High Risk of Advanced Colorectal Neoplasia in Patients With Primary Sclerosing Cholangitis Associated With Inflammatory Bowel Disease

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BACKGROUND & AIMS: **Patients with inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC, termed PSC-IBD) are at increased risk for colorectal cancer, but their risk following a diagnosis of low-grade dysplasia (LGD) is not well described. We aimed to determine the rate of advanced colorectal neoplasia (aCRN), defined as high-grade dysplasia and/or colorectal cancer, following a diagnosis of indefinite dysplasia or LGD in this population.**

METHODS: **We performed a retrospective, longitudinal study of 1911 patients with colonic IBD (293 with PSC and 1618 without PSC) who underwent more than 2 surveillance colonoscopies from 2000 through 2015 in The Netherlands or the United States (9265 patient-years of follow-up evaluation). We collected data on clinical and demographic features of patients, as well as data from each surveillance colonoscopy and histologic report. For each surveillance colonoscopy, the severity of active inflammation was documented. The primary outcome was a diagnosis of aCRN during follow-up evaluation. We also investigated factors associated with aCRN in patients with or without a prior diagnosis of indefinite dysplasia or LGD.**

RESULTS: **Patients with PSC-IBD had a 2-fold higher risk of developing aCRN than patients with non-PSC IBD. Mean inflammation scores did not differ significantly between patients with PSC-IBD (0.55) vs patients with non-PSC IBD (0.56) ($P = .89$), nor did proportions of patients with LGD (21% of patients with PSC-IBD vs 18% of patients with non-PSC IBD) differ significantly ($P = .37$). However, the rate of aCRN following a diagnosis of LGD was significantly higher in patients with PSC-IBD (8.4 per 100 patient-years) than patients with non-PSC IBD (3.0 per 100 patient-years; $P = .01$). PSC (adjusted hazard ratio [aHR], 2.01; 95% CI, 1.09–3.71), increasing age (aHR 1.03; 95% CI, 1.01–1.05), and active inflammation (aHR, 2.39; 95% CI, 1.63–3.49) were independent risk factors for aCRN. Dysplasia was more often endoscopically invisible in patients with PSC-IBD than in patients with non-PSC IBD.**

[a]Authors share co-first authorship.

Abbreviations used in this paper: aCRN, advanced colorectal neoplasia; aHR, adjusted hazard ratio; CRC, colorectal cancer; EHR, electronic health record; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease undifferentiated; IND, indefinite dysplasia; LGD, low-grade dysplasia; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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CONCLUSIONS: **In a longitudinal study of almost 2000 patients with colonic IBD, PSC remained a strong independent risk factor for aCRN. Once LGD is detected, aCRN develops at a higher rate in patients with PSC and is more often endoscopically invisible than in patients with only IBD. Our findings support recommendations for careful annual colonoscopic surveillance for patients with IBD and PSC, and consideration of colectomy once LGD is detected.**

Keywords: Surveillance; Colon Cancer; Crohn's Disease; Ulcerative Colitis; Primary Sclerosing Cholangitis.

Patients with inflammatory bowel disease (IBD) are at an increased risk of developing colorectal cancer (CRC).[1,2] The co-occurrence of primary sclerosing cholangitis (PSC),[1,3] a chronic liver disease characterized by progressive inflammation and fibrosis of the bile ducts,[4] increases this risk substantially.[5] Although an estimated 70% of patients with PSC have a concomitant diagnosis of IBD (termed PSC-IBD),[6] only 3% to 5% of patients with IBD have concomitant PSC, with the diagnosis more common in patients with ulcerative colitis (UC).[5,7] The PSC-IBD phenotype often is characterized by extensive colitis with rectal-sparing and backwash ileitis, albeit with a mild and often asymptomatic clinical course.[8–13] However, despite their mild clinical colitis, patients with PSC-IBD compared with patients with only IBD colitis have a 3- to 5-fold higher risk of CRC, and the cancers occur more often in the right colon.[14,15] As such, current guidelines recommend that patients with PSC-IBD be enrolled in a CRC surveillance program with an annual colonoscopy from the time of PSC diagnosis, regardless of their duration of IBD. This is in contrast to patients with IBD colitis and no PSC (non-PSC IBD), in which CRC surveillance is recommended after 8 years of colonic disease.[5,16–18]

The development of neoplasia in IBD colitis follows a multistep sequence from chronic inflammation and no dysplasia or indefinite dysplasia (IND) to low grade-dysplasia (LGD) and high-grade dysplasia (HGD), before final malignant transformation to adenocarcinoma. As such, the presence and grade of dysplasia remain the best current indicators of cancer risk in IBD. There is an increasing tendency to keep patients with LGD on intensive surveillance instead of recommending proctocolectomy.[19,20] However, very few studies have described the risk of advanced colorectal neoplasia (aCRN) in patients with PSC-IBD after a diagnosis of IND and/or LGD.[21,22] Furthermore, the studies that do report on the risk of neoplasia in patients with PSC-IBD were performed in an era in which imaging-enhanced endoscopy and high-resolution endoscopy were not used routinely.

The aims of the present study were to report on the risk of aCRN in a well-characterized cohort of patients with PSC-IBD enrolled in a surveillance program in the modern endoscopic era, and to describe the rate of aCRN after a diagnosis of IND and/or LGD in these patients compared with patients with non-PSC IBD and long-standing IBD colitis also undergoing surveillance.

Methods

Study Population and Case Identification

Patients with established IBD colitis undergoing colonoscopic surveillance between 2000 and 2015 were identified retrospectively from 2 databases: a Dutch database inclusive of 2 secondary and 6 tertiary centers and the Mount Sinai Hospital database in New York City inclusive of 1 tertiary IBD referral center. Cases were identified by query of the electronic health record (EHR)-linked database using both International Classification of Diseases, 9th and 10th revision codes, and free text searches for cases of IBD and also free text searches for PSC.

Patient Selection: Inclusion and Exclusion Criteria

After initial identification through the EHR query, individual charts were reviewed. For patients with PSC-IBD, a clinical diagnosis of PSC had to be confirmed by distinctive features on cholangiography or liver biopsy (for patients with small-duct PSC). Additional inclusion criteria were as follows: (1) diagnosis of IBD (UC, CD, IBD undifferentiated [IBD-U]) with colonic involvement confirmed endoscopically and histologically; (2) confirmed colonic disease duration of at least 8 years for patients with non-PSC IBD or any colonic disease duration for patients with PSC-IBD; (3) enrollment in a surveillance program; and (4) at least left-sided colitis (UC or IBD-U) or involvement of more than 30% of the colonic surface (CD or IBD-U). Patients with a history of colectomy before enrollment or a history of aCRN before or at the index colonoscopy during the defined study period were excluded. Surveillance procedures were defined as colonoscopies in which either segmental random biopsies or chromoendoscopy were used. Colonoscopies with other indications (eg, medically refractory disease), were excluded. The index colonoscopy was defined as the first surveillance colonoscopy performed within the study period (2000–2015).

Data Collection

Database coding was identical for all study populations. The date of study entry was set at the first surveillance colonoscopy in the database. The time of

onset of PSC or IBD was determined from EHR review. The date of the last colonoscopy was set as the last day of follow-up evaluation.

The following baseline demographic and clinical data were abstracted: date of birth, sex, date of PSC diagnosis (if applicable), date of IBD diagnosis, IBD type, maximum disease extent, and date of prior diagnosis of IND and/or LGD (if applicable). Maximum disease extent was defined as the maximum documented extent of endoscopic disease on any colonoscopy and was coded as follows: extensive/pancolitis (>50%) or intermediate/left-sided (30%–50%). Medication exposure (at least 1 prescription) was recorded for mesalamine, thiopurines, and biologics.

Data from each surveillance colonoscopy were recorded, including date of examination, quality of bowel preparation (adequate or inadequate), most proximal extent examined, use of chromoendoscopy, presence and severity of endoscopic inflammation, presence of post-inflammatory polyps (pseudopolyps), stricture(s), and visible lesions. Endoscopically detected neoplastic lesions were categorized based on morphology (polypoid/nonpolypoid). Endoscopically invisible neoplasia was defined as neoplasia detected in a random biopsy with no corresponding morphologic lesion seen on endoscopy. Right-sided lesions were defined as those proximal to the splenic flexure. Because this was a retrospective study, there was no a priori protocol in place to record endoscopic activity in a uniform way. Thus, for each surveillance colonoscopy, the severity of active endoscopic inflammation was scored on a 4-point scale for each colonic segment visualized to allow for standardization: 0, no inflammation/remission; 1, mild inflammation; 2, moderate inflammation; or 3, severe inflammation. A mean inflammatory severity score per patient and per colonoscopy was calculated by dividing the sum of inflammatory severity scores by the total number of colonic segments visualized per colonoscopy and then by the total number of surveillance colonoscopies.

Histology

Dysplasia was recorded as IND, LGD, or HGD. All histologic diagnoses were as reported in the original pathology report; no specimens were re-reviewed or altered for this study. Of note, it is routine clinical practice at each participating institution that colorectal neoplasia is reviewed at the time of diagnosis and agreed upon by at least 2 pathologists.

Primary and Secondary Outcomes

The primary outcome was a diagnosis of aCRN, defined as HGD or CRC, during follow-up evaluation. Secondary outcomes were a diagnosis of IND and/or LGD during follow-up evaluation and the development of aCRN after a diagnosis of IND and/or LGD. Factors associated with a diagnosis of aCRN in patients with PSC-IBD or patients with non-PSC IBD with or without a prior diagnosis of IND and/or LGD were explored.

Statistical Analysis

Basic descriptive statistics were generated for patients meeting inclusion criteria. Chi-square and Fisher exact tests were used to compare categoric variables and dichotomous outcomes, whereas the Student *t* test and the Mann–Whitney *U* test were used for analyzing continuous data. Incidence rates were calculated as the number of cases per 100 patient-years of follow-up evaluation. Univariate and multivariate Cox-regression modeling was used to identify factors associated with aCRN. The proportional hazards assumption of time-static covariates was assessed using log–log plots and Schoenfeld residuals. Because inflammatory scores were not stable over time, these were input as time-changing covariates into the models. Mean inflammation scores were recalculated at every time point for each patient to correct for the variable number of colonoscopies. A P value of .10 or less was used as the cut-off value for selecting variables for the multivariate analysis. Kaplan–Meier survival curves were generated to compare cumulative incidence rates. Follow-up data were censored at the last point of colonoscopic follow-up evaluation, aCRN diagnosis, or colectomy. All data analyses were performed using SPSS version 22 (IBM Corp, Armonk, NY).

Study Oversight

The Institutional Review Board at each of the included sites approved the creation and analysis of a longitudinal retrospective cohort database of patients with colonic IBD undergoing surveillance.

Results

Baseline Demographic and Clinical Characteristics

Of 1911 patients with colonic IBD in the combined database meeting inclusion criteria, 293 patients were confirmed to have PSC-IBD; the remaining 1618 patients with non-PSC IBD served as the comparison group (Figure 1). The main demographic and clinical features of the cohort are detailed in Table 1. Compared with the non-PSC IBD group, patients with PSC-IBD were more often male and younger at study entry, although the age at IBD diagnosis was similar between groups ($P = .11$). As expected, UC was the predominant IBD type in the PSC-IBD group. Patients with PSC-IBD were less frequently exposed to IBD therapy compared with patients with non-PSC IBD. In 151 patients (51.5%), the PSC diagnosis was established after the IBD diagnosis, while in 36 patients (12.3%) PSC was established before the IBD diagnosis. For the remainder, PSC and IBD were

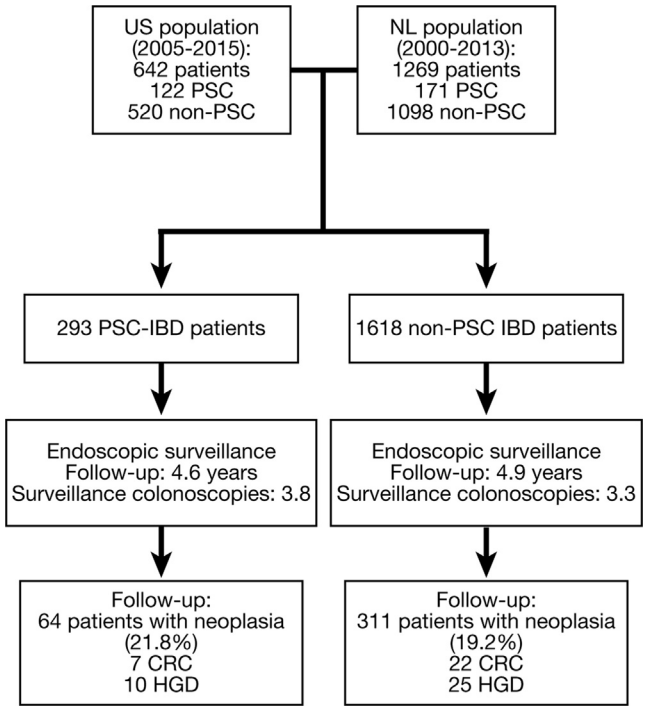

Figure 1. Description of patient selection and main outcomes in each database. NL, The Netherlands.

Table 1. Baseline Characteristics of the Study Population

	PSC-IBD (n = 293)	Non-PSC IBD (n = 1618)	*P* value
Male, %	205 (70.0%)	796 (49.2%)	<.001
Age at study inclusion, *y*, means (SD)	39 (14)	45 (13)	<.001
IBD type			<.001
Ulcerative colitis	203 (69.3%)	912 (56.4%)	
Crohn's colitis	76 (25.9%)	661 (40.9%)	
Indeterminate colitis	14 (4.8%)	45 (2.8%)	
Disease extent			<.001
Not specified	34 (11.8%)	154 (9.6%)	
Limited extent/proctitis	13 (4.5%)	49 (3.1%)	
Intermediate/left-sided	41 (14.2%)	572 (35.8%)	
Extensive/pancolitis	201 (69.6%)	823 (51.5%)	
Age at IBD diagnosis, *y*, mean (SD)	27 (13)	28 (12)	.11
IBD duration, *y*, mean (SD)	12 (10)	17 (9)	<.001
Age at PSC diagnosis, *y*, mean (SD)	32 (14)	-	-
Medication use			
Mesalamine	221 (75.4%)	1316 (81.3%)	.02
Thiopurines	93 (31.7%)	825 (51.0%)	<.001
Biologicals	38 (13.0%)	402 (24.8%)	<.001
Duration of follow-up evaluation after index colonoscopy, *y*			.10
Means (SD)	4.6 (3.2)	4.9 (3.0)	
Median	4.1	4.5	
Number of surveillance colonoscopies, mean	3.8	3.3	<.001

diagnosed within the same year or the sequence of diagnoses was not recorded.

The mean follow-up period for the total cohort was 4.8 years (SD, ±3.0 y), with a total of 9265 patient-years of follow-up evaluation; there was no difference in follow-up time between patients with PSC-IBD and patients with non-PSC IBD. The number of surveillance colonoscopies performed within the study period was higher in patients with PSC-IBD compared with patients with non-PSC IBD (3.8 vs 3.3; $P < .01$).

Inflammatory Activity

The endoscopic severity of inflammation on surveillance examinations was similar between patients with PSC-IBD and patients with non-PSC IBD (Supplementary Table 1). The proportion of procedures in which extensive active disease was observed in patients with PSC-IBD vs patients with non-PSC IBD patients was 27% vs 12% ($P < .01$), 23% vs 10% ($P < .01$), and 27% vs 10% ($P < .01$) for the first, second, and third surveillance colonoscopy, respectively. The proportion of patients in endoscopic remission on each of their surveillance colonoscopies during the entire study period was higher in patients with non-PSC IBD compared with patients with PSC-IBD ($P = .02$).

Occurrence of Advanced Colorectal Neoplasia and Associated Risk Factors

Among patients with PSC-IBD, aCRN was diagnosed in 17 patients (5.8%), with CRC in 7 (2.4%) and HGD in 10 patients (3.4%) (Table 2). The frequency of aCRN during follow-up evaluation was significantly lower in patients with non-PSC IBD (2.9%), with CRC and HGD diagnosed in 1.4% and 1.5% patients, respectively ($P = .01$). The incidence rate of aCRN in patients with PSC-IBD compared with patients with non-PSC IBD was significantly higher (1.3 vs 0.6/100 patient-years; $P < .01$) (Figure 2). Although aCRN was more often right-sided in patients with PSC-IBD compared with patients with non-PSC IBD, this was not statistically significant (53% vs 31%; $P = .12$). Among 40 patients with PSC-IBD (14%) in whom the diagnosis of PSC was newly established within the study period, 3 cases of aCRN occurred, with a mean duration of 4.0 years (±2.5 y) between the PSC diagnosis and aCRN occurrence. The primary outcomes stratified by study site are detailed in Supplementary Table 2.

On multivariate Cox-regression analysis, PSC (adjusted HR [aHR], 2.01; 95% CI, 1.09–3.71), increasing age (aHR, 1.03; 95% CI, 1.01–1.05), and active inflammation (aHR, 2.39; 95% CI, 1.63–3.49) remained independent predictors of aCRN diagnosis during follow-up evaluation (Table 3). Correcting for geography (United States vs The Netherlands) did not affect these findings (Supplementary Table 3).

Table 2. Description of the Outcomes During the Study Period

	PSC-IBD (n = 293)	Non-PSC IBD (n = 1618)	*P* value
Advanced neoplasia (aCRN)	17 (5.8%)	47 (2.9%)	.01
CRC	7 (2.4%)	22 (1.4%)	.19
HGD	10 (3.4%)	25 (1.5%)	.03
LGD, patients with ≥1 LGD lesion	60 (20.5%)	295 (18.2%)	.37
IND, patients with IND as highest grade lesion	27 (9.2%)	74 (4.6%)	.001
Time from IBD diagnosis to aCRN diagnosis, *y*, mean	19.4	24.3	.15
Time from database entry to aCRN diagnosis, *y*, mean	4.2	3.4	.31
Time from LGD to aCRN diagnosis, *y*, mean	0.7	1.7	.12

Risk of Advanced Colorectal Neoplasia After a Diagnosis of Indeterminate Dysplasia and/or Low-Grade Dysplasia

The number of patients in the total cohort with at least 1 diagnosis of IND was 147 (7.7%). In 101 patients (5.3%) no additional dysplasia was detected. Among patients with a diagnosis of IND, the rate of developing aCRN after detection of IND was higher in patients with PSC-IBD compared with patients with non-PSC IBD ($P = .02$) (Supplementary Figure 1). However, when patients with a synchronous or metachronous diagnosis of LGD (n = 46) were excluded from this analysis (ie, no grade of dysplasia higher than IND), this difference was no longer significant.

The occurrence of at least 1 LGD-containing lesion during the study period was similar for both patients with PSC-IBD and patients with non-PSC IBD (21% vs 18%; $P = .37$). Despite a similar proportion of patients with LGD, the rate of developing aCRN after detection of LGD was almost 3-fold higher in patients with PSC-IBD compared with patients with non-PSC IBD (8.4 vs 3.0/100 patient-years; $P = .01$) (Figure 3).

For the subgroup of patients with LGD, the number of patients in whom endoscopically invisible LGD was detected over the course of surveillance was higher in patients with PSC-IBD (38% vs 22%; $P = .01$). The proportion of invisible LGD cases among the total number of LGD cases (per-colonoscopy analysis) also was higher. In a subanalysis of The Netherlands population, we corrected for the total number of random biopsy specimens taken (107,745 biopsy specimens in total); the number of random biopsy specimens needed to detect invisible dysplasia was 826 in patients with PSC-IBD compared with 1703 in patients with non-PSC IBD.

On univariate Cox regression analysis, only PSC and multifocal dysplasia were associated with a higher risk of aCRN diagnosis after LGD detection, whereas polypoid morphology of the lesion (vs nonpolypoid or invisible) was associated with a lower risk. On multivariate analysis, only polypoid morphology remained significant and was associated with a reduced risk of aCRN (aHR, 0.31; 95% CI, 0.14–0.65) after LGD detection compared with nonpolypoid or endoscopically invisible lesions (Supplementary Table 4).

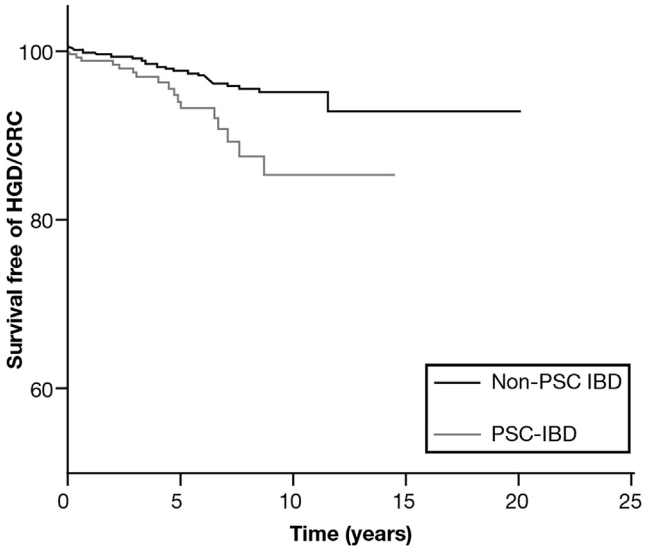

Figure 2. Kaplan–Meier time-to-event (aCRN) analysis, all patients since study entry.

Discussion

In this large, multicenter, cross-national, longitudinal cohort study of patients with confirmed IBD colitis undergoing colonoscopic CRC surveillance, we report a higher risk of aCRN in patients with concomitant PSC compared with those without PSC, in the current era of improved endoscopic technology and more effective medical therapy for inflammation. Although these findings corroborate previous studies, we further expand knowledge in the field by reporting an even higher risk of aCRN after detection of LGD (but not IND alone). That LGD was endoscopically invisible more often in patients with PSC-IBD compared with patients with non-PSC IBD justifies the more intensive management considerations for this population. Our findings suggest that although continued meticulous CRC surveillance with annual colonoscopy is indicated in the absence of dysplasia for patients with PSC-IBD, the detection of LGD or higher-grade pathology should lead to a careful weighting of the pros and cons of more aggressive therapeutic management, including colectomy.

In our well-characterized surveillance cohort of patients with PSC-IBD undergoing surveillance, we found

Table 3. Univariate and Multivariate Cox-Regression Analysis for the Overall Risk of aCRN: All Patients

Variable	Univariate			Multivariate		
	HR	95% CI	*P* value	aHR	95% CI	*P* value
Age, *y*	1.02	1.01–1.04	.03	1.03	1.01–1.05	.007
Age at IBD diagnosis	1.00	0.98–1.02	.78			
Sex, reference: male	1.83	1.08–3.08	.02	1.62	1.94–2.79	.08
PSC	2.13	1.22–3.70	.01	2.01	1.09–3.71	.03
Inflammation severity, mean (0–3)[a]	2.14	1.48–3.09	<.001	2.39	1.63–3.49	<.001
IBD type, reference: UC	0.99	0.60–1.61	.95			
Maximum disease extent, reference: pancolitis	1.43	0.85–2.41	.18			
Thiopurine exposure	0.84	0.51–1.40	.85			
Biological exposure	0.72	0.36–1.46	.36			
Mesalamine exposure	1.14	0.58–2.25	.70			
Number of surveillance procedures	0.96	0.84–1.09	.53			

[a]Entered as time-changing covariate; 0, no inflammation/remission; 1, mild; 2, moderate; 3, severe.

that having PSC-IBD is associated with a 2-fold higher risk of aCRN. This risk is slightly lower than prior studies and a recent meta-analysis of 16 studies that reported a 3.4-fold higher odds for colorectal neoplasia in patients with PSC-IBD.[23] Importantly, the increased risk in our study remained after correcting for active endoscopic inflammation over time (which was used as a time-changing covariate rather than a mean overall score). Endoscopic activity assessed during subsequent colonoscopies was associated strongly with the risk of future aCRN, congruent with studies in the population with non-PSC IBD.[24–26] Whether the outcomes of endoscopic inflammation compared with histologic inflammation are distinct remains a question for future investigation.

The increased risk of CRC in patients with PSC and concomitant colonic IBD has firmly been established, although the underlying mechanisms remain unclear.[3,27–30] The nearly 3-fold higher rate of aCRN (HGD and/or CRC) diagnosis after LGD detection, as well as the difference in location, morphology, and endoscopic conspicuousness of dysplasia in patients with PSC-IBD compared with patients with non-PSC IBD, suggests nuances in the pathogenesis of neoplasia between these groups. Several investigators have proposed a role for altered colonic bile composition in carcinogenesis. A right-sided predominance of neoplasia reinforces this hypothesis, as well as several studies directly measuring the bile acid composition in both animals and human beings.[29,31,32] There is also evidence supporting the notion that patients with PSC have an altered colonic microbiome irrespective of concurrent IBD or ursodeoxycholic acid treatment.[33] Still, whether these bacterial alterations are a cause or a consequence of the disease characteristics specific to PSC remains to be clarified. Patients with PSC also share a distinct genotype,[34] which may predispose them further to neoplastic progression. More likely, the underlying etiologies are multifactorial with roles for gene–environment interactions, the microbiome, and epigenetic modifications. Further investigations will hopefully open new avenues for novel therapeutic discovery and primary and secondary prevention.

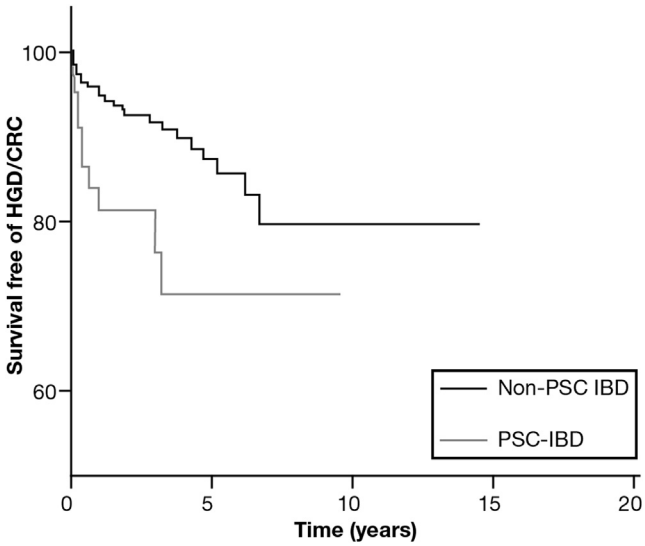

Figure 3. Kaplan–Meier time-to-event (aCRN) analysis, patients with LGD only.

All told, because the mechanisms underlying PSC as an independent risk factor for CRC in the setting of IBD colitis are unclear, the best strategy for CRC prevention in patients with PSC-IBD remains frequent, attentive surveillance colonoscopy. An important observation from our study that distinguishes patients with PSC-IBD from patients with non-PSC IBD, is that dysplasia was detected more often in random biopsies. Although previous retrospective studies have shown a low overall yield for dysplasia with random biopsies as opposed to only targeted biopsies of visible lesions, there was higher yield for dysplasia on random biopsy in patients with concurrent PSC.[35,36] Our data further add to this body of evidence, and it therefore can be questioned whether the current recommendation, based on the results of prospective studies, to move away from random biopsies as part of CRC surveillance should apply to patients with PSC-IBD.[37,38] During surveillance examinations, particular attention should be paid to the proximal colon because right-sided cancers seem to be more common in patients

with PSC-IBD compared with patients with non-PSC IBD colitis.[32] Although the proportion of right-sided aCRN was higher in the PSC-IBD subgroup, this difference was not statistically significant in the present study and may be owing to insufficient power; it also may reflect selection bias because one of our inclusion criteria for the non-PSC IBD subgroup was at least left-sided disease extent or more than 30% involvement, and thus may not represent the overall IBD population. Our study confirms that the date of PSC diagnosis is particularly relevant when risk-stratifying patients because it seems that the risk of neoplastic progression is highest within the first few years of the PSC diagnosis.[39] Thus, although CRC surveillance is recommended after a disease duration of 8 years in patients with colonic IBD and no PSC,[40] CRC surveillance at the time of diagnosis in the setting of PSC is recommended and further corroborated by our findings.

Our study had several strengths. In addition to being a large IBD surveillance cohort in the modern era, our cohort is particularly robust because each patient was confirmed to have colonic IBD and to be actively enrolled in a colonoscopic CRC surveillance program. Comprehensive data on disease history and endoscopic findings during surveillance allowed for more accurate neoplastic risk assessment, particularly with respect to measurement of inflammatory burden over time. Importantly, detailed information on inflammatory activity at each colonoscopy was incorporated into the analysis for more accurate assessment of aCRN development in patients with PSC-IBD.

Our study also had some limitations, most notably the retrospective design. Despite the large size of our PSC-IBD cohort, additional subanalyses, such as stratification according to IBD type or medication use, yielded insufficient power to permit meaningful conclusions. Although we combined surveillance cohorts from 2 different countries, we predefined the inclusion/exclusion criteria, variables to be assessed, and definitions of outcomes. Combining these 2 cohorts enhanced not only our power to detect meaningful differences, but also the generalizability of our findings given that our study population included patients from affiliated community-based sites as well as tertiary IBD referral centers. That said, there may be unmeasured differences in care pathways between The Netherlands and the United States, leading to heterogeneity in our study results. It is important to note, however, that after adjusting for study site and clinical–demographic differences between The Netherlands and US cohorts, our results remained significant (Supplementary Table 3). The lack of standardized guidelines for the use of chromoendoscopy for CRC surveillance in patients with IBD colitis unfortunately precluded a meaningful analysis of its impact on dysplasia detection because 10% or fewer examinations were performed with chromoendoscopy. Finally, although no samples were re-reviewed by pathologists for the purposes of this study, it is routine practice at all institutions participating in this study that whenever there is a diagnosis of CRN, that the specimen is reviewed by 2 pathologists and consensus is reached before final reporting.

In summary, using a large well-characterized cohort of patients with confirmed colonic IBD undergoing surveillance between 2000 and 2015, we substantiated prior smaller reports of the increased risk of aCRN in patients with concurrent PSC-IBD compared with patients with only IBD colitis undergoing surveillance. Novel findings of our study include the significantly higher rate of aCRN diagnosis after a diagnosis of LGD in the setting of PSC complicating IBD. This finding together with a higher risk of invisible dysplasia in patients with PSC-IBD highlights the need for an ongoing strict CRC surveillance program in these patients and a low threshold to advise colectomy once LGD is detected in this select population.

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.2018.01.023.

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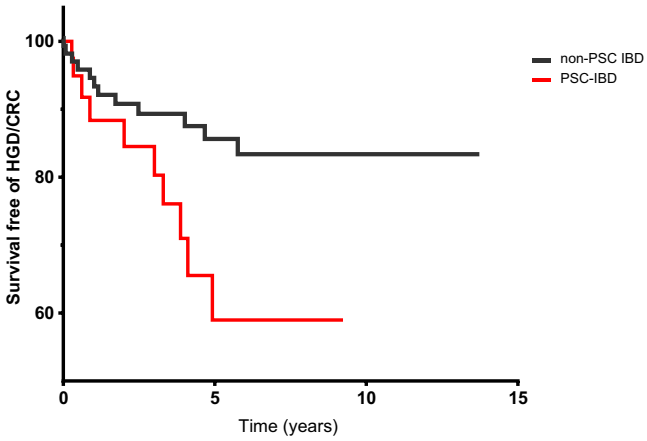

Supplementary Figure 1. Kaplan–Meier time-to-event (aCRN) analysis for patients with IND; time from first IND within study interval to event ($P = .02$, log-rank test). aCRN was defined as CRC and/or HGD.

Supplementary Table 1. Inflammatory Parameters During Surveillance

	PSC-IBD	Non-PSC IBD	*P* value
Severity of active inflammation, mean (0–3)[a]	0.55	0.56	.89
Extent of active inflammation, mean (0–3)[a]	1.36	1.17	.003
Activity ratio for all surveillance colonoscopies, active:inactive	45%	41%	.19
No inflammation on all surveillance colonoscopies	76 (27.1%)	546 (34.1%)	.02
Inflammation extent, first colonoscopy			.001
No activity	127 (53.6%)	864 (57.9%)	
Limited	7 (3.0%)	89 (6.0%)	
Intermediate	38 (16.0%)	363 (24.3%)	
Extensive/pancolitis	65 (27.4%)	176 (11.8%)	
Inflammation extent, second colonoscopy			<.001
No activity	125 (55.3%)	866 (61.2%)	
Limited	9 (4.0%)	109 (7.7%)	
Intermediate	40 (17.7%)	297 (21.0%)	
Extensive/pancolitis	52 (23.0%)	141 (10.0%)	
Inflammation extent, third colonoscopy			<.001
No activity	102 (57.3%)	584 (63.6%)	
Limited	6 (3.4%)	79 (8.6%)	
Intermediate	22 (12.4%)	164 (17.9%)	
Extensive/pancolitis	48 (27.0%)	92 (9.9%)	
Endoscopic inflammation severity, first colonoscopy			.20
No activity	160 (57.1%)	924 (57.8%)	
Mild	100 (35.7%)	495 (30.9%)	
Moderate	19 (6.8%)	131 (8.2%)	
Severe	1 (0.4%)	50 (3.1%)	
Endoscopic inflammation severity, second colonoscopy			.77
No activity	125 (53.6%)	864 (59.3%)	
Mild	89 (38.2%)	445 (30.5%)	
Moderate	16 (6.9%)	101 (6.9%)	
Severe	3 (1.3%)	48 (3.3%)	
Endoscopic inflammation severity, third colonoscopy			.17
No activity	102 (55.4%)	583 (61.6%)	
Mild	63 (34.2%)	276 (29.2%)	
Moderate	13 (7.1%)	64 (6.8%)	
Severe	6 (3.3%)	23 (2.4%)	

[a]Corrected for total number of surveillance colonoscopies per patient.

Supplementary Table 2. Database Characteristics: Comparison The Netherlands and the United States

	The Netherlands (n = 1269)	United States (n = 642)	*P* value
Male	674 (53.1%)	327 (50.9%)	.37
Age at study inclusion, means (SD)	45 (12)	41 (15)	<.001
Age at IBD diagnosis, means (SD)	29 (12)	26 (14)	<.001
PSC	171 (13.5%)	122 (19.0%)	.002
Age at PSC diagnosis, means (SD)	33 (12)	32 (16)	.37
IBD type			<.001
Ulcerative colitis	800 (63.0%)	315 (49.1%)	
Crohn's colitis	434 (34.2%)	303 (47.2%)	
Indeterminate colitis	35 (2.8%)	24 (3.7%)	
Extensive disease/pancolitis	686 (54.1%)	338 (52.6%)	.56
Medication use			
Mesalamines	999 (78.7%)	543 (83.8%)	.008
Thiopurines	556 (43.8%)	362 (56.4%)	<.001
Biologicals	156 (12.3%)	284 (44.2%)	<.001
Number of surveillance colonoscopies, means	3.4	3.3	.25
Interval between surveillance colonoscopies, *y*, means	1.6	1.2	<.001
Neoplasia outcomes			
CRC	17 (1.3%)	12 (1.9%)	.37
HGD	15 (1.2%)	20 (3.1%)	.003
LGD	264 (20.8%)	88 (13.7%)	<.001

Supplementary Table 3. Univariate and Multivariate Cox-Regression Analysis for the Overall Risk of aCRN (All Patients), Corrected for Study Site

	Univariate			Multivariate		
Variable	HR	95% CI	*P* value	aHR	95% CI	*P* value
PSC	2.13	1.22–3.70	.008	1.85	1.00–3.43	.049
Inflammation severity (0–3)[a]	2.14	1.48–3.09	<.001	2.08	1.42–3.07	<.001
Sex (reference: male)	1.83	1.08–3.08	.02	1.68	0.97–2.89	.06
IBD type (reference: UC)	0.99	0.60–1.61	.95			
Maximum disease extent (reference: pancolitis)	1.43	0.85–2.41	.18			
Age at IBD diagnosis	1.00	0.98–1.02	.78			
Age (years)	1.02	1.01–1.04	.03	1.03	1.01–1.05	.004
Thiopurine exposure	0.84	0.51–1.40	.85			
Biological exposure	0.72	0.36–1.46	.36			
5-aminosalicylate exposure	1.14	0.58–2.25	.70			
Number of surveillance procedures	0.96	0.84–1.09	.53			
Population (reference: US)	2.82	1.72–4.62	<.001	2.20	1.30–3.74	.003

NOTE. aCRN was defined as colorectal cancer and/or HGD.
[a]Entered as time-changing covariate; 0, no inflammation/remission; 1, mild; 2, moderate; 3, severe.

Supplementary Table 4. Univariate and Multivariate Cox-Regression Analysis for the Risk of aCRN After Detection of LGD

	Univariate			Multivariate		
Variable	HR	95% CI	*P* value	aHR	95% CI	*P* value
PSC	2.52	1.19–5.31	.02	1.79	0.83–3.88	.14
Sex, reference: male	1.23	0.60–2.49	.57			
Thiopurine exposure	1.20	0.60–2.40	.60			
Biological exposure	0.74	0.23–2.44	.74			
Mesalamine exposure	1.07	0.44–2.59	.88			
Dysplasia characteristics						
Distal location	1.69	0.77–4.32	.17			
Multifocality	2.46	1.22–4.95	.01	1.90	0.93–3.87	.08
Polypoid morphology	0.27	0.13–0.57	.001	0.31	0.14–0.65	.002
Invisible dysplasia	1.64	0.76–3.53	.21			
Nonpolypoid morphology	1.82	0.70–4.74	.22			

NOTE. aCRN was defined as colorectal cancer and/or HGD.