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Prognostic Factors for Advanced Colorectal Neoplasia in Inflammatory Bowel Disease: Systematic Review and Meta-analysis

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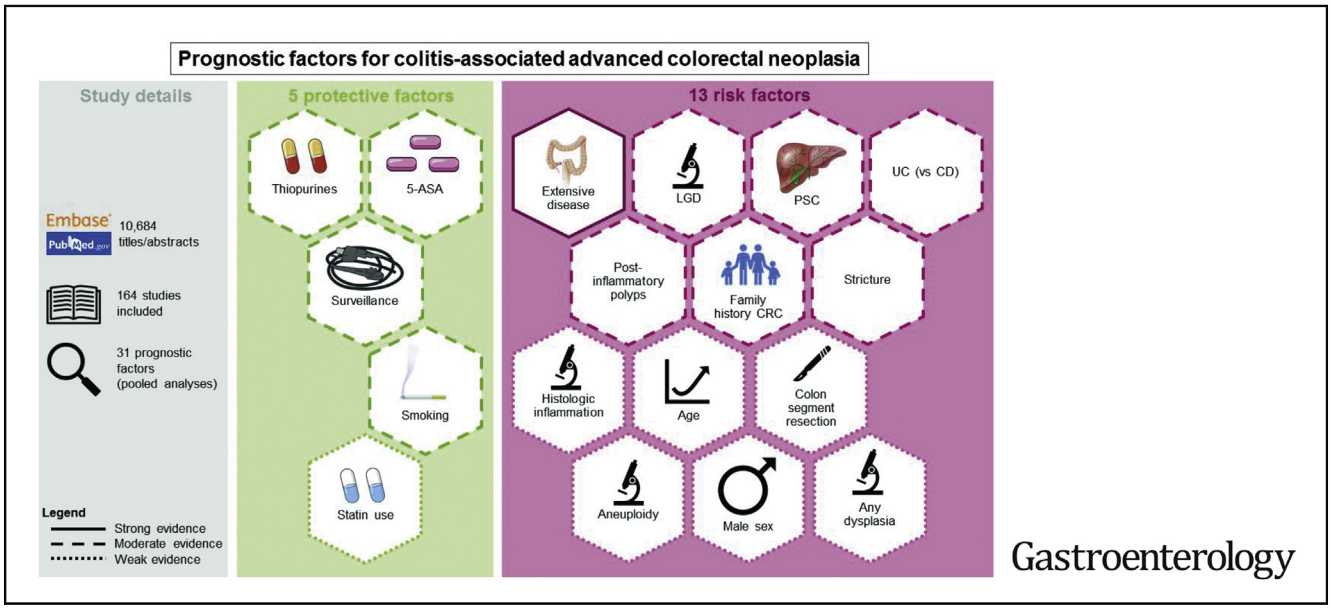

BACKGROUND AND AIMS: Patients with inflammatory bowel disease (IBD) have an increased risk of colorectal cancer (CRC). We performed a systematic review and meta-analysis to identify all prognostic factors for advanced colorectal neoplasia (aCRN, high-grade dysplasia, or CRC) in patients with IBD. **METHODS:** A systematic literature search was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Risk of bias was assessed using the Quality in Prognostic Studies tool. Random-effects models were created separately for odds and hazard ratios, different study designs, and univariable or multivariable data. The evidence for all prognostic factors was categorized as "weak", "moderate", or "strong", based on estimate of effect sizes, heterogeneity, and risk of bias. **RESULTS:** A total of 164 studies were included, allowing pooled analysis of 31 potential prognostic factors. In the univariable analysis, the evidence for extensive disease was classified as strong while evidence for low-grade dysplasia, strictures, primary sclerosing cholangitis, post-inflammatory polyps, family history of CRC, and ulcerative colitis versus Crohn's disease was considered moderate. Evidence for any dysplasia, colon segment resection, aneuploidy, male sex, and age was classified as weak. In addition, histologic inflammation was identified as a risk factor in multivariable analysis (weak evidence). The evidence for the protective factors colonoscopic surveillance, 5-Aminosalicylic Acid, thiopurines, and smoking was moderate in univariable analysis. Multivariable analysis provided weak evidence for statin use. **CONCLUSIONS:** In this systematic review and meta-analysis, we identified 13 risk factors and 5 protective factors for aCRN in IBD patients, based on univariable and/or multivariable pooled analyses. These findings might lay the groundwork for an improved CRC risk stratification-based surveillance in IBD.

Keywords: Risk Factor; Protective Factor; Ulcerative Colitis; Colorectal Cancer.

Patients with colonic inflammatory bowel disease (IBD) have a 1.7-fold increased risk of colorectal cancer (CRC).[1] Therefore, international guidelines recommend enrollment of patients with ulcerative or Crohn's colitis in surveillance programs to detect and remove dysplastic lesions before progression to advanced colorectal neoplasia (aCRN), high-grade dysplasia (HGD), and CRC occurs.[2–5] Indirect evidence indicates that endoscopic surveillance is effective in reducing CRC incidence and CRC-associated mortality.[6] However, effect sizes and levels of evidence of individual prognostic factors have not been incorporated into the stratification algorithms of current surveillance guidelines.

American guidelines recommend surveillance colonoscopies every 1 to 3 years, without stratifying the individual surveillance interval except for concomitant primary sclerosing cholangitis (PSC).[4,5] In contrast, European guidelines assign patients to a low-, moderate-, or high-risk category based on the presence of a number of clinical and histologic risk factors,[2,3] including concomitant PSC,[7] a history of low-grade dysplasia (LGD),[8] and extensive disease.[9] However, most recommendations in current guidelines are based on studies of diverse quality.

To provide an up-to-date overview of literature, with a focus on the overall strength of association of prognostic factors for aCRN, we performed a systematic review and meta-analysis.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Evidence for the use of prognostic factors in stratifying patients with inflammatory bowel disease for surveillance colonoscopies is only based on modest evidence.

NEW FINDINGS

This is the first systematic review and meta-analysis that evaluated all prognostic factors for advanced colorectal neoplasia, identifying 13 risk and 5 protective factors.

LIMITATIONS

The majority of studies included in this meta-analysis had a retrospective design. For several prognostic factors considerable heterogeneity between studies was found.

IMPACT

The results of this study can be used to guide future risk stratification models for colorectal cancer in inflammatory bowel disease.

Methods

We followed the guidelines for reporting developed by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. The study was registered on PROSPERO (CRD42019141345) before the literature search (MOOSE checklist provided in Supplementary File 1).[10]

Search Strategy

A comprehensive literature search using broad search criteria was conducted in the PubMed and Embase databases (on July 10, 2019) with aid of an experienced librarian. In short, the search terms included all key terms for IBD in combination with all terms for (a)CRN and terms for location in the colon. There were no language restrictions. Animal studies were excluded. Details on the search strategy are provided in Supplementary File 2. All reference lists of included studies and previous meta-analyses on prognostic factors were screened for additional eligible articles.

Study Selection

First, all titles and abstracts of identified studies were independently screened by 2 researchers (M.J. and A.W.) to exclude studies irrelevant for our aim. Discrepancies were resolved through a consensus discussion with the senior authors (F.H., M.L., S.E., B.O.). Case reports, conference abstracts, letters, and review articles were excluded.

Next, we assessed the full text of all potentially relevant studies for the following inclusion criteria: (1) cohort study or case-control study; (2) data on prognostic factors for aCRN in IBD with at least 1 event of aCRN; (3) reporting an odds ratio (OR) or a hazard ratio (HR) (with a 95% confidence interval [CI]) or providing data (number of events and patients in exposed and nonexposed group) that allowed for calculation of an OR and its standard error. Studies that reported prognostic factors for LGD and aCRN combined in a composite outcome or that only enrolled patients who had undergone a proctocolectomy were excluded. If more than 1 article assessed the impact of the same prognostic factor in identical or overlapping cohorts, we included the study that particularly focused on this prognostic factor (if not applicable, the most recent study was selected).

Data Extraction and Quality Assessment

The following data were collected from all eligible studies using an electronic data-entry sheet: first author, publication year, country, study design, inclusion and exclusion criteria, cohort size, duration of follow-up, IBD type, duration of IBD, number of patients with aCRN per prognostic factor, and univariable and multivariable estimates of effect (OR or HR).

[*] Authors share co-first authorship; [§] Authors share co-senior authorship.

Abbreviations used in this paper: 5-ASA, 5-aminosalicylic acid; aCRN, advanced colorectal neoplasia; CD, Crohn's disease; CI, confidence interval; CRC, colorectal cancer; CRN, colorectal neoplasia; HGD, high-grade dysplasia; HR, hazard ratio; IBD, inflammatory bowel disease; IND, indefinite dysplasia; IQR, interquartile range; LGD, low-grade dysplasia; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; OR, odds ratio; PIPs, postinflammatory polyps; PSC, primary sclerosing cholangitis; QUIPS, quality in prognostic studies; RoB, risk of bias; TNF, tumor necrosis factor; UC, ulcerative colitis.

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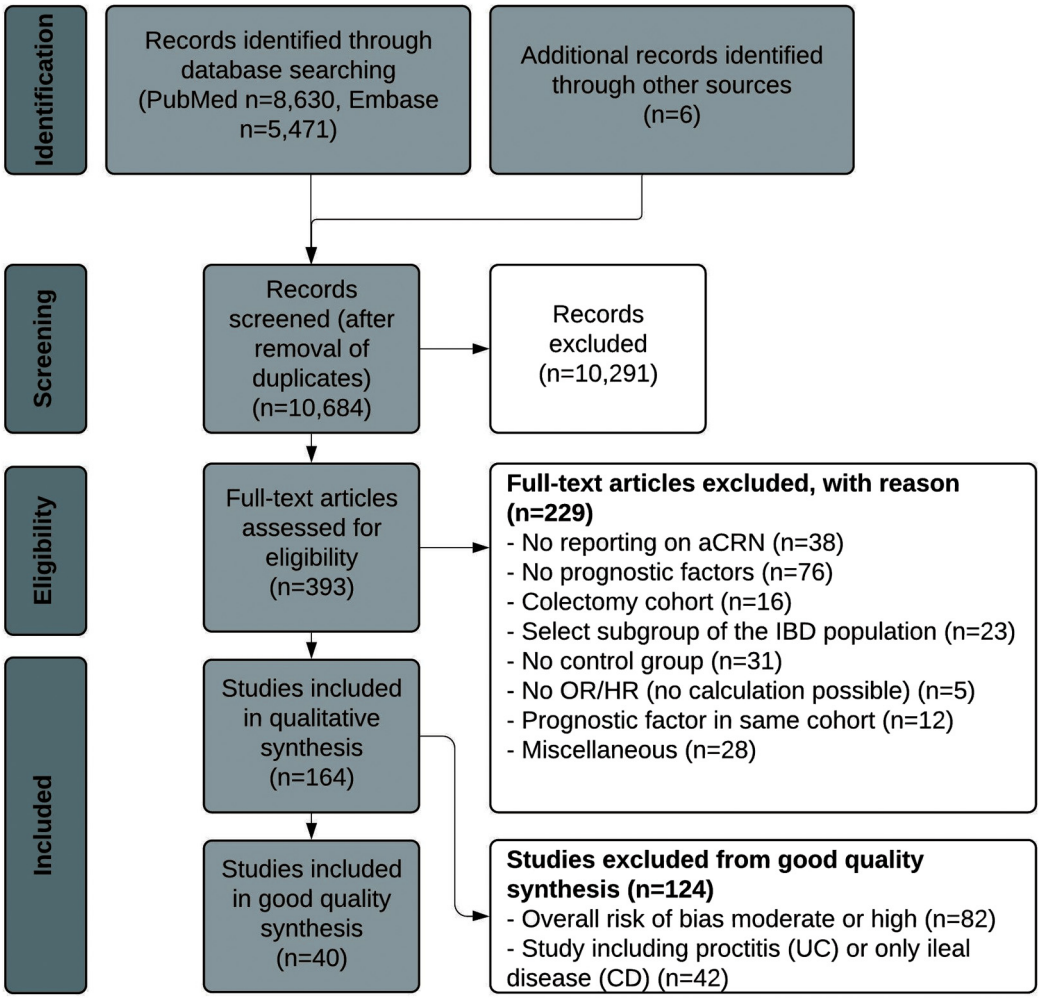


Figure 1. Flow diagram of the selection process.

Details of all included studies are provided in Supplementary File 3. If relative risks were reported and additional data were provided, we calculated the OR because only 6 studies reported a relative risk for our outcome. Adjusted estimates of effect were documented as multivariable results. The set of covariates that was adjusted for in each study is specified in Supplementary File 4. Data from all studies were extracted separately by M.J. and A.W., and discrepancies were resolved through discussion.

The quality of included studies was assessed using the Quality In Prognosis Studies (QUIPS) tool (Supplementary File 5).[11] The criteria of the QUIPS tool were expanded to enable grading of all included studies (Supplementary File 6). The overall quality of included studies was graded according to the methods previously described by Grooten et al.[12] If all QUIPS domains were rated as low risk of bias (RoB), or if all domains were rated as low RoB with 1 scoring moderate RoB, studies were categorized as low RoB. Studies were graded as high RoB if $\geq$1 domains were scored as high RoB or if $\geq$3 domains were scored as moderate RoB. The remaining studies were graded as moderate RoB. Domain 5, "study confounding," was not considered in grading the overall quality because few studies reported multivariable models.

Prognostic Factors

All potential prognostic factors reported in the literature were included without any preselection. All prognostic factors that were reported in $\geq$1 study are discussed in the Results, and related forest plots are shown in Supplementary Files 7–39. In addition, the factors endoscopic inflammation and p53 mutations were included, even though pooled analysis was not possible. The remaining factors are reported in Supplementary File 40. The definitions of the identified prognostic factors are specified in the Supplementary Files of each prognostic factor.

Statistical Analysis

A random-effects model was applied to pool the overall effect of a potential prognostic factor. We performed separate analyses to calculate the pooled univariable and multivariable ORs and HRs of potential prognostic factors. In addition, we performed secondary analyses by study design (cohort and case-control studies separately). We used I^2 statistics to assess the heterogeneity among studies. These were only reported here if $\geq$10 studies were included, because I^2 results in small meta-analyses tend to be inaccurate.[13] An $I^2 \geq 50\%$ indicates substantial (50% to 90%) to considerable (75% to 100%)

heterogeneity.[14] These analyses are provided in the supplementary files of the prognostic factor. Meta-analyses were performed using Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark).

R 3.5.1 (Metafor package) statistical software (The R Foundation for Statistical Computing, Vienna, Austria) was used to create funnel plots, to perform Egger's regression test for assessing publication bias, and to run meta-regression analyses.[15] Funnel plots were visually assessed for asymmetry. Egger's regression test was performed if ≥10 studies were available.[14] A *P* value of <.05 indicated substantial asymmetry of funnel plots, thereby implying publication bias.[16] Meta-regression analysis was performed for prognostic factors that might have changed over time and if ≥10 studies reporting on these prognostic factors were available.[14] Year of cohort was used as a covariate in meta-regression analysis, defined as the mean from start to end of the study period (if missing, publication year was used)."

Good-Quality Synthesis

A separate pooled analysis was performed with inclusion of only "good-quality studies." These studies had to meet the following criteria: (1) the overall quality of the study was graded as low RoB, and (2) only ulcerative colitis (UC) patients with at least left-sided disease or Crohn's disease (CD) patients with colonic involvement were included in the study.

Summary of All Identified Prognostic Factors

The quality of evidence for all identified prognostic factors was graded separately for univariable and multivariable analysis. Prognostic factors had to meet all criteria in the corresponding level of evidence; thus, all 4 criteria to be graded as "strong evidence."

- *Strong evidence*: OR/HR ≥2 (risk factors) or ≤0.50 (protective factors) *and* $P < .05$ *and* heterogeneity ≤50% *and* ≥5 studies in pooled analysis *and* $P < .05$ in pooled good-quality synthesis
- *Moderate evidence*: OR/HR ≥1.5 (risk factors) or ≤0.67 (protective factors) *and* $P < .05$ *and* ≥5 studies in pooled analysis
- *Weak evidence*: OR/HR >1 (risk factor) or <1 (protective factor) *and* $P < .05$ in pooled analysis

Prognostic factors were only included in the summary table if ≥2 studies were included in the pooled analysis. The pooled subgroup analysis (univariable HR or OR and multivariable OR or HR) including the largest number of studies was selected. If the number of included studies within both subanalyses was equal, grading of the level of evidence was based on the subanalysis with the lowest heterogeneity.

Results

Search Results

The initial search identified 10,674 unique articles from the PubMed and Embase libraries. An additional 6 articles were identified through manual screening of references. We excluded 10,291 articles after screening of titles and abstracts. After full-text screening of the remaining 393 articles, 164 articles remained eligible for inclusion. The main reasons for exclusion were no evaluation of prognostic factors for aCRN (n = 76), not reporting the exact number of aCRN (n = 38), and lack of a control group (n = 31). In addition, 12 studies were excluded based on overlapping cohorts. The flow diagram of the inclusion process is shown in Figure 1.

Study Characteristics and Quality Assessment

Among the 164 studies included were 120 cohort studies and 44 case-control studies. The characteristics of all included studies are shown in Supplementary File S3. A total of 83 studies were conducted in Europe, 44 in North America, 29 in Asia, 4 in Australia or New Zealand, 2 in Africa, and 2 in South America.

The overall quality of the included studies, as assessed using the QUIPS tool, was graded as low RoB in 83 studies, moderate RoB in 32 studies, and high RoB in 49 studies (Supplementary File 5).

Prognostic Factors

Figures 2 and 3 depict the pooled results from the univariable and the multivariable analyses (OR and HR). Meta-analysis was feasible for 31 prognostic factors.

Disease Characteristics and Demographics

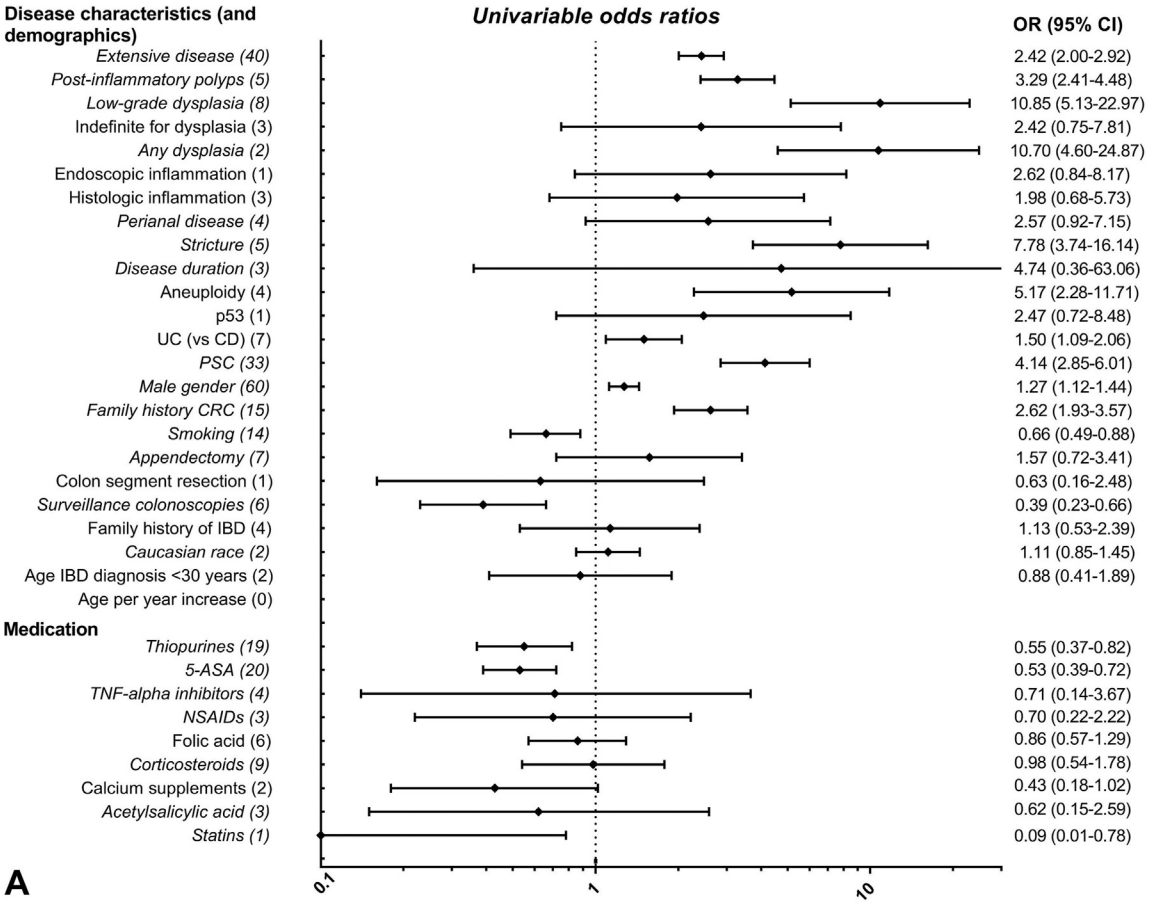
Disease Extent. The pooled univariable OR comparing extensive UC with left-sided UC was 2.43 (95% CI, 2.01-2.93; $I^2 = 0\%$), based on 40 studies. The pooled HR from 3 studies in UC was 3.48 (95% CI, 1.58-7.65). No study assessed the risk of >50% colonic involvement in patients with CD, but in 1 study, extensive CD, defined as involvement of more than two-thirds of the colon, was not associated with a higher risk compared with partial CD, defined as less than one-third of the colon (calculated OR, 0.35; 95% CI, 0.01-11.08) (Supplementary File S7*A*–*G*).[17]

Inflammatory Bowel Disease Type. The pooled univariable OR from 7 cohort studies comparing UC vs CD (ileocolonic or colonic disease) was 1.50 (95% CI, 1.09-2.06). No difference in aCRN risk between UC vs CD was found if UC patients who only had proctitis were included in the analysis (OR, 1.14; 95% CI, 0.79-1.64) (Supplementary File 8*A*–*F*).

History of Low-Grade Dysplasia. All analyses showed an increased risk of aCRN in IBD patients with a history of LGD (Supplementary File 9*A*–*E*). The pooled univariable OR from 8 studies was 10.85 (95% CI, 5.13-22.97). Although all studies reported an increased risk, the magnitude of this risk ranged widely, with ORs varying from 1.25 to 86.0. The multivariable HR of 4 studies was 3.67 (95% CI, 2.23-6.06).

History of Indefinite for Dysplasia. Four studies reported the risk of aCRN in patients with a history of indefinite for dysplasia (IND) lesions (Supplementary File 10*A*–*C*). The pooled univariable OR from 3 studies did not show a significantly increased risk (OR, 2.42; 95% CI, 0.75-7.81), but 1 cohort study with a multivariable model found a HR of 6.85 (95% CI, 1.78-26.36).[18]

Any Dysplasia (Grade Not Specified). This analysis includes only studies that did not specify the grade of


Disease characteristics (and demographics)
Univariable odds ratios
OR (95% CI)
Extensive disease (40)
2.42 (2.00-2.92)
Post-inflammatory polyps (5)
3.29 (2.41-4.48)
Low-grade dysplasia (8)
10.85 (5.13-22.97)
Indefinite for dysplasia (3)
2.42 (0.75-7.81)
Any dysplasia (2)
10.70 (4.60-24.87)
Endoscopic inflammation (1)
2.62 (0.84-8.17)
Histologic inflammation (3)
1.98 (0.68-5.73)
Perianal disease (4)
2.57 (0.92-7.15)
Stricture (5)
7.78 (3.74-16.14)
Disease duration (3)
4.74 (0.36-63.06)
Aneuploidy (4)
5.17 (2.28-11.71)
p53 (1)
2.47 (0.72-8.48)
UC (vs CD) (7)
1.50 (1.09-2.06)
PSC (33)
4.14 (2.85-6.01)
Male gender (60)
1.27 (1.12-1.44)
Family history CRC (15)
2.62 (1.93-3.57)
Smoking (14)
0.66 (0.49-0.88)
Appendectomy (7)
1.57 (0.72-3.41)
Colon segment resection (1)
0.63 (0.16-2.48)
Surveillance colonoscopies (6)
0.39 (0.23-0.66)
Family history of IBD (4)
1.13 (0.53-2.39)
Caucasian race (2)
1.11 (0.85-1.45)
Age IBD diagnosis <30 years (2)
0.88 (0.41-1.89)
Age per year increase (0)
Medication
Thiopurines (19)
0.55 (0.37-0.82)
5-ASA (20)
0.53 (0.39-0.72)
TNF-alpha inhibitors (4)
0.71 (0.14-3.67)
NSAIDs (3)
0.70 (0.22-2.22)
Folic acid (6)
0.86 (0.57-1.29)
Corticosteroids (9)
0.98 (0.54-1.78)
Calcium supplements (2)
0.43 (0.18-1.02)
Acetylsalicylic acid (3)
0.62 (0.15-2.59)
Statins (1)
0.09 (0.01-0.78)
0.1
1
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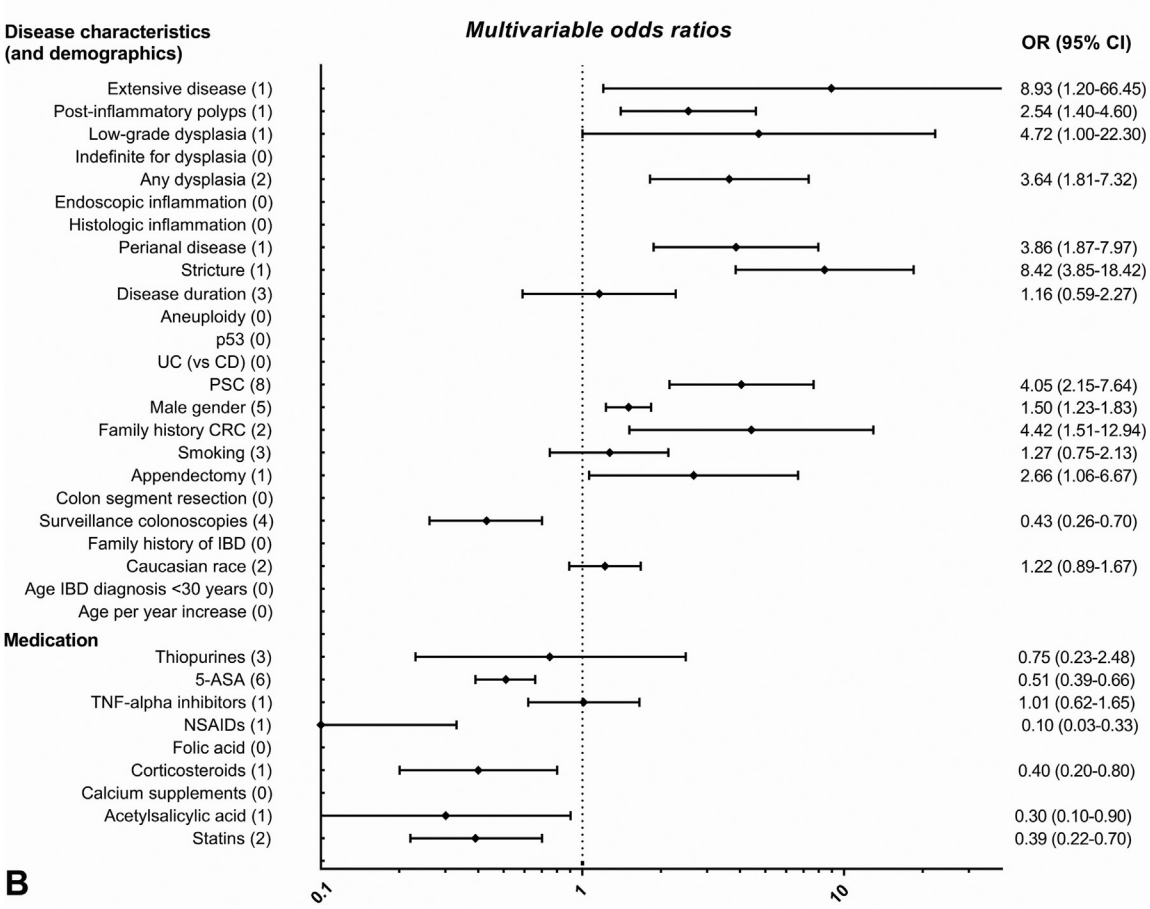

Disease characteristics (and demographics)
Multivariable odds ratios
OR (95% CI)
Extensive disease (1)
8.93 (1.20-66.45)
Post-inflammatory polyps (1)
2.54 (1.40-4.60)
Low-grade dysplasia (1)
4.72 (1.00-22.30)
Indefinite for dysplasia (0)
Any dysplasia (2)
3.64 (1.81-7.32)
Endoscopic inflammation (0)
Histologic inflammation (0)
Perianal disease (1)
3.86 (1.87-7.97)
Stricture (1)
8.42 (3.85-18.42)
Disease duration (3)
1.16 (0.59-2.27)
Aneuploidy (0)
p53 (0)
UC (vs CD) (0)
PSC (8)
4.05 (2.15-7.64)
Male gender (5)
1.50 (1.23-1.83)
Family history CRC (2)
4.42 (1.51-12.94)
Smoking (3)
1.27 (0.75-2.13)
Appendectomy (1)
2.66 (1.06-6.67)
Colon segment resection (0)
Surveillance colonoscopies (4)
0.43 (0.26-0.70)
Family history of IBD (0)
Caucasian race (2)
1.22 (0.89-1.67)
Age IBD diagnosis <30 years (0)
Age per year increase (0)
Medication
Thiopurines (3)
0.75 (0.23-2.48)
5-ASA (6)
0.51 (0.39-0.66)
TNF-alpha inhibitors (1)
1.01 (0.62-1.65)
NSAIDs (1)
0.10 (0.03-0.33)
Folic acid (0)
Corticosteroids (1)
0.40 (0.20-0.80)
Calcium supplements (0)
Acetylsalicylic acid (1)
0.30 (0.10-0.90)
Statins (2)
0.39 (0.22-0.70)
0.1
1
10
B

dysplasia. If grades of dysplasia were specified, the results were exclusively included in the analysis of IND or LGD. Four studies assessed the effect of any dysplasia on the risk of aCRN (Supplementary File 11*A*–*D*). Pooled univariable data of 2 cohort studies resulted in an OR of 10.70 (95% CI, 4.60-24.87).

Postinflammatory Polyps. The aCRN risk in patients with postinflammatory polyps (PIPs) was reported in 8 studies (Supplementary File 12*A*–*D*). The pooled univariable OR indicated that patients with PIPs were at higher risk (OR, 3.29; 95% CI, 2.41-4.48), but this association was not confirmed in the pooled HR analyses (univariable HR, 1.67 [95% CI, 0.99-2.82]; multivariable HR, 1.73 [95% CI, 0.88-3.40]).

Endoscopic Inflammation. Two studies evaluated the association of endoscopic inflammation with aCRN (Supplementary File 13*A*–*D*). One large cohort study reported a univariable HR of 2.14 (95% CI, 1.48-3.09) and a multivariable HR of 2.39 (95% CI, 1.63-3.50).[7] One case-control study calculated the mean score of endoscopic inflammation and found a higher risk of aCRN in patients with a higher score (OR, 2.62; 95% CI, 0.84-8.17 per 1-unit increase in score), although this did not reach statistical significance.[19]

Histologic Inflammation. Six studies assessed the impact of histologic inflammation on aCRN using different definitions (described in Supplementary File 14*D*). Three case-control studies provided data for calculation of a pooled univariable OR of 1.98; (95% CI, 0.68-5.73). The pooled multivariable HR of 2 cohort studies and 1 case-control study was 2.51 (95% CI, 1.75-3.61) (Supplementary File 14*A*–*D*).

Strictures. We identified 4 studies that evaluated the impact of colonic strictures on the development of aCRN. One of these studies provided data for separately analyzing UC (univariable OR, 12.74; 95% CI, 5.81-27.94) and CD (univariable OR, 4.14; 95% CI, 1.49-11.51).[20] Pooled analysis of all data on strictures in UC patients resulted in a pooled OR of 4.68 (95% CI, 0.45-48.25). Combining all data on strictures in CD patients resulted in a pooled OR of 8.03 (95% CI, 3.50-18.45). The pooled univariable analysis combining data from CD and UC patients resulted in an OR of 7.78 (95% CI, 3.74-16.18) (Figure 2). One study provided data on strictures and risk of CRC in IBD patients in a multivariable model (OR, 8.42; 95% CI, 3.85-18.42) (Supplementary File 15*A*–*C*).[20]

Perianal Disease. Risk estimates of rectal aCRN in patients with perianal disease were provided in 5 studies: 3 in CD[21–23] and 2 in CD and UC.[23,24] The pooled OR of 4 studies reporting univariable data was 2.57 (95% CI, 0.92-7.15) (Supplementary File 16*A* and *B*).

Disease Duration. Four studies evaluated the association of disease duration on the development of aCRN in predefined groups using different definitions (Supplementary File 17*A* and *B*). Both univariable and multivariable pooled analyses did not show a statistically significant difference.

Aneuploidy. Five studies evaluated the potential of DNA aneuploidy as a premalignant marker (Supplementary File 18*A*–*C*). The pooled univariable OR of 4 studies was 5.17 (95% CI, 2.28-11.71). Multivariable analysis showed a HR of 4.30 (95% CI, 2.50-7.40) in 1 case-control study.[25]

p53 Mutation. Two studies examined whether p53 mutations can serve as biomarkers for the development of aCRN (Supplementary File 19*A*–*C*). In a cohort of 95 patients with long-standing UC, p53 mutations were not predictive for aCRN (OR, 2.47; 95% CI, 0.72-8.48).[26] A case-control study found the presence of p53 mutations in random surveillance biopsy specimens was not associated with the development of CRC (multivariable HR, 1.70; 95% CI, 0.93-3.10).[25]

Primary Sclerosing Cholangitis. A concomitant diagnosis of PSC in IBD patients was associated with an increased aCRN risk, with a pooled univariable OR of 4.14 (95% CI, 2.85-6.01; $I^2 = 60\%$) based on 33 studies. There was substantial heterogeneity due to the wide range in ORs, yet almost all of the studies showed (a trend toward) an increased risk. The multivariable HR of 4 studies was 2.77 (95% CI, 1.76-4.38). Almost all separate analyses per study type demonstrated an increased risk in IBD patients with PSC (Supplementary File 20*A*–*D*).

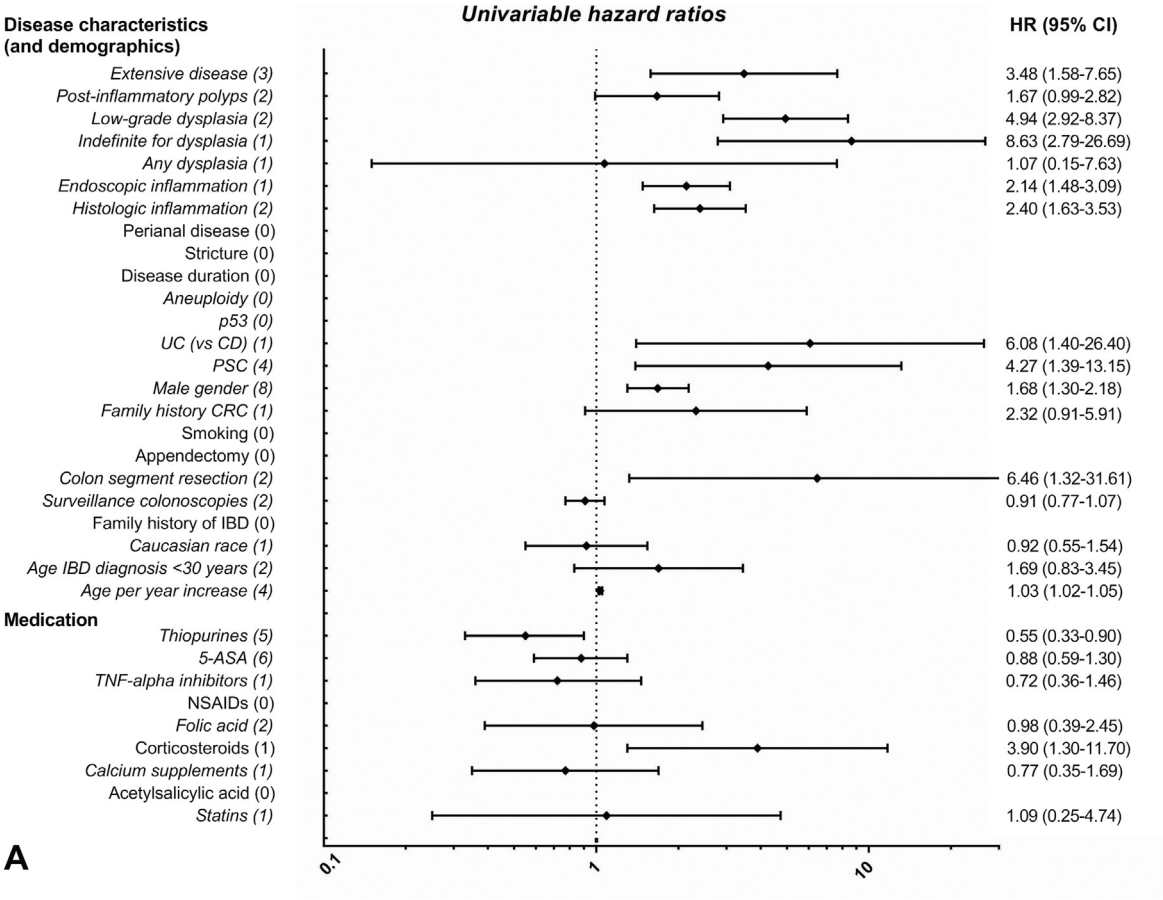
Sex. Pooled results from 60 studies showed that the aCRN risk was higher in male patients (OR, 1.27; 95% CI, 1.12-1.44; $I^2 = 30\%$). Male sex remained a significant risk factor for aCRN in the pooled multivariable HR and OR analyses (Supplementary File 21*A*–*D*).

Age. Age as a risk factor for aCRN was evaluated in 8 studies, using different definitions (Supplementary File 22*A*–*D*). Four studies used the definition "age per year increase," resulting in a pooled univariable HR of 1.031 per year (95% CI, 1.017-1.046). Three studies provided multivariable data, yielding a pooled multivariable HR of 1.036 per year (95% CI, 1.012-1.061).

Family History of Colorectal Carcinoma. Data from 15 studies showed that a positive family history of CRC was associated with a higher aCRN risk (OR, 2.62; 95% CI, 1.93-3.57; $I^2 = 0\%$) (Supplementary File 23*A*–*E*). Six studies restricted family history of CRC to first-degree relatives (pooled OR, 2.48; 95% CI, 1.49-4.14). A combination of the remaining 9 studies using different definitions (any relative, second-degree relative) or not providing one resulted in a pooled OR of 2.59 (95% CI, 1.59-4.21).

Family History of Inflammatory Bowel Disease. Four studies evaluating the impact of a positive family history of IBD on the aCRN risk did not report a significant association (univariable OR, 1.13; 95% CI, 0.53-2.39) (Supplementary File 24*A*).

Figure 2. (*A*) Univariable and (*B*) multivariable ORs of all potential prognostic factors. Prognostic factor (number of studies) (*right column*): OR and 95% CI from pooled analysis (pooled data if ≥2 studies were included in analysis). *NSAIDs*, nonsteroidal anti-inflammatory drugs.


Univariable hazard ratios
Disease characteristics (and demographics)
HR (95% CI)
Extensive disease (3) 3.48 (1.58-7.65)
Post-inflammatory polyps (2) 1.67 (0.99-2.82)
Low-grade dysplasia (2) 4.94 (2.92-8.37)
Indefinite for dysplasia (1) 8.63 (2.79-26.69)
Any dysplasia (1) 1.07 (0.15-7.63)
Endoscopic inflammation (1) 2.14 (1.48-3.09)
Histologic inflammation (2) 2.40 (1.63-3.53)
Perianal disease (0)
Stricture (0)
Disease duration (0)
Aneuploidy (0)
p53 (0)
UC (vs CD) (1) 6.08 (1.40-26.40)
PSC (4) 4.27 (1.39-13.15)
Male gender (8) 1.68 (1.30-2.18)
Family history CRC (1) 2.32 (0.91-5.91)
Smoking (0)
Appendectomy (0)
Colon segment resection (2) 6.46 (1.32-31.61)
Surveillance colonoscopies (2) 0.91 (0.77-1.07)
Family history of IBD (0)
Caucasian race (1) 0.92 (0.55-1.54)
Age IBD diagnosis <30 years (2) 1.69 (0.83-3.45)
Age per year increase (4) 1.03 (1.02-1.05)
Medication
Thiopurines (5) 0.55 (0.33-0.90)
5-ASA (6) 0.88 (0.59-1.30)
TNF-alpha inhibitors (1) 0.72 (0.36-1.46)
NSAIDs (0)
Folic acid (2) 0.98 (0.39-2.45)
Corticosteroids (1) 3.90 (1.30-11.70)
Calcium supplements (1) 0.77 (0.35-1.69)
Acetylsalicylic acid (0)
Statins (1) 1.09 (0.25-4.74)
0.1
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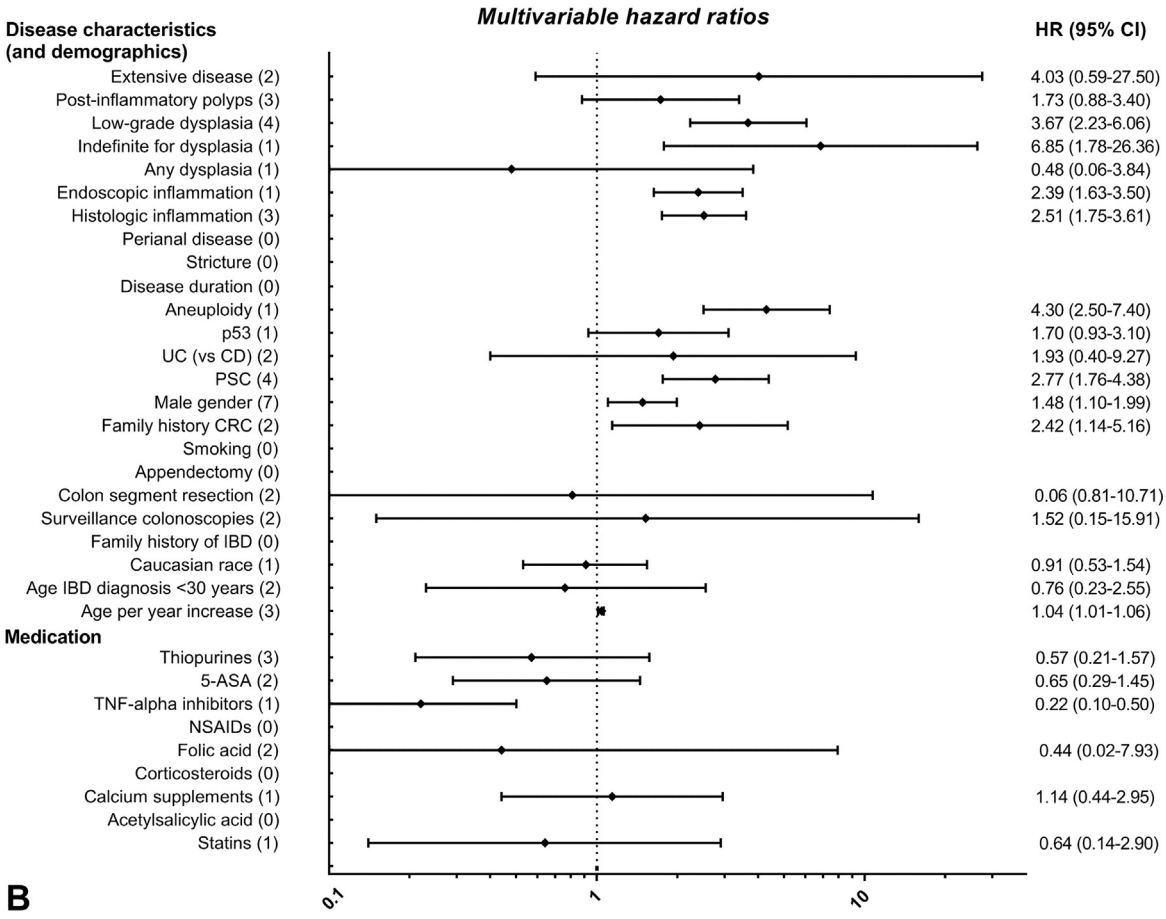
A


Multivariable hazard ratios
Disease characteristics (and demographics)
HR (95% CI)
Extensive disease (2) 4.03 (0.59-27.50)
Post-inflammatory polyps (3) 1.73 (0.88-3.40)
Low-grade dysplasia (4) 3.67 (2.23-6.06)
Indefinite for dysplasia (1) 6.85 (1.78-26.36)
Any dysplasia (1) 0.48 (0.06-3.84)
Endoscopic inflammation (1) 2.39 (1.63-3.50)
Histologic inflammation (3) 2.51 (1.75-3.61)
Perianal disease (0)
Stricture (0)
Disease duration (0)
Aneuploidy (1) 4.30 (2.50-7.40)
p53 (1) 1.70 (0.93-3.10)
UC (vs CD) (2) 1.93 (0.40-9.27)
PSC (4) 2.77 (1.76-4.38)
Male gender (7) 1.48 (1.10-1.99)
Family history CRC (2) 2.42 (1.14-5.16)
Smoking (0)
Appendectomy (0)
Colon segment resection (2) 0.06 (0.81-10.71)
Surveillance colonoscopies (2) 1.52 (0.15-15.91)
Family history of IBD (0)
Caucasian race (1) 0.91 (0.53-1.54)
Age IBD diagnosis <30 years (2) 0.76 (0.23-2.55)
Age per year increase (3) 1.04 (1.01-1.06)
Medication
Thiopurines (3) 0.57 (0.21-1.57)
5-ASA (2) 0.65 (0.29-1.45)
TNF-alpha inhibitors (1) 0.22 (0.10-0.50)
NSAIDs (0)
Folic acid (2) 0.44 (0.02-7.93)
Corticosteroids (0)
Calcium supplements (1) 1.14 (0.44-2.95)
Acetylsalicylic acid (0)
Statins (1) 0.64 (0.14-2.90)
0.1
1
10
B

Smoking. Patients with a history of smoking had a lower risk of developing aCRN in univariable but not in multivariable analysis. The pooled univariable OR in 14 studies was 0.66 (95% CI, 0.49-0.88; $I^2 = 28\%$). All studies but 2[27,28] included only UC patients. The pooled multivariable OR of 3 studies was 1.27 (95% CI, 0.75-2.13), based on 1 study providing data from a UC cohort[29] and 2 studies from IBD cohorts (Supplementary File 25*A*–*C*).

Appendectomy. Seven studies evaluated the impact of appendectomy on the aCRN risk (Supplementary File 26*A* and *B*). The pooled univariable OR was 1.57 (95% CI, 0.72-3.41). All data were derived from UC cohorts except for 1 study consisting of a CD cohort.[27] One study reporting a multivariable OR did show a higher risk of aCRN in patients with an appendectomy before the UC diagnosis (OR, 2.66; 95% CI, 1.06-6.67).[30]

Age at Inflammatory Bowel Disease Diagnosis. Studies that compared the impact of young vs old age at IBD diagnosis (n = 12) on aCRN development used a wide range of cutoff ages, ranging from 25 to 60 years (Supplementary File 27*A*–*G*); therefore, only a few studies could be pooled. The pooled univariable OR from 3 cohort studies comparing age <30 years vs ≥30 years was 1.00 (95% CI, 0.59-1.70). The pooled univariable HR of 2 studies was 1.69 (95% CI, 0.83-3.45), whereas data from 2 studies in a multivariable model reported a pooled HR of 0.76 (95% CI, 0.23-2.55).

Colon Segment Resection. Four studies evaluated the impact of colon segment resection on the development of aCRN. Three of these studies did not specify the indication for resection (Supplementary File 28*D*). The pooled univariable HR of 2 cohort studies (1 study including IBD patients and 1 study including UC and IBD unclassified patients) showed an increased risk of aCRN in patients with a history of a colon segment resection of 6.46 (95% CI, 1.32-31.61). In contrast, 1 case-control study in CD patients did not find an association (univariable OR, 0.63; 95% CI, 0.16-2.48).[27] The pooled multivariable analysis of 2 studies including IBD patients also did not find an association (HR, 0.81; 95% CI, 0.06-10.71). One of these studies, in which patients were excluded who received colon segment resection because of a diagnosis of neoplasia, reported a lower risk of aCRN (HR, 0.25; 95% CI, 0.07-0.89) (Supplementary File 28*A*–*D*).[31]

Surveillance Colonoscopies. The definition of surveillance colonoscopies varied widely between studies. Pooling of studies in which overlapping definitions were used (as specified in Supplementary File 29*E* and *F*) yielded conflicting results in subgroup analyses. Pooled univariable and multivariable OR analyses showed a lower risk of aCRN in patients enrolled in surveillance programs (univariable OR, 0.39; 95% CI, 0.23-0.66; multivariable OR, 0.43; 95% CI, 0.26-0.70). However, this protective effect was not observed in the pooled univariable and multivariable HR analyses. Of note, there was considerable heterogeneity between studies.

Race. Three studies evaluated the role of race as a risk factor for aCRN (Supplementary File 30*A*–*D*). No differences were found in studies comparing Caucasian race vs other race or African American race in all subanalyses (univariable OR of 2 studies, 1.11; 95% CI, 0.85-1.45).

Medication

Thiopurines. Thiopurine use was associated with a lower aCRN risk (pooled univariable OR, 0.55; 95% CI, 0.37-0.82; $I^2 = 66\%$). This pooled analysis included 19 studies. The pooled univariable HR from 5 studies was 0.55 (95% CI, 0.33-0.90). In contrast, the pooled multivariable OR and HR did not show a statistically significant protective effect (Supplementary File 31*A*–*E*).

5-Aminosalicylic Acid. Patients who ever received 5-aAminosalicylic acid (5-ASA) had a lower risk of aCRN, with a pooled univariable OR of 0.53 (95% CI, 0.39-0.72; $I^2 = 67\%$). Six studies that provided multivariable ORs showed a lower risk as well (pooled OR, 0.51; 95% CI, 0.39-0.66) (Supplementary File 32*A*–*E*).

Tumor Necrosis Factor-α Inhibitors. Six studies evaluated the use of tumor necrosis factor-α (TNF-α) inhibitors in relation to aCRN. Our pooled univariable analysis of 4 studies did not show a protective effect (OR, 0.71; 95% CI, 0.14-3.67). One cohort study did not report a protective effect of anti-TNF-α in a multivariable model (OR, 1.01; 95% CI, 0.62-1.65).[32] One case-control study showed a protective effect of anti-TNF-α in a multivariable hazard model (HR, 0.22; 95% CI, 0.10-0.50) (Supplementary File 33*A*–*E*).[33]

Nonsteroidal Anti-inflammatory Drugs. No significant effect of the use of nonsteroidal anti-inflammatory drugs on aCRN risk was found in 3 case-control studies. The pooled OR was 0.70 (95% CI, 0.22-2.22) (Supplementary File 34*A*–*C*). In contrast, the only study reporting nonsteroidal anti-inflammatory drugs use in a multivariable model did report a lower risk (OR, 0.10; 95% CI, 0.03-0.33).[29]

Folic Acid. Of 9 studies reporting on the effect of folic acid use, only 1 found a significant protective effect (Supplementary File 35*A*–*D*).[34] The pooled univariable OR of 6 studies was 0.86 (95% CI, 0.57-1.29). The pooled multivariable HR from 2 cohort studies was 0.44 (95% CI, 0.02-7.93).

Corticosteroids. The impact of corticosteroids on the risk of aCRN was studied in 10 studies. The pooled univariable analysis of 9 studies resulted in an OR of 0.98 (95% CI, 0.54-1.78) (Supplementary File 36*A*–*D*).

Statins. One cohort study found no lower risk in patients who used statins in a univariable model (HR, 1.09; 95% CI, 0.25-4.74).[35] In contrast, the pooled multivariable OR from 2 studies was 0.39 (95% CI, 0.22-0.70) (Supplementary File 37*A*–*E*).

Figure 3. (*A*) Univariable and (B) multivariable HRs of all potential prognostic factors. Prognostic factor (number of studies), *right column*: HR and 95% CI from pooled analysis (pooled data if ≥2 studies were included in analysis). *NSAIDs*, nonsteroidal anti-inflammatory drugs.

Calcium Supplements. Use of calcium supplements was associated with a nonsignificant decreased risk of aCRN in 2 studies (OR, 0.43; 95% CI, 0.18-1.02) (Supplementary File 38*A–D*).

Acetylsalicylic Acid. There was no association between the use of acetylsalicylic acid and aCRN. The pooled univariable OR from 3 studies was 0.62 (95% CI, 0.15-2.59). A multivariable analysis suggested a protective effect of acetylsalicylic acid in 1 other study (OR, 0.30; 95% CI, 0.10-0.90) (Supplementary File 39*A–C*).[29]

Other Factors

Potential prognostic factors reported in only 1 study are shown in Supplementary File 40*A–L*.

Good-Quality Synthesis

Forty studies fulfilled the criteria for "good quality" using the previously defined terms. The results of (pooled) analysis of these studies are shown in Figures 4 and 5. Extensive disease, LGD, UC (vs CD), aneuploidy, PSC, and male sex remained risk factors for aCRN in this analysis. Thiopurine use remained a protective factor for aCRN (Supplementary File 41*A–F*).

Summary

Figure 6 summarizes the quality of evidence of the identified prognostic factors categorized as strong, moderate, or weak.

Publication Bias

The Egger's regression test did not show statistically significant funnel plot asymmetry for any prognostic factor (Supplementary File 42). However, visual inspection of funnel plots suggests asymmetry and thus potential publication bias for male sex, family history of CRC, 5-ASA, and thiopurine use (Supplementary File 43).

Meta-regression (Univariable Odds Ratio Analyses)

Thiopurines, 5-ASA, and disease extent were evaluated in a meta-regression analysis to assess temporal changes of their respective prognostic values, using year of cohort as covariate. None showed statistically significant variation over time, although the scatterplot for thiopurines indicated a trend toward a reduced risk (results and interpretation are provided in Supplementary File 44*A–C*).

Discussion

Main Findings

This is the first systematic review and meta-analysis of all factors that potentially affect the risk of aCRN in IBD patients. Based on 164 studies, we identified 31 prognostic factors for which pooled analysis was possible. Using stringent criteria to summarize the level of evidence for all identified prognostic factors (Figure 6), we found strong evidence for the risk factor extensive disease, moderate evidence for LGD, strictures, PSC, PIPs, family history CRC, and IBD type, and weak evidence for any dysplasia, colon segment resection, aneuploidy, male sex, and age in univariable analysis. In multivariable analysis, there was weak evidence for histologic inflammation. Protective factors with moderate evidence in univariable analysis were surveillance colonoscopies, 5-ASA, thiopurines, and smoking. In multivariable analysis, there was weak evidence for statin use as a protective factor.

Summary of Identified Risk Factors for Advanced Colorectal Neoplasia

Several established premalignant markers were identified as risk factors for aCRN, including LGD, any dysplasia, and aneuploidy. IBD patients with LGD had an increased risk in both univariable and multivariable analyses, although the magnitude of the impact of LGD varied widely between studies ($I^2 = 69\%$). The latter can at least partially be ascribed to interobserver variability between pathologists,[36,37] the heterogeneous morphology of the lesions, differences in quality of endoscopic visualization techniques, and treatment variation (eg, biopsy, polypectomy, or surgery). Of note, the interobserver variance might even be greater for IND.[36] Aneuploidy seems to be a promising predictor of aCRN as well (pooled univariable OR of 4 studies, 5.17; 95% CI, 2.28-11.71). These results are in line with a previous meta-analysis that reported a high risk of CRC in patients with aneuploidy,[38] although this meta-analysis included patients with aneuploidy who already had developed dysplasia. The impact of p53 mutations was only assessed in 2 studies and did not reach statistical significance, and pooled analysis was not possible. The increased aCRN risk in IBD patients with premalignant lesions has been attributed to the concept of field cancerization. This concept implies that clonal molecular abnormalities in otherwise histologically normal-appearing mucosa throughout the colon causes colitis-associated cancer susceptibility.[39,40] Identification of these preneoplastic fields seems a promising and rational approach for surveillance of patients with long-standing colitis.

Although we identified colon segment resection as a risk factor for aCRN, the true impact of this factor remains uncertain. It is conceivable that segment resection was indicated for neoplastic lesions or therapy-refractory disease, which might have led to divergent effects on the risk of aCRN. Because most studies did not specify the indication for surgery, a clear answer to the question of whether resection protects against aCRN or is associated with a higher risk cannot be provided.

Several (surrogate) markers for chronic inflammation were found to be robust predictors of aCRN, ranging from histologic inflammation scores to disease extent, strictures, and possibly the presence of PIPs. Because studies reported different estimates of effects on endoscopic inflammation scores, a pooled analysis was not possible, although all studies showed promising results. Notable is that 1 cohort study reported endoscopic inflammation scored during

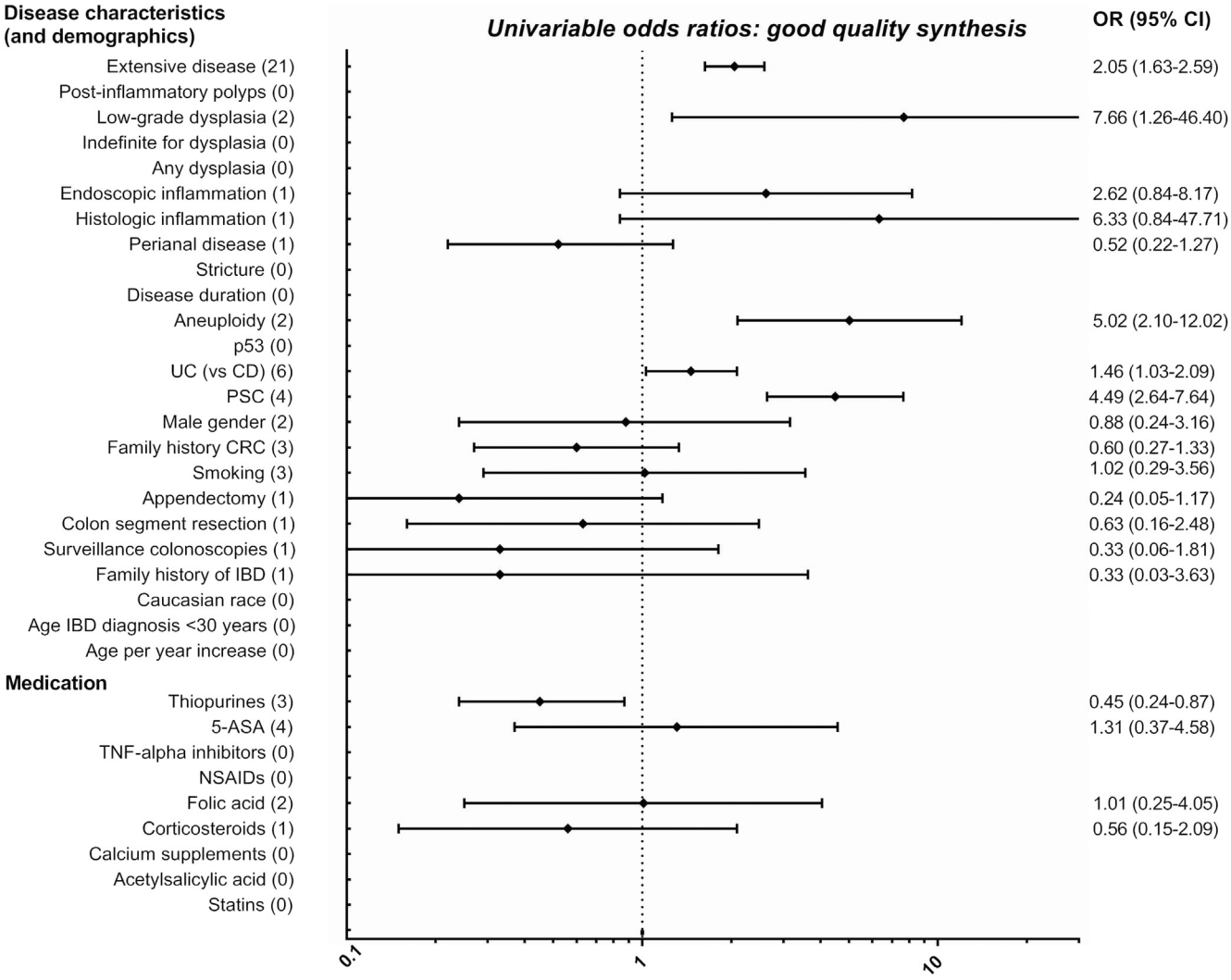


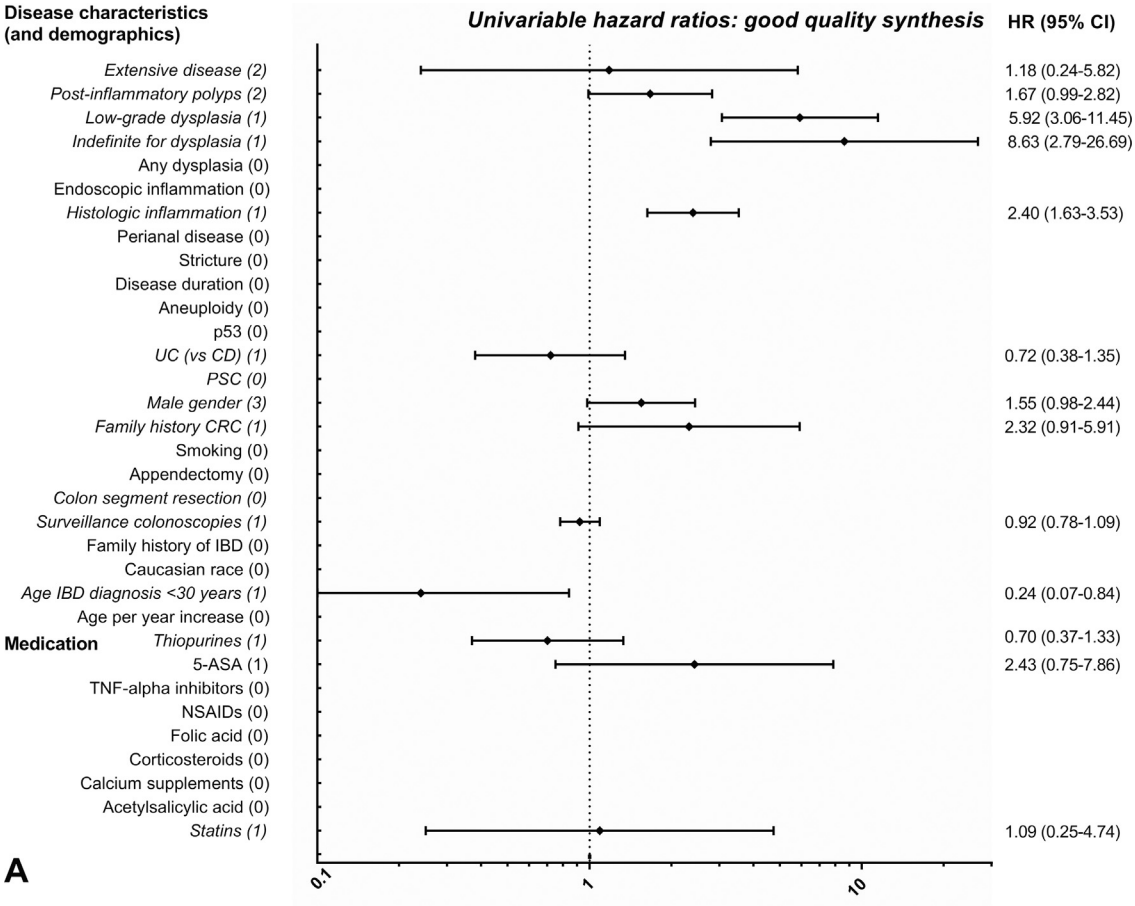
Figure 4. Univariable ORs good-quality synthesis. Prognostic factor (number of studies), *right column*: OR and 95% CI from pooled analysis (pooled data if ≥2 studies were included in analysis). *NSAIDs*, nonsteroidal anti-inflammatory drugs.

surveillance colonoscopies to remain a risk factor for aCRN in a multivariable model (HR. 2.39; 95% CI, 1.63-3.50).[7] To our knowledge, no previous meta-analysis evaluated these markers for inflammation as risk factors for aCRN. The observed negative association of thiopurine use, 5-ASA use, and smoking (in UC) with aCRN probably results from their anti-inflammatory effects. The protective effect of treatment with 5-ASA and thiopurines might be confounded by patient profile or additional excipients; therefore, the protective effect should not just be interpreted as a causal effect. Current guidelines use surrogate markers for inflammation, such as PIPs and strictures, to stratify patients in risk categories.[2–5]

Cumulative inflammatory burden scores have been hypothesized to be more direct and reliable predictors for the risk of (a)CRN. Indeed, recent studies support this concept,[41–43] although how to construct the optimal cumulative inflammatory burden score is not clear. It can be questioned whether surrogate markers for inflammation should still be used to stratify patients. For example, we observed that PIPs were not an independent risk factor for aCRN risk if outcomes were adjusted for the mean inflammation score.[44,45]

A concomitant diagnosis of PSC is an established risk factor for aCRN (univariable OR, 4.14 [95% CI, 2.85-6.01]; multivariable OR, 3.53 [95% CI, 1.83-6.79]). This increased risk is in line with the result of a previous meta-analysis that reported a pooled univariable OR for CRC of 3.41 (95% CI, 2.13-5.48).[46] Our study included several relevant new studies, and aCRN, instead of CRC only, was used as an outcome parameter. The mechanisms underlying the increased risk of CRC in IBD patients with PSC have yet to be clarified. Several studies suggested a role for the altered colonic bile composition in PSC, but intestinal dysbiosis[47] or a distinct genotype might also play a role.[48]

Genetic predisposition contributes importantly to CRC development in the general population,[49] but its role in IBD is less well-defined. We observed an increased risk of aCRN in IBD patients with a family history of CRC (OR, 2.62; 95%


Disease characteristics (and demographics)
Univariable hazard ratios: good quality synthesis
HR (95% CI)
Extensive disease (2)
1.18 (0.24-5.82)
Post-inflammatory polyps (2)
1.67 (0.99-2.82)
Low-grade dysplasia (1)
5.92 (3.06-11.45)
Indefinite for dysplasia (1)
8.63 (2.79-26.69)
Any dysplasia (0)
Endoscopic inflammation (0)
Histologic inflammation (1)
2.40 (1.63-3.53)
Perianal disease (0)
Stricture (0)
Disease duration (0)
Aneuploidy (0)
p53 (0)
UC (vs CD) (1)
0.72 (0.38-1.35)
PSC (0)
Male gender (3)
1.55 (0.98-2.44)
Family history CRC (1)
2.32 (0.91-5.91)
Smoking (0)
Appendectomy (0)
Colon segment resection (0)
Surveillance colonoscopies (1)
0.92 (0.78-1.09)
Family history of IBD (0)
Caucasian race (0)
Age IBD diagnosis <30 years (1)
0.24 (0.07-0.84)
Age per year increase (0)
Medication
Thiopurines (1)
0.70 (0.37-1.33)
5-ASA (1)
2.43 (0.75-7.86)
TNF-alpha inhibitors (0)
NSAIDs (0)
Folic acid (0)
Corticosteroids (0)
Calcium supplements (0)
Acetylsalicylic acid (0)
Statins (1)
1.09 (0.25-4.74)
0.1
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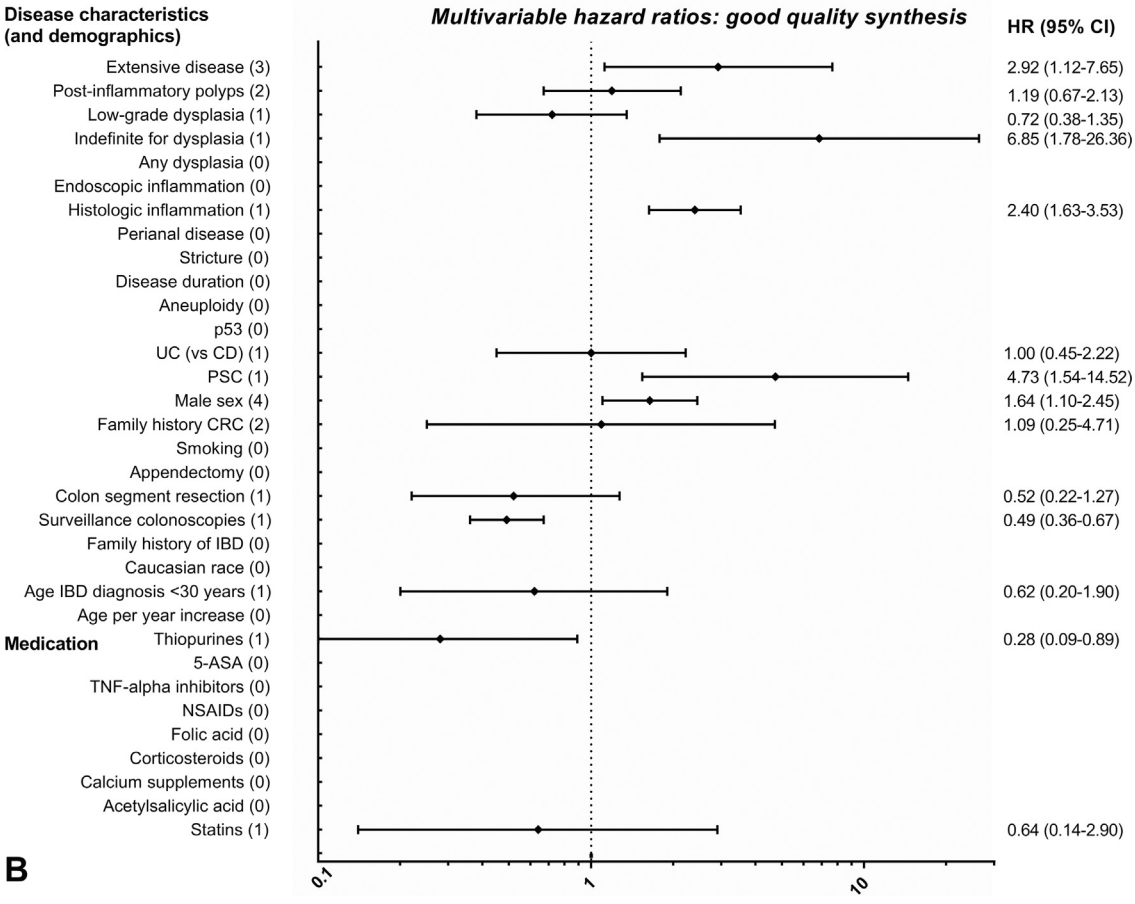
Disease characteristics (and demographics)
Multivariable hazard ratios: good quality synthesis
HR (95% CI)
Extensive disease (3)
2.92 (1.12-7.65)
Post-inflammatory polyps (2)
1.19 (0.67-2.13)
Low-grade dysplasia (1)
0.72 (0.38-1.35)
Indefinite for dysplasia (1)
6.85 (1.78-26.36)
Any dysplasia (0)
Endoscopic inflammation (0)
Histologic inflammation (1)
2.40 (1.63-3.53)
Perianal disease (0)
Stricture (0)
Disease duration (0)
Aneuploidy (0)
p53 (0)
UC (vs CD) (1)
1.00 (0.45-2.22)
PSC (1)
4.73 (1.54-14.52)
Male sex (4)
1.64 (1.10-2.45)
Family history CRC (2)
1.09 (0.25-4.71)
Smoking (0)
Appendectomy (0)
Colon segment resection (1)
0.52 (0.22-1.27)
Surveillance colonoscopies (1)
0.49 (0.36-0.67)
Family history of IBD (0)
Caucasian race (0)
Age IBD diagnosis <30 years (1)
0.62 (0.20-1.90)
Age per year increase (0)
Medication
Thiopurines (1)
0.28 (0.09-0.89)
5-ASA (0)
TNF-alpha inhibitors (0)
NSAIDs (0)
Folic acid (0)
Corticosteroids (0)
Calcium supplements (0)
Acetylsalicylic acid (0)
Statins (1)
0.64 (0.14-2.90)
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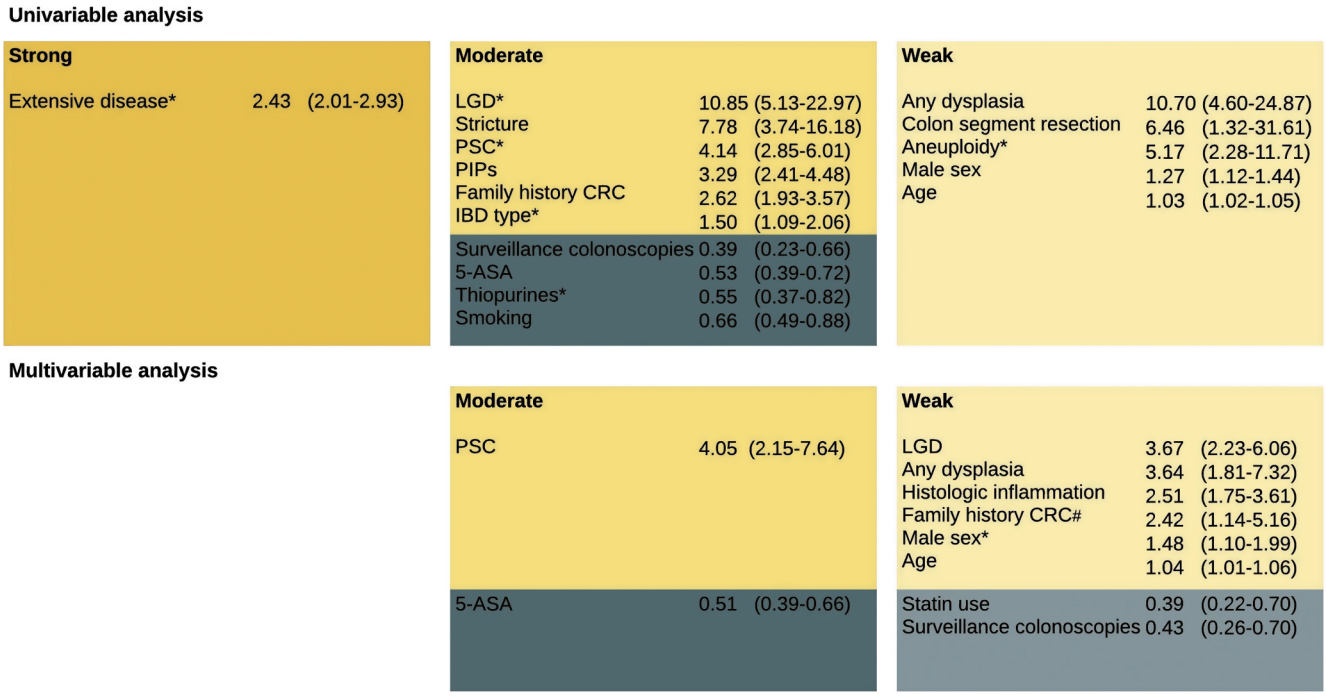

Figure 6. Summary of all identified risk and protective factors for aCRN. Prognostic factors were included in the summary table if pooled analysis was possible ($\geq$2 studies in the pooled analysis). Categorization based on the subanalysis (OR or HR) including most studies; if equal, the subanalysis with the lowest heterogeneity was selected. Level of evidence: **Strong evidence:** OR/HR $\geq$2 (risk factor) or $\leq$0.50 (protective factor) *and* $P < .05$ *and* heterogeneity $\leq$50% *and* $\geq$5 studies in pooled analysis *and* $P < .05$ in pooled good-quality synthesis. **Moderate evidence:** OR/HR $\geq$1.5 (risk factor) or $\leq$0.67 (protective factor) *and* $P < .05$ *and* $\geq$5 studies in pooled analysis. **Weak evidence:** OR/HR $>$1 (risk factor) or $<$1 (protective factor) *and* $P < .05$ in pooled analysis. *Significant prognostic factor in good-quality synthesis. #Equal number of studies and heterogeneity, estimate of effect is based on the smallest CI.

CI, 1.93-3.57) based on 15 studies. No other meta-analysis is available for comparison. The increased risk in male patients (OR, 1.27; 95% CI, 1.12-1.44), based on 60 studies, is in line with the male preponderance of CRC in the general population. In the general population, the cause of this increased risk is believed to be multifactorial.[50] We identified increasing age as a risk factor for aCRN in IBD patients, which is in line with data from the general population.[51] The remaining prognostic factors are discussed in Supplementary File 45.

Strengths and Limitations

Our study has several strengths. This meta-analysis was performed in accordance with the MOOSE guidelines for systematic reviews and meta-analysis.[10] An important contribution of this study is that we attempted to determine the level of evidence for all prognostic factors and to quantify the magnitude of impact of all published prognostic factors. The use of broad search terms and the lack of restrictions on country of origin ensured the identification of all prognostic factors for aCRN in IBD. We also included studies that did not report effect estimates but provided sufficient data to calculate the ORs. Moreover, the scale of our endeavor enabled us to perform subgroup analyses based on study design (case-control or cohort study) and type of outcome (univariable/multivariable and OR/HR). Last, we performed a separate synthesis, including only those studies that fulfilled the criteria of good quality.

Our study has several limitations worth noting. First, considerable heterogeneity between studies for several prognostic factors was found, possibly due to regional differences and changes over time with respect to screening and therapeutic strategies. Of note, the level of heterogeneity as expressed by I^2 could incorrectly be too high or too low in small meta-analyses.[13] By performing subgroup analyses per estimate of effect and per study design we aimed to reduce heterogeneity caused by methodology. Moreover, multivariable data on prognostic factors were derived from studies using different techniques of model building and taking into account a varying set of covariates (specified in Supplementary File 4).

Second, most of the included studies had a retrospective study design, introducing inherent biases such as selection, missing data, and lack of predefined end points. Moreover,

Figure 5. (*A*) Univariable and (*B*) multivariable HRs good-quality synthesis. Prognostic factor (number of studies), *right column*: HR and 95% CI from pooled analysis (pooled data if $\geq$2 studies were included in analysis). *NSAIDs*, nonsteroidal anti-inflammatory drugs.

we could not correct for the interval between surveillance colonoscopies because this information was rarely provided. Of note, prospective studies are often not performed in this field, given the large number of patients and the long-term follow-up that is needed.

Third, some of the included studies assessed the aCRN risk in patients with only proctitis (UC) or ileal disease (CD), which must have influenced the effect sizes of the prognostic factors. To overcome this problem, we adjusted the study selection criteria for the analysis of disease extent and IBD type as a risk factor (Supplementary Files 7*G* and 8*F*), and additional selection criteria were applied for the good-quality synthesis.

The present study provides information on all relevant predictors for aCRN and their respective effect sizes and can therefore help us and other research groups design novel prediction tools for patient stratification in this setting. We feel that a reliable and easy-to-use model should be based on a combination of clinical or endoscopic risk factors accounting for the number of risk factors present and the associated effect size of these factors rather than the presence of just 1 risk factor.

The addition of (a set of) biomarkers can be expected to considerably improve the predictive power of a new model. We identified several biomarkers for which the evidence is still incomplete, such as IND, aneuploidy, and p53 mutations. Future studies should clarify the impact of these factors.

In addition, whereas univariable data are abundant, there is a lack of evidence on prognostic factors for aCRN from multivariable models (only 37 of the 164 included studies reported multivariable data). This demonstrates the need for large surveillance cohorts with long-term follow-up that correct for important confounders.

Conclusion

In this systematic review and meta-analysis we provided more precise risk estimates of all known prognostic factors for aCRN in IBD patients. We identified 13 risk and 5 protective factors based on univariable and/or multivariable pooled analyses for aCRN in IBD patients. These findings may aid in the development of an improved CRC risk stratification model in IBD patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.12.036

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