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▶ **To cite this version:**

Julien Kirchgesner, Magali Svrcek, Guillaume Le Gall, Cécilia Landman, Xavier Dray, et al.. Nancy Index Scores of Chronic Inflammatory Bowel Disease Activity Associate With Development of Colorectal Neoplasia. Clinical Gastroenterology and Hepatology, 2020, 18 (1), pp.150-157.e1. 10.1016/j.cgh.2019.05.002 . hal-03347328

HAL Id: hal-03347328

https://hal.sorbonne-universite.fr/hal-03347328

Submitted on 17 Sep 2021

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Nancy Index Scores of Chronic Inflammatory Bowel Disease Activity Associate With Development of Colorectal Neoplasia

Short title: Neoplasia after colonoscopic surveillance in IBD

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Financial support: None.

Abbreviations used in this paper: IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; CRN: colorectal neoplasia; PSC: primary sclerosing cholangitis; CRC: colorectal cancer.

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Competing interests: The authors disclose the following: Xavier Dray has received consulting fees from Medtronic GI Solutions and Life Parterns Europe, and travel fees from Biocodex, Ferring, Hospira, and MSD. Anne Bourrier has received lecture fees from UCB. Harry Sokol has received consulting fees from Enterome, Astellas, Roche, Merck, Maat and Danone. Philippe Seksik has received consulting fees from Abbvie, Merck-MSD, and Biocodex, grants from Biocodex. Jacques Cosnes has received lecture fees from Abbvie, consulting fees from Vifor Pharma. Laurent Beaugerie has received consulting fees from Abbott, lecture fees from Abbott, Abbvie, MSD, Ferring Pharmaceuticals, Janssen, and research support from Abbott, Biocodex and Ferring Pharmaceuticals. Julien Kirchgesner, Magali Svrcek, Guillaume Le Gall, Cécilia Landman, Isabelle Nion-Larmurier, Nadia Hoyeau and Jean-François Fléjou disclose no conflicts.

Author contributions: J.K.: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript and statistical analysis. M.S.: study concept and design, acquisition of data, analysis and interpretation of data and critical revision of manuscript for important intellectual content. G.L.G, C.L., X.D., A.B., I.N.L., N.H., H.S., P.S. and J.C.: critical revision of manuscript for important intellectual content. J.F.F.: study concept and design, analysis and interpretation of data, critical revision of manuscript for important intellectual content. L.B.: study concept and design, analysis and interpretation of data, critical revision of manuscript for important intellectual content, and study supervision. All authors have approved the final draft submitted.

Acknowledgments: The authors would like to thank Mathieu Uzzan and Andrew Wisniewski for their comments on the manuscript.

List of collaborators of the Saint Antoine IBD Network: Lionel ARRIVE, Laurent BEAUGERIE, Anne BOURRIER, Marine CAMUS, Najim CHAFAI, Edouard CHAMBENOIS, Ulriikka CHAPUT, Clotilde DEBOVE, Charlotte DELATTRE, Xavier DRAY, Jean-François FLEJOU, Guillaume LE GALL, Nadia HOYEAU, Julien KIRCHGESNER, Cécilia LANDMAN, Jérémie LEFEVRE, Philippe MARTEAU, Chloé MARTINEAU, Laurence MONNIER-CHOLLEY, Violaine OZENNE, Yann PARC, Philippe SEKSIK, Harry SOKOL, Magali SVRCEK, Emmanuel TIRET.

Body text word count: 3978 words including references, figures and tables.

Abstract

Background & Aims: The degree of histological and endoscopic disease activity has been associated with an increased risk of colorectal neoplasia (CRN) in patients with inflammatory bowel diseases (IBD), but no histological scoring systems have been validated for determining risk of CRN. We investigated the association between histological and endoscopic disease activity and risk of first CRN in patients with IBD who had negative findings from a surveillance colonoscopy.

Methods: We performed a retrospective analysis of consecutive patients who underwent at least 2 colonoscopies at Saint Antoine Hospital in France from January 1, 1996 through March 1, 2015 and whose first procedure was a surveillance colonoscopy. Histological IBD activity was assessed by the Nancy histological index. Patients were followed for a mean 5.7±3.3 years. Logistic regression and generalized estimating equations were used to identify clinical, endoscopic and histologic factors associated with detection of neoplasia in the inflamed colon mucosa.

Results: Among 398 patients who underwent 1277 colonoscopies, we identified 45 patients with CRN. Factors associated with CRN were primary sclerosing cholangitis (odds ratio [OR], 2.65; CI 95%, 1.06-6.61; p=0.04), age (OR per 1-year increase, 1.04; CI 95%, 1.01-1.07; p=0.003) and mean Nancy histological index during follow-up (per 1-unit increase, OR, 1.69; CI 95%, 1.29-2.21; p<0.001). After adjustment for established factors, chronic disease activity defined as detection of ulcerations at more than 50% of colonoscopies was not associated with an increased risk of CRN (OR, 1.24; CI 95%, 0.53-2.91; p=0.62).

Conclusions: In addition to established risk factors, we associated Nancy histological index scores with development of CRN. Histologic findings based on the Nancy histological index should therefore be included in determining risk of colonic neoplasia in patients with IBD.

Keywords: colon cancer, prognostic factor, ulcerative colitis, Crohn's disease

Introduction

Inflammatory bowel disease (IBD) includes Crohn's disease (CD) and ulcerative colitis (UC). Patients with IBD are at increased risk of colorectal neoplasia.[1] The risk of colorectal neoplasia appears to be the same in UC and CD after adjustment for disease duration and extent of colitis.[2–4] This risk is mainly related to disease duration, extent of colitis and presence of primary sclerosing cholangitis (PSC).[5] Additional potential risk factors include first-degree family history of colorectal cancer (CRC), colonic strictures and pseudopolyps.[6,7] Thus, the degree of histological and endoscopic disease activity was variously associated with colorectal neoplasia,[7–11] but the lack of histological disease activity assessment based on a validated scoring system may affect the generalization of these findings.[12]

Surveillance colonoscopy programs rely on a baseline surveillance colonoscopy performed after a disease duration according to the presence of PSC.[1] Interval between surveillance colonoscopies is based on expert consensus and defined according to risk factors assessed in the whole IBD population.[13] However, risk factors of colorectal neoplasia were rarely assessed in IBD patients from the time of a surveillance colonoscopy negative for neoplasia. Identification of risk factors in this context may be the most appropriate for clinicians in order to assess the proper interval between surveillance colonoscopies, stratify the risk for colorectal neoplasia and adopt a personalized approach. The aim of our study was to assess the impact of histological and endoscopic disease activity on the risk for first colorectal neoplasia in IBD patients after a surveillance colonoscopy negative for neoplasia.

Patients and methods

Patients selection

All consecutive IBD patients who underwent at least two colonoscopies at Saint-Antoine Hospital between 1st January 1996 and 1st March 2015, and whose first procedure was a surveillance colonoscopy were identified through Saint Antoine Hospital's pathology department database. IBD diagnosis was based on clinical, endoscopic and pathological criteria. Patients with a history of colorectal neoplasia, presence of colorectal neoplasia at first surveillance colonoscopy or an interval between the first and last colonoscopy shorter than six months were excluded. Since neoplasia occurring in an area of active colitis has not the same significance as a polypoid adenoma developing outside an area of active colitis,[14,15] patients with sporadic adenomas were excluded. Lesions were defined as sporadic adenomas in case of raised lesions developed outside an area with previous or current inflammation based on imaging, endoscopy, and histology. In our center, patients were traditionally offered annual to triannual 5-year interval surveillance colonoscopies, according to risk factors, from 8 to 10 years after onset of IBD symptoms. Surveillance colonoscopy protocols (high-definition colonoscopy, chromoendoscopy or white-light endoscopy with 4 random biopsies every 10 cm, plus targeted biopsies) [13,16] were assessed using the Saint Antoine Hospital's pathology department database and endoscopic electronic medical records. Date of cohort entry was the date of first surveillance colonoscopy negative for colorectal neoplasia at Saint-Antoine hospital. Patients were followed until the last colonoscopy negative for neoplasia, first colonoscopy with neoplasia, total proctocolectomy or death.

Neoplasia diagnosis

Every biopsy was classified according to the Vienna classification;[17] lesion negative for dysplasia; indefinite for dysplasia; low-grade dysplasia; high-grade dysplasia and adenocarcinoma. If several neoplastic lesions were identified during the same procedure, the most severe lesion was included for the analysis. Lesions were classified as endoscopically visible and non-visible lesions [16] and localization was assessed. Diagnosis and classification of dysplasia were confirmed by a second expert gastrointestinal pathologist.[18]

Data collection

Variables were collected from the SUVIMIC registry (a prospective clinical database of all patients with IBD evaluated by Saint-Antoine Hospital digestive disease medical staff), endoscopic and medical records, and the Saint-Antoine Hospital's pathology department database.

The following variables were collected at cohort entry: gender, IBD type (indeterminate colitis cases were analyzed with the ulcerative colitis group), date of IBD diagnosis, disease extent, occurrence of digestive surgery during follow-up (subtotal colectomy and ileorectal anastomosis, segmental colectomy, ileocecal resection), concurrent diagnosis of PSC and family history of CRC defined as any first degree relative having a diagnosis of CRC. Disease extent was categorized as follows: pancolitis, extensive colitis (as defined by a proportion of the colonic mucosal area macroscopically or microscopically affected by disease > 50%) and non-extensive colitis (left colitis or right colitis for CD patients).

Treatment exposure was assessed for 5-aminosalicylates, thiopurines (azathioprine or mercaptopurine), methotrexate at cohort entry (first surveillance colonoscopy negative for neoplasia) and at last colonoscopy (neoplasia occurrence or end of follow-up).

Patients were considered treatment exposed when the therapeutic agents was taken for at least 6 months. Anti-tumor necrosis factor agents (anti-TNFs) were not assessed, since the follow-up period precede the marketing authorization of anti-TNFs and treatment exposure was only assessed at entry and end of follow-up.

Endoscopic and histological variables were assessed for each colonoscopy, and considered as positive when present, irrespective of the localization or number of biopsies affected. Endoscopic findings reported during colonoscopy included ulcerations, pseudopolyps and colonic strictures. The analyzed histological variables included: (i) the presence of chronic inflammatory infiltrate defined by lymphocytes, plasmocytes, or eosinophils in the lamina propria; (ii) the presence of acute inflammatory cell infiltrate defined by neutrophils in the lamina propria, in epithelium or the destruction of crypt by neutrophils; (iii) the presence of ulceration. The Nancy histological index was assessed for each colonoscopy (Figure 2).[19]

Statistical analysis

In order to assess the association between colorectal neoplasia risk and duration of histological and endoscopic disease activity, the impact of maximal and chronic histological and endoscopic disease activity were assessed. Occurrence of endoscopic disease activity variables were classified in two categories: 1) Ulcerations on at least one procedure; 2) Ulcerations on more than 50% of procedures during follow-up. Histological disease activity was classified as maximal Nancy histological index found in any of colonoscopies performed and mean Nancy histological index (defined as the sum of all Nancy histological index obtained from all colonoscopies performed divided by the total number of colonoscopies performed).

Continuous data are expressed as mean (standard deviation), and differences between groups were tested for significance by Student’s t–test or Wilcoxon test if

appropriate. Discrete data are given as percentages, and comparisons were made with Pearson's χ2 test or Fisher's test if appropriate**.** We considered differences to be statistically significant when the *P* value was <0.05 (all tests were two sided). Cumulative incidence of colorectal neoplasia was assessed in the whole cohort. Logistic regression was used to assess the relationship of clinical, endoscopic and histological variables to the risk of colorectal neoplasia. Variables significant at *P* < 0.20 were entered into a multivariate logistic regression model to assess the strength of the associations while controlling for possible confounding variables. Subgroups analyses according to IBD phenotype were performed.

Additionally, generalized estimating equations (GEE) were conducted to assess the impact of endoscopic and histological disease activity during any procedure on the risk of neoplasia. The binomial distribution with an exchangeable covariance structure was specified for repeated colonoscopies. Several sensitivity analyses were also performed in order to assess the robustness of the results. First, we excluded patients with ileo-rectal anastomosis at cohort entry because of a reduced mucosa surface at risk for colorectal neoplasia Second, we excluded patients with lesion indefinite for dysplasia. Analyses were carried out using SAS version 9.4 (Cary, NC).

Results

Patient Characteristics

Seven hundred and twenty six patients underwent at least two colonoscopies at Saint-Antoine Hospital between 1st January 1996 and 1st March 2015. Seventy-one had a history of colorectal neoplasia or colorectal neoplasia occurrence at first colonoscopy and the interval between first and last colonoscopy was shorter than six months for 31 patients. One hundred and thirty-five patients did not perform surveillance colonoscopy and no further colonoscopy was performed after surveillance colonoscopy for 85

patients. Among 51 patients with occurrence of neoplasia, neoplastic lesions were located outside an area of active colitis in 6 patients. The six lesions identified outside an area of active colitis were all adenomas with low-grade dysplasia.

Finally, 398 patients with a first surveillance colonoscopy negative for colorectal neoplasia and at least one follow up colonoscopy constituted the study population, including 45 patients with neoplasia in an area of active colitis. (Figure 1) Mean follow-up was 5.7 (SD 3.3) years. A total of 1137 and 140 colonoscopies were performed among patients without and with neoplasia, respectively. Among the 879 colonoscopies performed after the first surveillance colonoscopy, 721 (82.0%) were surveillance colonoscopies. The rates of cecal intubation rates was 93.6% (1195), 94.0% (1069) and 90.0% (126) in the overall cohort, patients without neoplasia during follow-up, and patients with neoplasia during follow-up, respectively. The vast majority of colonoscopies were performed after 2006 (81.7%, Supplementary Figure 1).

Patient characteristics at cohort entry are shown in Table 1. Overall, patients were predominantly female (n=217, 54.5%) and diagnosed with Crohn's disease (n=237, 59.5%). At cohort entry, mean age and disease duration were 40.3 (SD 13.3) and 12.2 (SD 7.9) years, respectively. Mean interval between two colonoscopies was 2.8 (SD 1.6) years, without statistically significant difference (P = 0.36) between groups (3.1 [SD 2.3] and 2.8 [SD 1.4] years in patients with and without neoplasia occurrence during follow-up, respectively). Treatment exposure status was similar at cohort entry and end of follow-up for 73.1%, 78.9%, and 91.2% regarding aminosalicylates, thiopurines, and methotrexate exposure, respectively. Rates of treatment modification between time of cohort entry and end of follow up were not different between patients with and without neoplasia.

In patients with colorectal neoplasia, 38 (84.4%) and 7 (15.6%) lesions were identified during surveillance colonoscopies and colonoscopies for disease activity assessment, respectively. Chromoendoscopy was used in 9 patients with surveillance colonoscopies (23.6%) and mostly performed after 2009 (70% of colonoscopies using chromoendoscopy). Among the 29 patients without chromoendoscopy, lack of chromoendoscopy was related to insufficient colonic preparation for 11 patients (37.9%), significant visible inflammation for 5 patients (17.2%) and obvious diagnosis of adenocarcinomas for one patient (3.4%).

Multifocal lesions were diagnosed in 10 patients. Among them, classification of colorectal neoplasia was similar for all lesions in 8 patients (6 lesions in low grade dysplasia and 2 lesions indefinite for dysplasia). The two remaining patients were diagnosed with adenocarcinoma, one had another lesion in low grade dysplasia and one another lesion in high grade dysplasia.

The cumulative incidence of neoplasia by disease duration was 2.2% (95% confidence interval (CI 95%) 1.0-4.1) at 10 years, 9.1% (CI 95% 6.0-13.1) at 20 years and 22.8% (CI 95% 15.7-30.8) at 30 years. Cumulative incidence of colorectal cancer was 0% at 10 years, 1.5% (CI 95% 0.4-4.1) at 20 years and 5.1% (CI 95% 1.9-10.9) at 30 years.

Predictors of neoplasia

By univariate analysis, age at last colonoscopy during follow-up, UC phenotype, and colonic stricture were associated with occurrence of first neoplasia (OR, 1.03; CI 95% 1.01-1.05 [per one year increase]; OR, 1.99; CI 95% 1.07-3.73; OR, 2.91; CI 95% 1.16-7.30, respectively) (Table 3). Regarding variables related to histological and endoscopic disease activity, mean and maximum Nancy histological index during follow-up were associated with the occurrence of neoplasia ([per one unit increase] OR, 1.62; CI 95% 1.27-2.06; OR, 1.29; CI 95% 1.03-1.61, respectively). Conversely,

treatment with thiopurines at the time of neoplasia occurrence or last colonoscopy was associated with a decreased risk of neoplasia (OR, 0.46; CI 95% 0.22-0.95). Because histological and endoscopic variables on at least one and more than 50% of procedures were significantly correlated to each other, only one of these variables was included in the multivariate analysis each time.

By multivariate analysis, age and PSC were significantly associated with colorectal neoplasia risk (OR, 1.04; CI 95% 1.01-1.07 [per one year increase]; OR, 2.65; CI 95% 1.06-6.61, respectively). Thiopurines exposure tends to be associated with an decreased risk of neoplasia occurrence, although not reaching statistical significance (OR, 0.55; CI 95% 0.25-1.21). (Table 3)

Mean Nancy histological index remained associated with an increased risk of neoplasia (OR, 1.69; CI 95% 1.29-2.21 [per one unit increase]), while maximum Nancy histological index reached statistical significance (OR, 1.30; CI 95% 1.03-1.64 [per one unit increase]). (Table 4) No significant association was found between neoplasia occurrence and endoscopic disease activity, defined by endoscopic ulcerations on at least one and on more than 50% of procedures (OR, 1.75; CI 95% 0.89-3.44; OR, 1.24; CI 95% 0.53-2.91, respectively). (Table 4) Results were consistent across IBD subtypes, although the impact of chronic endoscopic disease activity was numerically higher in patients with UC compared with CD. (Table 5)

Using multivariate generalized estimating equations modeling, a one point increase of the Nancy histological index was associated with an increased risk of neoplasia (OR, 1.04; CI 95% 1.02- 1.05). The odds ratio was 1.16 (CI 95% 1.09-1.24) per four points increase of the Nancy score during any procedures (i.e. histological ulcerations compared to the absence of chronic or acute inflammation cells infiltrate), while

presence of endoscopic ulcerations was also associated with an increased risk of neoplasia (OR, 1.08; CI 95% 1.02- 1.14).

In sensitivity analyses results remained unchanged after exclusion of patients with ileo-rectal anastomosis at cohort entry or exclusion patients with lesion indefinite for dysplasia (Supplementary Table 1). The number of patients with advanced neoplasia (defined as high-grade dysplasia or adenocarcinoma) was not sufficient to perform a multivariate analysis. By univariate analysis, mean Nancy histological index during follow-up was associated with the occurrence of advanced neoplasia ([per one unit increase] OR, 1.82 , CI95% 1.07-3.01).

Discussion

Our study demonstrates that the risk of first colorectal neoplasia in IBD patients after surveillance colonoscopy negative for neoplasia is associated with persistent histologically active disease assessed by the Nancy histological index, whereas no significant association between neoplasia occurrence and persistent endoscopically active disease defined as endoscopic ulcerations on more than 50% of procedures was observed. This is the first study using a validated histological activity score to assess the impact of histological disease activity on colorectal neoplasia.

A recent UK study reported significant associations between CRN and endoscopic inflammation.[11] However, the strength of association was generally weaker compared with outcomes based on histology, similarly as our study. The use of non-validated histological and endoscopic activity scores may also limit the generalization of these findings.[12] We used ulcerations as a surrogate marker of endoscopic disease activity, since validated endoscopic activity scores were not systematically reported in the endoscopic report. However, ‘ulcerations’ item is widely included in endoscopic disease activity scores.[13] Differences on the impact of endoscopic and

histological disease activity may be related to the accuracy between histological and endoscopic remission.[20]

We reported an association between chronic histological inflammation and colorectal neoplasia risk. The absence of differences in colonoscopy intervals between both groups allowed us to use mean Nancy histological index as a surrogate marker of histological chronic inflammation. The simplicity of its calculation and interpretation may ease its use in clinical practice. Several scores were developed to evaluate the risk of colorectal neoplasia by measuring the degree of histological disease activity,[8–11] but this is the first study using a validated score to assess its impact. It may help for the generalization of our findings and suggest the use of the Nancy histological index as a tool in the risk stratification strategy for colorectal neoplasia screening in IBD.

A one-point increase of the Nancy histological index was associated with an increased risk of colorectal neoplasia. Grade one of the Nancy histological index (presence of an increase in chronic inflammatory cells number that are easily apparent) on several subsequent biopsies may represent persistent histological disease. This was never considered so far as an independent factor of colorectal neoplasia risk, but Rubin et al. already suggested that a longer period of milder relapsing or chronically active disease did not confer the same risk compared to a short period of severe disease.[10] These results endorse the fact that mucosal healing, characterized by the resolution of crypt architectural distortion and significant inflammatory infiltrate,[18] is an important therapeutic goal. It also highlights the fact that histological disease activity assessed by the Nancy histological index may more accurately predict the risk of developing subsequent CRN compared to endoscopic disease activity.

Neither disease extent nor disease duration were associated with an increased risk of CRN. It may be related to the inclusion criteria with only patients undergoing surveillance colonoscopies, resulting in a vast majority of patients with long-standing extensive colitis at cohort entry. Similarly, a recent study did not report an increased risk of CRN associated with disease duration.[11] It may suggest that the predominant factor is persistent inflammation instead of disease duration itself. Discrepancies with old cohorts may be related to the modification of IBD management, with an increased use of immunosuppressants and higher proportion of patients having persistent remission.

Concurrent pseudopolyps were not associated with colorectal neoplasia risk. Several studies showed a positive association with pseudopolyps and colorectal neoplasia risk [6,21] and concluded that pseudopolyps are a surrogate marker for previous severe inflammation, which may be the risk factor for neoplasia. Our results suggest that the main histological driving factor is the duration of inflammation, whereas pseudopolyps can occur after one severe episode of inflammation. This could explain the absence of association between pseudopolyps and colorectal neoplasia in our study. Moreover pseudopolyps represent several types of lesions and the heterogeneity of pseudopolyps may explain differences observed between studies. Further characterization is needed to better understand the potential association with pseudopolyps and colorectal neoplasia risk.

We did not report a chemopreventive effect of aminosalicylates against colorectal neoplasia. It may be related to the inclusion of patients with Crohn's disease potentially not exposed to aminosalicylates. Our study provides further evidence of a chemopreventive effect of thiopurines against colorectal neoplasia. Assertion of a chemopreventive effect for this drug is still a matter of debate. Results from the

CESAME cohort suggest that thiopurines are only protective for a subset of patients with long-standing extensive colitis.[4] Our population is close to this definition and endorses the fact that thiopurines may be protective for this subset of IBD patients.

Several limitations of our study need to be addressed. First, endoscopic and histological variables were retrospectively collected from endoscopic electronic medical records and the Saint-Antoine Hospital's pathology department database. Future studies are required to prospectively assess the association between the colorectal neoplasia predictors identified in our study and colorectal neoplasia risk. Second, in this retrospective study, information on the procedures, such as bowel preparation quality, was often incomplete. Finally, patients were also included and followed in a tertiary referral center, which may impact the generalization of the results. However, the risk stratification strategy for colorectal neoplasia screening in IBD is well established and may be similar in non-referal and referral centers.

We included Crohn's colitis and ulcerative colitis patients in the same analysis. However, the risk of colorectal neoplasia appears to be the same in UC and CD after adjustment for disease duration and extent of colitis.[2–4] Moreover, the cumulative incidence of colorectal neoplasia in our cohort was comparable to historical data in ulcerative colitis.[15] We also used Nancy histological index in CD patients, since there is no fully validated histological scoring index for evaluation of Crohn's colitis activity.[22] Further studies are required to assess the accuracy between endoscopic and histological remission in CD since we reported a weaker association between chronic endoscopic disease activity and neoplasia occurrence in CD compared to UC.

We used treatment dispensed during more than six months at end of follow-up as a proxy for treatment exposure in univariate and multivariate analysis. However, treatment exposure at cohort entry and end of follow-up was similar for the vast

majority of patients. Patients with lesions indefinite for dysplasia were included, since these lesions modify the latter management of surveillance colonoscopy protocol and several studies suggest that a diagnosis of low-grade dysplasia versus indefinite for dysplasia does not predict etiological differences in disease progression.[15,23]

In conclusion, IBD patients undergoing endoscopic surveillance, the risk of first colorectal neoplasia is increased in case of persistence of histological acute inflammation and quiescent disease, assessed by the Nancy histological index. It suggests that the cumulative assessment of histological disease activity based on the Nancy histological index should be included in the risk stratification strategy for colorectal neoplasia screening in IBD.

Figure legends:

Figure 1. Study Population Flowchart

Figure 2. Algorithm of the Nancy histological index

Table 1. Patient characteristics at cohort entry

Table 2. Risk Factors of colorectal neoplasia: Univariate Analysis

Table 3. Risk Factors of colorectal neoplasia: Multivariate Analysis

Table 4. Endoscopic and histologic predictors of colorectal neoplasia according to IBD subtype: Multivariate Analysis

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Table 1. Patient characteristics at cohort entry

	Neoplasia n = 45	No neoplasia n= 353	Total N = 398
Male sex	25 (55.6)	156 (44.2)	181 (45.5)
Age at cohort entry (years)	45.4 (14.5)	39.6 (13.0)	40.3 (13.3)
Disease duration at cohort entry (years)	13.2 (8.7)	12.1 (7.8)	12.2 (7.9)
IBD phenotype			
Crohn's disease	20 (44.4)	217 (61.5)	237 (59.5)
Ulcerative colitis	25 (55.6)	136 (38.5)	161 (40.5)
Disease extension			
Pancolitis	23 (51.1)	171 (48.4)	194 (48.7)
Extensive colitis	16 (35.6)	134 (38.0)	150 (37.7)
Non-extensive colitis	6 (13.3)	48 (13.6)	54 (13.6)
Ileorectal anastomosis at cohort entry	4 (8.9)	23 (6.5)	27 (6.8)
Primary sclerosing cholangitis	9 (20.0)	41 (11.6)	50 (12.6)
Family history of CRC (first degree)	1 (2.2)	7 (2.0)	8 (2.0)
Colonoscopy interval (years)	3.1 (2.3)	2.8 (1.4)	2.8 (1.6)
No. of procedure per patient	3.1 (1.5)	3.2 (1.2)	3.2 (1.3)
Treatment exposure at cohort entry			
Aminosalicylates	19 (42.2)	158 (44.8)	177 (44.5)
Thiopurines	12 (26.7)	158 (44.8)	170 (42.7)
Methotrexate	3 (6.7)	25 (7.1)	28 (7.0)
Neoplasia			
Non-visible lesions	11 (24.5)		
Visible lesions	34 (75.5)		
Adenocarcinoma	7 (15.6)		
High-grade dysplasia	2 (4.4)		
Low-grade dysplasia	30 (66.7)		
Indefinite for dysplasia	6 (13.3)		

Results are expressed as mean (standard deviation) or number (%)

Table 2. Risk Factors of colorectal neoplasia: Univariate Analysis

	Odds ratio (CI 95%)	p
Age [a,b]	1.03 (1.01-1.05)	0.01
Male sex	1.58 (0.85-2.95)	0.15
Family history of CRC (first degree)	1.12 (0.14-9.35)	0.91
IBD phenotype, UC	1.99 (1.07-3.73)	0.03
IBD Disease duration [a,b]	1.01 (0.98-1.05)	0.59
Disease extension		
Non-extensive colitis	Ref	
Extensive colitis	0.96 (0.35-2.58)	0.82
Pancolitis	1.08 (0.41-2.79)	0.78
Primary sclerosing cholangitis	1.90 (0.86-4.23)	0.12
Current treatment during more than 6 months before neoplasia or end of follow-up		
Aminosalicylates	0.95 (0.51-1.77)	0.87
Thiopurines	0.46 (0.22-0.95)	0.04
Methotrexate	0.48 (0.06-3.70)	0.48
Endoscopic variables		
Colonic Strictures	2.91 (1.16-7.30)	0.02
Post-inflammatory polyps	0.69 (0.35-1.36)	0.28
Endoscopic ulcerations		
On more than 50% of colonoscopies	1.38 (0.63-3.04)	0.42
On at least one colonoscopy	1.65 (0.88-3.11)	0.12
Histological variables		
Mean Nancy histological index [c]	1.62 (1.27-2.06)	<0.001
Maximum Nancy histological index [c]	1.29 (1.03-1.61)	0.03

[a] per one year increase; [b] at neoplasia or end of follow-up; [c] per one unit increase

Table 3. Risk Factors of colorectal neoplasia: Multivariate Analysis

	Odds ratio (CI 95%)	p
Histological variables		
Mean Nancy histological index [a]	1.69 (1.29-2.21)	<0.001
Age [b,c]	1.04 (1.01-1.07)	0.003
Male sex	1.27 (0.64-2.52)	0.49
IBD phenotype, UC	1.73 (0.86-3.51)	0.13
Primary sclerosing cholangitis	2.65 (1.06-6.61)	0.04
Current treatment during more than 6 months before neoplasia or end of follow-up		
Thiopurines	0.55 (0.25-1.21)	0.14
Endoscopic variables		
Colonic Strictures	2.37 (0.84-6.75)	0.11

[a] per one unit increase; [b] at neoplasia or end of follow-up; [c] per one year increase

Table 4. Endoscopic and histologic predictors of colorectal neoplasia according to IBD subtype: Multivariate Analysis

	Inflammatory bowel disease		Ulcerative colitis		Crohn's disease	
	Odds ratio (CI 95%)	p	Odds ratio (CI 95%)	p	Odds ratio (CI 95%)	p
Histological variables						
Mean Nancy histological index [a]	1.69 (1.29-2.21)	<0.001	2.14 (1.39-3.29)	0.001	1.46 (1.01-2.11)	0.05
Maximum Nancy histological index [a]	1.30 (1.03-1.64)	0.03	1.31 (0.94-1.83)	0.11	1.28 (0.92-1.77)	0.14
Endoscopic variables						
Endoscopic ulcerations						
On more than 50% of colonoscopies	1.24 (0.53-2.91)	0.62	2.95 (0.86-10.1)	0.09	0.59 (0.15-2.42)	0.47
On at least one colonoscopy	1.75 (0.89-3.44)	0.11	1.88 (0.74-4.77)	0.18	1.58 (0.57-4.34)	0.38

[a] per one unit increase; adjusted for sex, age, primary sclerosing cholangitis, IBD phenotype, 5-aminosalicylates and thiopurines exposure, and colonic strictures

Figure 1. Study Population Flowchart

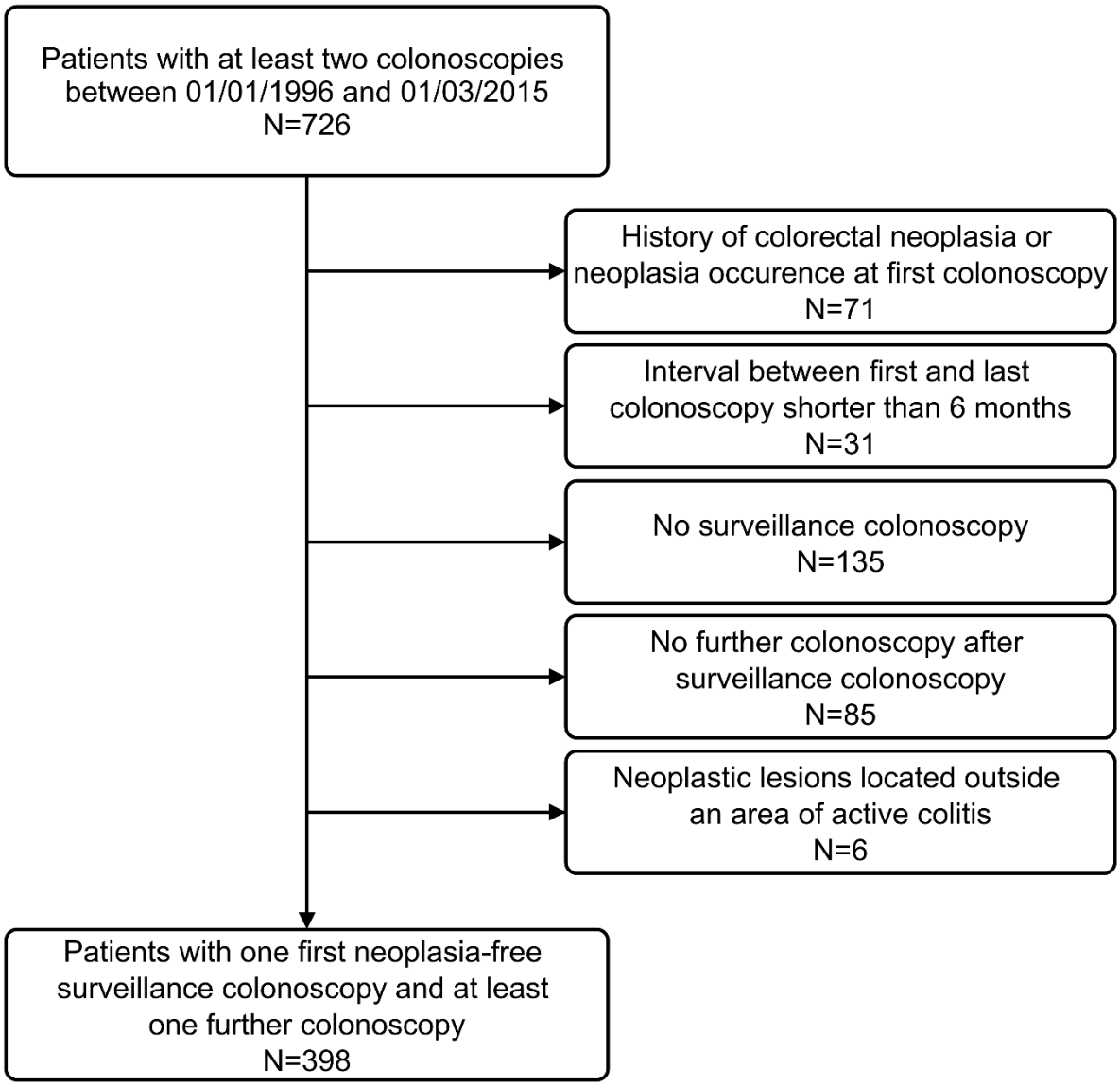
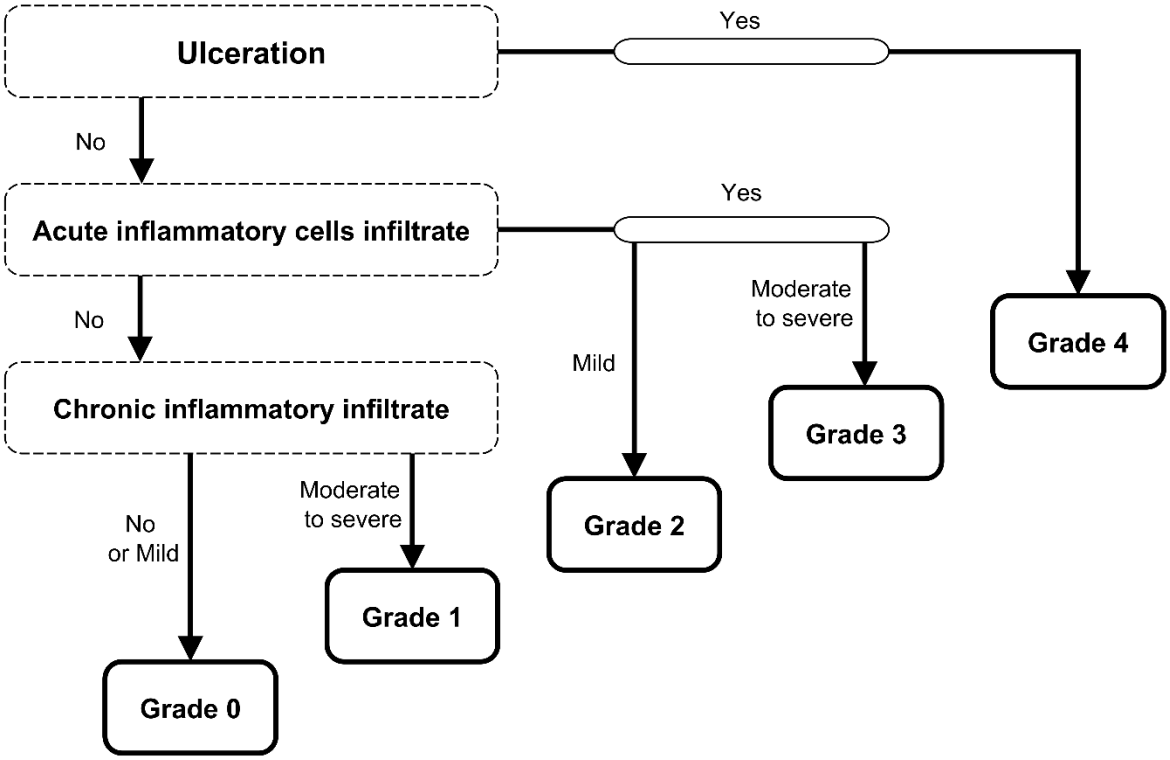


Figure 2. Algorithm of the Nancy histological index



Supplementary Material

Supplementary Table 1: Endoscopic and histologic predictors of colorectal neoplasia: Sensitivity Analysis

Supplementary Figure 1: Distribution of colonoscopies according to calendar year

Supplementary Table 1. Endoscopic and histologic predictors of colorectal neoplasia: Sensitivity Analysis

	Exclusion of patients with ileo-rectal anastomosis at cohort entry		Exclusion of patients with lesion indefinite for dysplasia	
	Odds ratio (CI 95%)	p	Odds ratio (CI 95%)	p
Histological variables				
Mean Nancy histological index [a]	1.58 (1.20-2.09)	0.001	1.58 (1.19-2.09)	<0.001
Maximum Nancy histological index [a]	1.24 (0.98-1.57)	0.07	1.27 (1.00-1.63)	0.05
Endoscopic variables				
Endoscopic ulcerations				
On more than 50% of colonoscopies	0.95 (0.36-2.51)	0.91	1.00 (0.39-2.58)	1.00
On at least one colonoscopy	1.49 (0.73-3.03)	0.27	1.79 (0.87-3.69)	0.12

[a] per one unit increase; adjusted for sex, age, primary sclerosing cholangitis, IBD phenotype, 5-aminosalicylates and thiopurines exposure, and colonic strictures

Supplementary Figure 1: Distribution of colonoscopies according to calendar year