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Quality of Surveillance Impacts the Colitis-Associated Advanced Neoplasia Risk: A Multicenter Case-Control Study

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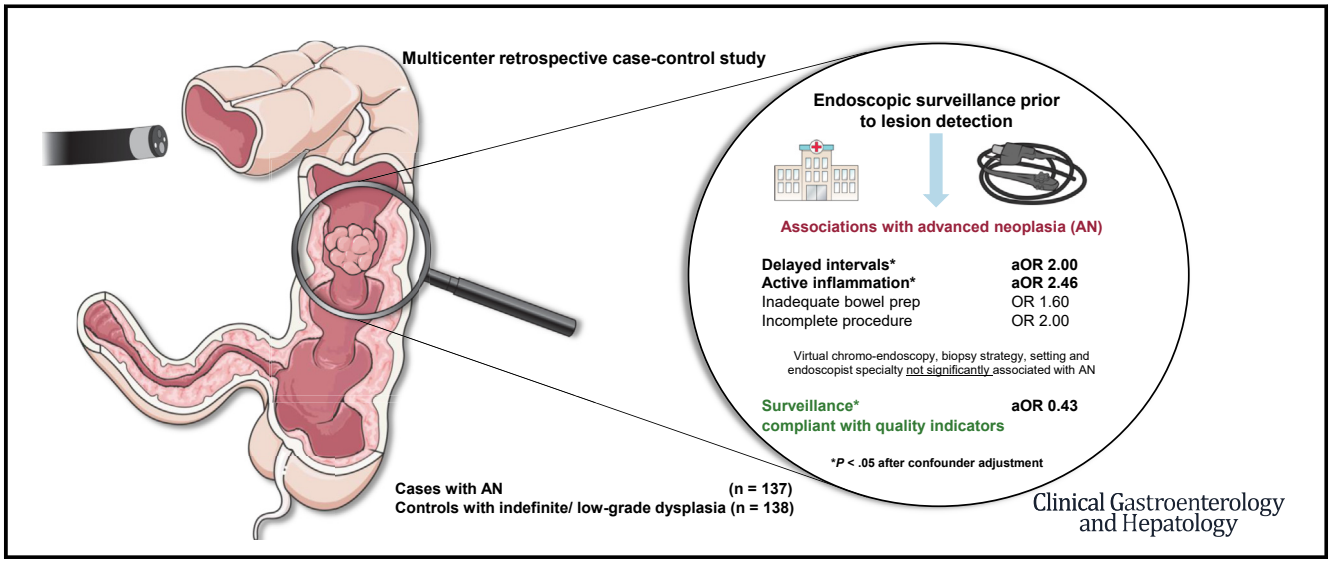

BACKGROUND AND AIMS: **Although colorectal cancer (CRC) surveillance is embedded in clinical inflammatory bowel disease (IBD) practice, a subset of patients still develops advanced neoplasia (AN) (high-grade dysplasia [HGD] and/or CRC). We aimed to assess the impact of surveillance quality on AN risk in IBD.**

METHODS: **In this multicenter case-control study, we searched the Dutch nationwide pathology databank to identify IBD cases with AN and controls with indefinite or low-grade dysplasia. The surveillance colonoscopy preceding the index lesion (first indefinite for dysplasia [IND]/low-grade dysplasia [LGD] or AN) was used to assess the impact of surveillance quality. We assessed intervals, bowel**

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Abbreviations used in this paper: AN, advanced neoplasia; aOR, adjusted odds ratio; BSG, British Society of Gastroenterology; CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease; IND, indefinite for dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; OR, odds ratio; PALGA, Dutch Nationwide Pathology Databank; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

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preparation, cecal intubation, and absence of inflammation as primary quality indicators. In addition, we assessed chromoendoscopy, endoscopist expertise, hospital setting, and biopsy strategy. Associations of quality indicators with AN risk were determined with multivariable logistic regression analyses with Firth's correction.

RESULTS: **We included 137 cases and 138 controls. Delayed intervals (58.2% vs 39.6%) and active inflammation (65.3% vs 41.8%) were frequently present in cases and controls and were associated with AN (delayed interval: adjusted odds ratio [aOR], 2.00; 95% confidence interval [CI], 1.07–3.81; $P = .03$; active inflammation: aOR, 2.46; 95% CI, 1.33–4.61; $P < .01$). Surveillance compliant with primary quality indicators was associated with a reduced AN risk (aOR, 0.43; 95% CI, 0.22–0.91; $P = .03$), similar to chromoendoscopy (OR, 0.11; 95% CI, 0.01–0.89; $P = .01$). Other indicators were not significantly associated with AN.**

CONCLUSIONS: **Surveillance compliant with primary quality indicators is associated with a reduced colitis-associated AN risk. Delayed surveillance intervals and active inflammation were associated with an increased AN risk. This underlines the importance of procedural quality, including endoscopic remission to optimize the effectiveness of endoscopic surveillance.**

Keywords: Colitis; Colon; Crohn's; Dysplasia; Screening.

Patients with inflammatory bowel disease (IBD) bear an increased risk of advanced neoplasia (AN) (including high-grade dysplasia [HGD] and colorectal cancer [CRC]) compared with the general population.[1–3] Endoscopic surveillance is recommended to attenuate this risk by detection and removal of dysplastic precursor lesions, including indefinite for dysplasia (IND) and low-grade dysplasia (LGD).[4,5] Despite current surveillance strategies, a significant number of IBD patients develops AN, resulting in morbidity and mortality.[5,6]

Endoscopic surveillance is widely implemented in daily IBD practice, although underlying evidence for its effectiveness is limited.[5,7] Development of AN can be used as a surrogate marker for effectiveness of endoscopic surveillance. Indeed, one meta-analysis concluded that endoscopic surveillance reduced CRC risk but was limited by a lack of information on quality of endoscopic surveillance.[5] High-quality surveillance is essential to ensure optimal mucosal visualization and prevent missed precursor lesions that may develop into AN.[8,9]

Although multiple studies have highlighted surveillance characteristics and performance in IBD, data regarding the effect of quality indicator compliance on surveillance effectiveness remain limited.[8] A recent study suggested that active inflammation might impede mucosal visualization of lesions,[10] although the exact impact of this limitation is unknown. Sufficient bowel preparation and cecal intubation are also relevant factors impacting mucosal visualization.[8,9] Endoscopic technique (white light vs chromoendoscopy), biopsy strategy (random and/or targeted biopsies), hospital setting (academic or community), and endoscopist expertise may impact the quality of surveillance as well.[11–13] Finally, surveillance intervals (CIs) are determined by risk stratification and delayed procedures may result in preventable interval AN.[14]

We hypothesized that reduced quality of endoscopic surveillance in IBD patients is associated with increased AN risk. In order to test this hypothesis, we designed a multicenter case-control study evaluating surveillance quality indicators and associated AN risk in IBD patients.

Materials and Methods

Study Design

We performed a retrospective multicenter case-control study to evaluate the impact of surveillance quality on the risk of AN (HGD or CRC) in IBD, with assessment of compliance to individual quality indicators including interval adequacy, bowel preparation, cecal intubation, and presence of active inflammation. Moreover, we assessed the impact of chromoendoscopy, biopsy strategy, hospital setting, and type of endoscopist.

Cases were patients with IBD and AN, as prevention of AN is one of the aims of endoscopic surveillance. Controls were patients with IBD and IND or LGD. We assumed that these controls with IND or LGD, rather than patients with IBD without dysplasia, would have intermediate to high AN risk profiles that are similar to cases. This provides a methodological setting that allows for a comparison of surveillance quality between higher-risk groups.

Patients

We searched the Dutch Nationwide Pathology Databank (PALGA) (lzv2019-87)[15] to identify IBD patients with IND, LGD, HGD, or CRC. PALGA has complete national coverage of both academic and nonacademic hospitals since 1991, with good accuracy in IBD.[16] All reports have a unique hash that allows identification of individual patients through electronic patient records. We performed a search combining search terms for IBD ("ulcerative colitis,"

"Crohn's disease," "indeterminate colitis," "chronic idiopathic inflammatory bowel disease") and for neoplasia ("indefinite for dysplasia," "low-grade dysplasia," "high-grade dysplasia," "carcinoma in situ," and "colorectal cancer"), located in the colon or rectum. Reports from January 1, 1991, to December 1, 2020, were collected.

All cases and controls from 5 academic and 2 community hospitals (with a cohort of 1923–3000 IBD patients),[17] were included if they fulfilled the following criteria: (1) an established histological diagnosis of colonic IBD (ulcerative colitis [UC], Crohn's disease [CD], or IBD unclassified), (2) a histological diagnosis of colorectal IND or LGD without AN (controls) or AN (cases), and (3) with available clinical and endoscopic data. Exclusion criteria comprised (1) familial CRC syndromes; (2) IND, LGD, or AN before IBD diagnosis; and (3) no indication for continued surveillance according to the British Society of Gastroenterology (BSG) 2019 guideline (ulcerative proctitis or <8 years of IBD in absence of primary sclerosing cholangitis [PSC]).[4]

What You Need to Know

Background

Quality of colonoscopy impacts outcomes in colorectal screening programs in non-inflammatory bowel disease (IBD) subjects. It is unknown whether compliance with endoscopic quality indicators reduces the risk of advanced neoplasia (defined as high-grade dysplasia or colorectal cancer) in patients with IBD.

Findings

Surveillance colonoscopy compliant with quality indicators is associated with advanced neoplasia risk reduction. By contrast, delayed intervals and active inflammation during surveillance are associated with an increased risk of advanced neoplasia.

Implications for patient care

Our findings underline the need for quality indicator registration and compliance for endoscopic surveillance in IBD, with focus on achieving endoscopic remission prior to scheduling surveillance colonoscopies.

Quality Assessment

Surveillance quality was primarily assessed by (1) surveillance intervals and (2) mucosal visualization, including bowel preparation, cecal intubation and presence of active inflammation. Secondary assessment included chromoendoscopy, biopsy strategy, hospital setting, and endoscopist expertise as potential quality indicators.

We used the last surveillance colonoscopy prior to index lesion (defined as first IND or LGD in controls or AN in cases) to assess the impact of quality indicators. We considered procedures as surveillance if they (1) were elective colonoscopies and (2) were not scheduled for assessment of (suspected) disease activity or therapeutic measures. In case only nonsurveillance endoscopies were performed prior to index lesion detection, this was considered as absence of surveillance.

Definitions of Quality Indicators

Considering the 2019 BSG guideline as a best-practice framework for surveillance, we assessed the following primary quality indicators by 2 researchers (M.t.G. and M.D.)[4]:

1. Surveillance intervals. Based on clinical CRC risk factors, the BSG guideline stratifies patients to a surveillance interval of 1, 3, or 5 years (Supplementary Figure 1). The start point of surveillance is 8 years after IBD diagnosis. In case of PSC, annual surveillance after IBD diagnosis is recommended. If the recommended surveillance interval was exceeded by more than a 3-month margin, we considered this a delayed interval.
2. Insufficient bowel preparation, defined as a Boston Bowel Preparation Scale score <6 and/or based on the endoscopists judgement as described in the endoscopy report. We classified the bowel preparation (if Boston Bowel Preparation Scale score was not reported) as insufficient if termed in the endoscopy report as insufficient, poor, or inadequate or if a repeat colonoscopy was requested due to bowel preparation.
3. Incompleteness of surveillance, defined as absence of cecal intubation.
4. Presence of endoscopic inflammation. Depending on the analysis, we assessed the impact of the presence or absence of (1) any grade and extent of active inflammation, (2) only moderate-to-severe inflammation, or (3) exclusion of E1 colitis patients on the AN risk. For each procedure the maximum endoscopic severity of inflammation in any colonic segment was scored using an ordinal score (normal/inactive = 1, mild = 2, moderate = 3, severe = 4) as previously published.[18] In case of hybrid descriptors (eg, moderate to severe) the maximum grade was recorded.

Secondary quality indicators included the following:

1. Endoscopic technique (chromoendoscopy, defined as dye-based or virtual chromoendoscopy vs white light endoscopy).
2. Biopsy strategy (targeted biopsies only vs random biopsies only or both).
3. Hospital setting (community vs academic hospital).
4. Expertise of the endoscopist (IBD specialist, gastroenterologist without IBD specialty, or resident).

Data Collection

We extracted the following data from the electronic patient files: sex, age, IBD type and behavior, disease duration, and maximum endoscopic and histologic IBD extent (UC: according to the Montreal classification; CD: more or less than 50% inflamed colonic mucosa).[19] Extensive disease was defined as E3 colitis for UC and >50% inflamed colonic mucosa for CD. Furthermore, we extracted data on index lesion characteristics (visible vs invisible, resection status), CRC family history, smoking status, PSC, and postinflammatory polyps. Data on all endoscopic procedures up to index lesion were collected, including date, type, and indication (surveillance vs other).

Statistical Analysis

Continuous outcomes were reported as median (interquartile range [IQR]) and categorical outcomes were reported as frequency and proportion. Differences between groups were assessed with the chi-square test, Student's *t* test, or nonparametric alternatives when appropriate. The impact of endoscopic quality indicators and surveillance intervals on AN risk was assessed employing a multivariable logistic regression model with Firth's correction to minimize low observation bias.[20] Selection of confounders was based on literature[21] and a study group consensus meeting and are displayed in a diagram, a priori developed in DAGitty (Supplementary Figure 2).[22] We attempted to account for the inherent AN risk associated with active inflammation (recorded as presence or absence) by adjustment for disease extent and endoscopic cumulative inflammatory burden score, and for this purpose we included all colonoscopies before index lesion detection (Supplementary Figure 3).[23] We performed multiple sensitivity analyses to assess the robustness of our methodology and results, including (1) colonoscopies with any type of indication (surveillance and other) and (2) only index lesions diagnosed after introduction of high-definition colonoscopes in 2005[24] or (3) after implementation of the first Dutch surveillance guideline in 2008.[25] Effects were presented as odds ratio (OR) and adjusted OR (aOR) with 95% CI. A 2-tailed *P* value of <.05 was considered statistically significant. All analyses were performed using SPSS v25 (IBM Corporation, Armonk, NY) and R (v3.5.3, package *logistf*; R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

This study was approved by the institutional review board of Radboud University Medical Center (2017–3219) and the scientific committee of PALGA.

Results

Baseline Characteristics

We included 275 patients with IBD (Figure 1), including 137 cases with AN (CRC: n = 78 [56.9%]; HGD: n = 59 [43.1%]) and 138 controls with LGD (n = 133 [96.4%]) or IND (n = 5 [3.6%]). Lesion characteristics are reported in Supplementary Table 1.

Cases with AN were diagnosed with IBD at a younger age (30.0 [IQR, 20.0–41.0] years vs 34.0 [IQR, 27.0–45.0] years; $P < .01$) and more frequently had extensive disease (77.4% vs 52.2%; $P < .01$) (Table 1). They more often had penetrating and stricturing CD (75.6% vs 34.4%; $P < .01$), strictures in UC (22.4% vs 10.5%;

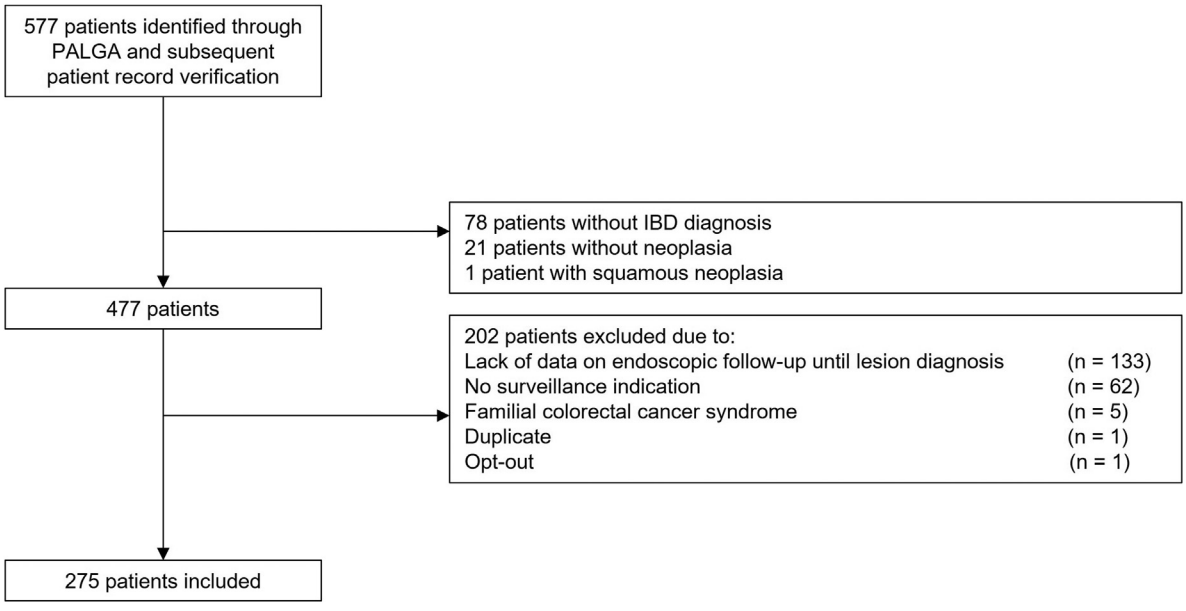

Figure 1. Patient identification.

Table 1. Baseline Characteristics of Cases and Controls

Characteristic	Cases (AN) (n = 137)	Controls (IND/LGD) (n = 138)	*P* Value
Male	78 (56.9)	80 (58.0)	.860
Disease			.079
UC	85 (62.0)	103 (74.6)	
CD	47 (34.3)	32 (23.2)	
IBD unclassified	5 (3.6)	3 (2.2)	
Age at IBD diagnosis, y	30.0 (20.0–41.0)	34.0 (27.0–45.0)	.004[a]
Disease duration	20.0 (15.0–28.0)	18.5 (13.8–27.0)	.189
Maximal endoscopic disease extent (Montreal)			.000[a]
E2 (UC)	16 (11.7)	44 (31.9)	
E3 (UC)	74 (54.0)	56 (40.6)	
<50% (CD)	15 (10.9)	22 (15.9)	
>50% (CD)	32 (23.4)	16 (11.6)	
Maximal histological disease extent (Montreal)[b]			.000[a]
E2 (UC)	12 (8.8)	26 (18.8)	
E3 (UC)	69 (50.4)	37 (26.8)	
<50% (CD)	14 (10.2)	53 (38.4)	
>50% (CD)	30 (21.9)	22 (15.9)	
Disease behavior (CD; Montreal)			.001[a]
B1	11 (23.4)	22 (66.7)	
B2	13 (27.7)	6 (18.2)	
B3	8 (17.0)	1 (3.0)	
B2+3	15 (31.9)	4 (12.1)	
p	19 (13.9)	11 (8.0)	.117
For ulcerative colitis/IBD unclassified: stricture	22 (22.4)	11 (10.5)	.011[a]
Guideline colorectal cancer risk stratification			.000[a]
Low	29 (21.2)	62 (44.9)	
Intermediate	42 (30.7)	43 (31.2)	
High	66 (48.2)	33 (23.9)	
Family history of colorectal cancer			.709
Yes	20 (14.6)	18 (13.0)	
No or unknown	117 (85.4)	120 (87.0)	
Smoking[c]			.045[a]
Yes	5 (4.5)	13 (9.4)	
No or stopped	106 (77.4)	96 (69.6)	
Primary sclerosing cholangitis	18 (13.1)	15 (10.9)	.563
Postinflammatory polyps	74 (54.0)	67 (48.6)	.365
Medication history			
Aminosalicylates	65 (48.5)	98 (71.5)	.000[a]
Thiopurines/methotrexate	28 (20.4)	55 (39.9)	.000[a]
Biologicals/small molecules	10 (7.5)	27 (19.7)	.004[a]

Values are n (%) or median (interquartile range).
AN, advanced neoplasia; CD, Crohn's disease; IBD, inflammatory bowel disease; IND, indefinite for dysplasia; LGD, low-grade dysplasia; UC, ulcerative colitis.
[a]$P < .05$.
[b]38 missing values.
[c]55 missing values.

$P = .01$), and a high CRC risk stratification according to the 2019 BSG guidelines (48.2% vs 23.9%; $P < .01$).[4] Furthermore, cases had a higher cumulative inflammatory burden score (median 14.5 [IQR, 6.2–25.9] vs 8.8 [IQR, 2.9–20.9]; $P < .01$).

The number of endoscopic procedures and follow-up time until the index lesion were similar between cases and controls (4 [IQR, 2–6] procedures vs 4 [IQR, 2–5] procedures; $P = .19$ and median 9 [IQR, 6–14] years vs 10 [IQR, 7–14] years; $P = .30$).

Quality Indicators

Patients frequently underwent endoscopic surveillance with delayed intervals (cases: 58.2% vs controls: 39.6%; $P = .01$) or active inflammation (cases: 65.3% vs

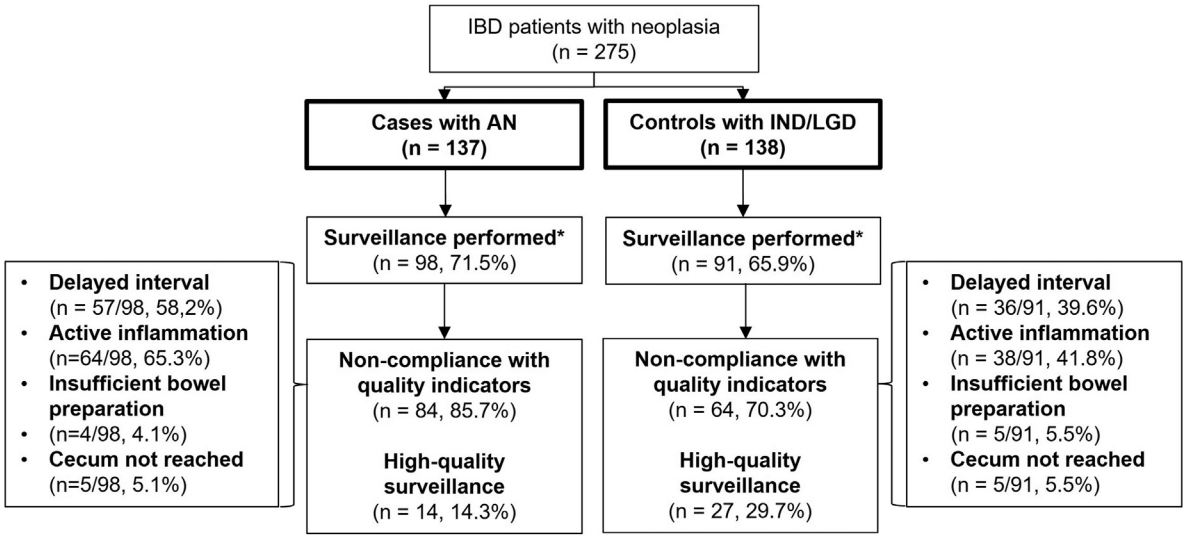

Figure 2. Surveillance enrollment showing absolute frequencies of primary quality indicator compliance. *Patients without surveillance had nonsurveillance colonoscopies prior to index lesion detection or lesions detected during the screening colonoscopy without a previous surveillance indication (Supplementary Table 2).

controls: 41.8%; $P < .01$) (Figure 2). Insufficient bowel preparation was observed in 4.1% vs 5.5% of cases and controls, respectively ($P = .53$). Incomplete procedures were reported in 5.1% of cases vs 5.5% of controls ($P = .92$). Fourteen (14.3%) cases vs 27 (29.7%) controls ($P = .04$) underwent endoscopic surveillance compliant with primary quality indicators prior to index lesion. This rate was similar between HGD and CRC cases (8.6% vs 10.3%; $P = .43$). By contrast, absence of any endoscopic surveillance until index lesion was observed in 27.7% of cases vs 31.2% of controls ($P = .39$) (Supplementary Table 2). No neoplasia was detected during the procedure that diagnosed IBD.

Dye-based chromoendoscopy was performed in 8 (8.8%) controls and 1 (1.0%) case during the surveillance colonoscopy prior to index lesion detection ($P = .01$) (Supplementary Table 3). Virtual chromoendoscopy was used in 4 (5.1%) cases and 4 (6.1%) controls ($P = .79$). There were no significant differences in biopsy strategy (random biopsies 67.5% vs 74.7%; $P = .33$) or number of random biopsies (median 20.5 [IQR, 9.8–27.0] vs 22.0 [IQR, 11.0–27.5]; $P = .61$) between cases and controls. In line, we did not observe differences in hospital setting (academic 78.6% vs 84.6%; $P = .29$) or endoscopist expertise (IBD specialist 29.5% vs 38.0%; $P = .33$) between cases and controls, respectively.

Impact of Surveillance Quality on AN Risk

Delayed surveillance intervals were associated with an increased AN risk (aOR, 2.00; 95% CI, 1.07–3.81; $P = .03$) (Table 2). The median surveillance delay did not differ between cases and controls (median 26.0 [IQR, 14.0–41.5] months vs 27.5 [IQR, 13.8–44.0] months; $P = .50$). The presence of active inflammation resulted in an increased AN risk (aOR, 2.46; 95% CI, 1.33–4.61; $P < .01$) (Table 2). Exclusion of patients with active E1 colitis or only mild inflammation resulted in a similar AN risk (Table 2). Cases had more often extensive disease (34.7% vs 16.5%; $P < .01$) and severe active inflammation (20.6% vs 3.3%; $P < .01$) compared with controls (Table 3). Dye-based chromoendoscopy resulted in a reduced AN risk (OR, 0.11; 95% CI, 0.01–0.89; $P = .01$). By contrast, insufficient bowel preparation, incomplete procedures, virtual chromoendoscopy, targeted only biopsies, hospital setting, and endoscopist expertise were not significantly associated with AN (Table 2). Patients who received endoscopic surveillance compliant with all primary quality indicators had a significantly lower risk of AN (aOR, 0.43; 95% CI, 0.22–0.91; $P = .03$). However, if surveillance irrespective of compliance with quality indicators was assessed, no significant effect on AN was found (aOR, 0.90; 95% CI, 0.51–1.59; $P = .71$).

Sensitivity Analyses

Results from the sensitivity analyses showed effect sizes in line with the main analyses. If colonoscopies with any type of indication (surveillance and other) were considered, delayed intervals resulted in a nonsignificantly increased AN risk (aOR, 1.87; 95% CI, 0.99–3.59; $P = .054$) (Table 2). Similarly, active inflammation was associated with a significantly increased AN risk (aOR, 2.69; 95% CI 1.20–6.20; $P = .02$). Exclusion of patients with an index lesion before introduction of high-definition surveillance or the first Dutch surveillance guideline showed increased ORs consistent with the main analyses (Table 2).

Discussion

In this multicenter case-control study including 275 patients with IBD and colorectal neoplasia, delayed

Table 2. Regression Results for the Associations Between Noncompliancy With Quality Indicators With Advanced Neoplasia Risk

	OR (95% CI)	*P* Value
Quality indicators—unadjusted		
Primary[a]		
Delayed interval	3.24 (1.47–7.14)	<.01[b]
Insufficient bowel preparation	1.60 (0.37–6.99)	.53
Incomplete procedure	2.00 (0.49–8.17)	.33
Active inflammation	3.37 (1.55–7.33)	<.01[b]
Secondary		
Dye-based chromoendoscopy (vs white light)	0.11 (0.01–0.89)	.01[b]
Virtual chromoendoscopy (vs white light)	1.21 (0.29–5.04)	.79
Targeted biopsies only (vs random only/both)	1.42 (0.71–2.85)	.33
Academic hospital (vs community)	0.67 (0.32–1.40)	.29
IBD-specialist (vs resident)	0.69 (0.33–1.46)	.33
	aOR (95% CI)	***P* Value**
Quality indicators—adjusted		
Delayed interval[c]	2.00 (1.07–3.81)	.03[b]
Active inflammation[d]	2.46 (1.33–4.61)	<.01[b]
Excluding patients with E1 colitis	2.45 (1.30–4.68)	<.01[b]
Excluding patients with mild inflammation	3.71 (1.73–8.25)	<.01[b]
Surveillance—adjusted		
Surveillance compliant with all primary quality indicators[e]	0.43 (0.20–0.91)	.03[b]
Irrespective of inflammation status	0.44 (0.20–0.98)	.04[b]
Irrespective of inflammatory burden score[f]	0.38 (0.17–0.78)	.01[b]
Surveillance irrespective of compliancy with quality indicators[e]	0.90 (0.51–1.59)	.71
Sensitivity analyses		
Colonoscopies with any type of indication		
Delayed interval[c]	1.87 (0.99–3.59)	.05
Active inflammation[d]	2.69 (1.20–6.20)	.02[b]
Surveillance compliant with all primary quality indicators[e]	0.43 (0.20–0.90)	.03[b]
After implementation of HD colonoscopes		
Delayed interval[c]	1.93 (1.03–3.65)	.04[b]
Active inflammation[d]	2.33 (1.25–4.37)	.01[b]
Surveillance compliant with all primary quality indicators[e]	0.45 (0.20–0.95)	.04[b]
After implementation of the first Dutch surveillance guideline		
Delayed interval[c]	2.02 (1.06–3.90)	.03[b]
Active inflammation[d]	2.15 (1.14–4.12)	.02[b]
Surveillance compliant with all primary quality indicators[e]	0.44 (0.20–0.94)	.04[b]

aOR, adjusted odds ratio; CI, confidence interval; HD, high-definition; IBD, inflammatory bowel disease; OR, odds ratio.
[a]Versus surveillance complaint with all primary quality indicators.
[b]$P < .05$.
[c]Adjusted for active inflammation, age at IBD diagnosis, colorectal cancer family history, primary sclerosing cholangitis, extensive disease, cumulative inflammatory burden, and strictures as covariates.
[d]Adjusted for extensive disease, strictures, cumulative inflammatory burden score, and delayed interval as covariates.
[e]Same as model 1, without active inflammation as covariate.
[f]Same as model 1, without active inflammation and cumulative inflammatory burden as covariates.

intervals and active inflammation were associated with an increased AN risk. Conversely, surveillance compliant with primary quality indicators was associated with a reduced AN risk.

Surveillance is widely endorsed in international IBD guidelines, although few studies have assessed the impact of surveillance quality on AN risk.[4,26] Our study showed an AN risk reduction in patients undergoing surveillance compliant with primary quality indicators. This finding is in line with a systematic review and meta-analysis which reports a pooled OR of 0.58 (95% CI, 0.24–0.80) for CRC development in patients who underwent surveillance (vs no surveillance). However, the latter study included historical cohorts, hampered by lack of quality assessment, different endoscopic techniques and adenoma detection methods.[5] More recent

Table 3. Extent and Severity of Active Inflammation at Last Surveillance Colonoscopy Prior Index Lesion Diagnosis and Endoscopic Cumulative Inflammatory Burden Score

		Cases (AN) (n = 98)	Controls (IND/LGD) (n = 91)	*P* Value
Severity[a]	Inactive disease (1)	32 (32.7)	52 (57.1)	<.01[b]
	Mild inflammation (2)	20 (20.6)	25 (27.5)	
	Moderate inflammation (3)	24 (24.5)	10 (10.9)	
	Severe inflammation (4)	20 (20.6)	3 (3.3)	
Extent[c]	E1	7 (7.7))	6 (6.6)	<.01[b]
	E2	12 (12.3)	11 (12.1)	
	E3	23 (23.7)	14 (15.4)	
	<50% (CD)	10 (10.3)	5 (5.5)	
	>50% (CD)	11 (11.3)	1 (1.1)	
Endoscopic cumulative inflammatory burden score	Points	14.5 (6.2–25.9)	8.8 (2.9–20.9)	<.01[b]

Values are n (%) or median (interquartile range).
AN, advanced neoplasia; CD, Crohn's disease; IND, indefinite for dysplasia; LGD, low-grade dysplasia.
[a]3 missing values.
[b]$P < .05$.
[c]2 missing values.

studies evaluating surveillance effectiveness reported conflicting results. One study reported a reduced CRC incidence, whereas the other reported a higher AN incidence in patients undergoing surveillance.[27,28] These differences might be the result from different study designs and definitions of surveillance. Importantly, both studies did not primarily assess quality of surveillance. Another study reported low CRC rates in a cohort with high guideline adherence but did not include a reference group for comparison.[29] Our study addressed these limitations and underlines the importance of surveillance procedures compliant with quality indicators to reduce the risk of missed precursor lesions (IND/LGD) and, subsequently, preventable AN.

We observed that delayed surveillance colonoscopies were independently associated with an increased AN risk, underlining the importance of the guidelines' recommended surveillance intervals.[4,26] Moreover, active inflammation during surveillance was associated with AN risk, regardless of severity or extent, as illustrated by the overlapping CIs. Active inflammation is considered the main driver of AN development in IBD but may also reduce mucosal visualization during surveillance, increase the risk of missed precursor lesions of AN, and impair histologic assessment.[8] The association of active inflammation with AN remained significant after adjustment for risk factors for AN, cumulative inflammatory burden, and extensive disease. Adjustment for these factors might not fully resolve residual confounding, but these findings support the dual role for mucosal inflammation both as a risk factor for AN and by reducing the quality of surveillance.[21,23] In line, a recent study showed an increased dysplasia yield of random biopsies in patients with active inflammation and dysplasia compared with controls with dysplasia and inactive disease, likely due to the inability to delineate lesions in inflamed mucosa.[10] Finally, insufficient bowel preparation and lack of cecal intubation showed ORs for AN risk in line with previous studies although statistically not significant, likely due to the low prevalence (4.1%–5.5%).[30,31]

We observed a reduced AN risk if dye-based chromoendoscopy was employed, confirming guideline recommendations for this modality as summarized in a recent meta-analysis.[11] In line with our findings, the benefits of virtual chromoendoscopy remain under debate.[32,33] Endoscopist expertise has previously been associated with colonoscopy outcomes, including the risk of missed neoplasia in the non-IBD population.[12] By contrast, we found a nonsignificant AN risk reduction if endoscopic surveillance was performed by an IBD specialist compared with residents. To our knowledge, there are no other IBD studies assessing endoscopic surveillance expertise. An academic setting did not significantly impact AN risk, in line with a study showing high-quality colonoscopy performance across different hospital types in the United States.[34]

Current guidelines recommend a shortened (1–3 yearly) surveillance interval in case of extensive disease and active inflammation detected during surveillance.[4] Our results indicate that these shortened intervals may not always be sufficient. This is illustrated by the relatively high rate (n = 22 [16.1%]) of cases with AN on a background of active inflammation at the preceding surveillance colonoscopy, despite adhering to these stricter guideline intervals. Even with the available biological and small molecule therapies, it remains challenging in clinical practice to achieve sufficient disease control in patients with severe IBD phenotypes similar to cases in this study. This underlines the need for more effective pharmacological interventions as well as enhanced endoscopic visualization techniques that may include the future use of artificial intelligence.

Importantly, almost 30% of the patients in our cohort did not undergo any endoscopic surveillance prior to diagnosis of the index lesion, without a significant difference between cases and controls. This might be the result of nonsurveillance (diagnostic or therapeutic) colonoscopies performed prior index lesion detection, limiting the risk of missed precursor lesions, as substantiated by our sensitivity analysis. Although the considerable proportion of patients without surveillance might be a consequence of contemporary guideline adherence and patient or physician preferences, these numbers confirm findings from previous studies. In a large cohort study using the U.S. Veterans Association database, only 30% of IBD patients underwent a surveillance colonoscopy within 5 years prior to CRC diagnosis.[7] A recent European cohort study reported that only 27% of patients received a timely first screening colonoscopy with subsequent surveillance according to guideline intervals.[28] Increasing participation of IBD patients in structured endoscopic surveillance programs is a first step toward reducing AN risk.

This study has several strengths. The PALGA search enabled us to create 2 large cohorts of IBD patients from academic and nonacademic hospitals. This is the first study in IBD primarily investigating the impact of surveillance quality indicators. The similar follow-up duration and number of endoscopic procedures between cases and controls prior to index lesion detection enabled us to calculate a cumulative inflammatory burden score. We used this score as confounder to assess active inflammation during surveillance as quality indicator for mucosal visualization. We used all colonoscopies for calculation, as patients frequently had inconsistently scheduled surveillance, potentially resulting in an underestimation of the inflammatory burden if only surveillance colonoscopies were used. We performed multiple sensitivity analyses to evaluate the robustness of our results.

There are also limitations to discuss, most importantly the retrospective design of this study. Consequently, data are lacking, such as withdrawal time, as this quality indicator is inconsistently reported in endoscopy reports. Although nationwide registries and randomized controlled trials would be beneficial in a definitive assessment of the effectiveness of surveillance without aforementioned limitations, these are not feasible in the foreseeable future due to ethical, time and financial constraints. We selected patients with a surveillance colonoscopy and IND or LGD or AN on subsequent colonoscopy as controls and cases, respectively. This methodological setting allowed for a comparison with patients with intermediate to high risk profiles similar to our cases with AN. This choice of controls may limit extrapolation of our findings to patients who do not develop dysplasia over their lifetime at all, although one could speculate that endoscopic surveillance is of greater clinical relevance for high-risk groups compared with low-risk patients with IBD who may never develop AN. The (virtual) chromoendoscopy rate in this study was low and might reflect local preferences, available expertise, and time-dependent trends.[28,35] Alternatively, one could hypothesize that active inflammation or insufficient bowel preparation resulted in the selection of white light endoscopy rather than chromoendoscopy. Last, patient adherence is an important factor in surveillance,[36] but the exact reasons for absent or delayed surveillance were rarely reported in patient files.

In conclusion, we observed in this multicenter case-control study including patients with IBD and colorectal neoplasia that surveillance compliant with primary quality indicators is associated with AN risk reduction. Active inflammation and delayed colonoscopy intervals are frequently present and limit the effectiveness of surveillance. These findings underline the need for participation in surveillance programs, quality indicator compliance, and focus on achieving endoscopic remission prior to scheduling surveillance colonoscopies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2022.12.010.

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Conflicts of Interest

The authors disclose no conflicts.

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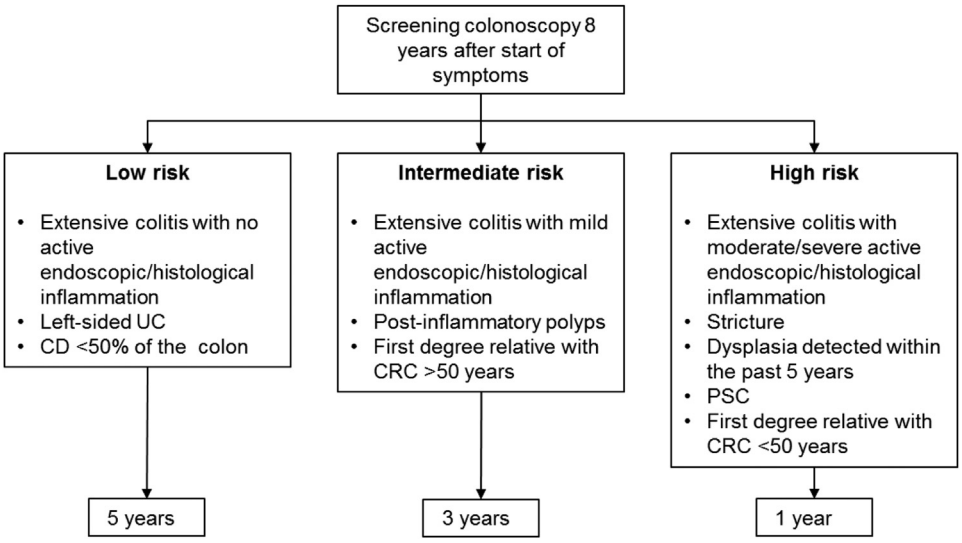
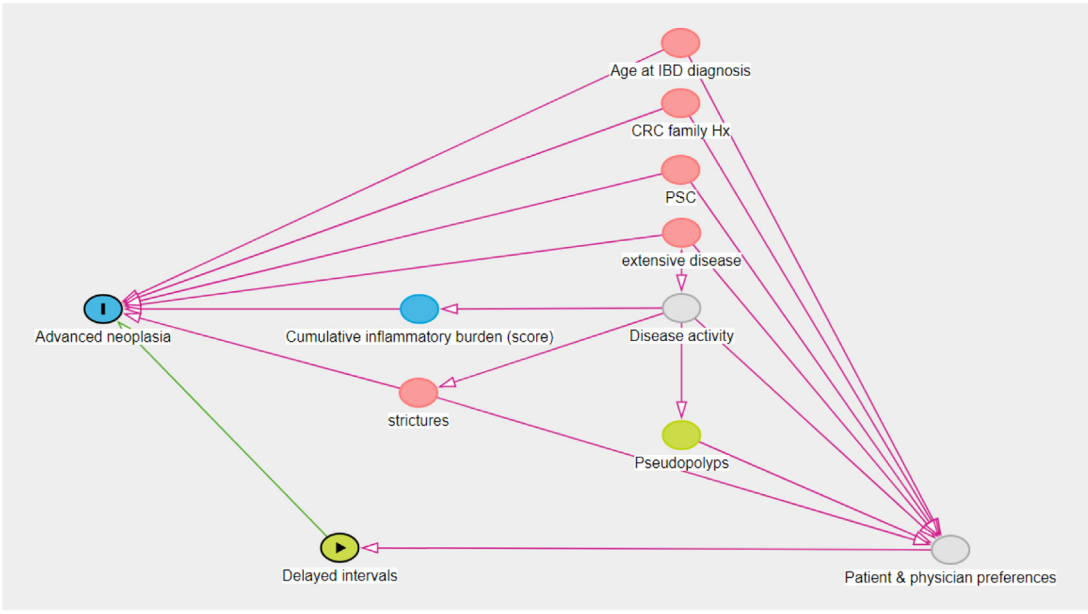
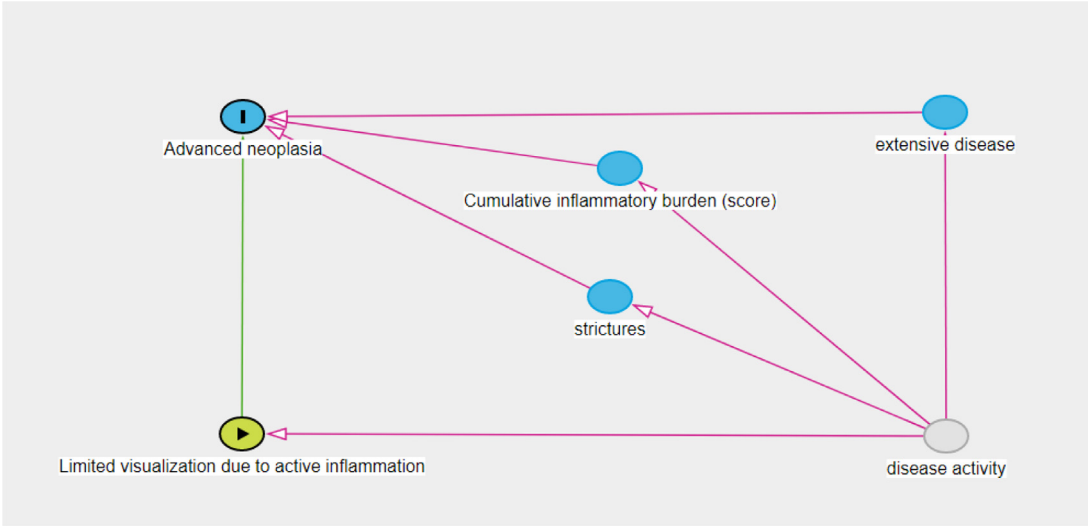
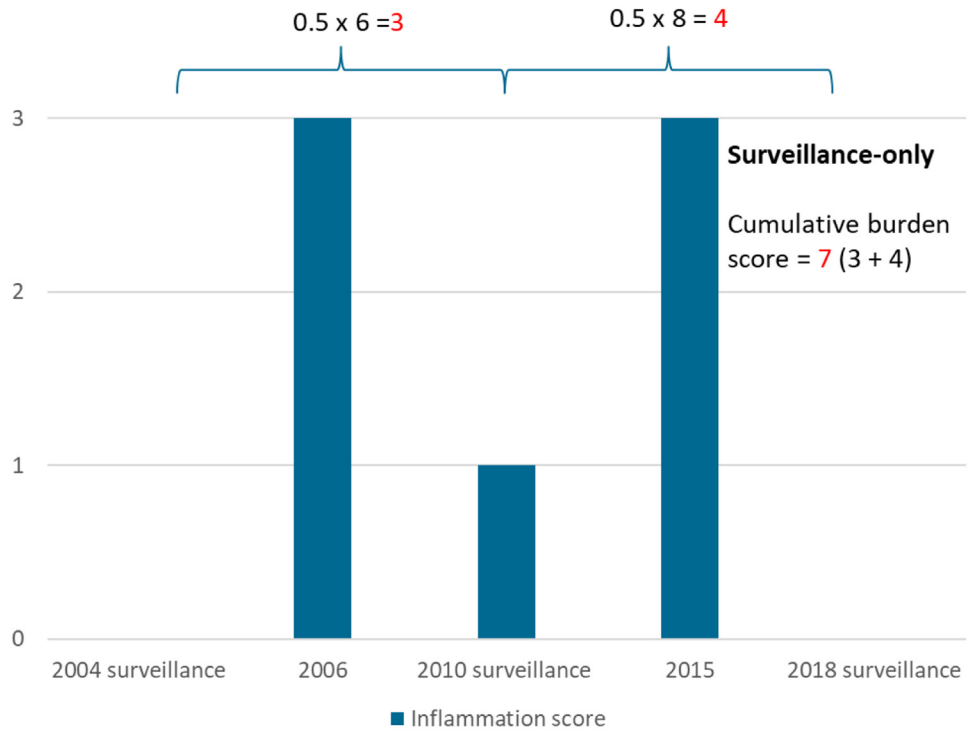


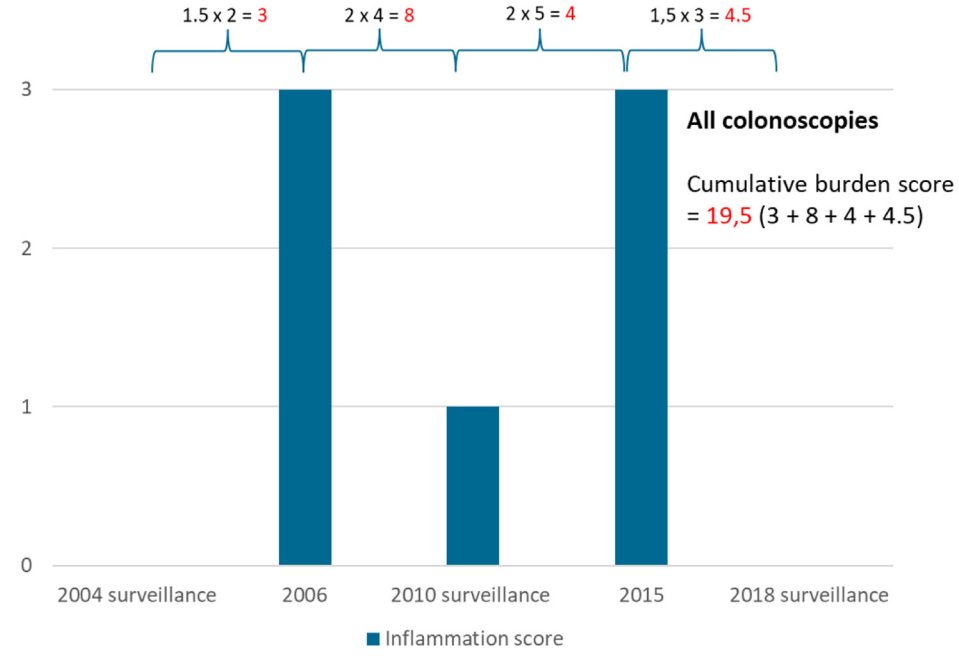
Supplementary Figure 1. Overview of the British Society of Gastroenterology surveillance guideline, risk stratification flowchart. CD, Crohn's disease; CRC, colorectal cancer; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.





Supplementary Figure 2. Causal diagrams made in Dagitty for assesment of confounding pathways between quality of surveillance and advanced neoplasia. Gray oval: unobserved/not quantifiable. Red oval: ancestor of exposure and outcome. Green oval: ancestor of exposure. Blue oval: ancestor of outcome. I: primary outcome. Triangle: exposure of interest. Green line: path of interest. Red lines: biasing paths. CRC, colorectal cancer; Hx, history; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.





Supplementary Figure 3. Example illustrating how the inflammatory burden score was calculated with a patient who had surveillance colonoscopies in 2004, 2010, and 2018 and nonsurveillance colonoscopies in 2006 and 2015. The mean endoscopic inflammation severity (0 = absence or inactive inflammation, 1 = mild, 2 = moderate, 3 = severe) between each interval is multiplied with the length of the interval and summed into the cumulative inflammatory burden score. As illustrated, omission of nonsurveillance colonoscopies results in an underestimation of the true inflammatory burden.

Supplementary Table 1. Index Lesion Characteristics

	Cases (AN) (n = 137)	Controls (IND/LGD) (n = 138)	Total (n = 275)
Neoplasia grade			
IND	0 (0.0)	5 (3.6)	5 (1.8)
LGD	0 (0.0)	133 (96.4)	133 (48.4)
HGD	59 (43.1)	0 (0.0)	59 (21.5)
CRC	78 (56.9)	0 (0.0)	78 (28.4)
Morphology			
Visible	126 (92.0)	125 (90.6)	251 (91.3)
Not resected	14 (10.2)	5 (3.6)	19 (6.9)
Invisible	11 (8.0)	8 (5.8)	19 (6.9)
Not resected	1 (0.7)	2 (1.4)	3 (1.1)
Unknown	0 (0.0)	5 (3.6)	5 (1.8)

Values are n (%).
AN, advanced neoplasia; CRC, colorectal cancer; HGD, high-grade dysplasia; IND, indefinite for dysplasia; LGD, low-grade dysplasia.

Supplementary Table 2. Absolute Frequencies of Quality of Surveillance Prior to Index Lesion Diagnosis, Including Simultaneous Occurrence of Reasons for Inadequate Surveillance

	Cases (AN) (n = 137)	Controls (IND/LGD) (n = 138)	Total (n = 275)
No surveillance[a]	38 (27.7)	43 (31.2)	81 (29.5)
Detected at screening colonoscopy	1 (0.7)	4 (2.8)	5 (1.8)
High-quality surveillance	14 (10.2)	27 (19.6)	41 (14.9)
Noncompliance with quality indicators			
Presence of			
Delayed interval	16 (11.7)	20 (14.5)	36 (13.1)
Inflammation	22 (16.1)	19 (13.8)	41 (14.9)
Inadequate BP	0 (0.0)	1 (0.7)	1 (0.4)
Incomplete procedure	0 (0.0)	3 (2.2)	3 (1.1)
Delayed interval + inflammation	38 (27.7)	15 (10.9)	53 (19.3)
Delayed interval + inadequate BP	2 (1.5)	1 (0.7)	3 (1.1)
Delayed interval + incomplete	1 (0.7)	1 (0.7)	2 (0.7)
Inflammation + inadequate BP	1 (0.7)	3 (2.2)	4 (1.5)
Inflammation + incomplete	3 (2.2)	1 (0.7)	4 (1.5)
Inadequate BP + incomplete	1 (0.7)	0 (0.0)	1 (0.4)
Subtotal >1	46 (33.6)	21 (15.2)	67 (24.4)
Subtotal	84 (61.3)	64 (46.4)	148 (53.8)

Values are n (%).
AN, advanced neoplasia; BP, bowel preparation; IND, indefinite for dysplasia; LGD, low-grade dysplasia.
[a]All with nonsurveillance endoscopies prior to the index lesion detection (colonoscopy: n = 18 [22.2%]; sigmoidoscopy: n = 63 [77.8%])

Supplementary Table 3. Secondary Quality Indicators for the Surveillance Colonoscopy Prior to Index Lesion Detection

	Cases (AN)	Controls (IND/LGD)	Total
Dye-based chromoendoscopy	1/98 (1.0)	8/91 (8.8)	9/189 (4.8)
Virtual chromoendoscopy	4/79 (5.1)	4/66 (6.1)	8/145 (5.5)[a]
Setting			
Academic hospital	77/98 (78.6)	77/91 (84.6)	154/189 (81.5)
Community hospital	21/98 (21.4)	14/91 (15.4)	35/189 (18.5)
Endoscopist expertise			
IBD specialist	23/78 (29.5)	30/79 (38.0)	53/157 (33.8)[b]
Gastroenterologist without IBD specialty	25/78 (32.1)	22/79 (27.8)	47/157 (29.9)[b]
Supervised resident	30/78 (38.5)	27/79 (34.2)	57/157 (36.3)[b]
Biopsy strategy			
Only random biopsies	21/77 (27.3)	29/79 (36.7)	50/156 (32.1)[c]
Only targeted biopsies	19/77 (24.7)	11 /79 (13.9)	30/156 (19.2)[c]
Both random and targeted biopsies	31/77 (40.3)	30/79 (38.0)	61/156 (39.1)[c]
No biopsies	6/77 (7.8)	9/79 (11.4)	15/156 (9.6)[c]
Number of random biopsies	20.5 (9.8-27.0)	22.0 (11.0-28.0)	22.0 (10.0-27.5)[c]

Values are n/n (%) or median (interquartile range).
AN, advanced neoplasia; CD, Crohn's disease; IBD, inflammatory bowel disease; IND, indefinite for dysplasia; LGD, low-grade dysplasia.
[a]44 missing values.
[b]32 missing values.
[c]33 missing values.