No Association Between Pseudopolyps and Colorectal Neoplasia in Patients With Inflammatory Bowel Diseases

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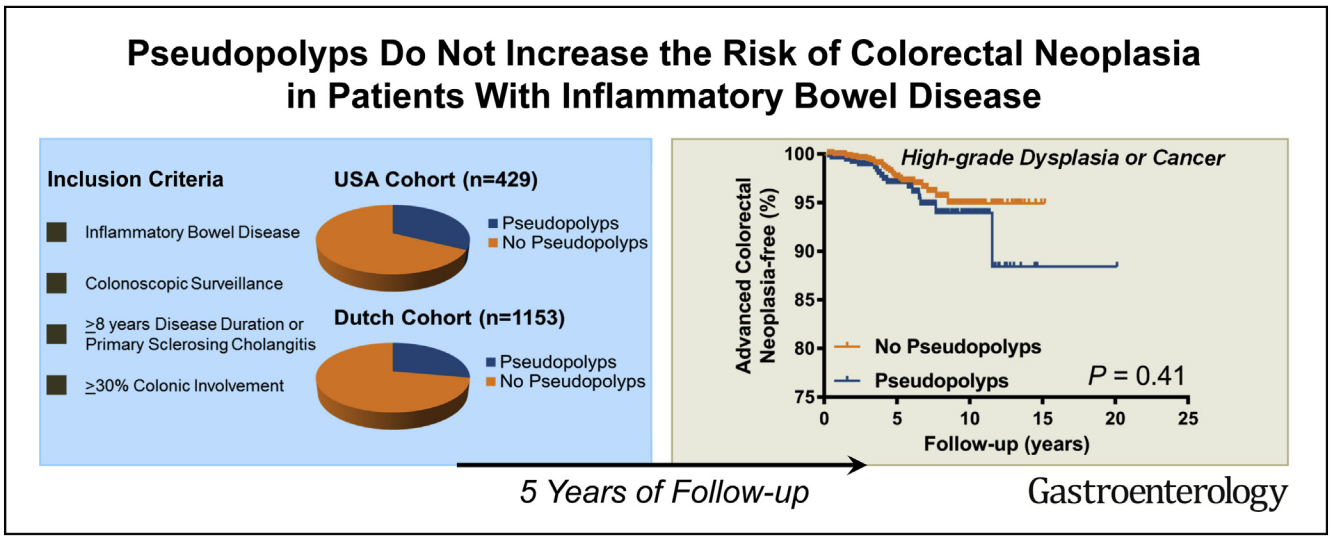
CLINICAL AT

This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e17. Learning Objective: Upon completion of this CME activity, successful learners will be able to recognize patients at high risk for colitis-associated colorectal cancer and apply current guidelines for colorectal neoplasia (CRN) surveillance in patients with inflammatory bowel disease (IBD).



BACKGROUND & AIMS: Patients with inflammatory bowel diseases who have postinflammatory polyps (PIPs) have an increased risk of colorectal neoplasia (CRN). European guidelines propose that patients with PIPs receive more frequent surveillance colonoscopies, despite limited evidence of this increased risk. We aimed to define the risk of CRN and colectomy in patients with inflammatory bowel diseases and PIPs. **METHODS:** We conducted a multicenter retrospective cohort study of patients with inflammatory bowel diseases who underwent colonoscopic surveillance for CRN, from January 1997 through January 2017, at 5 academic hospitals and 2 large nonacademic hospitals in New York or the Netherlands. Eligible patients had confirmed colonic disease with duration of at least 8 years (or any duration, if they also had primary sclerosing cholangitis) and no history of advanced CRN (high-grade dysplasia or colorectal cancer) or colectomy. The primary outcome was occurrence of advanced CRN according to PIP status; secondary outcomes were occurrence of CRN (inclusive of low-grade dysplasia) and colectomy. **RESULTS:** Of 1582 eligible patients, 462 (29.2%) had PIPs. PIPs were associated with more severe inflammation (adjusted odds ratio 1.32; 95% confidence interval [CI] 1.13–1.55), greater disease extent (adjusted odds ratio 1.92; 95% CI 1.34–2.74), and lower likelihood of primary sclerosing cholangitis (adjusted odds ratio 0.38; 95% CI 0.26–0.55). During a median follow-up period of 4.8 years, the time until development of advanced CRN did not differ significantly between patients with and those without PIPs. PIPs did not independently increase the risk of advanced CRN (adjusted hazard ratio 1.17; 95% CI 0.59–2.31). The colectomy rate was significantly higher in patients with PIPs ($P = .01$). **CONCLUSIONS:** In a retrospective analysis of data from 2 large independent surveillance cohorts, PIPs were associated with

greater severity and extent of colon inflammation and higher rates of colectomy, but were not associated with development of any degree of CRN. Therefore, intervals for surveillance should not be shortened based solely on the presence of PIPs.

Keywords: Primary Sclerosing Cholangitis; Ulcerative Colitis; Crohn Colitis; Crohn Disease.

Patients with longstanding inflammatory bowel disease (IBD) colitis are at increased risk of developing colorectal dysplasia and colorectal cancer (CRC).[1,2] Current guidelines recommend performing surveillance colonoscopies at regular intervals to screen for colorectal neoplasia (CRN; dysplasia or carcinoma).[3–6] Leading European guidelines stratify patients with IBD colitis into groups with low, intermediate, or high risk of CRC based on several risk factors, including the presence of post-inflammatory polyps (PIPs).[3,5,6] Commonly referred to as "pseudopolyps," PIPs are encountered in 20%–45% of patients with IBD and colonic involvement.[7–10] Previous case–control studies reported a 1.9- to 2.5-fold increased risk of CRC in patients with PIPs.[8,9,11] More recently, however, in a large retrospective cohort study of patients with ulcerative colitis (UC) undergoing CRN surveillance, PIPs did not independently predict CRN or predict progression from low-grade dysplasia (LGD) to advanced CRN (ACRN; defined as high-grade dysplasia [HGD] or CRC).[10,12]

Theoretically, the risk of CRN could be increased in patients with PIPs if their presence indicates prior severe inflammation. Alternatively, PIPs might obscure otherwise visible and resectable dysplastic lesions during surveillance. Direct malignant transformation of PIPs is generally considered unlikely.[13] Regardless of the mechanism, there is a gap in the literature as to whether PIPs are independent predictors of ACRN. Clarifying this risk has far-reaching implications for the burden of surveillance colonoscopies in patients with IBD and PIPs. If possible, safe lengthening of surveillance intervals would affect quality of life and promote cost containment and resource stewardship. Using a large multicenter cohort of patients with confirmed colonic IBD undergoing colonoscopic surveillance, we primarily aimed to determine whether PIPs are associated with increased risk of ACRN and secondarily aimed to determine whether PIPs are associated with CRN or colectomy. We also aimed to delineate predisposing or protective factors for PIPs and to define the prevalence of CRN in biopsied PIPs.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Despite limited evidence, shorter interval colonoscopic surveillance for colorectal neoplasia is recommended for patients with inflammatory bowel disease (IBD) and post-inflammatory polyps (PIPs).

NEW FINDINGS

In patients with IBD undergoing colonoscopic surveillance, PIPs were independently associated with more extensive and severe inflammation, and absence of concomitant primary sclerosing cholangitis. PIPs were not independently associated with colorectal neoplasia.

LIMITATIONS

This is a retrospective study and is subject to inherent bias. Density of PIPs as a predictor of colorectal neoplasia could only be studied for a subset of patients.

IMPACT

The interval for colorectal neoplasia surveillance in IBD should reflect evidence-based risk factors. Our findings suggest that the presence of PIPs should not influence risk stratification.

Methods

Study Design and Population

This retrospective cohort study identified patients with confirmed colitis undergoing colonoscopic surveillance for CRN from January 1997 through January 2017 in 2 large IBD cohorts: a USA cohort from Mount Sinai Hospital (New York, NY) and a Dutch cohort coordinated by the University Medical Center Utrecht (Utrecht, The Netherlands) composed of 5 academic hospitals and 2 large nonacademic hospitals. The search strategy has been described in detail previously.[14] Inclusion criteria were (1) diagnosis of IBD (UC, Crohn disease [CD], IBD–unclassified [IBD-U]); (2) confirmed colonic disease by endoscopy and histology of at least 8 years or of any duration if concomitant with primary sclerosing cholangitis (PSC; confirmed by endoscopic retrograde or magnetic resonance cholangiopancreatography or liver biopsy); (3) enrollment in a dysplasia surveillance program; (4) $\geq$2 surveillance colonoscopies with available colonoscopy and pathology reports or $\geq$1 surveillance colonoscopy if interval ACRN was diagnosed on pathology obtained by another method; (5) at least left-sided disease extent (UC), involvement of >30% of the colonic surface (CD or IBD-U), or any extent if concomitant with PSC; and, after meeting these inclusion criteria, (6) no history of ACRN or colectomy before (or within the 3 months after) the first surveillance colonoscopy within the predefined study period (ie, "index colonoscopy").

Data Collection

The following baseline and clinical data were collected from the electronic health record using the same data collection format and definitions for the 2 cohorts: date of birth, sex,

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Abbreviations used in this paper: **ACRN, advanced colorectal neoplasia; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; CD, Crohn disease; CRC, colorectal cancer; CRN, colorectal neoplasia; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IBD-U, inflammatory bowel disease—unclassified; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; MRD, medically refractory disease; OR, odds ratio; PIP, postinflammatory polyp; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.**

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age at IBD diagnosis, IBD type (UC, CD, or IBD-U), family history of CRC, diagnosis of PSC (confirmed by histology or endoscopic or radiologic cholangiography), and history of colonic dysplasia (defined as indefinite for dysplasia [IND] or LGD at or before the index colonoscopy). Maximum extent of colonic disease was determined based on history as documented in the electronic health record and maximal disease extent during colonoscopic surveillance according to endoscopic and/or histologic findings. Any documented exposure to medication was collected before and during follow-up, including 5-aminosalicylates, immunomodulators (azathioprine or 6-mercaptopurine), methotrexate, and biologicals (including infliximab, adalimumab, certolizumab, golimumab, ustekinumab, natalizumab and vedolizumab). Surveillance procedures were defined as colonoscopies in which segmental random biopsies or chromoendoscopy were used. Data from these procedures were collected from colonoscopy and pathology reports. In addition, data from any procedure (eg, colectomy) leading to a diagnosis of ACRN were recorded. Colonoscopies that did not meet these criteria were excluded. Endoscopic inflammation (1 = normal or inactive; 2 = mild; 3 = moderate; 4 = severe) and histologic inflammation (1 = normal; 2 = inactive; 3 = mild; 4 = moderate; 5 = severe) were scored per segment. A mean inflammation score was calculated by averaging the scores of the most severely inflamed segment of all recorded surveillance colonoscopies.

For each endoscopic (or surgical) procedure, the following data were collected: date of procedure, presence of PIPs, quality of bowel preparation (adequate [excellent or good] or inadequate [fair or poor]), extent of intubation, and endoscopic and/or histologic inflammation. Quality measures were reported relative to the number of surveillance procedures performed during follow-up (ie, percentage of procedures with adequate bowel preparation or cecal intubation). For the USA cohort only, if the endoscopy report described PIPs as "many," "limiting visibility," or "fields," patients were subclassified as having "many PIPs." In the absence of these descriptors, patients were subclassified as having "few PIPs." Furthermore, colonic location of PIPs, number of PIPs biopsied (including any lesion that was reported to be a PIP in the endoscopy or pathology report), and presence and grade of dysplasia in aforementioned lesions were extracted. These data were not available in the Dutch cohort.

Histologic diagnosis and highest grade of CRN (defined as LGD, HGD, or CRC) or IND were recorded per segment. At all participating institutions, specimens with suspected CRN are routinely reviewed by at least 2 pathologists. No samples were re-reviewed and no alterations to the finalized reports were made for this study.

Colectomy was defined as subtotal colectomy or total proctocolectomy. Colectomy date and indication (medically refractory disease [MRD], stricture, dysplasia [CRN of any degree, suspected or confirmed], or multiple [combination of the former]) were documented. Histologic findings from colectomy specimens (eg, dysplasia, cancer) were recorded. For colectomies, only the highest grade of CRN was recorded for this study. Thus, for example, an outcome of IND implies there was no synchronous diagnosis of LGD, HGD, or CRC.

The date of the index colonoscopy was set as the start of follow-up and the time at risk. The total duration of follow-up was defined as the interval from the index colonoscopy (time 0) to time x, which was the first occurrence of any of the following events: the primary outcome, any censoring event, or the predefined end of the study period (January 31, 2017). Patients were censored at colectomy, a diagnosis of ACRN, or last follow-up before the end of the study period.

Outcomes of Interest

The primary outcome of the study was the rate of occurrence of ACRN. Secondary outcomes were the rate of occurrence of CRN and colectomy. Furthermore, factors associated with presence or absence of PIPs and factors predictive of or protective against ACRN and CRN were explored.

Statistical Analyses

Descriptive statistics and comparative test statistics were reported according to the distribution of the data. Missing data were interpreted as the absence of a characteristic for categorical parameters and excluded for continuous parameters. Time-to-event analyses were conducted for ACRN, CRN (defined as LGD, HGD, or CRC), and colectomy. For analyses of CRN, patients with "prior dysplasia" (defined as IND or LGD diagnosed at or before the index colonoscopy) were excluded. There were no missing data for the primary analyses of (A)CRN. Survival analysis was performed using Kaplan-Meier curves with log-rank test for significance. Patients were censored as defined earlier. Cox regression analysis was used to identify predictors for ACRN and CRN (hazard ratio [HR]) for the joint cohort and stratified by cohort geography (USA vs Dutch cohort). Logistic regression was used instead of Cox regression to identify factors associated with PIPs (odds ratio) because most patients with PIPs had presented with PIPs at the index colonoscopy (ie, "prevalent cases" instead of "incident cases"). As the primary exposure of interest, PIPs were included a priori in all multivariable analyses. PSC also was included a priori in all models, because it is an established strong predictor of ACRN.[14–17] In addition, covariates with $P < .10$ at univariable analyses were included in the multivariable models. Interactions between covariates included in the multivariable models and the presence of PIPs were tested by comparing the log-likelihood ratios of the models that included the interaction term with the models that included these covariates as independent variables; no significant interactions were identified. We also performed the following time–trend analyses for our primary and secondary outcomes: (1) stratified analysis according to date of index colonoscopy; (2) sensitivity analysis excluding patients with colonoscopies before January 1, 2000; and (3) multivariable Cox regression analysis with year of the index colonoscopy included as an independent variable.

Reported HRs or odds ratios indicate risks or odds, respectively, per unit increase of corresponding parameters (eg, per 1 year for disease duration). Mean endoscopic and histologic inflammation were collinear; the latter was preferred and included in the regression models.[10] To limit the risk of immortal time bias for *incident* cases of PIPs, PIPs were included in the Cox regression models as a time-changing covariate.[18]

Statistical significance was set at a 2-tailed P value $<.05$. The Bonferroni method was used to correct for multiple testing in independent subgroup analyses where appropriate. All analyses were performed using SPSS 24 (IBM Corp, Armonk, NY).

Study Oversight

This study was reviewed and approved by the institutional review board at Mount Sinai Hospital. In the Netherlands, this study received exempt status from the institutional review board because it is exempt from the law of human-bound research.

Results

Patient Characteristics

Our search yielded 1582 eligible patients: 429 patients in the USA cohort and 1153 in the Dutch cohort (Figure 1). The accrual of the cohort is depicted in Figure 2. The median follow-up time was 4.8 years (interquartile range [IQR] 2.8–6.7), providing 8182 patient-years of follow-up. A comparison of characteristics of the USA and Dutch cohorts is presented in Supplementary Table 1.

Factors Associated With PIPs

PIPs were present in 462 patients (29.2%). A comparison of characteristics of patients with vs without PIPs is presented in Table 1. PIPs were prevalent in 300 patients (19.0%) and incident in 162 patients (10.2%) during follow-up. Of patients with PIPs, 273 (59.1%) had PIPs reported at multiple procedures. Of 140 patients in the USA cohort with PIPs, 94 (67.1%) were categorized as having "few" and the remaining were categorized as having "many." At multivariable logistic regression analysis, histologic inflammation, extensive disease, and cohort geography (USA vs Dutch cohort) were each independently associated with presence of PIPs. PSC was independently associated with absence of PIPs (Table 2).

Neoplastic Outcomes According to PIP Status

Rate of Occurrence of ACRN (Primary Outcome). During follow-up, 17 patients (3.7%) with PIPs developed ACRN compared with 24 (2.0%) without PIPs. There was no significant difference in occurrence of ACRN in patients with vs without PIPs ($P = .41$; Figure 3*A*), with a median time to ACRN of 3.8 years (IQR 2.1–6.3) vs 4.2 years (IQR 3.0–5.3), respectively. There was no difference in the rate of ACRN according to density of PIPs (few vs many, USA cohort only; $P = .36$; Supplementary Figure 1) or according to multiple reporting of PIPs (≥2 procedures) vs single reporting (1 procedure; $P = .41$). Statistical non-significance in rates of ACRN between patients with and those without PIPs remained in the following subgroups: patients with UC or IBD-U, patients with CD, Dutch cohort, USA cohort (Figure 3*C*–*F*), patients with vs without PSC, and patients with vs without prior dysplasia (data not shown; each $P > .10$).

Predictors of ACRN. At multivariable Cox regression analysis, PIPs were not predictive of ACRN (Table 3). PSC, disease duration, prior dysplasia, and mean histologic inflammation were independent positive predictors of ACRN occurrence, whereas cecal intubation was protective against ACRN. At stratified analysis by geographic cohort (USA vs Dutch cohort) and date of index colonoscopy (before vs after January 1, 2005), PIPs similarly did not independently predict ACRN. Furthermore, exposure to thiopurines was a significant, independent predictor of ACRN in the USA cohort only (adjusted HR [aHR] 0.29; 95% confidence interval [CI] 0.09–1.00), but not in the combined study cohort. In a subgroup analysis of patients without prior dysplasia, a diagnosis of LGD during follow-up increased the risk of subsequent ACRN by >5-fold (aHR 5.04; 95% CI 2.67–9.52; $P < .0005$) compared with patients without incident LGD.

Rate of Occurrence of CRN (Secondary Outcome). The analyses for CRN were restricted to patients without prior dysplasia (n = 1350). As defined earlier, CRN was inclusive of LGD, HGD and CRC. During follow-up, 188 patients (13.9%) were diagnosed with CRN, 64 (16.3%) with PIPs and 124 (13.0%) without PIPs. There was no significant difference in the rate of CRN occurrence between patients with and those without PIPs (Figure 3*B*). Similar to ACRN, time to CRN was not significantly different in patients with PIPs reported at multiple procedures (≥2) vs at only 1 procedure ($P = .84$). Statistical non-significance remained when comparing time to CRN in patients with vs without PIPs at subgroup analyses, including the USA cohort, Dutch cohort (Supplementary Figure 2*A* and 2*B*), patients with UC or IBD-U, patients with CD, and patients with vs without PSC (data not shown; $P > .30$ for all comparisons). PIPs did not independently predict CRN (aHR 1.25; 95% CI 0.88–1.77). Rather, male sex, increasing age, PSC, and disease duration were significant positive independent predictors of CRN. Increasing number of surveillance colonoscopies was protective (Supplementary Table 2). Similar to ACRN, stratified analyses based on geographic cohort and date of index colonoscopy confirmed that PIPs were not independently associated with CRN. Furthermore, biologicals were independently protective against CRN in the subgroup whose index colonoscopy was after 2005 (aHR 0.50; 95% CI 0.28–0.91). No other predictors of CRN were identified by additional time–trend analyses, as described in the Methods.

Presence of CRN in Biopsied PIPs (Descriptive, USA Cohort Only). In the USA cohort, 104 patients (74.2% of patients with PIPs in the USA cohort) had lesions biopsied or resected that were suspected or confirmed PIPs, yielding 360 biopsy jars with histologic data on PIPs. CRN was never detected in a histologically confirmed PIP. In PIPs identified by endoscopy, LGD was found in 3 patients (2.8%) and HGD was found in 1 (1%), but none of these lesions were histologically confirmed to be PIPs. In addition, 9 patients (8.7%) were diagnosed with IND in a PIP identified by the endoscopist, of which 6 (66.7%) were histologically confirmed PIPs.

Rate of Occurrence of Colectomy According to PIP Status (Secondary Outcome). Eighty-three patients (5.3%) underwent colectomy during follow-up. Patients with PIPs more frequently underwent colectomy compared with those without PIPs (8.4% vs 3.9%) and had a significantly shorter time to colectomy (3.9 years [IQR 2.6–6.3] vs 4.1 years [IQR 2.5–5.1], respectively; $P = .01$; Figure 4*A*). Before colectomy, ACRN and CRN had occurred in 26 and 18 patients, respectively. In 39 patients (19 with PIPs and 20 without PIPs; 2.5% of entire cohort), colectomy was performed before a CRN-related outcome was reached. These patients were censored for analyses of (A)CRN after a

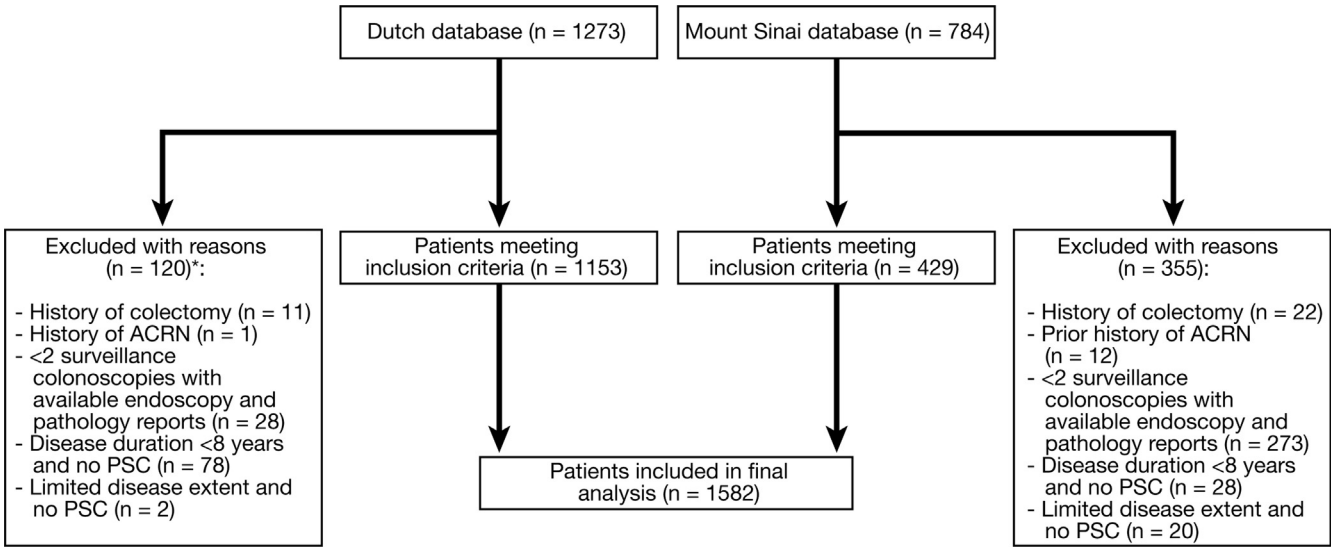

Figure 1. Flowchart of patient selection from databases. *The exclusion rate in the Dutch cohort is lower than that in the USA cohort, because most ineligible patients were excluded before data entry.

median 4.2-year follow-up. We further explored colectomy as an outcome at stratified analysis according to presence vs absence of PIPs and cohort geography (Figure 4*B* and *C*) and by comparing patients with vs without PIPs among 8 different subgroups (Dutch and USA cohort, patients with CD and UC or IBD-U, patients with and without PSC, and index colonoscopy before and after 2005). The Bonferroni correction for multiple testing was applied, resulting in a threshold for significance of $P < .006$ for comparing patients with vs without PIPs in 8 independent subgroups. Only in the CD subgroup did patients with PIPs vs without PIPs have a significantly higher risk of colectomy (data not shown; $P = .005$), but not in the USA cohort ($P = .54$; Figure 4*B*), patients with UC or IBD-U ($P = .30$), patients with concomitant PSC ($P = .02$) vs without PSC ($P = .01$), or in patients whose index colonoscopy was before 2005 ($P = .03$) vs after 2005 ($P = .10$; data not shown). Notably, in the subgroup of Dutch patients, the rate of colectomy was higher in patients with PIPs than in those without PIPs ($P = .008$; Figure 4*B*), but this was statistically

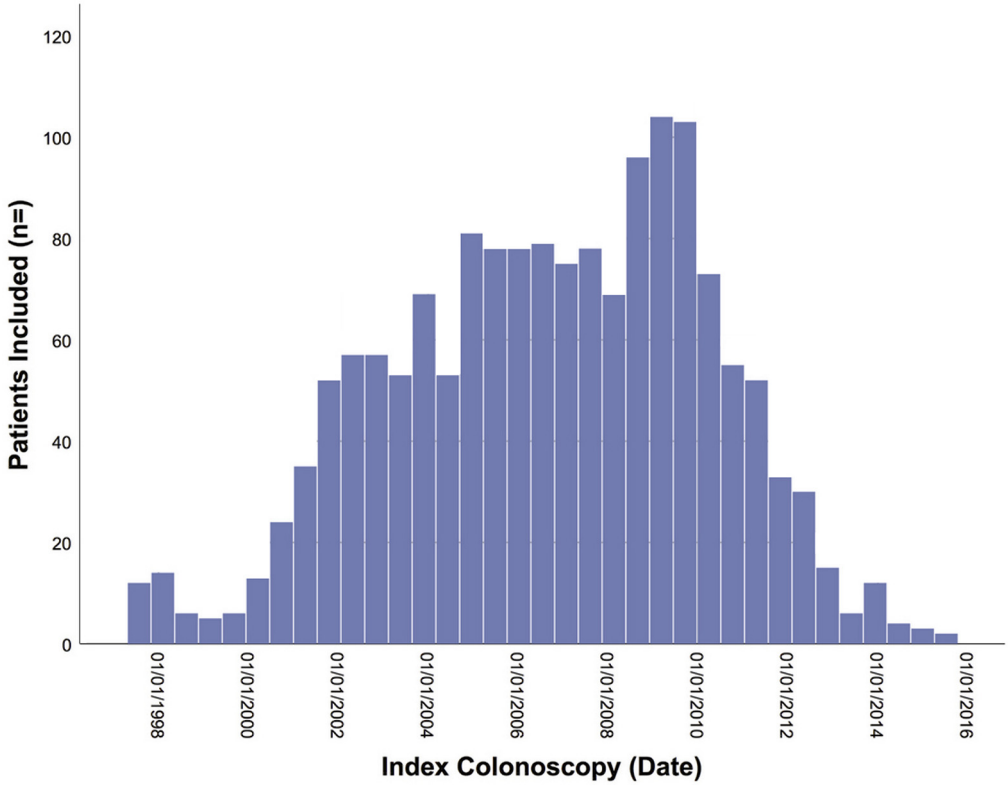

Figure 2. Accrual of cohort.

Table 1. Patient Characteristics and Follow-up Data Stratified by Presence of PIPs

	PIPs (n = 462)	No PIPs (n = 1120)	*P* value
Baseline and disease-related characteristics			
Age at index colonoscopy (*y*), median (IQR)	45 (36–56)	45.5 (35–54)	.43
Sex, n (%)			.42
Men	238 (51.1)	597 (53.3)	
Women	227 (48.9)	523 (46.7)	
IBD type, n (%)			.81
UC	279 (60.4)	230 (53.6)	
CD	170 (36.8)	181 (42.2)	
IBD-U	13 (2.8)	18 (4.2)	
Incident PIPs, n (%)	162 (35.1)	—	—
Follow-up before first diagnosis of PIPs (*y*), median (IQR)	2.9 (2.0–4.7)		
Family history of CRC, n (%)	29 (6.3)	64 (5.7)	.67
Disease duration at index colonoscopy (*y*), median (IQR)	14 (10–22)	14 (10–22)	.40
Dysplasia[a] at or before index colonoscopy, n (%)	70 (15.2)	163 (14.6)	.41
LGD	34 (7.4)	91 (8.1)	
IND	18 (3.9)	27 (2.4)	
Unspecified	17 (3.7)	45 (4.0)	
Extensive disease, n (%)	396 (88)	879 (83)	.01[b]
PSC, n (%)	38 (8.2)	196 (17.5)	<.0005[b]
Exposure to medication			
5-Aminosalicylates	393 (85.1)	893 (79.7)	.01[b]
Thiopurines	265 (57.4)	475 (42.4)	<.0005[b]
Methotrexate	30 (6.5)	60 (5.4)	.38
Biologicals	125 (27.1)	196 (17.5)	<.0005[b]
Colonoscopic surveillance details			
Procedures/y, median (IQR)	0.7 (0.6–1.0)	0.7 (0.6–1.0)	.49
Mean inflammation score			
Endoscopic	1.50 (1.00–2.00)	1.41 (1.00–1.80)	.001[b]
Histologic	2.60 (2.00–3.00)	2.50 (2.00–3.00)	<.0005[b]
Cecum intubated (% procedures), mean (SD)	86.0 (22.3)	87.4 (22.3)	.21
Adequate bowel preparation (% procedures), mean (SD)	97.6 (10.5)	98.1 (8.5)	.09
Duration of follow-up (*y*), median (IQR)	5.4 (3.3–7.6)	4.5 (2.7–6.6)	<.0005[b]

NOTE. Classification of PIPs in this table includes prevalent and incident PIPs.
SD, standard deviation.
[a]Patients with HGD at or before the index colonoscopy were excluded.
[b]Significant at $P < .05$ level.

nonsignificant after correction for multiple testing. However, when comparing indications for colectomy stratified by PIP status and cohort geography, there was a significant difference in colectomies performed for MRD between groups ($P = .004$; Figure 4*C*) and specifically between Dutch patients with and those without PIPs ($P = .001$). No other indications for colectomy were significantly different between these groups.

Discussion

In this multinational retrospective cohort study of nearly 1600 patients with confirmed colonic IBD undergoing colonoscopic CRN surveillance, PIPs were not a significant independent predictor of dysplasia or CRC. However, patients with PIPs had more severe histologic inflammation, more often had extensive colitis, and were significantly more likely to undergo colectomy. Our findings suggest that PIPs are related to the inflammatory burden, but are not themselves a dominant risk factor for CRN.

In contrast, previous studies broadly examining predictors of CRC in IBD have reported a significant, independent association between PIPs and CRC.[8,9,11] Limitations of these previous case–control studies include selection bias by comparing patients with CRC with low-risk controls, inadequate control for inflammation, and less sophisticated endoscopic techniques. Conversely, in this study we used a cohort design restricted to patients with confirmed colonic IBD undergoing CRN surveillance and distinctly controlled for histologic inflammation, a well-established predictor of ACRN.[7,10,19,20] Indeed, mean inflammation scores were highly predictive of ACRN and PIPs in our cohort. Similar to our findings, a recent cohort study of 987 patients with UC undergoing CRN surveillance also found that PIPs did not independently predict CRN risk after controlling for cumulative inflammatory burden.[10] In that study, patients with CD or IBD-U were excluded, and only 42 patients with PSC were enrolled. Further, PIPs were not the primary variable of interest in that study. In our study, we comprehensively evaluated PIPs and used sophisticated analytics to address

Table 2. Factors Associated With Presence of PIPs by Logistic Regression Analysis

		Univariable			Multivariable[d]		
Variable	PIPs, n (%)	OR	95% CI	*P* value	aOR	95%	*P* value
Patients with PIPs, N (%)	462 (100)						
Age at IBD diagnosis	—	1.00	0.99–1.01	.96			
Male sex	238 (51)	1.09	0.88–1.36	.42			
Extensive disease	396 (88)	1.51	1.09–2.08	.01[e]	1.92	1.34–2.74	<.0005[e]
USA cohort[a]	140 (30)	1.25	0.98–1.59	.06	1.40	1.04–1.88	.03[e]
Mean histologic inflammation[b]	—	1.39	1.21–1.60	<.0005[e]	1.32	1.13–1.55	.001[e]
PSC	38 (8.2)	0.42	0.29–0.61	<.0005[e]	0.38	0.26–0.55	<.0005[e]
CD[c]	170 (37)	1.06	0.84–1.32	.64			
Disease duration at index colonoscopy	—	1.01	1.00–1.02	.13			

aOR, adjusted odds ratio; OR, odds ratio.
[a]Reference category: Dutch cohort.
[b]Before first reported PIP.
[c]Reference category: UC or IBD-U.
[d]Seventy-seven patients (15 with PIPs) were excluded because of missing values.
[e]Significant at $P < .05$ level.

biases relevant to PIPs and CRN. We confirmed that no independent association between PIPs and ACRN exists in a broader population inclusive of patients with CD or PSC. In this context, a novel finding is that PSC was associated with a significantly lower likelihood of PIPs. This underscores the prevailing hypothesis that the phenotype of PSC-associated IBD colitis is distinct from non–PSC-associated IBD colitis, including clinically quiescent disease.[21] Regarding PIPs in Crohn colitis, data are scarce.[9] By enrolling a substantial number of patients with Crohn colitis, we provided evidence that PIPs do not independently predict (A)CRN in this group. Because IBD phenotype was not a predictor of (A)CRN, we suggest that surveillance intervals should be independent of IBD phenotype.

Although PIPs were not predictive of CRN, patients with PIPs did have significantly higher rates of colectomy. A key strength of our study is that all included patients were undergoing surveillance because of at least 8 years of colonic disease duration or a concomitant diagnosis of PSC. Thus, although patients with PIPs underwent colectomy more frequently than patient without PIPs, our cohort was universally at risk for ACRN at inclusion. Furthermore, very few patients underwent colectomy before a CRN-related outcome was reached, and the median follow-up in these patients was only slightly shorter compared with the entire cohort (4.2 vs 4.8 years, respectively). That said, we concede that early colectomy in patients with PIPs might obscure an increased risk of CRC. However, clinically, the competing risk of uncontrolled inflammation necessitating colectomy likely outweighs the risk of CRC in such patients. Indeed, in our cohort, patients with PIPs underwent significantly more colectomies indicated for MRD, but not for dysplasia. Moreover, this was found solely in the Dutch cohort. The reasons for this difference between the 2 geographic cohorts are unclear, but possibly reflect differences in clinical management and threshold for colectomy. Although it is certainly possible that those undergoing colectomy for MRD were at greater risk for ACRN in the long term, this risk is likely not driven by PIPs themselves, but by the well-established risk factor of colonic inflammation, also confirmed by our findings.[7,19,20,10]

There are some limitations to our study, beyond those that are inherent to retrospective research. Standardized scores were not used, but there was collinearity between endoscopic and histologic inflammation scores and an association with ACRN, as expected. Although we cannot provide absolute numbers on how often a dysplasia diagnosis was confirmed by a second expert pathologist, this is standard practice at each included institution. Indeed, confirmation of LGD by a pathology expert panel better predicts ACRN.[22] A second limitation is that reporting of PIPs by endoscopists was not standardized. In consequence, PIPs might be disregarded in the context of other pathologic findings (although, anecdotally, we expect such an occurrence to be exceedingly rare in our cohort, particularly for colonoscopies indicated specifically for surveillance). We improved the accuracy of identifying PIPs by including histologic evidence of PIPs where available. Notably, rates of (A)CRN did not differ according to how often PIPs were reported in colonoscopy reports. Because underreporting of PIPs might underestimate time at risk in patients with PIPs, we analyzed PIPs as a fixed parameter in survival analysis, which has the counter-effect of overestimating time at risk for patients with PIPs. We also analyzed PIPs as a time-changing covariate to account for incident PIPs after the index colonoscopy and minimize the risk of immortal time bias.[18] In these 2 analyses, PIPs still were not independent predictors of (A)CRN. Notably, in these same models, histologic inflammation independently predicted ACRN, and increasing number of surveillance colonoscopies was protective against CRN, findings that are consistent with the literature and support the internal validity of our findings.[7,10,19,20,23] All told, substantial misclassification of PIPs seems unlikely, because endoscopists have good

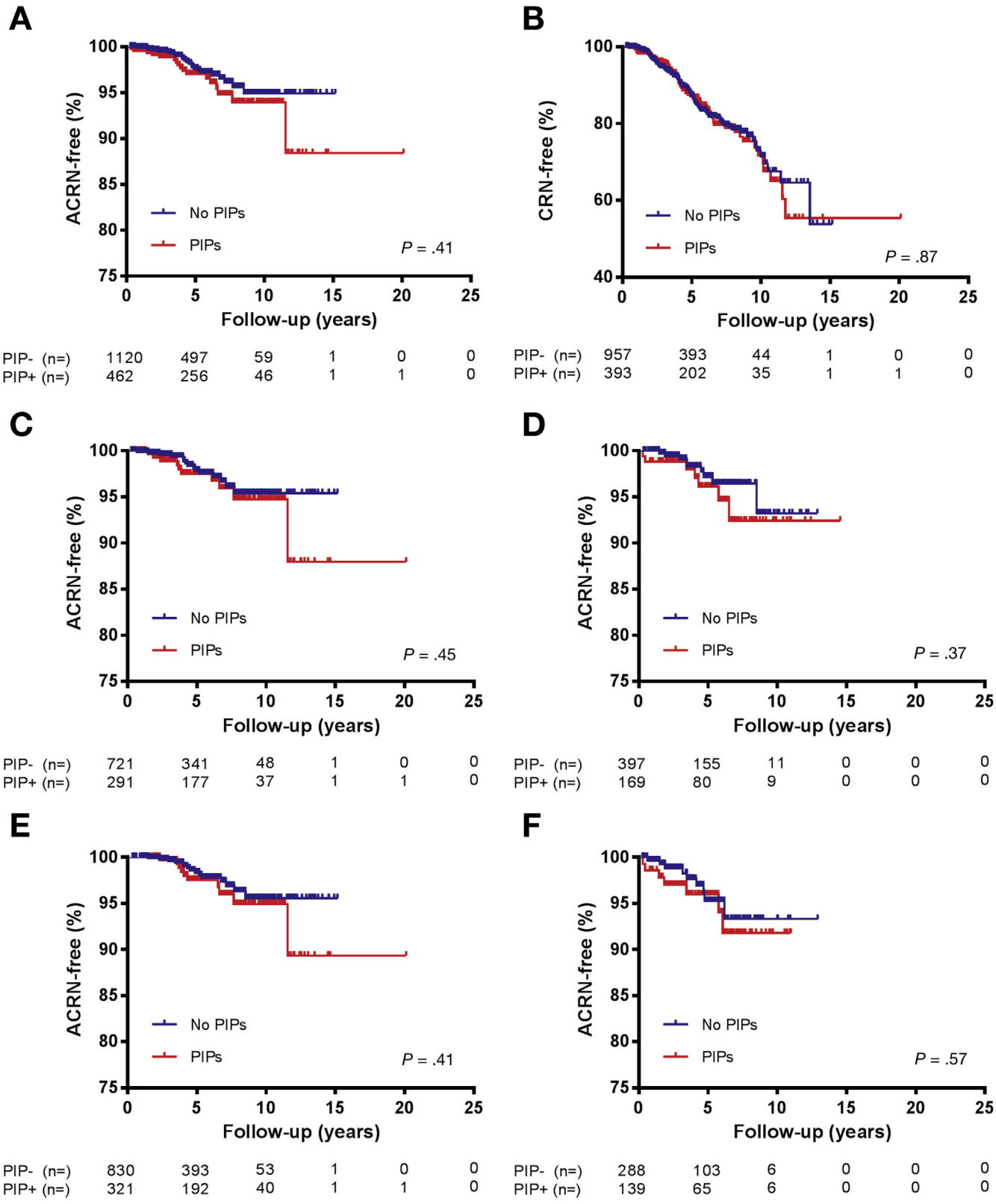

Figure 3. Kaplan-Meier curves for ACRN-free survival and CRN-free survival. (*A*) ACRN, All Patients; (*B*) CRN, All Patients; (*C*) ACRN, UC/IBD-U Patients; (*D*) ACRN, CD Patients; (*E*) ACRN, Dutch Cohort; (*F*) ACRN, USA Cohort.

Table 3. Predictors of ACRN by Cox Regression Analysis

Variable	ACRN, n (%)	Univariable			Multivariable[e]		
		HR	95% CI	*P* value	aHR	95% CI	*P* value
Patients with ACRN, N (%)	41 (100)						
Age at index colonoscopy	—	1.02	0.99–1.04	.17			
Male sex	27 (65.9)	1.77	0.93–3.38	.08	1.96	0.99–3.88	.06
USA cohort[a]	16 (39.0)	2.41	1.28–4.55	.01[f]	1.39	0.66–2.91	.39
Presence of PIPs[b]	17 (41.5)	1.56	0.82–2.96	.17	1.17	0.59–2.31	.65
PSC	9 (22.0)	1.70	0.81–3.57	.16	2.30	1.05–5.06	.04[f]
Dysplasia at or before index colonoscopy[c]	19 (46.3)	5.92	3.06–11.42	<.0005[f]	4.89	2.60–9.22	<.0005[f]
Mean histologic inflammation	—	2.40	1.63–3.53	<.0005[f]	2.11	1.34–3.34	<.001[f]
Disease duration at index colonoscopy	—	1.05	1.02–1.08	.003[f]	1.04	1.01–1.08	.005[f]
Cecum reached	—	0.11	0.01–0.85	.03[f]	0.09	0.01–0.68	.02[f]
Family history of CRC	5 (12.2)	2.32	0.91–5.91	.08	1.94	0.73–5.15	.18
Exposure to 5-aminosalicylates	38 (92.7)	2.42	0.75–7.86	.14			
CD[d]	16 (39.0)	1.38	0.74–2.60	.31			
Adequate bowel preparation	—	1.25	0.27–5.69	.78			
Exposure to biologicals	7 (17.1)	1.05	0.46–2.37	.91			
Number of surveillance colonoscopies	—	0.92	0.78–1.10	.36			
Exposure to thiopurines	—	0.70	0.37–1.33	.27			
Extensive disease	33 (80.5)	0.56	0.26–1.22	.15			

[a]Reference category: Dutch cohort.
[b]Time-changing covariate.
[c]IND or LGD.
[d]Reference category: UC or IBD-U.
[e]Thirty-eight patients (1 with ACRN) were excluded because of missing values.
[f]Significant at $P < .05$ level.

interobserver agreement for identifying PIPs based on endoscopic assessment.[24] For density of PIPs and ACRN risk, our study is unfortunately underpowered to draw conclusions regarding this issue. With this caveat, our data do suggest that even extensive PIPs in and of themselves might not grossly increase the risk of ACRN, but certainly inadequate visualization of the colonic mucosa and greater inflammatory burden in this setting are important considerations. Prospective, adequately powered studies are needed to better inform clinical decision making in this setting.

We further acknowledge some baseline differences between the 2 national cohorts, including more severe inflammation and greater use of biologicals in the USA cohort. The treatment approach concerning biologicals might differ between the USA and the Netherlands, particularly during the period of this study when data were still emerging regarding the (cost-)efficacy of biologicals. Alternatively, this difference also might indicate a more severe patient population given that the USA cohort represents a tertiary IBD referral center. In our cohort, exposure to biologicals was protective against CRN and not against ACRN, but only in the subgroup analysis of patients included after 2005 (presumably owing to more routine use in this period). Although this is compelling, our study was not designed to extensively assess the chemoprotective effect of medications, and the literature remains inconclusive regarding the potential chemoprotective effect of biologicals.[25,26] Regardless of these baseline differences between the 2 geographic cohorts, comprehensive subgroup analyses by country of origin, stratified Cox regression modeling, and including country of origin as an independent covariate in the multivariable models showed no modifying or interacting effect on the null association between PIPs and (A)CRN.

Our study has several strengths. One key strength is the large size of our surveillance cohort, with nearly 1600 patients who were well characterized for clinical, endoscopic, and histologic follow-up data. This large sample would have allowed us to detect a clinically relevant hazard rate for CRN and ACRN. Sample size is of pivotal importance, because ACRN is a rare outcome (incidence of 5.01 per 1000 patient-years in our surveillance cohort and comparable to a recent UC surveillance cohort).[10] Our analyses were robust with no missing data for our primary outcome. We controlled for several relevant covariates, including histologic inflammation, and evaluated PIPs as a fixed and as a time-changing covariate to account for underreporting of PIPs and immortal time bias, respectively. That we found already established predictive factors (eg, inflammation, disease duration, PSC, prior dysplasia) to be independently associated with ACRN supports the internal validity of our study. Furthermore, our findings were essentially validated in 2 independent surveillance cohorts because neither stratification by geography nor inclusion of geography as a covariate modified the null association between PIPs and our primary and secondary (A)CRN outcomes. It should be highlighted that

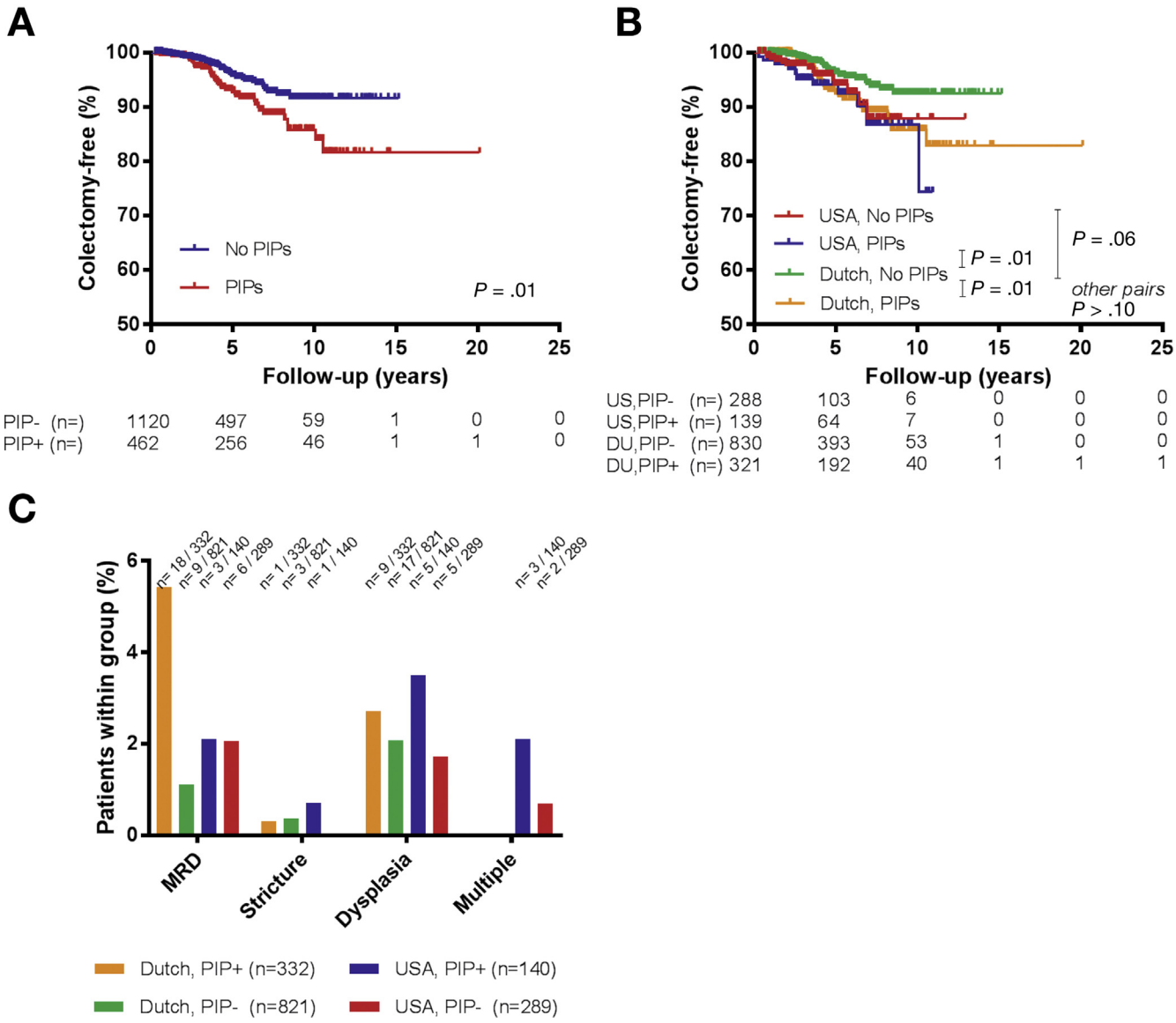

Figure 4. Kaplan-Meier curves and reasons for colectomy. (*A*) Time to Colectomy; (*B*) All Patients, Colectomy; (*C*) Reasons for Colectomy.

our cohort reflects a particularly high-risk population for ACRN, with a 14%–16% prevalence of PSC and the majority enrolled from tertiary IBD referral centers. Despite this enrichment of potential outcomes, we still did not find an independent association of PIPs with (A)CRN. The lower incidence of ACRN in recent compared with historical IBD cohorts might reflect improved management of patients with high inflammatory potential in our era of "treat-to-target" and "top-down" treatment paradigms. This is highly relevant to our study, because our findings indicate that PIPs are related to more severe and extensive inflammation. With a decreasing incidence of ACRN in most patients with IBD, the need for evidence-based risk factors to accurately identify high-risk patients only increases. Using a risk stratification model to guide surveillance intervals is less costly and equally effective as a program without risk stratification.[27]

In conclusion, the current practice of surveillance for CRN is resource intensive, costly, time consuming, inconvenient, and likely has a negative impact on the quality of life for patients with IBD. Appropriate categorization of patients with IBD according to their risk of CRC as part of an integrated surveillance program with intervals determined by an evidenced-based composite risk score should lower costs, optimize resource use, and maximize patients' quality of life. PIPs have had a reputation of being an ominous risk factor for developing CRN. Our findings should provide some degree of reassurance for clinicians and patients that PIPs are not, in themselves, the worrisome lesions they once were considered. Our data suggest that PIPs are not independently associated with increased risk of any degree of CRN at intermediate-term follow-up, an observation that should be considered in developing future IBD colonoscopic surveillance guidelines.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.11.067.

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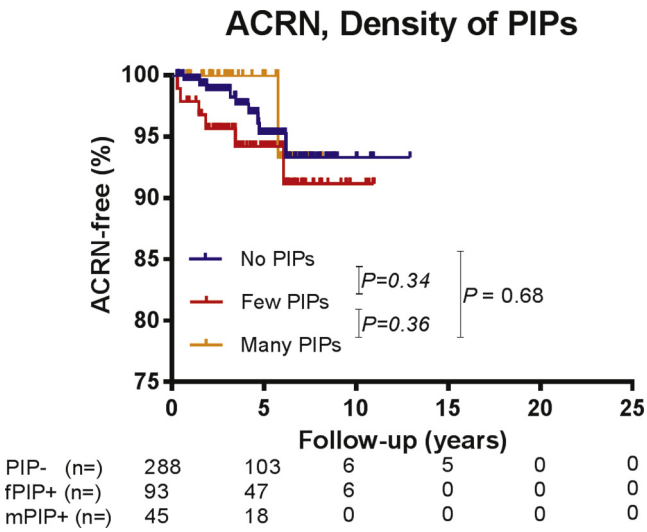
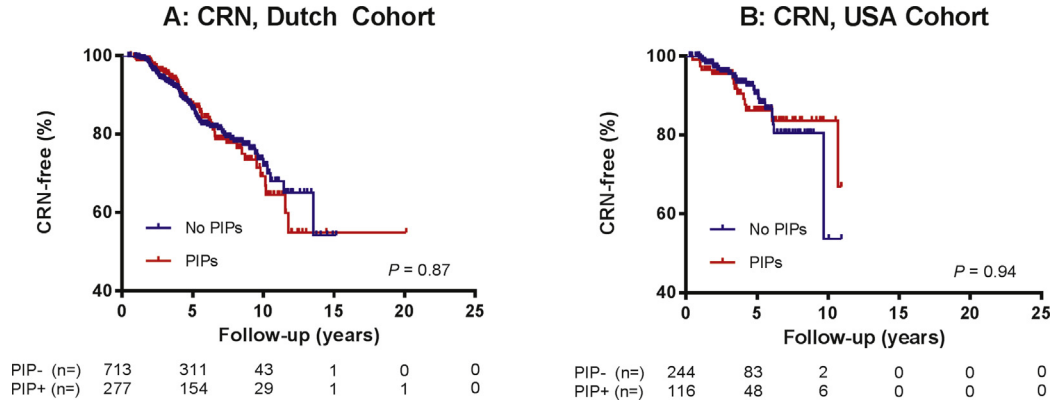
Author contributions: Remi Mahmoud designed the study, performed statistical analysis, and drafted the manuscript. Shailja C. Shah designed the USA database; contributed to data entry, statistical analysis, and study design; and drafted the manuscript. Joana Torres designed the USA database, contributed to data entry, and reviewed the manuscript. Joren R. ten Hove contributed to study design and analysis and reviewed the manuscript. Erik Mooiweer designed the Dutch database and reviewed the manuscript. Jason Glass, Jordan Elman, Akash Kumar, Jordan Axelrad, and Daniel Castaneda contributed to data collection and reviewed the manuscript. Thomas Ullman and Jean-Frederic Colombel reviewed the manuscript and provided important intellectual contributions. Bas Oldenburg and Steven H. Itzkowitz supervised the study and provided important contributions to all aspects of this project. The Dutch Initiative on Crohn and Colitis contributed to the identification and data entry of eligible patients in the Netherlands.

Conflicts of interest
Remi Mahmoud, Shailja C. Shah, Joren R. ten Hove, Erik Mooiweer, Daniel Castaneda, Jason Glass, Jordan Elman, Akash Kumar, Jordan Axelrad, and Steven H. Itzkowitz have no disclosures. Joana Torres has served as a consultant for Takeda and received speaker fees from Takeda, AbbVie, and Ferring. Thomas Ullman has served as consultant for Salix/Valeant and for Janssen. Jean-Frederic Colombel has served as consultant, advisory board member, or speaker for AbbVie, Amgen, Boehringer-Ingelheim, Celgene Corporation, Celltrion, Enterome, Ferring, Genentech, Janssen and Janssen, Lilly, Medimmune, Merck & Co, Pfizer, PPM Services, Protagonist, Second Genome, Seres, Shire, Takeda, Theradiag, and Theravance Biopharma; has stock options in Intestinal Biotech Development, and Genfit; and has received research grants from AbbVie, Takeda, and Janssen and Janssen. Bas Oldenburg has served as consultant for MSD, Takeda, AbbVie, Ferring, Cablon, and Janssen; received unrestricted grants from AbbVie, Ferring, Dr Falk, MSD, Takeda, and Janssen; and received speakers' fees from Ferring and MSD.



Supplementary Figure 1. Kaplan-Meier curves for ACRN-free survival according to density of PIPs in the USA cohort. fPIP, few PIPs; mPIP, many PIPs.



Supplementary Figure 2. Kaplan-Meier curves for CRN-free survival in patients without prior dysplasia in the USA and Dutch cohorts.

Supplementary Table 1. Patient Characteristics and Follow-up Data Stratified by Cohort

	Dutch cohort (n = 1153)	USA cohort (n = 429)	*P* value
Baseline and disease-related characteristics			
Age at index colonoscopy (*y*), median (IQR)	46 (37–54)	42 (31–55)	.002[b]
Sex, n (%)			.74
Men	610 (52.9)	223 (52)	
Women	543 (47.1)	206 (48)	
IBD type, n (%)			.001[b]
UC	734 (63.7)	230 (53.6)	
CD	387 (33.6)	181 (42.2)	
IBD-U	32 (2.8)	18 (4.2)	
Family history of CRC, n (%)	52 (4.5)	41 (9.6)	<.0005[b]
Disease duration at index colonoscopy[a] (y), median (IQR)	15 (11–22)	14 (9–22)	.02[b]
Dysplasia at or before index colonoscopy, n (%)	163 (14.1)	69 (16.1)	<.0005[b]
LGD	96 (8.3)	29 (6.8)	
IND	20 (1.7)	25 (5.8)	
Unspecified	47 (4.1)	15 (3.5)	
Extensive disease, n (%)	1038 (91)	237 (64)	<.0005[b]
PSC, n (%)	165 (14.3)	69 (16.1)	.38
Medication exposure, n (%)			
5-Aminosalicylates	911 (79.0)	375 (87.4)	<.0005[b]
Thiopurines	495 (42.9)	245 (57.1)	<.0005[b]
Methotrexate	61 (5.3)	29 (6.8)	.26
Biologicals	133 (11.5)	188 (43.8)	<.0005[b]
Colonoscopic surveillance details			
Presence of PIPs, n (%)	322 (27.9)	140 (32.6)	.07
Procedures/y, median (IQR)	0.7 (0.5–0.8)	1.0 (0.7–1.3)	<.0005[b]
Mean inflammation score			
Endoscopic	1.33 (1.00–1.67)	1.75 (1.33–2.00)	<.0005[b]
Histologic	2.33 (2.00–2.80)	3.00 (2.33–3.50)	<.0005[b]
Cecum intubated (% procedures), mean (SD)[a]	97.8 (8.9)	98.2 (9.9)	.15
Adequate bowel preparation (% procedures), mean (SD)	86.7 (21.7)	87.7 (23.8)	.05[b]
Duration of follow-up (y), median (IQR)	5.1 (3.1–7.3)	4.1 (2.2–5.8)	<.0005[b]

SD, standard deviation.
[a]Patients with HGD at or before the index colonoscopy were excluded.
[b]Significant at $P < .05$ level.

Supplementary Table 2. Predictors of CRN by Cox Regression Analysis

		Univariable			Multivariable[e]		
Variable	CRN, n (%)	HR	95% CI	*P* value	aHR	95% CI	*P* value
Patients with CRN, N (%)	188 (100)						
Age at index colonoscopy	—	1.04	1.03–1.05	<.0005[f]	1.03	1.01–1.05	<.0005[f]
Male sex	111 (59.0)	1.39	1.04–1.86	.03[f]	1.36	1.00–1.84	.05[f]
Presence of PIPs[a]	64 (34.0)	0.92	0.66–1.28	.61	1.25	0.88–1.77	.21
PSC	32 (17.0)	1.28	0.87–1.88	.20	2.38	1.58–3.58	<.0005[f]
Number of surveillance colonoscopies	—	0.58	0.51–0.65	<.0005[f]	0.54	0.48–0.62	<.0005[f]
Disease duration at baseline	—	1.03	1.02–1.05	<.0005[f]	1.02	1.00–1.07	.03[f]
Exposure to biologicals	22 (11.7)	0.64	0.41–1.00	.05	0.66	0.41–1.06	.09
Extensive disease	156 (83.9)	0.69	0.47–1.02	.06	0.89	0.59–1.33	.57
Family history of CRC	14 (7.4)	1.50	0.87–2.58	.15			
Exposure to 5-aminosalicylates	167 (88,8)	1.26	0.80–1.99	.31			
Adequate bowel preparation	—	1.22	0.61–2.42	.57			
Mean histologic inflammation[b]	—	1.02	0.83–1.26	.87			
CD[c]	58 (30.9)	0.97	0.71–1.32	.83			
USA cohort[d]	36 (19.1)	0.89	0.62–1.29	.54			
Exposure to thiopurines	78 (41.5)	0.89	0.66–1.19	.42			
Cecum reached	—	0.66	0.15–2.88	.58			

NOTE. Patients with a history of colonic dysplasia were excluded.
[a]Time-changing covariate.
[b]Before CRN.
[c]Reference category: UC or IND-U.
[d]Reference category: Dutch cohort.
[e]Seventy-eight patients (5 CRN cases) were excluded because of missing values.
[f]Significant at $P < .05$ level.