

Diverticulosis and neoplastic lesions in screening colonoscopy: a large, multicenter study

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Abstract

Background Data on the potential association between diverticulosis and colonic neoplastic lesions are still controversial. We investigated this issue in subjects who underwent screening colonoscopy.

Methods We reviewed the data of subjects with a positive fecal immunological test who underwent a first colonoscopy in the national colorectal screening program. Endoscopic and histological reports were evaluated, using both univariate and multivariate analyses to search for an association between diverticulosis and colonic neoplastic lesions.

Results Data from 5050 subjects (males: 52.2%; mean age: 61.7±6.5 years) observed in the 7 participating centers were considered. Diverticula were found in 2176 (43.1%) cases; at least 1 adenoma was detected in 2277 (45.1%) patients, at least 1 advanced adenoma in 842 (16.7%); and cancer was diagnosed in 159 (3.1%) cases. By univariate analysis, the prevalence of adenomas in patients with diverticula (46.7%, 95% confidence interval [CI] 44.6-48.8%) was significantly higher than in controls (43.8%, 95%CI 42.1-45.7%; P=0.041), while prevalences of both advanced adenomas (13.8%, 95%CI 16.3-19.5%) and cancers (2.4%, 95%CI 1.7-3.1% vs. 3.7%, 95%CI 3.1-4.4%) were lower. By multivariate analysis, only male sex (odds ratio [OR] range: 1.54-2.05) and age (OR range: 1.03-1.05) were found to be independent variables associated with different neoplastic lesions in the colon, whilst diverticulosis was not.

Conclusion This large, multicenter study found no significant association between diverticulosis and neoplastic lesions in subjects who underwent screening colonoscopy.

Keywords Diverticulosis, adenoma, cancer, screening, colonoscopy

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Conflict of Interest: None

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Introduction

During colonoscopies performed in routine practice, a concurrent presence of diverticula and adenomas is often detected. Indeed, diverticulosis is vastly prevalent in Caucasian populations, particularly in the elderly, and an increasing prevalence in subjects under 50 years old has also been reported [1,2]. On the other hand, colorectal cancer, which mainly develops from colonic adenomas, remains among the most frequent tumors in Western countries, and its incidence is growing in young subjects [3,4]. Based on these epidemiological observations, an association between diverticulosis and neoplastic lesions in the colon could be hypothesized. Data from 2 meta-analyses showed

that diverticulosis significantly increases (by 47-67%) the risk of adenomas, but not that of advanced adenomas or colorectal cancer [5,6]. However, a large cohort study based on a healthcare registry in Sweden found that diverticulosis was associated with a 71% greater risk of developing colorectal cancer [7]. Similarly, a 76% greater risk of developing early (<50 years) colorectal cancer in patients with preexisting diverticulosis was found by a United States of America study [4]. Conversely, a Taiwanese study found that the risk of colorectal cancer was not greater during the first year after a diverticulosis diagnosis [8]. Thus, the available data on the potential association between diverticulosis and colonic neoplastic lesions are still controversial. The conflicting results are probably due to heterogeneity among the studies, whose setting was widely ranging, from population-based retrospective studies to endoscopic, radiological or surgical series [5,6]. Moreover, some relevant differences were present regarding the clinical scenario, with studies mixing data from patients who underwent diagnostic or screening colonoscopy, as well as patients with diverticulosis or diverticulitis [9,10]. We designed the present study to further investigate this clinically relevant issue in subjects participating in an organized cancer screening program, using the fecal immunological test (FIT) and high-quality colonoscopy [11].

Patients and methods

Study design and setting

This was a retrospective cohort study of patients who participated in a National colorectal screening program.

Study population

Data from all 50-74-year-old subjects with a positive FIT (cutoff 100 ng/mL) who underwent a first colonoscopy in the participating centers were reviewed. In detail, endoscopic and histological reports were individually reviewed and anonymously entered into a specially prepared Excel database. In each center, all endoscopic examinations were performed by experienced endoscopists with a withdrawal time >7 min. Diverticulosis was categorized as either present, if at least 1 diverticulum was detected through the colon, or absent.

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Outcomes

The prevalence of adenomas, advanced adenomas and cancers, all confirmed at histological assessment, was calculated and compared between subjects with or without diverticulosis. Advanced adenoma was defined as an adenoma with either high-grade dysplasia or a size >1 cm evaluated at endoscopy, according to the updated guidelines [12]. Multiple adenomas were considered present when ≥ 5 adenomas were detected [12]. Hyperplastic polyps were not taken into account.

Ethical statements

Since no identification of patients was allowed, no experimental drugs were administered, no additional costs or procedures for the patients were required and no funds were received, the Investigational Review Boards waived formal approval for this retrospective analysis.

Statistical analysis

Demographic and clinical characteristics were expressed as mean and standard deviation for continuous variables, and as percentages with 95% confidence intervals (CI) for categorical variables. Comparisons of data between subjects with diverticulosis and controls were performed on univariate analysis using the chi-squared test or *t*-test, as appropriate. Mixed effects logistic regression models were used to evaluate the possible independent role of sex, age and diverticulosis on neoplastic lesions. A random intercept by centers was included to account for potential correlation of evaluations from physician belonging to the same center. Odds ratios (OR) and 95% CIs were calculated. A P-value less than 0.05 was considered significant. All analyses were performed using R software (version 4.0.2).

Results

Descriptive analysis

We analyzed data from 5050 subjects who underwent screening colonoscopy in the 7 participating centers, involving a total of 28 endoscopists. There were 2635 (52.2%) males, and the mean age was 61.7 ± 6.5 years. Diverticula were found in 2176 (43.1%) cases. Diverticulosis involved only the sigmoid tract in 1198 cases, but extended to the descending colon in 597 and the right colon in 332 cases, whilst in 49 patients diverticula were confined to the right colon. Overall, at least 1 adenoma was detected in 2277 (45.1%) patients, at least 1 advanced adenoma in 842 (16.7%), multiple (>5) adenomas in 89 (1.8%), and cancer was diagnosed in 159 (3.1%) cases.

Outcomes

On univariate analysis, sex distribution was significantly different between the cases with diverticula and controls (M/F: 1222/954 vs. 1413/1461, $P < 0.001$), whereas the age was similar (mean age: 62.7 ± 6.2 vs. 60.9 ± 6.5 years, $P = 0.9$). Overall, the prevalence of adenomas in patients with diverticula (46.7%, 95%CI 44.6-48.8%) was significantly higher than in controls (43.8%, 95%CI 42.1-45.7%), prevalences of both advanced adenomas (13.8%, 95%CI 16.3-19.5% vs. 15.7%, 95%CI 16.3-19.5%), and cancers (2.4%, 95%CI 1.7-3.1% vs. 3.7%, 95%CI 3.1-4.4%) were lower, while the frequency of multiple adenomas did not differ among groups (Table 1).

On multivariate analysis, sex and age were found to be independent variables associated with different neoplastic lesions in the colon, whereas diverticulosis, as well as all the other variables considered, were not (Table 2). Adenomas, advanced adenomas and cancers were less prevalent in female than in male patients, and their prevalence increased with age, whereas patients with diverticulosis showed a lower risk of cancer.

Discussion

Some epidemiological evidence has highlighted a potential association between diverticulosis and neoplastic lesions in the colon [4-9]. However, the literature provides conflicting data

on this issue. Indeed, the results of some meta-analyses showed that the presence of diverticulosis significantly increases the risk of adenomas, but not advanced adenomas or colorectal cancer [5,6]. Conversely, a significant association between diverticulosis and colorectal cancer emerged in some large nationwide studies based on healthcare registries [4,7], but not in others [8]. Furthermore, a recent meta-analysis, including data from more than 27,000 patients with diverticulosis, found a statistically significant association between diverticulosis and either adenomas or advanced adenomas, but not with colon cancer [13]. At least in part, these conflicting results may depend on the wide heterogeneity among these previous studies. Therefore, other data are needed to unravel the association; the findings of our large study certainly provide further information about this clinically relevant issue.

The potential association between diverticula and adenomas in the colon could be either causal or spurious: namely, the result of shared risk factors. For the former hypothesis, colonic microbiota might produce some toxic compounds that could be trapped in the diverticular tract, resulting in prolonged contact with the colonic mucosa and promoting adenoma development [14]. For the latter hypothesis, a dietary intake low in fiber and rich in saturated fat could play a role in both conditions. Indeed, a low-fiber diet predisposes to the disordered motility of the colonic wall responsible for the formation of diverticula, and a fat-rich diet has been shown to be strongly correlated with an increased risk of adenomas [14]. Irrespective of the process involved, the determination of an association between diverticula and adenoma may affect both preventive measures and follow-up procedures.

We performed this large study to search for a potential association between diverticula and colorectal neoplastic lesions in an organized screening program. Indeed, this setting would appear ideal for such a kind of investigation, when we consider that it represents a quite homogeneous population in term of age and sex distribution, and a sample rich in neoplastic lesions, given the positive FIT result. Moreover, a high-quality colonoscopy is performed by expert and retrained endoscopists [12]. The findings of this large study were that the significant association between diverticulosis and adenomas detected on univariate analysis was not confirmed by multivariate analysis. Indeed, we found an even lower risk of cancer in subjects with diverticulosis who underwent screening colonoscopy. This finding suggests that the results of those studies where multivariate analysis was lacking, and a positive association was observed only on univariate analysis, should be interpreted with caution [15-18]. Our observations are in contrast with data from a similar study performed on 970 subjects who underwent screening colonoscopy in a single center, where the presence of diverticulosis emerged as an independent risk factor for both adenoma detection rate (OR 1.58, 95% CI = 1.14-2.18) and advanced adenoma (OR 1.57, 95% CI = 1.10-2.24), but not for cancer, on multivariate analysis [19]. However, in the same study [19], male sex and age were found to be independent risk factor for adenomas and advanced adenomas, as emerged in our analysis. The potential "protective effect" of diverticulosis against colorectal cancer we detected remains unclear, when we take into account both data from epidemiological studies,

Table 1 Data from the univariate analysis

Variable	Diverticulosis (N=2176)	Control (N=2876)	P-value
Males/females	1222/954	1413/1461	<0.001
Mean age \pm SD; years	62.7 \pm 6.2	60.9 \pm 6.5	0.9
Adenomas	1017 (46.7)	1260 (43.8)	0.041
Advanced adenomas	390 (13.8)	452 (15.7)	0.038
Multiple adenomas (\geq 5)	42 (1.9)	47 (1.65)	0.49
Cancers	52 (2.4)	107 (3.7)	0.007

Numbers in parentheses are (%)
SD, standard deviation

Table 2 Variables associated with different neoplastic lesions on multivariate analysis

Lesion	OR	95%CI	P-value
Adenoma			
– Male vs. female	1.69	1.52-1.91	<0.001
– Age (years)	1.03	1.02-1.04	<0.001
Advanced adenoma			
– Male vs. female	1.54	1.32-1.80	<0.001
Cancer			
– Male vs. female	2.05	1.46-2.91	<0.001
– Age (years)	1.05	1.02-1.07	<0.001
– DD yes vs. no	0.55	0.39-0.78	<0.001

OR, odds ratio; CI, confidence interval; DD, diverticulosis

showing similar trend, and the shared risk factors, such as low-fiber diet, obesity and aging [20]. However, under-reporting of diverticula when a cancer is detected during colonoscopy [21], and missed lesions within the diverticular segment could be proposed as potential explanations [22]. Indeed, diverticulosis was found to be an independent predictor of interval cancer development in patients who underwent colorectal screening colonoscopy with an OR of 4.25 (95% CI = 2.58-7.00) and of 6.00 (95% CI = 5.57-6.46) in two studies [22,23].

An association between diverticulitis, rather than diverticulosis, and colon cancer has been proposed [24]. However, data from a recent Danish nationwide study showed that the prevalence of colon cancer was higher in diverticulitis (2.1%) than in matched controls (1.5%), but that the difference remained statistically significant only in during the first 6 months after a diverticulitis bout, whereas thereafter the risk was even significantly reduced (OR 0.8, 95%CI 0.7-0.9) [25]. It is likely that this was due to a missed cancer diagnosis at radiological evaluation in the acute setting, particularly in those patients with a complicated diverticulitis. Indeed, in a recent study of 91,993 colonoscopies performed following diverticulitis onset, it was found that colon cancer prevalence was significantly greater in patients with complicated (1.43%) but not uncomplicated (0.31%) diverticulitis, as compared to screening colonoscopies (0.33%) [26], confirming data from a previous systematic review [27]. Thus, the association between diverticulitis and colon neoplasia remains controversial.

In conclusion, this large, multicenter study found no significant association between diverticulosis and neoplastic lesions in subjects who underwent screening colonoscopy.

Summary Box

What is already known:

- Some epidemiological studies suggested an association between diverticulosis and neoplastic lesions in the colon, but data are conflicting
- Diverticula and colorectal cancer share some risk factors, including low-fiber diet and aging
- To find a significant association could affect both preventive measures and follow-up procedures

What the new findings are:

- Our data found that the significant association between diverticulosis and adenomas detected on univariate analysis is not confirmed by multivariate analysis
- In contrast to epidemiological evidence, this study showed even lower risk of cancer in subjects with diverticulosis who underwent screening colonoscopy
- Further studies are needed to unravel this clinically intriguing association

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