

# The incidence of colon cancer among patients diagnosed with left colonic or sigmoid acute diverticulitis is higher than in the general population

Jeremy Meyer · Theodoros Thomopoulos ·  
Massimo Usel · Ergys Gjika · Christine Bouchardy ·  
Philippe Morel · Frédéric Ris

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## Abstract

**Background** Considering the low incidence of colon cancer after an initial episode of colonic diverticulitis in some categories of patients, some authors suggested to exempt them from colonoscopy. However, this incidence has never been compared to that of a reference population, and predictors of cancer are still poorly investigated. We aimed to determine the 1-year incidence of colon cancer at the site of diverticulitis in patients diagnosed with left colonic or sigmoid acute diverticulitis, to compare this incidence to a reference population to state whether endoscopy is required or not, and to identify predicting factors of cancer to better target subpopulations needing that examination.

**Methods** All patients admitted at the University Hospitals of Geneva for left colonic or sigmoid acute diverticulitis were included. Patients with a previous history of colon cancer or non-available for follow-up were excluded. Demographic data, haemoglobin values, and the Hinchey score were documented. This cohort was matched with the Geneva Cancer Registry to look for cancer occurrence at the site of diverticulitis within 1 year. Predictors of cancer were assessed using univariate logistic regression and the risk of cancer by comparing observed cases to a reference population using standardized incidence ratios.

**Results** The final cohort included 506 patients. Eleven (2.2 %) had a diagnosis of cancer at the site of diverticulitis within 1 year. The mean age was significantly different between patients with cancer and others. No predictor of cancer could be identified, except a trend for an increased risk with advancing age ( $p = 0.067$ ). The standardized incidence ratios showed a 44-fold increased risk of cancer among the cohort compared to the reference population.

**Conclusions** Colonoscopy should be continued after an initial diagnosis of left colonic or sigmoid acute diverticulitis, irrespective of the clinical or radiological presentations.

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J. Meyer (✉) · T. Thomopoulos · E. Gjika · P. Morel · F. Ris  
Clinic for Visceral and Transplantation Surgery, Department of  
Surgery, University Hospitals of Geneva, Rue Gabrielle-Perret-  
Gentil 4, 1211 Geneva 14, Switzerland  
e-mail: jeremy.meyer@hcuge.ch

T. Thomopoulos  
e-mail: theothomopoulos@yahoo.com

E. Gjika  
e-mail: ergys.gjika@hcuge.ch

P. Morel  
e-mail: philippe.morel@hcuge.ch

F. Ris  
e-mail: frederic.ris@hcuge.ch

M. Usel · C. Bouchardy  
Geneva Cancer Registry, Global Health Institute, University of  
Geneva, Boulevard de la Cluse 55, 1205 Geneva, Switzerland  
e-mail: massimo.usel@unige.ch

C. Bouchardy  
e-mail: christine.bouchardymagnin@unige.ch

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## Abbreviations

CI Confidence interval  
CT Computed tomography  
Hb Haemoglobin  
OR Odds ratio  
SD Standard deviation  
SIR Standardized incidence ratio

Diverticulosis of the colon is a widespread disease in Western countries, involving 48 % of people over 50 years [1]. The lifelong risk of developing diverticulitis has been roughly estimated to be between 10 and 25 % [2], with a mean age of 61.8 years at presentation [3]. Discovery via abdominal computed tomography (CT) has become an essential step in the diagnostic procedure to confirm the disease and to stratify its severity, conditioning the prognosis and the therapeutic management [4–7]. However, difficulties in distinguishing acute diverticulitis of the colon from colon carcinoma persist because these conditions both induce the inflammation of an intestinal segment and can share the same radiological presentation [8].

The leading societies of gastroenterology and colorectal surgery therefore recommend performing a colonoscopy after an episode of acute diverticulitis of the colon to seek alternative aetiologies, notably any neoplastic processes [9, 10]. This recommendation is based on low-quality evidence 1C [9] and has been applied to all patients, regardless of their risk factors or warning signs for colon carcinoma. However, the use of colonoscopy should be limited to at-risk populations because of its limited availability, high cost, and the risk for complications, which are certainly low in prevalence but have a relevant impact on morbidity and mortality [11].

The short-term incidence of colon carcinoma in a population diagnosed with acute diverticulitis has therefore been recently investigated by some authors [12–21], whose results have been summarized by a meta-analysis, and was found to be 1.6 % [22]. This incidence was described to be lower in patients presenting with uncomplicated diverticulitis compared to complicated disease, with reported incidences of, respectively, 0.3 and 7.6 % [22]. Considering the lower incidence of colon carcinoma in patients with uncomplicated diverticulitis, it was suggested that these patients be exempt from endoscopic evaluation. This assertion was further confirmed by another recent systematic review, which recommends not performing routine colonoscopy after an episode of uncomplicated diverticulitis in the absence of other clinical signs of colorectal carcinoma, unless this examination is regarded for screening in individuals aged 50 and older [23].

However, these recommendations were systematically based on comparison with published general population risks of colon carcinoma from registries of screening colonoscopies, which were estimated to be between 0.8 and 1 % [24, 25], and not with the adjusted risk in the local reference populations. In addition, the conditional exemption mentioned by some authors, based on certain criteria, such as the absence of warning signs of colon carcinoma, disregards the fact that the supposed predictors of cancer were not assessed in a diverticulitis population.

Considering the lack of evidence regarding these fundamental questions, the purposes of this study were to determine the 1-year incidence of colon carcinoma at the site of diverticulitis in a cohort of patient diagnosed with left colonic or sigmoid acute diverticulitis, to compare this incidence with a reference population to clearly state whether endoscopy is required or not after an episode of diverticulitis, and to identify predicting factors of cancer to better target subpopulations needing an endoscopic screening.

## Materials and methods

### Setting

This single-centre retrospective cohort study was performed at the University Hospitals of Geneva, which constitute the only public hospital system in the Swiss canton of Geneva, responsible for 75 % of admissions of approximately half a million inhabitants [26].

### Inclusion process

Considering that CT is an essential step in the diagnostic procedure of diverticulitis, an informatics research was performed across all CT reports from the emergency department from 1 January 2005 to 31 December 2009, looking for keywords related to left colonic or sigmoid diverticulitis. The reports were read by the investigators to confirm that the radiological findings were compatible with an acute inflammation of a diverticular segment of the left or sigmoid colon and the hospital files consulted to complete medical information including symptoms, haemoglobin (Hb) value, and diverticulitis severity at the time of diagnosis. Previous colonoscopies were not documented and follow-up CT non-considered. The hospital cohort was matched with the Geneva population-based Cancer Registry and the Cantonal Office of the Population datasets. Exclusion criteria were defined as patients with symptomatology incompatible with an episode of acute diverticulitis (no abdominal pain or no fever), with a previous history of colon carcinoma, who were not resident in the canton, or who had incomplete follow-up by the Geneva Cancer Registry at 1 year after the diagnosis. Recurrences of CT-proven diverticulitis occurring during the studied period were also excluded, and only the first episode was considered. Doubtful cases were solved by consensus. The investigators and radiologists who produced the CT reports were blinded during the inclusion process for the occurrence of colon carcinoma. The final cohort included 506 patients (Fig. 1). The protocol was approved by the ethics

committee of the University Hospitals of Geneva (reference number 12-090).

### Variables of interest

Age, sex, Hb value, and diverticulitis gravity classified according to the modified Hinchey score of Wasvary et al. [27] within 24 h after admission were considered relevant variables for identifying an increased risk of colon carcinoma. Anaemia was defined as a Hb value below 130 g/l for males and below 120 g/l for females. Uncomplicated diverticulitis refers to a Hinchey score of 1a, and complicated diverticulitis to a Hinchey score >1a. The Geneva Cancer Registry was searched for all diagnoses of colon carcinoma at the site involved in the inflammatory process within 1 year after the CT.

### Statistical analysis

Differences between patients with and without colon carcinoma at the site of diverticulitis were compared using the two-sided Student's test, the Pearson's Chi-squared test, or the Fisher's exact test, as appropriate. Continuous variables were transformed into categorical variables if required. Variables were expressed as proportions for categorical variables and means for continuous ones; 95 % confidence intervals (95 % CIs) and standard deviations (SDs) were

reported. An a posteriori power calculation was performed for each of the assessed variables, using the two-sided Pearson's Chi-squared test to compare two independent proportions or the two-sided Satterthwaite's test to compare two independent means, as appropriate. The alpha value was set at 0.05.

Factors linked to cancer occurrence were identified by age-adjusted univariate logistic regression, considering as "cases" patients with cancer and as "controls" other patients.

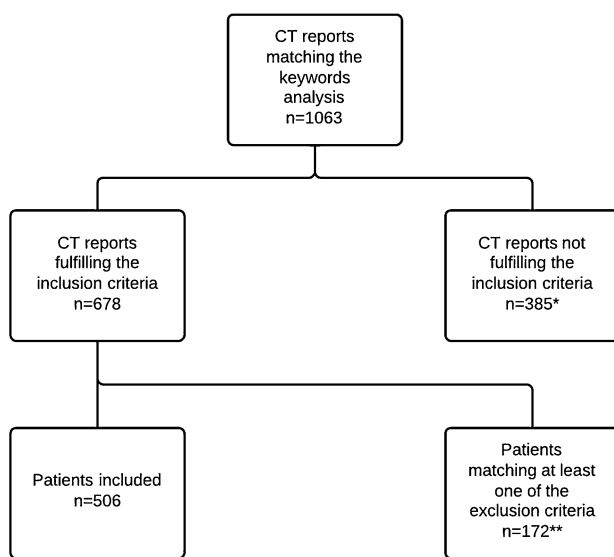
To assess the risk of colon carcinoma in our cohort, we compared the number of cases occurring at the site of diverticulitis within 1 year after the CT in the cohort (observed cases [O]) to those occurring at the same site, expected during the same period, in the resident population of Geneva [expected cases (E)], using age-standardized incidence ratios (SIR), i.e. the ratio of O/E. The SIRs with 95 % CIs were calculated using the PYRS software [28]. The two-sided *p* value was obtained with the OpenEpi software [29]. The Mid-P exact test was chosen for the present analysis considering the low number of observed cases, as previously described [30]. Subgroup analyses were done according to gender and Hinchey score.

All statistical analyses were performed using the STATA software [31]. The null hypothesis was rejected at  $p < 0.05$ .

### Results

Overall, 1063 CT reports matched the informatics research criteria. Three-hundred and eighty-five of the reports were non-considered after revision for not fulfilling the inclusion criteria, and 172 were excluded, leaving 506 patients for the present analysis (Fig. 1). The sex ratio was 2:3 in favour of females, and the mean age at diverticulitis was 67.4 years. In total, 403 (79.6 %) episodes of acute diverticulitis were classified as uncomplicated, and 103 (20.4 %) as complicated; 150 (30.3 %) patients were considered anaemic. Eleven patients (2.2 %) were found to have an invasive colon carcinoma at the site involved in the inflammatory process within 1 year after the diagnosis of diverticulitis, as reported by the Geneva Cancer Registry. Ten of these cancers (90.9 %) were located at the sigmoid colon and one (9.1 %) was located at the recto-sigmoid junction. A mean time of 68.6 days elapsed between the CT and the final diagnosis of cancer.

Table 1 compares the characteristics of patients according to the presence or not of cancer at the site of interest and provides the risk of having cancer at the same site derived from age-adjusted logistic regression. The mean age was significantly different between patients with cancer and those with a final diagnosis of diverticulitis



**Fig. 1** Flowchart of the inclusion process. \*347 patients without diverticulitis, 10 patients with diverticulitis of another colonic segment and 28 CT reports on part of the follow-up of an active diverticulitis. \*\*54 patients with a symptomatology incompatible with an acute diverticulitis, 44 patients non-covered by the Geneva Cancer Registry for the 1-year follow-up, 14 patients with a previous history of colon carcinoma, 49 cases of recurrences and 11 patients with missing data

**Table 1** Distribution of characteristics of patients with diverticulitis according to the presence or not of colon cancer at the site of diverticulitis

Characteristics	Total <i>N</i> = 506 (100 %)	Patients with cancer <i>N</i> = 11 (100 %)	Patients without cancer <i>N</i> = 495 (100 %)	<i>p</i> value from group comparison	Power (%)	Odds ratio (95 % CI) <sup>b</sup>	<i>p</i> value from logistic regression <sup>b</sup>
Age in continuous (SD)	67.4 (15.5)	76.1 (12.4)	67.2 (15.6)	0.020	65.17	1.04 (1.00–1.09) <sup>c</sup>	0.067 <sup>c</sup>
Age group				0.122	42.06		0.097 <sup>c</sup>
≥65 years	281 (55.5 %)	9 (81.8 %)	272 (55.0 %)			3.69 (0.79–17.25) <sup>c</sup>	
<65 years	225 (44.5 %)	2 (18.2 %)	223 (45.1 %)			1 (reference)	
Gender				0.214	29.08		0.318
Female	306 (60.5 %)	9 (81.8 %)	297 (60.0 %)			2.24 (0.46–10.90)	
Male	200 (39.5 %)	2 (18.2 %)	198 (40.0 %)			1 (reference)	
Hb in continuous (SD)	131.4 (19.1)	123.5 (14.7)	131.6 (19.1)	0.949	43.02	0.99 (0.95–1.03)	0.496
Anaemia <sup>a</sup>				0.269	24.33		0.671
Yes	150 (30.3 %)	5 (45.5 %)	145 (30.0 %)			1.32 (0.37–4.69)	
No	345 (69.7 %)	6 (54.6 %)	339 (70.0 %)			1 (reference)	
Hinchey score				0.474	11.80		0.539
>1a	103 (20.4 %)	3 (27.3 %)	100 (20.2 %)			1.53 (0.40–5.90)	
1a	403 (79.6 %)	8 (72.7 %)	395 (79.8 %)			1 (reference)	

Hb haemoglobin, CI confidence interval, SD standard deviation

<sup>a</sup> Hb < 120 g/l for females and <130 g/l for males; 11 missing values

<sup>b</sup> Age-adjusted logistic regression

<sup>c</sup> Crude value, i.e. not adjusted for age

(mean age of 76.1 vs. 67.2 years,  $p = 0.02$ ). All patients with cancer were aged 50 years and more (data not shown). The risk of having colon carcinoma was higher for patients with advanced age, females, patients with anaemia, or Hinchey >1a. However, because of the few numbers of patients having a cancer, none of these results reached significance. The a posteriori calculation of the power to show a potential difference between patients with cancer and those without cancer was lower than 80 % for each of the assessed variables. Age-adjusted univariate logistic regression did not identify age, gender, Hb value, or Hinchey score as predictors of colon carcinoma. However, a trend for age towards significance emerged ( $p = 0.07$ ). A multivariate analysis was not performed due to the absence of any significance among the supposed predictors on univariate analysis and due to the low number of positive cases.

Table 2 presents the overall risk of cancer of pertinent site in the cohort of patients with diverticulitis and the effect of factors on that risk, separately for males and females. Eleven carcinomas were observed at the site of interest in the cohort, whilst only 0.25 were expected, therefore providing a 44-fold increased risk of cancer at the site of diverticulitis in the cohort compared to the general reference population (SIR 44, 95 % CI 23–76,  $p < 0.001$ ). That risk was increased for both males (SIR 17, 95 % CI 3–55,  $p = 0.007$ ) and females (SIR 60, 95 % CI 29–110,  $p < 0.001$ ). A Hinchey score >1a versus ≤1a increased the risk from 40-fold (95 % CI 19–76,  $p < 0.001$ ) to 50-fold

(95 % CI 13–136,  $p < 0.001$ ) and the presence of an anaemia versus not from 38-fold (95 % CI 15–78,  $p < 0.001$ ) to 63-fold (95 % CI 23–139,  $p < 0.001$ ). Among females, the risk was significantly increased for uncomplicated and complicated diverticulitis alike (SIR 50, 95 % CI 20–104,  $p < 0.001$ , and SIR 100, 95 % CI 25–272,  $p < 0.001$ , respectively). Among males, the effects of Hinchey score and anaemia were not estimable because no cancer was observed among patients with a Hinchey score >1a or without anaemia.

## Discussion

As mentioned before, the short-term incidence of colon carcinoma in a population diagnosed with acute diverticulitis has been only recently investigated by some authors [12–21], whose results have been summarized by a meta-analysis [22]. Twenty-two cases of colon carcinomas were identified among 1970 pooled patients whose colons were evaluated by imaging or endoscopy, giving an incidence of 1.6 % [22]. More recent studies described similar incidences of cancer, with such findings as 2.7 % (17/633 patients) [32], 1.6 % (4/249 patients) [33], and 1.9 % (8/422 patients) [34]. In our cohort of 506 patients, we found out that 2.2 % had colon carcinoma diagnosed at the site of the inflammatory process within 1 year after the initial CT, thus confirming these previous results. The SIR values

**Table 2** Risk of colon cancer at the site of diverticulitis within 1 year among patients with acute diverticulitis by gender, Hinchey score, and anaemia

Characteristics	Number of persons at risk	Observed cancers	Expected cancers	Age-standardized incidence ratio (95 % CI)	<i>p</i> value
Both genders					
Hinchey 1a	403	8	0.20	40.00 (18.58 - 75.96)	<0.001
Hinchey > 1a	103	3	0.06	50.00 (12.72 - 136.10)	<0.001
No anaemia <sup>a</sup>	345	6	0.16	37.50 (15.26 - 78.00)	<0.001
Anaemia <sup>a</sup>	150	5	0.08	62.50 (22.90 - 138.50)	<0.001
Total	506	11	0.25	44.00 (23.14 - 76.48)	<0.001
Males					
Hinchey 1a	148	2	0.08	25.00 (4.19 - 82.60)	<0.001
Hinchey > 1a	52	0	0.03	–	–
No anaemia <sup>a</sup>	152	0	0.08	–	–
Anaemia <sup>a</sup>	45	2	0.03	66.67 (11.18 - 220.30)	<0.001
Total	200	2	0.12	16.67 (2.79 - 55.06)	0.0069
Females					
Hinchey 1a	255	6	0.12	50.00 (20.27 - 104.00)	<0.001
Hinchey > 1a	51	3	0.03	100.0 (25.44 - 272.20)	<0.001
No anaemia <sup>a</sup>	193	6	0.08	75.00 (30.40 - 156.00)	<0.001
Anaemia <sup>a</sup>	105	3	0.05	60.00 (15.26 - 163.30)	<0.001
Total	306	9	0.15	60.00 (29.26 - 110.10)	<0.001

CI confidence interval

<sup>a</sup> Hb < 120 g/l for females and <130 g/l for males; 11 missing values

noted a 44-fold global increased risk of colon carcinoma diagnosis within 1 year after the diagnosis of diverticulitis compared to our age-matched reference population.

Considering that diverticular disease itself does not seem to be associated with the development of colon cancer in the light of current knowledge [35], we suppose that this increased risk might be explained by the persistent difficulties in distinguishing acute diverticulitis from colon carcinoma solely on a radiological basis. Eight out of the 11 colon carcinomas found in our cohort were discovered within 2 months after the initial CT, which represents the average time required to obtain a definitive endoscopic or surgical diagnosis. In their case–control study on 2,477 patients, Granlund et al. [35] similarly identified an increased risk of colon carcinoma in the first 6 and 12 months after admission for diverticular disease, with odds ratios (ORs) of 22.75 and 1.67, respectively, but that analysis was performed for all diagnoses related to diverticular disease and not limited to diverticulitis.

Subgroup analysis usually enables risk stratification depending on the severity of diverticulitis. The incidence of colon carcinoma was found to be lower in patients presenting with uncomplicated diverticulitis compared to complicated disease, with reported incidences of, respectively, 0.3 % (5/1,497) and 7.6 % (6/79) in the meta-analysis cited above [22], compared to 0 % (0/533 patients)

and 17 % (17/100 patients) [32] and 0 % (0/175 patients) and 5.4 % (4/74 patients) [33] in the latest studies. Considering these results, some of these authors proposed to exempt patients diagnosed with uncomplicated diverticulitis from an endoscopic evaluation in the absence of other signs warranting that examination [17, 22, 32–34].

Surprisingly, we did not find any statistically significant difference in term of cancer in our population, with incidences of 1.8 % (8/403) and 2.9 % (3/103) between the uncomplicated and complicated subgroups, respectively. Moreover, the subgroup analysis performed on SIR values showed a 50-fold increased risk of colon carcinoma for females with uncomplicated diverticulitis compared to the general population and a 100-fold increase for those with complicated diverticulitis, thus confirming an increased risk, regardless of the Hinchey score.

Similarly, only age presented significance as a continuous variable after group comparisons between patients with cancer and others, and a trend towards significance on univariate logistic regression (OR 1.04, 95 % CI 1.00–1.09, *p* 0.07). Despite our cohort's relatively large number of included subjects and our very similar incidence of colon carcinoma compared to other studies [12–21, 32–34], no other variables, such as gender, Hb value, the presence of an anaemia, or a Hinchey score >1a, were identified as predictors of colon carcinoma.



Previous studies also failed to reach consensus about the latters', therefore highlighting the difficulties in identifying patients needing an endoscopic evaluation after an initial diagnosis of diverticulitis. The presence of an abscess, suspicion of a cancer by the radiologist, thickness of the affected colon  $\geq 15$  mm, the absence of diverticulosis of the affected segment, or the presence of undiagnosed metastases were associated with colon carcinoma, whilst neither age  $>60$  years, recurrence, anaemia, extraluminal air, ascites, signs of occlusion, an affected colon shorter than 10 cm nor the presence of mesenteric or para-aortic lymphadenopathies were associated with carcinoma on multivariate logistic regression analysis in the study by Sallinen et al. [32]. On their side, Brar et al. [33] identified complicated diverticulitis and age as risk factors for the presence of colon carcinoma, excluding the participation of anaemia and recurrence. Noteworthy, none of these studies investigated anamnestic or clinical findings, such as positive familial history or hematochezia, which could constitute better indicators of cancer.

This lack of significance of potential predictors to identify patients with colon carcinoma in this setting could be the result of a true absence of association, or more likely due to the low number of positive events in our cohort and in the previous studies, as reflected by the low power resulting from group comparison, rendering the probability of a type II error occurring to be very high.

The strengths of our study are (1) the comparison of the incidence of colon carcinoma in patients diagnosed with diverticulitis to that of an age-matched reference population using the Geneva Cancer Registry and the Cantonal Office of the Population datasets, performed for the first time to our knowledge, allowing to clearly assess the risk of cancer in our cohort, and (2) the a posteriori power calculation from group comparison between patients with cancer and others, proving that predictors of cancer cannot be accurately evaluated in our cohort, and by extension in previous studies, and calling for larger sample sizes before drawing conclusions about subpopulations needing an endoscopic screening. The shortcomings of this study are (1) its retrospective nature, rendering the inclusion process less accurate and the collection of data limited to documented variables, (2) the few number of positive cases, preventing the identification of predictors of cancer, and (3) its limitation to patients referred to our university hospital, non-considering patients treated in ambulatory setting or those hospitalized in private hospitals, therefore giving a risk of a selection bias of patients with severe disease. This latter assertion should be weighted with the proportion of complicated disease of 20.4 % (103/506 patients) in our cohort, which is very similar to that reported by the literature [15, 32, 33], and thus speaks in disfavour of that bias.

However, the results of the present study are sufficient to draw definitive conclusions, as they strongly indicate that colonoscopy should be continued after an initial diagnosis of diverticulitis of the left or sigmoid colon, regardless of the clinical or radiological presentations. Large-scale population-based well-conducted prospective studies remain necessary to confirm the increased incidence of colon cancer exhibited by this population and to further identify its predictors, aiming to better target subgroups requiring an endoscopic evaluation.

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