Risk of Development of More-advanced Lesions in Patients With Inflammatory Bowel Diseases and Dysplasia

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BACKGROUND & AIMS: **Patients with inflammatory bowel diseases (IBD) have increased risks of dysplasia and colitis-associated cancer (CAC). We evaluated the risk of development of high-grade dysplasia (HGD) or CAC after diagnosis of dysplasia using data from a national cohort of patients with IBD.**

METHODS: **We performed a multicenter retrospective analysis of data collected from 7 tertiary referral regional or academic centers in Belgium. In searches of IBD pathology databases, we identified 813 lesions (616 low-grade dysplasias [LGDs], 64 high-grade dysplasias [HGDs], and 133 CACs) in 410 patients with IBD: 299 had dysplasia (73%) and 111 had CAC (27%). The primary aim was to determine the risk of more-advanced lesions after diagnosis of LGD or HGD.**

RESULTS: **Of the 287 patients with LGD, 21 (7%) developed more-advanced lesions (HGD or CAC) after a median time period of 86 months (interquartile range, 34–214). Of the 28 patients with HGD, 4 (14%) developed CAC after a median time period of 180 months (interquartile range, 23–444). The overall cumulative incidence of CAC at 10 years after an initial diagnosis of HGD was 24.3% and after an initial diagnosis of LGD was 8.5% ($P < .05$). Metachronous lesions, non-polypoid lesions, and colonic stricture were associated with risk of occurrence of more-advanced lesions after LGD ($P < .05$). Of the 630 dysplastic lesions identified during endoscopy, 545 (86%) were removed during the same procedure or during a follow-up endoscopy or by surgery. Of 111 patients with CAC, 95 (86%) did not have prior detection of dysplasia and 64 of these 95 patients (67%) developed CAC outside of the screening or surveillance period recommended by the European Crohn's and Colitis Organisation.**

CONCLUSIONS: **In an analysis of pathology data from 7 medical centers in Belgium, we found a low rate of detection of more-advanced lesions following detection of LGD or HGD—taking into account that most of the lesions were removed. Main risk factors for development of more-advanced lesions after LGD were metachronous lesions, non-polypoid lesions, and colon strictures.**

Keywords: Colorectal Cancer; CRC; Endoscopy Resection; Crohn's Disease; Ulcerative Colitis.

Abbreviations used in this paper: **CAC, colitis-associated colorectal cancer; CD, Crohn's disease; CE, chromoendoscopy; CI, confidence interval; CRC, colorectal cancer; ECCO, European Crohn's and Colitis Organisation; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IQR, interquartile range; LGD, low-grade dysplasia; PSC, primary sclerosing cholangitis; RR, relative risk; SE, standard error; UC, ulcerative colitis.**

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Patients with inflammatory bowel disease (IBD) (Crohn's disease [CD] and ulcerative colitis [UC]) are at increased risk of colorectal cancer (CRC), namely colitis-associated colorectal cancer (CAC).[1,2] Carcinogenesis in IBD follows the inflammation-dysplasia-cancer sequence from inflammation to indefinite, low-grade dysplasia (LGD), high-grade dysplasia (HGD), with some progressing to cancer.[3] Screening/surveillance colonoscopy is therefore recommended to detect and treat dysplasia.

Recent meta-analysis reported a 2-fold risk of developing CAC compared with the general population.[4] The pivotal role of inflammation is supported by disease duration, extent, and activity (both endoscopically and histologically) as main risk factors for developing CAC.[1,5,6] Primary sclerosing cholangitis (PSC),[7] family history of CRC,[8] post-inflammatory polyps,[9] and dysplasia at colonoscopy surveillance represent additional risks factors.

A few recent studies suggest decreasing incidence and mortality rates of CAC that may be related to improved IBD patient management, increased adherence to screening/surveillance recommendations, and enhanced quality criteria in performing colonoscopy and detecting/removing lesions.[10] CAC originates from either flat (endoscopically invisible) or raised (visible) dysplastic lesions as precursor lesions.[11] Detection of dysplasia relies on both pathologic examination from random biopsies to identify invisible dysplasia and from targeted biopsies of visible (polypoid and non-polypoid) lesions. With the improvement of endoscopic techniques, most dysplastic lesions discovered in IBD patients are reported to be visible.[12]

The reported risk of CAC associated with HGD or LGD varies greatly between studies.[13–16] Few studies have looked at the long-term outcome of endoscopically visible lesions removed by endoscopy. In nearly all studies, the treatment status is not even reported, and this might partly explain the different rates and risks of progression of dysplasia to more advanced lesion across these studies. Moreover, the term *progression* used in all studies is somewhat confusing when visible resectable lesions are for the most part removed as recommended in the management of dysplasia in IBD.

The aim of the study was to evaluate the risk of development of more advanced lesions after diagnosis of LGD or HGD in a large cohort of IBD patients with dysplasia.

What You Need to Know

Background

Patients with inflammatory bowel diseases (IBD) have increased risks of dysplasia and colitis-associated cancer (CAC). We evaluated the risk of development of high-grade dysplasia (HGD) or CAC after diagnosis of dysplasia using data from a national cohort of patients with IBD.

Findings

In an analysis of pathology data from 7 medical centers, we found a low rate of detection of more advanced lesions following detection of LGD or HGD—taking into account that most of the lesions were removed. Main risk factors for development of more advanced lesions after LGD were metachronous lesions, non-polypoid lesions, and colon strictures.

Implications for patient care

Description of long-term outcome of endoscopically visible lesions removed by endoscopy or surgery and identification of risk factors for development of more advanced lesions could help increase awareness and adherence of clinicians to international guidelines in screening or surveillance endoscopy programs and in detection or treatment modalities of dysplasia.

Methods

This large national cohort study is a long-term follow-up retrospective study conducted across 7 Belgian tertiary centers within the Belgian Inflammatory Bowel Disease Research and Development Group. Patients with histologically confirmed IBD who were diagnosed with at least 1 episode of dysplasia and/or CAC between January 1, 1990 and December 31, 2016 were retrospectively identified through IBD and pathology databases after Ethics Committee agreement (reference number: P2013/331 approved February 25, 2014). Endoscopic, histologic, and clinical data were collected by electronic chart review. All authors had access to the study data and had reviewed and approved the final manuscript. Advanced neoplasia was defined as HGD or CAC and did not refer to the size, number, and villous content of the neoplasia. Patients were classified according to the most advanced lesion that the patients developed during colonoscopy or at surgery performed during their follow-up (Supplementary Materials).

Characterization of the Dysplastic/Colitis-associated Colorectal Cancer Lesions

Each episode of dysplasia was graded according to the 1983 Inflammatory Bowel Disease Dysplasia Morphology Study group classification in LGD or HGD.[17] Lesions indefinite for dysplasia were excluded. Because of poor interobserver agreement in grading dysplasia among pathologists,[18] central review has been done by an independent expert IBD pathologist (P.D.). Lesions were categorized according to their macroscopic shape reported on endoscopy report. The Paris[19] or SCENIC[20] classifications could not always be applied because of incomplete endoscopy reports. Therefore, lesions were defined as follows: Visible lesions include polypoid lesions (Paris type 0-I lesions) and non-polypoid lesions (Paris type 0-II, 0-III, irregular, or plate-like lesions); invisible lesions were defined as absence of documented

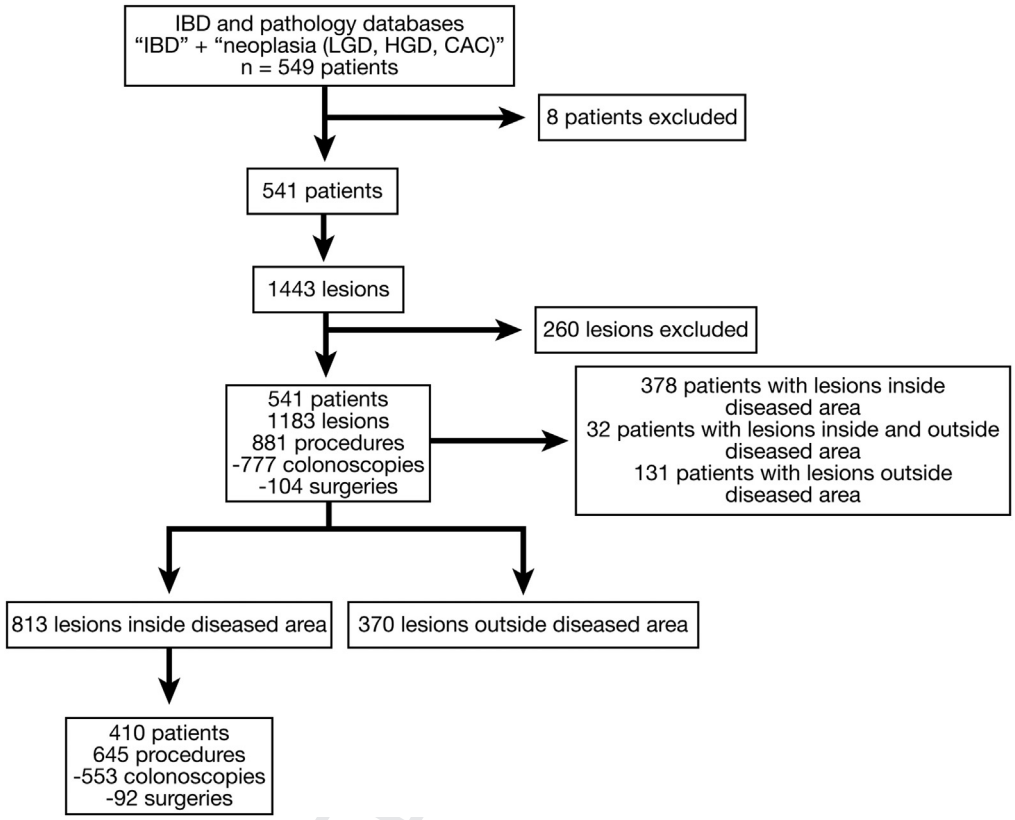

Figure 1. CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; LGD, low-grade dysplasia.

endoscopic abnormalities. Outside diseased area lesions, duplicates, misdiagnosed lesions, and recurrence were defined in Supplementary Materials. Screening/surveillance periods, namely the starting time of screening after IBD diagnosis and the interval of endoscopic surveillance, were defined according to European Crohn's and Colitis Organisation (ECCO) guidelines.[21] Patients were stratified as high, intermediate, or low risk according to those recommendations. Lesions were diagnosed outside screening/surveillance period when diagnosed before screening period or out of screening/surveillance period. Lesions were diagnosed out of screening/surveillance period when screening colonoscopy was not performed on time or when intervals between surveillance colonoscopies were too long according to the risk stratification profile (Supplementary Materials). The term *development* was used on purpose in this study rather than "progression" used in all studies. In this study, development of more advanced lesion can be either a newly developed lesion or a recurrence when the index lesion has been removed, and progression to more advanced lesion was used when index lesion has been left untreated. Therefore, resected and unresected lesions are considered for data analyses.

Statistical Analysis

Data were analyzed using MedCalc Statistical Software (version 18.5; MedCalc Software bvba, Ostend, Belgium). Continuous variables were reported as medians with interquartile ranges (IQRs) or ranges (minimum-maximum). Comparisons of continuous variables were performed by using Mann-Whitney or Kruskal-Wallis test. Categorical variables were reported as numbers (n) and proportions (%). Comparisons of categorical variables were performed by using Fisher exact test or Pearson χ^2 test for trend. Results of logistic regression were expressed in odds ratios with 95% confidence intervals (CIs). Rates of development of more advanced lesion were analyzed using Kaplan–Meier survival analysis. Comparison of incidences was performed by using log-rank test. Results of Cox proportional hazards regression were expressed in Exp(b) and 95% CI for Exp(b). Exp(b) can be interpreted as the instantaneous relative risk (RR) of an event, at any time, for an individual. A P value $<.05$ was considered statistically significant.

Results

Study Population

A total of 549 IBD patients were diagnosed with LGD, HGD, or CAC between January 1, 1990 and December 31, 2016 (Figure 1). After exclusion of some patients and lesions (Supplementary Materials), patients were grouped according to the location of lesions within or outside diseased area. Finally, 410 IBD patients with 813 lesions inside diseased area from 645 procedures were included in the study.

Patient Characteristics

Demographics and clinical variables of the study population are summarized in Table 1. Among UC patients, 5 (2%) had proctitis, 68 (27%) had left-side colitis, and 175 (71%) had pancolitis. As of December 31, 2016, 266 patients (65%) were still under follow-up (median, 70 months; IQR, 35–122), 60 patients (15%) died (median, 36 months; IQR, 6–85) (CAC [n = 32] and non-CAC [(n = 28] related mortality), and 84 patients (20%) were lost to follow-up (median, 40 months; IQR, 11–90). Of the 410 patients, 299 (73%) had only dysplasia (266 LGDs and 33 HGDs), whereas 111 (27%) had CAC during their follow-up. When comparing patients with CAC with those with dysplasia (LGD and HGD), median age at IBD diagnosis was lower (29 [IQR, 22–49] vs 41 (IQR, 28–54) years; $P = .0001$), and median IBD disease duration at time of detection of index lesion was longer (19 [IQR, 10–28] vs 10 (IQR, 2–19] years; $P < .0001$). There were more metachronous (39% vs 29%; $P = .036$) and multifocal synchronous lesions (38% vs 24%; $P = .004$) among patients with advanced neoplasia (HGD or CAC) compared with those with LGD.

Lesion Characteristics

Characteristics of the 813 dysplasia/CAC lesions are summarized in Table 2. Six hundred sixteen lesions were LGDs, 64 HGDs, and 133 CACs. Most of the lesions were endoscopically visible lesions (92%) that include polypoid (64%) and non-polypoid (36%) lesions. LGD lesions were more likely to be invisible than advanced neoplasia lesions (57/616, 9% vs 6/197, 3%; $P = .003$). Advanced neoplasia lesions were more likely to be

Table 1. Demographics and Clinical Variables for Patients With Dysplasia/Neoplasia (Most Advanced Grade) (n = Number of Patients)

Variable	Study population (n = 410)	LGD (n = 266)	HGD (n = 33)	CAC (111)	*P* value[a]
Type of IBD, n (%)					NS
- CD	162 (39)	99 (37)	9 (27)	54 (49)	
- UC	248 (61)	167 (63)	24 (73)	57 (51)	
Male, n (%)	248 (60)	158 (59)	23 (70)	67 (60)	NS
Age (*y*) at IBD diagnosis, median (IQR)	37 (26–53) (n = 394)	41 (29–53) (n = 258)	40 (26–61) (n = 27)	29 (22–49) (n = 109)	**<.01**
Follow-up duration (*y*) after IBD diagnosis, median (IQR)	19 (10–29) (n = 396)	16 (9–26) (n = 260)	16 (10–27) (n = 27)	25 (16–33) (n = 109)	**<.01**
Deceased, n (%)	60 (15)	20 (8)	4 (12)	36 (32)	**<.01**
Smoking status, n (%)					NS
- Active	36 (9)	24 (9)	1 (3)	11 (10)	
- Stopped	88 (21)	57 (21)	7 (21)	24 (22)	
- No	139 (34)	90 (34)	12 (36.5)	37 (33)	
- Unknown	147 (36)	95 (36)	13 (39.5)	39 (35)	
Age (*y*) at diagnosis of index lesion, median (IQR)	55 (45–65) (n = 408)	54 (46–65) (n = 264)	61 (40–72) (n = 33)	55 (45–62) (n = 111)	NS
Duration (*y*) of IBD at diagnosis of index lesion, median (IQR)	13 (4–22) (n = 396)	10 (2–19) (n = 260)	10 (2–20) (n = 27)	19 (10–28) (n = 109)	**<.01**
Follow-up duration (*mo*) after diagnosis of index lesion, median (IQR)	60 (24–105) (n = 410)	56 (24–105) (n = 266)	77 (46–119) (n = 33)	53 (20–93) (n = 111)	NS
No. of neoplastic lesions per patient during follow-up, median (IQR; range)	1 (1–2; 1–12) (n = 410)	1 (1–2; 1–12) (n = 266)	2 (1–5; 1–10) (n = 33)	1 (1–3; 1–11) (n = 111)	**<.01**
No. of neoplastic lesions diagnosis procedures per patient during follow-up, median (IQR; range)	1 (1–2; 1–9) (n = 410)	1 (1–1; 1–6) (n = 266)	2 (1–4; 1–9) (n = 33)	1 (1–2; 1–5) (n = 111)	**<.01**
Metachronous lesions, n (%)	132 (32) (n = 410)	76 (29) (n = 266)	19 (58) (n = 33)	37 (33) (n = 111)	**<.01**
Multifocal lesions, n (%)	117 (29) (n = 410)	63 (24) (n = 266)	18 (55) (n = 33)	36 (32) (n = 111)	**<.01**
Family history of CRC, n (%)	36 (9)	28 (11)	1 (3)	7 (6)	NS
- First degree	- 15	- 13	- 0	- 2	
- Other degree	- 20	- 14	- 1	- 5	
- Unknown	- 1 (n = 410)	- 1 (n = 266)	- 0 (n = 33)	- 0 (n = 111)	
Associated PSC, n (%)	39 (10) (n = 410)	20 (8) (n = 266)	5 (15) (n = 33)	14 (13) (n = 111)	NS

CAC, colitis-associated colorectal cancer; CD, Crohn's disease; CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IQR, interquartile range; LGD, low-grade dysplasia; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.
[a]*P* value for two-sided χ^2 test or Kruskal-Wallis test. Bold values are significant.

non-polypoid (151/191, 79% vs 121/559, 22%; $P < .0001$) and ≥1 cm than LGD lesions (117/127, 92% vs 118/422, 28%; $P < .0001$) (Supplementary Materials for risk factors associated with CAC.)

Diagnosis of Dysplasia and Colitis-associated Colorectal Cancer

Fourteen patients (3%) had their first lesion diagnosed before IBD diagnosis, 27 (7%) at IBD diagnosis, 111 (27%) before 8 years of disease, and 22 (5%) between 8 and 10 years of disease. In total, 37% and 42% of the patients had their first lesion diagnosed before 8 and 10 years of disease, respectively. Seventy-six CACs (57%) were diagnosed during colonoscopy and 57 (43%) at surgery. Four CACs (3%) were diagnosed before IBD diagnosis, 4 (3%) at IBD diagnosis, 8 (6%) before screening period, 59 (44%) during screening/surveillance period, and 58 (44%) out of screening/surveillance period according to ECCO recommendations. Seventeen percent and 21% of the patients had their CAC diagnosed before 8 and 10 years of disease, respectively (Supplementary Materials for more details about diagnostic circumstances of dysplasia and CAC).

Treatment of Dysplasia and Colitis-associated Colorectal Cancer

Among the 630 dysplastic lesions reported during endoscopy, the majority were removed at the time of the endoscopy detection (436/630, 69%) or at a second follow-up procedure (endoscopy or surgery) (109/630, 17%), whereas only a minority were left untreated (61/630, 10%) or had an unknown treatment status (24/630, 4%) (Supplementary Materials for more details). Median duration between diagnostic and second procedure was significantly longer for LGD lesions compared with HGD lesions (103 [IQR, 58–240] vs 48 days (IQR, 40–123); $P = .0039$). Concerning the 76 CACs that were diagnosed during colonoscopy, 59 (78%) had surgery secondarily after a median duration of 35 days (IQR, 21–105).

Rate of Development to More Advanced Lesions

Two hundred eighty-seven patients were initially diagnosed with LGD, 28 with HGD, and 95 with CAC. Table 3 and Figure 2 show the most advanced lesion that the patients developed during colonoscopies or at surgery performed during follow-up after the index lesion was diagnosed, according to the grade of this lesion. Twenty-one of 287 patients (7%) who were initially diagnosed with LGD developed more advanced lesions (9 HGDs and 12 CACs) after a median time of 86 months (IQR, 34–214) (137 [IQR, 40–232] for CAC vs 43 [IQR, 12–118] for HGD; $P = .0466$), whereas 202 of 287 (71%) did not develop any further lesion. Four of 28 patients (14%) who were initially diagnosed with HGD developed CAC after a median time of 180 months (IQR, 23–444), whereas 15 of 2 (54%) did not develop any further Q4 lesion (Supplementary Materials for more details). Sixteen patients (14%) (12 with prior LGD, 4 with prior HGD) developed CAC secondarily after a median follow-up of 137 months (IQR, 39–260), whereas 95 (86%) were diagnosed with CAC without evidence of prior

Table 2. Lesion Characteristics (N = Number of Lesions)

Variable	Study population (n = 813)	LGD (n = 616)	HGD (n = 64)	CAC (n = 133)	*P* value[a]
Macroscopic shape					**<.01**
- Visible	750 (92%)	559 (91%)	58 (91%)	133 (100%)	
- Invisible	63 (8%)	57 (9%)	6 (9%)	0 (0%)	
For visible lesions					**<.01**
- Polypoid	478 (64%)	438 (78%)	29 (50%)	11 (8%)	
- Non-polypoid	272 (36%)	121 (22%)	29 (50%)	122 (92%)	
Size of the lesion					**<.01**
- <1 cm	235 (31%)	118 (21%)	25 (43%)	92 (69%)	
- ≥1 cm	314 (42%)	304 (54%)	9 (16%)	1 (1%)	
- Unknown	201 (27%)	137 (25%)	24 (41%)	40 (30%)	
Diagnosis circumstances					**<.01**
- Colonoscopy	706 (87%)	576 (94%)	54 (84%)	76 (57%)	
- Surgery	107 (13%)	40 (6%)	10 (16%)	57 (43%)	
Treatment status of lesions diagnosed during endoscopy					**<.01**
- During the same procedure	443 (63%)	410 (71%)	26 (48%)	7 (9%)	
- During a second procedure	168 (24%)	89 (15%)	20 (37%)	59 (78%)	
- No treatment	71 (10%)	55 (10%)	6 (11%)	10 (13%)	
- Unknown	24 (3%)	22 (4%)	2 (4%)	0 (0%)	

CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.
[a]*P* value for two-sided χ^2 test. Bold values are significant.

Table 3. Findings on Follow-up Colonoscopies and Surgery Based on Index Lesion (Number of Patients)

	Most advanced follow-up lesion				
Index lesion	No dysplasia or CAC	LGD	HGD	CAC	Total
LGD	202 (71%)	64 (22%)	9 (3%)	12 (4%)	287
HGD	15 (54%)	7 (25%)	2 (7%)	4 (14%)	28
CAC	77 (81%)	5 (5%)	3 (3%)	10 (11%)	95
Total	294	76	14	26	410

CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

detected dysplasia. Sixty-seven percent of the patients diagnosed with CAC without prior detected dysplasia were diagnosed outside screening/surveillance period. Details are described in Supplementary Materials. Whereas 25 of 315 patients (8%) with LGD or HGD as index lesion developed more advanced lesion, 290 of 315 patients (92%) with LGD or HGD did not develop more advanced lesion (Supplementary Materials for more details about completeness of follow-up).

Overall cumulative incidence of HGD or CAC development at 1 and 10 years after initial LGD diagnosis was 2.3% (standard error [SE], 1%) and 13.8% (SE, 3.2%), respectively (Figure 3*A*). Rate of development of CAC was higher after HGD compared with LGD ($P = .0364$) (Figure 3*B*), with an overall cumulative incidence of CAC development at 1 and 10 years after LGD diagnosis of 0.5% (SE, 0.5%) and 8.5% (SE, 2.7%), respectively, whereas at 1 and 10 years after HGD diagnosis it was 9.1% (SE, 6.2%) and 24.3% (SE, 14.8%), respectively.

Risk Factors Associated With the Development of More Advanced Lesions

In univariate analysis, metachronous lesions ($P = .0003$), multifocal lesions ($P = .0014$), non-polypoid lesions ($P < .0001$), associated PSC ($P = .0032$), invisible lesions ($P = .0048$), and colonic stricture ($P < .0001$) were associated with the risk of development of more advanced lesions. In multivariate analysis, metachronous lesions ($P = .0119$), non-polypoid lesions ($P = .0006$), and colonic stricture ($P = .0496$) remained associated with the risk of development of more advanced lesions (Supplementary Table 4) (Supplementary Materials for risk factors associated with the development of CAC after dysplasia).

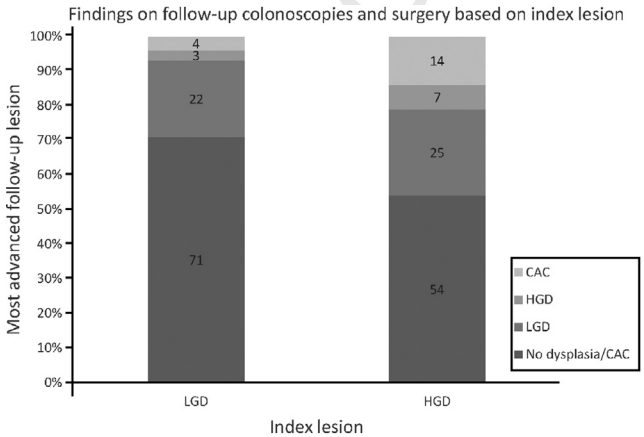

Figure 2. CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Discussion

This large national cohort study revealed that the rate of development of more advanced lesions after LGD was low (7%), and only 14% of the patients who were initially diagnosed with HGD developed CAC, considering that nearly all lesions had been removed. Most of the dysplastic lesions diagnosed during endoscopy were treated during the same procedure or at a second follow-up by endoscopy or surgery (86%). Main risk factors for development of more advanced lesion were the presence of metachronous lesions, non-polypoid lesions, and colonic stricture. Advanced neoplasia lesions were more likely to be visible, non-polypoid, ≥1 cm, metachronous, and multifocal synchronous than LGD lesions. Our rate of invisible LGD lesions (9%) is close to the one reported in SCENIC consensus[20] (9.4% by high definition white light endoscopy and 9.8% by chromoendoscopy [CE]) or in study by Choi et al[22] (9.3%). Importantly, the majority of IBD patients with CAC (86%) were diagnosed without prior detected dysplasia, mainly because of outside screening/surveillance period for 67% of them.

The SCENIC international consensus statement on surveillance of dysplasia in IBD[20] recommends complete endoscopic removal of resectable polypoid dysplastic lesions, followed by surveillance colonoscopy. However, in addition to poor reproducibility of Paris classification[23] and no validation in IBD, it is not clear that the risk of CAC is the same for visible and invisible dysplastic lesions and for polypoid and non-polypoid dysplastic lesions. Very few studies have looked at long-term outcome of visible lesions removed by endoscopy because there are limited follow-up data especially for non-polypoid lesion resected by endoscopic submucosal dissection.[24] In many studies, treatment status is not even reported, and this might partly explain the different incidence rates for more advanced lesions across these studies in which CAC incidence was between 2% and 13% after a mean follow-up period of 36–82 months.[13–15] In our study, overall cumulative incidence of HGD or CAC development at 1 year after initial LGD diagnosis was 1.9%, which is much lower than the incidence of 10.9% at 1 year previously reported.[22] This difference can be explained by the fact that we excluded all misdiagnosed lesions. Indeed, median time to progression varied from 10.5 to 13 months,[22] depending on whether LGD lesions on biopsies from

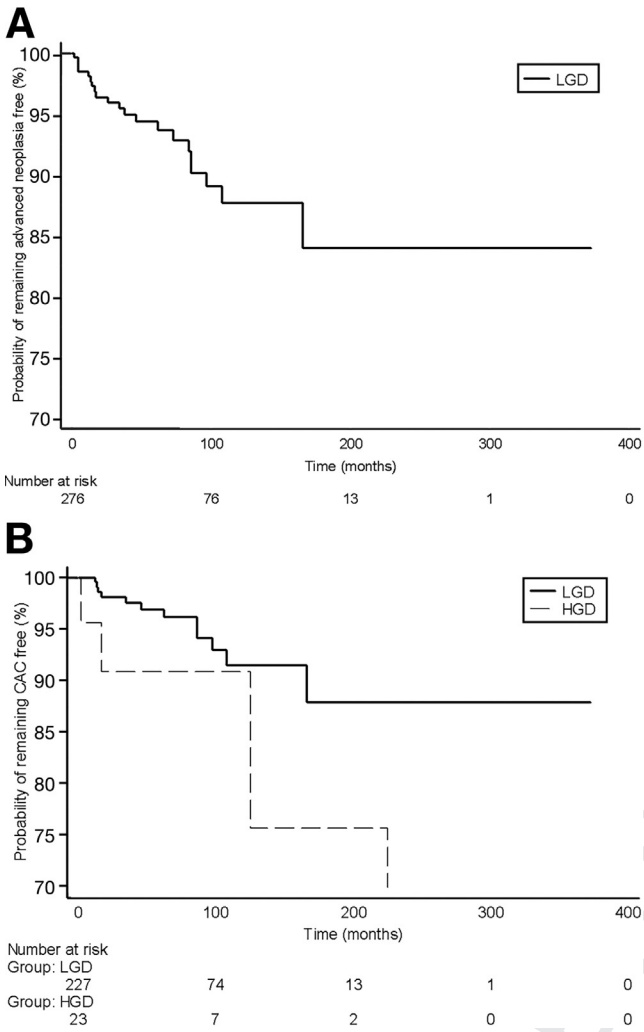

Figure 3. CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

colonoscopy progressed to CAC or HGD. This short time of progression suggests more hidden or missed HGD or CAC at the time of colonoscopy than real progression from LGD lesions. Such lesions were reported in our study directly as HGD or CAC diagnosed at surgery performed for preexisting dysplasia (even if LGD) on biopsies from colonoscopy. Also, those patients were considered to be diagnosed with HGD or CAC without evidence of prior dysplasia because this is the same lesion (misdiagnosed lesion); indeed, the time between colonoscopy and surgery is very short (median, 57 days). This may explain why 86% of the patients with CAC were diagnosed without evidence of prior dysplasia, whereas 14% developed CAC secondarily after a median follow-up of 137 months. Our results are therefore more in concordance with those reported in 2 meta-analyses.[4,16] Thus, patients with IBD have a low risk of development of more advanced lesions after resection of dysplastic lesions.

Although many studies have examined risk factors associated with CAC, very few have examined risk factors associated with the risk of development of more advanced lesion after diagnosis of dysplasia. We have shown that in IBD patients, non-polypoid lesions are the most important risk factor of development of CAC with a RR of 15, which is consistent with another study.[22] They reported that dysplastic lesions that are non-polypoid, endoscopically invisible, $\geq$1 cm, or preceded by indefinite dysplasia were associated with increased risk of progression to advanced lesion. Previous studies have shown that patients with polypoid LGD lesions have a low risk of development of CAC.[25] PSC was also an important risk factor (3.4-fold increase) in our study to the same extent as in the meta-analysis by Fumery et al,[4] where invisible dysplasia and multifocal dysplasia were also significantly associated with progression to advanced lesion.

Dysplasia is a reliable marker for the risk of developing or having CAC. Indeed, when indication of surgery was HGD, 42% of the patients had CAC in their surgical specimen. For those who had colectomy for LGD, more advanced lesions were found in 23% of cases (CAC in 19% of cases). This is a little lower than the percentages reported by Choi et al[22] (46% and 39%, respectively). In the meta-analysis by Fumery et al,[4] 30% of the patients who underwent colectomy for LGD had more advanced lesions. Yet, CAC can develop in patients without history of dysplasia or from invisible dysplastic lesions. Also, not all patients with LGD may pass through a phase of detectable HGD before developing CAC.[26] In this cohort, 86% of patients were diagnosed with CAC without prior detected dysplasia. This can be easily explained with 67% of them diagnosed outside screening/surveillance period; dysplasia had therefore not been previously reported in these patients. Previous colonoscopies may have been false negative in patients diagnosed with CAC inside screening/surveillance period because of suboptimal conditions (eg, inflammation, low rate of CE/random biopsies performed, and poor colonic preparation). Low quality endoscopy measures may likely play a role and are difficult to evaluate because of the retrospective design of the study. Nevertheless, only 57% of CACs were diagnosed during colonoscopy. When CAC was diagnosed at surgery, surgery was initially performed for detected preexisting neoplasia in only 56% of the cases. Thus, low rate of detected preexisting neoplasia heralds the need for improved training in the detection of dysplastic lesions.

Most cases of CACs are believed to arise from dysplasia. Endoscopic screening/surveillance guidelines have been developed to enable the detection and potential removal of precancerous lesions. This strategy aims at decreasing the incidence of CAC and related mortality.[27] However, we and others have shown that CACs are most often detected outside screening/surveillance period: at IBD diagnosis, before or out of screening/surveillance period. In a princeps study,[28] only 25 of 149 patients (17%) were diagnosed with CAC during screening/surveillance period, and 22% developed CAC before 8 or 15 years of surveillance for pancolitis and left-side colitis, respectively. Eleven

percent of CACs were diagnosed before screening period and 17% before 8 years of disease in our cohort. Today, several guidelines recommend starting surveillance after 8–10 years of first symptoms.[21,26] In the CESAME cohort,[29] colonoscopy surveillance rate was surprisingly low in IBD patients with longstanding extensive colitis, with only 54% of the patients who had at least 1 surveillance colonoscopy during the study period. Thus, the high rate of CACs outside screening/surveillance period in all the studies might be explained by poor adherence in routine practice to screening/surveillance programs according to recommendations.

This study has several limitations. This is a retrospective study. We may underestimate the risk of development of more advanced lesions because of high number of CACs diagnosed without evidence of prior dysplasia and outside screening/surveillance period. This means that we can assume that if they had had proper surveillance, it is possible that dysplastic lesions would have been identified before the CAC diagnosis. The consensus statement by Rutter et al[30] could help to better define diagnostic circumstances of neoplastic lesions to limit the occurrence of interval lesions in the future management of dysplastic lesions in IBD.

In conclusion, the rate of development of more advanced lesion after LGD is low in patients in whom the majority of the lesions have been routinely removed. This reassuring real-life data must be balanced with the high rate of patients diagnosed with CAC without detected preexisting dysplasia. This heralds the need for improved training in the detection of dysplastic lesions, together with increased awareness of colon cancer screening and surveillance in IBD patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.05.062.

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Supplementary Materials

Methods

The Pathology database was established by using the International Classification of Diseases 9th revision code for the identification of IBD patients and neoplastic lesions, with additional chart review performed to confirm IBD diagnosis. We optimized case retrieval by double cross-check through hand chart review using IBD registries. Patients with not enough information about their IBD and/or dysplastic/CAC lesion were excluded as well as those whose lesion(s) did not show dysplasia or CAC after central review by an independent expert IBD pathologist (P.D.). Patients' demographics, IBD phenotypic characteristics, and data regarding IBD-related therapies were collected. Information on family history of IBD or CRC was also obtained.

Patients were classified according to the most advanced lesion during colonoscopy or at surgery performed at follow-up. The index lesion was the first lesion diagnosed in a patient during colonoscopy or surgery. When more than 1 lesion was found during the procedure, we considered the lesion with maximal grade of dysplasia or CAC. The follow-up lesion is the most advanced lesion developed at follow-up procedure (either colonoscopy or surgery) after the index lesion. When more than 1 dysplasia/CAC lesion was found and more than 1 procedure was done during follow-up, the categorization of the follow-up lesion was based on the maximal grade of dysplasia or CAC. If no lesion was detected during follow-up, the follow-up lesion is reported as no dysplasia/CAC. Patients were considered to have multifocal neoplastic lesions when they had more than 1 lesion during the same procedure. They were considered to have metachronous neoplastic lesions when they had more than 1 episode of neoplasia in minimum 2 procedures during their follow-up.

Patients were considered lost to follow-up if in December 2016 they had not been seen at their IBD center for more than 1 year.

Patients were considered to have family history of CRC if he/she had either first-, second-, or third-degree relatives who had CRC at any age.

Patients were considered to have associated PSC only if the diagnosis was confirmed radiologically and/or histologically.

Characterization of the dysplastic/colitis-associated colorectal cancer lesions. Only lesions with available pathologic report after surgery or colonoscopy were taken into account. Lesions outside diseased area and lesions where dysplasia or CAC was not confirmed at review were excluded. A diseased area was defined as a colonic area that is histologically and/or endoscopically affected at least once in the follow-up of the patient. Lesions outside diseased area were therefore lesions located in a part of the colon that has not been histologically (even without apparent endoscopic involvement) and/or endoscopically involved. Duplicates, defined as lesions being found either in the same procedure on different slides (same lesions in same procedure) or in another procedure that follows the diagnostic procedure if the lesions have not been treated or treated incompletely (same lesions in different procedures), were also excluded. In the same way were excluded misdiagnosed lesions (same lesions in different procedures with a different grade of neoplasia), defined as lesions being found in another procedure that follows the diagnostic procedure if the lesions have not been treated or treated incompletely and have a different grade of neoplasia. Lesions affecting the small intestine were excluded. Recurrence, defined as a lesion occurring in the same diseased area as a lesion previously diagnosed and treated, was considered as a new lesion and not as a duplicate in the follow-up of the patient.

Data concerning the diagnostic circumstances (colonoscopy or surgery) and the indication of the diagnostic procedure (eg, surveillance colonoscopy or colonoscopy for therapeutic management) as well as the treatment of the lesion either at initial diagnosis procedure or during a following procedure and the follow-up of untreated lesions were collected. The treatment was defined as unknown when it was not specified in the endoscopy report whether the lesion was resected or not. Information about location of the lesions within or outside a diseased area (active or quiescent) and extension of the disease (Montreal classification) was also collected. Data on the presence or absence of a documented episode of colonic stricture or post-inflammatory polyp were collected.

ECCO guidelines[1,2] were retrospectively applied to our study population to be able to categorize neoplastic lesions as diagnosed before, during, or out of screening/surveillance period. According to ECCO guidelines, screening colonoscopy should be offered 8 years after the onset of colitis symptoms to all patients (UC and Crohn's colitis) to reassess disease extent and exclude dysplasia. Patients were stratified as high, intermediate, or low risk for surveillance interval according to those guidelines. Ongoing surveillance should be performed in all patients apart from those with proctitis or Crohn's colitis involving only 1 segment of colorectum. Patients with high risk features (stricture or dysplasia detected within the past 5 years, PSC, extensive colitis with severe active inflammation, or a family history of CRC in a first-degree relative when younger than 50 years) should have next surveillance colonoscopy scheduled for 1 year. In patients with concurrent PSC, annual surveillance colonoscopy should be performed after the diagnosis of PSC, irrespective of disease activity, extent, and duration. Patients with intermediate risk factors should have their next surveillance colonoscopy scheduled for 2–3 years. Intermediate risk factors include extensive colitis with mild or moderate active inflammation, post-inflammatory polyps, or a family history of CRC in a first-degree relative at 50 years and older. Patients with

neither intermediate nor high risk features should have their next surveillance colonoscopy scheduled for 5 years.

Nevertheless, because of the difficulty of retrospectively determining the onset of colitis symptoms in all patients, it was the disease diagnosis rather than the onset of symptoms that was considered to define the screening period, namely the starting time of screening after disease diagnosis.

Lesions were diagnosed out of screening/surveillance period when screening colonoscopy was not performed on time (more than 8 years after disease diagnosis) or when intervals between surveillance colonoscopies were too long according to the risk stratification profile (more than 1 year in high risk patients, 3 years in intermediate risk patients, and 5 years in low risk patients). Lesions were diagnosed outside screening/surveillance period when diagnosed before screening period (before 8 years after the disease diagnosis) or out of screening/surveillance period.

Results

Study population. Eight patients were excluded for the following reasons: no neoplasia after pathology review (n = 6), no IBD (n = 1), and lack of clinical information (n = 1). Among the 541 remaining patients, 1443 lesions were identified. Two hundred sixty lesions were excluded for the following reasons: no neoplasia after pathology review (n = 21), same lesion in same procedure (n = 36), same lesion in different procedures (n = 142), ileal location of the lesion (n = 7), lack of clinical/pathologic information (n = 14), and misdiagnosed lesion (n = 40).

Risk factors associated with colitis-associated colorectal cancer. In univariate analysis performed by logistic regression, CD, younger age at IBD diagnosis, and longer follow-up duration after IBD diagnosis were significantly associated with the risk of developing a CAC, whereas in multivariate analysis, younger age at IBD diagnosis and longer follow-up duration after IBD diagnosis remained statistically significant (Supplementary Table 1).

Diagnosis of dysplasia and colitis-associated colorectal cancer. Ninety-four percent of LGDs were diagnosed during colonoscopy performed for IBD diagnosis in 6% of the cases, therapeutic management in 19% of the cases, screening in 11% of the cases, and surveillance in 64% of the cases. Eighty-four percent of HGDs were diagnosed during colonoscopy performed for IBD diagnosis in 7% of the cases, therapeutic management in 32% of the cases, screening in 9% of the cases, and surveillance in 52% of the cases. Fifty-seven percent of CACs were diagnosed during colonoscopy performed for IBD diagnosis in 2% of the cases, therapeutic management in 54% of the cases, screening in 5% of the cases, and surveillance in 39% of the cases.

Chromoendoscopy was performed in 15% of the patients, and 32 random biopsies were performed in less than 1% of the patients. Method of resection as well as completeness of resection was specified in less than 50% of the endoscopy reports. For this reason, it was assumed that in case of resection and in the absence of additional precision, the lesions were completely resected.

Indications for surgeries when colitis-associated colorectal cancer was diagnosed at surgery. Regarding indications for surgery when CAC was diagnosed at surgery, surgery was initially performed for preexisting dysplasia on the biopsies from a colonoscopy in 22 CACs (39%) (13 preexisting HGDs, 9 preexisting LGDs), of which 10 had an associated stricture (5 HGDs and 5 LGDs). Those 22 CACs were diagnosed at surgery performed after a median time of 57 days (IQR, 28–86) after colonoscopy and were part of what we considered as misdiagnosed lesions. Ten synchronous CACs (18%) were diagnosed at surgery performed for another CAC diagnosed during colonoscopy. Surgery was performed because of a high clinical suspicion of CAC based on computed tomodensitometry in 7 CACs (12%). The last 18 CACs (33%) were diagnosed at surgery performed for IBD therapeutic management, mostly stricture (8 CACs) but also fistula or intra-abdominal collection (3 CACs), occlusion (3 CACs), refractory disease to medical treatment (1 CAC), and presence of a suspicious mass at endoscopy with negative pathology (3 CACs).

Indications for surgeries for the entire study population. Of the study population (n = 410), 194 patients (47%) underwent 1 or more colonic surgical interventions during follow-up, with a total of 212 surgical interventions. The indications for surgery and the most advanced grade of neoplasia found on surgical specimens for the 194 patients and 212 surgeries are shown in Supplementary Tables 2 and 3, respectively. Twenty-five percent of the patients diagnosed with dysplasia (n = 78/315; 31 HGDs, 47 LGDs) underwent surgery (partial or total colectomy) for dysplasia as indication. Histologic analysis of their surgical specimen revealed CAC in 22 patients (28%), HGD in 7 (9%), LGD in 25 (32%), and no neoplasia in 24 patients (31%). Overall, when the indication for surgery was HGD, 42% of the patients (13/31) had CAC in their surgical specimen. For those who had surgery for LGD, HGD or CAC was found in 23% of cases (11/47). Indication for surgery was CAC in 63 surgeries, of which histologic analysis showed CAC in 59 specimens (94%), no neoplasia after chemoradiotherapy for rectal CAC in 1 specimen (1.5%), and dysplasia (2 LGDs, 1 HGD) in 3 specimens (4.5%) after CAC endoscopic resection. Sixty IBD patients with no previous dysplasia underwent surgery for therapeutic management (refractory disease, stenosis, fistula, collection) but also for high clinical suspicion of CAC based on computed tomodensitometry, and CAC was found on the surgical specimen in 21 patients (35%), whereas dysplasia was found in 16 patients (27%) (15 LGDs, 1 HGD).

Treatment of dysplastic/colitis-associated colorectal cancer lesions. Among the 61 dysplastic lesions left untreated, 55 were LGD and 6 HGD. Twenty-nine LGDs

were visible lesions (7 polypoid, 22 non-polypoid), whereas 26 were invisible lesions. Five HGDs were visible lesions (2 polypoid, 3 non-polypoid), and 1 was invisible lesion. Among the 24 dysplastic lesions with an unknown treatment status, all were visible lesions, with 17 polypoid (1 HGD, 16 LGD) and 7 non-polypoid lesions (1 HGD, 6 LGD).

Rate of development of more advanced lesions. Among the 25 patients (21 LGDs and 4 HGDs) who developed more advanced lesions during their follow-up, all but 2 were treated previously for their dysplastic lesions. Indeed, only 2 patients had untreated LGD and progressed to HGD. One of the LGDs was a non-polypoid lesion left in place because of limited life expectancy, and the second one was an invisible lesion.

As of December 2016, 15 of the 290 patients who did not develop more advanced neoplasia during their follow-up had total colectomy during follow-up, 49 had no surveillance colonoscopy after index lesion diagnosis, and the remaining 226 patients had their last surveillance colonoscopy after a median follow-up of 55 months (IQR, 25–95). To analyze overall cumulative incidence of HGD and/or CAC development at 1 and 10 years after LGD or HGD diagnosis, patients who had total colectomy during follow-up after index lesion diagnosis and patients who had no surveillance colonoscopy were excluded.

Diagnostic circumstances of the patients diagnosed with high-grade dysplasia without prior detected low-grade dysplasia. Among the 28 patients diagnosed with HGD without prior LGD, 1 was diagnosed 20 months before IBD diagnosis with no colonoscopy performed before; 3 at IBD diagnosis with no colonoscopy performed before; 5 before screening colonoscopy after a mean time after IBD diagnosis of 65 months (IQR, 53–86) and with a mean interval to prior colonoscopy of 18 months (IQR, 14–23); 11 during screening or surveillance period according to the risk stratification profile (1 year in high risk patients, 3 years in intermediate risk patients, and 5 years in low risk patients) with a mean interval to prior colonoscopy of 18 months (IQR, 14–24); and 8 out of screening/surveillance period (when screening/surveillance colonoscopy was not performed on time (more than 8 years after disease diagnosis or when intervals between surveillance colonoscopies were too long according to the risk stratification profile). Most of the patients diagnosed out of screening/surveillance period had an inappropriate follow-up, with a mean interval to prior colonoscopy of 8 years (IQR, 7–9). Sixty-one percent of the patients diagnosed with HGD without prior LGD were therefore diagnosed outside screening/surveillance period.

Diagnostic circumstances of the patients diagnosed with colitis-associated colorectal cancer without prior detected dysplasia. Among the 95 patients diagnosed with CAC without prior detected dysplasia, 4 (4%) were diagnosed before IBD diagnosis with a mean interval before IBD diagnosis of 31 months (IQR, 12–51) with either no colonoscopy performed before in 3 patients or a colonoscopy performed 5 years before the CAC diagnosis in 1 patient; 4 (4%) at IBD diagnosis with either no colonoscopy performed before in 3 patients or a colonoscopy performed 13 years before the CAC diagnosis in 1 patient; 8 (8%) before screening colonoscopy after a mean time after IBD diagnosis of 31 months (IQR, 2–57) and with a mean interval to prior colonoscopy of 12 months (IQR, 2–25); 31 (33%) during screening or surveillance period according to the risk stratification profile with a mean interval to prior colonoscopy of 15 months (IQR, 4–19); and 48 (51%) out of screening/surveillance period with a mean interval to prior colonoscopy of 8 years (IQR, 2–12).

Risk factors associated with the development of colitis-associated colorectal cancer after dysplasia. In univariate analysis, metachronous lesions ($P = .0086$), multifocal lesions ($P = .005$), non-polypoid lesions ($P = .0014$), associated PSC ($P = .0005$), and colonic stricture ($P = .0017$) were significantly associated with the risk of development of CAC after dysplasia. In multivariate analysis, only the presence of non-polypoid lesions ($P = .0106$) and associated PSC ($P = .033$) were significantly associated with the risk of development of CAC after dysplasia (Supplementary Table 5).

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Supplementary Table 1. Risk Factors Associated With CAC

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value[a]	Odds ratio	95% CI	*P* value[a]
CD	**1.68**	**1.08–2.60**	**.02**	1.55	0.97–2.46	.07
Age at IBD diagnosis	**0.97**	**0.96–0.99**	**<.01**	**0.98**	**0.97–0.99**	**.01**
Follow-up duration after IBD diagnosis	**1.04**	**1.02–1.06**	**<.01**	**1.03**	**1.01–1.05**	**<.01**
Female	1.00	0.65–1.57	.97			
Smoking status	1.08	0.63–1.87	.77			
Metachronous lesions	1.07	0.68–1.71	.76			
Multifocal lesions	1.29	0.81–2.07	.29			
Family history of CRC	0.63	0.27–1.47	.28			
Associated PSC	1.58	0.79–3.17	.20			

CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.
[a]*P* value for logistic regression. Bold values are significant.

Supplementary Table 2. Indication for Surgery During Follow-up and the Maximal Grade of Neoplasia Found in Surgical Specimen (Number of Surgeries)

Indication for surgery	Findings in surgical specimen				
	No neoplasia	LGD	HGD	CAC	Total
LGD	**16**	**22**	**2**	**9 (18%)**	49
HGD	**8**	**6**	**5**	**13 (41%)**	32
CAC	**1**	**2**	**1**	**59 (94%)**	63
Other reason	**23**	**17**	**1**	**27 (40%)**	68
Total	48	47	9	108	212

CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Supplementary Table 3. Indication for Surgery During Follow-up and the Maximal Grade of Neoplasia Found in Surgical Specimen (Number of Patients)

Indication for surgery	Findings in surgical specimen				
	No neoplasia	LGD	HGD	CAC	Total
LGD	**16**	**20**	**2**	**9 (19%)**	47
HGD	**8**	**5**	**5**	**13 (42%)**	31
CAC	**1**	**2**	**1**	**52 (93%)**	56
Other reason	**23**	**15**	**1**	**21 (35%)**	60
Total	48	42	9	95	194

CAC, colitis-associated colorectal cancer; HGD, high-grade dysplasia; LGD, low-grade dysplasia.

Supplementary Table 4. Risk Factors Associated With Development of More Advanced Lesion (HGD or CAC)

Variable	Univariate analysis			Multivariate analysis		
	Relative risk	95% CI	*P* value[a]	Relative risk	95% CI	*P* value[a]
Metachronous lesions	14.50	3.39–61.90	**<.01**	6.99	1.54–31.77	**.01**
Multifocal lesions	3.99	1.71–9.34	**<.01**	0.94	0.34–2.59	.90
Non-polypoid lesions	20.94	4.92–89.17	**<.01**	13.78	3.11–61.19	**<.01**
Associated PSC	3.78	1.56–9.14	**<.01**	1.45	0.52–4.03	.48
Invisible lesions	3.18	1.42–7.11	**<.01**	2.36	0.93–5.99	.07
Colonic stricture	7.48	3.08–18.17	**<.01**	2.64	1.00–6.96	**<.05**
Age at IBD diagnosis	0.99	0.97–1.01	.40			
Family history of CRC	0.76	0.16–3.69	.73			
Smoking status	0.37	0.12–1.17	.09			
Age at diagnosis of the index lesion	1.01	0.98–1.03	.71			
Family history of IBD	0.58	0.12–2.80	.50			

CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.
[a]*P* value for Cox proportional hazards regression. Bold values are significant.

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Supplementary Table 5. Risk Factors Associated With Development of Colitis-associated Colorectal Cancer

Variable	Univariate analysis			Multivariate analysis		
	Relative risk	95% CI	*P* value[a]	Relative risk	95% CI	*P* value[a]
Metachronous lesions	7.47	1.67–33.42	**<.01**	3.72	0.76–18.21	.10
Multifocal lesions	5.17	1.64–16.27	**<.01**	1.44	0.41–5.05	.57
Non-polypoid lesions	26.94	3.55–204.35	**<.01**	14.96	1.88–119.25	**.01**
Associated PSC	6.35	2.26–17.85	**<.01**	3.41	1.10–10.56	**.03**
Colonic stricture	6.33	2.00–20.00	**<.01**	1.85	0.5550–6.18	.32
Invisible lesions	2.60	0.94–7.19	.07			
Age at IBD diagnosis	0.98	0.95–1.01	.21			
Family history of CRC	0.43	0.05–3.62	.44			
Smoking status	0.36	0.07–1.77	.21			
Age at diagnosis of the index lesion	1.00	0.96–1.03	.92			
Family history of IBD	0.89	0.17–4.71	.89			

CI, confidence interval; CRC, colorectal cancer; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.
[a]*P* value for Cox proportional hazards regression. Bold values are significant.