Diverticular disease as a risk factor for sigmoid colon adenomas

S. Morini
C. Hassan
A. Zullo
V. De Francesco[1]
V. Festa[2]
F. Barberani[2]
D. Faleo[1]
T. Stroffolini

Background. *Diverticular disease and colorectal neoplasia share similar epidemiological features and risk factors.*
Aim. *To evaluate a possible association between diverticular disease and both adenomas and colorectal cancer in patients undergoing total colonoscopy.*
Methods. *Overall, 630 consecutive patients were recruited from the 3 Units. Inclusion criteria were age over 45 years and the performance of total colonoscopy. Demographic and clinical data were recorded. Adenomas were defined as advanced when their size was >1 cm in diameter, and/or the percentage of the villous component was >30% and/or high grade dysplasia was present.*
Results. *At endoscopy, 291 (47%) out of 630 patients presented evidence of diverticular disease. Adenomas were found in 92 (31.9%) patients with diverticular disease and in 98 (28.9%) patients without (p=ns). The prevalence of adenomas located in the sigmoid colon was significantly higher in patients with diverticula than in controls (64.1% vs 41.8%; p<0.05). Similarly, the detection of advanced adenomas located in the sigmoid colon was more likely in patients with diverticula than in controls (59.6% vs 37.5%; p<0.05). Colorectal cancer prevalence was similar in patients with and without diverticula (8.3% vs 7.1%; p=ns), and no difference was detected regarding site, between the two groups.*
Conclusions. *Patients with diverticular disease have a higher risk of harbouring adenomas and advanced adenomas in the sigmoid colon. This observation should be taken into account in screening and surveillance programmes for colorectal neoplasia.*

Digest Liver Dis 2002;34:635-9

Key words: colorectal cancer; diverticular disease; sigmoid colon adenoma

From
Gastroenterology and Digestive Endoscopy Unit, "Nuovo Regina Margherita" Hospital, Rome; [1] Gastroenterology and Digestive Endoscopy Unit, "Riuniti" Hospital, Foggia; [2] Gastroenterology and Digestive Endoscopy Unit, "San Camillo de Lellis" Hospital, Rieti, Italy.

Address for correspondence
Prof. S. Morini, Ospedale Nuovo "Regina Margherita", Gastroenterologia ed Endoscopia Digestiva, via Morosini 30, 00153 Roma, Italy.
Fax: +39-06-58446533.
E-mail: s.morini@flashnet.it

Submitted September 17, 2001.
Accepted after revision February 12, 2002.

Introduction

Colonic neoplasia and diverticular disease have shared a common epidemiological trend since the last Century [1-4]. Their prevalence has increased dramatically in Western countries, especially in the elderly. Indeed, colorectal neoplasia has become a major cause of cancer-associated morbidity and mortality in the United States and Europe, reaching a cumulative lifetime risk of approximately 6% [5]. Similarly, prevalence of diverticular disease, in autopsy series, has risen since 1910 from 5% to more than 50% [6].
In most cases, colorectal cancer is thought to be the result of an adenoma-carcinoma sequence [7], and many risk factors involved in its development, such as age and Western diet (low in fibre and rich in dietary fat), are also claimed to play a role in the pathogenesis of diverticular disease [8 9]. However, an association between these diseases is still debatable, and very few data have been reported [10 11].
Aim of the present study was to further evaluate a possible association be-

tween diverticular disease and both adenomas and colorectal cancer in patients undergoing total colonoscopy.

Patients and methods

Consecutive patients from the 3 Units were prospectively enrolled in the study between January and July 2000. Inclusion criteria were: age over 45 years and need for a total colonoscopy. Exclusion criteria were: previous radiographic or endoscopic studies of the colon, a personal history of either colonic neoplasia, diverticular disease, inflammatory bowel disease or large bowel resection, a family history of hereditary colorectal cancer. Those patients with more than 10 adenomatous polyps or evidence of inflammatory bowel disease at endoscopy were also excluded. Prior to endoscopy, patients answered a questionnaire regarding family history, indication for endoscopy according to the American Society of Gastrointestinal Endoscopy (ASGE) guidelines, bowel habits, and previous abdominal surgery [12].

At endoscopy, patients were classified into two groups according to the presence or absence of diverticula. Diverticular disease was endoscopically specified in terms of location and segmental extension. The severity of diverticulosis was classified as follows: a) spastic colon diverticulosis: presence of multiple diverticula with increased thickness of the bowel wall and reduction of the lumen due to overlapping folds; b) simple massed diverticulosis: presence of numerous diverticula with little or no thickening of the wall; c) right-sided diverticulosis: presence of some diverticula confined to the right colon with no alteration of the wall [6 13]. Prediverticular state and single diverticulum were not taken into account. For the purpose of the study, the size of the polyps was estimated during endoscopy, and all polyps were removed for histological examination. Dysplasia of adenomas was defined as low-grade or high-grade according to criteria reported elsewhere [14], whereas hyperplastic polyps were not considered. Adenomas were defined as advanced if greatest than 1 cm in size, and/or the percentage of the villous component was >30% and/or a high grade dysplasia was present [14]. In the case of multiple polyps, the most severe adenoma was identified – by ranking histopathology from extremely severe to not very severe – and considered for statistical analysis. All cancers were documented histologically.

Statistical analysis

Differences in proportions and in means were calculated by χ^2 test and Student t test, respectively. A $p<0.05$ value was considered to be significant. The Odds Ratio (OR), adjusted for the confounding influence of age, was computed by the Mantel-Haenszel method to assess the association between the presence of diverticular disease and sigmoid adenomas.

Results

Overall, 630 consecutive patients were included in the study. Of these, 291 (47%) had diverticular disease at endoscopy. Demographic and clinical characteristics of the two groups, and indications for colonoscopy are given in Tables I and II. Patients with diverticula were significantly older (66.8 vs 61.5 years; $p<0.01$), and complained of constipation more frequently than controls (43% vs 28.6%; $p<0.01$), whereas no difference between the two groups was found regarding indication for endoscopy, family history of neoplasia, and previous extra-colonic abdominal surgery. Diverticular disease involved the sigmoid colon in 286 cases (98.2%), extending also to the descending colon in 68,

Table I. Clinical and demographic data.

Variable	Diverticular patients (n=291)	Controls (n=339)	p value
Age, mean (range), years	66.8 (45-81)	61.5 (45-76)	<0.01
Sex, M/F	148/143	178/161	ns
First-degree familiarity for colorectal neoplasia (%)	55 (19)	68 (20)	ns
Bowel habit (%)			
Normal	128 (44)	182 (53.7)	ns
Constipation	125 (43)	97 (28.6)	<0.01
Diarrhoea	26 (8.9)	43 (12.7)	ns
Irregular	12 (4.1)	17 (5)	ns
Previous surgery (%)			
Appendicectomy	45 (15.5)	46 (13.6)	ns
Gynaecological	24 (8.2)	20 (5.9)	ns
Cholecystectomy	37 (12.7)	39 (11.5)	ns
Others	24 (8.2)	25 (7.4)	ns

Table II. Indications for colonoscopy.

Indication	Diverticular patients n=291 (%)	Control sn=339 (%)	p value
Rectal bleeding	84 (28.9)	103 (30.4)	ns
Constipation	42 (14.4)	35 (10.3)	ns
Diarrhoea	17 (5.8)	24 (7.1)	ns
Anaemia	20 (6.9)	26 (7.7)	ns
Abdominal pain	94 (32.3)	114 (33.7)	ns
Increased tumoural markers	3 (1)	5 (1.5)	ns
Others	31 (10.6)	32 (9)	ns

and as far as the right colon in 53, respectively, whereas the remaining 5 (1.8%) cases had right-sided diverticulosis. Among the 286 patients with left-sided or diffuse diverticulosis, spastic colon diverticulosis of the sigma was present in 189 (66.1%) cases, and simple massed diverticulosis in the remaining 97 (33.9%). Neoplasia, either adenoma or carcinoma, was detected in 116 (39.8%) patients with diverticula, and in 122 (35.9%) of those without (p = ns). In detail, adenomas were found in 92 (31.9%) patients with diverticular disease and in 98 (28.9%) patients without diverticula (p = ns). In the diverticular disease patients, adenomas were found in 62 (32.3%) patients with spastic colon diverticulosis and in 30 (30.9%) patients with simple massed diverticulosis (p = ns). As shown in Table III, 52.6% of all polyps detected were confined to the sigmoid colon. Indeed, the prevalence of adenomas located in the sigmoid colon was significantly higher in patients with diverticula than in those without (64.1% vs 41.8%; p<0.05). Since the prevalence of diverticular disease increases with age, the disturbing influence of this variable should be removed in the analysis. Adjusting for the confounding effect of age (≤60 years vs >60 years), the association between the presence of diverticular disease and the presence of sigmoid colonic adenomas was, nevertheless, still observed [OR_{MH}: 2.4; 95% confidence interval (CI)=1.3-4.6]. Regarding advanced adenomas, the overall number was similar in the two groups, although the anatomic distribution was different. Indeed, the percentage of advanced adenomas in the left colon of patients with diverticular disease was 76.9% compared to 55.3% in those without diverticula (p<0.05). In detail, the prevalence of advanced adenomas located in the sigmoid colon was significantly higher in patients with diverticula than in controls (59.6% vs 37.5%; p<0.05), whereas no difference for the descending colon was found (17.3% vs 17.8%; p = ns). Regarding the shape of the adenomas, pedunculated polyps were significantly more frequent in diverticular disease patients than in controls (46.7% vs 31.6%; p<0.05).

Cancer prevalence was similar in patients with and without diverticula (8.3% vs 7.1%; p = ns), and no difference regarding site was detected between the two groups (Table III).

Table III. Distribution of adenomas and cancers.

Finding	Diverticular patients n=291 (%)	Controls n=339 (%)	p value
Adenomas (%)	92 (31.6)	98 (28.9)	ns
Rectum	8 (8.7)	15 (15.3)	ns
Sigmoid colon	59 (64.1)	41 (41.8)	0.03
Descending colon	12 (13)	12 (12.2)	ns
Transverse colon	5 (5.4)	8 (8.2)	ns
Ascending colon	5 (5.4)	11 (11.2)	ns
Caecum	3 (3.3)	11 (11.2)	ns
Advanced adenomas (%)	52 (17.8)	56 (16.5)	ns
Rectum	3 (5.7)	9 (16.1)	ns
Sigmoid colon	31 (59.6)	21 (37.5)	0.02
Descending colon	9 (17.4)	10 (17.9)	ns
Transverse colon	3 (5.7)	5 (8.9)	ns
Ascending colon	4 (7.8)	5 (8.9)	ns
Caecum	2 (3.8)	6 (10.7)	ns
Cancer	24 (8.3)	24 (7.1)	ns
Rectum	9 (37.5)	4 (16.7)	ns
Sigmoid colon	7 (29.2)	8 (33.3)	ns
Descending colon	2 (8.3)	-	ns
Transverse colon	1 (4.2)	4 (16.7)	ns
Ascending colon	1 (4.2)	4 (16.7)	ns
Caecum	4 (16.7)	4 (16.7)	ns

Discussion

Diverticular disease and colorectal neoplasia share similar epidemiological features and risk factors [1-4 8 9]. Nevertheless, whether or not an association between the two diseases really exists is still unclear, and only very few data are available. Although the overall prevalence of colon cancer was found to be the same between patients with diverticulosis and normal controls [10, 11], a cohort study on 7159 patients with diverticular disease revealed an increased risk for left-colon cancer in these patients as compared to the general population [15].

The present study has been performed to assess the relationship between diverticular disease and both adenomas and carcinomas in consecutive patients undergoing total colonoscopy. To avoid referral bias, patients who had already had a previous colonic study (endoscopy or radiology) were not included. Our data showed a 2.4-fold increased risk for sigmoid location of adenomas in patients with diverticula as compared to controls. Similarly, the prevalence of advanced adenomas in the sigmoid colon was higher in these patients than in controls. Since the presence of advanced adenomas is regarded as a risk factor for developing cancer over time [16-19], our findings are consistent with the finding of a higher risk of left-sided colon cancer in diverticular disease than previously reported [15]. In our study, no difference in left-sided colon cancer was detected between diverticular disease patients and controls, although the percentage of carcinomas detected in the distal colon was similar to that reported in a recent study [20]. This observation, however, may depend on the limited overall number of cancers detected in our study. Similarly, the lack of a higher prevalence of adenomas in sites other than the sigmoid tract in patients with diffuse or right-sided diverticulosis could be explained by the small sample size. Therefore, larger studies are recommended in this field.

Although the reason for the association between diverticular disease and adenomas in the sigmoid colon is still unclear, some plausible biological explanations may be advanced. In theory, the presence of common pathogenic factors or a causal relationship between the two diseases may explain this association. As far as the former hypothesis is concerned, the Western diet, low in dietary fibre and rich in saturated fat, may play a pivotal role [21 22]. Indeed, a low-fibre diet predisposes to the disordered motility of the colonic wall responsible for the formation of diverticula [23], and a fat-rich diet has been shown to be strictly correlated with an increased risk of left colon adenomas, presumably due to the larger amount of carcinogens produced by colonic bacteria [24]. In the latter hypothesis, the toxic compounds produced by the bacteria in the left colon could have become trapped both in the diverticulas and in the diverticular tract resulting in a protracted contact with the colonic mucosa and, therefore, favouring the carcinogenic process [15]. Indeed, in our series, the prevalence of constipation in diverticular disease patients was significantly higher than in controls. Alternatively, diverticular disease is associated, in some cases, with chronic inflammation of the sigmoid mucosa [25 26]. In turn, this event may increase the proliferation of the colonic crypts leading to a higher rate of somatic mutations of the epithelial cells, not unlike that seen in ulcerative colitis [27]. Further studies, to evaluate also cell kinetics in the sigmoid colon of patients with diverticulosis, are needed to clarify this aspect.

Our study also showed that polyps were more frequently pedunculated in diverticular disease patients than in controls. It is likely that the high intraluminal pressures and the spastic contraction described in colonic diverticulosis enhance the process of mucosal redundancy responsible for stalk development, as occurs in the "polypoid prolapsing mucosal folds" associated with diverticular disease [28 29].

In conclusion, although the present study did not reveal a higher overall prevalence of neoplastic lesions in patients with diverticular disease than in controls, our data demonstrate that patients with diverticular disease have a higher risk of harbouring adenomas, particularly advanced, in the sigmoid colon, when compared to controls. This observation should be taken into account in the screening and surveillance programmes for colorectal cancer. For this purpose, lower endoscopy would appear more accurate than barium enema in detecting sigmoid polyps in diverticular disease patients [30].

List of abbreviations

ASGE: American Society of Gastrointestinal Endoscopy; CI: confidence interval; OR: odds ratio.

References

[1] Burkitt DP. Epidemiology of cancer of the colon and rectum. Cancer 1971;28:3-13.

[2] Adanja B, Gledovic Z, Pekmezovic T, Vlajinac H, Jarebinski M, Zivaljevic V, et al. Mortality trends of malignant tumours of digestive organs in Belgrade, Yugoslavia, 1975-1997. Digest Liver Dis 2000;32:386-91.

[3] Burkitt DP, Walker AR, Painter NS. Dietary fiber and disease. J Am Med Ass 1974;229:1068-74.

[4] Painter NS, Burkitt DP. Diverticular disease of the colon: a 20th Century problem. Clin Gastroenterol 1975;4:3-21.

[5] Inadomi JM, Sonnenberg A. The impact of colorectal cancer screening on life expectancy. Gastrointest Endosc 2000;51:517-23.

[6] Almy TP, Howell DA. Diverticular disease of the colon. N Engl J Med 1980;302:324-31.

[7] Ponz de Leon M, Roncucci L. The cause of colorectal cancer. Digest Liver Dis 2000;32:426-39.

[8] Howe GR, Benito E, Castelleto R, Cornee J, Esteve J, Gallagher RP, et al. Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. J Natl Cancer Inst 1992;84:1887-96.

[9] Aldoori WH, Giovannucci EL, Rockett HR, Sampson L, Rimm EB, Willett WC. A prospective study of dietary fiber types and symptomatic diverticular disease in men. J Nutr 1998;128:714-9.

[10] McCallum A, Eastwood MA, Smith AN, Fulton PM. Colonic diverticulosis in patients with colorectal cancer and in controls. Scand J Gastroenterol 1988;23:284-6.

[11] Morini S, de Angelis P, Manurita L, Colavolpe V. Association of colonic diverticula with adenomas and carcinomas. Acolonoscopic experience. Dis Colon Rectum 1988;31:793-6.

[12] The American Society for Gastrointestinal Endoscopy. Appropriate use of gastrointestinal endoscopy. Manchester, Mass: American Society for Gastrointestinal Endoscopy, 1992.

[13] Naitove A, Smith RE. Diverticular disease. In: Sleisenger MH, Fordran JS, editors. Gastrointestinal disease. Philadelphia: Saunders; 1993. p. 1347-63.

[14] O'Brien MJ, Winawer SJ, Zauber AG, Gottlieb LS, Sternberg SS, Diaz B, et al. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology 1990;98:371-9.

[15] Stefansson T, Ekbom A, Sparen P, Pahlman L. Increased risk of left sided colon cancer in patients with diverticular disease. Gut 1993;34:499-502.

[16] Noshirwani KC, van Stolk RU, Rybicki LA, Beck GJ. Adenoma size and number are predictive of adenoma recurrence: implications for surveillance colonoscopy. Gastrointest Endosc 2000;51:433-7.

[17] Atkin WS, Morson BC, Cuzick J. Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med 1992;326:658-62.

[18] Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. Gastroenterology. 1987;93:1009-13.

[19] Otchy DP, Ransohoff DF, Wolff BG, Weaver A, Ilstrup D, Carlson H, et al. Metachronous colon cancer in persons who have had a large adenomatous polyp. Am J Gastroenterol 1996;91:448-54.

[20] Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? Symptoms, duration and clues to location. Am J Gastroenterol 1999;94:3039-45.

[21] Jenkins DJ, Jenkins AL, Wolever TM, Rao AV, Thompson LU.

Fiber and starchy foods: gut function and implications in disease. Am J Gastroenterol 1986;81:920-30.

[22] Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol 1999;94:3110-21.

[23] Hodgson J. Diverticular disease. Possible correlation between low residue diet and raised intracolonic pressures in the rabbit model. Am J Gastroenterol 1974;62:116-23.

[24] Giovannucci E, Stampfer MJ, Colditz G, Rimm EB, Willett WC. Relationship of diet to risk of colorectal adenoma in men. J Natl Cancer Inst 1992;84:91-8.

[25] Pereira MC. Diverticular disease-associated colitis: progression to severe chronic ulcerative colitis after sigmoid surgery. Gastrointest Endosc 1998;48:520-3.

[26] Imperiali G, Meucci G, Alvisi C, Fasoli R, Ferrara A, Girelli CM, et al. Segmental colitis associated with diverticula: a prospective study. Am J Gastroenterol 2000;95:1014-6.

[27] Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. N Engl J Med 1990;323:1228-33.

[28] Yoshida M, Kawabata K, Kutsumi H, Fujita T, Soga T, Nishimura K, et al. Polypoid prolapsing mucosal folds associated with diverticular disease in the sigmoid colon: usefulness of colonoscopy and endoscopic ultrasonography for the diagnosis. Gastrointest Endosc 1996;44:489-91.

[29] Mathus-Vliegen EM, Tytgat GN. Polyp-simulating mucosal prolapse syndrome in (pre-) diverticular disease. Endoscopy 1986;18:84-6.

[30] Boulos PB, Karamandis DG, Salmon PR, Clark CG. Is colonoscopy necessary in diverticular disease? Lancet 1984;1:95-6.