

CONCLUSIONS

The presence of family history of CD was strongly associated with CD of the pouch in patients who underwent restorative proctocolectomy. The patients with UC or IC undergoing restorative proctocolectomy who had a family history of CD may be informed the increased risk for having CD of the pouch. In addition, a diagnosis of CD of the pouch was associated with a high risk for pouch failure.

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ABBREVIATIONS

ASCA	<i>anti-saccharomyces cerevesiae</i>
CD	Crohn's disease
CI	confidence interval
FAP	familial adenomatous polyposis
IBD	inflammatory bowel disease
IC	indeterminate colitis
IPAA	Ileal pouch-anal anastomosis
IPS	irritable pouch syndrome
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PDAI	Pouchitis Disease Activity Index
UC	ulcerative colitis

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Figure 1.
Diagnostic Algorithm for Crohn's Disease of the Pouch

Table 1

Demographic and Clinic Data of 558 Patients with Pouches

Variable	Mean ± Standard Deviation or Frequency (%)
Age, yrs	45.7 ± 13.8
Female Gender	257 (46.1%)
Caucasian Race	549 (98.4%)
Smoking Status	
Ex-smoker	104 (18.6%)
Active	52 (9.3%)
Duration of Pouch, yrs	8.7 ± 5.5
Duration of Inflammatory Bowel Disease, yrs	17.2 ± 9.8
J Pouch	527 (94.4%)
2-Stage Pouch Surgery	437 (78.3%)
Colectomy for Refractory Disease	483 (86.5%)
Pre-operative Pancolitis	514 (92.1%)
Toxic Megacolon or Fulminant Colitis at Colectomy	54 (9.7%)
Pre-op Diagnosis	
UC	522 (93.5%)
Indeterminate Colitis	30 (5.4%)
Crohn's Colitis	6 (1.1%)
Pre-colectomy Biological Therapy	18 (3.2%)
Duration of Follow-up, yrs	2.7 ± 1.7
Post-operative Use of Immunomodulators	12.9 (%)
Post-operative Use of Biologics	7.3%
Pouch Failure	
Yes- Due to surgical complications	11 (2.0%)
Yes – due to inflammatory disorder of the pouch	23 (4.1%)
Hospitalization due to Pouch Disorder	476 (85.3%)
Extra-intestinal manifestations	
Arthralgia or Arthropathy	224 (40.4%)
Cutaneous Lesions	4 (0.7%)
Ocular Lesions	10 (1.8%)
Thromboembolic Events	9 (1.6%)
Primary Sclerosing Cholangitis	26 (4.7%)

Table 2**Family History of Inflammatory Bowel Disease**

Variable	Frequency (%)
Family History of Inflammatory Bowel Disease	
Crohn's Disease	31 (5.6%)
Ulcerative Colitis	89 (15.9%)
Crohn's Disease and Ulcerative Colitis	5 (0.9%)
Neither Crohn's Disease Nor Ulcerative Colitis	433 (77.6%)
Number of First-degree Relatives with Inflammatory Bowel Disease	
0	483 (86.6%)
1	69 (12.4%)
2	6 (1.1%)
Total Family Members with Inflammatory Bowel Disease	
0	433 (77.6%)
1	97 (17.4%)
2	22 (3.9%)
3	1 (0.2%)
4	3 (0.5%)
5	2 (0.4%)
First-degree Relatives with Crohn's Disease	
0	541 (97.0%)
1	17 (3.0%)
Total Family Members with Crohn's Disease	
0	522 (93.5%)
1	30 (5.4%)
2	3 (0.5%)
3	1 (0.2%)
4	2 (0.4%)

Table 3

Association between a Diagnosis of Crohn's Disease and Family History of Crohn's Disease and Covariates - Multivariable Logistic Regression Model

Variable	OR (95% CI)	P-value
Age *	0.84 (0.76 – 0.93)	0.001
Gender= Female	1.31 (0.85 – 2.01)	0.22
Smoking = Ex	1.11 (0.62 – 1.98)	0.73
Smoking = Active	1.36 (0.68 – 2.71)	0.38
Duration of Pouch *	1.44 (1.16 – 1.80)	0.001
Duration of Inflammatory Bowel Disease *	1.08 (0.93 – 1.26)	0.30
Pre-op Diagnosis of Indeterminate Colitis or Crohn's Disease	1.32 (0.58 – 2.99)	0.51
Family History of Crohn's Disease	3.22 (1.56 – 6.67)	0.002

* Parameter estimate and odds ratio relative to a five year difference

Table 4

Association between a Diagnosis of Crohn's Disease and Number of First-degree Relatives with Crohn's Disease and Covariates - Multivariable Logistic Regression Model

Variable	OR (95% CI)	P-value
Age *	0.84 (0.76 – 0.93)	0.001
Gender = Female	1.29 (0.84 – 1.98)	0.25
Smoking = Ex	1.18 (0.66 – 2.12)	0.58
Smoking = Active	1.49 (0.75 – 2.94)	0.26
Duration of Pouch *	1.42 (1.14 – 1.78)	0.002
Duration of Inflammatory Bowel Disease *	1.08 (0.92 – 1.25)	0.34
Pre-op Diagnosis of Indeterminate Colitis or Crohn's Disease	1.34 (0.60 – 3.03)	0.48
Number of First-degree Relatives with Crohn's Disease **	4.18 (1.48 – 11.8)	0.007

* Parameter estimate and odds ratio relative to a five-year difference

** Parameter estimate and odds ratio relative to a difference of one relative

Table 5

Association between a Diagnosis of Crohn's Disease and Total Number of Family Member with Crohn's Disease and Covariates - Multivariable Logistic Regression Model

Variable	OR (95% CI)	P-value
Age *	0.84 (0.76 – 0.93)	0.001
Gender = Female	1.29 (0.84 – 1.98)	0.25
Smoking = Ex	1.08 (0.60 – 1.94)	0.80
Smoking = Active	1.44 (0.73 – 2.85)	0.29
Duration of Pouch *	1.43 (1.15 – 1.79)	0.001
Duration of Inflammatory Bowel Disease *	1.09 (0.93 – 1.27)	0.28
Pre-op Diagnosis of Indeterminate Colitis or Crohn's Disease	1.34 (0.59 – 3.02)	0.48
Total Number of Family Members with Crohn's Disease **	2.00 (1.19 – 3.37)	0.009

* Parameter estimate and odds ratio relative to a five year difference

** Parameter estimate and odds ratio relative to a difference of one family member