Colonic diverticulosis is associated with an increased adenoma detection rate in patients undergoing first-time screening colonoscopy

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Background: Diverticulosis is a common finding in patients undergoing colonoscopy. The effect of colonic diverticulosis on the colorectal adenoma detection rate (ADR) and other colonoscopy quality indicators remains unclear.

Objectives: To determine if colonic diverticulosis is associated with differences in (1) colorectal ADR and (2) other quality indicators and operating characteristics in patients undergoing first-time screening colonoscopy.

Methods: Retrospective cohort study conducted at an outpatient surgical center affiliated with an academic medical center.

Results: 300 consecutive patients (190 women) with a median age of 57 years (range: 23-70 years) who underwent colonoscopy for various indications were included. 108 (36%) of these 300 patients had diverticulosis found on colonoscopy. 142 (47.3%) of these patients (88 women, median age of 52 years) underwent their first screening colonoscopy. In this population, the frequency of colonic diverticula was 39.2%, and the ADR was 47.5% for patients with diverticulosis and 27.4% for patients without diverticulosis. Multivariate analysis revealed that the presence of diverticulosis had an associated odds ratio of 2.3 (p=0.04) in favor of finding at least one adenoma. No statistically significant differences were found among the rates of total colonoscopy, median scope insertion and withdrawal times, and the amounts of midazolam and fentanyl required for sedation when patients with diverticulosis were compared to those without diverticulosis.

Conclusion: Colonic diverticulosis was associated with an increased ADR in patients undergoing first-time screening colonoscopy. The presence of colonic diverticulosis did not adversely affect the cecal intubation rate, scope insertion or withdrawal times, or sedation requirements.

Introduction

Colorectal cancer (CRC) is the second most common cause of cancer death in the United States.[1] Most CRCs arises from pre-existing adenomatous polyps, which represent one-half to two-thirds of all colorectal polyps.[2-4] Total colonoscopy with polypectomy of neoplastic polyps has been associated with a reduced incidence of CRC and decreased mortality.[5-7] The adenoma detection rate (ADR) is a widely accepted indicator of colonoscopic quality in individuals undergoing first-time screening exams,[8] and the ADR was recently demonstrated to be an independent predictor of the risk of interval colorectal cancer after screening colonoscopy.[9]

Diverticulosis is a commonly diagnosed condition in patients undergoing colonoscopy, and the incidence of diverticula-related disease appears to be increasing.[10] The prevalence of diverticular disease is age-dependent, increasing from less than 5% at 40 years, to about 30% by 60 years, and to greater than 40% by 80 years.[11] Increasing age is also a major risk factor for sporadic CRC. CRC is a rare diagnosis before the age of 40 years; the incidence begins to increase significantly between the ages of 40 and 50 years, and age-specific incidence rates increase in each succeeding decade thereafter.[12] Despite this apparent commonality with advancing age, it is not clear if there is an association between colonic diverticulosis and colorectal neoplasia, as only a few conflicting studies have been published.[13-17] Furthermore, those prior studies did not examine the relationship between diverticulosis and the ADR in patients undergoing first-time screening colonoscopy. Lastly, possible associations between diverticulosis and other indicators of colonoscopic quality (ie, cecal intubation rates, scope insertion and withdrawal times, and sedation requirements) have not been described.

The aims of this study were (1) to determine if the presence of colonic diverticulosis is associated with a difference in the colorectal ADR in patients undergoing a first-time screening colonoscopy, and (2) to determine if the presence of colonic diverticulosis is associated with differences in cecal intubation

rates, scope insertion times, withdrawal times, or sedation requirements, which are commonly used indicators of colonoscopic quality.

Methods

A retrospective, single-center, cohort study was conducted that included patients who underwent colonoscopy performed by one of five experienced attending gastroenterologists (without the assistance of trainees) at an outpatient surgical center. Patients were identified using a hospital database and electronic medical records were reviewed. This study was approved by our local institutional review board.

All patients included in this study underwent colonoscopy performed with a high-definition adult or a high-resolution pediatric, variable-stiffness colonoscope (CF-H180AL or PCF-Q180AL; Olympus America, Center Valley, Penn). All polyps found were completely resected for pathological analysis by using a variety of techniques, including cold biopsy, cold snare, hot snare, and saline-lift-assisted hot-snare polypectomy.

Subjects received conscious sedation using intravenous midazolam and fentanyl with or without diphenhydramine. A total colonoscopy was denoted by successful cecal intubation resulting in identification of the appendiceal orifice, ileocecal valve, and cecal strap, which then allowed for a careful exam of the colorectal mucosa on withdrawal of the scope. Colonoscope insertion time was defined as the time from insertion into the rectum to the time of cecal intubation and identification of the appendix. Colonoscope withdrawal time was defined as the time from cecal identification to the time when the colonoscope was withdrawn across the anus. In most cases, the time taken for polypectomy was included in the withdrawal time. The number of polyp, their location, and method of removal were recorded at the time of the procedure. Patients were administered either 4 L of polyethylene glycol (PEG) 3350 with electrolytes or with 2 L of PEG 3350 with electrolytes and bisacodyl for preprocedural bowel preparation. The quality of bowel preparation was documented as, "excellent," "good," "fair," and "poor '' as per ASGE guidelines.[8]

Statistical methods

Categorical data were summarized as frequencies and percentages, and continuous scaled data were summarized by the median and the range of the measurement distribution.

Polyp and adenoma detection rates

For calculation of the ADR, patients undergoing a first-time screening colonoscopy were counted as positive if they had one or more adenomas found on colonoscopy. Patients with multiple adenomas were considered only once in calculating the ADR. For calculation of the polyp detection rate, patients with either hyperplastic or adenomatous polyps were included in the rate calculations.

The frequency data for polyp and ADR on first-time screening colonoscopies were analyzed via univariate and multivariate logistic regression. For the univariate and multivariate logistic regression analyses, the response variables were binary variables, and the binary variables indicated whether or not one or more polyps/adenomas were detected during the colonoscopy procedure. For the univariate analyses, the sole independent predictor variable was the patients' diverticulosis status; while for the multivariate analyses, three predictor variables were included in the logistic regression model. The primary predictor variable was the patients' diverticulosis status, while colon preparation-quality and gender functioned as concomitant adjustment variables. For both the univariate and multivariate analyses, tests of association were based on the Wald chi-squared statistic, and a $p \leq 0.05$ decision rule was utilized as the criterion for rejecting the null hypothesis of no independent versus dependent variable association. 95% confidence interval construction for the odds ratio was based on the Wald confidence interval method.

Procedural operating characteristics

Colonoscopy operating characteristics including scope insertion times, withdrawal times, and the amounts of medication required were compared between the patients who had diverticulosis and those who did not by way of permutation tests.[18] For the purposes of analysis of overall drug utilization and sedative requirement, midazolam 1 mg IV was considered equivalent to fentanyl 25 mcg IV and to diphenhydramine 25 mg IV.

Withdrawal time and ADR

Multivariate logistic regression analyses (adjusted for colon preparation quality and gender) were conducted to determine if increased withdrawal time was associated with an increased ADR in patients undergoing first-time screening colonoscopy irrespective of diverticulosis status. Additionally, colon-preparation- and gender-adjusted multivariate Poisson regression analyses were conducted to determine if the number of adenomatous polyps detected per patient on first-time screening colonoscopes increased with longer withdrawal time. For both types of regression analysis, the test of association was based on the Wald chi-squared statistic, and a $p \leq 0.05$ decision rule was utilized as the criterion for rejecting the null hypothesis of no independent versus dependent variable association. 95% confidence interval construction for the odds ratio and the mean detection rate ratio was based on the Wald confidence interval method.

Statistical software

The GENMOD procedure of SAS version 9.2.2 (SAS Institute Inc., Cary, NC) was utilized to conduct the logistic regression and Poisson regression analyses. Spotfire Splus 8.1 (TIBCO Inc., Palo Alto, CA) was utilized to conduct the permutation tests.

Results

Patient characteristics and frequency of diverticulosis

300 consecutive patients (190 women) with a median age of 57 years (range: 23-70 years) who underwent colonoscopy for any indication were reviewed and included in this study. 142 (47.3%) of these patients (88 women, median age of 52 years, range: 40-70 years) underwent their first colonoscopy for colorectal cancer

and adenoma screening.

108 (36%) of these 300 patients had diverticulosis (in any colonic segment) found on colonoscopy. The frequency of colonic diverticula was 39.2% (40/142) in this screening population (**Table 1**). The first-time screening ADR for patients irrespective of diverticulosis status (when one or more adenomas were found) was 33.1% (47/142, 95% CI: 30.0 to 35.5). Refer to **Table 2** for data regarding the presence and location of polyps as stratified by the distribution of diverticulosis.

Association between diverticulosis and colorectal adenomas and polyps

In patients undergoing a first-time screening colonoscopy, the detection rate for all polyps was 62.5% (25/40) for patients

Table 1. Patient characteristics

	Diverticulosis (+) [n (%)]	Diverticulosis (-) [n (%)]	Total [n (%)]
All patients (n=300)			
Men	44 (40.0)	66 (60.0)	110 (36.7)
Women	64 (33.7)	126 (66.3)	190 (63.3)
	Men vs. women, p=0.318		
Characteristics of colonic diverticulosis			
Mild	74 (68.5)	-	-
Moderate	14 (13.0)	-	-
Severe	9 (8.3)	-	-
Unspecified	11 (10.2)	-	-
Left-sided	97 (89.8)	-	-
Right-sided	2 (1.8)	-	-
Pan-diverticulosis	9 (8.3)	-	-
Quality of bowel preparation			
Poor	2 (1.9)	10 (5.2)	
Fair	21 (19.4)	32 (16.7)	
Good	85 (78.8)	150 (78.1)	
First-time screening colonoscopy patients (n=142)			
Men	21 (38.9)	33 (61.1)	54 (38.0)
Women	19 (21.6)	69 (78.4)	88 (62.0)
	Men vs. women, p=0.034		
1st degree FH of CRC	2 (14.3)	12 (85.7)	14 (9.9)
1st degree FH of polyps	1 (14.3)	6 (85.7)	7 (4.9)
1st degree FH of CRC or polyps	3 (15.0)	17 (85.0)	20 (14.1)
Characteristics of colonic diverticulosis			
Mild	28 (70.0)	-	-
Moderate	5 (12.5)	-	-
Severe	2 (5.0)	-	-
Unspecified	5 (12.5)	-	-
Left-sided	36 (90.0)	-	-
Right-sided	1 (2.5)	-	-
Pan-diverticulosis	3 (7.5)	-	-
Average-risk, first-time screening colonoscopy patients (n=122)			
Men	19 (38.0)	31 (62.0)	50 (41.0)
Women	18 (25.0)	54 (75.0)	72 (59.0)
	Men vs. women, p=0.161		
Characteristics of colonic diverticulosis			
Mild	26 (70.3)	-	-
Moderate	4 (10.8)	-	-
Severe	2 (5.4)	-	-
Unspecified	5 (13.5)	-	-
Left-sided	33 (89.2)	-	-
Right-sided	1 (2.7)	-	-
Pan-diverticulosis	3 (8.1)	-	-

with diverticulosis and 44.3% (44/102) for patients without diverticulosis. In patients undergoing a first-time screening exam, the ADR was 47.5% (19/40) for patients with diverticulosis and 27.4% (28/102) for patients without diverticulosis (p=0.03 on univariate analysis)(**Table 3**). Multivariate analysis (adjusted for colon preparation quality and gender) revealed that the presence of diverticulosis had an associated odds ratio of 2.3 (p=0.04) in favor of finding at least one adenoma (**Table 4**).

When patients undergoing a first-time screening exam (n=142) with diverticulosis were compared to those without diverticulosis, there were no statistically significant differences in their respective median scope insertion times (6 min vs. 5 min, p=0.22), median withdrawal times (12 min vs. 11 min, p=0.27), or rates of total colonoscopy (100% vs. 97%, p=0.56).

When only considering average-risk patients undergoing first-time colonoscopy, excluding those patients with first-degree family history of CRC or adenomas (in this case a family history of any type of polyp), the ADR was 37.7% (95% CI: 30.3 to 42.2%). In this population, multivariate analysis (adjusted for colon preparation quality and gender) resulted in an odds ratio of 1.94 (95% CI: 0.85 to 4.39, p=0.11) showing a trend towards an association between colonic diverticulosis and ADR on first-time screening colonoscopy.

Longer withdrawal times are associated with increased ADR and more adenomas detected per patient

Multivariate analysis (adjusted for colon preparation and gender) showed that increasing withdrawal time was associated with an increased ADR in patients undergoing first-time screening colonoscopy (OR 1.87, 95% CI: 1.34 to 2.63, p<0.001). Similarly, preparation- and gender-adjusted multivariate analysis found that the number of adenomatous polyps detected per patient on first-time screening colonoscopes increased with longer withdrawal times (mean rate ratio for number of adenomas detected was 1.52, 95% CI: 1.33 to 1.76, p<0.001).

Diverticulosis does not affect other colonoscopy operating characteristics

When all 300 patients were analyzed, total colonoscopy was achieved in 97.4% of patients without diverticulosis and in 99.1% of patient with diverticulosis (p=0.42). No statistically significant differences were found between the median scope insertion times (p=0.16) and median withdrawal times (p=0.72) when all patients with diverticulosis were compared to those without diverticulosis (**Table 5**).

Analysis of the amount of midazolam and fentanyl administered to perform colonoscopy showed no statistically significant difference in amount of medication required in patients with or without diverticulosis (**Table 5**). When comparing "dose equivalents" (with 1 dose equivalent=1 mg of IV midazolam=25 mcg of IV fentanyl=25 mg of IV diphenhydramine), there was also no statistically significant difference (p=0.26) in the amount of drugs required to perform colonoscopy in patients with or without diverticulosis (**Table 5**).

Discussion

The prevalence of colonic diverticulosis and colorectal neoplasia both increase with advancing age. However, a positive association between these two diseases remains unclear. There have been a handful of conflicting, heterogeneous clinical reports published over the past two decades that explore the possibility of a

Table 2. Presence and location of polyps as stratified by the distribution of diverticulosis

	Pts (n)	Without polyps [n (%)]	≥1 Polyp [n (%)]	≥1 Polyp in the left colon [n (%)]	≥1 Polyp in the right colon [n (%)]	≥1 Polyp in both sides of the colon [n (%)]
Left-sided diverticulosis	97	49 (51)	48 (49)	20 (42)	17 (35)	11(23)
Right-sided diverticulosis	2	1 (50)	1 (50)	1 (100)	0 (0)	0 (0)
Pan diverticulosis	9	2 (22)	7 (78)	2 (29)	3 (43)	2 (29)

Table 3. Polyp and adenoma detection rates found on first-time screening colonoscopies as stratified by diverticulosis status (univariate analysis)

	Detection rate		p†
	(+) Diverticulosis	(+) Diverticulosis	
≥1 polyp	25/40 (62.5%)	44/102 (44.3%)	0.118
≥1 adenoma	19/40 (47.5%)	28/102 (27.4%)	0.029

† Determined via univariate logistic regression.

Table 4. Multivariate analysis of the association between polyp or adenoma detection rates and diverticulosis status found on first-time screening colonoscopies (adjusted for colon preparation quality and gender)

	Diverticulosis ratio	Odds ratio	95% CI	p†
Polyp detection rate *	Yes: No	1.93	0.85 to 4.39	0.113
Adenoma detection rate **	Yes: No	2.26	1.04 to 4.92	0.039

*Patients were counted once if they had multiple polyps; **Patients were counted once if they had multiple adenomas; †Determined via multivariate logistic regression..

relationship between colonic diverticular disease and colorectal polyps or cancer.[13-17]

Our study found on adjusted multivariate analysis a statistically significant association between colonic diverticulosis and the colorectal ADR in patients undergoing a first-time colonoscopy for colorectal cancer screening. When patients with a reported first-degree family history of colorectal cancer or colorectal polyps (presumed to be adenomas) were excluded in order to isolate only "average-risk" patients, further decreasing the sample size, adjusted multivariate analysis still demonstrated a trend towards an association between diverticulosis and an increased ADR. As most patients do not know if a family member actually had adenomatous or hyperplastic polyps, our excluding patients with a first-degree family history of colon polyps likely removed average-risk patients whose family history was significant only for hyperplastic polyps; thereby reducing our statistical power to detect a significant association. On subgroup analysis comparing the severity of diverticulosis to the number of adenomas detected, no association was found, which could have been due to lack of statistical power, as our study was not constructed to answer this specific question (data not shown, p=0.987).

The positive association found between colonic diverticulosis and colorectal adenomas in all patients undergoing first-time screening colonoscopy corroborates previous reports by Morini,[13] Kieff,[15] Stefansson,[17] and Hirata.[14] Morini et al[13] found in a study of Italian patients undergoing total colonoscopy significantly more adenomas (64.1% vs. 41.8%, p<0.05) and more advanced adenomas (59.6% vs. 37.5%, p<0.05) in the sigmoid colon of patients with diverticula than in controls. Kieff et al[15] found that U.S. women with diverticulosis were more likely to have advanced distal colorectal neoplasia on age-adjusted multivariate analysis (OR 3.9, CI: 1.2 to 13.0). Stefansson et al[17] found on review of 7159 patients over an 18 year period that there was a significantly increased risk of cancer of the left colon (RR 1.8, 95% CI: 1.1 to 2.7). Hirata et al[14] found in a retrospective review of Japanese patients undergoing total colonoscopy after hemorrhoidectomy for rectal bleeding that on multivariate logistic regression analysis adjusted for age and sex there was a statistically significant association between diverticulosis in any portion of the colon and colon polyps in all locations (OR 1.7, 95% CI: 1.1 to 2.5, p=0.01). In contrast to these studies, Meurs-Szojda et al[16] found in 4,241 patients that there was no relation between patients with diverticulosis and a higher incidence of polyps or CRC when using an age-stratified analysis (p=0.478).

This present study differs from previous studies as these prior studies did not examine the relationship between diverticulosis and the ADR in patients undergoing first-time screening colonoscopy. Furthermore, this study might be one of the first to assess the impact, if any, that diverticulosis might have with respect to other commonly used indicators of colonoscopic quality. Looking at the years of publication, it is likely that the previous studies were conducted using low-resolution colonoscopes. In contrast, each colonoscopy in this study was conducted using either a high-definition or a high-resolution colonoscope with narrow-band imaging (NBI) capability. Several recent prospective studies have shown that high-definition colonoscopy is associated with a reduced adenoma miss rate (using high-definition NBI)[19] and an increased number of adenomas detected per person (using high-definition white light).[20] Among asymptomatic patients undergoing screening colonoscopy, adenomas should be detected in ≥25% of men and ≥15% women more than 50 years old.[8,21] The ADR for all patients undergoing first-time screening colonoscopy irrespective of diverticulosis status was 33.1% in this study. This high ADR may be attributable to use of high-definition or high-resolution colonoscopes and to careful examinations denoted by a median withdrawal time of 11 minutes, which was in excess of the minimum 6-8 minutes withdrawal time that has been recommended in recent studies[22,23] and by ASGE guidelines on "Quality Indicators for Colonoscopy."[8]

It should be noted that most polyps were removed during scope withdrawal, and the time required for polypectomy was also included in the withdrawal time. As such, the association between ADR and withdrawal time, which although is still valid, may be artificially augmented as finding an adenoma would also add time to the scope withdrawal. However, as a sizable number of polyps found and removed were non-neoplastic, this would somewhat mitigate this effect.

Although the pathophysiology of colonic diverticula is incompletely understood, it is generally assumed that aging and low dietary fiber are involved in this disease. A low fiber diet has been associated with both colonic diverticulosis and colorectal neoplasia.[15] Low dietary fiber contributes to decreased colonic transit time, a reduction in stool volume, and segmentation of the colon, which has been associated with increased intraluminal pressure that leads to mucosal and submucosal herniation through the weakened muscularis propria; consequently, colonic diverticula may develop.[24-26]

However, several other pathophysiological theories exist that might explain how colonic diverticula could be linked to colorectal neoplasia. Studies have posited that bacteria produce

Table 5. Colonoscopy operating characteristics including scope insertion times, withdrawal times, and amounts of sedative medications required as stratified by diverticulosis status in all patients (n=300)

	(+) Diverticulosis	(-) Diverticulosis	p†
Insertion time (median)	6 min (range: 2-37 min)	6 min (range: 2-34 min)	0.16
Withdrawal time (median)	11 min (range: 4-24 min)	11 min (range: 5-43 min)	0.72
Midazolam (median)	6 mg (range: 2-10 mg)	6 mg (range: 0-10 mg)	0.24
Fentanyl (median)	150 mcg (range: 50-250 mcg)	125 mcg (range: 0-250 mcg)	0.25
Drug equivalents (median)*	12.0 (range: 4-19)	11.0 (range: 0-23)	0.26

†Determined via a permutation test.

*1 drug equivalent=1 mg of IV midazolam=25 mcg of IV fentanyl=25 mg of IV diphenhydramine.

carcinogens and can degrade biliary steroids in feces in to co-carcinogens, which might then accumulate in diverticula.[27,28] Morini et al[29] showed an upward shifting of cellular proliferation in the sigmoid mucosa of patients with diverticular as compared to age-matched controls. Furthermore, Tursi et al[30] showed an upward shifting of cellular proliferation of the colonic mucosa in patients with different degrees of diverticular disease. These investigators also found in patients with asymptomatic diverticulosis a cell proliferation index three-fold higher than that of healthy controls and similar to that of patients with ulcerative colitis in remission, which led them to conclude that asymptomatic diverticulosis might confer the same risk for colonic carcinoma as that of ulcerative colitis. Lastly, Wassenaar et al. conducted a case-control study that found that patients with cured or controlled acromegaly had an increased risk of colonic diverticula (OR 3.6, 95% CI: 1.4 to 5.7) and colon adenomas (OR 4.1, 95% CI: 1.9 to 6.4), which was also associated with elevated insulin-like growth factor (IGF-1) concentrations at the time of diagnosis of acromegaly. These investigators theorized that diverticula developed due to disturbed matrix regulation caused by excess growth hormone (GH) and IGF-1.[26] Although none of the patients in this study had known acromegaly, a possible link between elevated GH and IGF-1 levels and colonic diverticulosis and colorectal adenomas in non-acromegalic patients is intriguing.

It might be speculated that the presence of diverticulosis prompts an endoscopist to conduct a more careful exam, although the scope withdrawal times measured in this study did not support this presumption. In fact, this study did not find any association between colonic diverticulosis and differences in the rates of cecal intubation (total colonoscopy), scope insertion times, withdrawal times, or sedation requirements, which are other commonly used colonoscopy quality indicators.[8,21] These results do not support commonly held notions that colonic diverticulosis is associated with a more complex or difficult colonoscopic procedure for either the patient or the endoscopist. A limitation of these data is that they were derived from a retrospective cohort study. Furthermore, although 300 consecutive patients were included, this study may have been underpowered to detect a statistically significant association in "average risk" patients who did not have a family history of colorectal cancers or polyps.

Although these data should not be overstated, they do suggest that colonic diverticulosis might be associated with an increased ADR in patients undergoing a first-time screening colonoscopy. Furthermore, the presence of colonic diverticulosis was not associated with differences in the rate of total colonoscopy, scope insertion or withdrawal times, or sedation requirements during colonoscopy. A large prospective study is warranted to confirm these findings.

Conflict of interests

Dr. Vanessa M. Shami discloses that she is a consultant for Olympus and Merit Medical Endotek. All other authors have no relevant financial relationships to disclose with respect to this article.

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