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The Yield of Colonoscopy in Patients With Non-Constipated Irritable Bowel Syndrome: Results From a Prospective, Controlled US Trial

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Abstract

OBJECTIVES—There are limited data on the yield of colonoscopy in patients with irritable bowel syndrome (IBS). This study compared the prevalence of structural colonic lesions in patients with suspected non-constipation-predominant IBS and healthy volunteers. We also determined the yield of rectosigmoid biopsies in patients with suspected IBS.

METHODS—This was a prospective, case – control study conducted at three US sites. Patients with suspected non-constipation-predominant IBS (Rome II) underwent colonoscopy with rectosigmoid biopsies. Healthy persons undergoing colonoscopy for colorectal cancer screening or

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CONFLICT OF INTEREST

Guarantor of the article : William D. Chey, MD, AGAF, FACG, FACP.

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Potential competing interests : William D. Chey is a consultant for Albireo, Aryx, AstraZeneca, Ironwood, McNeil, Proctor & Gamble, Prometheus, Salix, Smart Pill Corporation, Takeda, and Xenoport and has been a speakers' bureau member for Axcan, Prometheus, Salix, and Takeda. Borko Nojkov, Joel H. Rubenstein, and Richard R. Dobhan have no conflict of interest relevant to this study. Joel K. Greenson is a consultant for Millennium Pharmaceuticals, Glaxo-SmithKline, and Roche/Genentech. He is a shareholder in Amirsys Corporation. Brooks D. Cash is a consultant for Salix, Takeda, and Prometheus and has received research grants from Salix. He has been a speakers' bureau member for Takeda, Salix, and Prometheus.

polyp surveillance comprised the control group. Abnormalities identified at colonoscopy were compared between suspected IBS and control groups.

RESULTS—In all, 466 suspected IBS patients and 451 controls were enrolled. Suspected IBS patients were significantly younger ($P < 0.0001$) and more frequently female ($P < 0.0001$) than controls. The most common lesions in suspected IBS patients were hemorrhoids (18.2%), polyps (14.6%), and diverticulosis (8.8%). Suspected IBS patients had a lower prevalence of adenomas (7.7% vs. 26.1%, $P < 0.0001$) and diverticulosis (8.8% vs. 21.3%, $P < 0.0001$) and higher prevalence of mucosal erythema or ulceration (4.9% vs. 1.8%, $P < 0.01$) compared with controls. Logistic regression found the between-group differences in adenoma prevalence to be robust after correction for demographic factors. The overall prevalence of microscopic colitis in suspected IBS patients was 1.5% (7/466) and 2.3% (4/171) in those ≥45 years of age.

CONCLUSIONS—The prevalence of structural abnormalities of the colon is no higher in suspected non-constipation IBS patients than in healthy controls. Microscopic colitis can be identified in a small proportion of persons with IBS symptoms.

INTRODUCTION

The irritable bowel syndrome (IBS) is a symptom-based condition in which affected individuals report recurrent bouts of abdominal pain or discomfort associated with altered bowel habits (1). Population-based studies from the United States report that the prevalence of IBS is 7–15% and that this condition occurs more commonly in women than men (2–4). IBS is heterogeneous both in terms of pathophysiology and symptom expression. IBS patients are typically subgrouped on the basis of differences in predominant bowel pattern as diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), or a mixture of both diarrhea and constipation-related features (IBS-M).

The lack of reliable biomarkers and overlap of IBS symptoms with other organic conditions cause most health-care providers to consider IBS a " diagnosis of exclusion" (5). Owing to concerns about mislabeling a patient with an organic disease with IBS, health-care providers often order a battery of tests in patients with suspected IBS. Physicians are particularly concerned about missing colorectal cancer (CRC) or inflammatory bowel diseases (IBDs) such as ulcerative colitis or Crohn's disease in patients with IBS symptoms, especially those that include a diarrheal component. Owing to this, patients with typical IBS symptoms commonly undergo colonoscopy. For example, community-based surveys indicate that half of IBS patients undergo colonoscopy as part of the evaluation of their symptoms (6). Furthermore, a recent national database analysis found that roughly a quarter of all colonoscopies performed in the United States are for IBS-related symptoms, and 1 in 10 colonoscopies performed in patients under the age of 50 are for IBS symptoms (7). Despite such broad use of colonoscopy in the evaluation of IBS symptoms, data addressing the actual prevalence of colonic structural abnormalities in patients with IBS are limited.

Another potential concern in patients with IBS symptoms are the microscopic colitides. The microscopic colitides are characterized by normal endoscopic appearance of the colon but an intense mucosal inflammatory infiltrate on mucosal biopsies. On the basis of the nature of the inflammatory infiltrate and the thickness of the sub-mucosal collagen band, the microscopic colitides can be broadly separated into two entities, lymphocytic colitis and collagenous colitis (8,9). The principal clinical manifestation of microscopic colitides is diarrhea. However, it is not uncommon for affected patients to report abdominal cramping or discomfort (8). A recent retrospective study from Olmstead County suggested that a significant proportion of patients with lymphocytic and collagenous colitis had symptoms suggestive of IBS or had been diagnosed with IBS before eventually being diagnosed with

microscopic colitis (10). No studies have prospectively evaluated the prevalence of the microscopic colitides in patients with IBS symptoms.

We performed a prospective, multi-center US trial to compare the prevalence of structural lesions of the colon including diverticulosis, polyps, or malignancy found during colonoscopy in patients with non-constipated IBS and healthy volunteers undergoing routine CRC screening. We also aimed to determine the prevalence of IBDs including ulcerative colitis, Crohn's disease, and microscopic colitis in patients with non-constipated IBS.

METHODS

Study population

This prospective, observational case–control study was conducted at three US sites (National Naval Medical Center Bethesda, MD; Naval Medical Center Portsmouth, Portsmouth, VA; University of Michigan, Ann Arbor, MI) between August 2003 and August 2008 (11). The IBS group was composed of consecutive patients with symptoms suggestive of non-constipation-predominant IBS who had no "alarm features." The control group consisted of asymptomatic healthy persons undergoing colonoscopy for CRC screening or surveillance based on a personal history of adenomatous polyps.

Study populations

Patients with symptoms suggestive of IBS were identified in the Gastroenterology Clinics at the participating sites. Eligible patients with suspected IBS fulfilled the Rome II criteria as determined during a structured interview with a study coordinator (12). Patients who fulfilled the Rome II criteria for IBS-C were not eligible for enrollment. All other patients who fulfilled the Rome II criteria for IBS (non-constipation-predominant IBS) were eligible for enrollment (Table 1).

Patients with previously identified co-morbid illnesses that could have explained their gastrointestinal (GI) symptoms (e.g., celiac disease, colon cancer, IBD, scleroderma, small bowel bacterial overgrowth, uncontrolled thyroid disease, or diabetes) were not eligible for enrollment. Patients who had undergone previous structural evaluation of the GI tract for their IBS symptoms were not eligible. Further, patients with previous gastrointestinal or colonic surgery (except appendectomy or cholecystectomy) were also excluded. Patients reporting "alarm symptoms" including unexplained weight loss (> 10 lb over 6 months), fever, significant gastrointestinal bleeding (patients with spotting of red blood on the toilet tissue after a bowel movement were eligible), or those reporting a family history of a first degree relative with colon cancer, celiac disease, or IBD were not eligible for enrollment. In addition, we excluded women who were pregnant or breast feeding, and patients that had been previously evaluated for their IBS symptoms. On the basis of these exclusion criteria, the majority of the IBS population consisted of patients referred directly from primary care physicians.

The control group consisted of healthy individuals who were scheduled for screening or surveillance colonoscopy. Controls were recruited in the procedure units of the participating study sites before their colonoscopy. All controls completed a GI symptom questionnaire to confirm the absence of IBS symptoms. There were no differences in the preparations, equipment, or endoscopists used between the IBS and control groups.

Experimental protocol

All patients with suspected IBS underwent colonoscopy by an experienced board-certified gastroenterologist after bowel preparation with 4 l polyethylene glycol or oral phosphosoda

(13). During colonoscopy, all abnormalities identified were recorded. Polyps and/or mucosal abnormalities were biopsied and/or treated as deemed appropriate by the performing endoscopist. At least two random biopsies from the sigmoid colon and rectum were obtained in all patients with suspected IBS.

Similar to the IBS group, any abnormalities identified during colonoscopy in the control group were recorded. Biopsies and/or endoscopic therapy were performed as deemed clinically appropriate by the performing endoscopist. Colon biopsies were only performed in controls when a visible abnormality was identified during colonoscopy, thus random sampling of colonic tissue was not performed in the control group.

Findings of interest abstracted during colonoscopy included polyps, diverticulosis, mucosal erythema or ulceration, CRC, arterio-venous malformations, hemorrhoids, and anal fistula. Results of interest abstracted from the random rectosigmoid biopsies obtained from the IBS group included adenomatous and hyperplastic polyps, colorectal adenocarcinoma, Crohn's disease/ulcerative colitis, microscopic colitis (lymphocytic or collagenous colitis), and solitary rectal ulcer syndrome. All histological specimens were evaluated by experienced GI pathologists at the participating centers.

The diagnosis of lymphocytic colitis required an increase in intraepithelial lymphocytes (more than 15 lymphocytes/100 epithelial cells) and surface epithelial damage with increased lamina propria plasma cells and absent or minimal crypt architectural disruption. For a diagnosis of collagenous colitis, an increase/irregularity in sub-epithelial collagen (> 10 μM) that typically trapped superficial capillaries was required as well as the other inflammatory changes seen in lymphocytic colitis (8). All suspected cases of lymphocytic and collagenous colitis were confirmed by a single expert pathologist at the University of Michigan (J.K.G.).

Statistical analysis

Statistical comparisons of findings between the IBS and control groups were performed by χ^2 or Fisher's exact test. On the basis of an assumed adenomatous polyps prevalence of 20% in general middle-aged population, we calculated a required sample size of at least 329 participants in each of the two groups to detect 10% absolute difference in the mean proportions of adenomas with a power of 95% and α of 0.05. Logistic regression was used to adjust for differences in age, gender, race, level of education, tobacco, and alcohol use between groups.

RESULTS

Study population

Four hundred and sixty-six patients with suspected IBS and 451 healthy volunteers were enrolled in this study. The demographic characteristics of the IBS and control groups are shown in Table 2. Patients with suspected IBS were significantly younger and more likely to be female compared with the control group (mean age 41.1 years vs. 53.8 years, $P < 0.0001$, 69% vs. 41% female, $P < 0.0001$, respectively). There were no significant differences in the racial makeup of the two groups with the largest proportions of study participants being Caucasian (80–85%) or African-American (~10%).

Colonoscopic findings

More than 95% of patients and controls had procedures, which reached the cecum and were deemed "satisfactory clean" (good to excellent prep). The prevalence of colonic lesions identified during colonoscopy among participants in the suspected IBS and control groups

are shown in Table 3. The most common lesions in patients with suspected IBS were hemorrhoids (18.2%) followed by polyps (14.6%), diverticuli (8.8%), erythema, or ulceration (4.9%). The prevalence of macroscopically visible mucosal erythema ($n = 23$) or ulceration ($n = 2$) was significantly higher in patients with suspected IBS when compared with healthy controls (4.9% vs. 1.8%, $P < 0.01$).

In the control group, the most common findings were polyps (34.4%) followed by diverticuli (21.3%), and hemorrhoids (16.4%). Healthy controls had a significantly higher prevalence of polyps and diverticulosis compared with patients with suspected IBS (34.4% vs. 14.6%, $P < 0.0001$ and 21.3% vs. 8.8%, $P=0.0001$, respectively). Other lesions including CRC, arterio-venous malformations, and fistula were uncommon in both groups.

Histological findings

The most common lesions identified by histology in IBS patients were hyperplastic polyps (8.4%) and adenomas (7.7%). There were two patients (0.4%) in the IBS group that were confirmed to have IBD (one patient with Crohn's disease and one with ulcerative colitis).

In the control group, adenomas were most commonly found (26.1%) followed by hyperplastic polyps (11.5%). Healthy controls had a significantly higher prevalence of adenomatous polyps compared with patients with suspected IBS ($P = 0.0001$). There was no significant difference between the two groups in the prevalence of hyperplastic polyps, IBD, CRC, or solitary rectal ulcer syndrome (Table 4).

When colonic mucosal biopsies from the IBS group were reviewed, microscopic colitis was identified in 7 of 466 patients (1.5%). Among the patients with microscopic colitis, four patients had lymphocytic colitis and three had collagenous colitis. The mean age of the patients with microscopic colitis was 49.1 years (age range 35–66 years) and six of seven patients were female. The prevalence of microscopic colitis increased to 2.3% in IBS patients over the age of 45 years. All of the patients with microscopic colitis had normal appearing colonic mucosa on their colonoscopy. Evaluation with serologies for celiac disease and IBD was negative in all patients with microscopic colitis. Details regarding the patients with microscopic colitis can be found in Table 5.

Logistic regression analysis

Logistic regression was performed to estimate the risk of adenomas, diverticulosis, and hemorrhoids in IBS patients vs. controls after adjusting for the following factors: age, gender, race, level of education, tobacco, and alcohol use. The adjusted odds ratio for the presence of adenomas in patients with suspected IBS vs. controls corrected for the above factors was 0.33 (95% CI = 0.20–0.56). The adjusted odds ratios for the presence of diverticulosis and hemorrhoids in the IBS group compared with controls was 0.68 (95% CI = 0.42–1.1) and 1.2 (95% CI = 0.75–1.8), respectively.

DISCUSSION

This study represents the largest prospective, controlled evaluation of the diagnostic yield of colonoscopy and mucosal biopsy in patients with IBS-D or IBS-M. In this cohort of patients fulfilling the Rome II criteria for IBS without warning signs, colonoscopy did not alter the diagnosis of IBS in 457/466 (98.1%). Structural lesions of the colon including adenomatous and hyperplastic polyps, CRC, angiodysplasia, diverticulosis, hemorrhoids, and anal fissure were no more likely in IBS patients vs. controls.

Our results are consistent with previously published studies. In a *post hoc* analysis of data from two placebo-controlled IBS trials, Hamm (14) examined the yield of flexible

sigmoidoscopy in study participants < 50 years of age or colonoscopy/flexible sigmoidoscopy and barium enema in enrollees ≥ 50 years of age. Three hundred and six of 1,452 (21%) study participants were included in this *post hoc* analysis. Colonic imaging identified important structural lesions in four patients (1.3%, three IBD, one colonic obstruction). Unfortunately, the results of this *post hoc* analysis are difficult to interpret, as the proportion of patients who underwent sigmoidoscopy vs. colonoscopy were not reported. Additionally, patients only underwent colonic imaging if they had not undergone such imaging within 2 years of study enrollment. Furthermore, the proportion of IBS patients who had undergone previous colonic imaging were not reported.

Tolliver (15) evaluated the yield of sigmoidoscopy and barium enema and/or colonoscopy in an uncontrolled, prospective trial that included 196 subjects with suspected IBS. Forty-three colonic structural abnormalities were found in 34 subjects. Similar to our study, most of abnormalities found were felt to be incidental and not responsible for patient's GI symptoms (benign polyps, diverticulosis, hemorrhoids, lipomata, and melanosis coli). Two (1.0%) patients were found to have abnormalities (one IBD, one cancer) that could have explained their IBS symptoms. Again, there are several issues that complicate interpretation of the results from this study including the inclusion of patients with warning signs (family history of colon cancer and fecal occult blood test positive stool), the absence of a control group, and failure to report the percentage of IBS patients who underwent each type of examination.

In an uncontrolled study, Francis *et al*. (16) studied the yield of flexible sigmoidoscopy, barium enema, or colonoscopy in 125 patients who fulfilled the Rome I criteria for IBS. With the exception of diverticular disease that was judged to be an incidental finding, no structural lesions were identified which changed the diagnosis of IBS.

Vanner (17) performed a prospective study in 95 patients referred to general gastroenterology clinics over a 9-month period in 1995–1996 who met the Rome criteria and lacked warning signs. Ninety-one percent of patients over 45 years of age underwent barium enema or colonoscopy. Two patients declined investigation and one patient had a flexible sigmoidoscopy. Only 45% of patients under the age of 45 years underwent colon imaging. Sigmoidoscopy alone was carried out in 21% of these patients. One patient with rectal bleeding was found to have ulcerative proctitis. Otherwise no colonic abnormalities were identified (17).

The finding of a reduced prevalence of adenomatous polyps in patients with IBS compared with controls deserves further comment. We initially thought that this result was the consequence of between-group differences in demographic factors, such as age and gender. However, IBS patients were found to have a reduced prevalence of adenomas compared with controls even after adjusting for age and gender in a multivariable logistic regression analysis. Two other important factors that could have influenced our results deserve mention. First, our study included healthy controls who were undergoing an initial screening colonoscopy or a surveillance colonoscopy for a personal history of adenomatous polyps. Unfortunately, we did not collect data on the indication for colonoscopy in controls (screening or surveillance) at all of the study sites. We were able to obtain these data from one of the sites (National Naval Medical Center). Of the controls enrolled at this site, 78 underwent their first colonoscopy, 68 underwent a surveillance colonoscopy, and in 44 it was unknown if the study colonoscopy was a first or follow-up procedure. Thus, at least 36% of the controls at this site had a history of adenomas during a previous colonoscopy. In addition, 42/190 (22%) controls had a family history of colon polyps or cancer. Of the 42 controls with a family history of colon polyps or cancer, 11 were in the surveillance group– thus a substantial minority of controls undergoing their first colonoscopy, or for which these

data were not available, had a family history of colon polyps or cancer. On the other hand, patients with a family history of colon cancer were not eligible for inclusion in the non-IBS-C group. These disparities are likely to have contributed to the between-group adenoma detection rate found in this study. Further evaluation of this interesting observation is warranted.

Our study found that colonoscopy and colonic mucosal biopsies identified an alternative diagnosis in 9/466 (1.9%) patients with suspected IBS. Of these nine patients, seven had microscopic colitis, one had Crohn's disease, and one had ulcerative colitis. Our study differs from the only other prospective study by MacIntosh (18), which evaluated flexible sigmoidoscopy and rectal biopsy in 89 patients with suspected IBS and 59 controls who underwent colonoscopy for "cancer surveillance or investigation of blood loss." Among the IBS cohort, 84% fulfilled the Rome I criteria, whereas in the control group only 5% fulfilled the Rome I criteria. These authors reported that no IBS patients or controls had macroscopic or microscopic findings that resulted in a change of diagnosis from IBS. Specifically, the authors identified no patients or controls with microscopic colitis.

Other studies have found that microscopic colitis can be mistakenly diagnosed as IBS (10,19–21). Previously, published studies addressing this potential association have been retrospective cohort analyses of patients diagnosed with microscopic colitis. These studies have found that a variable proportion of patients with microscopic colitis report abdominal pain or discomfort in addition to diarrhea-related complaints. For example, a retrospective study by Limsui *et al*. (10) found that 56% of 131 patients from Olmstead County, MN diagnosed with micoscopic colitis fulfilled the Rome II criteria for IBS and that 33% had been labeled as suffering with IBS before the diagnosis of microscopic colitis. A recent retrospective analysis from the Kaiser Permanente Group in Los Angeles, CA found that 43/376 (11%) patients with lymphocytic colitis and 30/171 (18%) patients with collagenous colitis had been labeled as suffering from IBS before receiving the diagnosis of microscopic colitis (21).

This study provides the first prospectively collected data set addressing the prevalence of microscopic colitis in patients with non-constipated IBS and no warning signs. We found the overall prevalence of microscopic colitis to be 1.5% in our large cohort of non-constipated IBS patients. Similar to earlier studies, we found that microscopic colitis tended to occur in Caucasian females. Unlike other large series of patients with microscopic colitis, which have reported a mean age at diagnosis in the seventh decade (10,21), we report a mean age at diagnosis of 49 years. The discrepancy in age may represent the consequence of lead-time bias given that we performed random biopsies in all patients who fulfilled the Rome II criteria for IBS–regardless of whether a patient's symptoms were mild or severe. In a subgroup analysis of IBS patients over the age of 45 years, the prevalence of microscopic colitis was 2.3% (4/171). All subjects with microscopic colitis were at least 35 years of age. The clinical data collected at patient enrollment did not allow the accurate division of the IBS cohort into IBS-D and mixed bowel habit IBS (IBS-M) subgroups. It should also be pointed out that the Rome II criteria, which were used to identify patients with suspected IBS in this study, provide criteria for IBS-D but not IBS-M (11). We did carefully review the medical records of the seven patients diagnosed with microscopic colitis (Table 5). Interestingly, all of the patients with microscopic colitis qualified for the diagnosis of IBS-D by the Rome II criteria. If one accepts the available literature that states that 30–50% of the overall IBS population falls into the IBS-M subgroup (22–24), the prevalence of microscopic colitis in this study was almost certainly higher than 1.5% in those with symptoms suggestive of IBS-D. It is possible that our study underestimated the true prevalence of microscopic colitis in IBS patients as the protocol required the endoscopist to obtain only two biopsies from the sigmoid and rectum. The optimal number and location of

colonic mucosal biopsies needed to diagnose microscopic colitis remains controversial. A recent review on this topic suggested that between 18 and 34% of patients with collagenous colitis may not be identified if only rectosigmoid biopsies are obtained (25).

Another interesting observation from this study involves the significantly higher prevalence of ulceration and erythema identified during colonoscopy in suspected IBS patients compared with controls. The two patients in the IBS group with frank ulceration were found to have Crohn's disease (one) and ulcerative colitis (one). Of the remaining patients with mucosal erythema, a significant proportion had "nonspecific" inflammation on histological evaluation. These findings might be explained by ascertainment bias resulting from the lack of blinding of the endoscopist to the patient's indication for colonoscopy, which was typically abdominal pain and diarrhea. A more provocative explanation involves recent literature that suggests that low-grade inflammation might be responsible for symptoms in a subset of IBS sufferers. More studies on this contentious issue are warranted.

A number of weaknesses should be considered when considering our results. We have already discussed in detail some of the between-group differences in important demographic factors as well as indication for colonoscopy, which might have influenced our results. For practical and cost-related reasons, we did not routinely obtain random rectosigmoid biopsies in the control group. As such, we cannot definitively say that microscopic colitis is more prevalent in patients with non-IBS-C symptoms than healthy controls. In addition, our study did not include patients with IBS-C and thus cannot be generalized to the entire universe of IBS patients. Future prospective studies of colonoscopy in IBS-C are encouraged. We also did not systematically collect data on complication rates associated with the performance of colonoscopy in patients and controls. This information would certainly have been helpful in a risk/benefit analysis of colonoscopy in patients with non-IBS-C.

In summary, the prevalence of common structural abnormalities of the colon such as polyps, hemorrhoids, CRC, and diverticulosis are no higher in non-constipated IBS patients without warning signs than in healthy controls undergoing colonoscopy for CRC screening or surveillance. Less than 1% of the IBS cohort was found to have IBD. A small proportion of patients with symptoms suggestive of non-constipated IBS were found to have microscopic colitis on rectosigmoid mucosal biopsies. The likelihood of identifying microscopic colitis is likely to be greater in patients with symptoms of IBS-D and in persons over the age of 35 years. The findings from this study lend support to the recent recommendations of the American College of Gastroenterology Task Force (26), which state "*routine colonic imaging is not recommended in patients younger than 50 years of age with typical IBS symptoms and no alarm features. Colonoscopic imaging should be performed in IBS patients with alarm features to rule out organic diseases and in those over the age of 50 years for the purpose of colorectal cancer screening. When colonoscopy is performed in patients with IBS-D, obtaining random biopsies should be considered to rule out microscopic colitis.*"

Study Highlights

WHAT IS CURRENT KNOWLEDGE

Irritable bowel syndrome (IBS) is a symptom-based disorder that affects quality of life and work productivity.

On the basis of data from retrospective analyses or uncontrolled prospective studies, which show a low yield of important structural abnormalities in patients with typical IBS symptoms, the American College of Gastroenterology has recommended that

routine colonoscopy be reserved for patients with typical IBS symptoms over the age of 50 years or in whom warning signs are present.

Retrospective studies suggest that microscopic colitis may be confused with IBS.

WHAT IS NEW HERE

In a large, prospective case–control study, the prevalence rates of hyperplastic polyps, colorectal cancer (CRC), inflammatory bowel disease, angiodysplasia, hemorrhoids, and anal fissure were not significantly greater in patients with suspected non-constipated IBS than in healthy controls undergoing colonoscopy for CRC screening or polyp surveillance.

The prevalence rates of adenomatous polyps and diverticulosis were lower in patients with suspected non-constipated IBS than in controls.

The prevalence of microscopic colitis was 1.5% in patients with suspected non-constipated IBS.

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Table 1

Rome II recruitment criteria for non-constipation-predominant IBS

At least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features
i. Relieved with defecation; and/or
ii. onset associated with a change in frequency of stool; and/or
iii. onset associated with a change in form (appearance) of stool.
Diarrhea-predominant IBS patients were recruited if at least one of the following three criteria was present
i. More than three bowel movements per day.
ii. Loose (mushy) or watery stools.
iii. Urgency (having to rush to have a bowel movement).
Patients were excluded if having any of the following three criteria for constipation-predominant IBS
i. Fewer than three bowel movements a week.
ii. Hard or lumpy stools.
iii. Straining during a bowel movement.

IBS, irritable bowel syndrome.

Table 2

Demographic characteristics of participating subjects

	All ages			Age > 45 years		
Variable	**IBS patients (*n* = 466)**	**Controls (*n* = 451)**	***P* value**	**IBS patients (*n* =171)**	**Controls (*n* = 428)**	***P* value**
Age (mean)	41.1 (12.9)	53.8 (7.7)	< 0.0001	54.4 (8.4)	55.3 (6.9)	NS
n (%) females	322 69.1)	185 (41)	< 0.0001	120 (70.2)	182 (42.5)	< 0.0001
Caucasian	374 (80.3)	376 (83.4)	NS	146 (85.4)	362 (84.6)	NS
African American	47 (10)	48 (10.6)	NS	12 (7)	44 (10.3)	NS
Hispanic	19 (4.1)	6 (1.3)	0.01	2 (1.2)	3 (0.7)	NS
Asian	9 (1.9)	12 (2.7)	NS	3 (1.8)	11 (2.6)	NS
American Indian	2 (0.4)	0	NS	1 (0.6)	0	NS
Other	2 (0.4)	7 (1.6)	NS	0	6 (1.4)	NS

IBS, irritable bowel syndrome; NS, not significant.

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Table 3

Colonoscopic findings in IBS patients and controls

Lesion	IBS patients (*n* = 466), *n* (%)	Controls (*n* = 451), *n* (%)	*P* value
Polyps	68 (14.6)	155 (34.4)	<0.0001
Mass	0 (0)	1 (0.2)	NS
Mucosal erythema or ulceration	23 (4.9)	8 (1.8)	<0.01
Diverticulosis	41 (8.8)	96 (21.3)	<0.0001
Angiodysplasia	1 (0.2)	2 (0.4)	NS
Hemorrhoids	85 (18.2)	74 (16.4)	NS
Anal fistula	0	1 (0.2)	NS

IBS, irritable bowel syndrome; NS, not significant.

Table 4

Histological findings in IBS patients and controls

Lesion	IBS patients (*n* = 466), *n* (%)	Controls (*n* = 451), *n* (%)	*P* value
Adenomas	36 (7.7)	118 (26.1)	<0.0001
Hyperplastic polyps	39 (8.4)	52 (11.5)	NS
Colorectal adenocarcinoma	0 (0.0)	1 (0.2)	NS
IBD	2 (0.4)	0	NS
Microscopic colitis	7 (1.5)	N/A[a]	N/A
Solitary rectal ulcer syndrome	1 (0.2)	1 (0.2)	NS

IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NS, not significant.

[a]Number of controls with microscopic colitis is not recorded, as those participants did not undergo systematic random colon mucosa biopsies.

Table 5

Demographic and clinical characteristics of IBS patients diagnosed with microscopic colitis (MC)

	Microscopic colitis
Patients (*n*)	7
Lymphocytic/Collagenous (*n*)	4/3
n (%) females	6 (86%)
Mean age (years)	49.1 ± 11.1
Age range (years)	35–66
n (%) Caucasian	7 (100%)
n (%) presenting as IBS-diarrhea	7 (100%)
Co-morbidities	2 GERD 1 Hashimoto thyroiditis
Medications used before recruitment	2 NSAID, 2 SSRI, 1 PPI, 2 H_2blocker, 2 Loperamide
Colonoscopy findings	Normal in all patients except 1 with an adenomatous polyp and diverticulosis 1 with a hyperplastic polyp
Laboratory (CBC, BMP, thyroid panel)	Normal in all patients
Celiac disease serology panel [a]	Negative in all patients
IBD serology panel [b]	Negative in all patients

BMP, basic metabolic profile; CBC, complete blood count; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NSAID, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors.

[a] Included analyses anti-gliadin antibodies (IgA and IgG), antibodies to tissue transglutaminase (IgA), anti-endomysial antibodies (IgA).

[b] Included analyses anti- *Saccharomyces cerevisiae* antibody (IgA, IgG), perinuclear anti-neutrophil cytoplasmic antibodies, anti-OmpC IgA.