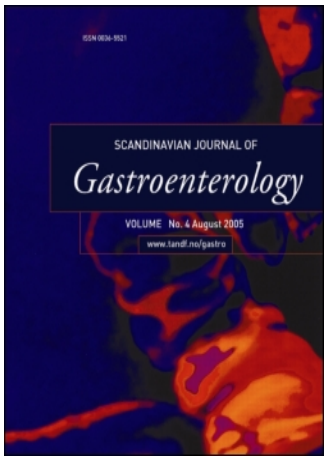

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Association between sigmoid diverticulitis and left-sided colon cancer: a nested, population-based, case control study

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Association Between Sigmoid Diverticulitis and Left-sided Colon Cancer: a Nested, Population-based, Case Control Study

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Background: An increased risk of left-sided colon cancer in patients with diverticular disease of the sigmoid colon has been reported. The aim of this study was to investigate to what extent patients with diverticulitis of the sigmoid colon differ in long-term risk of colon cancer compared to patients with diverticulosis of the colon without any clinical signs of diverticulitis. **Methods:** A total of 7159 patients (2478 M, 4681 F) discharged with a diagnosis of diverticulosis or diverticulitis in 1965–83 in the Uppsala Health Care Region were followed-up with the Swedish Cancer Registry. Sixty-four cases with colon cancer were identified and compared with 123 controls without cancer matched for sex, age and year of first discharge. Based on information from the patients' charts, an independent observer blinded to the outcome assigned a clinical diagnosis of diverticulitis or not diverticulitis to cases and controls. **Results:** In patients classified as having sigmoid diverticulitis there was an increased risk of left-sided colon cancer compared with patients with diverticulosis without any clinical signs of diverticulitis (odds ratio = 4.2, 95% CI 1.3–13.0) which remained after mutually adjusting for several clinical parameters in a multivariate conditional logistic regression analysis. **Conclusion:** The results of the study indicate a causal association between sigmoid diverticulitis and a long-term increased risk of left-sided colon cancer.

Key words: Colon; colon cancer; diverticular disease; diverticulitis of the sigmoid colon

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There is a 20-fold variation in the incidence of colon cancer in the world (1). The incidence is already tending to increase with migration and Westernization within the first generation (2) and is most prominent in men (3) and in the sigmoid colon (4–6). The prevalence of diverticulosis of the sigmoid colon is higher in the developed countries in Western Europe and North America compared to countries in Africa and Asia (7). The prevalence of colon diverticulosis increases in a population moving from a low-risk area to a high-risk area (8, 9). These findings support the hypotheses of environmental risk factors in the aetiology of colorectal cancer and colon diverticulosis and a common aetiology of these diseases has been proposed (10). In a previous publication we found an increased long-term effect of left-sided colon cancer in patients with sigmoid diverticular disease (11). The effects of inflammation or exposure to intraluminal carcinogens from diet trapped in the diverticulum were proposed as possible biological explanations.

The aim of this study was to carry out a further and more detailed examination of the potential association between sigmoid diverticulitis and colon cancer in a case control study nested within a cohort of 7159 patients with diverticular disease (11).

Subjects and Methods

The cohort

The Uppsala Health Care Region, which covers six counties, is located in central Sweden and had, during the study period, a population of 1.2–1.3 million people. As there is almost no private inpatient treatment in Sweden, hospital-provided medical services are population based and referable to the county in which the patient lives. From 1965 through 1983, the Swedish National Board of Health and Welfare received annual reports from all inpatient medical institutions in Sweden and recorded data on individual hospital admissions and discharges in the Inpatient Register for all inhabitants within the Uppsala Health Care Region.

As well as a national registration number (a unique personal identifier assigned to all Swedish citizens), each record contains data on place of residence, hospital department, surgical procedures and up to eight discharge diagnoses. These diagnoses were coded according to the seventh revision of the International Classification of Diseases (ICD 7) through 1968 and according to the eighth revision (ICD 8) thereafter. In a recent publication it was estimated that the overall extent of under-reporting to the inpatient register was

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Table I. Characteristics of cases and controls

	Cases	Controls
Sex		
Males	21	42
Females	43	81
Age at diagnosis of diverticular disease		
<60	5	11
60–70	20	35
≥70	39	77
First hospitalization for diverticular disease		
1965–70	24	46
1971–76	17	32
1977–83	23	45
Total	64	123

less than 2%. Severe under-reporting occurred in certain counties during a limited period representing a few percent of the estimated total number of hospital admissions (12).

All patients with records in the Inpatient Register containing a diagnostic code for diverticulosis (ICD 7 code 572.12 and ICD 8 code 562.10) or diverticulitis (ICD 7 code 572.11 and ICD 8 code 562.11) of the colon were considered for inclusion in the study. The national registration number (13) allowed us to select the first recorded discharge with this diagnosis for each individual. A total of 7630 individuals had been given a discharge diagnosis of diverticulosis or diverticulitis at least once during 1965–83 and were potentially eligible. We excluded 128 of these individuals because they were entered in the Inpatient Register with an incomplete or inconsistent national registration number and were not available for follow-up. Record linkage based on the national registration number, to the nation-wide Register of Causes of Death led to information on the date of death among those deceased through 1991. A total of 343 cases were not found in any of the registers used for follow-up, probably because they were entered in the Inpatient Register with an erroneous national registration number, and they were therefore excluded. Through the National Census Bureau and the Emigration Register we were able to confirm that the remaining members of the cohort were alive and living in Sweden on 31 December 1983. The number of patients available to follow-up was thus 7159 (2478 M, 4681 F). At first discharge, 1410 patients were under 60 years of age, 1665 were 60 to 69 years old and 4084 were 70 years or older.

Identification of cases

The National Swedish Cancer Registry, founded in 1958 (14, 15), was used to ascertain all 140 incident cancers of the colon diagnosed in the cohort from start of follow-up until the end of 1991. We excluded 75 cancer cases because they were detected during the first two years after the first discharge due to diverticulosis or diverticulitis. The reason for this approach was to eliminate or to reduce the possible impact of selection bias. Such bias would occur in patients where the symptoms of the cancer were the reason for the hospitalization and the patients were given the discharge diagnosis of diverticulosis or diverticulitis. The medical records of the remaining 65 colon cancer cases were reviewed. One of the cases had been erroneously classified as sigmoid diverticulitis instead of duodenal diverticulitis, and was excluded, leaving us with 64 cancer cases for analysis (left-sided: 30, right-sided: 30 and indefinite site: 4) (Table I).

Table II. Exposure status of cases and controls

	Cases	Controls
Categorized as diverticulitis	46 (72%)	65 (53%)
Categorized as not having diverticulitis	18 (28%)	58 (47%)
	64 (100%)	123 (100%)

Identification of controls

Two controls per case were randomly chosen from the cohort matched by age (±1 year), sex and calendar year of the first recorded discharge with a diagnosis of diverticular disease. Each control subject had to be alive and without a colon cancer when the case was diagnosed as colon cancer. Eight controls served as controls twice owing to the small sample size. One of the potential controls had been operated on for a colon cancer before the date of the diagnosis of diverticular disease and was excluded. It was impossible to retrieve the patient charts for 4 controls and they were excluded, leaving 123 controls for analysis.

Exposure information

The patient charts for the first admission for diverticular disease of the colon were retrieved in a uniform manner for cases and controls. From the charts we then assessed the following exposures, which were categorized as discrete dichotomous variables:

Relapsing disease: If the patient had a medical history of a previous clinical diagnosis of diverticulitis versus not.

Duration of illness: If the patient had abdominal symptoms for more than one month at the time of the first admission versus symptoms for less than one month.

Lower abdominal pain: The presence of a recorded history of lower abdominal pain in the patient chart versus none.

Lower abdominal tenderness: Tenderness in the lower abdominal part at a clinical examination at the first admission versus no tenderness recorded.

Elevated body temperature: Body temperature exceeding 37.5 °C versus normal body temperature.

Elevated erythrocyte sedimentation rate: Sedimentation rate exceeding the reference value versus a rate within the reference values (women 20–40 years old: 16 mm, <40 years old: 35 mm; men <60 years old: 13 mm, >60 years old: 24 mm).

Elevated white cell count: White cell count exceeding 9.0×10^9 per L versus less than 9.0×10^9/L.

Number of diverticula: Among those with a barium examination the number of diverticula as a measurement of

Table III. Univariate analysis

	All colon		Right colon		Left colon	
	OR	95% CI	OR	95% CI	OR	95% CI
Sigmoid diverticulitis	3.1	1.5–6.3	2.4	0.9–6.0	4.2	1.3–13.0
Relapsing disease	1.8	0.9–4.0	2.5	0.7–8.6	1.5	0.5–4.3
Duration of illness	2.8	1.2–6.6	2.7	0.7–9.7	2.2	0.7–7.2
Lower abdominal pain	1.1	0.6–2.1	1.5	0.6–3.8	0.9	0.2–2.3
Lower abdominal tenderness	1.0	0.5–1.9	0.8	0.3–2.0	1.4	0.3–1.7
Body temperature	1.0	0.5–2.1	1.2	0.4–3.6	0.7	0.3–1.7
Erythrocyte sedimentation rate	0.9	0.4–1.8	0.8	0.3–2.2	0.7	0.2–2.2
White cell count	1.4	0.3–2.9	0.6	0.2–1.9	3.5	1.1–11.8
Number of diverticula	1.9	0.9–4.2	4.0	1.1–14.6	1.2	0.4–3.8
Irregularity in the colonic mucosa	1.2	0.3–2.8	0.9	0.3–2.5	1.2	0.5–3.0

Odds ratio (OR) and 95% confidence interval (CI) for colon cancer in all colon, right colon and left colon according to exposure (sigmoid diverticulitis, relapsing disease, duration of illness, lower abdominal pain, lower abdominal tenderness, erythrocyte sedimentation rate, white cell count, number of diverticula and irregularity of the colonic mucosa).

the magnitude of diverticulosis was always assessed by the radiologist. We divided this assessment into three categories: none, less than 10 and more than 10 diverticula. In the analysis, the variable was analysed as a dichotomous variable where none and less than 10 diverticula constituted the reference value.

Irregularity in the colon mucosa: Irregularities in the mucosa of the sigmoid colon often combined with contractions or strictures in the same segment have been used as an indicator for sigmoid diverticulitis by radiologists (16, 17). Patients with these features on the barium enema were compared with those without such features.

Through the information acquired from the charts, cases and controls were finally categorized as either a case of sigmoid diverticulitis or not. As it sometimes was obvious in patients' charts, if the patient had or had not subsequently developed colon cancer, a standardized summary of the charts was prepared in a uniform manner for cases and controls. This summary was then used as an instrument to categorize patients with or without sigmoid diverticulitis, which was done by one of us (AE) blinded to the final outcome, i.e. colon cancer or not.

To be categorized with a diagnosis of diverticulitis of the colon, a patient had to have diverticulosis on a barium enema, lower abdominal symptoms at first admission and one of the following: fever, elevated white cell count or elevated sedimentation rate at first admission. Mucosal changes in the sigmoid colon interpreted by the radiologist as diverticulitis in combination with a medical history of probable sigmoid diverticulitis were sufficient for the patient to be categorized with a diagnosis of diverticulitis. Diverticulitis was ruled out in all patients with no diverticula on the barium enema.

Statistical analysis

In a matched analysis, we used a conditional logistic regression model to study the difference in exposures in cases and controls. The results were given as odd ratios for the risk of colon cancer as one entity but also, in a second analysis, stratified by outcome in left- and right-sided colon cancer. The confidence limits were calculated as 95%. In a second stage in a multivariate analysis, mutual adjustments were made for certain exposures of interest.

Results

Clinical data for cases and controls are presented in Table II. From the results of the univariate analysis (Table III) it is obvious that patients categorized with a diagnosis of diverticulitis of the sigmoid colon were at higher risk for colon cancer than those with just diverticulosis (OR = 3.1; 95% CI 1.5–6.3). The increased risk was most prominent for cancer of the left colon (OR = 4.2; 95% CI 1.3–13.0). There was, however, also a tendency towards an increased risk for cancer of the right colon (OR = 2.4; 95% CI 0.9–6.0). Duration of symptoms exceeding a month prior to the first admission also entailed an increased risk for colon cancer (OR = 2.8; 95% CI 1.2–6.6) but did not reach significance when analysed separately for right- and left-sided colon cancer. Elevated white cell count was, however, associated with an increased risk of left-sided colon cancer (OR = 3.5; 95% CI 1.1–11.8). Somewhat surprisingly, more than 10 diverticula in the sigmoid colon were associated with an increased risk of right-sided colon cancer (OR = 4.0; 95% CI 1.1–14.6) but not with left-sided colon cancer. No other exposures were associated with a significant increase of either left- or right-sided colon cancer. After mutually adjusting for a diagnosis of diverticulitis and other variables, a slight decrease in the point estimate for a diverticulitis diagnosis was evident (Table IV). The increased risk, however, remained significant in most cases both for colon cancer as one entity and for left-sided colon cancer (Table IV). Furthermore, in most cases there was a clear tendency for other associations present in the univariate analysis to decrease or disappear altogether, but a clear tendency for an association between elevated white cell count and left-sided

Table IV. Multivariate analysis

	All colon		Right colon		Left colon	
	OR	95% CI	OR	95% CI	OR	95% CI
Sigmoid diverticulitis	2.6	1.2–5.5	2.1	0.4–5.5	3.9	1.2–12.9
Duration of illness (>1 month/<1 month)	1.9	0.8–4.7	1.9	0.5–7.4	1.3	0.4–4.6
Sigmoid diverticulitis	3.1	1.5–6.5	2.6	1.0–6.8	3.2	0.9–11.2
White cell count ($>9 \times 10^9$ /L/$<9 \times 10^9$/L)	1.0	0.4–2.2	0.5	0.1–1.7	2.0	0.5–7.7
Sigmoid diverticulitis	2.9	1.4–6.1	1.8	0.7–4.8	4.7	1.4–15.7
Number of diverticula (Many/none or few)	1.3	0.5–3.0	3.2	0.8–12.6	0.7	0.2–2.4
Sigmoid diverticulitis	3.2	1.5–6.6	2.6	1.0–6.9	4.2	1.3–13.4
Irregularity in the colonic mucosa	0.9	0.4–1.8	0.7	0.2–1.9	1.0	0.4–2.6

Odds ratio (OR) and 95% confidence interval (CI) for colon cancer (all colon, right colon and left colon) in patients categorised as having the diagnosis sigmoid diverticulitis mutually adjusted for duration of illness, white cell count, number of diverticulas and irregularity in the bowel lumen.

colon cancer still remained in the multivariate analysis (Table IV).

Discussion

The main result in this study is the association between a prior diagnosis of diverticulitis and a long-term increased risk of left-sided colon cancer. This increased risk still remains after mutually adjusting for other exposures, such as prior medical history and exposures associated with an inflammation process. In a previous study, we found an increased long-term risk of left-sided colon cancer after a discharge diagnosis of diverticular disease of the colon (11). One of the feasible biological explanations for that association was that the presence of an inflammation process increased the risk for a malignant transformation. This hypothesis is supported in a new reference where elevated C-reactive protein is associated with an increase in the risk of developing colorectal cancer (18) and the hypothesis is further strengthened by the findings in the present study. An alternative hypothesis was also presented, that the increased risk could be due to a common aetiology for colon cancer and diverticulosis of the colon. This hypothesis is to some extent refuted by the results in the present study, as diverticulosis of the colon in the multivariate analysis is not associated with any increase in the risk for left-sided colon cancer but solely due to a diagnosis of diverticulitis. In the previous cohort study we found a more than 2-fold increased risk of left-sided colon cancer still present 10 years after the first discharge because of a diverticular disease of the colon (11). The results from the present study indicate, however, that the subgroup of patients being at risk are those with diverticulitis, indicating that the estimate of a 2-fold increase is too low, especially as only 52% of the controls were classified with diverticulitis. A long-term 4–5-fold increased risk for left-sided colon cancer compared to the general population is probably a more valid risk estimate, thus indicating a causal association between the two disease entities.

In the univariate analysis the presence of diverticulosis was associated with an increased risk of right-sided colon cancer (OR = 4.0; 95% CI 1.1–14.6) as opposed to left-sided colon cancer where no association was found. Although the point estimate was markedly reduced in the multivariate analysis, the underlying reason for this association is difficult to explain. Besides chance, one other feasible explanation could be that a right-sided colon cancer has a longer lead-time than left-sided colon cancer and the arbitrarily chosen limit of two years is too short in the case of right-sided colon cancer. Another explanation may be that there are common aetiologic factors for diverticulosis of the colon and right-sided colon cancer, a hypothesis that perhaps merits further studies. Since the inherited form of colon cancer (HNPCC) usually occurs in the right colon, this could be an interesting hypothesis (19). It is not known whether diverticulosis is an inherited disease or if it is solely an environmental disease. However, if diverticulosis or underlying reasons for diverticulosis are inherited, there could be a genetic explanation to the association. Detection bias is of lesser concern in the case of left-sided colon cancer. Cancer in the left colon often mimics symptoms of sigmoid diverticulitis and therefore initially is misclassified as diverticulitis. It is unlikely that a left-sided colon cancer would remain undetected for more than two years, as the natural history of left-sided colon cancer as opposed to right-sided colon cancer is often associated with obstructive symptoms that become more prominent as time passes.

Another weakness of the study is the categorization of diverticulitis as a dichotomous variable. This approach makes it impossible to analyse to what extent increasing severity is associated with an increased risk of colon cancer. However, the specificity of the clinical diagnosis of diverticulitis is low (20), which makes it likely that non-differential misclassification exists in the present study. This is further substantiated by the tendency towards an increased risk of especially left-sided colon cancer among those with an elevated white cell count, even after mutually adjusting for the diagnosis of diverticu-

litis. This variable is probably the most sensitive for the existence of an inflammation process and there are therefore reasons to believe that some patients with 'real' diverticulitis were classified as non-diverticulitis. The existence of non-differential misclassification, however, tends to decrease the point estimate and will not show as an increased odds ratio. The assessment of the risk estimates found in the present study for the association between diverticulitis and left-sided colon cancer is therefore probably too low.

Colorectal cancer screening has been recommended in populations with a 2–3-fold average risk for developing colorectal cancer (21, 22). In this study we have shown a 4–5-fold increase in relative risk of developing colonic cancer in a long-time follow-up for those who have sigmoid diverticulitis. In a previous study we showed an 18-fold increase in the occurrence of colonic cancer in individuals with a clinical diagnosis of sigmoid diverticulitis during the first two years after a diagnosis of sigmoid diverticulitis (11). Therefore patients who have had diverticulitis of the sigmoid colon should probably be recommended for colonoscopic screening every 5 years as those who are first-degree relatives to patients with colorectal cancer (23).

Another question that remains to be answered is what exposures will determine whether a patient with diverticulosis of the colon will succumb to diverticulitis. Various motility disorders as underlying reasons could be one such exposure (24), a hypothesis further substantiated by other studies showing an association between malignant transformation in the colon and a motility disorder such as constipation (25).

We conclude that there seems to be a causal association between diverticulitis of the colon and left-sided colon cancer. No association seems to exist between diverticulosis of the colon and left-sided colon cancer, which argues against a common aetiology of those two disease entities. Furthermore, colorectal cancer screening should be considered and recommended for patients who have had sigmoid diverticulitis.

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