

Risk Factors Associated With Small Bowel Adenocarcinoma in Crohn's Disease: A Case–Control Study

Gaël Piton, M.D.,¹ Jacques Cosnes, M.D., Ph.D.,² Elisabeth Monnet, M.D., Ph.D.,³ Laurent Beaugerie, M.D., Ph.D.,² Philippe Seksik, M.D., Ph.D.,² Guillaume Savoye, M.D., Ph.D.,⁴ Guillaume Cadiot, M.D., Ph.D.,⁵ Bernard Flourie, M.D., Ph.D.,⁶ Philippe Capelle, M.D.,⁷ Philippe Marteau, M.D., Ph.D.,⁸ Marc Lemann, M.D., Ph.D.,⁹ Jean Frédéric Colombel, M.D., Ph.D.,¹⁰ Elie Khouri, M.D.,¹¹ Bruno Bonaz, M.D., Ph.D.,¹² and Franck Carbonnel, M.D., Ph.D.¹

¹Service de Gastroentérologie et Nutrition, Centre Hospitalier Universitaire de Besançon; ²Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine; ³Département de Santé Publique, Centre Hospitalier Universitaire de Besançon; ⁴Service de Gastroentérologie, Centre Hospitalier Universitaire de Rouen; ⁵Service de Gastroentérologie, Centre Hospitalier Universitaire de Reim; ⁶Service de Gastroentérologie, Centre Hospitalier Universitaire Lyon Sud; ⁷Service de Gastroentérologie, Institut Mutualiste Montsouris, Paris; ⁸Service de Gastroentérologie, Hôpital Lariboisière, Paris; ⁹Service de Gastroentérologie, Hôpital Saint-Louis, Paris; ¹⁰Service de Gastroentérologie, Centre Hospitalier Universitaire de Lille; ¹¹Service de Gastroentérologie, Centre Hospitalier de Chaumont; and ¹²Service de Gastroentérologie, Centre Hospitalier Universitaire de Grenoble, France

- BACKGROUND AND AIMS:** It is well established that Crohn's disease (CD) is associated with an increased risk of small bowel adenocarcinoma (SBA). The data concerning SBA risk factors in CD are scanty. The aim of this study was to identify them.
- METHODS:** In 11 French centers affiliated with the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif), we identified 29 patients with CD and SBA. Eighty-seven CD controls without SBA recruited in a single center were matched to the cases for sex, age, duration, and CD site. A conditional logistic regression, taking into account the matching between cases and controls, was performed.
- RESULTS:** In univariate analysis, the cases had had significantly less small bowel resection and received prolonged treatment with salicylates (more than 2 yr), less often than the controls (odds ratio, OR [95% confidence interval, CI] 0.07 [0.01–0.32] and 0.29 [0.10–0.82], respectively). In multivariate analysis, both associations remained significant (OR 0.04 [0.01–0.28], $P = 0.001$; OR 0.16 [0.03–0.79], $P = 0.02$, respectively).
- CONCLUSION:** This study suggests that small bowel resection and prolonged salicylates use may protect against SBA in CD patients.

(Am J Gastroenterol 2008;103:1–7)

INTRODUCTION

Colorectal cancer (CRC) in ulcerative colitis (UC) has been thoroughly studied (1–5). However, there have been relatively few studies dedicated to small bowel adenocarcinoma (SBA) in Crohn's disease (CD). It is well established that there is an increased risk of SBA in patients with CD. A recent meta-analysis of five population-based cohort studies has shown that ratios of observed to expected SBA rates in CD patient cohorts ranged from 3.4 to 66.7, giving a 27-fold increased overall risk of SBA in CD patients (standardized incidence

ratio 27.1, 95% confidence interval [CI] 14.9–49.2) (6). In another meta-analysis pooling population-based as well as hospital or specialist center-based series, the overall pooled estimate of relative risk of SBA in CD was found to be 33.2 (95% CI 15.9–60.9) (7). According to one population-based study where the standardized incidence ratio estimate was as high as 200, the SBA risk increase could be even higher in patients with ileal CD (95% CI 54–512) (8). Given the extremely low incidence of SBA in the general population, it is thought that even this large relative risk does not result in a high rate of SBA. However, in a recent study, based upon a hospital

cohort of 1,935 patients with small bowel involvement, the cumulative risk of SBA in CD (95% CI) was estimated to be 2 (0–8) and 22 per 1,000 patients (7–64) after 10 and 25 yr of follow-up, respectively (9). In the same series, SBA accounted for 50% and 66% of the risk of gastrointestinal carcinoma after 10 and 25 yr of small bowel CD, respectively. Similarly, in the Copenhagen county population-based study, 4 out of 7 intestinal cancers observed in 374 patients after a median time of 17 yr were SBA (8).

In clinical practice, SBA often presents as an ominous surprise, after a median time of 15 yr from CD diagnosis (range 0–37 yr) (9). In most cases, SBA diagnosis is not suspected preoperatively and is made either during laparotomy or by the pathological examination of the ileal resection specimen in a patient with longstanding, but recently aggravated, ileal CD (9). The median survival is only 24 months and the median age is 46 yr, 21 yr less than the median age of SBA cases in the general population (9).

Thus, SBA seems to be more common than previously thought, occurs in young patients, and carries a poor prognosis. Considerable progress is needed in the prevention, screening, diagnosis, and therapy of SBA in CD patients. The identification of risk factors is a prerequisite for defining screening and prevention strategies. The aim of the present study was to define SBA risk factors in CD patients. To achieve this goal, we performed a case-control study in which we compared CD patients, with or without SBA, in a ratio of 3 controls (patients without SBA) for one case (patient with SBA).

MATERIALS AND METHODS

Patients

CASES. Patients with CD and SBA were identified in French centers affiliated with the GETAID. GETAID is a French-speaking association of gastroenterologists that coordinates multicenter clinical research in the field of inflammatory bowel disease. The centers affiliated with the GETAID are located in the university hospitals of Belgium, France, and Switzerland. These centers were asked to collect data on patients who had SBA and CD between 1986 and 2006. The CD diagnosis relied on the usual criteria and was made or confirmed in the GETAID centers. The SBA diagnosis was based on the pathological examination of the small bowel or, in one case, hepatic metastases.

CONTROLS. Patients with CD without SBA were recruited from the MICISTA Registry, a tertiary clinical database of all inflammatory bowel disease (IBD) patients evaluated by the same staff of physicians at Rothschild Hospital (Paris, France) between 1974 and 2002 and then at the Saint-Antoine Hospital (Paris, France). In total, 3,492 patients with CD were seen between 1986 and 2006. This series comprised 1,361 men and 2,131 women, with a median age at diagnosis of 25 yr (interquartile range 20–34 yr) and a median follow-up of 96 months (interquartile range 37–176 months; complete

follow-up in 70% of patients). Three control patients were matched to each case. The matching criteria were sex, CD site during the first 6 months of the disease, date of birth (range of 5 yr), and calendar year of CD diagnosis (range of 5 yr). In these patients, the whole clinical history of the disease was reviewed until July 2006 in order to verify the absence of SBA in controls.

Data Collection

For patients with SBA, medical charts were screened by a single investigator (GP) using a predefined, standardized questionnaire. For patients without SBA, the variables were taken from the MICISTA registry, except for those variables related to medical or surgical treatment that were screened in the medical charts of the patients. These data were taken by the same investigator (GP) using the same standardized, predefined questionnaire. We retrospectively studied the CD history of cases and controls. The beginning of follow-up was the date of CD diagnosis, and the end point of follow-up was either the date of SBA in cases or the date that matched SBA diagnosis in the corresponding controls.

Studied Variables

We recorded treatment and nontreatment variables as the possible risk factors for SBA among CD patients.

NONTREATMENT VARIABLES. The following nontreatment variables were studied for the cases and controls: smoking (previous or ongoing smoker), cholecystectomy, appendectomy, family history of CD or UC, dates of first symptoms and of CD diagnosis, and extraintestinal manifestations. The CD duration was calculated as the time elapsed from the date of CD diagnosis until SBA diagnosis in the cases or until the date that matched SBA diagnosis in the corresponding controls. CD was classified at three dates according to the Montreal classification: 5 yr after CD diagnosis, 3 yr before that of SBA, and the date of SBA diagnosis for each case (10). The same variables were recorded in the controls, taking into account the date that matched SBA diagnosis in the corresponding cases.

TREATMENT VARIABLES. We noted the medical treatment of CD: salicylates (salazosulfapyridine, 5-aminosalicylates), steroids, and immunosuppressive drugs (azathioprine or 6-mercaptopurine, methotrexate, or infliximab). For each drug, the cumulative duration of use before SBA diagnosis in cases or for an equivalent follow-up time in controls was estimated. The duration of use was categorized into two classes using the median value observed in the whole group. Eventually, the dates and sites (jejunum, ileum) of small bowel resections were studied. For each patient, the CD duration without small bowel resection was calculated as follows: for nonoperated patients, from the date of CD diagnosis to the date of SBA diagnosis in cases or the date that matched SBA diagnosis of the corresponding case in controls. For

Table 1. Clinical Details of Cases (CD and SBA) and Controls (CD Without SBA)

| | | Cases (N = 29) | Controls (N = 87) |
|---|-------------------------------|------------------------|------------------------|
| Sex, N (%) | Male | 15 (52) | 45 (52) |
| | Female | 14 (48) | 42 (48) |
| Median age in years (range) | At first CD symptoms | 30 (11–63) | 30 (11–63) |
| | At CD diagnosis | 35 (15–63) | 34 (13–63) |
| | At SBA diagnosis | 46 (29–72) | 45 (29–74)* |
| Median duration in years (range), [mean duration] (standard deviation) | From first CD symptoms to SBA | 15 (0–37) | 10 (0–52) |
| | From CD diagnosis to SBA | 11 (0–37) [11] (11.32) | 7 (0–52)† [11] (11.44) |
| | | | |
| Montreal classification: localization during the first 6 months of the CD, N (%) | L1 = small bowel | 22 (76) | 61 (70) |
| | L2 = colon | 1 (3) | 2 (2) |
| | L3 = small bowel + colon | 6 (21) | 24 (28) |
| | L4 = upper digestive tract | 0 (0) | 0 (0) |

*Age at the date that matched SBA diagnosis of the corresponding case.
 †Date that matched SBA diagnosis of the corresponding case.

operated patients, the CD duration without resection extended from the date of the last small bowel resection until the date of SBA diagnosis in cases or the date that matched SBA diagnosis of the corresponding case in controls. Furthermore, a history of previous stricturoplasty and intestinal bypass was investigated.

Statistical Analysis

The link between the clinical and treatment variables and SBA was assessed using a conditional logistic regression, taking into account the matching of cases and controls. First, the link for each of these variables was examined, adjusting for the CD duration and age at diagnosis. These analyses are labeled as univariate analyses throughout this text. Second, a multivariate analysis was conducted, using a backward elimination conditional logistic regression model, to identify a final set of variables independently associated with SBA. A significance level of $\alpha = 0.05$ was used to retain the variables in the multivariate model. All results are presented as odds ratios (OR) with the associated 95% CI. The CIs not con-

taining unity were regarded as statistically significant. The analyses were carried out with NCSS 2004 and PASS Trial software (Number Cruncher Statistical Systems, Kaysville, Utah, USA.)

RESULTS

Study Population

The clinical details of the 29 cases (14 women) and the 87 controls (42 women) are shown in Table 1. The intervals between CD diagnosis or first symptoms and SBA for each case are shown in Figures 1 and 2, respectively. The median interval from CD diagnosis to SBA was 11 yr (range 0–37 yr) for cases, whereas for controls, the median interval from CD diagnosis to the date that matched SBA diagnosis of the corresponding case was 7 yr (range 0–52 yr). This difference was not statistically significant ($P = 0.66$). In 8 cases, the time interval between CD diagnosis and SBA diagnosis was less than 1 yr. These 8 cases were defined as concomitant.

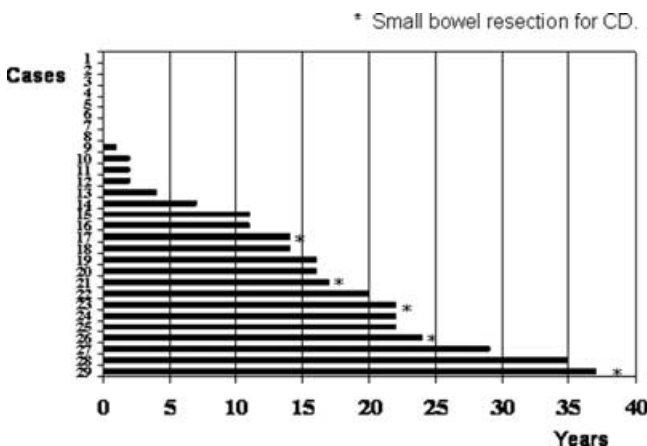


Figure 1. CD duration from CD diagnosis to SBA diagnosis in 29 cases.

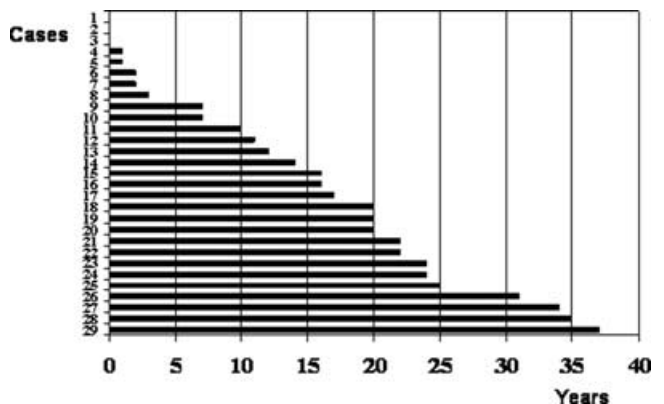


Figure 2. CD duration from first CD symptoms to SBA diagnosis in 29 cases.

Table 2. Univariate Analysis of Nontreatment Variables Associated With SBA

| | Cases (N = 29) | Controls (N = 87) | OR* | 95% CI |
|---|----------------|-------------------|----------------|-----------|
| Tobacco smoking, N (%) | 18 (62) | 57 (66) | 0.87 | 0.36–2.09 |
| History of cholecystectomy, N [†] (%) | 5 (17) | 9 (10) | 2.18 | 0.55–8.64 |
| History of appendectomy, N (%) | 10 (34) | 41 (47) | 0.59 | 0.24–1.47 |
| Family history of IBD, N (%) | 4 (14) | 19 (22) | 0.58 | 0.17–1.98 |
| Behavior 5 yr after CD diagnosis [‡] , N (%) | | | | |
| B1 | 6 (35) | 21 (39) | 1.00 | |
| B2 | 8 (47) | 14 (26) | 1.83 | 0.51–6.61 |
| B3 | 3 (18) | 19 (35) | 0.45 | 0.10–1.95 |
| Behavior 3 yr before SBA diagnosis [§] , N (%) | | | | |
| B1 | 17 (59) | 42 (48) | 1.00 | |
| B2 | 7 (24) | 18 (21) | 0.68 | 0.18–2.54 |
| B3 | 5 (17) | 27 (31) | 0.35 | 0.09–1.28 |
| Behavior at SBA diagnosis, N (%) | | | | |
| B1 | 0 (0) | 34 (39) | Not calculable | |
| B2 | 13 (45) | 21 (24) | Not calculable | |
| B3 | 16 (55) | 32 (37) | Not calculable | |
| Extraintestinal manifestations | 6 (21) | 19 (22) | 0.89 | 0.29–2.72 |

*Odds ratio estimated from a conditional logistic regression including the matching factors and the individual characteristic listed.

[†]4 cases with unknown value excluded.

[‡]45 patients (12 cases, 33 controls) with disease duration less than 5 yr excluded.

[§]SBA diagnosis for cases; for controls, date that matched SBA diagnosis of the corresponding case.

Univariate Analysis

The variables were studied in the whole population of cases and controls (N = 116), except for those concerning medical and surgical treatment, for which the analysis was restricted to the nonconcomitant patients and their matched controls (N = 84).

NONTREATMENT VARIABLES. The results are shown in Table 2. There was no significant association between SBA and smoking status, cholecystectomy, appendectomy, family history of CD, extraintestinal manifestations, or disease behavior (according to the Montreal classification) 5 yr after the date of CD diagnosis or 3 yr before SBA diagnosis. In contrast, at the date of SBA diagnosis, none of the cases *versus* 34 controls (39%) had an inflammatory form (B1), whereas 13 cases (45%) *versus* 21 controls (24%) had a stricturing disease form (B2). These results show that, although a stricturing phenotype is associated with SBA at the time of diagnosis, it does not appear earlier in the course of CD.

TREATMENT VARIABLES (Table 3). In univariate analysis, small bowel resection was less frequent in cases (5 patients, 24%) than in controls (46 patients, 73%) (OR [95% CI] 0.07 [0.01–0.32], $P = 0.0007$). The median CD du-

ration (range) without small bowel resection was significantly longer in cases (15.6 yr [1.4–37.1]) than in controls (8.2 yr [0.1–35.8], $P = 0.02$). Strictureplasty was performed in 1 out of 29 cases, and in 6 control patients (including 3 patients with a single strictureplasty and 3 patients with several strictureplasties). No intestinal bypass was performed, neither in cases nor in controls. The cases were less likely than the controls to have received salicylates for 2 yr or more (6 [29%] *vs* 36 [57%], respectively, OR [95% CI] 0.29 [0.10–0.82], $P = 0.02$). On the other hand, neither steroid therapy nor azathioprine/6-mercaptopurine, methotrexate or infliximab was found to be significantly associated with SBA.

Multivariate Analysis (Table 4)

Table 4 shows results of the backward elimination conditional logistic analysis. Only two factors were independently associated with SBA: small bowel resection and salicylates for more than 2 yr (OR [95% CI] 0.04 [0.01–0.28], $P = 0.001$ and OR [95% CI] 0.16 [0.03–0.79], $P = 0.02$, respectively). Figure 3 shows the distribution of these two risk factors in the cases and controls.

Subgroup Analysis

We performed a subgroup analysis restricted to the nonconcomitant cases (N = 11) and controls (N = 33) recruited in

Table 3. Univariate Analysis of Treatment Variables Associated With SBA During CD

| | Cases (N = 21) | Controls (N = 63) | OR* | 95% CI |
|--------------------------------------|----------------|-------------------|----------------|------------|
| ≥2 yr of salicylates, N (%) | 6 (29) | 36 (57) | 0.29 | 0.10–0.82 |
| ≥6 months of steroids, N (%) | 15 (71) | 32 (51) | 1.94 | 0.71–5.34 |
| Azathioprine/6-mercaptopurine, N (%) | 6 (29) | 17 (27) | 1.02 | 0.33–3.17 |
| Methotrexate, N (%) | 1 (5) | 1 (2) | 3.61 | 0.22–59.12 |
| Infliximab, N (%) | 0 | 1 (2) | Not calculable | |
| Small bowel resection, N (%) | 5 (24) | 46 (73) | 0.07 | 0.01–0.32 |

*Odds ratio estimated from a conditional logistic regression including the matching factors and the individual characteristic listed.

Table 4. Final Multivariate Model of Significant Factors Independently Associated With SBA in CD

| | OR* | 95% CI |
|-----------------------|------|-----------|
| ≥2 yr of salicylates | 0.16 | 0.03–0.79 |
| Small bowel resection | 0.04 | 0.01–0.28 |

*Odds ratio based on a backward elimination conditional logistic regression model.

the Saint Antoine hospital. In univariate analysis, the same risk factors were found to be significantly associated with SBA risk. The ORs were 0.14 (0.03–0.74) for salicylates therapy for more than 2 yr and 0.09 (0.02–0.48) for small bowel resection. These two variables were collinear, and a multivariate analysis could not be performed.

DISCUSSION

There are relatively few data concerning SBA risk factors in CD patients. We are aware of two case–control studies of SBA in CD (11, 12). The study by Lashner was based upon 7 patients with SBA and 28 CD controls (11). It was found that proximal small bowel disease, 6-mercaptopurine use, and hazardous occupations were associated with SBA in patients with CD. The study by Solem *et al.*, published in 2004, compared 9 patients with CD and SBA and 18 CD controls (12). No significant risk factors were identified, but it suggested that salicylates might have a protective effect against SBA. To our knowledge, the present study is the largest ever reported. Although, in this study, the cases and controls were not taken from the same population, the results were not altered when the analysis was restricted to the cases and controls recruited in the Saint Antoine hospital. Its main finding is that small bowel resection and salicylates therapy for more than 2 yr are less common in SBA patients than in matched controls.

In this study, the surgical removal of the inflammatory ileum was associated with a significant and dramatic reduction in the SBA odds. In UC, proctocolectomy abolishes the CRC risk by removing the whole colonic tissue. In CD,

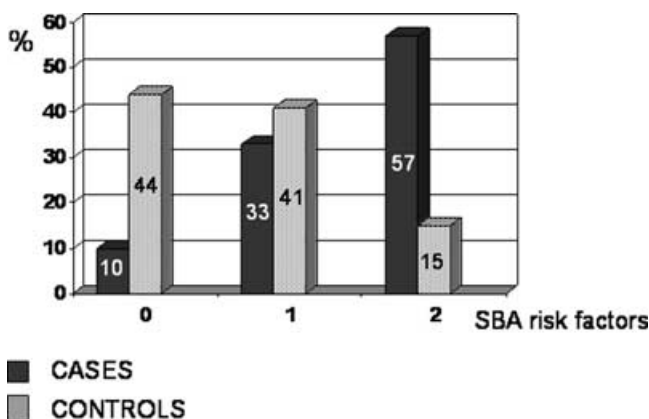


Figure 3. Percentage of cases (N = 21) and controls (N = 63) with 0, 1, and 2 small bowel adenocarcinoma risk factors (salicylate therapy for less than 2 yr and absence of small bowel resection for CD).

the small bowel resection markedly reduces SBA risk, but does not eliminate it. Indeed, 5 patients with SBA had undergone a small bowel resection for CD 14–37 yr prior to SBA diagnosis (Fig. 1). CD recurrences are common after ileal resection and SBA may develop from them. Recently, a decision analysis compared azathioprine with ileocecal resection in a steroid-dependent, short-segment, terminal ileal CD (13). Both treatment strategies were found to be reasonable. Our findings show that surgical resection reduces SBA odds, whereas azathioprine does not. This should be kept in mind when deciding between medical therapy and surgery in a patient with longstanding symptomatic CD of the terminal ileum. The decision could be refined by the findings of preneoplastic changes. However, there are currently no effective methods to screen for SBA (14). There have been very few studies concerning dysplasia in CD-associated SBA. In a pathological study of eight SBA, epithelial dysplasia was found adjacent to the carcinoma in 7 cases, suggesting that, like CRC in UC, SBA in CD develops from dysplasia (15). More data are needed in this field. If the high prevalence of dysplasia in the vicinity of SBA is confirmed, perendoscopic biopsies may become a useful tool for screening dysplasia in SBA, although they may require balloon dilatation in patients with stricturing disease. Videocapsule endoscopy carries the risk of intestinal obstruction in patients with CD stricturing disease. In addition, the morphological diagnosis of SBA is often difficult in CD patients. SBA diagnosis is seldom made preoperatively but rather during laparotomy or by careful histological examination of the resection specimen (9). Thus, videocapsule sensitivity may be too low to screen for SBA.

The second protective factor of SBA found in this study is the salicylates prescription for more than 2 yr. Several case–control studies and a recent meta-analysis strongly suggest that salicylates exert a protective effect on CRC in UC (16–18). Moreover, a regular 5-aminosalicylate use tends to demonstrate a protective effect on CRC in CD (OR 0.30, 95% CI 0.05–1.17, $P = 0.10$) (19). Most of the patients in the present study who were prescribed salicylates received formulations with release in the small bowel, and this could explain the protective effect of salicylates observed. However, the negative association between salicylates and SBA is not necessarily causal. In UC, it has been found that the activity of the disease was associated with an increased risk of CRC (3). It can be argued that salicylates prescription is a marker of mild activity or better follow-up and has no preventive effect *per se*. Alternatively, salicylates prescription may reduce inflammation, and thereby, decrease the risk of SBA. The only way to resolve this issue would be a randomized study. Assessing a cumulative SBA risk of 3 per 1,000 nontreated CD patients after 10 yr (assuming that 40% of the patients are treated with salicylates), a study evaluating the protective effect of salicylates with a relative risk of 0.16 would have to include 6,500 CD patients in each arm, with a 10-yr follow-up. It is unlikely that such a study will ever be carried out. However, further confirmative studies are needed before the preventive use of salicylates can be recommended in small

bowel CD. In conclusion, this study delineates a subgroup of patients who carry a higher risk of SBA: those who have not been resected and who have been treated with salicylates for less than 2 yr. Future screening and prevention strategies should target these patients.

ACKNOWLEDGMENTS

We are indebted to Vanessa Palascak-Juif for the help in data collection, Vincent Di Martino for the fruitful statistical comments, and Pamela Albert for the expert assistance in English writing.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Crohn's disease (CD) is associated with an increased risk of small bowel adenocarcinoma (SBA).
- The data concerning SBA risk factors in CD are scanty.

What Is New Here

- This is the largest study on this topic.
- Small bowel resection and prolonged salicylates use may protect against SBA in CD patients.

Reprint requests and correspondence: Franck Carbonnel, M.D., Ph.D., Service de Gastroentérologie et Nutrition, Centre Hospitalier Universitaire de Besançon, France.

Received October 18, 2007; accepted January 7, 2008.

REFERENCES

1. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: A meta-analysis. *Gut* 2001;48:526–35.
2. Ekobom A, Helmick C, Zack M, et al. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990;323:1228–33.
3. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126:451–9.
4. Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;130:1030–8.
5. Velayos FS, Loftus EV Jr, Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. *Gastroenterology* 2006;130:1941–9.
6. Jess T, Gamborg M, Matzen P, et al. Increased risk of intestinal cancer in Crohn's disease: A meta-analysis of population-based cohort studies. *Am J Gastroenterol* 2005;100:2724–9.
7. Canavan C, Abrams KR, Mayberry J. Meta-analysis: Colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment Pharmacol Ther* 2006;23:1097–104.
8. Jess T, Winther KV, Munkholm P, et al. Intestinal and extra-intestinal cancer in Crohn's disease: Follow-up of a population-based cohort in Copenhagen county, Denmark. *Aliment Pharmacol Ther* 2004;19:287–93.
9. Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. *Inflamm Bowel Dis* 2005;11:828–32.
10. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a working party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;19(Suppl A):5–36.
11. Lashner BA. Risk factors for small bowel cancer in Crohn's disease. *Dig Dis Sci* 1992;37:1179–84.
12. Solem CA, Harmsen WS, Zinsmeister AR, et al. Small intestinal adenocarcinoma in Crohn's disease: A case-control study. *Inflamm Bowel Dis* 2004;10:32–5.
13. Kennedy ED, Urbach DR, Krahn MD, et al. Azathioprine or ileocolic resection for steroid-dependent terminal ileal Crohn's disease? A Markov analysis. *Dis Colon Rectum* 2004;47:2120–30.
14. Friedman S. Cancer in Crohn's disease. *Gastroenterol Clin North Am* 2006;35:621–39.
15. Sigel JE, Petras RE, Lashner BA, et al. Intestinal adenocarcinoma in Crohn's disease: A report of 30 cases with a focus on coexisting dysplasia. *Am J Surg Pathol* 1999;23:651–5.
16. Pinczowski D, Ekobom A, Baron J, et al. Risk factors for colorectal cancer in patients with ulcerative colitis: A case-control study. *Gastroenterology* 1994;107:117–20.
17. van Staa TP, Card T, Logan RF, et al. 5-aminosalicylate use and colorectal cancer risk in inflammatory bowel disease: A large epidemiological study. *Gut* 2005;54:1573–8.
18. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: A systematic review and meta-analysis of observational studies. *Am J Gastroenterol* 2005;100:1345–53.
19. Siegel CA, Sands BE. Risk factors for colorectal cancer in Crohn's colitis: A case-control study. *Inflamm Bowel Dis* 2006;12:491–6.

CONFLICT OF INTEREST

Guarantor of the article: Franck Carbonnel.

Specific author contributions: Gaël Piton collated and analyzed the data. He also wrote the different versions of the manuscript. Jacques Cosnes contributed to the conception of the study and was involved in the diagnosis, data collection, and clinical care of many cases and all controls. Elisabeth Monnet contributed to the analysis of the data. Laurent Beaugerie, Philippe Seksik, Guillaume Savoye, Guillaume Cadiot, Bernard Flourie, Philippe Capelle, Philippe Marteau, Marc Lemann, Jean Frédéric Colombel, Elie Khouri, and Bruno Bonaz were involved in the diagnosis, data collection, and clinical care of the subjects. Franck Carbonnel conceived the study. All authors contributed to the drafting of the manuscript and revising it for important intellectual content.

Financial support: No financial support was received for the study. The invitation of GP to the Digestive Disease Week, 2007, in Washington DC, for oral presentation of this study, was paid by Ferring Laboratories.

Potential competing interests: Jean Frédéric Colombel has received grant support from Ferring and participated in continuing medical education events supported by unrestricted educational grants from Ferring. Philippe Marteau has received honoraria for consulting and participated in continuing medical education events supported by unrestricted educational grants from Ferring. Marc Lemann par-

ticipated in continuing medical education events supported by unrestricted educational grants from Ferring and has received honoraria from Shire for consulting. Franck Carbonnel participated in continuing medical education events supported by unrestricted educational grants from Ferring and Norgine. Laurent Beaugerie has received grant support from Ferring.
