# No Increased Risk of Colorectal Neoplasia in Patients With Inflammatory Bowel Disease and Postinflammatory Polyps

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**Background:** Patients with inflammatory bowel disease (IBD) who have postinflammatory polyps (PIPs) may have an increased risk of developing colorectal neoplasia. Current guidelines recommend an intensified surveillance strategy in these patients, although the evidence for this recommendation is conflicting. The aim of our study was to assess whether IBD patients with PIPs are at increased risk of colorectal neoplasia.

**Methods:** We established a retrospective cohort in a tertiary IBD center with IBD patients undergoing colorectal cancer (CRC) surveillance in the current era. We compared cumulative incidences of colorectal neoplasia since IBD diagnosis between patients with and without PIPs and corrected for confounders. Second, we compared the risk of receiving a colectomy.

**Results:** In our cohort with >22 years of median follow-up, 154 of 519 patients had PIPs. PIPs were associated with extensive disease (odds ratio [OR], 2.76; 95% confidence interval [CI], 1.61–4.42; $P < 0.001$) and with more severe inflammation at colonoscopy (OR, 3.54; 95% CI, 2.28–5.50; $P < 0.001$). After correction for confounders, the presence of PIPs was not associated with development of colorectal neoplasia (hazard ratio [HR], 1.28; 95% CI, 0.85–1.93; $P = 0.24$) or with development of advanced neoplasia (HR, 1.38; 95% CI, 0.52–3.68; $P = 0.52$). There was a higher risk of colectomy in patients with PIPs (HR, 3.41; 95% CI, 1.55–7.54; $P = 0.002$).

**Conclusion:** In this cohort, PIPs were associated with disease extent, inflammation, and higher rates of colectomy. However, the presence of PIPs was not associated with the development of neoplasia. These findings suggest that patients with PIPs may not need an intensified surveillance strategy.

**Key Words:** inflammatory bowel disease, postinflammatory polyps, colorectal cancer, neoplasia

## INTRODUCTION

Patients with inflammatory bowel disease (IBD) bear an increased risk of colorectal cancer (CRC).[1] Therefore, IBD patients undergo surveillance colonoscopies to detect and remove premalignant dysplastic lesions such as low-grade dysplasia (LGD) and high-grade dysplasia (HGD). This may

prevent progression to CRC and allow early detection of CRC, minimizing the morbidity and mortality associated with invasive cancer.[1] The leading European surveillance guideline recommends surveillance intervals based on risk stratification, categorizing IBD patients into low-, medium-, and high-risk groups based on several risk factors.[2] Likewise, the American Gastroenterological Association (AGA) recommends an increased surveillance frequency in patients with certain risk factors.[3] One of these risk factors includes the presence of postinflammatory polyps (PIPs), although evidence for PIPs as a risk factor for CRC in IBD patients is limited.

PIPs, commonly referred to as "pseudopolyps," are nonneoplastic lesions that look like polyps or loose mucosal tags. The overall prevalence of PIPs in IBD patients is estimated at 20%–40%. PIPs are the remnants of severe inflammation that are formed of stromal and epithelial components and inflammatory cells, and they are associated with longstanding IBD.[4–7] Patients with PIPs may be at increased risk of advanced neoplasia (ie, HGD or CRC), as PIPs may indicate longstanding severe inflammation, which is associated with an increased CRC risk. In addition, PIPs may mask otherwise visible and resectable dysplasia. It is considered unlikely that PIPs have a direct malignant potential.[5]

Case–control studies from previous decades showed a 1.9–2.5-fold increased CRC risk in patients with PIPs.[4, 6, 7] By contrast, a recent large retrospective cohort study did not find an increased advanced neoplasia risk in patients with PIPs, although the study did report an increased risk of undergoing

a (sub)total colectomy.[8] These conflicting data result in an ongoing debate regarding the necessity of an intensified surveillance strategy in patients with PIPs. Clarification of the risk of advanced neoplasia in patients with PIPs has important implications, as safe extension of surveillance intervals could reduce the high burden associated with frequent colonoscopies and may reduce health care costs.

In the present study we aimed to (1) assess whether IBD patients with PIPs are at increased risk of colorectal neoplasia, (2) determine whether PIPs are associated with an increased risk of (sub)total colectomy, and (3) identify factors associated with the development of PIPs.

## METHODS

### Study Design

We performed a retrospective single-center cohort study to determine (1) the cumulative risk of developing advanced neoplasia (ie, HGD or CRC) and colorectal neoplasia (ie, LGD, HGD, or CRC) and (2) the risk of colectomy in IBD patients with PIPs compared with patients without PIPs. In addition, we identified factors associated with the development of PIPs.

### Patient Selection

We established a cohort including all IBD patients in the IBD surveillance program at the Radboud University Medical Center. Patients were identified with an electronic search in the local endoscopy database. This search included key terms for "surveillance" and/or "colonoscopy" in combination with key terms for IBD ("ulcerative colitis," "Crohn's disease," "inflammatory bowel disease") or key terms for PIPs ("postinflammatory polyp," "pseudopolyp").

### Ethical Considerations

The study was approved by the medical ethical committee of the Radboud University Medical Center Nijmegen (2017–3645).

### Inclusion and Exclusion Criteria

After initial patient identification, all medical data from the identified patients were reviewed from patient charts by 2 authors (V.G. and M.J.). Inclusion criteria were as follows: (1) confirmed IBD diagnosis (Crohn's disease [CD], ulcerative colitis [UC], or IBD-unclassified [IBD-U]); (2) colonic disease of ≥8 years, or of any duration when diagnosed with concomitant primary sclerosing cholangitis (PSC); (3) having at least left-sided disease (UC) or involvement of >30% of the colonic surface (CD/IBD-U), or PSC with any disease extent; (4) receiving ≥1 surveillance colonoscopy between January 2012 and December 2017. Exclusion criteria included disease activity limited to the ileum (CD), familial CRC syndromes such as familial adenomatous polyposis or lynch syndrome, lack of any surveillance colonoscopy, and colorectal neoplasia before IBD diagnosis.

### Data Collection

The following baseline characteristics were extracted from the patients' medical charts: age, sex, diagnosis of concomitant PSC, and family history of CRC. Regarding IBD, we collected information on IBD type, age at IBD diagnosis, maximum disease extent, and IBD medication use including 5-aminosalicylic acid (5-ASA), thiopurines, methotrexate, and biologicals (anti–tumor necrosis factor, anti-$\alpha 4\beta 7$ integrin monoclonal antibody, or interleukin 12/interleukin 23 inhibitor). Extensive disease was defined as inflammation extending proximal to the splenic flexure in UC or colonic involvement of >50% in CD. Nonextended disease included left-sided UC or segmental CD with <50% colonic involvement. In addition, dates and outcomes of IBD colonoscopies were extracted. As adapted from the study of Mahmoud et al.,[8] a mean inflammation score, reflecting the average extent of inflammation at colonoscopies, was calculated by averaging the inflammation scores of all colonoscopies (no inflammation = 0, nonextensive inflammation = 1, extensive inflammation = 2). In view of our primary outcome, we extracted the date and type of colorectal neoplasia (indefinite for dysplasia, LGD, HGD, and CRC). Re-evaluation of dysplasia by a second pathologist is standard practice in our center, and therefore no histologic re-evaluation of the dysplasia diagnosis was performed for this study. For our secondary outcome, we extracted the date, type, and indication of colectomy. A colectomy was defined as either a subtotal (ie, a colectomy only leaving the rectum in situ) or a total colectomy. To compare outcomes based on the presence of PIPs, we reported the date and number of PIPs. Patients with a sporadic PIP (described as "a single" or "one" PIP) were considered patients without PIPs due to the lack of consequences in clinical practice. Per the study of Mahmoud et al.,[8] patients with PIPs were subclassified as having "many" PIPs if the colonoscopy reports described PIPs as "many," "fields," "limiting visibility," "PIPs throughout the whole colon," and/or if fields of PIPs were present on images and video recordings of colonoscopy procedures. In the absence of the abovementioned criteria for "many" PIPs, patients were subclassified as having "few" PIPs.

### Statistical Analysis

Descriptive statistics were used to describe the baseline characteristics. Continuous outcomes are presented as means and standard deviations if normally distributed and as medians with interquartile ranges (IQRs) if non–normally distributed. Baseline factors between patients with and without PIPs were compared using the chi-square test and independent *t* test. Missing data were regarded as the absence of a characteristic for categorical parameters; there were no missing data on continuous outcomes.

To compare cumulative incidences of colorectal and advanced neoplasia between patients with and without PIPs, we used Kaplan-Meier curves and log-rank analyses. Time to event was calculated from the moment of IBD diagnosis until neoplasia or censoring. Patients were censored at last follow-up surveillance colonoscopy or, if performed, at the moment of (sub)total colectomy, given the low subsequent CRC risk.[9]

We performed an additional analysis comparing the cumulative incidence of colorectal neoplasia and advanced neoplasia in patients with "no" PIPs vs "many" PIPs.

Subsequently, we used a Cox regression model to adjust for potential confounders impacting CRC risk. The following potential confounders were assessed: IBD type, sex, concomitant PSC, age at IBD diagnosis, maximum disease extent, medication use (categorized as 5-ASA, thiopurines, methotrexate, and biologicals), family history of CRC, and mean inflammation score. A potential confounder was included in the final model when the beta coefficient of the variable of interest (PIP yes/no) changed by ≥10%. Of note, PIP was included as a fixed factor in the multivariable model, as our aim was to investigate whether this factor increases colorectal neoplasia risk.

Next, we performed a sensitivity analysis including all potential confounders as fixed covariates in our Cox regression model, as all variables are known risk factors for CRC development.[2, 10–15]

Cumulative incidences of colectomy were compared using the log-rank test. Incidence rates were calculated as the number of cases per 1000 patient-years of follow-up. Logistic regression analysis was performed to identify factors associated with PIPs. Factors with a *P* value <0.1 were included in the multivariable logistic regression model. A *P* value of <0.05 was considered statistically significant. All analyses were performed using SPSS statistical software (version 22; IBM, Chicago, IL, USA).

## RESULTS

### Patient Selection

A total of 519 IBD patients were eligible for inclusion (Fig. 1). PIPs were present in 154/519 (29.7%) patients (Table 1). A total of 80/519 (15%) patients had "many" PIPs. The mean follow-up duration after IBD diagnosis was 21.6 (±10.7) years in patients with PIPs and 22.9 (±11.2) years in patients without PIPs. The total patient-years of follow-up was 11,424 years (3534 vs 7890 years). The mean time between colonoscopies from first surveillance colonoscopy was 2.4 (±1.3) vs 2.3 (±1.1) years in patients with and without PIPs, respectively (*P* = 0.50). The cecum was reached in 96.9% of colonoscopies in patients with PIPs and 95% of colonoscopies in patients without PIPs.

### Factors Associated With the Presence of PIPs

Baseline characteristics of patients with and without PIPs are shown in Table 1. Patients with PIPs more often had extensive disease (*P* < 0.001) and had a higher mean inflammation score (*P* < 0.001). Patients with "many" PIPs, especially, more often had extensive disease (75/80, 94%) compared with patients with "few" PIPs (55/74, 74%; *P* = 0.001) and patients with no PIPs (215/365, 59%; *P* < 0.001).

Multivariable logistic regression analyses identified extensive disease (odds ratio [OR], 2.76; 95% confidence interval [CI], 1.61–4.42; *P* < 0.001) and inflammation score (OR, 3.54; 95% CI, 2.28–5.50; *P* < 0.001) as independent factors associated with PIPs (Table 2).

## Association Between PIPs and Colorectal Neoplasia

### Association of PIPs with development of colorectal neoplasia

Thirty-six of 154 (23.4%) patients with PIPs were diagnosed with colorectal neoplasia during follow-up (27 LGD, 3 HGD, 6 CRC), compared with 65/365 (17.8%; 55 LGD, 3 HGD, 7 CRC) in the group without PIPs. This resulted in a cumulative incidence of colorectal neoplasia of 11.9% (PIPs) and 10.7% (no PIPs) after 20 years in both groups. The cumulative incidence of colorectal neoplasia was comparable between patients with and without PIPs (hazard ratio [HR], 1.28; 95% CI, 0.85–1.93; *P* = 0.24) (Fig. 2), and thus no association between PIPs and colorectal neoplasia development was found in univariable analysis. There was no association between PIPs and colorectal neoplasia in either UC (HR, 1.21; 95% CI, 0.73–2.00; *P* = 0.46) or CD (HR, 1.22; 95% CI, 0.57–2.64; *P* = 0.61). Similarly, multivariable analyses with confounder correction did not show an association between PIPs and colorectal neoplasia development. In our multivariable model, there were no confounders changing the *β* of PIPs >10%, not allowing entry of additional confounders in our final model in addition to PIPs. Moreover, our multivariable sensitivity analysis including all confounders found no association between PIPs and colorectal neoplasia development (HR, 1.08; 95% CI, 0.66–1.75; *P* = 0.76).

Subsequently, we performed an additional analysis classifying patients as having "no," "few," or "many" PIPs (Supplementary Fig. 1). Univariable analysis showed a higher cumulative incidence in patients with "many" PIPs compared with patients with "no" PIPs (HR, 1.68; 95% CI, 1.05–2.70; *P* = 0.03). However, after adjustment for all confounders, no association between "many" PIPs and colorectal neoplasia was found (HR, 1.46; 95% CI, 0.82–2.63; *P* = 0.20).

### Association of PIPs with development of advanced neoplasia

The cumulative incidence of advanced neoplasia was 2.7% and 1.7% after 20 years in patients with and without PIPs, respectively. The cumulative incidence of advanced neoplasia was comparable between patients with and without PIPs (HR, 1.93;
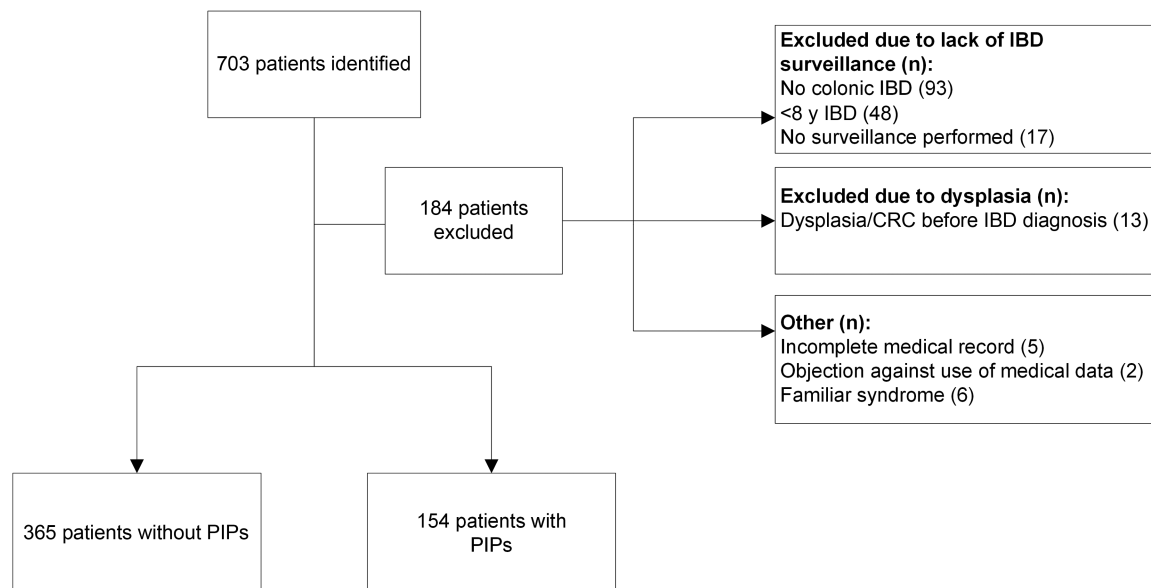
FIGURE 1. Flowchart of patient inclusion.

**TABLE 1.** Baseline Characteristics of Included IBD Patients With and Without PIPs

| Characteristic | Patients With PIPs (n = 154) | Patients Without PIP (n = 365) | *P* |
|---|---|---|---|
| Male sex, No. (%) | 73 (47.4) | 211 (57.8) | 0.27 |
| Disease, No. (%) | | | 0.19 |
|    Ulcerative colitis | 87 (56.5) | 179 (49.0) | |
|    Crohn's disease | 63 (40.9) | 180 (49.3) | |
|    IBD-unclassified | 4 (2.6) | 6 (1.6) | |
| Age at IBD diagnosis, mean (±SD), y | 28.5 (±11.8) | 28.9 (±12.4) | 0.74 |
| Family history of CRC, No. (%) | 26 (16.9) | 48 (13.2) | 0.27 |
| Concomitant PSC, No. (%) | 9 (5.8) | 18 (4.9) | 0.67 |
| Extensive disease, No. (%) | 130 (84.4) | 215 (58.9) | <0.001 |
| Follow-up after IBD diagnosis, mean (±SD), y | 21.6 (±10.7) | 22.9 (±11.2) | 0.20 |
| Mean (±SD) inflammation score during follow-up | 0.74 (±0.41) | 0.39 (±0.47) | <0.001 |
| Mean cecal intubation rate (±SD) | 96.9 (±8.1) | 95.0 (±14.4) | 0.12 |

**TABLE 2.** Factors Associated With the Presence of PIPs

| Baseline | OR Univariable | 95% CI | *P* | OR Multivariable (Final Model) | 95% CI | *P* |
|---|---|---|---|---|---|---|
| Ulcerative colitis | 1.41 | 0.96–2.06 | 0.08 | 1.25 | 0.83–1.88 | 0.29 |
| Male sex | 1.24 | 0.85–1.80 | 0.28 | | | |
| PSC | 1.20 | 0.53–2.73 | 0.67 | | | |
| Extensive disease | 3.78 | 2.33–6.12 | <0.001 | 2.67 | 1.61–4.42 | <0.001 |
| Higher age at IBD diagnosis | 1.00 | 0.98–1.01 | 0.74 | | | |
| Inflammation score | 4.53 | 2.97–6.93 | <0.001 | 3.54 | 2.28–5.50 | <0.001 |

95% CI, 0.78–4.75; *P* = 0.15) (Fig. 3). This applied for both UC (HR, 1.56; 95% CI, 0.50–4.87; *P* = 0.44) and CD (HR, 2.38; 95% CI, 0.53–10.69; *P* = 0.26). In multivariable analysis, concomitant PSC and the mean inflammation score changed the β of PIPs more than 10%, and these factors were therefore included as confounders. This resulted in an adjusted HR of PIPs of 1.38 (95% CI, 0.52–3.68; *P* = 0.52). In our multivariable sensitivity analysis, with inclusion of all confounders, the presence of PIPs remained not associated with development of advanced neoplasia (HR, 1.26; 95% CI, 0.42–3.74; *P* = 0.68).

Subsequently, in the analysis comparing patients with "no," "few," or "many" PIPs (Supplementary Fig. 2), the cumulative incidence of advanced neoplasia in patients with "many" PIPs compared with patients with "no" PIPs was comparable in both univariable (HR, 2.49; 95% CI, 0.90–6.87; *P* = 0.08) and multivariable sensitivity analyses (HR, 1.83; 95% CI, 0.59–6.86;

*P* = 0.37). Likewise, there was no difference between "many" and "few" PIPs (HR, 1.84; 95% CI, 0.46–7.41; *P* = 0.39).

## Risk of Colectomy

Of the patients with PIPs, 16/154 (10.4%) underwent a (sub)total colectomy, vs 10/365 (2.7%) in patients without PIPs. The cumulative incidence rate of colectomy was higher in patients with PIPs (HR, 3.41; 95% CI, 1.55–7.54; *P* = 0.002) (Fig. 4). Reasons for (sub)total colectomy in patients with PIPs were as follows: inflammation (n = 8), dysplasia (n = 4), CRC (n = 1), stenosis (n = 2), perforation at colonoscopy (n = 1); and in patients without PIPs: inflammation (n = 4), dysplasia (n = 3), CRC (n = 1), stenosis (n = 1), B-cell lymphoma (n = 1) (Supplementary Fig. 3).

Of all patients with CRC (n = 13), 4 patients received a (sub)total colectomy, 2 a hemi-colectomy, 5 a rectosigmoid resection, 1 an endoscopic removal of a T1 CRC, and 1 patient received palliative treatment.

## DISCUSSION

In this cohort study including 519 patients with colonic IBD undergoing CRC surveillance, we found no association between PIPs and the development of colorectal and advanced neoplasia. PIPs were associated with more extensive disease and higher inflammation scores at follow-up colonoscopies. Furthermore, we found that IBD patients with PIPs were more likely to undergo colectomy.

Current guidelines recommend an intensified surveillance strategy in patients with PIPs.[2, 16] However, the evidence for this recommendation is limited, as it is based on a few studies from previous decades that reported on risk factors for CRC in general. Two case–control studies reported that patients with UC and PIPs had 2.1- and 2.5-fold higher odds of developing colorectal neoplasia and advanced neoplasia,
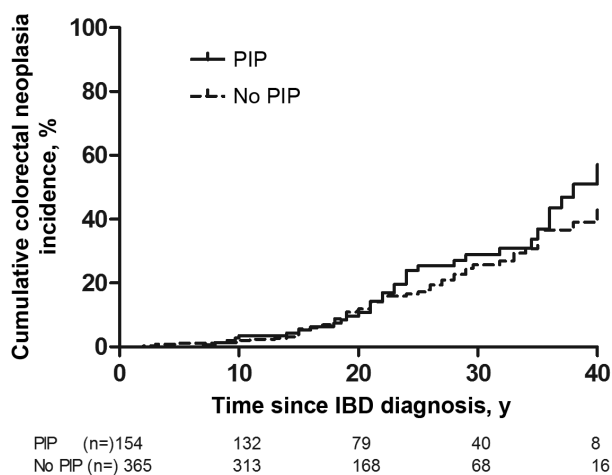


| PIP | (n=)154 | 132 | 79 | 40 | 8 |
| No PIP | (n=) 365 | 313 | 168 | 68 | 16 |

FIGURE 2. Cumulative incidence of colorectal neoplasia in patients with PIPs vs patients without PIPs.



| PIP | (n=)154 | 136 | 83 | 45 | 12 |
| No PIP | (n=) 365 | 316 | 180 | 77 | 24 |
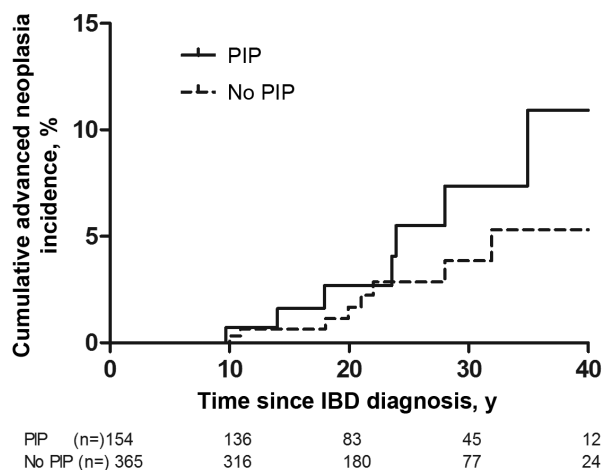
FIGURE 3. Cumulative incidence of advanced neoplasia in patients with PIPs vs patients without PIPs.



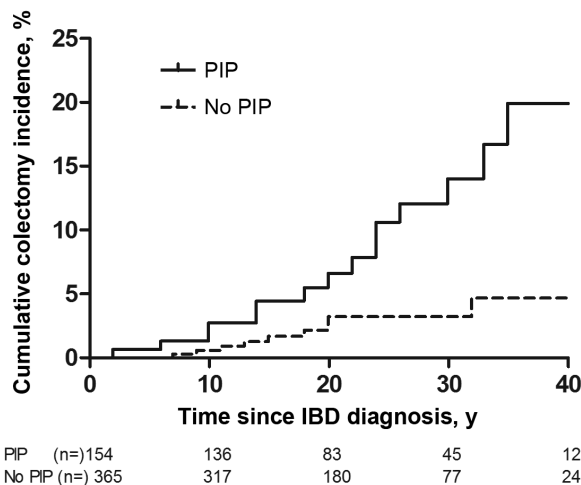| PIP | (n=)154 | 136 | 83 | 45 | 12 |
| No PIP | (n=) 365 | 317 | 180 | 77 | 24 |

FIGURE 4. Cumulative incidence of colectomy in patients with PIPs vs patients without PIPs.

respectively. However, these results were not corrected for the presence of inflammation at follow-up colonoscopies. Furthermore, these results may not be representative for the current era with improved endoscopic visualization techniques and surveillance strategies. A case–control cohort study from 2011, including 565 CD and UC patients undergoing surveillance, reported a 1.92-fold higher rate of CRC in patients with PIPs.[4, 6, 7] By contrast, a more recent, large retrospective multicenter study did not find an increased risk of advanced neoplasia compared with patients without PIPs.[8] These findings are supported by another study not reporting PIPs as an independent risk factor for advanced neoplasia development in patients with UC and LGD.[17]

In line with the 2 most recent studies, we did not identify an association between PIPs and colorectal neoplasia or advanced neoplasia development. However, univariable analysis showed an increased cumulative colorectal neoplasia incidence in IBD patients with large fields of PIPs compared with patients without PIPs (HR, 1.68; $P = 0.03$). One can speculate that these large fields of PIPs indicate severe inflammation, resulting in an increased colorectal neoplasia risk. Indeed, we found that higher inflammation scores and extensive disease are associated with the presence of PIPs. In addition, inadequate visualization of the entire colonic mucosa may hamper detection of true neoplastic lesions among the fields of PIPs and consequently may lead to an increased advanced neoplasia risk, as these neoplastic lesions may progress to CRC when not removed.[5, 7] However, after adjustment for all confounders in multivariable analyses, no association was found between "many" PIPs and colorectal neoplasia development (HR, 1.46; $P = 0.20$) or advanced neoplasia development (HR, 1.83; $P = 0.37$). The findings of our study suggest that the presence of PIPs alone is insufficient reason for an intensified surveillance strategy. Alternatively, the severity of inflammation during the disease course may be more accurate for risk stratification. Indeed, previous studies reported a strong association between the severity of inflammation and the development of neoplasia.[8, 18] Prospective studies are needed to support our findings and aid in clinical decision-making on endoscopic surveillance intervals.

The strengths of our study include the rigorous collection of data of patients undergoing surveillance and adjustment of our results for important confounders like inflammation during follow-up, concomitant PSC, and the extent of disease. The setting of an IBD population undergoing CRC surveillance in the current era makes our cohort representative for clinical practice. Moreover, we established a relatively large cohort including >500 IBD patients with >100 cases of neoplasia. However, there are also some limitations to this study that should be addressed. First, the retrospective study design brings some limitations, such as the absence of a standardized surveillance interval. However, there was no difference in mean time between subsequent colonoscopies between patients with and without PIPs. In addition, there was

no standardized reporting of PIPs. Although unlikely, there might be misclassification of PIPs, as other lesions might have been regarded as PIPs incorrectly. However, classification of PIPs by an endoscopist is often reliable, as demonstrated by the good interobserver agreement between pathologists and endoscopists.[19] To further reduce misclassification, we combined data from pathology reports, endoscopy reports, and endoscopy images/videos. Second, selection bias might be present, as this is a single-center study in a tertiary referral center, with in general a trend toward more complex IBD phenotypes. Third, due to the lower incidence of advanced neoplasia, one can hypothesize that there is a lack of power to detect a significant difference for advanced neoplasia. However, our findings correspond with the results of recently published studies that also found a higher colectomy rate but no association between PIPs and advanced neoplasia.[8] We acknowledge that the higher colectomy rate in patients with PIPs may have resulted in a lower CRC risk. However, this finding reflects current clinical practice in which PIPs are outcomes of severe inflammation, thus resulting more frequently in a colectomy.

In conclusion, in a well-characterized cohort of IBD patients undergoing CRC surveillance in the current era, PIPs were not associated with development of colorectal neoplasia. These findings add to the growing body of evidence suggesting that IBD patients with PIPs may not require an intensified surveillance strategy.

## SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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