

# Diverticulosis and diverticulitis form no risk for polyps and colorectal neoplasia in 4,241 colonoscopies

M. M. Meurs-Szojda · J. S. Terhaar sive Droste ·  
D. J. Kuik · C. J. J. Mulder · R. J. F. Felt-Bersma

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## Abstract

**Background and aims** There are conflicting data concerning the association between diverticular disease and colorectal carcinoma (CRC). This study was performed to determine the prevalence and association of diverticulosis, diverticulitis, polyps, and CRC.

**Materials and methods** In a cross-sectional, retrospective study, we analyzed the colonoscopy reports of complete colonoscopies and patho-histological results of all patients referred for colonoscopy in a period of 3 months in 18 hospitals in The Netherlands. Diverticulosis was defined as three or more diverticula present and diverticulitis as diverticulosis with inflammation. Polyps were also coded according to localization and size. Advanced neoplastic lesions were defined as polyps  $\geq 10$  mm in diameter and/or villous architecture and/or adenomas with high grade dysplasia and/or invasive cancer. Actual and previous described CRC were registered.

**Results** A total of 4,241 patients were included in the study [1,996 (47%) male], mean age of 59 and range 18–95. Diverticula, diverticulitis, and polyps were seen in 1,052 (25%), 75 (2%), and 1,282 (30%) patients, respectively. No association was found between patients with polyps and those with and without diverticulosis ( $p=0.478$ ). Invasive adenocarcinoma and adenomas  $\geq 10$  mm were most frequently

observed. CRC was present in 372 (9%) patients. Negative relation between diverticulosis and CRC and invasive adenocarcinoma was observed. No association was found between polyps and CRC and patients with diverticulitis and CRC. In conclusion, there is no relation between patients with diverticulosis and higher incidence of polyps or CRC when using age-stratified analysis. No increased risk for polyps or CRC was found in patients with diverticulitis.

**Keywords** Diverticulosis · Diverticular disease · Diverticulitis · Polyps · Colorectal carcinoma

## Introduction

The prevalence of diverticulosis and subsequently diverticulitis is increasing in the last decades [1, 2]. Diverticulosis increases with age; it is estimated less than 10% in those under the age of 40 and increases to 65–70% in those above 65 years of age [3–5]. Besides diverticulosis, the prevalence of colon cancer is also increasing in the western world [3, 6]. Colorectal cancer is a leading cause of cancer mortality in the Western world, with more than 1,000,000 new cases per year and with 500,000 deaths per year worldwide [7]. The estimated lifetime risk is 5–6%, where incidence rates increase sharply after the age of 50 years [8]. In The Netherlands, colorectal cancer is diagnosed in about 10,000 patients each year and causes 4,400 deaths per year [9, 10]. Colorectal cancer is the third most common cancer in men and the second commonest in women in this country. Certain groups are at risk, like autosomal dominant syndromes, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer (HNPCC), Peutz–Jegher’s syndrome, acromegaly, and Gardner syndrome [11, 12]. Patients who are at risk are included in colonoscopic surveillance programs [13, 14].

M. M. Meurs-Szojda · J. S. T. s. Droste · C. J. J. Mulder ·  
R. J. F. Felt-Bersma (✉)  
Department of Gastroenterology and Hepatology,  
VU University Medical Centre,  
P.O. Box 7057, 1007 MB Amsterdam, The Netherlands  
e-mail: R.JF.Felt@vumc.nl

D. J. Kuik  
Department of Clinical Epidemiology and Biostatistics,  
VU University Medical Centre,  
P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

The relationship of diverticulosis, diverticulitis, colon polyps, and the occurrence of cancer is complicated and conflicting. There are studies in patients with diverticulosis that found an increased incidence of polyps [1, 15, 16] and colorectal carcinoma (CRC), [17, 18] a decreased incidence of polyps [19] and colon carcinoma [1, 19], or no difference in CRC [20]. In patients with diverticulitis, an increased [21] and decreased risk [19] for CRC was described.

When diverticulosis and diverticulitis form an increased risk for CRC, a different view concerning colorectal screening should be taken.

The aim of this study was to establish the relationship between diverticulosis, diverticulitis, polyps, advanced neoplastic lesions (ANL), and colon carcinoma in a retrospective, cross-sectional study.

## Materials and methods

### Patients

In a 3-month period from September to November 2006, 4,241 outpatients who underwent colonoscopy in 18 hospitals in the region of North Holland were included. Of all the hospitals which took a part in our study, 17 were peripheral hospitals and 1 was tertiary clinic (our hospital).

The indications for colonoscopy included uncomplicated lower abdominal pain of at least 2 months' duration, hematochezia, gastrointestinal hemorrhage, unexplained changes in bowel habit, weight loss, iron-deficiency anemia, chronic obstipation without positive reaction on the treatment, chronic diarrhea, surveillance after colonic polypectomy, and screening for and follow-up of colorectal cancer. Permission was granted from the central medical ethics review board of the VUMC medical center.

### Methods

The reports of 3 months complete colonoscopies and pathohistological results were entered in a database coding for age, sex, indication, medical history as present, endoscopic findings like inflammation, diverticula, polyps, CRC, and pathohistological results. Diverticulosis was defined as three or more diverticula present. Diverticulosis with inflammation was coded as diverticulitis. Any detected polyp was coded separately according to localization and size. Any described or earlier diagnosed macroscopic CRC was coded as CRC. ANL were defined as an adenomas  $\geq 10$  mm or more in diameter,  $>25\%$  villous architecture and/or adenomas with a high-grade dysplasia and/or an invasive cancer. Benign polyps were defined as hyperplastic polyps and adenomas  $<10$  mm with low/intermediate grade dysplasia.

### Statistical analysis

The frequency, location, and size of polyps are described in patients with diverticulosis and diverticulitis as well as frequency of colorectal cancer. Results are presented as mean and SD; statistical testing was done with the chi-square test, when appropriate corrected for age with the Mantel–Haenszel test (age stratified analysis in 10 years classes). Calculations were made with the SPSS program (SPSS 14.0).

## Results

A total of 4,241 patients were included in the study [1,996 (47%) male and 2,245 (53%) female], mean age of 59 and range 18–95. Patients with diverticulosis, polyps, and cancer were significant older than those without: mean age 69 vs. 56, 64 vs. 57, 68 vs. 58, respectively,  $P < 0.0001$ . Diverticula were seen in 1,052 (25%), diverticulitis in 75 (2%), polyps in 1,282 (30%), and CRC in 372 (9%) patients.

In 98% of the patients, predominantly left-sided diverticulosis was found. In 21 (2%) patients, mainly right-sided diverticula were seen. The mean age of the patients with diverticular disease was 69.5 (SD 11.8) as compared with 55.9 (SD 16.8) in those without ( $P < 0.0001$ ). No gender difference existed in patients with diverticulosis.

Polyps were seen significantly more in men than in women [703 (55%) vs. 579 (45%);  $p < 0.0001$ ]. No difference in distribution of ANL was found between men and women, 348 (53%) vs. 258 (39%), respectively ( $P = 0.12$ ). ANL were seen more often in the recto-sigmoid colon than the rest of the colon, 465 (36%) vs. 386 (30%),  $P = 0.002$  (Table 1). Invasive adenocarcinoma and adenomas  $\geq 10$  mm were most frequently observed (Table 1).

Though unstratified analysis seemed to show an association between patients with polyps and diverticulosis and those without diverticulosis [916 (71 %) vs. 366 (29%)], however, age stratified analysis showed no relationship ( $P = 0.478$ ).

A negative relation was observed between diverticulosis and CRC and invasive adenocarcinoma in age-stratified analysis ( $P < 0.0001$  and  $P = 0.002$ , respectively). No association was found between polyps and CRC and patients with diverticulitis and CRC (Table 2).

## Discussion

In this retrospective, cross-sectional study, we examined the relationship between diverticulosis, diverticulitis, polyps, ANL, and CRC in a group of 4,241 consecutive patients undergoing colonoscopy for various reasons.

**Table 1** Histopathological results and location of the polyps

Localization of the polyps	Advanced neoplastic lesions					Benign polyps N (%)	Total N (%)
	Adenomas $\geq 10$ mm N (%)	Invasive adenoca. N (%)	Villous adenoma N (%)	High grade dysplasia N (%)	Total N (%)		
Rectum	59 (37)	154 (38)	30 (79)	19 (34)	262 (40)	153 (25)	415 (32)
Sigmoid	48 (30)	131 (32)	2 (5)	22 (39)	203 (31)	233 (38)	436 (34)
Colon descendens	10 (6)	30 (7.5)	0	1 (2)	41 (6)	61 (10)	102 (8)
Transversum	9 (5)	17 (4)	1 (3)	1 (2)	28 (4)	46 (7)	74 (6)
Colon ascendens	21 (13)	36 (9)	4 (10)	8 (14)	69 (10)	82 (13)	151 (12)
Cecum	14 (9)	38 (9.5)	1 (3)	5 (9)	58 (9)	46 (7)	104 (8)
Total	161 (24)	406 (61.5)	38 (6)	56 (8.5)	661 (51.5)	621 (48.5)	1,282 (100)

In our study, diverticulosis was reported in 25% of patients. Underreporting and selection bias may play a role. Diverticulitis was seen in 2% of the patients, which is less than the previously reported prevalence of 5% [22]. This is probably due to the fact that, in many cases, computer tomography is performed when diverticulitis is suspected, rather than colonoscopy.

Polyps were observed in 30% of the patients, of which half (51%) were ANL. The polyps and ANL were found predominantly in the recto-sigmoid colon. This finding is consistent with other studies, where the left colon is the principal site of ANL and polyps [23–25].

CRC was present in 9% of the patients. This included patients with a previously resected CRC. Since the reason for colon resection was not always reported, underreporting also might play a role here.

The prevalence of both diverticulosis and adenomas increases with advanced age [3–5, 23, 26] as was also shown in our results.

We have not observed any gender domination in patients with diverticulosis, ANL, and CRC. However, polyps were seen more often in men than in women. The increasing prevalence of polyps in young male patients was already observed in a recently published study [24].

We observed a negative correlation between diverticular disease and CRC as well as invasive adenocarcinoma. Furthermore, we did not find any association between polyps and CRC or diverticulitis and CRC.

How can this discrepancy in the literature, including our results, be explained? Table 3 summarizes the studies regarding this subject.

There are nine studies, including ours, concerning diverticulosis, polyps, and CRC [1, 15–21]. Three studies described an increased incidence of polyps in patients with diverticulosis [1, 15, 16]. However, only one of these studies considered the confounding influence of age [15]. We did not find any relation between patients with polyps and incidence of diverticulosis when using age-stratified analysis. In the light of our results, it seems vital to make an age-stratified analysis.

One study only included first time colonoscopies without prior polypectomy, colorectal surgery, or inflammatory bowel disease [16]. Although the number of included patients was only 502, selection bias was minimal. Another study [19] found a lower incidence of polyps. Since these are retrospective studies, underreporting might be due to the fact that a substantial part of colonoscopies performed, consisted of follow-up colonoscopies after polypectomy or after partial colon resection.

**Table 2** Relationship between diverticulosis/diverticulitis with polyps, colorectal carcinoma (CRC), and invasive adenocarcinoma

	Polyps (%)	<i>P</i> value	OR	CI
Diverticulosis	916 (71)	0.478	0.94	0.8–1.1
Diverticulitis	23 (1.8)	0.695	0.87	0.5–1.4
CRC (%)				
Diverticulosis	88 (23.6)	<0.0001	0.54	0.4–0.7
Diverticulitis	3 (0.8)	0.116	0.36	1.1–1.2
Polyps	133 (35.7)	0.824	0.03	0.2–0.3
Invasive adenocarcinoma (%)				
Diverticulosis	175 (26.4)	0.002	0.66	0.5–0.8
Diverticulitis	11 (1.6)	0.43	0.66	0.2–1.5

**Table 3** Review of literature: relationship between diverticulosis, diverticulitis, polyps, and colon carcinoma

Author	Year	Diverticulosis	Diverticulitis	Polyp	Carcinoma	Note
Stefanson et al. [17]	1993	+			Left side ↑	Mixed diverticulosis and diverticulitis
Loffeld et al. [1]	2002	+		↑	↓	Many polyp surveillance
Morini et al. [15]	2002	+		Sigmoid ↑ ANL in sigmoid ↑	=	
Kieff et al. [16]	2004	+		Women ↑ distal and advanced		No previous polypectomy or surgery
Stefanson et al. [21]	2004	+			=	Longitudinal, case control study
Krones et al. [19]	2006	+	+	↓	4.2 ↑	Only 18% diverticulosis in CRC
Soran et al. [20]	2006	+			↓	10% diverticula in colonca
Choi et al. [18]	2007	+			Prognosis after colonca =	after resection for colonca
Meurs-Szojda	2008	+		=	Both left and right sided ↑	No previous polypectomy or surgery
			+	=	↓	Many polyp surveillance
				=	=	

ANL Advanced neoplastic lesion

Eight studies, including our own, concern the relationship between diverticulosis and carcinoma [1, 15, 17–21]. One recent study from Korea found an increased risk of CRC in both patients with left- or right-sided diverticulosis without prior polypectomy or surgery in the affected area [18]. Three studies showed no relationship between diverticulosis and CRC, one of them being a longitudinal study [21]. The two other studies showed no prognostic difference in patients with and without diverticulitis after removal of CRC [20] and the same prevalence of CRC in both groups of patients [15]. Two studies [1, 19] besides ours found less CRC in patients with diverticular disease. Again, selection bias could play a role.

There are two studies besides ours concerning the relationship between diverticulitis and CRC [19, 21] and one regarding polyps [19]. Stefanson describes a longitudinal, case control study in 7,159 patients with a prior diverticulitis and a follow up of at least 20 years in which he finds an increased risk (OR=4.2) for left-sided CRC [21]. Krones et al. [19] looked retrospective at resected specimen for CRC for diverticulitis and in resected diverticulitis for ANP. In the CRC group, the incidence of diverticulosis was only 18% and ANP in the diverticulitis group only 6%, both very low numbers [23–25]. Subsequently, a negative relationship was found. Our study showed no difference and also suffers from confounding factors like underreporting and previously removed polyps and CRC.

Although only one study [21] has demonstrated the relationship between prior diverticulitis and development of CRC, the sequence seems logic. Many patients with diverticulitis will experience recurrent attacks, and chronic inflammation can lead to overt carcinoma as is well known

in patients with inflammatory bowel disease [27, 28] and *Helicobacter pylori* [29].

This concept is supported by studies in vitro, although contradictory results are also found in this study. One study showed an elevated C-reactive protein concentration in blood of the persons who developed colonic cancer after several years [30]. One of the possible explanations for the association between diverticular disease and colorectal cancer is that the presence of an inflammation process increases the risk for a malignant transformation [30] since, in the Western population, both diseases occur usually in the left colon. A study in patients with diverticular disease demonstrated that hyperproliferation of the colonic mucosa was localized in the upper third of the colonic crypts [31]. Hyperproliferation of the colonic mucosa was detectable in the whole length of the colonic crypts in the patients not only with symptomatic diverticulosis and acute diverticulitis but also in patients with asymptomatic diverticulosis [32]. This suggests that not only patients with acute diverticulitis but also those with asymptomatic diverticulosis are at a risk of developing adenomas and CRC. Recently, an abnormal expression of M1/MUC5AC mucin [found in (pre)cancerous lesions] in the distal colon of 26% of patients with diverticulitis was found [33]. In contrast, a different matrix microenvironment was found between the colonic tissue architecture of the patients with colon cancer and those with diverticular disease, thus implying no predisposition for cancer in diverticular disease [34].

Now, what should we believe? Clearly, a longitudinal study following cohorts of patients with diverticulosis or diverticulitis is the best. However, some firm conclusions can be drawn. Considering the fact that more than 60% of

patients above the age of 60 will have diverticula, it is obvious that screening from this point of view is useless, even if there were a very slight increased risk.

How about diverticulitis? This is more complicated. In our group, there were not so many patients with diverticulitis (75) compared to the group of Stefansson et al. [21] (7,159), which were also followed as a cohort and found a positive relationship. But the surgical resection specimens of Krones et al. [19] were thoroughly examined, and he found less polyps and cancer. The difference could lie in the moment of endoscopy or surgery. Some find surgery mandatory after a first recurrence while others follow a more liberated policy [35]. Furthermore, additional or more adequate treatment may alter the disease and lead to less recurrences [36], thus reducing the chance for chronic inflammation. It seems that the common practice to perform a colonoscopy after a cured diverticulitis to rule out a malignancy is valuable. If any polyps are found, surveillance can occur as usual. Probably, the patient with continuous inflammation or frequent attacks of diverticulitis merit more attention.

Increasing diverticular disease and therefore diverticulitis around the world poses interesting questions regarding the long-time consequences for these patients and possible colonoscopy screening. This certainly merits more attention and research. Further longitudinal studies and awareness of underreporting are necessary, which can be overcome by standardized endoscopy reports.

In conclusion, no relationship between diverticular disease and colon neoplastic disease was found. Although some critical points can be made about the study design, some conclusion can be drawn from this study and the existing literature. Diverticulosis probably bears no relationship with colonic neoplastic lesions. Maybe, some patients with chronic or recurrent diverticulitis are at risk. The general clinical practice that patient should have a colonoscopy after a cured diverticulitis to rule out a carcinoma holds true. Those with polyps should enter a surveillance program. Probably, the patient with recurrent attacks of diverticulitis merit more attention.

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