Prognostic factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis

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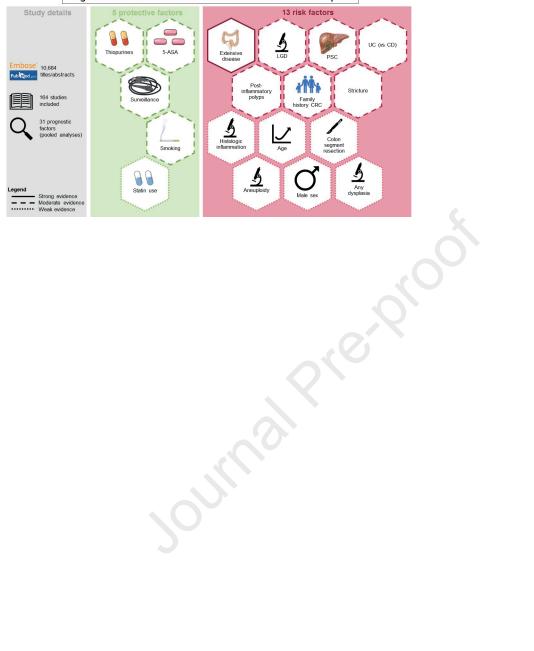
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Prognostic factors for colitis associated advanced colorectal neoplasia



Prognostic factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis

Short title: Prognostic factors for aCRN in IBD

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List of abbreviations

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

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HR	hazard ratio
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease unclassified
IND	indefinite dysplasia
IQR	interquartile range
LGD	low-grade dysplasia
NSAIDs	non-steroidal anti-inflammatory drugs
n	number
OR	odds ratio
PIPs	post-inflammatory polyps
PSC	primary sclerosing cholangitis
QUIPS	quality in prognostic studies
RoB	risk of bias
S	supplementary file
TNF	tumor necrosis factor
UC	ulcerative colitis

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Disclosures

All authors declare no conflicts of interest

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M.L: Study concept and design; study supervision; interpretation of data; drafting of manuscript.

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S.E.: Study concept and design; study supervision; interpretation of data; drafting of manuscript.

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ABSTRACT

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 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-ASA, thiopurines, and smoking was moderate in univariable analysis. Multivariable analysis provided weak evidence for statin use.

Conclusion: 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.

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INTRODUCTION

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 terms of a reduced 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 1-3 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 histological 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.

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) prior to the literature search (checklist MOOSE provided in supplementary file 1 (S1)).¹⁰

Search strategy

A comprehensive literature search using broad search criteria was conducted in the PubMed and EMBASE databases (date: July 10th, 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 S2. 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 two 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 one 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 non-exposed 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 one 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 dataentry 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). Details of all included studies are provided in S3. If relative risks (RR) were reported and additional data were provided we calculated the OR because only 6 studies reported a RR 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 S4. 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 (S5).¹¹ The criteria of the QUIPS tool were expanded to enable grading of all included studies (S6). 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 one scoring moderate RoB, studies were categorized as low RoB.

Studies were graded as high RoB if one or more domains were scored as high RoB or if ≥3 domains were scored as moderate RoB. Remaining studies were graded as moderate RoB. Domain five, 'study confounding', was not considered in grading the overall quality since few studies reported multivariable models.

Prognostic factors

All potential prognostic factors reported in literature were included without any preselection. All prognostic factors that were reported in \geq 1 study are discussed in the results section while related forest plots are shown in S7-S39. In addition, the factors endoscopic inflammation and p53 mutations were included, even though pooled analysis was not possible. The remaining factors are reported in S40.

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). I² statistics were used to assess the heterogeneity among studies. These were only reported in the manuscript if ≥10 studies were included, because I² results in small meta-analyses tend to be inaccurate.¹³ An I² ≥ 50% indicates substantial (50% to 90%) to considerable (75% to 100%) heterogeneity.¹⁴ These analyses were provided in the supplementary files of the prognostic factor. Meta-analyses were performed using Review Manager, version 5.3 (Cochrane

Collaboration, Copenhagen, Denmark). R statistical software, version 3.5.1 (Metafor package), 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 \geq 10 studies were available.¹⁴ A p-value < .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 \geq 10 studies reporting on these prognostic factors were available.¹⁴ Year of cohort was used as a covariate in meta-regression analysis, defined as 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', 2) only UC patients with at least left-sided disease or 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 four criteria to be graded as 'strong evidence').

Strong evidence: OR/HR ≥2 (risk factor) or ≤0.50 (protective factor) and P-value < .05 and heterogeneity ≤50% and ≥5 studies in pooled analysis and P-value < .05 in pooled good quality synthesis

- Moderate evidence: OR/HR ≥1.5 (risk factor) or ≤0.67 (protective factor) and
 P-value < .05 and ≥5 studies in pooled analysis
- Weak evidence: OR/HR >1 (risk factor) or <1 (protective factor) and P-value <
 .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 sub-analyses was equal, grading of the level of evidence was based on the sub-analysis with the lowest heterogeneity.

RESULTS

Search results

The initial search identified 10,674 unique articles from PubMed and Embase libraries. An additional 6 articles were identified through manual screening of references. A total of 10,291 articles were excluded 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 (number (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

A total of 164 studies were included (120 cohort studies, 44 case-control studies). The characteristics of all included studies are shown in 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 (S5).

Prognostic factors

Figure 2 and figure 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 one study, extensive CD, defined as involvement of >2/3rd of the colon was not associated with a higher risk as compared to partial CD (less than 1/3rd of the colon) (calculated OR 0.35, 95%CI 0.01-11.08) (S7A-G).¹⁷

IBD type

The pooled univariable OR from 7 cohort studies comparing UC versus CD (ileocolonic or colonic disease) was 1.50 (95%CI 1.09-2.06. No difference in aCRN

risk between UC versus CD was found if UC patients who only had proctitis were included in the analysis (OR 1.14 (95%CI 0.79-1.64) (S8A-F).

History of LGD

All analyses showed an increased risk of aCRN in IBD patients with a history of LGD (S9A-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 on the risk of aCRN in patients with a history of indefinite for dysplasia (IND) lesions (S10A-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 one 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 dysplasia. If grades of dysplasia were specified, the results were exclusively included in the analysis of IND or LGD. Four studies assessed the impact of any dysplasia on the risk of aCRN (S11A-D). Pooled univariable data of 2 cohort studies resulted in an OR of 10.70 (95%CI 4.60-24.87).

Post-inflammatory polyps

The aCRN risk in patients with post-inflammatory polyps (PIPs) was reported in 8 studies (S12A-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 (S13A-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 S14D). Three case-control studies provided data for calculation of a pooled univariable OR (1.98, 95%CI 0.68-5.73). The pooled multivariable HR of 2 cohort studies and one case-control study was 2.51 (95%CI 1.75-3.61) (S14A-D).

Strictures

Four studies were identified in which the impact of colonic strictures on development of aCRN was evaluated. One of these studies provided data for analyzing UC and CD separately (UC: univariable OR 12.74, 95%CI 5.81-27.94; 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, shown in 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) (S15A-C).²⁰

Perianal disease

Five studies provided risk estimates of rectal aCRN in patients with perianal disease (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) (S16A-B).

Disease duration

Four studies evaluated the association of disease duration on the development of aCRN in predefined groups using different definitions (S17A-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 (S18A-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 one case-control study.²⁵

P53 mutation

Two studies examined whether p53 mutations can serve as biomarkers for development of aCRN (S19A-C). In a cohort of 95 patients with longstanding UC, p53 mutations were not predictive for aCRN (OR 2.47, 95%CI 0.72-8.48).²⁶ In a case-control study, the presence of p53 mutations in random surveillance biopsies was not associated with the development of CRC (multivariable HR of 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, I²=60%) based on 33 studies. There was substantial heterogeneity due to the wide range in ORs, yet almost all studies showed (a trend towards) 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 (S20A-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, I² 30%). Male sex remained a significant risk factor for aCRN in the pooled multivariable HR and OR analyses (S21A-D).

Age

Age as a risk factor for aCRN was evaluated in 8 studies, using different definitions (S22A-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%Cl 1.93-3.57, I²=0%) (S23A-E). Six studies restricted family history of CRC to first-degree relatives (pooled OR 2.48, 95%Cl 1.49-4.14). 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%Cl 1.59-4.21).

Family history of IBD

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, S24A).

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 two^{27, 28} included only UC patients. The pooled multivariable OR of 3 studies was 1.27 (95%CI 0.75-2.13), based on one study providing data from a UC cohort²⁹ and 2 studies from IBD cohorts (S25A-C).

Appendectomy

Seven studies evaluated the impact of appendectomy on the aCRN risk (S26A-B). The pooled univariable OR was 1.57 (95%CI 0.72-3.41). All data were derived from UC cohorts except for one 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 UC diagnosis (OR 2.66, 95%CI 1.06-6.67).³⁰

Age at IBD diagnosis

Studies that compared the impact of young versus old age at IBD diagnosis (n=12) on aCRN development used a wide range of cut-off ages, ranging from 25 to 60 years (S27A-G). Therefore, only a few studies could be pooled. The pooled univariable OR from 3 cohort studies comparing age <30 years versus \geq 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), while 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 (S28D). The pooled univariable HR of 2 cohort studies (one study including IBD patients and one study including UC and IBD-U patients) showed an increased risk of aCRN in patients with a history of a colon segment resection 6.46 (95%CI 1.32-31.61). In contrast, one case-control study in CD patients did not find an association (univariable OR 0.63, 95%CI 0.16-2.48).³¹ The pooled multivariable analysis of two studies including IBD patients did not find an association as well (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) (S28A-D).³²

Surveillance colonoscopies

The definition of 'surveillance colonoscopies' varied widely between studies. Pooling of studies in which overlapping definitions were used (as specified in S29E and S29F) 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 (S30A-D). No differences were found in studies comparing Caucasian race versus 'other race' or 'African-American race' in all sub-analyses (univariable OR of two 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, I²=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 (S31A-E).

5-Aminosalicylic acid

Patients who ever received 5-Aminosalicylic acid (5-ASA) had a lower risk of aCRN, with a pooled univariable OR of 0.53 (95%CI 0.39-0.72, I²=67%). Six studies that provided multivariable ORs showed a lower risk as well (pooled OR 0.51, 95%CI 0.39-0.66) (S32A-E).

Tumor necrosis factor (TNF)-alpha inhibitors

Six studies evaluated the use of TNF-alpha 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 in a multivariable model (OR 1.01, 95%CI 0.62-1.65).³³ One case-control study showed a protective effect of anti-TNF in a multivariable hazard model (HR 0.22, 95%CI 0.10-0.50) (S33A-E).³⁴

Non-Steroidal Anti-Inflammatory Drugs

No significant effect of the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) on aCRN risk was found in 3 case-control studies. The pooled OR was 0.70 (95%CI 0.22-2.22) (S34A-C). In contrast, the only study reporting on NSAID use in a multivariable model did report a lower risk (OR 0.10, 95%CI 0.03-0.33).³⁵

Folic acid

Of 9 studies reporting on the effect of folic acid use, only one found a significant protective effect (S35A-D).³⁶ 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, S36A-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).³⁷ In contrast, the pooled multivariable OR from 2 studies was 0.39 (95%CI 0.22-0.70, S37A-E).

Calcium supplements

Use of calcium supplements was associated with a non-significant decreased risk of aCRN in 2 studies (OR 0.43, 95%CI 0.18-1.02) (S38A-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 one other study (OR 0.30, 95%CI 0.10-0.90) (S39A-C).²⁹

Other factors

Potential prognostic factors reported in only one study are shown in S40A-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 figure 4 and 5. Extensive disease, LGD, UC (versus CD), aneuploidy, PSC and male sex remained risk factors for aCRN in this analysis. Thiopurine use remained a protective factor for aCRN (S41A-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 (S42). 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 (S43).

Meta-regression (univariable OR analyses)

5-ASA, thiopurines 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 towards a reduced risk (results and interpretation are provided in S44A-C).

DISCUSSION

Main findings

This is the first systematic review and meta-analysis of all factors that potentially impact 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), there was strong evidence for the risk factor extensive disease; moderate evidence for LGD, strictures, PSC, PIPs, family history CRC, IBD type; and weak evidence for any dysplasia, colon segment resection, aneuploidy, male sex, 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.

Summary of identified risk factors for aCRN

Several established pre-malignant 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 (I² 69%). The latter can at least partially be ascribed to inter-observer variability between pathologists^{38, 39}, the heterogeneous morphology of the lesions, differences in quality of endoscopic visualization techniques, and treatment variation (e.g. biopsy, polypectomy, or surgery). Of note, the inter-observer variance might even be greater for IND.³⁸ Aneuploidy seems to be a promising predictor of aCRN as well (pooled univariable OR of four 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,⁴⁰ although this meta-analysis included patients with aneuploidy who already had developed dysplasia. The impact of p53 mutations was only assessed in two 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.^{41, 42} 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. Since most studies did not specify the indication for surgery a clear answer 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 histological inflammation scores to disease extent, strictures, and possibly the presence of PIPs. Since studies reported different estimates of effects on endoscopic inflammation scores, a pooled analysis was not possible, although all studies showed promising results. Notable is the fact that one cohort study reported endoscopic inflammation scored during 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 It has been hypothesized that cumulative inflammatory burden scores are more direct and reliable predictors for the risk of (a)CRN. Indeed, recent studies support this concept,⁴³⁻⁴⁵ although it is currently not clear how to construct the optimal cumulative inflammatory burden score. 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.^{46, 47}

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).⁴⁸ In our study, several relevant new studies were included 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 dysbiosis⁴⁹ or a distinct genotype might also play a role.⁵⁰

Genetic predisposition contributes importantly to CRC development in the general population,⁵¹ 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%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%Cl 1.12-1.44, 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.⁵² We identified increasing age as a risk factor for aCRN in IBD patients, which is in line with data from the general population⁵³. The remaining prognostic factors are discussed in S45.

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 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 I² 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 was derived from studies using different techniques of model building and taking into account a varying set of covariates (specified in S4). Second, the majority of included studies had a retrospective study design, introducing inherent biases such as selection, missing data, and lack of predefined endpoints. Moreover, we could not correct for the interval between surveillance colonoscopies as 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 (S7G and S8F), 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 one 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.

Figure legends

Figure 1: Flow diagram of the selection process

N=number, OR=odds ratio, HR=hazard ratio.

Figure 2: Univariable (A) and multivariable (B) odds ratios of all potential prognostic factors

Prognostic factor (number of studies), right column: odds ratio (OR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 3: Univariable (A) and multivariable (B) hazard ratios of all potential prognostic factors

Prognostic factor (number of studies), right column: hazard ratio (HR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 4: Univariable odds ratios good quality synthesis

Prognostic factor (number of studies), right column: odds ratio (OR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

Figure 5: Univariable (A) and multivariable (B) hazard ratios good quality synthesis

Prognostic factor (number of studies), right column: hazard ratio (HR) and confidence interval (CI) from pooled analysis (pooled data if ≥2 studies included in analysis).

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 (≥2 studies in pooled analysis)
- Categorization based on the sub-analysis (OR or HR) including most studies, if equal, the subanalysis with the lowest heterogeneity was selected.
- Level of evidence:
 - Strong evidence: OR/HR ≥2 (risk factor) or ≤0.50 (protective factor) and P-value < .05 & heterogeneity ≤50% and ≥5 studies in pooled analysis and P-value < .05 in pooled good quality synthesis
 - **Moderate evidence**: OR/HR ≥1.5 (risk factor) or ≤0.67 (protective factor) *and* P-value < .05 *and* ≥5 studies in pooled analysis
 - Weak evidence: OR/HR >1 (risk factor) or <1 (protective factor) and P-value < .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.

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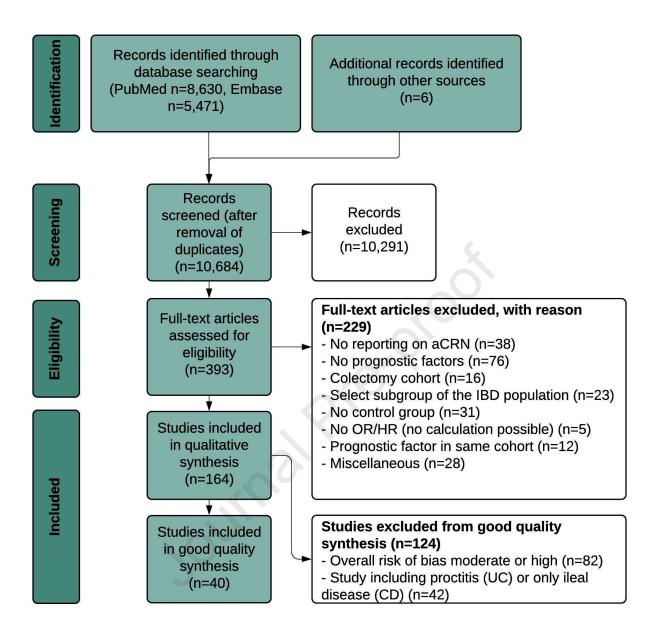
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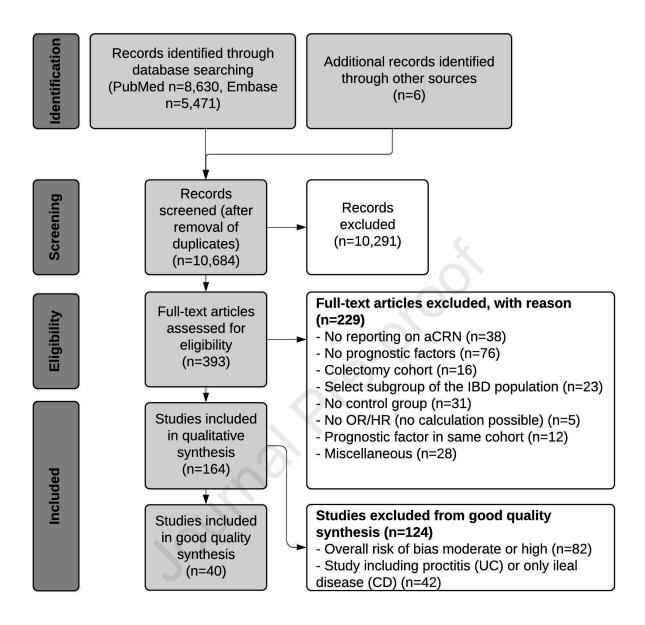
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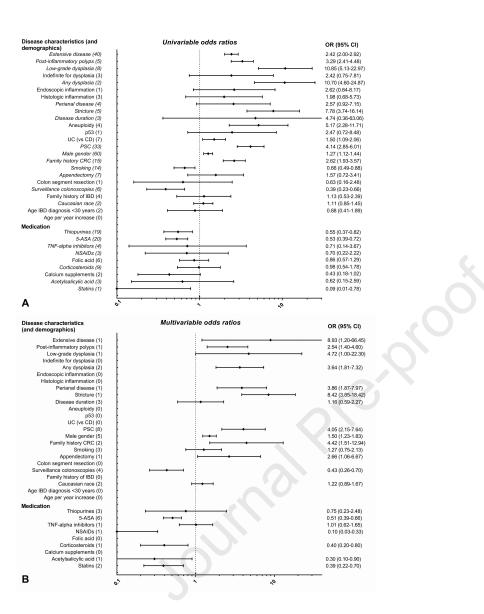
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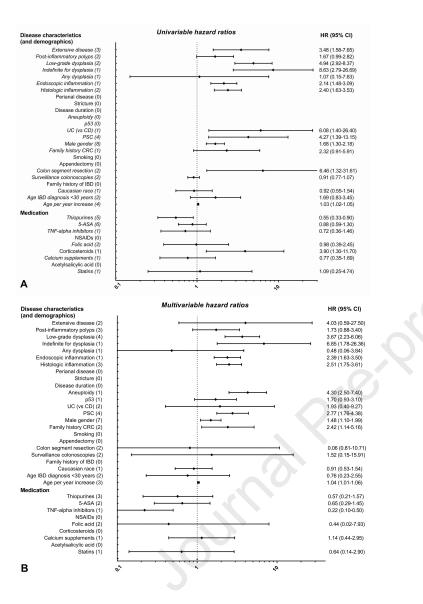
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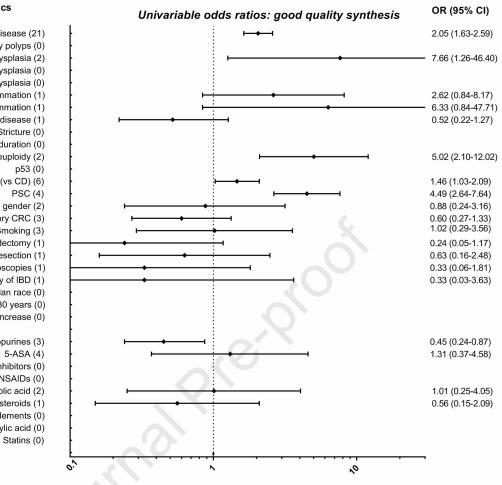
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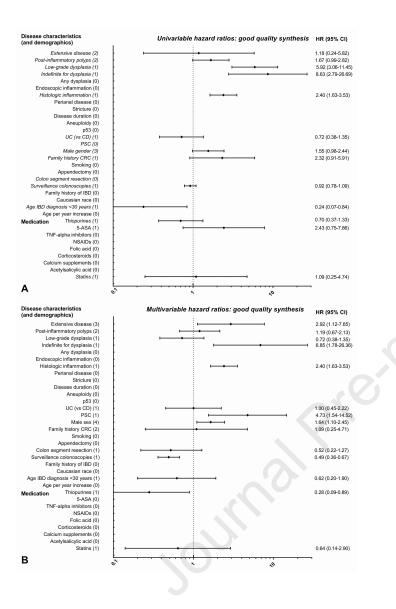


Disease characteristics (and demographics) Extensive disease (21) Post-inflammatory polyps (0) Low-grade dysplasia (2) Indefinite for dysplasia (0) Any dysplasia (0) Endoscopic inflammation (1) Histologic inflammation (1) Perianal disease (1) Stricture (0) Disease duration (0) Aneuploidy (2) p53 (0) UC (vs CD) (6) PSC (4) Male gender (2) Family history CRC (3)

- Smoking (3)
- Appendectomy (1)
- Colon segment resection (1)
- Surveillance colonoscopies (1)
- Family history of IBD (1)
- Caucasian race (0)
- Age IBD diagnosis <30 years (0)
- Age per year increase (0)

Medication

- Thiopurines (3) 5-ASA (4)
- TNF-alpha inhibitors (0)
- NSAIDs (0)
 - Folic acid (2)
- Corticosteroids (1)
- Calcium supplements (0)
 - Acetylsalicylic acid (0)



Univariable analysis

Strong	
Extensive disease*	2.43 (2.01-2.93)

Moderate		
LGD*	10.85	(5.13-22.97)
Stricture	7.78	(3.74-16.18)
PSC*	4.14	(2.85-6.01)
PIPs	3.29	(2.41-4.48)
Family history CRC	2.62	(1.93-3.57)
IBD type*	1.50	(1.09-2.06)
Surveillance colonoscopie	s 0.39	(0.23-0.66)
5-ASA	0.53	(0.39-0.72)
Thiopurines*	0.55	(0.37-0.82)
Smoking	0.66	(0.49-0.88)

Weak	
Any dysplasia	10.70 (4.60-24.87)
Colon segment resection	6.46 (1.32-31.61)
Aneuploidy*	5.17 (2.28-11.71)
Male sex	1.27 (1.12-1.44)
Age	1.03 (1.02-1.05)

Multivariable analysis

3				
	Moderate			Weak
	PSC		(2.15-7.64)	LGD Any dyspl Histologic Family his Male sex* Age
	5-ASA	0.51	(0.39-0.66)	Statin use Surveillan

Weak		
LGD Any dysplasia Histologic inflammation Family history CRC# Male sex* Age	3.64 2.51 2.42 1.48	(2.23-6.06) (1.81-7.32) (1.75-3.61) (1.14-5.16) (1.10-1.99) (1.01-1.06)
Statin use Surveillance colonoscopies	0.39 0.43	(0.22-0.70) (0.26-0.70)

Univariable analysis

Strong		
Extensive disease*	2.43	(2.01-2.93)

Moderate		
LGD* Stricture PSC* PIPs Family history CRC IBD type*	7.78 4.14	(5.13-22.97) (3.74-16.18) (2.85-6.01) (2.41-4.48) (1.93-3.57) (1.09-2.06)
Surveillance colonoscopies 5-ASA Thiopurines* Smoking	0.39 0.53 0.55 0.66	(0.23-0.66) (0.39-0.72) (0.37-0.82) (0.49-0.88)

Weak	
Any dysplasia	10.70 (4.60-24.87)
Colon segment resection	6.46 (1.32-31.61)
Aneuploidy*	5.17 (2.28-11.71)
Male sex	1.27 (1.12-1.44)
Age	1.03 (1.02-1.05)

Multivariable analysis

Moderate			Weak
PSC		(2.15-7.64)	LGD Any dysplasia Histologic inflamm Family history CR Male sex* Age
5-ASA	0.51	(0.39-0.66)	Statin use Surveillance color

Weak		
LGD Any dysplasia Histologic inflammation Family history CRC# Male sex* Age	3.64 2.51 2.42 1.48	(2.23-6.06) (1.81-7.32) (1.75-3.61) (1.14-5.16) (1.10-1.99)
Age	1.04	(1.01-1.06)
Statin use Surveillance colonoscopies	0.39 0.43	(0.22-0.70) (0.26-0.70)

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.

LAY SUMMARY

This comprehensive systematic review and meta-analysis identified 13 risk factors and 5 protective factors for advanced colorectal neoplasia in inflammatory bowel disease.

Supplementary files 1 - 46

boundance

Supplementary file 1: MOOSE checklist

Reporting Criteria	Reported (Yes/No)	Reported on Page
Reporting of Background		
Problem definition	Yes	7
Hypothesis statement	No	N/A
Description of Study Outcome(s)	Yes	7-9
Type of exposure or intervention used	Yes	10
Type of study design used	Yes	8
Study population	Yes	8
Reporting of Search Strategy		
Qualifications of searchers (e.g., librarians	Yes	8
and investigators)		
Search strategy, including time period	Yes	8; S1
included in the synthesis and keywords		
Effort to include all available studies,	Yes	8 (no contact with authors)
including contact with authors		
Databases and registries searched	Yes	8
Search software used, name and	No	N/A
version, including special features used	0	
(e.g., explosion)		
Use of hand searching (e.g., reference	Yes	8
lists of obtained articles)		
List of citations located and those	Yes	S42; figure 1
excluded, including justification		
Method for addressing articles	Yes	8
published in languages other than		
English		
Method of handling abstracts and	Yes	8
unpublished studies		
Description of any contact with authors	No	N/A
Reporting of Methods		
Description of relevance or	Yes	8-9
appropriateness of studies assembled for		
assessing the hypothesis to be tested		
Rationale for the selection and coding of	Yes	9
data (e.g., sound clinical principles or		
convenience)		
Documentation of how data were	Yes	9
classified and coded (e.g., multiple raters,		
blinding, and interrater reliability)		
Assessment of confounding (e.g.,	Yes	11, S4
comparability of cases and controls in		
studies where appropriate		
Assessment of study quality, including	Yes	9, 13; S4-5
blinding of quality assessors;		
stratification or regression on possible		

predictors of study results		
Assessment of heterogeneity	Yes	11; S6-40
Description of statistical methods (e.g.,	Yes	11
complete description of fixed or random		
effects models, justification of whether		
the chosen models account for predictors		
of study results, dose-response models,		
or cumulative meta-analysis) in sufficient		
detail to be replicated		
Provision of appropriate tables and	Yes	S2-42; figures 1-6
graphics		
Reporting of Results		
Table giving descriptive information for	Yes 🕻	S2
each study included		
Results of sensitivity testing (e.g.,	Yes	S6-40
subgroup analysis)		
Indication of statistical uncertainty of	Yes	S6-40
findings		
Reporting of Discussion		
Quantitative assessment of bias (e.g.,	Yes	11, 24; S41-42
publication bias)		
Justification for exclusion (e.g., exclusion	Yes	8, 9, 13; figure 1
of non–English-language citations)		
Assessment of quality of included studies	Yes	Figure 4-5; S4-5
Reporting of Conclusions		
Consideration of alternative explanations	Yes	25-29
for observed results		
Generalization of the conclusions (e.g.,	Yes	30-31
appropriate for the data presented and		
within the domain of the literature review)		
Guidelines for future research	Yes	30-31
Disclosure of funding source	Yes	31

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology

(MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. JAMA.

2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

Supplementary file 2: Search strategies Embase and PubMed

Embase

('inflammatory bowel disease'/exp OR 'inflammatory bowel disease*':ti,ab,kw OR 'ibd':ti,ab,kw OR 'proctocolitis'/exp OR 'proctocolitis':ti,ab,kw OR 'ulcerative rectocolitis':ti,ab,kw OR 'ulcerative proctocolitis':ti,ab,kw OR 'ulcerative colitis':ti,ab,kw OR 'colitis gravis':ti,ab,kw OR 'colitis ulcerosa':ti,ab,kw OR 'crohn*':ti,ab,kw)

AND

('colorectal cancer'/mj OR 'colorectal carcinoma'/exp OR 'rectum cancer'/exp OR 'Rectum tumor'/mj OR 'sigmoid cancer'/exp OR 'colon carcinoma'/exp OR 'colon adenocarcinoma'/exp OR 'colon tumor'/mj OR 'cecum cancer'/exp OR 'intestine tumor'/mj OR 'intestine cancer'/mj OR 'large intestine cancer'/mj OR 'Colorectal tumor'/mj OR 'malignant neoplasm'/exp OR 'malignant neoplas*':ti,ab,kw OR 'malignancy':ti,ab,kw OR 'neoplas*':ti,ab,kw OR 'neoplasm'/exp OR 'adenocarcinoma'/mj OR 'adenocarcinoma in situ'/exp OR 'adenocarcinoma*':ti,ab,kw OR 'cancer*':ti,ab,kw OR 'carcinoma*':ti,ab,kw OR 'dysplasia'/exp OR 'dysplasia':ti,ab,kw OR 'high grade dysplasia':ti,ab,kw OR 'Precancerous condition*':ti,ab,kw OR 'Tumour*':ti,ab,kw OR 'Tumor*':ti,ab,kw OR 'surveillance':ti,ab,kw OR 'screening':ti,ab,kw)

AND

('large intestine':ti,ab,kw OR 'large intestine'/mj OR 'colon'/mj OR 'colon':ti,ab,kw OR 'sigmoid'/exp OR 'sigmoid':ti,ab,kw OR 'colon sigmoideum':ti,ab,kw OR 'colon, sigmoid':ti,ab,kw OR 'rectum'/exp OR 'rectum':ti,ab,kw OR 'Rectal':ti,ab,kw OR 'Colorectal':ti,ab,kw OR 'ascending colon'/exp OR 'ascending colon':ti,ab,kw OR 'colon ascend*':ti,ab,kw OR 'proximal colon':ti,ab,kw OR 'descending colon'/exp OR 'descending colon':ti,ab,kw OR 'colon descend*':ti,ab,kw OR 'distal colon':ti,ab,kw OR 'cecum'/exp OR 'Cecum':ti,ab,kw OR 'Coecum':ti,ab,kw)

AND

'article'/it

NOT

('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'mouse

model'/de OR 'nonhuman'/de)

AND

[embase]/lim

PubMed

("Inflammatory Bowel Diseases"[Mesh] OR "Inflammatory Bowel Disease*"[Title/Abstract] OR "inflammatory bowel disorder*"[Title/Abstract] OR IBD[Title/Abstract] OR ulcerative colitis[Title/Abstract] OR colitis ulcerosa[Title/Abstract] OR "Proctocolitis"[Mesh] OR "Idiopathic Proctocolitis"[Title/Abstract] OR "Ulcerative rectocolitis"[Title/Abstract] OR "Ulcerative proctocolitis"[Title/Abstract] OR "Colitis Gravis"[Title/Abstract] OR Crohn*[Title/Abstract])

AND

("Colorectal Neoplasms"[Mesh] OR "Intestinal Neoplasms"[Mesh:NoExp] OR "Cecal neoplasms"[Mesh:NoExp] OR "Precancerous Conditions"[Mesh:noexp] OR "Population Surveillance"[Mesh:noexp] OR "Cancer*"[Title/Abstract] OR "Carcinoma*"[Title/Abstract] OR "Tumor*"[Title/Abstract] OR "Tumour*"[Title/Abstract] OR "Adenocarcinoma*"[Title/Abstract] OR "Adenocarcinoma"[Mesh] OR "Dysplasia"[Title/Abstract] OR "Neoplasms"[Mesh:NoExp] OR "Neoplas*"[Title/Abstract] OR "Malignancy"[Title/Abstract] OR "High grade dysplasia"[Title/Abstract] OR Surveillance[Title/Abstract] OR Screening[Title/Abstract])

AND

("Intestine, large" [Mesh] OR "Large intestine" [Title/Abstract] OR "Cecum" [Title/Abstract] OR

"Colon"[Title/Abstract] OR "Colon ascendens"[Title/Abstract] OR "Ascending colon"[Title/Abstract] OR

"Colon descendens"[Title/Abstract] OR "Descending colon"[Title/Abstract] OR "Proximal

colon"[Title/Abstract] OR "Distal colon"[Title/Abstract] OR "Sigmoid"[Title/Abstract] OR "Sigmoid

colon"[Title/Abstract] OR "Rectum"[Title/Abstract] OR "Colorectal"[Title/Abstract])

NOT

(((((animals[mh] NOT humans[mh])))))

Supplementary file 3: Study characteristics included studies

Author [Year]			Description	0.01	01	Final	Nerrelean	Number		Prognostic
	Country	Study design	Prospective or retrospective design	OR/ HR	Start study period	End study period	Number of patients	of events (aCRN)	IBD type	factors
Ananthakrishnan [2014] ¹	USA	Cohort	Retrospective	OR	1996		11001	167	UC, CD	18*
Ananthakrishnan [2014a] ²	USA	Cohort	Retrospective	OR			2809	41	UC, CD	35*
Ananthakrishnan [2014b] ³	USA	Cohort	Retrospective	OR			4726	33	UC, CD	35*
Ananthakrishnan [2015] ⁴	USA	Cohort	Retrospective	OR			6823	154	UC, CD, IBD -U	15*,18,19,28, 25,35
Ananthakrishnan [2016] ⁵	USA	Cohort	Retrospective	OR	1998	2010	11001	317	UC, CD	19*, 20,23*, 25*,28*,32*,35*
Askling [2001] ⁶	Sweden	Cohort	Retrospective	OR	1955	1995	19876	143	UC, CD	21
Baars [2011] ⁷	The Netherla nds	Case control	Retrospective	OR	1990	2006	566	173	UC, CD	7,18,19, 21,26,27,28,29, 30,31,33,34,35
Bansal [1996] ⁸	USA	Cohort	Retrospective	OR	1981	1993	11446	371	UC	18*,19*,25*,35*
Beaugerie [2013] ⁹	France	Cohort	Prospective	OR HR	2004	2007	19486	57	UC, CD, IBD -U	3*,19*,20*,26*,3 5
Beaugerie [2018] ¹⁰	France	Case control	Prospective	OR	2004	2007	19486	22	UC, CD, IBD -U	11
Bergeron [2010] ¹¹	France	Case control	Partial	OR HR	1994	2010	855	33	UC, CD	11,14*,18*,21*,2 3,26,27
Bernstein [2011] ¹²	Canada	Cohort	Retrospective	HR	1995	2008	8744		UC, CD	27
Biancone [2016] ¹³	Italy	Case control	Partial	OR	2012	2014	522	19	UC, CD	11*,35*
Boland [1984] ¹⁴	USA	Cohort	Prospective	OR	1979	1982	18	1	UC	35
Bopanna[2017] ¹⁵	India	Cohort	Partial	OR HR	2004	2015	1012	20	UC	2,7,18,19
Braden [2012] ¹⁶	United Kingdo m	Case control	Retrospective	OR			382	5	UC, CD, IBD -U	18

		Case	Prospective	OR			45	8	UC	18
Brentnall [1996] ¹⁷	USA	control	Trospective				45	0	00	10
Broomé [1995] ¹⁸	Sweden	Case control	Retrospective	OR	1973	1984	40	18	UC	18
Brostróm [1986] ¹⁹	Sweden	Cohort	Retrospective	OR	1945	1979	1274	25	UC	19
Campos [2013] ²⁰	Brazil	Cohort	Prospective	OR	1984	2007	1607	17	UC, CD	2,18,19
Camus [2013] ²¹	France	Case control	Prospective	OR	1986	2011	660		CD	26
Carrat [2017] ²²	France	Case control	Prospective	OR	2004	2007	420		UC, CD, IBD -U	18*,23*,26*,27*, 35*
Cheddani [2016] ²³	France	Cohort	Retrospective	OR	1988	2006	844	15	UC, CD	18
Choi [2019] ²⁴	United Kingdo m	Cohort	Retrospective	OR	2003	2012	987		UC	4
Chow [2009] ²⁵	China	Cohort	Prospective	OR	1985	2006	172	1	UC	2,19
Connell [1994] ²⁶	United Kingdo m	Case control	Prospective	OR	1962	1991	266	23	UC	26
Cosnes [2002] 27	France	Cohort	Partial	OR	1997	2000	638	11	UC	24
De Dombal [1966] ²⁸	United Kingdo m	Cohort	Retrospective	OR	1952	1963	465	8	UC	7,10
de Jong [2019] ²⁹	The Netherla nds	Cohort	Retrospective	HR		2017	519	19	UC, CD	7*
Desai [2015] ³⁰	India	Cohort	Prospective	OR	2005		430	12	UC	2,19,22,23,26
Eaden [2000] ³¹	United Kingdo m	Case control	Retrospective	OR			204	62	UC	15*,21*,23,27*,3 1,34,35*
Ekbom [1990a] ³²	Sweden	Cohort	Retrospective	OR	1958	1984	3117	91	UC	2,19
Florin [2004] ³³	Australi a	Cohort	Retrospective	OR	1995	2002	372	11	UC	18,24
Fraga [2017] ³⁴	Switzerl and	Cohort	Prospective	OR	2006	2014	1188	11	UC, CD	18
Fraser [2002] ³⁵	New Zealand	Cohort	Retrospective	OR			1349	36	UC, CD	2,26
Freeman [2001] ³⁶	Canada	Cohort	Retrospective	OR	1979	1998	877	6	CD	19

							-			
Fujita [2010] ³⁷	Japan	Cohort	Retrospective	OR	1998	2006	314	7	UC	2,19,21,23,27,3 1
Fuson [1980] ³⁸	USA	Cohort	Retrospective	OR	1972	1977	75	11	UC	19
Gerrits [2011] ³⁹	The Netherla nds	Case control	Retrospective	HR	1985	2008	54	26	UC, CD, IBD -U	4*,9*,16*,17*
Gilat [1974] ⁴⁰	Israel	Cohort	Retrospective	OR	1961	1970	504	4	UC	19
Gillen [1994a] ⁴¹	Sweden and United Kingdo m	Cohort	Retrospective	OR	1945	1975	611	37	UC, CD	3
Gomez-Garcia [2013] ⁴²	Spain	Cohort	Retrospective	OR	1996	2013	812	12	UC, CD	26
Gong [2012] ⁴³	China	Cohort	Retrospective	OR	1998	2009	3922	34	UC	2*,6,15,19,27*,3 1,35
Gordillo [2015] ⁴⁴	Spain	Cohort	Retrospective	OR	2006	2010	831	45	UC	2,12*,13,15*,18* ,19*,21,22,23,24 *,26*,27,31,35*
Greenstein [1979] ⁴⁵	USA	Cohort	Retrospective	OR	1960	1976	267	26	UC	2
Gupta [2007] ⁴⁶	USA	Cohort	Retrospective	HR	1996	1997	418	15	UC	9*,13,15*,19,26, 27,30,31
Hajek [2005] ⁴⁷	Czech	Cohort	Retrospective	OR	1993	2003	353	3	UC, CD	19
Hou [2012] ⁴⁸	USA	Cohort	Retrospective	HR	1998	2009	20949	168	UC	13*,15,19*,25*,3 5*
Hovde [2017] ⁴⁹	Norway	Cohort	Prospective	OR	1990		756		UC, CD	19
Jablonska [1993] ⁵⁰	Czech	Cohort	Prospective	OR			191	9	UC	2,19
Jacobsen [1994] ⁵¹	Norway	Cohort	Retrospective	OR	1979	1988	641	6	UC, CD, IBD -U	19
Jess [2012] ⁵²	Denmar k	Cohort	Retrospective	OR	1979	2008	47374	338	UC, CD	19
Jonsson [1994] ⁵³	Sweden	Cohort	Prospective	OR	1977	1991	131	8	UC	2
Joo [2009] ⁵⁴	USA	Case control	Retrospective	OR	1989	2005	80	4	UC	18
Jung [2017] ⁵⁵	Korea	Case	Retrospective	OR	2010	2014	15644	28	UC,	3,19,26,27,28,3

		control							CD	5
Jussila [2013] ⁵⁶	Finland	Cohort	Retrospective	OR	1987	2010	21964	190	UC, CD	19
Kamiya [2012] ⁵⁷	Japan	Cohort	Retrospective	OR	1998	2010	174	2	CD	19,21
Katzka [1983] ⁵⁸	USA	Cohort	Retrospective	OR	1955	1980	258	9	UC	2
Kishikawa [2018] ⁵⁹	Japan	Cohort	Retrospective	HR	1979	2014	289	15	UC	2,13*,19*
Kobayashi [2002] ⁶⁰	Japan	Cohort	Retrospective	OR	1987	2001	246	7	UC	2,19
Kochhar [1991] ⁶¹	India	Cohort	Retrospective	OR	1977	1988	436	8	UC	2,19
Kopylov [2015] ⁶²	Canada	Case control	Retrospective	OR			19582	343	UC, CD	19
Kottachchi [2009] ⁶³	Canada	Cohort	Retrospective	OR	1980	2005	141	3	UC	2
Kuo [2014] ⁶⁴	Taiwan	Cohort	Retrospective	OR	2000	2010	2617	6	UC, CD	19
Kvist [1989] ⁶⁵	Denmar k	Cohort	Retrospective	OR	1964	1983	759	20	UC	2,19
Lai [2015] ⁶⁶	USA	Case control	Retrospective	OR	1989	2004	111	9	UC, CD	5
Laish [2017] ⁶⁷	Isreal	Cohort* *	Retrospective	OR	2005	2014	229	5	UC	2,18
Lakatos [2004] ⁶⁸	Hungary	Cohort	Retrospective	OR	1991	2001	812	12	UC, CD, IBD -U	3
Lakatos [2006] ⁶⁹	Hungary	Cohort	Partial	OR	1974		723	13	UC	2,4*,6*,12*,18*,1 9*,22,23,24,26,3 1,35*
Lakatos [2011] ⁷⁰	Hungary	Cohort	Partial	OR	1977	2008	506	5	CD	19,35
Langholz[1992] ⁷¹	Denmar k	Cohort	Partial	OR	1962	1987	1161	6	UC	19
Lashner [1989a] ⁷²	USA	Cohort	Prospective	OR	1977	1985	99	12	UC	4
Lashner [1989] ⁷³	USA	Cohort	Retrospective	OR	1986	1992	98	15	UC	30
Lashner [1990] ⁷⁴	USA	Cohort	Retrospective	OR	1984	1986	186	18	UC	15
Lashner [1999] ⁷⁵	USA	Cohort	Retrospective	OR	1986	1992	95	23	UC	17
Lee[2015] ⁷⁶	South Korea	Cohort	Partial	OR	1989	2013	5212	30	UC, CD	2,3,11,13, 18,19

Leidenius [1991] ⁷⁷	Finland	Cohort	Retrospective	OR	1976	1989	66	1	UC	2
Leidenius [1997] ⁷⁸	Finland	Case control	Retrospective	OR	1984	1995	90	8	UC	18
Lennard-Jones [1977] ⁷⁹	United Kingdo m	Cohort	Prospective	OR	1966	1976	229	14	UC	4
Lennard-Jones [1990] ⁸⁰	United Kingdo m	Cohort	Prospective	OR	1966	1987	401	34	UC	19
Lim [2003] ⁸¹	United Kingdo m	Cohort	Retrospective	OR	1978	2000	128	7	UC	4,19
Lindberg [1999] ⁸²	Sweden	Cohort	Prospective	OR	1984	1997	147	11	UC	16
Lindberg [2001] ⁸³	Sweden	Cohort	Partial	OR		1993	143	17	UC	18,27
Lindberg[2005] ⁸⁴	Sweden	Cohort	Prospective	OR	1977	2002	211	15	UC	2
Lindström [2011] ⁸⁵	Denmar k	Case control	Retrospective	OR	1978	2005	74	4	CD	18
Löfberg [1991] ⁸⁶	Sweden	Cohort	Prospective	OR			24	1	CD	2,16
Loftus [2005] ⁸⁷	USA	Case control	Prospective	HR	1987	1992	213	18	UC, CD	18
Lovasz [2013] ⁸⁸	Hungary	Cohort	Retrospective	OR	1977	2011	640	6	CD	10,19
Lutgens [2015] ⁸⁹	The Netherla nds	Case control	Retrospective	HR	1990	2009	528	186	UC, CD	4*,7*,13*,18*,28
MacDougall [1954] ⁹⁰	United Kingdo m	Cohort	Unclear	OR	1947	1951	126	5	UC	19
Madanchi [2016] ⁹¹	Switzerl and	Cohort	Retrospective	OR	2007	2014	1026	4	UC, CD, IBD -U	19
Mahmoud [2019] ⁹²	USA and the Netherla nds	Cohort	Retrospective	HR	1997	2017	1582	41	UC, CD, IBD -U	2*,3,4*,7*,9*,15, 19*,21*,26,27, 35*
Mahmoud [2019b] ⁹³	USA and the Netherla nds	Cohort	Retrospective	HR	2001	2017	492	32	UC, CD, IBD -U	5*,15*
Manninen [2013] ⁹⁴	Finland	Cohort	Retrospective	OR	1986	2007	1915	21	UC, CD, IBD	2,3,13,18,19

									-U	
Maratka [1985] ⁹⁵	Czech Republi c	Cohort	Retrospective	OR	1942	1984	959	6	UC	2,19
Markowitz [1997] ⁹⁶	USA	Cohort	Prospective	OR	1992	1995	35	2	UC, CD	2
Mir-Madjlessi [1986] ⁹⁷	USA	Cohort	Retrospective	OR		1984	1160	82	UC	2
Navaneethan [2016] ⁹⁸	USA	Case control	Retrospective	OR	1985	2012	202	18	CD	18
Nieminen [2014] ⁹⁹	Finland	Case control	Retrospective	OR			190	31	UC, CD	9,18,26,27,35
Nkontchou [1996] ¹⁰⁰	France	Cohort	Retrospective	OR	1962	1993	130	6	UC	19
Nowacki [2015] ¹⁰¹	German y	Cohort	Retrospective	OR	2002	2013	434	15	UC	2,12,18,19,20,2 6,27,28,35*
Nuako [1998] ¹⁰²	USA	Case control	Retrospective	OR	1976	1994	342	171	UC	18*
Nuako [1998a] ¹⁰³	USA	Case control	Retrospective	OR	1976	1994	297	147	UC	21
Nugent [1991] ¹⁰⁴	USA	Cohort	Prospective	OR	1974	1986	213		UC	4,5
Paris [1994] ¹⁰⁵	Italy	Cohort	Retrospective	OR	1987	1992	74	1	UC	19
Peng [2015] ¹⁰⁶	Taiwan	Cohort	Retrospective	HR	1998	2011	10650	59	UC, CD	19*
Peng [2017] ¹⁰⁷	Taiwan	Case control	Retrospective	OR	1998	2010	1050		UC, CD	3,20,35
Picazo-Ferrera [2011] ¹⁰⁸	Mexico	Case control	Retrospective	OR	2007	2010	114		UC	24
Pinczowski [1994] ¹⁰⁹	Sweden	Case control	Retrospective	OR			298	102	UC	23,27,35
Prior [1982] ¹¹⁰	United Kingdo m	Cohort	Retrospective	OR	1940	1976	676	35	UC	19
Radford-Smith [2002] ¹¹¹	Australi a	Case control	Retrospective	OR	1995	1999	307	6	UC	24
Ray [2011] ¹¹²	India	Cohort	Partial	OR	2003	2009	50	5	UC, CD	2, 12*
Rozen [1995] ¹¹³	Israel	Cohort	Prospective	OR	1976	1994	154	13	UC	2,19
Rubin [2013] ¹¹⁴	USA	Case control	Retrospective	OR			200	20	UC	9,18,19,21,23,2 6,27,30

Rubio [2009] ¹¹⁵	Sweden	Cohort	Retrospective	OR	1996	2007	121	6	CD	19
Rutegard [1988] ¹¹⁶	Sweden	Cohort	Retrospective	OR	1961	1983	127	3	UC	2
Rutegard [1988b] ¹¹⁷	Sweden	Cohort	Retrospective	OR	1984	1987	73	2	UC	16
Rutter [2004] ¹¹⁸	United Kingdo m	Case control	Retrospective	OR	1988	2002	204	22	UC	8,9,21,23,26,27, 30
Rutter[2006] ¹¹⁹	United Kingdo m	Cohort	Partial	OR	1971	2001	600	57	UC	19
Samadder [2011] ¹²⁰	Israel	Case control	Partial	OR	1998	2004	60	5	UC, CD, IBD -U	32,35*
Samadder [2018] ¹²¹	USA	Cohort	Retrospective	HR	1996	2011	9505	101	UC, CD, IBD -U	18,19,20,21
Satchi [2013] ¹²²	USA	Case control	Retrospective	OR			54	13	UC, CD	26
Scharl [2018] ¹²³	Switzerl and	Cohort	Retrospective	HR	2006	2016	3119		UC, CD, IBD -U	14,20,26,35
Selinger [2014] ¹²⁴	Australi a	Cohort	Retrospective	OR HR	1977	1992	881	29	UC, CD	2,35
Senanayake [2013] ¹²⁵	Sri Lanka	Cohort	Retrospective	OR	1995	2002	348	2	UC	2
Setshedi [2012] ¹²⁶	South- Africa	Cohort	Retrospective	OR	1960	2007	959	12	UC, CD, IBD -U	26
Shah [2018] ¹²⁷	USA	Cohort	Retrospective	HR	2000	2015	1911	64	UC, CD, IBD -U	8*,13,18*,20*,28
Shah[2019] ¹²⁸	USA	Cohort	Retrospective	OR	2005	2016	642	60	UC, CD, IBD -U	32*
Shetty [1999] ¹²⁹		Case control	Retrospective	OR	1976	1994	329	38	UC	18
Shi [2016] ¹³⁰	China	Cohort	Partial	OR	1981	2013	1255	15	UC	13

Shivakumar [2013] ¹³¹	India	Cohort	Prospective	OR	2008	2012	29	4	UC	2
Siegel [2006] ¹³²	USA	Case control	Retrospective	OR	1990	2004	54	27	CD	14,15,21,22, 23,24,27,30,31, 35
Söderlund [2009] ¹³³	Sweden	Cohort	Partial	OR	1960	2004	7607	188	UC, CD	2,3
Söderlund [2010] ¹³⁴	Sweden	Cohort	Partial	OR	1960	2004	7607	196	UC, CD	19
Söderlund [2011] ¹³⁵	Sweden	Cohort	Retrospective	OR	1982		245	12	CD, IBD -U	16
Sokol [2008] ¹³⁶	France	Case control	Partial	OR	1974		225	9	UC, CD, IBD -U	18*
Sonnenberg [2015] ¹³⁷	USA	Case control	Retrospective	OR	2008	2014	53568	98	UC, CD, IBD -U	6*,10*,19*,20*
Sørensen [2018] ¹³⁸	Denmar k	Case control	Retrospective	HR	1977	2011	8453	11	UC, CD, IBD -U	18
Stewénius [1995] ¹³⁹	Sweden	Cohort	Prospective	OR	1958	1990	571	12	UC, IBD -U	2,3,19
Stolwijk [2013] ¹⁴⁰	The Netherla nds	Cohort	Prospective	HR	1980	2005	293	23	UC	2,4,15,18,19
Tang [2010] ¹⁴¹	USA	Case control	Retrospective	OR	1970	2005	48	18	UC, CD	21,23,26,27*,30
Ten Hove [2019] ¹⁴²	USA and the Netherla nds	Cohort	Retrospective	OR			775	12	UC, CD, IBD -U	15
Terdiman [2007] ¹⁴³	USA	Case control	Retrospective	OR	2001	2003	1536	364	UC, CD	15,26,27, 29, 31,35
Terg [2008] ¹⁴⁴	Argentin a	Case control	Prospective	OR	1990	2003	106	9	UC	18
Triantafillidis [1998] ¹⁴⁵	Greece	Cohort	Prospective	OR	1978	1993	413	6	UC	2
Triantafillidis [2000] ¹⁴⁶	Greece	Cohort	Prospective	OR	1981	1996	155	3	CD	19

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Triantafillidis [2001] ¹⁴⁷	Greece	Cohort	Retrospective	OR			413	3	UC	13
Ullman [2008] ¹⁴⁸	USA	Cohort	Retrospective	OR HR	1994	2001	393	31	UC	4,5,27
Ünal [2019] ¹⁴⁹	Turkey	Cohort	Retrospective	OR	1993	2016	801	11	UC	2,7,18,19,21,23
van den Heuvel [2016] ¹⁵⁰	The Netherla nds	Cohort	Prospective	OR	1991	2013	2801	23	UC, CD	2,3,19
van Schaik [2012] ¹⁵¹	Van Schaik	Cohort	Retrospective	HR	2001	2009	2578	28	UC, CD, IBD -U	6*,14*,19*,20*,2 6*,27*,30,33*
van Schaik [2013] ¹⁵²	The Netherla nds	Case control	Retrospective	HR	1995	2005	233	25	UC, CD, IBD -U	3*,4*,18*,19*,26 *,27*
van Staa [2005] ¹⁵³	United Kingdo m	Case control	Retrospective	OR	1987	2001	700	100	UC, CD	27*
Velayos [2006] ¹⁵⁴	USA	Case control	Retrospective	OR	1976	2002	376	188	UC	7,15*,18*,21*,23 *,26*,27*,29*,30, 31*,33,34*,35
Venkataraman [2005] ¹⁵⁵	India	Cohort	Retrospective	OR	1978	2002	532	6	UC	2
Walmsley [1997] ¹⁵⁶	United Kingdo m	Cohort	Retrospective	OR	1970	1993	62	4	CD	19
Wang [2013] ¹⁵⁷	China	Cohort	Retrospective	OR	2000	2012	603	4	UC	19
Winther [2004] ¹⁵⁸	Denmar k	Cohort	Retrospective	OR	1962	1987	1160	13	UC	2,13,19
Wright [1983] ¹⁵⁹	South Africa	Cohort	Retrospective	OR	1975	1980	220	2	UC	2,19
Yamazaki [1991] ¹⁶⁰	USA	Cohort	Retrospective	OR	1959	1985	980	15	CD	10
Yano [2008] ¹⁶¹	Japan	Cohort	Retrospective	OR	1985	2005	512	6	CD	11
Yano [2013] ¹⁶²	Japan	Cohort	Retrospective	OR	1985	2010	770	3	CD	19
Ye [2011] ¹⁶³	Korea	Case control	Retrospective	OR	1977	2009	84	3	UC	18
Zhang [2015] ¹⁶⁴	China	Cohort	Retrospective	OR	2000	2012	642	4	UC	19,27,35
	1	1		1	1	1	1	1		1

 Prognostic factors: 2 = Disease extent; 3 = IBD type; 4 = Low-grade dysplasia; 5 = Indefinite for dysplasia; 6 =

 Any dysplasia (not specified); 7 = Post-inflammatory polyps; 8 = Endoscopic inflammation; 9 = Histological

 inflammation; 10 = Stricture; 11 = Perianal disease; 12 = Disease duration; 13 = Age at IBD diagnosis; 14 = Colon

 segment resection; 15 = Surveillance colonoscopies; 16 = Aneuploidy; 17 = P53 mutation; 18 = Primary

sclerosing cholangitis; 19 = Sex; 20 = Age; 21 = Family history of colorectal carcinoma; 22 = Family history of IBD; 23 = Smoking; 24 = Appendectomy; 25 = Race; 26 = Thiopurines; 27 = 5-Aminosalicylates; 28 = TNF-alpha inhibitors; 29 = NSAIDs; 30 = Folic acid; 31 = Corticosteroids; 32 = Statins; 33 = Calcium supplements; 34 = Acetylsalicylic acid; 35 = Other risk factors;

* = multivariable analysis

** = original case-control; we only used UC part

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Supplementary file 4: Covariates within multivariable and adjusted models

Study	Author [Year]	Multivariable	Covariates
ID		or adjusted	
		model	
1	Ananthakrishnan	Multivariable	PSC,Gender,anti-TNF/biological,Duration of
0	[2014]1	model	followup,Immunomoduators,Race
2	Ananthakrishnan	Adjusted model	Age,Gender,IBD type,Duration followup,
	[2014a]2	model	Immunosuppression use,Season measurement,Race,Plasma 25(OH)D
3	Ananthakrishnan	Multivariable	Age,Gender,IBD type,PSC,CRP,ESR,Race,Duration
5	[2014b]3	model	followup
4	Ananthakrishnan	Multivariable	IBD type,PSC,Age,Disease duration,Gender,Recent
	[2015]4	model	colonoscopy within 3 years
5	Ananthakrishnan	Multivariable	Gender,IBD type,anti-
	[2016]5	model	TNF/biological,Smoking,PSC,Age,Statin use,
			Increased inflammatory markers, Colonoscopy within 3
			years,Race,Duration followup
8	Bansal [1996]8	Multivariable	Age,Gender,IBD type,PSC,Race,NSAID associated
-		model	diagnoses
9	Beaugerie	Multivariable	Gender, Age, Disease duration, Extent
	[2013]9	model	disease, Thiopurine, IBD type, Age, Gender, IBD type
11	Bergeron [2010]11	Multivariable model	PSC, Family history CRC, Colon segment resection
13	Biancone	Multivariable	Perianal disease, Colon segment resection, Extent
	[2016]13	model	disease,Smoking,Disease duration,Age,Disease
			duration,,Remark UC and CD multivarible analyses
	0 / [0047]00		seperatly,Montreal behaviour,Surgery
22	Carrat [2017]22	Multivariable	5-ASA, Thiopurine, PSC, Smoking, 1 or more surgical
20	de Jong [2019]29	model Multivariable	procedures over the 5 years preceding cancer
29	de Jong [2019]29	model	Pseudopolyps, All confounders
31	Eaden [2000]31	Multivariable	5-ASA,Family history CRC,Contact with hospital
0.		model	doctor,Colonoscopies after diagnosis
39	Gerrits [2011]39	Multivariable	LGD, Aneuploidy, Aneuploidy, p53 mutation, Endoscopic
		model	inflammation
43	Gong [2012]43	Multivariable	Disease duration, Extent disease, LGD, 5-ASA
		model	
44	Gordillo [2015]44	Multivariable	Gender,Extent
		model	disease,Age,PSC,Appendectomy,Disease
			duration, Thiopurine, Included in surveillance
			program,Corticosteroids,5ASA or thiopurine versus no use
46	Gupta [2007]46	Multivariable	Histologic inflammation,One or more colonoscopies
40	Gupta [2007]40	model	per year
48	Hou [2012]48	Multivariable	IBD age at onset, Gender, Race, Deyo score, Priority
		model	level,History of endoscopy in VA,VA encounters,UC
			index year
59	Kishikawa	Multivariable	Gender,Extent disease,IBD age at onset
	[2018]59	model	
69	Lakatos [2006]69	Multivariable	Gender, Disease duration, LGD, Extent
		model	disease,PSC,Chronic continuous disease
89	Lutgens [2015]89	Multivariable	Age,Extent disease,PSC,Pseudopolyps,anti-
		model	TNF/biological,HGD
92	Mahmoud	Multivariable	Gender, Pseudopolyps, PSC, Histologic
	[2019]92	model	inflammation, Disease duration, Family history
			CRC,USA cohort,Cecum reached,LGD or IND before
93	Mahmoud	Multivariable	index scopy IND,Age,LGD,PSC,Histologic inflammation,Disease
90	IVIAIIIIIUUU	wwwwanable	IND, AYE, LOD, FOO, AISOIOYIC IIIIIaMMalion, Disease

	[2019b]93	model	duration, Extent disease, 5- ASA, Immunomodulators, Surveillance colonoscopies
101	Nowacki [2015]101	Multivariable model	Anti inflammatory and or immunosuppresive therapy, Disease duration 9-15 years, Disease duration
102	Nuako [1998]102	Adjusted model	more than 15 years PSC,Disease duration,Extent disease,IBD age at onset
107	Peng [2017]107	Adjusted	Age,Gender,Cholecystectomy,Comorbidities
112	Ray [2011]112	Multivariable model	Disease duration, Unclear
120	Samadder [2011]120	Adjusted model	Age,Gender,Smoking,Family history CRC,Other,Ethnic group,Vegetable consumption,NSAIDs,Statin use
127	Shah [2018]127	Multivariable model	Age,Gender,PSC,Endoscopic inflammation
128	Shah[2019] 128	Adjusted model	Age,Gender,PSC,Disease duration,Thiopurine,anti- TNF/biological,Histologic inflammation,Number of colonoscopies
136	Sokol [2008]136	Multivariable model	PSC,PSC,5- ASA,Immunomosuppressors,Extraintestinal manifestations,Initial sigmoi colon involvement
137	Sonnenberg [2015]137	Multivariable model	Age,Gender,IBD type,IBD type,Stricture
140	Stolwijk [2013]140	Multivariable model	Gender, Extent disease, Age at first surveillance
141	Tang [2010]141	Multivariable model	5-ASA,Folic acid
151	van Schaik [2012]151	Multivariable model	5-ASA,Thiopurine,IBD type,Gender,Age,Disease duration,Extent disease,Colon segment resection,History of dysplasia,Folic acid
152	van Schaik [2013]152	Multivariable model	LGD,Gender,IBD type,Extent disease,5- ASA,Thiopurine,PSC
153	van Staa [2005]153	Adjusted model	5-ASA,Disease duration,Other,BMI,History colorectal polyps,NSAIDs,Paracetamol,Immunosuppressants,GI ucocorticosteroids,Prior gastrointestinal hospitalisation,Recorded colonoscopies
154	Velayos [2006]154	Multivariable model	Family history, Smoking, PSC, Pseudopolyps, 5-ASA, NSAIDs, Surveillance colonoscopies, Corticosteroid use, Immunosuppressive use, Aspirin

Supplementary file 5: Risk of bias assessment (QUIPS)

Study ID	Author [Year]	Q1: Study Participatio n	Q2: Study Attrition	Q3: Prognostic Factor Measureme nt	Q4: Outcome Measureme nt	Q5: Study Confoundin g (Covariates)	Q6: Statistical Analysis and Reporting	Overall quality assesment
1	Ananthakrishnan [2014]1	Low	Moderate	Low	Moderate	Low	Low	Moderate
2	Ananthakrishnan [2014a]2	Moderate	Moderate	Low	Moderate	Moderate	Low	High
3	Ananthakrishnan [2014b]3	Moderate	Moderate	Low	Moderate	Low	Low	High
4	Ananthakrishnan [2015]4	Low	Low	Low	Moderate	Low	Low	Low
5	Ananthakrishnan [2016]5	Low	Moderate	Low	Moderate	Low	Low	Moderate
6	Askling [2001]6	Low	Low	Moderate	Moderate	High*	Low	Moderate
7	Baars [2011]7	Low	Low	Low	Low	Low	Low	Low
8	Bansal [1996]8	Moderate	High	Moderate	Moderate	Low	Low	High
9	Beaugerie [2013]9	Low	Low	Low	Low	Low	Moderate	Low
10	Beaugerie [2018]10	Low	Low	Low	Low	Moderate	Low	Low
11	Bergeron [2010]11	Low	Low	Low	Low	Low	Low	Low
12	Bernstein [2011]12	Moderate	Moderate	Low	Moderate	Moderate	Low	High
13	Biancone [2016]13	Low	Low	Low	Low	Low	Moderate	Low
14	Boland [1984]14	High	Low	Low	Low	High	Moderate	High
15	Bopanna[2017]15	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
16	Braden [2012]16	Low	Low	Low	Low	High*	Low*	Low
17	Brentnall [1996]17	High	Moderate	Low	Low	High*	Moderate	Moderate
18	Broomé [1995]18	Low	Moderate	Low	Low	High*	Moderate	Moderate
19	Brostróm [1986]19	Low	Low	Low*	Low	High*	Moderate*	Low
20	Campos [2013]20	Low	Low	Low	Low	High	Moderate*	Low
21	Camus [2013]21	High	Low	Low	Low	High*	Moderate*	High
22	Carrat [2017]22	Low	Low	Low	Low	Low	Low	Low
23	Cheddani [2016]23	Moderate	Low	Low	Low	High*	Moderate*	Moderate
24	Choi [2019]24	Low	Low	Low	Low	High*	Moderate*	Low
25	Chow [2009]25	Low	Low	Low	Low	High*	Moderate*	Low
26	Connell [1994]26	Low	Low	Low	Low	High*	Moderate*	Low
27	Cosnes [2002] 27	Low	Low	Low	Low	High*	Moderate*	Low
	De Dombal [1966]28	Low	High	Low	Low	High*	Moderate*	High
	de Jong [2019]29	Low	Low	Low	Low	Low	Low	Low
30		Low	Moderate	Moderate	Low	High*	Moderate*	High
31	Eaden [2000]31	Moderate	Low	Low	Low	Low	Low	Low
32		Low	Low	Low	Low	High*	Moderate*	Low
33		Low	High	Low	Low	High*	Moderate*	High
34	0	Low	Moderate	Low	Moderate	High*	Moderate*	High
35		Low	Low	Low	Low	High	Moderate	Low
36		Low	Low	Moderate*	Low	High*	Moderate*	Moderate
37	Fujita [2010]37	Low	Moderate	High	Moderate	High*	Moderate*	High
38		Low	High	Low*	Low	High*	Moderate*	High
39	Gerrits [2011]39	Moderate	Low	Low	Low	Low	Low	Low
40	Gilat [1974]40	Low	Low	Low	Low	High*	Moderate*	Low
41	Gillen [1994a]41	Low	Low	Low	Low	High*	Moderate*	Low
42		Low	Low	Low	Low	High*	Moderate*	Low
43	Gong [2012]43	Low	Moderate	Low	Low	Moderate	Moderate*	Moderate
44	Gordillo [2015]44	Low	Low	Low	Low	Low High*	Low Moderate*	Low
45	Greenstein [1979]45	High	Low	Low	Low	High*	Moderate*	High

46 Gupta [2007]46	Low	Low	Low	Low	Low	Low Mederate*	Low
47 Hajek [2005]47	Moderate	Low	Low	Moderate	High*	Moderate*	High
48 Hou [2012]48	Moderate	Low	Moderate	Moderate	Moderate	Low	High
49 Hovde [2017]49	Low	Moderate	Low	Low	High*	Moderate*	Moderat
50 Jablonska [1993]50	Low	Low	Low	Low	High*	Moderate*	Low
51 Jacobsen [1994]51	Low	Low	Low	Low	High*	Moderate*	Low
52 Jess [2012]52	Moderate	Low	Low	Moderate	High*	Moderate*	High
53 Jonsson [1994]53	Low	Low	Low	Low	High*	Moderate*	Low
54 Joo [2009]54	Moderate	Low	Low	Low	High*	Moderate*	Moderat
55 Jung [2017]55	Moderate	Low	Low	Moderate	Moderate	Low	Moderat
56 Jussila [2013]56	Moderate	Moderate	Low*	Low	High*	Moderate*	High
57 Kamiya [2012]57	Low	Moderate	Low*	Low	High*	Moderate*	Moderat
58 Katzka [1983]58	Moderate	Low	Low	Low	High*	Moderate*	Moderat
59 Kishikawa [2018]59	Low	Moderate	Low	Low	Low	Low	Low
60 Kobayashi [2002]60	Low	Low	Low	Low	High*	Moderate*	Low
61 Kochhar [1991]61	Low	High	Moderate	Low	High*	Moderate*	High
62 Kopylov [2015]62	Moderate	Moderate	Low*	Moderate	High*	Moderate*	High
63 Kottachchi [2009]63	Low	Low	Low	Low	High*	Moderate*	Low
64 Kuo [2014]64	Moderate	Low	Low*	Moderate	High*	Moderate*	High
65 Kvist [1989]65	Low	Low	Low	Low	High*	Moderate*	Low
	1. Contract (1997)						
66 Lai [2015]66	Low	Low Moderate*	Low	Low	High*	Moderate*	Low
67 Laish [2017]67	Moderate*	Moderate*	Low	Low	High*	Moderate*	High
68 Lakatos [2004]68	Low	Moderate	Low	Low	High*	Moderate	Moderate
69 Lakatos [2006]69	Low	Low	Low	Low	Moderate	Moderate	Low
70 Lakatos [2011]70	Low	Low	Low	Low	High*	Moderate*	Low
71 Langholz[1992]71	Low	Low	Low	Low	High*	Moderate*	Low
73 Lashner [1989] 73	Moderate	High	Moderate	Low	High*	Moderate	High
72 Lashner [1989a]72	Low	Low	Low	Low	High*	Moderate*	Low
74 Lashner [1990]74	Moderate	Low	Low	Low	High*	Moderate*	Moderate
75 Lashner [1999]75	Moderate	Low	Low	Low	High*	Moderate*	Moderat
76 Lee[2015]76	Low	Low	Low	Low	High*	Moderate*	Low
77 Leidenius [1991]77	Low	Low	Low	Low	High*	Moderate*	Low
78 Leidenius [1997]78	Moderate	Low	Low	Low	High*	Moderate*	Moderat
79 Lennard-Jones [1977]79	Moderate	Low	Low	Low	High*	Moderate*	Moderate
80 Lennard-Jones [1990]80	Moderate	Low	Low	Low	High*	Moderate*	Moderate
			1			Moderate*	Moderat
81 Lim [2003]81	Moderate	Low	Low	Low	High*	moderate	
81 Lim [2003]81	Moderate Low	Low Low	Low			Moderate*	Low
				Low Low Low	High*		
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 	Low Low	Low Low	Low Low	Low Low	High* High*	Moderate* Moderate*	Low Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 	Low Low Low	Low	Low	Low Low Low	High* High* High*	Moderate* Moderate* Moderate*	Low Low Moderate
 Lim [2003]81 Lindberg [1999]82 Lindberg [2001]83 Lindberg[2005]84 Lindström [2011]85 	Low Low Low Low	Low Low Low Low	Low Low Moderate Low	Low Low Low Low	High* High* High* High*	Moderate* Moderate* Moderate* Moderate*	Low Low Moderate Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 	Low Low Low Low High	Low Low Low Low Low	Low Low Moderate Low Moderate	Low Low Low Low Low	High* High* High* High* High*	Moderate* Moderate* Moderate* Moderate* Moderate*	Low Low Moderate Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 	Low Low Low Low High Low	Low Low Low Low Low Low	Low Low Moderate Low Moderate Low	Low Low Low Low Low Low	High* High* High* High* High* High*	Moderate* Moderate* Moderate* Moderate* Moderate* Low	Low Low Moderat Low High Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 	Low Low Low Low High Low	Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Moderate	Low Low Low Low Low Low Low Low	High* High* High* High* High* High*	Moderate* Moderate* Moderate* Moderate* Moderate* Low Moderate*	Low Low Moderat Low High Low Moderat
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 89 Lutgens [2015]89 	Low Low Low Low Low Low Low	Low Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Moderate Low	Low Low Low Low Low Low Low	High* High* High* High* High* High* High*	Moderate* Moderate* Moderate* Moderate* Low Moderate* Low	Low Low Moderat Low High Low Moderat Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg [2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 89 Lutgens [2015]89 90 MacDougall [1954]90 	Low Low Low Low Low Low Low Low	Low Low Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Moderate Low	Low Low Low Low Low Low Low Low Low	High* High* High* High* High* High* Low High*	Moderate* Moderate* Moderate* Moderate* Moderate* Low Moderate* Low	Low Low Moderat Low High Low Moderat Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 89 Lutgens [2015]89 90 MacDougall [1954]90 91 Madanchi [2016]91 	Low Low Low Low Low Low Low Low	Low Low Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Low Low	Low Low Low Low Low Low Low Low Low Low	High* High* High* High* High* High* Low High* High*	Moderate* Moderate* Moderate* Moderate* Low Low Moderate* Low	Low Low Moderat Low High Low Moderat Low Low Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 89 Lutgens [2015]89 90 MacDougall [1954]90 91 Madanchi [2016]91 92 Mahmoud [2019]92 	Low Low Low Low Low Low Low Low Low Low	Low Low Low Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Low Low Low	Low Low Low Low Low Low Low Low Low Low	High* High* High* High* High* High* Low High* Low	Moderate* Moderate* Moderate* Moderate* Low Moderate* Low Moderate* Moderate* Moderate*	Low Low Moderate Low High Low Low Low Low Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 89 Lutgens [2015]89 90 MacDougall [1954]90 91 Madanchi [2016]91 92 Mahmoud [2019]92 93 Mahmoud [2019b]93 	Low Low Low Low Low Low Low Low	Low Low Low Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Low Low	Low Low Low Low Low Low Low Low Low Low	High* High* High* High* High* High* Low High* High* Low	Moderate* Moderate* Moderate* Moderate* Moderate* Low Moderate* Moderate* Moderate* Moderate*	Low Low Moderate Low High Low Moderate Low Low Low
 81 Lim [2003]81 82 Lindberg [1999]82 83 Lindberg [2001]83 84 Lindberg[2005]84 85 Lindström [2011]85 86 Löfberg [1991]86 87 Loftus [2005]87 88 Lovasz [2013]88 89 Lutgens [2015]89 90 MacDougall [1954]90 91 Madanchi [2016]91 92 Mahmoud [2019]92 	Low Low Low Low Low Low Low Low Low Low	Low Low Low Low Low Low Low Low Low Low	Low Low Moderate Low Moderate Low Low Low Low	Low Low Low Low Low Low Low Low Low Low	High* High* High* High* High* High* Low High* Low	Moderate* Moderate* Moderate* Moderate* Low Moderate* Low Moderate* Moderate* Moderate*	Low Low Moderate Low High Low Low Low Low Low

97	Mir-Madjlessi [1986]97	Low	Moderate	Low	Low	High*	Moderate*	High
98	Navaneethan [2016]98	Low	Low	Low	Low	High*	Moderate*	Low
99	Nieminen [2014]99	Low	Low	Low	Low	Moderate	Low	Low
100	Nkontchou [1996]100	Moderate	High	Low	Moderate	High*	Moderate*	High
101	Nowacki [2015]101	Low	Low	Low	Low	Low	Low	Low
102	Nuako [1998]102	Low	Low	Low	Low	Low	Low	Low
103	Nuako [1998a]103	Moderate	Unclear	Low	Low	Low	Low	Low
104	Nugent [1991]104	Low	Moderate	Low	Low	High*	Moderate*	Moderate
105	Paris [1994]105	Low	High	Low	Moderate	High*	Moderate*	High
106	Peng [2015]106	Moderate	Low	Low	Moderate	High*	Moderate*	High
107	Peng [2017]107	Moderate	Low	Low	Moderate	Moderate	Moderate	High
108	Picazo-Ferrera [2011]108	Low	Moderate	Low	Low	High	High	High
109	Pinczowski [1994]109	Moderate	High	Low	Low	High	Moderate	High
110	Prior [1982]110	Low	Low	Low	Low	High*	Moderate*	Low
111	Radford-Smith [2002]111	Low	High	Low	Low	High*	Moderate*	High
112	Ray [2011]112	Low	Low	Low	Low	Moderate	Moderate*	Low
113	Rozen [1995]113	Low	Low	Low	Low	High*	Moderate*	Low
114		Low	Low	Low	Low	Low	Low	Low
115	Rubio [2009]115	High	High	Low	Low	High*	Moderate*	High
116	Rutegard [1988]116	Low	Low	Low	Low	High*	Moderate*	Low
117	Rutegard [1988b]117	Low	High	Low	Low	High*	Moderate*	High
118	Rutter [2004]118	Moderate	Low	Low	Low	Low	Low	Low
119	Rutter[2006]119	Moderate	Low	Low	Low	High*	Moderate*	Moderate
120	Samadder [2011]120	Moderate	High	Moderate	Moderate	Moderate	Moderate	High
120	Samadder [2018]121	Moderate	Moderate	Moderate	Moderate	High*	Moderate	High
122	Satchi [2013]122	Moderate	Low	Low	Low	High*	Moderate*	Moderate
122	Scharl [2018]123	Low	Low	Low	Low	Moderate	Moderate	Moderate
124	Selinger [2014]124	Low	Low	Low	Low	High	Moderate	Low
124	• • •	Low	Moderate	Low	Moderate	High*	Moderate*	High
126	Setshedi [2012]126		Moderate	Low	Moderate	High*	Moderate*	High
120	Shah [2018]127	Low	Low	Low	Low	Low	Low	Low
128								
	Shetty [1999] 129	Low	Low Low	Low Low	Low Low	Low High*	Low Moderate*	Low
130 131	Shi [2016]130 Shivakumar [2013]131	Low Low	Low Moderate	Low Low	Low Low	High*	Moderate* Moderate*	Low Moderate
		1				High*		
132 133	• • •	Low	Low	Low	Low	Low High*	Low Moderate*	Low Low
		Low	Low	Low	Low	High*		
134		Low	Low	Low	Low	High*	Moderate*	Low
135		Low	Low	Low	Low	High*	Moderate*	Low
136		Low	Low	Low	Low	Low	Low	Low
	. .	Moderate	High	High	Low	Moderate	Low	High
137	• • • • • • • • • • • • • • • • • • •	Low	Low	Low	Low	Moderate	Low	Low
138						High*	Moderate*	Low
138 139	Stewénius [1995]139	Low	Low	Low	Low			
138 139 140	Stewénius [1995]139 Stolwijk [2013]140	Low Low	Low	Low	Low	Low	Low	Low
138 139 140 141	Stewénius [1995]139 Stolwijk [2013]140 Tang [2010]141	Low Low Low				Low Moderate	Low Moderate	Low Low
138 139 140 141 142	Stewénius [1995]139 Stolwijk [2013]140 Tang [2010]141 Ten Hove [2019]142	Low Low Low Moderate	Low Low Low	Low Low Low	Low Low Low	Low Moderate High*	Low Moderate Moderate*	Low Low Moderate
138 139 140 141	Stewénius [1995]139 Stolwijk [2013]140 Tang [2010]141 Ten Hove [2019]142 Terdiman [2007]143	Low Low Low	Low Low	Low Low Low Moderate	Low Low	Low Moderate High* Low	Low Moderate Moderate* Low	Low Low Moderate High
138 139 140 141 142 143 144	Stewénius [1995]139 Stolwijk [2013]140 Tang [2010]141 Ten Hove [2019]142 Terdiman [2007]143 Terg [2008]144	Low Low Moderate Moderate Low	Low Low Low High Low	Low Low Low Moderate Low	Low Low Low Moderate Low	Low Moderate High* Low High*	Low Moderate Moderate* Low Moderate*	Low Low Moderate High Low
138 139 140 141 142 143 144 145	Stewénius [1995]139 Stolwijk [2013]140 Tang [2010]141 Ten Hove [2019]142 Terdiman [2007]143	Low Low Low Moderate Moderate	Low Low Low High	Low Low Low Moderate	Low Low Low Moderate	Low Moderate High* Low	Low Moderate Moderate* Low	Low Low Moderate High

4.40		1	1	1	1	h e an	Ma	1
148	Ullman [2008]148	Low	Low	Low	Low	High	Moderate*	Low
149	Ünal [2019]149	Low	Low	Moderate	Low	High*	Moderate*	Moderate
150	van den Heuvel [2016]150	Low	Low	Low	Low	High*	Moderate*	Low
151	van Schaik [2012]151	Moderate	Low	Low	Low	Low	Low	Low
152	van Schaik [2013]152	High	Low	Low	Low	Low	Low	High
153	van Staa [2005]153	Moderate	Low	Moderate	Moderate	Low	Low	High
154	Velayos [2006]154	Low	Low	Low	Low	Low	Low	Low
155	Venkataraman [2005]155	Low	Moderate	High*	Low	High	High	High
156	Walmsley [1997]156	High	Low	Low	Low	High*	Moderate*	High
157	Wang [2013]157	Moderate	Low	Low	Low	High*	Moderate*	Moderate
158	Winther [2004]158	Low	Low	Moderate	Moderate	High*	Moderate*	High
159	Wright [1983]159	Moderate	Low	Low	Moderate	High*	Moderate*	High
160	Yamazaki [1991]160	Low	Moderate	High	Moderate	High*	Moderate*	High
161	Yano [2008]161	Low	Low	Moderate	Low	High*	Moderate*	Moderate
162	Yano [2013]162	Low	Low	Low	Low	High*	Moderate*	Low
163	Ye [2011]163	Low	Low	Low	Low	High*	Moderate*	Low
164	Zhang [2015]164	Low	High	Moderate	Low	High	Moderate	High

* The risk of bias is high because the aim of the study was not specifically to study the impact of risk factors on the advanced colorectal neoplasia risk, but data to calculate an OR was provided. Therefore it was not possible to analyze these risk factors adjusted for important covariates.

Supplementary file 6: Risk of bias: QUIPS explanation

In addition to the QUIPS tool, through consensus, we have stated additional criteria to evaluate risk of bias in the included studies. The main reason for this addition is the fact that the majority of the included studies was originally not intended for prognostic factor research or did not provide sufficient information to be able to grade in accordance with the original QUIPS tool. As a recent Cochrane systematic review has done, we added a fourth 'unclear' option to the QUIPS tool.¹

Q1: Study participation

Low risk: Surveillance cohort or cohort of total IBD population. Moderate risk: ICD codes (or comparable codes) without chart review; sub-selection of IBD patients (e.g. only extensive disease, only above a certain age). High risk: Extreme selection (e.g. only patients using 5-ASA or another prescription); no random selection of cohort or the selection process is not described.

Q2: Study Attrition

Low risk: Documentation of follow-up and actions are undertaken to retrieve information from these cases.

Moderate risk: Intermediate.

High risk: No information or mentioning on loss-to follow-up.

Q3: Prognostic factor (PF) Measurement

Low risk: Definition of PF is provided and reproducible. The risk of misclassification is extremely low (e.g. sex; dose of medication).

Moderate risk: Definition is given, but not specific (e.g. unclear definition of

medication use)

High risk: No clear definition given for all factors.

Q4: Outcome Measurement

Low risk: Definition of outcome is provided and reproducible. The risk of misclassification is extremely low. Chart review was executed (pathology or patient chart). Moderate risk: Definition is given, outcome is based on coding (no revision of patient chart).

High risk: No clear definition of outcome is given or process of collection information on occurrence of outcomes is not described.

Q5: Study Confounding (Covariates)

Low risk: Most important covariates were evaluated and the result was either adjusted for these variables or reported in a multivariable model.

Moderate risk: Some important covariates were unadjusted for or missing in the cohort. High risk: Only univariable analysis was provided or we calculated or own OR based on data in article (last category indicated with an asterisk).

Q6: Statistical analysis and Reporting

Low risk: A fitting analysis was undertaken (e.g. conditional logistic regression in the setting of a case-control design); steps in model building were undertaken well and adequate reporting (univariable as well as multivariable).

Moderate: Only univariable data are provided in a study in which a multivariable model could have been performed. Or we calculated or own OR from either a case-control study or cohort study.

High risk: Multivariable analysis is performed with a low number of cases.

Reference

^{1.} Aldin A, Umlauff L, Estcourt LJ, Collins G, Moons KG, Engert A, et al. Interim PET-results for prognosis in adults with Hodgkin lymphoma: a systematic review and meta-analysis of prognostic factor studies. The Cochrane database of systematic reviews. 2020;1:CD012643.

DISEASE CHARACTERISTICS (AND DEMOGRAPHICS)

Supplementary file 7A-G Disease extent

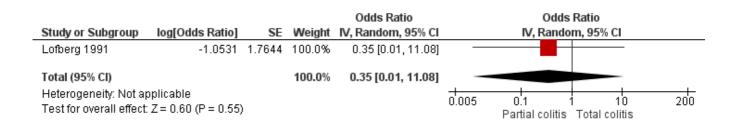
Supplementary Figure 7A: Forest plot of univariable ORs extensive disease versus

non-extensive disease in UC (cohort studies)

~		-		Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]			IV, Random, 95% Cl		IV, Random, 95% Cl
Greenstein 1979		0.5143	3.5%	3.19 [1.16, 8.74]		-
Wright 1983		1.5561	0.4%	5.74 [0.27, 121.26]		
Katzka 1983		0.8124	1.4%	4.67 [0.95, 22.94]		
Maratka 1985		1.1215	0.7%	2.96 [0.33, 26.70]		
Mir-Madjlessi 1986		0.3774	6.5%	7.42 [3.54, 15.55]	1986	
Rutegard 1988		1.5228	0.4%	4.75 [0.24, 93.85]	1988	
Kvist 1989	0.0679	0.4919	3.8%	1.07 [0.41, 2.81]	1989	
Ekbom 1990a	1.2471	0.2763	12.0%	3.48 [2.02, 5.98]	1990	
Kochhar 1991	2.0067	0.8235	1.4%	7.44 [1.48, 37.36]	1991	
Leidenius 1991	1.3115	1.6517	0.3%	3.71 [0.15, 94.52]	1991	
Jablonská 1993	0.8602	0.7305	1.7%	2.36 [0.56, 9.89]	1993	
Jonsson 1994	0.8204	0.8366	1.3%	2.27 [0.44, 11.71]	1994	
Stewenius 1995	1.0385	0.8783	1.2%	2.82 [0.51, 15.80]	1995	
Rozen 1995	-0.1405	0.7822	1.5%	0.87 [0.19, 4.03]		
Markowitz 1997	0.7621	1.7015	0.3%	2.14 [0.08, 60.16]		
Triantafillidis 1998	-1.1236	1.5237	0.4%	0.33 [0.02, 6.44]		←
Fraser 2002	0.4223	0.4259	5.1%	1.53 [0.66, 3.52]		
Kobayashi 2002		1.4896	0.4%	2.72 [0.15, 50.40]		
Winther 2004		0.6763	2.0%	1.63 [0.43, 6.14]		
Venkataraman 2005		1.4719	0.4%	6.91 [0.39, 123.74]		
Lindberg 2005		0.8303	1.3%	1.56 [0.31, 7.93]		
Lakatos 2006		0.5778	2.8%	3.54 [1.14, 10.99]		
Chow 2009		1.6431	0.3%	2.13 [0.09, 53.36]		
Kottachchi 2009		1.5225	0.4%	4.15 [0.21, 82.03]		
Söderlund 2009		0.2218	18.7%	1.57 [1.02, 2.43]		_ _
Fujita 2010		1.4666	0.4%	7.26 [0.41, 128.69]		
		1.5319	0.4%			
Ray 2011	1.382	0.361	7.1%	5.00 [0.25, 100.67]		
Gong 2012 Shively may 2012				3.98 [1.96, 8.08]		
Shivakumar 2013		1.5601	0.4%	7.00 [0.33, 148.95]		
Campos 2013		1.0528	0.8%	6.48 [0.82, 51.02]		
Senanayake 2013		1.4207	0.5%	1.72 [0.11, 27.87]		
Manninen 2013		0.5202	3.4%	1.17 [0.42, 3.24]		
Selinger 2014		0.4676	4.2%	1.64 [0.66, 4.10]		
Desai 2015	1.3376	0.791	1.5%	3.81 [0.81, 17.96]		
Lee 2015		0.7514	1.6%	5.86 [1.34, 25.54]		
Gordillo 2015		0.5144	3.5%	2.11 [0.77, 5.78]		
Nowacki 2015		0.6555	2.1%	1.46 [0.40, 5.28]		
van den Heuvel 2016		0.6158	2.4%	2.27 [0.68, 7.59]		
Laish 2017		0.9257	1.1%	1.45 [0.24, 8.88]		
Ünal 2019	0.4568	0.611	2.5%	1.58 [0.48, 5.23]	2019	
Total (95% CI)			100.0 %	2.43 [2.01, 2.93]		•
Heterogeneity: Tau² = 0			= 0.57);1	P= 0%		0.05 0.2 1 5 20
Test for overall effect: Z	= 9.26 (P < 0.000	11)				Left-sided Extensive disease

Supplementary Figure 7B: Forest plot of univariable ORs extensive disease versus

non-extensive disease in CD (cohort study)



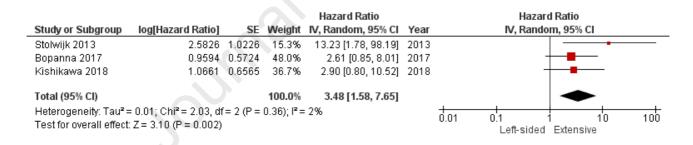
Supplementary Figure 7C: Forest plot of univariable HRs extensive disease versus

non-extensive disease in IBD (cohort studies)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Year	Hazard Ratio IV, Random, 95% Cl
Mahmoud 2019	-0.5741	0.3944	100.0%	0.56 [0.26, 1.22]	2019	→ -■+
Total (95% CI)			100.0%	0.56 [0.26, 1.22]		
Heterogeneity: Not ap	•					
Test for overall effect:	Z = 1.46 (P = 0.15)					Left-sided Extensive

Supplementary Figure 7D: Forest plot of univariable HRs extensive disease versus

non-extensive disease in UC (cohort studies)



Supplementary Figure 7E: Forest plot of multivariable ORs extensive disease versus

non-extensive disease in UC (cohort study)

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Gong 2012	2.1894	1.024	100.0%	8.93 [1.20, 66.45]	
Total (95% CI)			100.0%	8.93 [1.20, 66.45]	
Heterogeneity: Not ap	•				
Test for overall effect:	Z = 2.14 (P = 0.03)	I			Left sided Extensive disease

Supplementary Figure 7F: Forest plot of multivariable HRs extensive disease versus

non-extensive disease in all IBD (cohort studies)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Year	Hazard Ratio IV, Random, 95% Cl
Stolwijk 2013	2.6034	1.0228	39.6%	13.51 [1.82, 100.29]	2013	_ >
Mahmoud 2019	0.5988	0.4592	60.4%	1.82 [0.74, 4.48]	2019	+
Total (95% CI)			100.0%	4.03 [0.59, 27.50]		
Heterogeneity: Tau ² = Test for overall effect:		= 1 (P =	0.07); I² =	69%		0.02 0.1 1 10 50 Left sided Extensive disease

Supplementary notation 7G: Definition disease extent

To assess extent of disease we included studies that provided data on patients with left-sided UC versus extensive disease (inflammation extending at least proximal of the splenic flexure). In CD, an estimated involvement of >50% of the colon was regarded as extensive disease. Studies not clearly defining disease extent were excluded.

Supplementary file 8A-F IBD type

Supplementary Figure 8A: Forest plot Univariable analysis OR cohort studies (UC

excluding proctitis versus CD (ileo-)colitis)

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Gillen 1994a	-0.0747	0.4126	13.8%	0.93 [0.41, 2.08]	1994	
Lakatos 2004	0.4605	0.7806	4.2%	1.58 [0.34, 7.32]	2004	
Söderlund 2009	0.8802	0.2726	27.8%	2.41 [1.41, 4.11]	2009	_
Manninen 2013	0.2954	0.5155	9.2%	1.34 [0.49, 3.69]	2013	
Beaugerie 2013	0.5594	0.3736	16.5%	1.75 [0.84, 3.64]	2013	
Lee 2015	0.3631	0.3741	16.4%	1.44 [0.69, 2.99]	2015	
van den Heuvel 2016	-0.2399	0.4438	12.1%	0.79 [0.33, 1.88]	2016	
Total (95% CI)			100.0%	1.50 [1.09, 2.06]		
Heterogeneity: Tau ² = (0.02; Chi ^z = 6.72, df	f= 6 (P =	0.35); I² =	:11%		
Test for overall effect: 2						0.5 0.7 1 1.5 2 Crohn's disease Ulcerative colitis
						oronna disease Orcerative contis

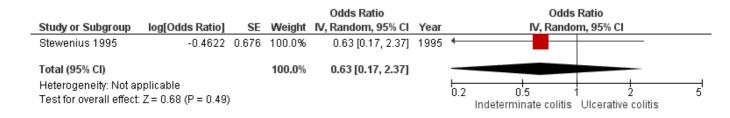
Supplementary Figure 8B: Forest plot Univariable analysis OR cohort studies (UC

including proctitis versus CD (ileo-)colitis)

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Gillen 1994a	-0.0747	0.4126	14.8%	0.93 [0.41, 2.08]	1994	
Lakatos 2004	0.2553	0.7803	5.1%	1.29 [0.28, 5.96]	2004	• •
Söderlund 2009	0.7104	0.2673	25.7%	2.03 [1.21, 3.44]	2009	
Beaugerie 2013	0.1176	0.4354	13.6%	1.12 [0.48, 2.64]	2013	
Manninen 2013	0.1181	0.5154	10.5%	1.13 [0.41, 3.09]	2013	
Lee 2015	0.0189	0.3739	17.0%	1.02 [0.49, 2.12]	2015	
van den Heuvel 2016	-0.6613	0.4435	13.3%	0.52 [0.22, 1.23]	2016	• •
Total (95% CI)			100.0%	1.14 [0.79, 1.64]		
Heterogeneity: Tau ² = (0.06; Chi ² = 8.15, dt	f= 6 (P =	0.23); l² =	: 26%		
Test for overall effect: Z	(= 0.69 (P = 0.49)					0.5 0.7 1 1.5 2 Crohn's disease Ulcerative colitis

Supplementary Figure 8C: Forest plot Univariable analysis OR cohort studies

(indeterminate colitis versus UC)

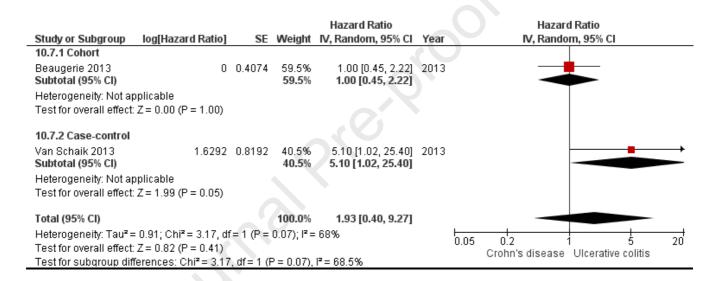


Supplementary Figure 8D: Forest plot of Univariable analysis HR case-control (UC

versus CD)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Hazard Ratio IV, Random, 95% Cl
Van Schaik 2013	1.8049	0.7492	100.0%	6.08 [1.40, 26.40]	
Total (95% CI)			100.0%	6.08 [1.40, 26.40]	
Heterogeneity: Not ap Test for overall effect:					0.05 0.2 1 5 20 Crohn's disease Ulcerative colitis

Supplementary Figure 8E: Forest plot of Multivariable analysis HR (UC versus CD)



Supplementary notation 8F: Definition IBD type

To compare the risk of UC versus CD we only included studies that reported the risk of aCRN in IBD patients with colonic involvement. Studies were excluded if the provided data did not allow for calculation of the OR after exclusion of patients without colonic involvement.

Supplementary file 9A-E Low-grade dysplasia

Supplementary Figure 9A: Forest plot of Univariable OR (cohort studies)

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Lennard-Jones 1977	3.9723	1.5682	4.6%	53.11 [2.46, 1148.16]	1977	
Lashner 1989a	1.6514	0.6469	12.9%	5.21 [1.47, 18.53]	1989	
Nugent 1991	4.4543	0.8694	9.9%	86.00 [15.65, 472.62]	1991	+
Lim 2003	0.9868	0.7953	10.8%	2.68 [0.56, 12.75]	2003	
Lakatos 2006	2.9601	0.6559	12.8%	19.30 [5.34, 69.80]	2006	
Uliman 2008	2.3804	0.4741	15.5%	10.81 [4.27, 27.37]	2008	
Stolwijk 2013	1.0804	0.4771	15.5%	2.95 [1.16, 7.50]	2013	_
Choi 2019	2.92	0.3106	18.0%	18.54 [10.09, 34.08]	2019	
Total (95% CI)			100.0%	10.85 [5.13, 22.97]		6 •
Heterogeneity: Tau ² = 0	.72; Chi² = 22.27, o	: #f = 7 (P =	= 0.002); I	I²= 69%		
Test for overall effect: Z						0.01 0.1 1 10 100 LGD protective LGD risk factor

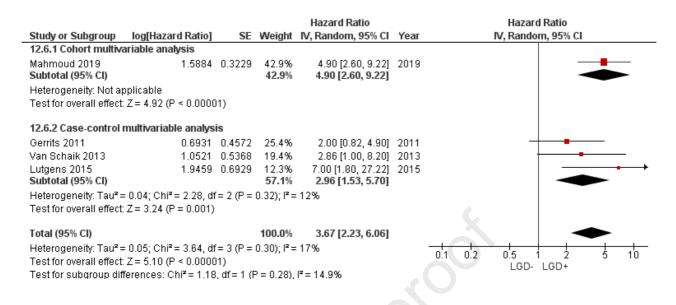
Supplementary Figure 9B: Forest plot of Univariable HR

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
12.2.1 Cohort						
Mahmoud 2019 Subtotal (95% CI)	1.7783	0.3367	63.8% 63.8 %	5.92 [3.06, 11.45] 5.92 [3.06, 11.45]	2019	-
Heterogeneity: Not ap	plicable					
Test for overall effect:	Z = 5.28 (P < 0.0000)1)				
12.2.2 Case-control						
Van Schaik 2013 Subtotal (95% CI)	1.2809	0.4467	36.2% 36.2 %	3.60 [1.50, 8.64] 3.60 [1.50, 8.64]	2013	
Heterogeneity: Not ap	plicable					
Test for overall effect:	Z = 2.87 (P = 0.004)					
Total (95% CI)			100.0%	4.94 [2.92, 8.37]		-
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diff	Z = 5.94 (P < 0.0000)1)			-	0.1 0.2 0.5 1 2 5 10 LGD- LGD+

Supplementary Figure 9C: Forest plot of Multivariable OR (cohort study)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Year			rd Ratio om, 95% Cl	
Lakatos 2006	1.5518	0.7922	100.0%	4.72 [1.00, 22.30]	2006				———
Total (95% CI)			100.0%	4.72 [1.00, 22.30]					
Heterogeneity: Not ap Test for overall effect:						0.05	0.2 LGD	1 5 - LGD+	i 20

Supplementary Figure 9D: Forest plot of Multivariable analysis HR



Supplementary Table 9E: Characteristics of LGD

Author	Number of LGD	Number of aCRN	Morphology
Lennard-Jones 1977	20	2	not specified
Lashner 1989a	20	6	not specified
Nugent 1991	18	7	not specified
Lim 2003	29	3	not specified
Lakatos 2006	not specified	not specified	not specified
Ullman 2008	26	10	Flat
Stolwijk 2013	55	10	not specified
Choi 2019	not specified	not specified	Flat
Mahmoud 2019	not specified	not specified	not specified
Van Schaik 2013	42	18	Flat and polypoid
Gerrits 2011	not specified	not specified	Flat and polypoid
Lutgens 2015	not specified	not specified	Polypoid

Supplementary file 10A-C Indefinite for dysplasia

Supplementary Figure 10A: Forest plot of Univariable OR (cohort studies)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio IV, Random, 95% Cl
Nugent 1991	2.3143	0.8552	27.6%	10.12 [1.89, 54.08]	1991	_
Uliman 2008	0.2854	0.5757	39.9%	1.33 [0.43, 4.11]	2008	
Lai 2015	0.4106	0.732	32.5%	1.51 [0.36, 6.33]	2015	
Total (95% CI)			100.0%	2.42 [0.75, 7.81]		
Heterogeneity: Tau² = Test for overall effect:			= 0.12); l²	²= 52%		0.02 0.1 1 10 50 IND protective IND risk factor

Supplementary Figure 10B: Forest plot of Univariable HR (cohort study)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Year			rd Ratio om, 95% Cl		
Mahmoud 2019b	2.1552	0.5761	100.0%	8.63 [2.79, 26.69]	2019					
Total (95% CI)			100.0%	8.63 [2.79, 26.69]						
Heterogeneity: Not a Test for overall effect	••	!)				0.05	0.2 IND-	1 (IND+	ō	20

Supplementary Figure 10C: Forest plot of Multivariable HR (cohort study)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Voar			rd Ratio om, 95% Cl	
Study of Subgroup	log[nazaru Natio]	JL	weight	W, Nandom, 55% CI	rear		iv, Nanu	011, 3370 CI	
Mahmoud 2019b	1.9242	0.6876	100.0%	6.85 [1.78, 26.36]	2019				
Total (95% CI)			100.0%	6.85 [1.78, 26.36]					
Heterogeneity: Not a	pplicable					-		<u> </u>	+ +
Test for overall effect	 .: Z = 2.80 (P = 0.005)					0.05	0.2	1	Ś 20
							IND-	· IND+	

Supplementary file 11A-D Any dysplasia (not specified)

Supplementary Figure 11A: Any dysplasia (not specified), univariable OR cohort

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl			Ratio m, 95% Cl	
Lakatos 2006	2.966	0.6529	34.3%	19.41 [5.40, 69.80]			_	
Gong 2012	2.0596	0.4098	65.7%	7.84 [3.51, 17.51]				
Total (95% CI)			100.0%	10.70 [4.60, 24.87]			-	
Heterogeneity: Tau² = Test for overall effect:			= 0.24); l ^a	²= 28%	0.02	0.1 Protective factor	1 10 Risk factor	50

Supplementary Figure 11B: Any dysplasia (not specified), univariable HR cohort

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl		Hazard Ratio IV, Random, 95% Cl	
Van Schaik 2012	-0.734	1.061	100.0%	0.48 [0.06, 3.84]			
Total (95% CI) Heterogeneity: Not ap Test for overall effect: J	•		100.0%	0.48 [0.06, 3.84]	0.02	0.1 1 10 50 Protective factor Risk factor	† 0

Supplementary Figure 11C: Any dysplasia (not specified), multivariable OR cohort

				Odds Ratio		Odds	Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl		IV, Rando	m, 95% Cl	
Lakatos 2006	1.5523	0.792	20.2%	4.72 [1.00, 22.30]				
Sonnenberg 2015	1.2267	0.399	79.8%	3.41 [1.56, 7.45]				
Total (95% CI)			100.0 %	3.64 [1.81, 7.32]				
Heterogeneity: Tau² = Test for overall effect		-	P = 0.71);	I ² = 0%	0.1	0.2 0.5 Protective factor	1 2 5 Risk factor	10 5 10

Supplementary Figure 11D: Any dysplasia (not specified), multivariable HR cohort

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl		Hazard IV, Randor		
Van Schaik 2012	0.0677	1.0025	100.0%	1.07 [0.15, 7.63]				
Total (95% CI)			100.0%	1.07 [0.15, 7.63]				
Heterogeneity: Not ap Test for overall effect:	•				0.05	0.2 1 Protective factor	5 Risk factor	20

Supplementary Files 12A-D Post-inflammatory polyps (PIPs)

Supplementary Figure 12A: Forest plot of univariable ORs PIPs

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
2.2.1 Cohort						
De Dombal 1966	1.0913	0.8312	3.6%	2.98 [0.58, 15.19]	1966	
Bopanna 2017	0.7931	0.5249	9.0%	2.21 [0.79, 6.18]	2017	
Ünal 2019	0.9855	0.6856	5.3%	2.68 [0.70, 10.27]	2019	
Subtotal (95% CI)			17.9%	2.48 [1.20, 5.16]		
Heterogeneity: Tau ² =	: 0.00; Chi ² = 0.11,	df = 2 (P	= 0.95); l ^a	²= 0%		
Test for overall effect:	Z = 2.44 (P = 0.01)					
2.2.2 Case-control						
Velayos 2006	0.9313	0.3035	27.0%	2.54 [1.40, 4.60]	2006	· · · · · · · · · · · · · · · · · · ·
Baars 2011	1.4095	0.2128	55.0%	4.09 [2.70, 6.21]	2011	
Subtotal (95% CI)			82.1%	3.39 [2.14, 5.36]		
Heterogeneity: Tau ² =	: 0.05; Chi ² = 1.66,	df = 1 (P	= 0.20); P	²= 40%		
Test for overall effect:	Z=5.21 (P < 0.00	001)				
Total (95% CI)			100.0%	3.29 [2.41, 4.48]		
Heterogeneity: Tau ² =	: 0.00: Chi ² = 2.47.	df = 4 (P	= 0.65); l ^a	²= 0%		
Test for overall effect:						0.1 0.2 0.5 1 2 5 10
Test for subaroup dif	•		(P = 0.48)	i), ² = 0%		PIPs protective PIPs risk factor
		· - • · · ·				

Supplementary Figure 12B: Forest plot of univariable HRs PIPs (cohort studies)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Hazard Ratio IV, Random, 95% Cl
de Jong 2019	0.6548	0.4609	33.6%	1.92 [0.78, 4.75]	
Mahmoud 2019	0.4434	0.3275	66.4%	1.56 [0.82, 2.96]	
Total (95% CI)			100.0%	1.67 [0.99, 2.82]	
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.14, df=	⇒1 (P = I	0.71); I ^z =	: 0%	
Test for overall effect	Z = 1.93 (P = 0.05)				0.2 0.5 1 2 5 PIPs protective PIPs risk factor

Supplementary Figure 12C: Forest plot Multivariable OR (case-control study)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio IV, Random, 95% Cl
Velayos 2006	0.9313	0.3035	100.0%	2.54 [1.40, 4.60]	2006	
Total (95% CI)			100.0 %	2.54 [1.40, 4.60]		
Heterogeneity: Not ap Test for overall effect:	•	2)				0.05 0.2 1 5 20 PIPs protective PIPs risk factor

Supplementary Figure 12D: Forest plot of Multivariable analysis HR

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
2.7.1 Cohort multiva	riable analysis					
Mahmoud 2019	0.157	0.3493	37.4%	1.17 [0.59, 2.32]	2019	
de Jong 2019 Subtotal (95% CI)	0.2258	0.5578	23.5% 60.9 %	1.25 [0.42, 3.74] 1.19 [0.67, 2.13]	2019	
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.01, df	= 1 (P =	0.92); l² =	:0%		
Test for overall effect	Z = 0.60 (P = 0.55)					
2.7.2 Case-control m	ultivariable analysis					
Lutgens 2015 Subtotal (95% CI)	1.1139	0.3285	39.1% 39.1 %	3.05 [1.60, 5.80] 3.05 [1.60, 5.80]	2015	
Heterogeneity: Not ap	oplicable					
Test for overall effect:	Z = 3.39 (P = 0.0007)				
Total (95% Cl)			100.0%	1.73 [0.88, 3.40]		
Heterogeneity: Tau ² =	= 0.20° Chi² = 4.51. df	= 2 (P =	0 11) [,] P=	. , 1		
Test for overall effect:		- 0	//-			0.2 0.5 1 2 5
Test for subgroup dif	· · ·	. df = 1 (F	° = 0.03),	I ² = 77.8%		PIPs protective PIPs risk factor

- u.03), I^z = 77.8%

Supplementary file 13A-D Endoscopic inflammation

Supplementary Figure 13A: Forest plot of Univariable OR (case-control study)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year		Odds Ratio IV, Random, 95			
Rutter 2004	0.9632	0.5804	100.0%	2.62 [0.84, 8.17]	2004					
Total (95% CI) Heterogeneity: Not a) Test for overall effect:		ļ	100.0%	2.62 [0.84, 8.17]		0.1 0.2	0.5 1 Protective Risk	+ 2	 5 10	

Supplementary Figure 13B: Forest plot Univariable HR (cohort study)

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Shah 2018	0.7608	0.1881	100.0%	2.14 [1.48, 3.09]	2018	
Total (95% CI)			100.0%	2.14 [1.48, 3.09]		
Heterogeneity: Not app Test for overall effect: 2)				0.5 0.7 1 1.5 2 Protective Risk

Supplementary Figure 13C: Forest plot of Multivariable HR (cohort study)

				Hazard Ratio			Hazar	d Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year		IV, Rando	m, 95% Cl	
Shah 2018	0.8713	0.1953	100.0%	2.39 [1.63, 3.50]	2018				
Total (95% CI)			100.0%	2.39 [1.63, 3.50]					
Heterogeneity: Not ap Test for overall effect:		11)				0.2	0.5 Protective	l 2 Risk	5

Supplementary Table 13D: Definitions used in studies used in pooled analysis

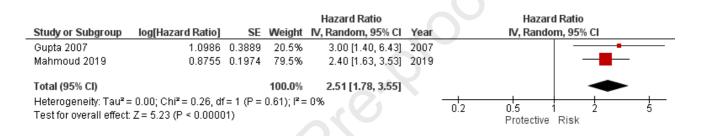
Study, year	Definition	Supplementary figure
Rutter, 2004	Scoring per segment providing a mean endoscopic score (0-4). The mean endoscopic score for all segments of each colonoscopy was calculated and the mean endoscopic score for all surveillance colonoscopies performed in one patient.	13A
Shah, 2018	For each surveillance colonoscopy the severity of active endoscopic inflammation was scored on a 4-point scale for each colonic segment visualized. A mean inflammatory severity score per patient and per colonoscopy was calculated.	13B, 13C

Supplementary file 14A-D Histologic inflammation

Supplementary Figure 14A: Forest plot of Univariable OR (case-control studies)

				Odds Ratio			Odds Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year		IV, Random, 95% Cl	
Rutter 2004	1.8453	1.0305	20.8%	6.33 [0.84, 47.71]	2004			-
Rubin 2013	0.9708	0.6846	35.9%	2.64 [0.69, 10.10]	2013			
Nieminen 2014	-0.1165	0.5721	43.3%	0.89 [0.29, 2.73]	2014			
Total (95% CI)			100.0%	1.98 [0.68, 5.73]				
Heterogeneity: Tau² = Test for overall effect:			= 0.19); l ^a	²= 40%		0.05	0.2 1 5 Protective Risk	20

Supplementary Figure 14B: Forest plot of Univariable HR (cohort studies)



Supplementary Figure 14C: Forest plot of Multivariable analysis HR

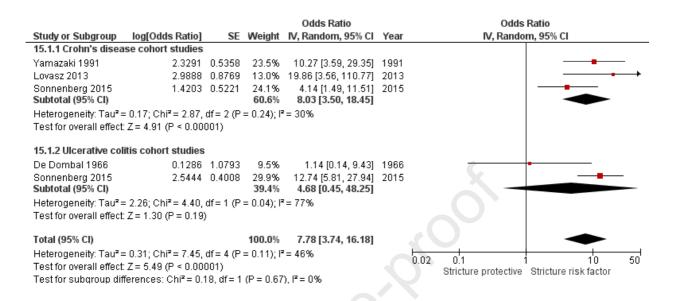
				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio] SE Weight IV, Random, 95% Cl Year		IV, Random, 95% CI			
22.5.1 Cohort multiv	ariable analysis 🔪					
Gupta 2007	1.335	0.4104	20.4%	3.80 [1.70, 8.49]	2007	_
Mahmoud 2019 Subtotal (95% Cl)	0.7467	0.2316	63.9% 84.3 %	2.11 [1.34, 3.32] 2.57 [1.49, 4.42]	2019	
Heterogeneity: Tau ² : Test for overall effect		,	0.21); F=	: 36%		
22.5.2 Case-control	multivariable analys	is				
Gerrits 2011 Subtotal (95% Cl)	1.0986	0.4675	15.7% 15.7 %	3.00 [1.20, 7.50] 3.00 [1.20, 7.50]	2011	
Heterogeneity: Not a Test for overall effect						
Total (95% CI)			100.0%	2.51 [1.75, 3.61]		•
Heterogeneity: Tau ² :	= 0.00; Chi ² = 1.73, df					
Test for overall effect						0.2 0.5 1 2 5 Protective Risk
Test for subgroup dif	ferences: Chi² = 0.08	, df = 1 (F	^o = 0.78),	I ² = 0%		FIDIECTIVE RISK

Study, year	Definition	Supplementary figure
Rutter, 2004	Scoring per segment providing a mean histologic score (0-4). The mean histologic score for all segments of each colonoscopy was calculated and the mean histologic score for all surveillance colonoscopies performed in one patient.	14A
Rubin, 2013	6-point histologic inflammatory activity scale (each biopsy taken at each surveillance colonoscopy was taken into account). Two summative inflammation scores were calculated: mean score (average inflammation of each procedure; and the average of all procedure scores) and maximum score (the maximum score for any single biopsy was reported as the maximum score).	14A
Nieminen, 2014	Histological activity of IBD of index patients was based on corresponding endoscopy or operative sample. Score 0- 2. The last colonoscopy examination of the control patients served as score for control patients.	14A
Gupta, 2007	'Inflammation summarized in 3 different ways and each included as a time-changing covariate: (1) mean inflammatory score (IS-mean), (2) binary inflammatory score (IS-bin), and (3) maximum inflammatory score (IS- max)'. Scores were documented at biopsy level.	14B, 14C
Mahmoud, 2019	Score 1-5 per segment. A mean inflammation score was calculated by averaging the scores of the most severely inflamed segment of all recorded surveillance colonoscopies.	14B, 14C
Gerrits, 2011	Degree of inflammation was reevaluated by one expert gastrointestinal pathologist using the Geboes scoring system. Patients were classified according to the most severe abnormality present in the biopsy specimens.	14C

Supplementary Table 14D: Definitions used in studies used in pooled analysis

Supplementary file 15A-C Stricture

Supplementary Figure 15A: Forest plot of Univariable OR (cohort studies)



Supplementary Figure 15B: Forest plot Multivariable OR (cohort study)

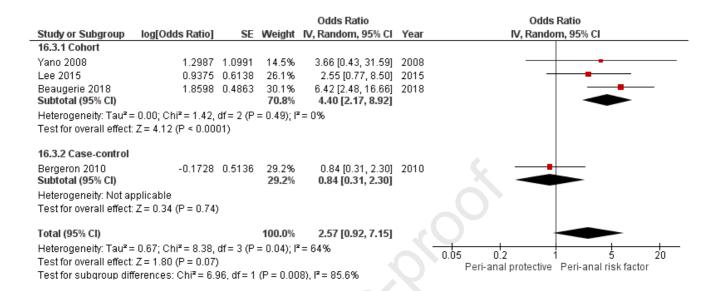
				Odds Ratio	Odds Ratio				
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year		IV, Rando	m, 95% Cl	
Sonnenberg 2015	2.1306	0.3993	100.0%	8.42 [3.85, 18.42]	2015				
Total (95% CI)			100.0%	8.42 [3.85, 18.42]					
Heterogeneity: Not ap Test for overall effect:	•	001)				0.05	0.2 Stricture-	1 5 Stricture+	20

Supplementary Table 15C: Definitions used in studies used in pooled analysis

Study, year	Definition	Supplementary figure
Yamazaki, 1991	Fixed and localized colonic narrowing, defined by radiologists, endoscopists, surgeons or pathologists. Strictures were identified as benign or malignant on the basis of radiology and histology.	15A
Lovasz, 2013	Stenosing disease in patients with colonic Crohn's disease. Stenotic lesion seen by endoscopy.	15A
Sonnenberg, 2015	Colonic stricture diagnosed by the endoscopists base on endoscopic appearance.	15A
De Dombal, 1966	Stricture is defined as a constant narrowing of the lumen of the colon or rectum. Diagnosed by barium enema or found upon examination of the bowel after excision.	15A, 15B

Supplementary file 16A-B Perianal disease

Supplementary Figure 16A: Forest plot Univariable analysis OR

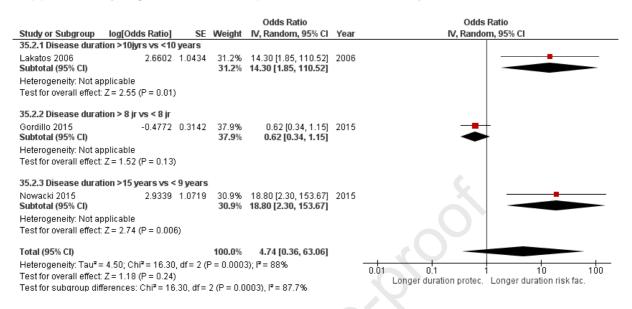


Supplementary Figure 16B: Forest plot Multivariable OR (case-control study)

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Biancone 2016	1.3507	0.3698	100.0%	3.86 [1.87, 7.97]	2016	
Total (95% CI)			100.0%	3.86 [1.87, 7.97]		
Heterogeneity: Not ap	oplicable					
Test for overall effect: Z = 3.65 (P = 0.0003)						P- P+

Supplementary file 17A- B Disease duration

Supplementary Figure 17A: Forest plot of Univariable analysis OR , cohort studies

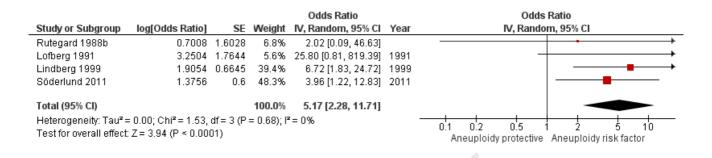


Supplementary Figure 17B: Forest plot of Multivariable analysis OR, cohort studies

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
35.1.1 Disease durat	ion >10jyrs vs <10	years				
Lakatos 2006	2.164	1.0555	9.0%	8.71 [1.10, 68.91]	2006	
Ray 2011 Subtotal (95% CI)	0.0169	0.0066	60.6% 69.7 %	1.02 [1.00, 1.03] 2.30 [0.30, 17.69]	2011	
Heterogeneity: Tau² = Test for overall effect:			= 0.04); P	²= 76%		
35.1.2 Disease durat	ion > 8yrs vs < 8ye	ears				
Gordillo 2015 Subtotal (95% CI)	-0.1863	0.4406	30.3% 30.3 %	0.83 [0.35, 1.97] 0.83 [0.35, 1.97]	2015	
Heterogeneity: Not ap Test for overall effect:	·)				
Total (95% CI)			100.0%	1.16 [0.59, 2.27]		-
Heterogeneity: Tau² = Test for overall effect: Test for subgroup diff	Z = 0.43 (P = 0.66)		0.02 0.1 1 10 50 Longer duration protec. Longer duration risk fac.			

Supplementary file 18A-C Aneuploidy

Supplementary Figure 18A: Forest plot of Univariable OR (cohort studies)



Supplementary Figure 18B: Forest plot of Multivariable HR (case-control study)

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Gerrits 2011	1.4586	0.2767	100.0%	4.30 [2.50, 7.40]	2011	
Total (95% CI)			100.0%	4.30 [2.50, 7.40]		
Heterogeneity: Not applicable Test for overall effect: Z = 5.27 (P < 0.00001)				-	0.1 0.2 0.5 1 2 5 10	
Test for overall effect	: Z = 5.27 (P < 0.0000	л) -				Aneuploidy- Aneuploidy+

Supplementary Table 18C: Definitions used in studies used in pooled analysis

Study, year	Definition aneuploidy	Supplementary figure
Rutegard 1988	Aneuploidy before HGD or CRC. Biopsy samples with more than one peak in the histogram were judged as aneuploidy	18A
Lofberg 1991	Aneuploidy before HGD or CRC. An aneuploid cell population was considered to be present when, in addition to the diploid peak, another distinct peak in the DNA histogram was observed.	18A
Lindberg 1999	Aneuploidy before HGD or CRC. Samples with more than one peak in the histogram were judged as aneuploid	18A
Söderlund 2011	Aneuploidy (unifocal, unifocal reproducible or extensive) before HGD or CRC. Any DNA aneuploidy findings were classified as unifocal if occurring only once in one fraction, unifocal reproducible if occurring in one fraction but repeatedly in the same fraction over several examinations, and multifocal if occurring in several (at least four fractions).	18A
Gerrits 2011	The DNA index (DI) was calculated as the ratio of the abnormal G0/G1 mean peak channel number to the normal diploid G0/G1 mean peak channel number. Histograms displaying a G0/G1 peak with a coefficient of variation (CV) of 1%≤CV≤10% were included in the analysis.Samples were considered diploid when the	18B

DNA index was 0.95≤DI≤1.05, near diploid in case of 1.06≤DI≤1.34, and aneuploid in case of a DI >1.34 [11,	
321	

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Supplementary file 19A-C P53 mutation

Supplementary Figure 19A: Forest plot Univariable OR (cohort study)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio r IV, Random, 95% Cl
Lashner 1999	0.9056	0.6285	100.0%	2.47 [0.72, 8.48]	1999)
Total (95% CI) Heterogeneity: Not ap Test for overall effect:	•	I	100.0%	2.47 [0.72, 8.48]		0.2 0.5 1 2 5 p53 mutation- p53 mutation+

Supplementary Figure 19B: Forest plot Multivariable HR (case-control study)

				Hazard Ratio			Hazaı	rd Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year		IV, Rande	om, 95% Cl	
Gerrits 2011	0.5306	0.3065	100.0%	1.70 [0.93, 3.10]	2011				
Total (95% CI)			100.0%	1.70 [0.93, 3.10]					
Heterogeneity: Not a Test for overall effect						0.2	0.5 p53-	1 2 p53+	5

Supplementary Table 19C: Definitions used in studies used in pooled analysis

Study, year	Definition P53 mutation	Supplementary figure
Lashner 1999	P53 mutation in colonic biopsy specimens in patients with long standing pancolitis. Risk of cancer in patients with ever p53 versus patients without ever a p53 mutation. Biopsy specimens were considered positive for the p53 mutation if \pm 5% of the epithelial cells in a biopsy specimen exhibited dark brown intranuclear staining	19A
Gerrits 2011	Case-control study. Hazard rate in patients with a p 53 mutation in a biopsy specimen, separately calculated at each follow-up moment. Overexpression of p53 was defined as moderate and intense brown staining in >15% of the nucle	19B

Supplementary file 20A-D Primary Sclerosing Cholangitis

Supplementary Figure 20A: Forest plot of Univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Woight	Odds Ratio IV, Random, 95% Cl	Voar	Odds Ratio IV, Random, 95% Cl
1.1.1 Cohort		3L	weight	IV, Nanuom, 55% CI	Tear	IV, Kandolii, 55% Ci
Lindberg 2001	1.3507	0 6077	3.9%	3.86 [1.22, 12.21]	2004	
Florin 2004	1.1385		4.2%	3.12 [1.12, 8.67]		
Lakatos 2006	3.2995		4.2%	27.10 [7.98, 92.03]		
Campos 2008	2.4671		2.9%	11.79 [2.35, 59.03]		
Manninen 2013	1.9705		2.9%	7.17 [2.04, 25.27]		
Stolwijk 2013		0.8109	2.9%			
_ee 2015		0.7729	2.9%	3.14 [0.64, 15.37] 11.86 [2.61, 53.94]		
Lee 2015 Ananthakrishnan 2015	0.3026		4.8%			_
Gordillo 2015	2.2219	0.4087	4.6%	1.35 [0.61, 3.02]		
Nowacki 2015	1.7121		4.0%	9.22 [3.77, 22.59]		
				5.54 [1.36, 22.61]		
Cheddani 2016 Denonno 2017	2.0304		1.2%	7.62 [0.38, 153.82]		
Bopanna 2017 Leich 2017	2.2683		1.2%	9.66 [0.45, 207.69]	2017	
_aish 2017	0.3536		1.3%			
Fraga 2017	2.8911			18.01 [0.84, 386.17]	2017	
Ünal 2019 Subtotal (95% CI)	1.8758	1.2525	1.7% 43.6 %	6.53 [0.56, 75.99]	2019	
				5.76 [3.45, 9.59]		
Heterogeneity: Tau² = 0.4			: 0.03); F	= 44%		
Test for overall effect: Z =	6.72 (P < 0.00001)					
1.1.2 Case-control						
Broomé 1995	1.3751	0.531	4.2%	3.96 [1.40, 11.20]	1005	·
Brentnall 1996	0.8938		4.2 %	2.44 [0.51, 11.80]		
Leidenius 1997	1.1963		2.9%			
Leidenius 1997 Nuako 1998	0.1711		2.070 5.4%	3.31 [0.63, 17.36]		
Shetty 1999	1.8061		0.4% 4.8%	1.19 [0.67, 2.11] 6.09 [2.77, 13.36]		
Velayos 2006	0.0923	0.4013	4.0%			
,	2.1178	0.304		1.10 [0.60, 1.99]		
Terg 2008 Deltal 2009			2.8%	8.31 [1.64, 42.21]		
Sokol 2008	2.8787		2.1%	17.79 [2.18, 145.10]		
Joo 2009 Doursen 2010	2.3012		1.3%	9.99 [0.52, 191.91]		
Bergeron 2010		0.5305	4.2%	2.38 [0.84, 6.72]		
Ye 2011	1.8758		1.7%	6.53 [0.56, 75.99]		
Lindström 2011	1.6864		1.8%	5.40 [0.53, 54.69]		
Baars 2011	2.1323		4.2%	8.43 [3.06, 23.26]		
Braden 2012 Dubia 2012	-0.0746		2.5%	0.93 [0.15, 5.62]		
Rubin 2013	2.0218		1.1%	7.55 [0.29, 196.30]		
Nieminen 2014	-2.2504		1.8%	0.11 [0.01, 1.11]		
Navaneethan 2016	1.0669		3.0%	2.91 [0.63, 13.51]		
Carrat 2017 Subtotal (95% CI)	1.8321	0.4868	4.4% 56.4%	6.25 [2.41, 16.22]	2017	
	7. OKR 11.50 H	47.00		3.16 [1.93, 5.18]		
Heterogeneity: Tau ² = 0.5			: 0.0003);	17 = 102%		
	4.57 (P < 0.00001)					
Test for overall effect: Z =						
			100 0%	4 14 [2 95 6 04]		
Total (95% CI)	0. OKR - 20.00 -K	- 22 (P	100.0%	4.14 [2.85, 6.01]		◆

Supplementary Figure 20B: Forest plot of Univariable analysis HR

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Hazard Ratio IV, Random, 95% Cl
1.5.1 Cohort					
Samadder 2018	1.1217	0.3409	27.8%	3.07 [1.57, 5.99]	— —
Shah 2018 Subtotal (95% CI)	0.7561	0.2843	28.7% 56.5 %	2.13 [1.22, 3.72] 2.47 [1.61, 3.80]	•
Heterogeneity: Tau ² =	0.00; Chi ² = 0.68, df	= 1 (P =	0.41); I ² =	:0%	
Test for overall effect:	Z = 4.15 (P < 0.0001)			
1.5.2 Case-control					
Loftus 2005	0.6363	0.9389	16.9%	1.89 [0.30, 11.90]	
Sørensen 2018 Subtotal (95% CI)	3.0634	0.409	26.7% 43.5 %	21.40 [9.60, 47.70] 7.37 [0.69, 78.10]	
Heterogeneity: Tau ² =	2.42; Chi ² = 5.62, df	= 1 (P =	0.02); I² =	82%	C
Test for overall effect:	Z = 1.66 (P = 0.10)				X
Total (95% CI)			100.0%	4.27 [1.39, 13.15]	
Heterogeneity: Tau ² = Test for overall effect: Test for subgroup diffe	Z = 2.53 (P = 0.01)				0.02 0.1 1 10 50 PSC no risk factor PSC risk factor

Supplementary Figure 20C: Forest plot of Multivariable analysis OR

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
1.9.1 Cohort multivariab	le analysis					
Bansal 1996	1.2302	0.2639	16.0%	3.42 [2.04, 5.74]	1996	_
Lakatos 2006	2.2517	0.7396	9.2%	9.50 [2.23, 40.50]	2006	_
Ananthakrishnan 2014	1.6106	0.2964	15.5%	5.01 [2.80, 8.95]	2014	_
Gordillo 2015 Subtotal (95% Cl)	2.39	0.545	11.9% 52.6 %	10.91 [3.75, 31.76] 5.21 [3.19, 8.51]	2015	
Heterogeneity: Tau ² = 0.0	09; Chi² = 4.78, df =	3 (P = 0.	.19); I ² = 3	37%		
Test for overall effect: Z =						
1.9.2 Case-control multi	ivariable analysis					
Nuako 1998	0.2029	0.3474	14.8%	1.22 [0.62, 2.42]	1998	
Velayos 2006	0.0699	0.3893	14.2%	1.07 [0.50, 2.30]	2006	
Sokol 2008	2.3795	0.5465	11.8%	10.80 [3.70, 31.52]	2008	
Carrat 2017	2.1181	1.0006	6.6%	8.32 [1.17, 59.10]	2017	
Subtotal (95% Cl)			47.4%	2.82 [0.91, 8.77]		
Heterogeneity: Tau ² = 1.0	02; Chi ² = 16.04, df =	= 3 (P = I	0.001); I ^z :	= 81%		
Test for overall effect: Z =	= 1.79 (P = 0.07)					
Total (95% CI)			100.0%	4.05 [2.15, 7.64]		•
Heterogeneity: Tau ² = 0.6	59; Chi² = 30.89, df =	= 7 (P < I	0.0001); I	²= 77%		
Test for overall effect: Z =		-				0.05 0.2 1 5 20 PSC no risk factor PSC risk factor
Test for subgroup differe	ences: Chi² = 0.95, d	f=1 (P =	= 0.33), I ^z	= 0%		FOCHUTISKIALUF FOCHSKIALUF

Supplementary Figure 20D: Forest plot of Multivariable analysis HR

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
1.7.1 Cohort multiva	riable analysis					
Shah 2018 Subtotal (95% CI)	0.6986	0.3125	55.6% 55.6 %	2.01 [1.09, 3.71] 2.01 [1.09, 3.71]	2018	-
Heterogeneity: Not a	pplicable					
Test for overall effect	Z = 2.24 (P = 0.03)					
1.7.2 Case-control n	nultivariable analysis	5				
Bergeron 2010	1.5537	0.5724	16.6%	4.73 [1.54, 14.52]	2010	
Van Schaik 2013	1.351	0.8713	7.1%	3.86 [0.70, 21.30]	2013	
Lutgens 2015 Subtotal (95% Cl)	1.3391	0.5116	20.7% 44.4%	3.82 [1.40, 10.40] 4.14 [2.09, 8.21]	2015	
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.09, df	= 2 (P =	0.96); l² =	:0%		
Test for overall effect	: Z = 4.07 (P < 0.0001)				6
Total (95% CI)			100.0%	2.77 [1.76, 4.38]		•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2.46, df	= 3 (P =	0.48); I ^z =	: 0%	+	0.2 1 5 2
Test for overall effect	: Z = 4.38 (P < 0.0001)			0.05	0.2 1 Ś 2 PSC no risk factor PSC risk factor
Test for subgroup dif	ferences: Chi ² = 2.37	, df = 1 (i	P = 0.12),	I² = 57.9%		1 SC HOHSK IACTOR 1 SC HSK IACTOR

Supplementary file 21A-D Sex

Supplementary Figure 21A: Forest plot of Univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio IV, Random, 95% Cl
3.1.1 Cohort						
Macdougall 1954	-0.0888		0.5%	0.92 [0.15, 5.68]		
Gilat 1974 Fuson 1980	0.6332 0.7156	1.228	0.3% 0.6%	1.88 [0.17, 20.91] 2.05 [0.40, 10.34]		
Prior 1982	-0.2206	0.445	1.7%	0.80 [0.34, 1.92]		
Wright 1983	1.7558		0.2%	5.79 [0.27, 121.97]		
Maratka 1985	0.3325		0.6%	1.39 [0.28, 6.94]		
Broström 1986	-0.0595	0.4043	2.0%	0.94 [0.43, 2.08]	1986	
Kvist 1989	1.1302		1.3%	3.10 [1.08, 8.88]		
Lennard-Jones 1990	0.0754		1.7%	1.08 [0.45, 2.58]		
Ekborn 1990a Kaabbar 1991	0.0419	0.215	4.5%	1.04 [0.68, 1.59]		
Kochhar 1991 Langholz 1992	0.8302	0.8222	0.6% 0.5%	2.53 [0.51, 12.70] 2.29 [0.42, 12.57]		
Jablonská 1993	0.0449		0.8%	1.05 [0.27, 4.02]		
Paris 1994	0.6875		0.2%	1.99 [0.08, 50.49]		
Jacobsen 1994	1.4231		0.3%	4.15 [0.48, 35.72]		
Stewenius 1995	-1.0088	0.7134	0.8%	0.36 [0.09, 1.48]	1995	
Rozen 1995	2.6675		0.2%	14.40 [0.81, 256.79]		
Bansal 1996		0.1098	7.1%	1.27 [1.03, 1.58]		-
Nkontchou 1996	0.2231		0.4%	1.25 [0.17, 9.15]		
Nalmsley 1997 Triantafillidis 2000	0.069	1.0339	0.4% 0.3%	1.07 [0.14, 8.13]		
Freeman 2001	2.8256		0.3%	1.27 [0.11, 14.31] 16.87 [0.95, 300.42]		
Kobayashi 2002	-0.0167		0.6%	0.98 [0.19, 4.97]		
Lim 2003	1.0341		0.5%	2.81 [0.52, 15.07]		
Winther 2004	0.2921		1.2%	1.34 [0.45, 4.01]		
Hájek 2005	0.6245	1.2294	0.3%	1.87 [0.17, 20.78]	2005	
Rutter 2006	-0.0826		2.6%	0.92 [0.48, 1.78]		
Lakatos 2006	-0.2613		1.2%	0.77 [0.26, 2.31]		
Rubio 2009	-0.5713	0.886	0.5%	0.56 [0.10, 3.21]		
Chow 2009 Söderlund 2010	1.0405 0.4637		0.2% 6.0%	2.83 [0.11, 70.46]		
Fujita 2010	-1.9944		0.0%	1.59 [1.19, 2.13] 0.14 [0.02, 1.14]		•
Lakatos 2011	2.4338		0.2%	11.40 [0.63, 207.30]		
Kamiya 2012		1.5589	0.2%	1.73 [0.08, 36.76]		
Gong 2012	-0.5206	0.3499	2.5%	0.59 [0.30, 1.18]		
Hou 2012	0.6162	0.4551	1.7%	1.85 [0.76, 4.52]	2012	
Jess 2012	0.1727		7.1%	1.19 [0.96, 1.47]		+-
Campos 2013	0.6455		1.4%	1.91 [0.72, 5.04]		
Manninen 2013 Juggilo 2012	0.1693		1.7%	1.18 [0.50, 2.82]		
Jussila 2013 Yano 2013	0.1824 -1.5112		5.7% 0.8%	1.20 [0.87, 1.65] 0.22 [0.05, 0.89]		
Lovasz 2013	2.5775		0.2%	13.16 [0.74, 234.64]		
Beaugerie 2013	0.6646		3.5%	1.94 [1.14, 3.32]		_
Wang 2013	0.8547		0.4%	2.35 [0.33, 16.76]		
Peng 2015	-0.0733	0.2614	3.6%	0.93 [0.56, 1.55]	2015	
Zhang 2015	-0.2202		0.4%	0.80 [0.11, 5.73]		
Gordillo 2015	0.6624		2.7%	1.94 [1.02, 3.70]		
Lee 2015	-0.5053		2.3%	0.60 [0.29, 1.24]		
Desai 2015 Kuo 2015	-0.6549 1.0984		1.1% 0.3%	0.52 [0.16, 1.66] 3.00 [0.35, 25.71]		
Nowacki 2015	-0.3624		0.3%	0.70 [0.20, 2.44]		
Ananthakrishnan 2015	0.515		5.6%	1.67 [1.21, 2.31]		
Kopylov 2015		0.1092	7.1%	1.08 [0.87, 1.34]		+
van den Heuvel 2016	-0.3308	0.4289	1.8%	0.72 [0.31, 1.67]	2016	
Madanchi 2016	1.0245		0.3%	2.79 [0.29, 26.88]		
Jung 2017	-0.0035		2.9%	1.00 [0.54, 1.84]		
Hovde 2017 Ümel 2010	0.8806		1.0%	2.41 [0.75, 7.79]		
Ünal 2019 Subtotal (95% CI)	1.1406	0.7851	0.6% 94.3 %	3.13 [0.67, 14.58] 1.22 [1.09, 1.37]	2019	
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =		= 57 (P =				•
. Source of order encoul Z =	0.41 (i → 0.0007)					
3.1.2 Case-control						
Baars 2011	0.9005	0.1877	5.1%	2.46 [1.70, 3.56]	2011	
Rubin 2013	1.2524	0.8066	0.6%	3.50 [0.72, 17.00]	2013	+
Subtotal (95% CI)			5.7%	2.51 [1.75, 3.59]		
Heterogeneity: Tau² = 0.(Test for overall effect: Z =			.67); I² = 0	1%		
Fotal (95% CI)			100.0%	1 27 [1 12 1 44]		
Heterogeneity: Tau ² = 0.0	15· Chiz - 01 00 44	- 60 /0 -		1.27 [1.12, 1.44]		_
						0.05 0.2 1 5 20

Hazard Ratio Hazard Ratio IV, Random, 95% CI Study or Subgroup log[Hazard Ratio] SE Weight IV, Random, 95% CI Year 3.2.1 Cohort Gupta 2007 0.9155 0.5809 5.2% 2.50 [0.80, 7.80] 2007 Van Schaik 2012 0.3759 0.3738 12.6% 1.46 [0.70, 3.03] 2012 Stolwijk 2013 0.3067 0.4257 9.7% 1.36 [0.59, 3.13] 2013 Bopanna 2017 0.3785 0.5268 6.3% 1.46 [0.52, 4.10] 2017 Samadder 2018 0.7655 0.2326 32.5% 2.15 [1.36, 3.39] 2018 Kishikawa 2018 0.2852 0.52 6.5% 1.33 [0.48, 3.69] 2018 16.2% Mahmoud 2019 1.77 [0.93, 3.38] 2019 0.5727 0.3292 Subtotal (95% CI) 89.0% 1.77 [1.34, 2.33] Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 6 (P = 0.91); I² = 0% Test for overall effect: Z = 4.07 (P < 0.0001) 3.2.2 Case-control Van Schaik 2013 1.10 [0.50, 2.40] 2013 0.0912 0.4002 11.0% Subtotal (95% CI) 11.0% 1.10 [0.50, 2.40] Heterogeneity: Not applicable Test for overall effect: Z = 0.23 (P = 0.82) 1.68 [1.30, 2.18] Total (95% CI) 100.0% Heterogeneity: Tau² = 0.00; Chi² = 3.43, df = 7 (P = 0.84); l² = 0% 0.7 1.5 0.5 ż Test for overall effect: Z = 3.91 (P < 0.0001) Male protective Male risk factor Test for subgroup differences: Chi² = 1.28, df = 1 (P = 0.26), l² = 22.0%

Supplementary Figure 21B: Forest plot of Univariable analysis HR

Supplementary Figure 21C: Forest plot of Multivariable analysis OR (cohort studies)

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Bansal 1996	-0.0113	0.3279	9.3%	0.99 [0.52, 1.88]	1996	
Lakatos 2006	-0.1744	0.6392	2.4%	0.84 [0.24, 2.94]	2006	•
Sonnenberg 2015	0.3286	0.2506	15.9%	1.39 [0.85, 2.27]	2015	
Gordillo 2015	0.5675	0.3725	7.2%	1.76 [0.85, 3.66]	2015	
Ananthakrishnan 2016	0.4896	0.1239	65.1%	1.63 [1.28, 2.08]	2016	
Total (95% CI)			100.0%	1.50 [1.23, 1.83]		-
Heterogeneity: Tau ² = 0.1	00; Chi² = 3.18, df =	4 (P = 0.	.53); I² = 0)%		0.5 0.7 1 1.5 2
Test for overall effect: Z =						Male protective Male risk factor

Supplementary Figure 21D: Forest plot of Multivariable analysis HR

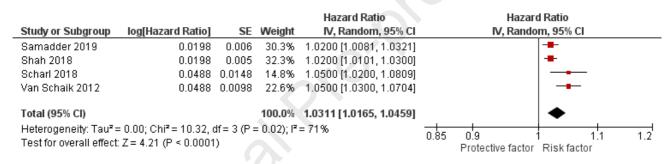
				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
3.9.1 Cohort multiva	riable analysis					
Hou 2012	0.3026	0.4594	10.9%	1.35 [0.55, 3.33]	2012	
Van Schaik 2012	0.0363	0.4611	10.8%	1.04 [0.42, 2.56]	2012	
Beaugerie 2013	0.6259	0.2801	29.4%	1.87 [1.08, 3.24]	2013	
Stolwijk 2013	0.3784	0.4337	12.3%	1.46 [0.62, 3.42]	2013	
Kishikawa 2018	0.1914	0.5224	8.4%	1.21 [0.43, 3.37]	2018	
Mahmoud 2019 Subtotal (95% CI)	0.6729	0.3485	19.0% 90.8 %	1.96 [0.99, 3.88] 1.57 [1.15, 2.15]	2019	
Heterogeneity: Tau² = Test for overall effect		= 5 (P =	0.85); l² =	: 0%		
3.9.2 Case-control m	nultivariable analysis	;				
Van Schaik 2013 Subtotal (95% Cl)	-0.2231	0.5004	9.2% 9.2 %	0.80 [0.30, 2.13] 0.80 [0.30, 2.13]	2013	
Heterogeneity: Not a						<u>S</u>
Test for overall effect	:: Z = 0.45 (P = 0.66)					
Total (95% CI)			100.0%	1.48 [1.10, 1.99]		
Heterogeneity: Tau ² =	= 0.00; Chi ² = 3.64, df	= 6 (P =	0.73); l²=	: 0%		
Test for overall effect	: Z = 2.57 (P = 0.01)					Male protective Male risk factor
Test for subaroup dif	fferences: Chi ² = 1.66	. df = 1 (ł	P = 0.20).	I ² = 39.6%		Male protective Male HSK factor

Supplementary file 22A-D Age

Supplementary Figure 22A: Cohort univariable OR, different age categories/definitions

			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]		IV, Random, 95% Cl	IV, Random, 95% Cl
38.2.1 Cohort OR 'differ	ence of 10 years o	f age'		
Nowacki 2015	0.0392	0.02	1.04 [1.00, 1.08]	t -
38.2.2 Age per year incr	ease			
Ananthakrishnan 2016	0.0392	0.0049	1.04 [1.03, 1.05]	ŀ
38.2.3 >50 years vs <49	years (=ref)			
Peng 2017	1.3917	0.7713	4.02 [0.89, 18.24]	+++++++++++++++++++++++++++++++++++++++
				0.5 0.7 1 1.5 2 Protective factor Risk factor

Supplementary Figure 22B: Cohort univariable HR, age per year increase



Supplementary Figure 22C: Cohort multivariable OR, Old age (OR reflects change over

the entire age range)

Study or Subgroup	log[Odd	ls Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl			Ratio m, 95% Cl	
Sonnenberg 2015		3.5065	0.7569	100.0%	33.33 [7.56, 146.94]				
Total (95% CI)				100.0%	33.33 [7.56, 146.94]				
Heterogeneity: Not ap Test for overall effect:	•	(P < 0.00)	001)			0.01	0.1 Protective factor	1 10 Risk factor	100

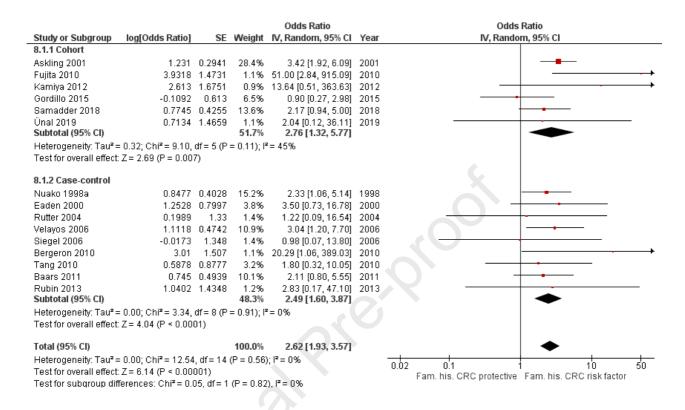
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Year	Hazard Ratio IV, Random, 95% Cl
Van Schaik 2012	0.0677	0.0194	23.8%	1.0700 [1.0301, 1.1115]	2012	_
Beaugerie 2013	0.0198	0.0152	31.6%	1.0200 [0.9901, 1.0508]	2013	
Shah 2018	0.0296	0.01	44.6%	1.0300 [1.0101, 1.0504]	2018	
Total (95% CI)			100.0%	1.0362 [1.0124, 1.0606]		•
Heterogeneity: Tau ² = Test for overall effect:			0.13); I² =	51%		0.85 0.9 1 1.1 1.2 Protective factor Risk factor

Supplementary Figure 22D: Cohort multivariable HR, age per year increase

ounding

Supplementary file 23A-E Family history of colorectal carcinoma

Supplementary Figure 23A: Forest plot of Univariable analysis OR



Supplementary Figure 23B: Forest plot of Univariable analysis HR cohort study

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Mahmoud 2019	0.8412	0.4773	100.0%	2.32 [0.91, 5.91]	
Total (95% CI)			100.0%	2.32 [0.91, 5.91]	
Heterogeneity: Not ap Test for overall effect:	•				0.02 0.1 1 10 50 Fam CRC no risk factor Fam CRC risk factor

Supplementary Figure 23C: Forest plot of Multivariable analysis OR case-control

studies

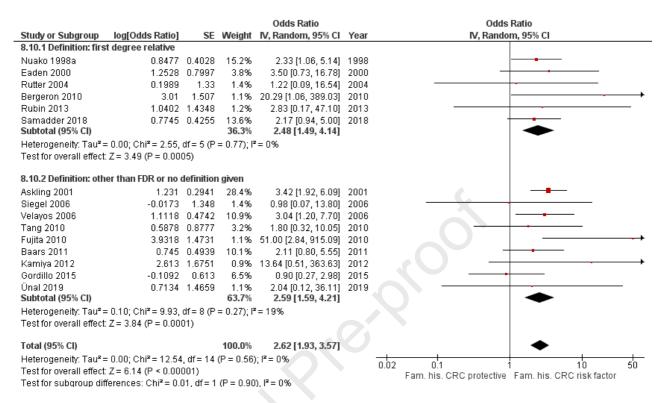
				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Eaden 2000	1.8532	0.9611	32.5%	6.38 [0.97, 41.97]	2000	
Velayos 2006	1.3083	0.6675	67.5%	3.70 [1.00, 13.69]	2006	
Total (95% CI)			100.0%	4.42 [1.51, 12.94]		
Heterogeneity: Tau² = Test for overall effect:		•		0.01 0.1 1 10 100 Fam CRC no risk factor Fam CRC risk factor		

Supplementary Figure 23D: Forest plot of Multivariable analysis HR

				Hazard Ratio	Hazard Ratio
Study or Subgroup lo	g[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
8.7.1 Case-control multi	variable analysis				
Bergeron 2010 Subtotal (95% CI)	1.2149	0.6098	40.1% 40.1 %	3.37 [1.02, 11.13] 3.37 [1.02, 11.13]	
Heterogeneity: Not appli	cable				
Test for overall effect: Z =	: 1.99 (P = 0.05)				
8.7.2 Cohort multivariab	le analysis				
Mahmoud 2019 Subtotal (95% CI)	0.6627	0.4987	59.9% 59.9 %	1.94 [0.73, 5.16] 1.94 [0.73, 5.16]	
Heterogeneity: Not appli	cable				
Test for overall effect: Z =	: 1.33 (P = 0.18)				
Total (95% CI)			100.0%	2.42 [1.14, 5.16]	
Heterogeneity: Tau ² = 0.0	00; Chi² = 0.49, df =	= 1 (P =	0.48); l ² =	0%	
Test for overall effect: Z =	2.29 (P = 0.02)	-			0.1 0.2 0.5 1 2 5 10 Fam CRC no risk factor Fam CRC risk factor
Test for subgroup differe	nces: Chi ² = 0.49.	df = 1 (F	P = 0.48).	² = 0%	

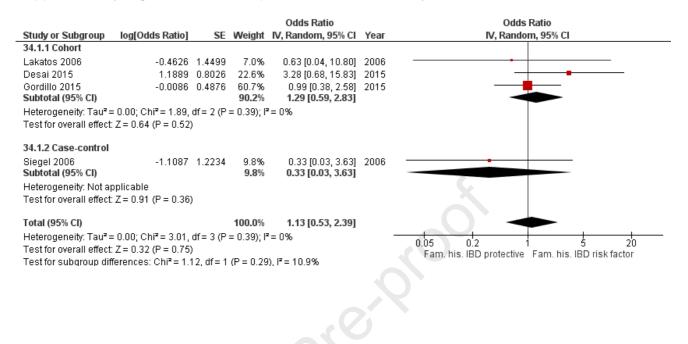
Supplementary Figure 23E: Forest plot of Univariable analysis cohort and case-control

OR (separated for first-degree relative and any relative)



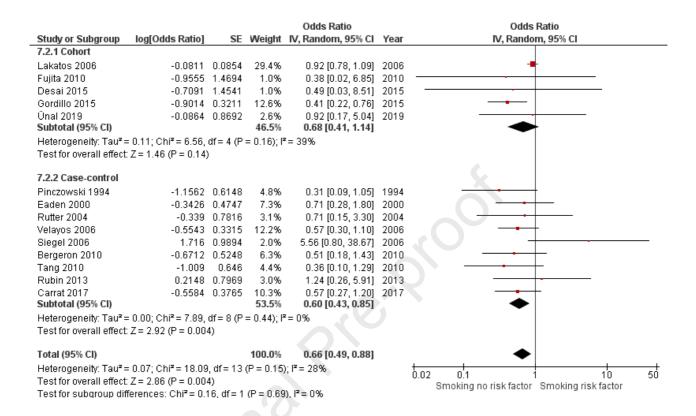
Supplementary file 24A Family history of IBD

Supplementary Figure 24A: Forest plot of Univariable analysis OR



Supplementary 25A-C Smoking

Supplementary Figure 25A: Forest plot of Univariable analysis OR



Supplementary Figure 25B: Forest plot of Multivariable analysis OR

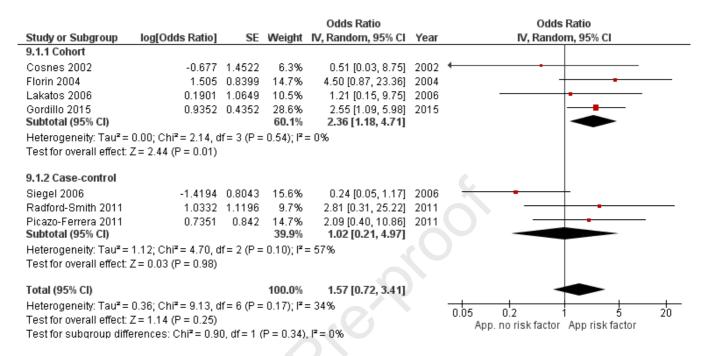
				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
7.7.1 Cohort multivaria	ble analysis					
Ananthakrishnan 2016 Subtotal (95% Cl)	0.6152	0.135	44.1% 44.1%	1.85 [1.42, 2.41] 1.85 [1.42, 2.41]	2016	
Heterogeneity: Not appl	icable					
Test for overall effect: Z	= 4.56 (P < 0.00001)					
7.7.2 Case-control mult	tivariable analysis					
Velayos 2006	0.0144	0.2512	34.4%	1.01 [0.62, 1.66]	2006	
Carrat 2017 Subtotal (95% Cl)	-0.1795	0.4297	21.5% 55.9 %	0.84 [0.36, 1.94] 0.97 [0.63, 1.48]	2017	
Heterogeneity: Tau ² = 0.	.00; Chi² = 0.15, df =	1 (P = 0.	70); I ^z = 0	1%		
Test for overall effect: Z	= 0.16 (P = 0.87)					
Total (95% CI)			100.0%	1.27 [0.75, 2.13]		
Heterogeneity: Tau ² = 0.	.14; Chi² = 6.63, df =	2 (P = 0.	04); l ² = 7	'0%	-	
Test for overall effect: Z	= 0.90 (P = 0.37)					0.5 0.7 1 1.5 2 Smoking no risk factor Smoking risk factor
Test for subgroup differ	ences: Chi² = 6.48, d	lf = 1 (P =	= 0.01), I ²	= 84.6%		Shoking to tak lactor Shoking lisk lactor

Study, year	Definition smoking	Supplementary figure
Lakatos 2016	Yes and previous smoking versus never smoking	25A
Fujita 2010	Yes and previous smoking versus never smoking	25A
Desai 2015	History of smoking versus no history of smoking	25A
Gordillo 2015	History of smoking versus no history of smoking	25A
Unal 2019	Currently smoking and former smoker versus non-smoker	25A
Pinczowski 1994	Ever having smoked versus no known history of smoking	25A
Eaden 2000	Smoking history at moment of UC diagnosis	25A
Rutter 2004	Smoked since onset of colitis versus not smoked from	25A
	moment of onset of colitis	
Velayos 2006	Current smoker and ex-smoker versus nonsmoker	25A + 25B
Siegel 2006	History of smoking versus no history of smoking	25A
Bergeron 2010	Smoking during the 5 years before neoplasia or censoring	25A
Tang 2010	Current and former smoking versus non-smoker	25A
Rubin 2013	Ever smoked versus non-smoker	25A
Ananthakrishnan 2016	Ever smoked versus non-smoker	25B
Carrat 2017	Active smoking versus not active smoking	25B

Supplementary Table 25C: Definitions used in studies used in pooled analysis

Supplementary file 26A-B Appendectomy

Supplementary Figure 26A: Forest plot of Univariable analysis OR

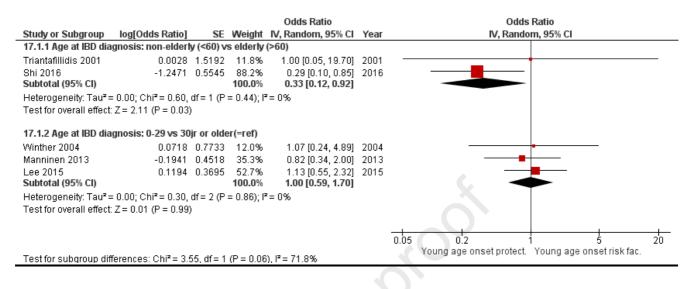


Supplementary Figure 26B: Forest plot of Multivariable OR cohort study

				Odds Ratio			Odds	Ratio		
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl			IV, Rando	om, 95% Cl		
Gordillo 2015	0.9783	0.4694	100.0%	2.66 [1.06, 6.67]						
Total (95% CI)			100.0%	2.66 [1.06, 6.67]						
Heterogeneity: Not ap Test for overall effect					0.2	0. Appendector	5 ny no risk fact	1 Appendector	1 2 ny risk facto	or 5

Supplementary file 27A-G Age at IBD diagnosis

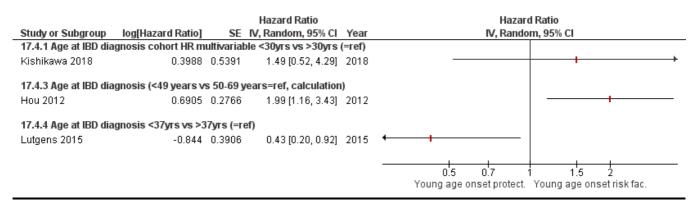
Supplementary Figure 27A: Forest plot of Univariable analysis OR, cohort studies



Supplementary Figure 27B: Forest plot of Univariable analysis HR, cohort studies

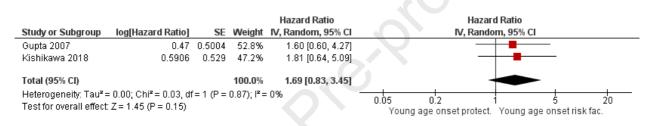
			Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
17.2.1 Age at IBD dia	gnosis cohort HR <2	5yrs vs	>25 years(=ref)		
Gupta 2007	0.47	0.5004	1.60 [0.60, 4.27]	2007	
17.2.2 Age at IBD dia	gnosis (no clear def	inition gi	ven, unclear young ve	s old or old vs young	g)
Shah 2018	0	0.0103	1.00 [0.98, 1.02]	2018	t
17.2.3 Age at IBD dia	gnosis (<49 years v	s 50-69 y	/ears=ref)		
Hou 2012	-0.6425	0.27	0.53 [0.31, 0.89]	2012	
17.2.4 Age at IBD dia	gnosis cohort HR <3	Oyrs vs	>30 years(=ref)		
Kishikawa 2018	0.5906	0.529	1.81 [0.64, 5.09]	2018	
					0.2 0.5 1 2 5 Young age onset protect. Young age risk fac.

Supplementary Figure 27C: Forest plot of Multivariable analysis HR , cohort studies



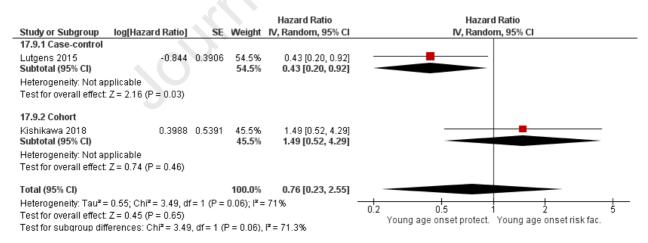
Supplementary Figure 27D: Forest plot of Univariable analysis HR cohort studies

(definition: <25/30 years versus >25/30 years, see definitions above)



Supplementary Figure 27E: Forest plot of Multivariable analysis HR studies

(definition: <30/37 years versus >30/37 years, see definitions above)



Supplementary Figure 27F: Forest plot of age at UC diagnosis above versus below

median of study (univariable)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year		Odds IV, Randoi		
Gordillo 2015	0.925	0.3446	100.0%	2.52 [1.28, 4.96]	2015				
Total (95% CI) Heterogeneity: Not ap Test for overall effect:		7)	100.0%	2.52 [1.28, 4.96]		0.2	0.5 1 Below median	2 Above medi	5 an

Supplementary Figure 27G: Forest plot of age at UC diagnosis above versus below

median of study (multivariable)

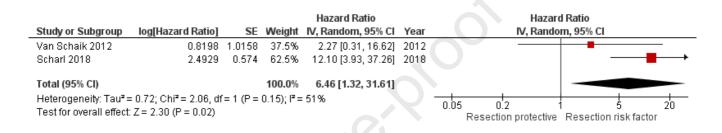
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year		Odds Ratio IV, Random, 95% Cl	
Gordillo 2015	0.7885	0.3872	100.0%		2015			
Total (95% CI)			100.0%	2.20 [1.03, 4.70]				-
Heterogeneity: Not ap Test for overall effect:						0.2	0.5 1 2 Below median Above median	5
				\mathbf{O}				

Supplementary file 28A-D Colon segment resection

Supplementary Figure 28A: Forest plot of Univariable OR case-control studies

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio IV, Random, 95% Cl
Siegel 2006	-0.462	0.6993	100.0%	0.63 [0.16, 2.48]	2006	
Total (95% CI) Heterogeneity: Not ap	nlicable		100.0%	0.63 [0.16, 2.48]		
Test for overall effect:	•					0.2 0.5 i ż ś Resection protective Resection risk factor

Supplementary Figure 28B: Forest plot of Univariable HR cohort studies



Supplementary Figure 28C: Forest plot of Multivariable analysis HR

			Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
18.4.1 Cohort multiv	ariable analysis				
Van Schaik 2012 Subtotal (95% CI)	1.2641 1.0	999 44.4% 44.4%	3.54 [0.41, 30.57] 3.54 [0.41, 30.57]	2012	
Heterogeneity: Not ap	oplicable				
Test for overall effect	: Z = 1.15 (P = 0.25)				
18.4.2 Case-control	multivariable analysis				
Bergeron 2010 Subtotal (95% CI)	-1.3863 0.64	495 55.6% 55.6 %	0.25 [0.07, 0.89] 0.25 [0.07, 0.89]	2010	
Heterogeneity: Not a	oplicable				
Test for overall effect	Z = 2.13 (P = 0.03)				
Total (95% CI)		100.0%	0.81 [0.06, 10.71]		
Heterogeneity: Tau ² =	= 2.70; Chi ² = 4.31, df = 1 ((P = 0.04); I ² =	77%		
Test for overall effect	Z = 0.16 (P = 0.87)				0.05 0.2 1 5 20 Resection protective Resection risk factor
Test for subgroup dif	ferences: Chi² = 4.31, df =	1 (P = 0.04),	I² = 76.8%		Resection protective Resection risk lactor

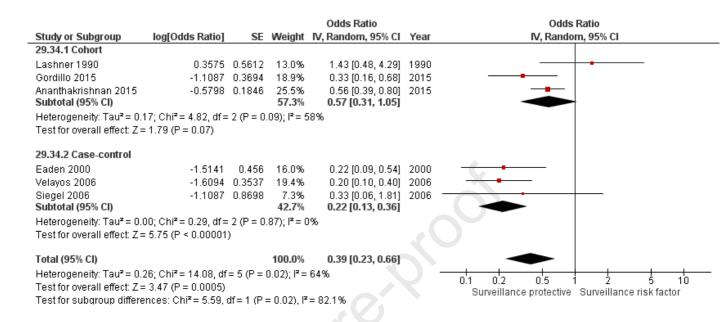
Study, year	Definition	Supplementary figure
Siegel 2006	Prior partial colonic resection could be any amount of colon, but patients had to have at least one third of their colon intact to be included in this study. Not specified which operation indication. Crohn colitis patients.	28A
Van Schaik 2012	History of partial colonic resection, not specified which operation indication (patients with a previous subtotal or total colectomy were excluded). IBD patients.	28B, 28C
Scharl 2018	Intestinal surgery not specified which operation indication; Patients who had non-CRC related colectomy were excluded from at risk population for CRC development. HR based on UC/IBD-U patients	28B
Bergeron 2010	Previous segmental colectomy during the course of the disease before diagnosis of neoplasia or date of censoring (IBD pancolitis patients)	28C

Supplementary table 28D: Definitions used in studies used in pooled analysis

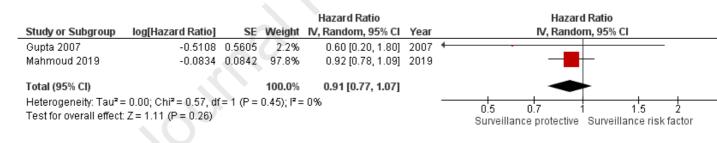
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Supplementary file 29A-F Surveillance colonoscopies

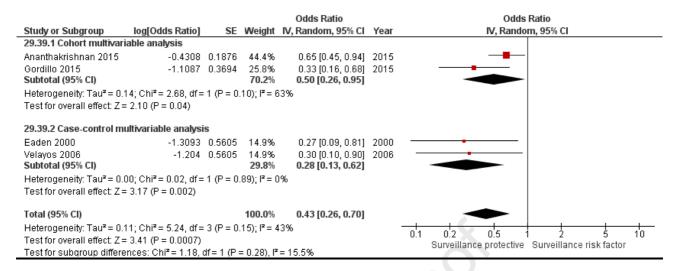
Supplementary Figure 29A: Forest plot of Univariable analysis OR



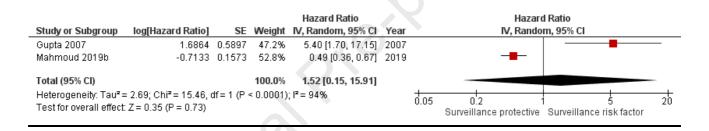
Supplementary Figure 29B: Forest plot of Univariable analysis HR cohort



Supplementary Figure 29C: Forest plot of Multivariable analysis OR



Supplementary Figure 29D: Forest plot of Multivariable analysis HR cohort studies



Supplementary Table 29E: Definitions used in studies used in pooled analysis

Study, year	Definition	Supplementary figure
Lashner 1990	Surveillance versus no surveillance	29A
Eaden 2000	1 to 2 colonoscopies during FU (compared to none)	29A
Eaden 2000	1-2 colonoscopies after diagnosis versus <1	29C
Siegel 2006	Prior surveillance colonoscopy	29A
Velayos 2006	Surveillance colonoscopy > 2 case-control	29A, 29C
Gupta 2007	One or more colonoscopies per year	29B, 29D
Ananthakrishn an 2015	Colonoscopy < 3 yrs cohort	29A, 29C
Gordillo 2015	Surveillance versus no surveillance	29A, 29C
Mahmoud 2019	Number of adequate surveillance colonoscopies	29B
Mahmoud 2019b	Number of adequate surveillance colonoscopies	29D

Supplementary Table 29F: Other definitions used, data not pooled

Journal Pre-proof

Study, year	Study design	Univariable or multivariable analysis?	Definition	Effect size [95% CI]
Siegel 2006	Case- control	Univariable OR	Colonoscopy indication surveillance	0.21 [0.04, 1.10]
Siegel 2006	Case- control	Univariable OR	Colonoscopy indication change in symptoms case-control	4.67 [1.30, 16.78]
Terdiman 2007	Case- control	Univariable OR	Colonoscopy 61-365 days before index date case-control	0.76 [0.58, 1.00]
Gong 2012	Cohort	Univariable OR	Colonoscopy follow up	1.86 [0.94, 3.69]
Stolwijk 2013	Cohort	Univariable HR	Age at 1st surveillance, yrs	1.00 [0.97, 1.03]
Stolwijk 2013	Cohort	Multivariable HR	Age at 1st surveillance, yrs	1.01 [0.98, 1.04]
Ten Hove 2019	Cohort	Univariable OR	1 negative colonoscopy (no neoplasia or other abnormalities) versus 1 positive colonoscopy	0.11 [0.01, 0.88]

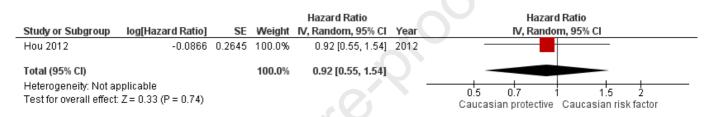
Journal Pre

Supplementary file 30A- D Race

Supplementary Figure 30A: Forest plot of Univariable analysis OR (Caucasian versus other races)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Odds Ratio IV, Random, 95% Cl
Ananthakrishnan 2015	-0.0907	0.2427	31.1%	0.91 [0.57, 1.47]	
Bansal 1996	0.1961	0.1629	68.9%	1.22 [0.88, 1.67]	
Total (95% CI)			100.0%	1.11 [0.85, 1.45]	
Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	• •	1 (P = 0.	.33); I² = 0)%	0.7 0.85 1 1.2 1.5 Caucasian protective Caucasian risk factor

Supplementary Figure 30B: Forest plot of Univariable analysis HR (Caucasian versus African-American)



Supplementary Figure 30C: Forest plot of Multivariable analysis OR (Caucasian versus other races)

				Odds Ratio			Odds	Ratio	
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year		IV, Rando	m, 95% Cl	
Bansal 1996	0.0488	0.1649	53.2%	1.05 [0.76, 1.45]	1996		-	-	
Ananthakrishnan 2016	0.3709	0.1841	46.8%	1.45 [1.01, 2.08]	2016				
Total (95% CI)			100.0%	1.22 [0.89, 1.67]				•	
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =		1 (P = 0.	19); I² = 4	1%		0.01	0.1 Caucasian protective	l 10 Caucasian risk factor	100

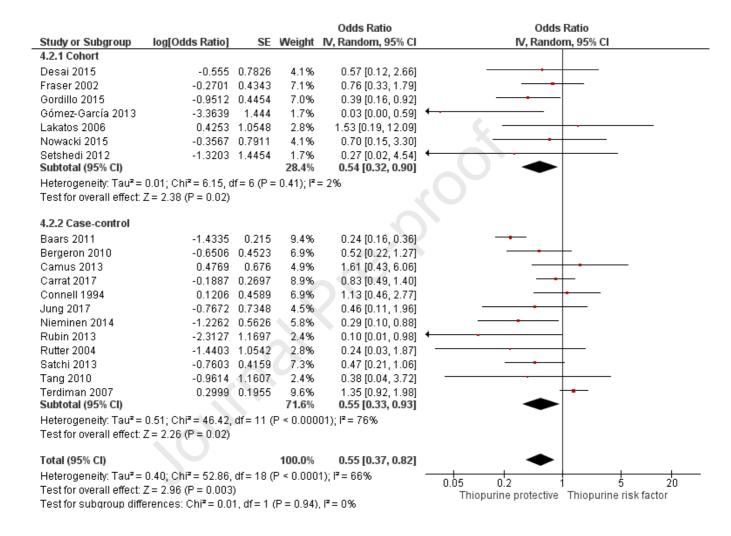
Supplementary Figure 30D: Forest plot of Multivariable analysis HR (Caucasian versus African-American)

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Hou 2012	-0.0954	0.2705	100.0%	0.91 [0.53, 1.54]	2012	
Total (95% CI)			100.0%	0.91 [0.53, 1.54]		
Heterogeneity: Not ap Test for overall effect:						0.5 0.7 1 1.5 2 Caucasian protective Caucasian risk factor

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Supplementary file 31A-E Thiopurines

Supplementary Figure 31A: Forest plot of Univariable analysis OR



Supplementary Figure 31B: Forest plot of Univariable analysis HR

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
4.5.1 Cohort						
Gupta 2007	-0.1054	0.5605	16.2%	0.90 [0.30, 2.70]	2007	
Van Schaik 2012	-1.35	0.5999	14.5%	0.26 [0.08, 0.84]	2012 —	
Scharl 2018	-1.4668	0.6084	14.2%	0.23 [0.07, 0.76]	2018	
Mahmoud 2019 Subtotal (95% Cl)	-0.3534	0.327	34.0% 78.9 %	0.70 [0.37, 1.33] 0.49 [0.26, 0.92]	2019	-
Heterogeneity: Tau ² = 0	0.16; Chi² = 4.92, df	= 3 (P =	0.18); I ² =	: 39%		
Test for overall effect: Z	(= 2.22 (P = 0.03)					
4.5.2 Case-control						
Van Schaik 2013	-0.2811	0.4709	21.1%	0.75 [0.30, 1.90]	2013	
Subtotal (95% CI)			21.1%	0.75 [0.30, 1.90]		
Heterogeneity: Not app	licable					
Test for overall effect: Z	(= 0.60 (P = 0.55)					
Total (95% CI)			100.0%	0.55 [0.33, 0.90]		-
Heterogeneity: Tau ² = 0	0.08; Chi² = 5.36, df	= 4 (P =	0.25); l² =	25%		
Test for overall effect: Z	(= 2.37 (P = 0.02)				0.1	0.2 0.5 1 2 5 10 Thiopurine No thiopurine
Test for subgroup diffe	rences: Chi ^z = 0.58	. df = 1 (F	^o = 0.45),	I ^z = 0%		

Supplementary Figure 31C: Forest plot of Multivariable analysis OR

Church an Curbana	la stOdda Datial	er	L& Controlled	Odds Ratio	V	Odds Ratio
Study or Subgroup	log[Odds Ratio]	35	weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
4.10.1 Cohort multiva	ariable analysis					
Gordillo 2015	-1.5573	0.6409	30.8%	0.21 [0.06, 0.74]	2015	_
Subtotal (95% CI)			30.8%	0.21 [0.06, 0.74]		
Heterogeneity: Not ap	pplicable					
Test for overall effect	: Z = 2.43 (P = 0.02)	1				
4.10.2 Case-control	multivariable analy	/sis				
Velayos 2006	1.1267	0.7568	27.2%	3.09 [0.70, 13.60]	2006	
Carrat 2017	-0.2757	0.29	42.1%	0.76 [0.43, 1.34]	2017	
Subtotal (95% CI)			69.2%	1.29 [0.34, 4.87]		
Heterogeneity: Tau ² =	= 0.65; Chi ² = 2.99,	df = 1 (P	= 0.08); P	²= 67%		
Test for overall effect	: Z = 0.37 (P = 0.71)	ł				
Total (95% CI)			100.0%	0.75 [0.23, 2.48]		
Heterogeneity: Tau ² =	= 0.80; Chi ² = 7.40,	df = 2 (P	= 0.02); P	²= 73%		
Test for overall effect	: Z = 0.47 (P = 0.64))				0.1 0.2 0.5 1 2 5 10 Thiopurine no risk factor Thiopurine risk factor
Test for subgroup dif	ferences: Chi ² = 3.7	/5, df = 1	(P = 0.05	5), I² = 73.3%		

Supplementary Figure 31D: Forest plot of Multivariable analysis HR

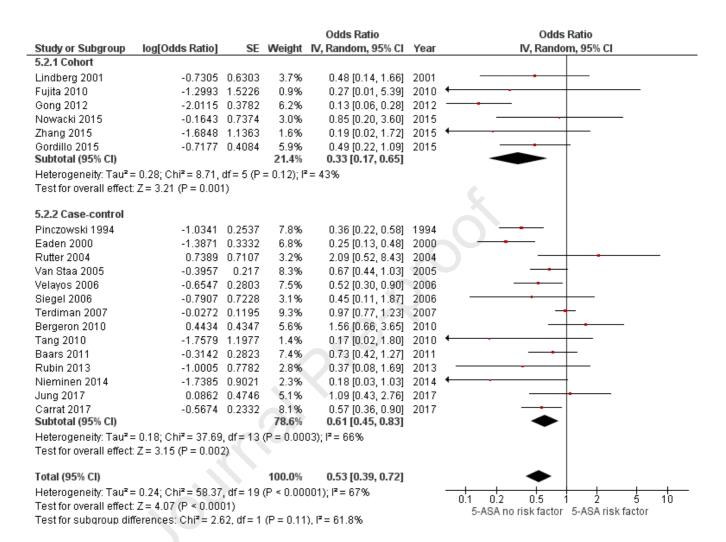
				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
4.7.1 Cohort multivaria	able analysis					
Van Schaik 2012	-2.4464	1.1014	16.3%	0.09 [0.01, 0.75]	2012	•
Beaugerie 2013	-0.47	0.3577	47.6%	0.63 [0.31, 1.26]	2013	
Subtotal (95% CI)			63.8%	0.31 [0.05, 1.97]		
Heterogeneity: Tau ² = 1	(.28; Chi ² = 2.91, df	= 1 (P = 1	0.09); l² =	- 66%		
Test for overall effect: Z	1= 1.25 (P = 0.21)					
4.7.2 Case-control mu	ltivariable analysis	;				
Van Schaik 2013	0.1682	0.5533	36.2%	1.18 [0.40, 3.50]	2013	
Subtotal (95% CI)			36.2%	1.18 [0.40, 3.50]		
Heterogeneity: Not app	Jicable					
Test for overall effect: Z	1= 0.30 (P = 0.76)					
T-4-1/05% OB			100.00			
Total (95% CI)			100.0%			
Heterogeneity: Tau² = 0		= 2 (P = 1	0.10); l² =	- 56%		0.02 0.1 1 10
Test for overall effect: Z	2= 1.08 (P = 0.28)					Thiopurine no risk factor Thiopurine risk factor
Test for subgroup differ	rences: Chi ² = 1.51	<u>, df = 1 (F</u>	^o = 0.22),	I² = 33.9%		·····

Study, year	Definition thiopurines	Supplementary figure
Desai 2015	Use of azathioprine	31A
Fraser 2002	Use of azathioprine	31A
Gordillo 2015	Use of any thiopurine	31A & 31C
Gómez-Garcia 2013	Use of azathioprine or mercaptopurine	31A
Lakatos 2006	Use of azathioprine	31A
Nowacki 2015	Use of any thiopurine	31A
Setshedi 2012	Use of azathioprine or mercaptopurine	31A
Baars 2011	Use of any thiopurine	31A
Bergeron 2010	Use of azathioprine or 6-mercaptopurine greater than 1 or 0.5 mg / kg per day, respectively, during the 5 years before neoplasia or censoring	31A
Camus 2013	Use of azathioprine	31A
Carrat 2017	Exposure to thiopurines during the year of cancer diagnosis	31A & 31C
Connell 1994	Use of azathioprine	31A
Jung 2017	Use of azathioprine or mercaptopurine	31A
Nieminen 2014	Use of azathioprine or mercaptopurine	31A
Rubin 2013	Any use of azathioprine, 6-mercaptopurine, or methotrexate	31A
Rutter 2004	Use of azathioprine	31A
Satschi 2013	Use of mercaptopurine	31A
Tang 2010	Use of azathioprine or mercaptopurine	31A
Terdiman 2007	Use of immunomodulators	31A
Gupta 2007	Use of azathioprine or mercaptopurine	31B
Van Schaik 2012	Use of azathioprine or mercaptopurine	31B & 31D
Scharl 2018	Use of azathioprine	31B
Mahmoud 2019	Use of azathioprine or mercaptopurine	31B
Van Schaik 2013	Use of azathioprine or mercaptopurine	31B & 31D
Velayos 2006	Use of azathioprine or mercaptopurine	31C
Beaugerie 2013	Use of any thiopurine	31D

Supplementary Table 31E: Definitions used in studies used in pooled analysis

Supplementary file 32A-E 5-Aminosalicylates (5-ASA)

Supplementary Figure 32A: Forest plot of Univariable analysis OR



Supplementary Figure 32B: Forest plot of Univariable analysis HR

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
5.5.1 Cohort						
Gupta 2007	-0.7136	0.8107	5.7%	0.49 [0.10, 2.40]	2007	• •
Uliman 2008	-0.3567	0.6392	8.8%	0.70 [0.20, 2.45]	2008	
Bernstein 2011	0.041	0.2252	42.3%	1.04 [0.67, 1.62]	2011	
Van Schaik 2012	-0.6705	0.3861	20.7%	0.51 [0.24, 1.09]	2012	
Mahmoud 2019	0.8871	0.5994	9.9%	2.43 [0.75, 7.86]	2019	
Subtotal (95% CI)			87.3%	0.88 [0.54, 1.43]		
Heterogeneity: Tau² =	= 0.10; Chi ² = 6.02, df	í= 4 (P =	0.20); l² =	34%		
Test for overall effect:	Z = 0.53 (P = 0.60)					
5.5.2 Case-control						
Van Schaik 2013	-0.1855	0.5196	12.7%	0.83 [0.30, 2.30]	2013	•
Subtotal (95% CI)			12.7%	0.83 [0.30, 2.30]		
Heterogeneity: Not ap	oplicable					
Test for overall effect:	Z = 0.36 (P = 0.72)					
Total (95% CI)			100.0 %	0.88 [0.59, 1.30]		
Heterogeneity: Tau² =	= 0.04; Chi² = 6.05, df	f= 5 (P =	0.30); l² =	17%		0.2 0.5 1 2 5
Test for overall effect:	Z = 0.65 (P = 0.52)					5-ASA no risk factor 5-ASA risk factor
Test for subgroup dif	ferences: Chi² = 0.01	. df = 1 (F	P = 0.93),	I ² = 0%		

Supplementary Figure 32C: Forest plot of Multivariable analysis OR

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
5.11.1 Cohort multiva	ariable analysis					
Gong 2012 Subtotal (95% Cl)	-1.2755	0.3902	11.7% 11.7 %	0.28 [0.13, 0.60] 0.28 [0.13, 0.60]	2012	
Heterogeneity: Not ap	oplicable					
Test for overall effect:	: Z = 3.27 (P = 0.001)				
5.11.2 Case-control	multivariable analys	sis				
Eaden 2000	-0.7571	0.3863	11.9%	0.47 [0.22, 1.00]	2000	
/an Staa 2005	-0.5042	0.2364	31.8%	0.60 [0.38, 0.96]	2005	_
/elayos 2006	-0.8574	0.3837	12.1%	0.42 [0.20, 0.90]	2006	-
Tang 2010	-1.0728	1.2417	1.2%	0.34 [0.03, 3.90]	2010	• • • • • • • • • • • • • • • • • • • •
Carrat 2017 Subtotal (95% CI)	-0.5281	0.2379	31.4% 88.3 %	0.59 [0.37, 0.94] 0.55 [0.41, 0.72]	2017	•
Heterogeneity: Tau ² =	= 0.00: Chi ² = 1.02. d	if = 4 (P :	= 0.91); l ^a	'= 0%		-
Test for overall effect:			,,,			
Total (95% CI)			100.0%	0.51 [0.39, 0.66]		•
Heterogeneity: Tau ² =	= 0.00; Chi ² = 3.64, d	lf = 5 (P :	= 0.60); l ^a	²= 0%		
Test for overall effect:	Z = 5.11 (P < 0.000	01)				0.2 0.5 1 2 5 5ASA no risk factor 5ASA risk factor
Test for subgroup dif	ferences: Chi ² = 2.6	3, df = 1	(P = 0.11), I² = 61.9%		SAGA TO TAK ACTOL SAGA TAK ACTOL

Supplementary Figure 32D: Forest plot of Multivariable analysis HR

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
5.8.1 Cohort multivari	iable analysis					
Van Schaik 2012 Subtotal (95% Cl)	0.0477	0.8455	23.8% 23.8 %	1.05 [0.20, 5.50] 1.05 [0.20, 5.50]	2012	
Heterogeneity: Not ap	plicable					
Test for overall effect:	Z = 0.06 (P = 0.96)					
5.8.2 Case-control m	ultivariable analysis	;				
Van Schaik 2013 Subtotal (95% Cl)	-0.5888	0.4721	76.2% 76.2 %	0.55 [0.22, 1.40] 0.55 [0.22, 1.40]	2013	
Heterogeneity: Not ap	plicable					
Test for overall effect:	Z = 1.25 (P = 0.21)					
Total (95% CI)			100.0%	0.65 [0.29, 1.45]		
Heterogeneity: Tau ² =	0.00; Chi ² = 0.43, df	= 1 (P =	0.51); l ² =	:0%		
Test for overall effect:	Z = 1.06 (P = 0.29)					0.2 0.5 1 2 5 5ASA no risk factor 5ASA risk factor
Test for subgroup diff	erences: Chi ² = 0.43	. df = 1 (F	^o = 0.51),	I² = 0%		SAGA TO TAK ACTOL SAGA TAK ACTOL

Supplementary Table 32E: Definitions used in studies used in pooled analysis

Study, year	Definition 5-aminosalicylates	Supplementary figure
Lindberg 2001	Use of 5-ASA or sulfasalazine for at least 6 months	32A
Fujita 2010	Use of 5-ASA	32A
Gong 2012	Use of 5-ASA or sulfasalazine	32A
Nowacki 2015	Use of 5-ASA	32A 32A
Zhang 2015	Use of 5-ASA	32A 32A
Gordillo 2015	Use of 5-ASA	32A 32A
Pinczowski 1994	Use of sulfasalazine	32A 32A
Eaden 2000		32A & 32C
Rutter 2004	Regular use of mesalazine at a dose of 1.2g/day or greater	32A & 32C
	Use of sulfasalazine > 3 months up to 10 years	32A & 32C
Van Staa 2005	Any 5-ASA (mesalazine, balsalazide, olsalazine, sulfasalazine)	32A & 32C
Velayos 2006	Use of sulfasalazine > 3 months up to 10 years	32A & 32C
Siegel 2006	Use of 5-ASA	32A
Terdiman 2007	Use of at least 1 prescription of mesalamine or sulfasalazine or balsalazide	32A
Tang 2010	Use of sulfasalazine, olsalazine, mesalazine klysma, mesalazine rectal suppository	32A & 32C
Bergeron 2010	Use of 5-ASA, mean dose greater dan 1g/day during the 5 years before event	32A
Baars 2011	Use of 5-ASA	32A
Rubin 2013	Use of sulfasalazine (results for non-sulfasalazine were similar)	32A
Nieminen 2014	Use of 5-ASA	32A
Carrat 2017	Use of mesalamine, sulfasalazine, olsalazine and balsalazide	32A & 32C
Jung 2017	Use of 5-ASA at least 1 month	32A
Gupta 2008	Use of mesalamine-based agents	32B
Ullman 2008	Use of mesalamine, dose 2.0 g/day (or an equivalent dose of balsalazide or sulfasalazine or olsalazine)	32B
Bernstein 2011	Use of 5-ASA > 1 year	32B
Van Schaik 2012	Use of mesalazine at a dose of at least 1.2 g/day during 6 monthas, or an equivalent dos of sulfasalazine or olsalazine	32B & 32D

Mahmoud 2019	Use of 5-ASA	32B & 32D
Van Schaik 2013	Use of 5-ASA	32B
Gong 2012	Use of 5-ASA <u>></u> 1.5 g/day or sulfasalazine <u>></u> 2g/day	32C

Journal Prevention

Supplementary file 33A-E Tumor necrosis factor alpha inhibitors

Supplementary Figure 33A: Forest plot of Univariable analysis OR

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
6.2.1 Cohort					
Ananthakrishnan 2015	0.4116	0.2741	31.3%	1.51 [0.88, 2.58]	+
Nowacki 2015	0.5076	1.0801	21.0%	1.66 [0.20, 13.80]	
Subtotal (95% CI)			52.4%	1.52 [0.90, 2.56]	◆
Heterogeneity: Tau ² = 0.0	10; Chi² = 0.01, df =	1 (P = 0)	.93); I ² = 0)%	
Test for overall effect: Z =	1.57 (P = 0.12)				
6.2.2 Case-control					
Baars 2011	-2.2114	0.514	28.9%	0.11 [0.04, 0.30]	
Jung 2017	0.3385	1.2545	18.8%	1.40 [0.12, 16.40]	
Subtotal (95% CI)			47.6%	0.30 [0.03, 3.51]	
Heterogeneity: Tau ² = 2.3	3; Chi ² = 3.54, df =	1 (P = 0)	.06); I^z = 7	72%	
Test for overall effect: Z =	0.96 (P = 0.34)				
Total (95% CI)			100.0%	0.71 [0.14, 3.67]	
Heterogeneity: Tau ² = 2.1	6; Chi ² = 20.79, df	= 3 (P = I	0.0001); I	²= 86%	
Test for overall effect: Z =					 0.05 0.2 1 5 20 Biological no risk factor Biological risk factor
Test for subgroup differe	nces: Chi ² = 1.59, (df = 1 (P :	= 0.21), I ^z	'= 37.2%	Diological no hisk lactor Diological HSK lattor

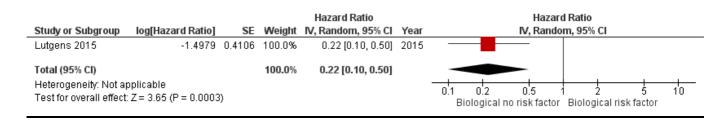
Supplementary Figure 33B: Forest plot of Univariable HR cohort studies

				Hazard Ratio	Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
Shah 2018	-0.3216	0.3572	100.0%	0.72 [0.36, 1.46]		
Total (95% CI)			100.0%	0.72 [0.36, 1.46]		
Heterogeneity: Not ap Test for overall effect:	· · · · · · · · · · · · · · · · · · ·				0.2 0.5 1 2 Biological no risk factor Biological risk factor	5

Supplementary Figure 33C: Forest plot of Multivariable OR cohort studies

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Ananthakrishnan 2016	0.01	0.249	100.0%	1.01 [0.62, 1.65]	2016	
Total (95% CI)			100.0 %	1.01 [0.62, 1.65]		
Heterogeneity: Not applie Test for overall effect: Z =						0.5 0.7 1 1.5 2 Biological no risk factor Biological risk factor

Supplementary Figure 33D: Forest plot of Multivariable HR cohort studies



Supplementary Table 33E: Definitions used in studies used in pooled analysis

Study, year	Definition biologic	Supplementary figure
Ananthakrishnan 2015	Use of infliximab, adalimumab, and certolizumab	33A
Nowacki 2015	Use of anti-TNF	33A
Baars 2011	Use of anti-TNF	33A
Jung 2017	Use of infliximab or adalimumab	33A
Shah 2018	Use of biologics	33B
Ananthakrishnan 2016	Use of infliximab, adalimumab, and certolizumab	33C
Lutgens 2015	Use of anti-TNF	33D

Supplementary file 34A-C NSAIDs

Supplementary Figure 34A: Forest plot of Univariable OR case-control studies

				Odds Ratio		Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Velayos 2006	-1.6094	0.3537	33.4%	0.20 [0.10, 0.40]	2006	B
Terdiman 2007	-0.0305	0.1381	37.2%	0.97 [0.74, 1.27]	2007	
Baars 2011	0.6729	0.511	29.5%	1.96 [0.72, 5.34]	2011	
Total (95% CI)			100.0%	0.70 [0.22, 2.22]		
Heterogeneity: Tau ² =	0.90; Chi ² = 20.29	, df = 2 (F	• < 0.000	1); I² = 90%		
Test for overall effect:	Z = 0.60 (P = 0.55))				0.1 0.2 0.5 1 2 5 10 NSAID protective NSAID risk factor

Supplementary Figure 34B: Forest plot of Multivariable OR case-control studies

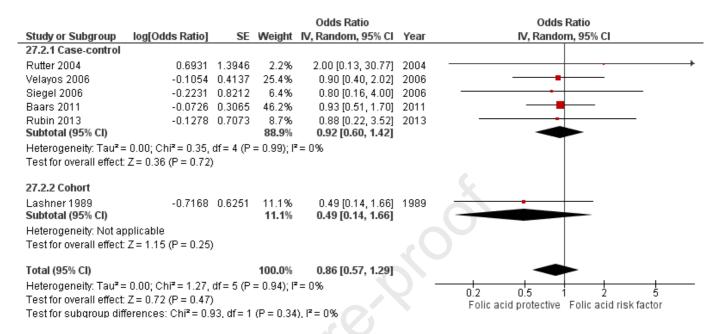
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% Cl	Year			s Ratio om, 95% Cl	
Velayos 2006	-2.3026	0.6143	100.0%	0.10 [0.03, 0.33]	2006				
Total (95% CI)			100.0%	0.10 [0.03, 0.33]					
Heterogeneity: Not ap Test for overall effect:)2)				0.02 0.1 NSAI	1 ID protective	1 10 NSAID risk factor	50

Study, year	Definition NSAID	Supplementary figure
Velayos 2006	Use of NSAIDs noted on at least 2 office visits	34A & 34B
Terdiman 2007	Ever use of NSAID	34A
Baars 2011	Ever use of NSAID	34A

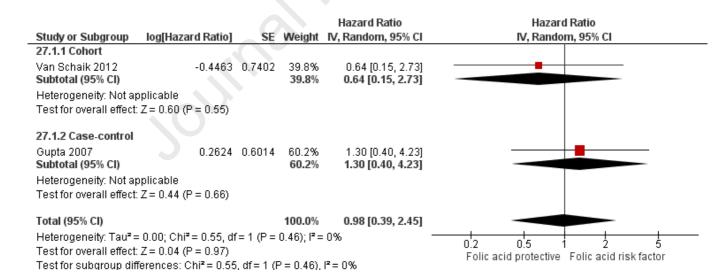
Supplementary Table 34C: Definitions used in studies used in pooled analysis

Supplementary file 35A-D Folic acid

Supplementary Figure 35A: Forest plot of Univariable analysis OR



Supplementary Figure 35B: Forest plot of Univariable analysis HR



Supplementary Figure 35C: Forest plot of Multivariable HR cohort studies

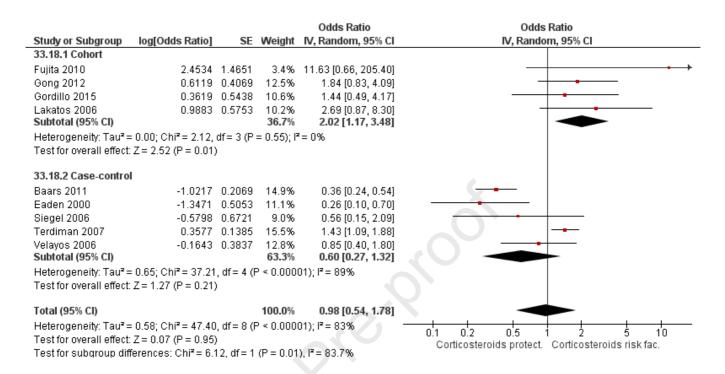
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Hazard Ratio IV, Random, 95% Cl
Tang 2010	-2.2073	0.3093	53.0%	0.11 [0.06, 0.20]	
Van Schaik 2012	0.7467	0.7884	47.0%	2.11 [0.45, 9.89]	
Total (95% CI)			100.0%	0.44 [0.02, 7.93]	
Heterogeneity: Tau ² = Test for overall effect:		df=1(P∶	= 0.0005)	; l² = 92%	0.01 0.1 1 10 100 Folic acid protective Folic acid risk factor

Supplementary Table 35D: Definitions used in studies used in pooled analysis

Study, year	Definition folic acid	Supplementary figure
Rutter 2004	Ever use of folic acid	35A
Velayos 2006	Use of folic acid, noted on at least 2 office visits	35A
Siegel 2006	Ever use of folic acid	35A
Baars 2011	Ever use of folic acid	35A
Rubin 2013	Ever use of folic acid	35A
Van Schaik 2012	Concurrent use of folic acid	35B & 35C
Gupta 2007	Ever use of folic acid	35B
Tang 2010	Ever use of folic acid	35C

Supplementary file 36A-D Corticosteroids

Supplementary Figure 36A: Forest plot of Univariable analysis OR



Supplementary Figure 36B: Forest plot of Univariable analysis HR cohort study

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Gupta 2007	1.361	0.5605	100.0%	3.90 [1.30, 11.70]	
Total (95% CI)			100.0%	3.90 [1.30, 11.70]	
Heterogeneity: Not a	pplicable				
Test for overall effect	: Z = 2.43 (P = 0.02)				0.05 0.2 1 5 20 Corticosteroids protect. Corticosteroids risk fac.

Supplementary Figure 36C: Forest plot of Multivariable analysis OR case-control study

Study or Subgroup	log[Odds Ratio]	SE	Mojaht	Odds Ratio IV, Random, 95% Cl				Ratio m, 95% Cl		
Study of Subgroup	log[odds Ratio]	36	weight	IV, Rahuom, 95% Ci			rv, ranuu	m, 95% CI		
Velayos 2006	-0.9163	0.3537	100.0%	0.40 [0.20, 0.80]						
Total (95% CI)			100.0%	0.40 [0.20, 0.80]						
Heterogeneity: Not ap	oplicable								I	_
					0.05	0	2	1	5	20
Test for overall effect:	: Z = 2.59 (P = 0.010	J)			С	orticoste	eroids protect.	Corticosteroi	ds risk fac.	

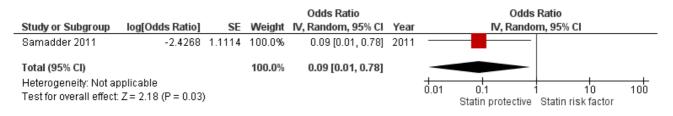
Study, year	Definition corticosteroids	Supplementary figure
Fujita 2010	Use of steroids	36A
Gong 2012	Use of steroids	36A
Gordillo 2015	Use of systemic steroids	36A
Lakatos 2006	Use of steroids	36A
Baars 2011	Use of steroids	36A
Eaden 2000	Use of systemic or local steroids	36A
Siegel 2006	Use of steroids	36A
Terdiman 2007	Use of steroids	36A
Velayos 2006	Use of steroids >1 year	36A & 36B
Gupta 2007	Use of steroids	36B

Supplementary Table 36D: Definitions used in studies used in pooled analysis

oundipreserves

Supplementary file 37A-E Statins

Supplementary Figure 37A: Forest plot of Univariable analysis OR case-control (definition > 5 years use, self-reported)



Supplementary Figure 37B: Forest plot of Univariable analysis HR cohort

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Shah 2019	0.0849	0.7506	100.0%	1.09 [0.25, 4.74]	2019	
Total (95% CI)			100.0 %	1.09 [0.25, 4.74]		
Heterogeneity: Not ap Test for overall effect:	•					0.1 0.2 0.5 1 2 5 10 Statin protective Statin risk factor

Supplementary Figure 37C: Forest plot of Multivariable analysis OR

				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
41.2.1 Cohort multivarial	ble analysis				
Ananthakrishnan 2016 Subtotal (95% CI)	-0.8675	0.2069	94.5% 94.5 %	0.42 [0.28, 0.63] 0.42 [0.28, 0.63]	
Heterogeneity: Not applic	able				
Test for overall effect: Z =	4.19 (P ≤ 0.0001)				
41.2.2 Case-control adju	sted (definition > 5	5 years u	ıse, self-ı	reported)	
Samadder 2011 Subtotal (95% Cl)	-2.1676	1.2437	5.5% 5.5 %	0.11 [0.01, 1.31] 0.11 [0.01, 1.31]	
Heterogeneity: Not applic	able				
Test for overall effect: Z =	1.74 (P = 0.08)				
Total (95% CI)			100.0%	0.39 [0.22, 0.70]	◆
Heterogeneity: Tau² = 0.0 Test for overall effect: Z = Test for subgroup differen	3.17 (P = 0.002)				0.01 0.1 1 10 100 Statin protective Statin risk factor

Supplementary Figure 37D: Forest plot of Multivariable analysis HR cohort

				Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Shah 2019	-0.4507	0.7732	100.0%	0.64 [0.14, 2.90]	2019	
Total (95% CI)			100.0%	0.64 [0.14, 2.90]		
Heterogeneity: Not a Test for overall effect						0.1 0.2 0.5 1 2 5 10 Statin protective Statin risk factor

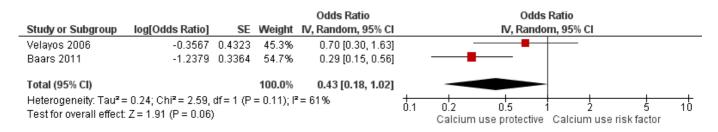
Study, year	Definition statin use	Supplementary figure
Samadder 2011	Statin use at least 5 years (as recalled by the patient)	37A & 37C
Shah 2019	Statin use at least 3 months	37B & 37D
Ananthakrishnan 2016	Statin use at least 6 months	37C

Supplementary Table 37E: Definitions used in studies used in pooled analysis

ounding

Supplementary file 38A-D Calcium supplements

Supplementary Figure 38A: Forest plot of Univariable analysis OR case-control



Supplementary Figure 38B: Forest plot of Univariable analysis HR cohort

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl	Hazard Ratio IV, Random, 95% Cl
Van Schaik 2012	-0.2614	0.4023	100.0%	0.77 [0.35, 1.69]	
Total (95% CI)			100.0%	0.77 [0.35, 1.69]	
Heterogeneity: Not ap Test for overall effect:				<u> </u>	0.5 0.7 1 1.5 2 Calcium use protective Calcium use risk factor

Supplementary Figure 38C: Forest plot of Multivariable analysis HR cohort

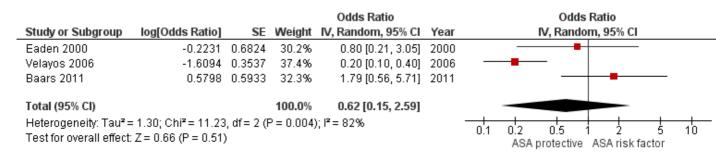
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% Cl			azard Ratio andom, 95		
Van Schaik 2012	0.131	0.4857	100.0%	1.14 [0.44, 2.95]					
Total (95% CI)			100.0%	1.14 [0.44, 2.95]					
Heterogeneity: Not app Test for overall effect: 2					0.2 Calc	0.5 ium use prote	1 ctive Calc	2 ium use risk	5 factor

Study, year	Definition calcium supplements	Supplementary figure
Velayos 2006	Use of calcium, noted on at least 2 office visits	38A
Baars 2011	Use of calcium	38A
Van Schaik 2012	Concurrent use of calcium	38B & 38C
Van Schaik 2012		38B & 38C

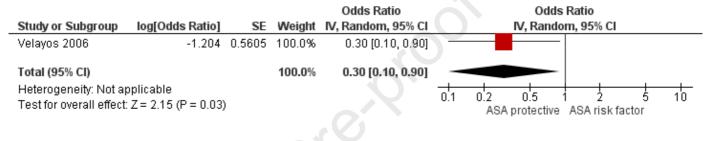
Supplementary Table 38D: Definitions used in studies used in pooled analysis

Supplementary file 39A-C Acetylsalicylic acid (ASA)

Supplementary Figure 39A: Forest plot of Univariable analysis OR case-control



Supplementary Figure 39B: Forest plot of Multivariable analysis OR case-control



Study, year	Definition ASA	Supplementary figure
Eaden 2000	Use of ASA	39A
Velayos 2006	Use of ASA, noted on at least 2 office visits	39A & 39B
Baars 2011	Use of ASA	39A

Supplementary Table 39C: Definitions used in studies used in pooled analysis

Supplementary file 40A-L Other prognostic factors

Supplementary Figure 40A: Medication other, univariable OR

Study or Subgroup	log[Odds Ratio]	SE.	Odds Ratio IV, Random, 95% Cl	Voar	Odds Ratio IV, Random, 95% Cl
36.2.1 Multivitamin case	<u> </u>	ЭL	IV, Nandolli, 55% CI	rear	TV, Nandolfi, 55% CI
Velayos 2006	-0.5108	0.3945	0.60 [0.28, 1.30]	2006	+
36.2.2 At least one thera	py with Antibiotics	6			
Scharl 2018	-2.0092	1.0246	0.13 [0.02, 1.00]	2018	←
36.2.3 Contraceptive us	e cohort				
Lakatos 2006	-0.1625	0.7382	0.85 [0.20, 3.61]	2006	+
36.2.4 Treatment with 'a	ny drug' vs never/	<3 mont	hs case-control		6
Pinczowski 1994	-1.0061		0.37 [0.22, 0.60]	1994	
36.2.5 Thiopurine and bi	ological 'ever' use	versus '	never' case-control		
Jung 2017	9	1.4146		2017	
36.2.6 Anti-inflammatory	/ and/or immunosu	uppressi	ve treatment cohort		
Nowacki 2015		0.5605	0.30 [0.10, 0.90]	2015	
36.2.7 Methotrexaat cas	e-control				
Baars 2011	-1.5878	0.7433	0.20 [0.05, 0.88]	2011	
36.2.8 Any use of azathi	oprine, 6-mercapto	opurine.	or methotrexate		
Ananthakrishnan 2015	-0.3973	· . ·	0.67 [0.46, 0.99]	2015	-+-
					0.05 0.2 1 5 20
					n'n5 n'2 i 5 2n

Supplementary Figure 40B: Medication other, multivariable OR

		Odds Ratio		Odds Ratio
log[Odds Ratio]	SE	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
ne versus no use o	cohort			
-0.6539	1.3087	0.52 [0.04, 6.76]	2015	5
ne, 6-mercaptopur	ine, or m	ethotrexate cohort		
0.1387	0.1658	1.15 [0.83, 1.59]	2016	3 1
/ and/or immunosu	ippressi	ve treatment cohort		
-0.9163	0.7073	0.40 [0.10, 1.60]	2015	5+
				0.05 0.2 1 5 20 Protective factor Risk factor
ľ	ne versus no use o -0.6539 ne, 6-mercaptopur 0.1387 / and/or immunosu	ne versus no use cohort -0.6539 1.3087 ne, 6-mercaptopurine, or m 0.1387 0.1658	ne versus no use cohort -0.6539 1.3087 0.52 [0.04, 6.76] ne, 6-mercaptopurine, or methotrexate cohort 0.1387 0.1658 1.15 [0.83, 1.59] v and/or immunosuppressive treatment cohort	ne versus no use cohort -0.6539 1.3087 0.52 [0.04, 6.76] 2015 ne, 6-mercaptopurine, or methotrexate cohort 0.1387 0.1658 1.15 [0.83, 1.59] 2016 v and/or immunosuppressive treatment cohort

Supplementary Figure 40C: Inflammatory markers, univariable OR cohort

Study of Subgroup	leg[Oddo Dotio]	er.	Odds Ratio	Odds Ratio	
Study or Subgroup 30.26.1 Highest CRP quar	log[Odds Ratio]	36	IV, Random, 95% Cl	IV, Random, 95% Cl	
Ananthakrishnan 2014b		0.5559	3.27 [1.10, 9.72]	I	
30.26.2 Highest BSE quar	tile vs lowest				
Ananthakrishnan 2014b	0.9203	0.2835	2.51 [1.44, 4.38]	- +	
				0.2 0.5 1 2 Protective factor Risk factor	<u> </u> 5

Supplementary Figure 40D: Inflammatory markers, multivariable OR

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio IV, Random, 95% Cl
30.9.1 CRP multivariable	<u> </u>				
Ananthakrishnan 2014b	1.0006	0.5367	2.72 [0.95, 7.79]	2014	
30.9.2 ESR multivariable	cohort				
Ananthakrishnan 2014b	0.7227	0.3019	2.06 [1.14, 3.72]	2014	
30.9.3 Increased inflamm	natory markers mu	ıltivariab	le cohort		
Ananthakrishnan 2016	0.5988	0.1678	1.82 [1.31, 2.53]	2016	
				+	2 0.5 1 2 5 Protective factor Risk factor

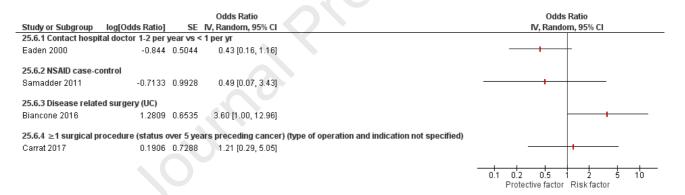
Supplementary Figure 40E: Cohort multivariable analysis OR

			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	IV, Random, 95% Cl	IV, Random, 95% Cl
26.22.1 More extensiv	e colitis (any locatio	n)		
Lakatos 2006	0.5663	0.2834	1.76 [1.01, 3.07]	+
26.22.2 Chronic contin	uous disease			
Lakatos 2006	1.0338	0.7967	2.81 [0.59, 13.40]	
26.22.3 NSAID associa	ited colitis			
Bansal 1996	-0.1744	0.1308	0.84 [0.65, 1.09]	-+-+
26.22.4 Duration of foll	ow up evaluation			
Ananthakrishnan 2016	-0.1863	0.0188	0.83 [0.80, 0.86]	+
				0.5 0.7 1 1.5 2 Protective factor Risk factor

Supplementary Figure 40F: Cohort multivariable analysis HR

			Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
26.15.1 Coecum rea	ched				
Mahmoud 2019	-2.4079	1.1211	0.09 [0.01, 0.81]	2019	<u>← </u>
26.15.2 UC index yea	ır				
Hou 2012	0.0953	0.2684	1.10 [0.65, 1.86]	2012	— <u>+</u>
26.15.6 History of en	doscopy in VA				
Hou 2012	0.5365	0.1765	1.71 [1.21, 2.42]	2012	-+
26.15.7 VA encounte	ers (1 year post UC ir	ıdex'			
Hou 2012	0.207	0.0955	1.23 [1.02, 1.48]	2012	+-
26.15.8 Priority level	(1-6 vs 7-8'				
Hou 2012	0.0677	0.1881	1.07 [0.74, 1.55]	2012	× +
26.15.9 Deyo score (1 versus 0)				
Hou 2012	0.0296	0.1971	1.03 [0.70, 1.52]	2012	\sim +
					0.1 0.2 0.5 1 2 5 10
					Protective factor Risk factor

Supplementary Figure 40G: Case-control multivariable analysis OR



Supplementary Figure 40H: Case-control multivariable analysis HR

			Hazard Ratio		Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	IV, Random, 95% Cl	Year	r IV, Random, 95% Cl	
Peng 2017	-0.2744	0.5673	0.76 [0.25, 2.31]	2017	7	
					0.01 0.1 1 10 100	0
					Protective factor Risk factor	

Supplementary Figure 40I: Case-control univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SF	Odds Ratio IV, Random, 95% Cl	Year	Odds Ratio IV, Random, 95% Cl
24.1.1 Sulfa allergy	logicationation	02	10,14,14,14,00,10,00,10	Tour	
Velayos 2006	0	0.3537	1.00 [0.50, 2.00]	2006	
24.1.2 NSAID/ascal us	e				
Samadder 2011	-0.755	0.6966	0.47 [0.12, 1.84]	2011	< <u>+</u> + − − −
24.1.3 CD involving the	e large intestine v	ersus of	ther subtypes IBD		
Terdiman 2007	0.5933	0.2588	1.81 [1.09, 3.01]	2007	
24.1.4 Pancolitis vs of	ther subtypes IBD				
Terdiman 2007	0.4511	0.1815	1.57 [1.10, 2.24]	2007	
24.1.5 Hospitalisation					
Terdiman 2007	1.3218	0.1276	3.75 [2.92, 4.82]	2007	
24.1.6 CD colitis alone	e versus ileocoliti	s			
Siegel 2006	0.6931	0.7843	2.00 [0.43, 9.30]	2006	
24.1.7 Fistulizing dise	ase				
Siegel 2006	0.3365	0.6653	1.40 [0.38, 5.16]	2006	
24.1.8 > 1 exacerbation	on per year				O T
Pinczowski 1994	-0.4884	0.2544	0.61 [0.37, 1.01]	1994	
24.1.9 Raised alkalic	phosphatase				
Eaden 2000	0.131	0.5218	1.14 [0.41, 3.17]	2000	
24.1.10 Contact with I	nospital doctor (1	2 comp	ared to none)		
Eaden 2000	-1.1394	0.4218	0.32 [0.14, 0.73]	2000	←
24.1.11 1 exacerbatio	n / 10 years				
Eaden 2000	-0.1625	0.3846	0.85 [0.40, 1.81]	2000	
24.1.12 Rectal sparing	g at onset IBD				
Baars 2011	-0.3711	0.5832	0.69 [0.22, 2.16]	2011	• • • •
24.1.13 Colon surgery	/ before onset IBC				
Baars 2011	1.16	0.385	3.19 [1.50, 6.78]	2011	│
24.1.14 Disease durat	tion per year				
Nieminen 2014	0.1133	0.0349	1.12 [1.05, 1.20]	2014	+
					Protective factor Risk factor

Supplementary Figure 40J: Case-control univariable analysis HR

			Hazard Ratio		Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Peng 2017	0.2151	0.5524	1.24 [0.42, 3.66]	2017	0.5 0.7 1 1.5 2 Protective factor Risk factor

Supplementary Figure 40K: Cohort univariable analysis OR

Study or Subgroup	log[Odds Ratio]	SE	Odds Ratio IV, Random, 95% Cl		Odds IV, Rando	
23.1.1 Disease duration (in years)					
Gong 2012	0.0579	0.0205	1.06 [1.02, 1.10]			
23.1.2 Severity of diseas	e					
Zhang 2015	2.6086	1.1593	13.58 [1.40, 131.73]			→
23.1.3 Chronic iron defici	iency					
Lakatos 2006	1.9169	0.6614	6.80 [1.86, 24.86]			+
23.1.4 B2 vs B1/B2 CD						
Lakatos 2011	3.8464	1.4815	46.82 [2.57, 854.13]			++
23.1.5 Chronic continuou	s disease					
Lakatos 2006	1.8563	0.6196	6.40 [1.90, 21.56]			
23.1.6 1 point increase p	lasma 25-hydroxi v	vit D (adju	usted model)			
Ananthakrishnan 2014a	-0.0619	0.0165	0.94 [0.91, 0.97]		1	
23.1.7 abnormalities of g	oblet cell glycocor	njugates	had been detected in t	he initial biopsy at the beginning of the study		
Boland 1984	-1.0986	1.5275	0.33 [0.02, 6.65]		+	
23.1.8 Longstanding exte	ensive colitis (10 y	ears and	l a cumulative estimat	ed percentage of the colonic mucosa surface affected by IBD of ≥50%)		
Beaugerie 2013	1.8116	0.2657	6.12 [3.64, 10.30]			-+
					0.02 0.1	
					Protective factor	

Supplementary Figure 40L: Cohort univariable analysis HR

			Hazard Ratio			Hazard Ratio	
Study or Subgroup	log[Hazard Ratio]	SE	IV, Random, 95% CI	Year		IV, Random, 95% Cl	
23.4.1 Disease durat	ion (in years)						
Scharl 2018	0.063	0.0185	1.07 [1.03, 1.10]	2018		t t	
23.4.2 Diagnosis bef							
Selinger 2014	1.6474	0.5579	5.19 [1.74, 15.50]	2014			→
23.4.3 Adequate bow	al proportion of he	ooline					
•							
Mahmoud 2019	0.2231	0.7819	1.25 [0.27, 5.79]	2019			
23.4.4 Coecum react	hor						
Mahmoud 2019	-2.3838	1 1 2 2 4	0.09 [0.01, 0.85]	2010			
Mannouu 2019	-2.3030	1.1554	0.09 [0.01, 0.03]	2019			
23.4.5 UC index year	2003-2008 (ref 199	8-2002)					
Hou 2012	-0.0834	0.1772	0.92 [0.65, 1.30]	2012		+	
23.4.6 History of end	oscopy in VA						
Hou 2012	0.4886	0.1563	1.63 [1.20, 2.21]	2012		- + -	
23.4.7 VA encounter	s (1 year post UC ind	lex'					
Hou 2012	0.3221	0.0713	1.38 [1.20, 1.59]	2012		+	
22.4.0 D-iit-level.4	4.0 7.01						
23.4.8 Priority level (
Hou 2012	0.2231	0.1733	1.25 [0.89, 1.76]	2012			
23.4.9 Deyo score (1	versus ())						
Hou 2012		0.1965	1.22 [0.83, 1.79]	2012		_ 	
H00 2012	0.1969	0.1900	1.22 [0.05, 1.79]	2012			
						0.2 0.5 1 2 5 1	0
					ł	Protective factor Risk factor	

Supplementary file 41A-H: Good quality synthesis

Supplementary Figure 41A: Forest plot of univariable OR cohort studies

	log[Odds Dati-1	er	Moint	Odds Ratio	Voor	Odds Ratio
	log[Odds Ratio]	SE	weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
7.4.1 IBD type	0.0747		45.000	0.00.00.44.0.000	4004	
}illen 1994a	-0.0747		15.0%	0.93 [0.41, 2.08]		
Söderlund 2009		0.2726	26.5%	2.41 [1.41, 4.11]		
Reaugerie 2013		0.3736	17.4%	1.75 [0.84, 3.64]		
fanninen 2013		0.5155	10.5%	1.34 [0.49, 3.69]		
.ee 2015		0.3741	17.4%	1.44 [0.69, 2.99]		
an den Heuvel 2016	-0.2399	0.4438	13.4%	0.79 [0.33, 1.88]	2016	
Subtotal (95% CI)			100.0%	1.46 [1.03, 2.09]		•
leterogeneity: Tau² = 0.0 est for overall effect: Z =		f= 5 (P =	0.24); I² =	26%		
7.4.2 Extensive diseas	e					
1aratka 1985	1.0864	1.1215	1.1%	2.96 [0.33, 26.70]	1985	
1aratka 1985	1.0864	1.1215	1.1%	2.96 [0.33, 26.70]	1985	
Rutegard 1988	1.5571	1.5228	0.6%	4.75 [0.24, 93.85]	1988	
(vist 1989	0.0679	0.4919	5.8%	1.07 [0.41, 2.81]	1989	
kbom 1990a	1.2471	0.2763	18.4%	3.48 [2.02, 5.98]	1990	
eidenius 1991.	1.3115	1.6517	0.5%	3.71 [0.15, 94.52]	1991	
ablonská 1993	0.8602	0.7305	2.6%	2.36 [0.56, 9.89]	1993	
onsson 1994	0.8204	0.8366	2.0%	2.27 [0.44, 11.71]		
Rozen 1995	-0.1405		2.3%	0.87 [0.19, 4.03]		
Stewenius 1995	1.0385	0.8783	1.8%	2.82 [0.51, 15.80]		
raser 2002		0.4259	7.8%	1.53 [0.66, 3.52]		
(obayashi 2002		1.4896	0.6%	2.72 [0.15, 50.40]		
akatos 2006		0.5778	4.2%	3.54 [1.14, 10.99]		
how 2009		1.6431	0.5%	2.13 [0.09, 53.36]		
öderlund 2009		0.2218	28.6%	1.57 [1.02, 2.43]		
(ottachchi 2009		1.5225	0.6%	4.15 [0.21, 82.03]		
Ray 2011		1.5319	0.6%	5.00 [0.25, 100.67]		
ampos 2013		1.0528	1.3%	6.48 [0.82, 51.02]		
fanninen 2013		0.5202	5.2%	1.17 [0.42, 3.24]		
Selinger 2014		0.4676	6.4%	1.64 [0.66, 4.10]		
.ee 2015		0.7514	2.5%	5.86 [1.34, 25.54]		
ordillo 2015		0.75144	2.3% 5.3%			
Subtotal (95% CI)	0.7400	0.0144	100.0%	2.11 [0.77, 5.78] 2.05 [1.63, 2.59]	2015	
abtotal (55% cl)			100.070	2.00 [1.00, 2.00]		•
leteroneneity: Tou ² – 0 (10: Chi2 - 15 /1	Mf = 21 /P	- 0.80) ⁻ P			
leterogeneity: Tau² = 0.0 est for overall effect: Z =			= 0.80); i			
est for overall effect: Z =	6.07 (P < 0.0000		= 0.80); i			
est for overall effect: Z = 7.4.3 Low-grade dyspla	: 6.07 (P < 0.0000 asia)1)		* = 0%	2012	
est for overall effect: Z = 7.4.3 Low-grade dyspla Stolwijk 2013	: 6.07 (P < 0.0000 asia 1.0804	01) 0.4771	48.1%	* = 0% 2.95 [1.16, 7.50]		
Test for overall effect: Z = (7.4.3 Low-grade dyspl a Stolwijk 2013 Schoi 2019	: 6.07 (P < 0.0000 asia 1.0804)1)	48.1% 51.9%	² = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08]		
est for overall effect: Z = 7.4.3 Low-grade dyspla Stolwijk 2013	: 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi ^a = 10.44, r	01) 0.4771 0.3106	48.1% 51.9% 100.0 %	² = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40]		
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% CI) teterogeneity: Tau ² = 1.4 Test for overall effect: Z =	: 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi ^a = 10.44, r	01) 0.4771 0.3106	48.1% 51.9% 100.0 %	² = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40]		- t
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Stolwidk 2019 Subtotal (95% CI) Tau ² = 1.9 Test for overall effect: Z = 7.4.5 Aneuploidy	6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, 2.22 (P = 0.03)	01) 0.4771 0.3106 df = 1 (P =	48.1% 51.9% 100.0 % = 0.001); F	² = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ² = 90%	2019	
est for overall effect: Z = 7.4.3 Low-grade dyspl stolwijk 2013 shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.4 rest for overall effect: Z = 7.4.5 Aneuploidy indberg 1999	 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, 2.22 (P = 0.03) 1.9054 	01) 0.4771 0.3106 df = 1 (P = 0.6645	48.1% 51.9% 100.0% = 0.001); F 44.9%	² = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ² = 90% 6.72 [1.83, 24.72]	2019 1999	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.3 rest for overall effect: Z = 7.4.5 Aneuploidy Söderlund 2011	6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, 2.22 (P = 0.03)	01) 0.4771 0.3106 df = 1 (P =	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1%	 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ² = 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 	2019 1999	
est for overall effect: Z = 7.4.3 Low-grade dyspl stolwijk 2013 shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.4 rest for overall effect: Z = 7.4.5 Aneuploidy indberg 1999	6.07 (P < 0.000) asia 1.0804 2.92 53; Chi ² = 10.44, (2.22 (P = 0.03) 1.9054 1.3756 D0; Chi ² = 0.35, dr	0.4771 0.3106 df = 1 (P = 0.6645 0.6	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0%	2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ² = 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02]	2019 1999	
iest for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Subtotal (95% CI) Heterogeneity: Tau ² = 1.4 iest for overall effect: Z = 7.4.5 Aneuploidy Söderlund 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 0.4	6.07 (P < 0.000) asia 1.0804 2.92 53; Chi ² = 10.44, (2.22 (P = 0.03) 1.9054 1.3756 D0; Chi ² = 0.35, dr	0.4771 0.3106 df = 1 (P = 0.6645 0.6	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0%	2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ² = 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02]	2019 1999	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.9 est for overall effect: Z = 7.4.5 Aneuploidy Söderlund 2011 Söderlund 2011 Söderlund 2011 Soutotal (95% CI) Heterogeneity: Tau ² = 0.0 est for overall effect: Z = 7.4.8 Male sex	6.07 (P < 0.000) asia 1.0804 2.92 53; Chi ² = 10.44, (2.22 (P = 0.03) 1.9054 1.3756 D0; Chi ² = 0.35, dr	01) 0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 3)	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F=	² = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ² = 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0%	2019 1999 2011	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.3 rest for overall effect: Z = 7.4.5 Aneuploidy Soderlund 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 rest for overall effect: Z = 7.4.8 Male sex Macdougall 1954	 6.07 (P < 0.000) asia 1.0804 2.92 53; Chi^a = 10.44, 2.22 (P = 0.03) 1.9054 1.3756 00; Chi^a = 0.35, dt 3.62 (P = 0.003) 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 3) 0.9313	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2%	 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ?= 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 	2019 1999 2011 1954	
est for overall effect: Z = 7.4.3 Low-grade dyspl tolwijk 2013 boli 2019 tubtotal (95% CI) leterogeneity: Tau ² = 1.4 est for overall effect: Z = 7.4.5 Aneuploidy indberg 1999 öderlund 2011 subtotal (95% CI) leterogeneity: Tau ² = 0.1 est for overall effect: Z = 7.4.8 Male sex facdougal 1954 factougal 1985	 6.07 (P < 0.000) asia 1.0804 2.92 53; Chi² = 10.44, 2.22 (P = 0.03) 1.9054 1.3756 D0; Chi² = 0.35, di 3.62 (P = 0.003) 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 3) 0.9313	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8%	 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ?= 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 	2019 1999 2011 1954	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.3 rest for overall effect: Z = 7.4.5 Aneuploidy Soderlund 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 rest for overall effect: Z = 7.4.8 Male sex Macdougall 1954	 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, 2.22 (P = 0.03) 1.9054 1.3756 00; Chi² = 0.35, dt -0.0888 -0.1677 00; Chi² = 0.00, dt 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 f = 1 (P = 3) 0.9313 0.9171	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 	2019 1999 2011 1954	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.4 For overall effect: Z = 7.4.5 Aneuploidy Söderlund 2011 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.4 For overall effect: Z = 7.4.8 Male sex Macdougall 1954 Maratka 1985 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.4 Heterogeneity: Tau ² = 0.4	 6.07 (P < 0.000) asia 1.0804 2.92 53; Chi^a = 10.44, 1 2.22 (P = 0.03) 1.9054 1.3756 00; Chi^a = 0.35, dt -0.0888 -0.1677 00; Chi^a = 0.00, dt 0.20 (P = 0.84) 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 3) 0.9313 0.9171 f = 1 (P =	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 	2019 1999 2011 1954	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.3 rest for overall effect: Z = 7.4.5 Aneuploidy Soderlund 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 rest for overall effect: Z = 7.4.8 Male sex Macdougall 1954 Maratka 1985 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 rest for overall effect: Z =	 6.07 (P < 0.000) asia 1.0804 2.92 53; Chi^a = 10.44, 1 2.22 (P = 0.03) 1.9054 1.3756 00; Chi^a = 0.35, dt -0.0888 -0.1677 00; Chi^a = 0.00, dt 0.20 (P = 0.84) 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 0.9313 0.9313 0.9171 f = 1 (P = colitis	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ?= 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 0% 	2019 1999 2011 1954 1985	
iest for overall effect: Z = 7.4.3 Low-grade dyspla itolwijk 2013 iest for overall effect: Z = 7.4.5 Aneuploidy indberg 1999 oderlund 2011 iubtotal (95% Cl) iest for overall effect: Z = 7.4.8 Male sex facadougall 1954 facatka 1985 iubtotal (95% Cl) feterogeneity: Tau ² = 0.1 iest for overall effect: Z = 7.4.9 IBD type UC versa	 6.07 (P < 0.000) asia 1.0804 2.92 53; Chi² = 10.44, 1 2.22 (P = 0.03) 1.9054 1.3756 00; Chi² = 0.35, dt -0.0888 -0.1677 00; Chi² = 0.00, dt 0.20 (P = 0.84) us indeterminate 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 0.9313 0.9313 0.9171 f = 1 (P = colitis	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0% 0.95); F=	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 	2019 1999 2011 1954 1985	
est for overall effect: Z = 7.4.3 Low-grade dyspl Stolwijk 2013 Shoi 2019 Subtotal (95% Cl) Heterogeneity: Tau ² = 1.4 For overall effect: Z = 7.4.5 Aneuploidy Söderlund 2011 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.4 For overall effect: Z = 7.4.8 Male sex Macdougall 1954 Maratka 1985 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.4 For overall effect: Z = 7.4.9 IBD type UC versu Stevenius 1995 Subtotal (95% Cl)	 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, 2.22 (P = 0.03) 1.9054 1.3756 00; Chi² = 0.35, dri 3.62 (P = 0.0003 -0.0888 -0.1677 00; Chi² = 0.00, dri 0.20 (P = 0.84) us indeterminate -0.4622 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 0.9313 0.9313 0.9171 f = 1 (P = colitis	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 0% 	2019 1999 2011 1954 1985	
iest for overall effect: Z = 7.4.3 Low-grade dyspla itolwijk 2013 itolwijk 2013 ibio 2019 jubtotal (95% Cl) deterogeneity: Tau ² = 1.3 iest for overall effect: Z = 7.4.5 Aneuploidy indberg 1999 iddfund 2011 jubtotal (95% Cl) deterogeneity: Tau ² = 0.1 feterogeneity: Tau ² = 0.1 idetougall 1985 iadcougall 1985 iadcougall 1985 iabtotal (95% Cl) ieterogeneity: Tau ² = 0.1	 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, i 2.22 (P = 0.03) 1.9054 1.3756 00; Chi² = 0.35, dr -0.0888 -0.1677 00; Chi² = 0.00, dr 0.20 (P = 0.84) is indeterminate -0.4622 cable 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 0.9313 0.9313 0.9171 f = 1 (P = colitis	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 0% 	2019 1999 2011 1954 1985	
est for overall effect: Z = 7.4.3 Low-grade dyspla Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.9 (7.4.5 Aneuploidy indberg 1999 Söderlund 2011 Stotal (95% CI) Heterogeneity: Tau ² = 0.1 (7.4.8 Male sex Hacdougal 1954 Haratka 1985 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 (7.4.9 IBD type UC versu Stevenius 1995 Subtotal (95% CI) Heterogeneity: Stau ² = 0.1 (7.4.9 IBD type UC versu Stevenius 1995 Subtotal (95% CI) Heterogeneity: Not appli	 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, i 2.22 (P = 0.03) 1.9054 1.3756 00; Chi² = 0.35, dr -0.0888 -0.1677 00; Chi² = 0.00, dr 0.20 (P = 0.84) is indeterminate -0.4622 cable 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 0.9313 0.9313 0.9171 f = 1 (P = colitis	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 0% 	2019 1999 2011 1954 1985	
est for overall effect: Z = 7.4.3 Low-grade dyspla Stolwijk 2013 Shoi 2019 Subtotal (95% CI) Heterogeneity: Tau ² = 1.9 (7.4.5 Aneuploidy indberg 1999 Söderlund 2011 Stotal (95% CI) Heterogeneity: Tau ² = 0.1 (7.4.8 Male sex Hacdougal 1954 Haratka 1985 Subtotal (95% CI) Heterogeneity: Tau ² = 0.1 (7.4.9 IBD type UC versu Stevenius 1995 Subtotal (95% CI) Heterogeneity: Stau ² = 0.1 (7.4.9 IBD type UC versu Stevenius 1995 Subtotal (95% CI) Heterogeneity: Not appli	 6.07 (P < 0.0000 asia 1.0804 2.92 53; Chi² = 10.44, i 2.22 (P = 0.03) 1.9054 1.3756 00; Chi² = 0.35, dr -0.0888 -0.1677 00; Chi² = 0.00, dr 0.20 (P = 0.84) is indeterminate -0.4622 cable 	0.4771 0.3106 df = 1 (P = 0.6645 0.6 (= 1 (P = 0.9313 0.9313 0.9171 f = 1 (P = colitis	48.1% 51.9% 100.0% = 0.001); F 44.9% 55.1% 100.0% 0.55); F= 49.2% 50.8% 100.0%	 = 0% 2.95 [1.16, 7.50] 18.54 [10.09, 34.08] 7.66 [1.26, 46.40] ≈ 90% 6.72 [1.83, 24.72] 3.96 [1.22, 12.83] 5.02 [2.10, 12.02] 0% 0.92 [0.15, 5.68] 0.85 [0.14, 5.10] 0.88 [0.24, 3.16] 0% 	2019 1999 2011 1954 1985	

Supplementary figure 41B.1: Forest plot of univariable OR case-control studies, pooled analysis possible

ooleu allaiysis	possible				
				Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
37.3.4 Smoking					_
Bergeron 2010	-0.6506		44.8%	0.52 [0.22, 1.27]	
Rutter 2004		0.7816	31.0%	0.71 [0.15, 3.30]	
Siegel 2006	1.716	0.9894	24.2%	5.56 [0.80, 38.67]	
Subtotal (95% CI)			100.0%	1.02 [0.29, 3.56]	
Heterogeneity: Tau² = Test for overall effect:			= 0.09); P	²= 58%	
37.3.5 Family history	CRC				_
Bergeron 2010	-0.6506	0.4523	81.4%	0.52 [0.22, 1.27]	
Rutter 2004	0.1989	1.33	9.4%	1.22 [0.09, 16.54]	
Siegel 2006	-0.0173	1.348	9.2%	0.98 [0.07, 13.80]	
Subtotal (95% CI)			100.0%	0.60 [0.27, 1.33]	
Heterogeneity: Tau ² =			= 0.77); P	²=0%	X
Test for overall effect:	Z = 1.26 (P = 0.21)	1			
37.3.6 Folic acid					
Rutter 2004	0.6931	1.3946	25.7%	2.00 [0.13, 30.77]	
Siegel 2006	-0.2231		74.3%	0.80 [0.16, 4.00]	
Subtotal (95% CI)			100.0%	1.01 [0.25, 4.05]	
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.32.	df = 1 (P	= 0.57); P	²=0%	
Test for overall effect:			/1		
	,				
					0.05 0.2 1 5 20 Bratactive factor Dick factor
					Protective factor Risk factor

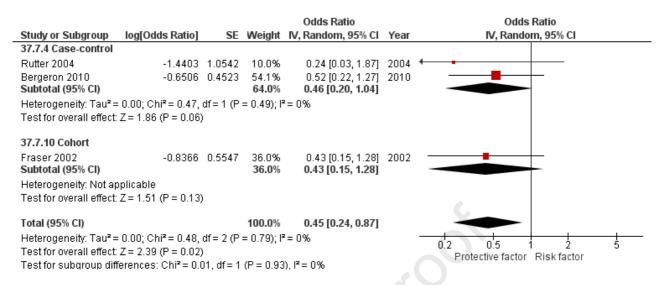
Supplementary figure 41B.2: Forest plot of univariable OR case-control studies, no pooled analysis

			Odds Ratio	Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	IV, Random, 95% Cl	IV, Random, 95% Cl
37.9.8 Endoscopic in	flammation			
Rutter 2004	0.9632	0.5804	2.62 [0.84, 8.17]	++
37.9.9 Histologic infl	ammation			
Rutter 2004		1.0305	6.33 [0.84, 47.71]	,
11011212004	1.0455	1.0000	0.00 [0.04, 47.71]	•
37.9.10 Peri-anal dis	ease			
Bergeron 2010	-0.6506	0.4523	0.52 [0.22, 1.27]	+
37.9.11 Appendector	-			
Siegel 2006	-1.4194	0.8043	0.24 [0.05, 1.17]	
37.9.12 Colon segme	ent recention			X
-		0 0000	0 60 10 4 6 0 401	
Siegel 2006	-0.462	0.6993	0.63 [0.16, 2.48]	
37.9.13 CD colitis alo	ne versus ileocoli	tis		
Siegel 2006	0.6931	0.7843	2.00 [0.43, 9.30]	
37.9.14 Fistulizing dis	sease			
Siegel 2006	0.3365	0.6653	1.40 [0.38, 5.16]	
37.9.15 Prior surveill				.
Siegel 2006	-1.1087	0.8698	0.33 [0.06, 1.81]	
37.9.16 Corticostero	ide			
Siegel 2006	-0.5798	0.6724	0.56 [0.15, 2.09]	
olegel 2000	-0.5730	0.0721	0.50 [0.15, 2.03]	
37.9.17 Family histor	y IBD			
Siegel 2006	-1.1087	1.2234	0.33 [0.03, 3.63]	<
-				
				0.05 0.2 1 5 20
				Protective factor Risk factor

Supplementary figure 41C.1: Forest plot PSC of univariable OR cohort and casecontrol studies pooled

			Odds Ratio			Odds Ratio
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
37.6.6 Cohort						
Lindberg 1999	1.9054	0.6645	16.7%	6.72 [1.83, 24.72]	1999	
Stolwijk 2013	1.143	0.8109	11.2%	3.14 [0.64, 15.37]	2013	
Subtotal (95% CI)			27.9%	4.95 [1.81, 13.55]		
Heterogeneity: Tau ^z :	= 0.00; Chi ² = 0.53,	df = 1 (P	= 0.47); P	²=0%		
Test for overall effect	: Z = 3.11 (P = 0.00)	2)				
37.6.10 Case-contro	d					
Shetty 1999	1.8061	0.4013	45.8%	6.09 [2.77, 13.36]	1999	_
Bergeron 2010	0.865	0.5305	26.2%	2.38 [0.84, 6.72]	2010	
Subtotal (95% CI)			72.1%	4.05 [1.63, 10.11]		
Heterogeneity: Tau ² =	= 0.22; Chi ² = 2.00,	df = 1 (P	= 0.16); P	²= 50%		
Test for overall effect	: Z = 3.00 (P = 0.00	3)				
Total (95% CI)			100.0%	4.49 [2.64, 7.64]		-
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2.58,	df = 3 (P	= 0.46); l ^a	²=0%	_	
Test for overall effect	: Z = 5.53 (P < 0.00	001)				0.1 0.2 0.5 1 2 5 10 Protective factor Risk factor
Test for subgroup dif	fferences: Chi² = 0.0	08. df = 1				

Supplementary figure 41C.2: Forest plot Thiopurines of univariable OR cohort and case-control studies pooled



Supplementary figure 41C.3: Forest plot 5-ASA of univariable OR cohort and casecontrol studies pooled

				Odds Ratio			Odds Ratio		
Study or Subgroup	log[Odds Ratio]	SE	Weight	IV, Random, 95% Cl	Year		IV, Random, 95	% CI	
37.8.7 Cohort									
Lindberg 1999 Subtotal (95% CI)	1.9054	0.6645	24.5% 24.5 %	6.72 [1.83, 24.72] 6.72 [1.83, 24.72]	1999		-		
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z = 2.87 (P = 0.004	4)							
37.8.10 Case-control	I								
Rutter 2004	0.7389	0.7107	23.6%	2.09 [0.52, 8.43]	2004				
Siegel 2006	-0.7907	0.7228	23.4%	0.45 [0.11, 1.87]	2006				
Bergeron 2010 Subtotal (95% CI)	-0.6506	0.4523	28.6% 75.5 %	0.52 [0.22, 1.27] 0.73 [0.31, 1.75]	2010				
Heterogeneity: Tau ² =	0.22; Chi ² = 3.16,	df = 2 (P	= 0.21); l ^a	²= 37%					
Test for overall effect:	Z = 0.70 (P = 0.49)								
Total (95% CI)			100.0%	1.31 [0.37, 4.58]					
Heterogeneity: Tau ² =	: 1.22; Chi ² = 12.46	, df = 3 (F	^o = 0.006)); I² = 76%		0.05	n2 1		20
Test for overall effect:	Z = 0.42 (P = 0.67)					0.05		5 factor	20
Test for subgroup differences: Chi² = 7.68, df = 1 (P = 0.006), l² = 87.0%								i si e ce l	

Supplementary figure 41D: Forest plot of univariable HR cohort studies, pooled analysis

Study or Subgroup	log[Hazard Ratio]	ee.	Mojaht	Hazard Ratio IV, Random, 95% Cl	Voor	Hazard Ratio IV, Random, 95% Cl
37.15.3 Post-inflamn		30	weight	iv, Ranuom, 95% Ci	real	IV, Randolli, 95% Ci
de Jong 2019		0.4609	33.6%	1.92 [0.78, 4.75]	2019	_
Mahmoud 2019		0.3275	66.4%	1.56 [0.82, 2.96]		
Subtotal (95% CI)			100.0%	1.67 [0.99, 2.82]		
Heterogeneity: Tau ² = Test for overall effect:		7=1 (P=	0.71); l² =	:0%		
37.15.4 Male sex	,					
Stolwijk 2013	0.3067	0.4257	29.9%	1.36 [0.59, 3.13]	2013	_
Kishikawa 2018	0.2852	0.52		1.33 [0.48, 3.69]		
Mahmoud 2019		0.3292		1.77 [0.93, 3.38]		_
Subtotal (95% CI)			100.0%	1.55 [0.98, 2.44]	2010	
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.35, dt	= 2 (P =	0.84); l ² =			
Test for overall effect:						
37.15.5 Disease exte	ent					
Kishikawa 2018	1.0661	0.6565	44.9%	2.90 [0.80, 10.52]	2018	
Mahmoud 2019	-0.5741			0.56 [0.26, 1.22]		
Subtotal (95% CI)			100.0%	1.18 [0.24, 5.82]		
						0.2 0.5 1 2 5 Protective factor Risk factor
				2		

Supplementary figure 41E: Forest plot of univariable HR cohort studies, no pooled analysis

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Random, 95% Cl	Year	Hazard Ratio IV, Random, 95% Cl
37.6.1 Coecum reach					
Mahmoud 2019	-2.4079	1.1211	0.09 [0.01, 0.81]	2019	←
37.6.2 IBD-duration p	er 1 vear increase				
Beaugerie 2013		0.0253	1.01 [0.96, 1.06]	2013	+
-					
37.6.6 Age at IBD diag					
Kishikawa 2018	-1.4355	0.6452	0.24 [0.07, 0.84]	2018	
37.6.7 Thiopurines					
Mahmoud 2019	-0.3534	0.327	0.70 [0.37, 1.33]	2019	+
					C .
37.6.8 5-ASA	0.0074	0 5004	2 42 10 75 7 001	204.0	
Mahmoud 2019	0.0071	0.5994	2.43 [0.75, 7.86]	2019	
37.6.9 Family history	CRC				
Mahmoud 2019	0.8412	0.4773	2.32 [0.91, 5.91]	2019	
37.6.10 IBD type					
Mahmoud 2019	-0.3268	0 3203	0.72 [0.38, 1.35]	2010	
Marinioda 2013	-0.3200	0.0200	0.72 [0.00, 1.00]	2013	
37.6.11 LGD					
Mahmoud 2019	1.7783	0.3367	5.92 [3.06, 11.45]	2019	
37.6.12 Histologic inf	lammation				
Mahmoud 2019	0.8755	0 1 9 7 4	2.40 [1.63, 3.53]	2019	
	0.0100	00	1.10[1.00]0.00]	2010	
37.6.13 Coecum read					
Mahmoud 2019	-2.3838	1.1334	0.09 [0.01, 0.85]	2019	←↓
37.6.14 Adequate bo	wel preparation at b	aseline			
Mahmoud 2019	0.2231		1.25 [0.27, 5.79]	2019	
37.6.15 Number of ac					
Mahmoud 2019	-0.0834	0.0842	0.92 [0.78, 1.09]	2019	
37.6.16 IND					
Mahmoud 2019b	2.1552	0.5761	8.63 [2.79, 26.69]	2019	i →
27647800	un voillon oc				
37.6.17 Age at first st Stolwijk 2013		0.0155		2012	
3101WIJK 2013	U	0.0100	1.00 [0.97, 1.03]	2013	
37.6.18 Statin use					
Shah 2019	0.0849	0.7506	1.09 [0.25, 4.74]	2019	
					0.1 0.2 0.5 1 2 5 10
					Protective factor Risk factor

Supplementary figure 41E: Forest plot of multivariable HR cohort (and case-control study if mentioned), pooled analysis possible

Study or Subgroup	log[Hazard Ratio]	6E	Moight	Hazard Ratio IV, Random, 95% Cl	Vear	Hazard Ratio IV, Random, 95% Cl
37.3.3 Male sex	ισθίμαται η κατιοί	36	weight	IV, Rahuom, 95% Ci	Teal	
Stolwijk 2013	0.3784	0.4337	22.1%	1.46 [0.62, 3.42]	2013	
Beaugerie 2013		0.3833	28.3%	1.63 [0.77, 3.46]		
Kishikawa 2018	0.2852	0.52	15.4%	1.33 [0.48, 3.69]		
Mahmoud 2019	0.6729	0.3485	34.2%	1.96 [0.99, 3.88]	2019	
Subtotal (95% CI)			100.0%	1.64 [1.10, 2.45]		◆
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.50, df	= 3 (P =	0.92); l² =	:0%		
Test for overall effect	: Z = 2.43 (P = 0.01)					
37.3.7 Post-inflamm	atory polyps					
de Jong 2019	0.2258	0.5578	28.2%	1.25 [0.42, 3.74]	2019	
Mahmoud 2019	0.157	0.3493	71.8%	1.17 [0.59, 2.32]	2019	
Subtotal (95% CI)			100.0 %	1.19 [0.67, 2.13]		
Heterogeneity: Tau ² =	= 0.00; Chi ² = 0.01, df	= 1 (P =	0.92); l² =	:0%		
Test for overall effect	: Z = 0.60 (P = 0.55)					
37.3.8 Disease exter	nt					
Stolwijk 2013	2.6034	1.0228	18.2%	13.51 [1.82, 100.29]	2013	
Kishikawa 2018	0.9322	0.6799	32.5%	2.54 [0.67, 9.63]		
Mahmoud 2019	0.5988	0.4592	49.2%	1.82 [0.74, 4.48]	2019	+
Subtotal (95% CI)			100.0%	2.92 [1.12, 7.65]		
Heterogeneity: Tau ² =	= 0.28; Chi ² = 3.20, df	= 2 (P =	0.20); l² =	: 37%)
Test for overall effect	: Z = 2.18 (P = 0.03)					
37.3.15 Family histor	ry CRC (2010 case-c	ontrol, 20	019 coho	rt)		
Bergeron 2010	-0.6506	0.4523	50.5%	0.52 [0.22, 1.27]	2010	
Mahmoud 2019	0.8412	0.4773	49.5%	2.32 [0.91, 5.91]	2019	+ e
Subtotal (95% CI)			100.0 %	1.09 [0.25, 4.71]		
Heterogeneity: Tau ² = Test for overall effect		'= 1 (P =	0.02); l² =	: 81%		
	•					
						Protective factor Risk factor

Supplementary figure 41F: Forest plot of multivariable HR cohort and case-control studies, no pooled analysis

Study or Subgroup	log[Hazard Ratio]	SE	Hazard Ratio IV, Random, 95% Cl	Year	Hazard Ratio IV, Random, 95% CI
37.1.1 Coecum reac			, , , , , , , , , , , , , , , , , , , ,		, , , , , , , , , , , , , , , , , , , ,
Mahmoud 2019	-2.4079	1.1211	0.09 [0.01, 0.81]	2019	<
37.1.2 IBD-duration p	er 1 year increase				
Beaugerie 2013	0.0087	0.0253	1.01 [0.96, 1.06]	2013	+
37.1.4 IBD type					
Beaugerie 2013	-0.0045	0.4097	1.00 [0.45, 2.22]	2013	
37.1.5 Thiopurine the	erapy (ongoing versu	ıs never	received)		
Beaugerie 2013	-1.2622	0.5846	0.28 [0.09, 0.89]	2013	
37.1.6 Age at first su	rveillance colonosc	ору			
Stolwijk 2013	0.01	0.0154	1.01 [0.98, 1.04]	2013	
37.1.9 Age at IBD dia	gnosis cohort HR m	ultivarial	ole <30yrs vs >30yrs	(=ref)	
Kishikawa 2018	-0.4838	0.5743	0.62 [0.20, 1.90]	2018	
37.1.10 Statin use					
Shah 2019	-0.4507	0.7732	0.64 [0.14, 2.90]	2019	+
37.1.11 LGD					
Mahmoud 2019	-0.3268	0.3203	0.72 [0.38, 1.35]	2019	
37.1.12 Histologic in	flammation				
Mahmoud 2019	0.8755	0.1974	2.40 [1.63, 3.53]	2019	_+
37.1.13 Number of a	dequate surveillance	e colonos	scopies		
Mahmoud 2019b	-0.7133	0.1573	0.49 [0.36, 0.67]	2019	-+
37.1.14 IND					
Mahmoud 2019b	1.9242	0.6876	6.85 [1.78, 26.36]	2019	+
37.1.16 Colon segme	ent resection case-c	ontrol st	tudy		
Bergeron 2010	-0.6506	0.4523	0.52 [0.22, 1.27]	2010	
37.1.17 PSC case-co	ontrol study				
Bergeron 2010	1.5537	0.5724	4.73 [1.54, 14.52]	2010	
					0.1 0.2 0.5 1 2 5 10 Protective factor Risk factor

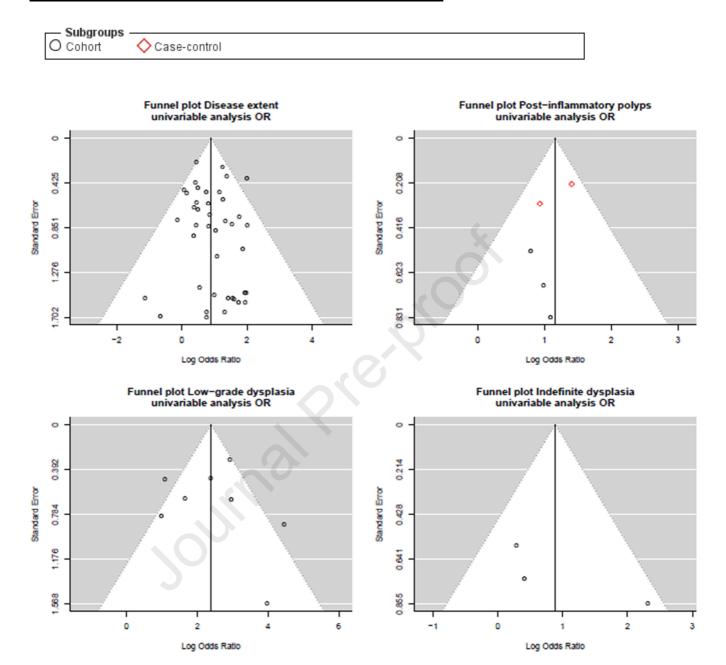
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factor	Index	Reference	N of studies	P-value Egger	N of cohorts	N of case- controls
PSC	PSC	No PSC	32	0.268	15	17
Sex	Male sex	Female sex	60	0.196	58	2
Thiopurine	Thiopurines	No thiopurines	20	0.141	8	12
5-ASA	5-ASA use	No 5-ASA use	20	0.336	6	14
Smoking	Smoking	No smoking	13	0.923	5	8
Family history CRC	Positive family history CRC	No family history CRC	15	0.558	6	9
Disease extent	Extensive disease	No extensive disease	41	0.667	41	0

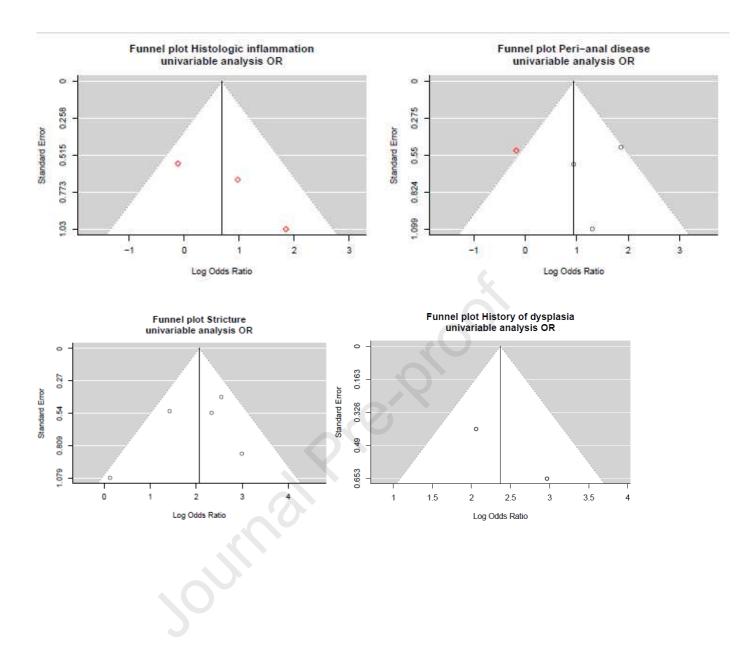
Supplementary file 42: Egger's regression test univariable analysis OR (≥ 10 studies)

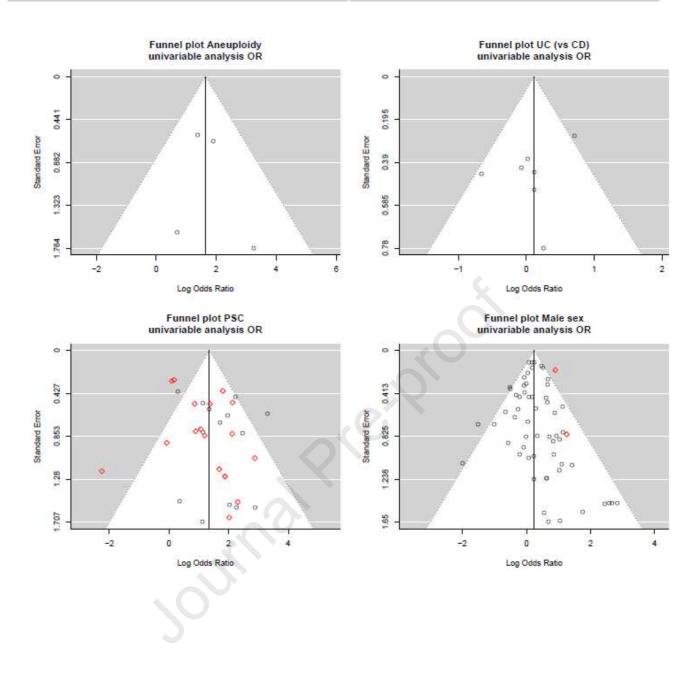
99

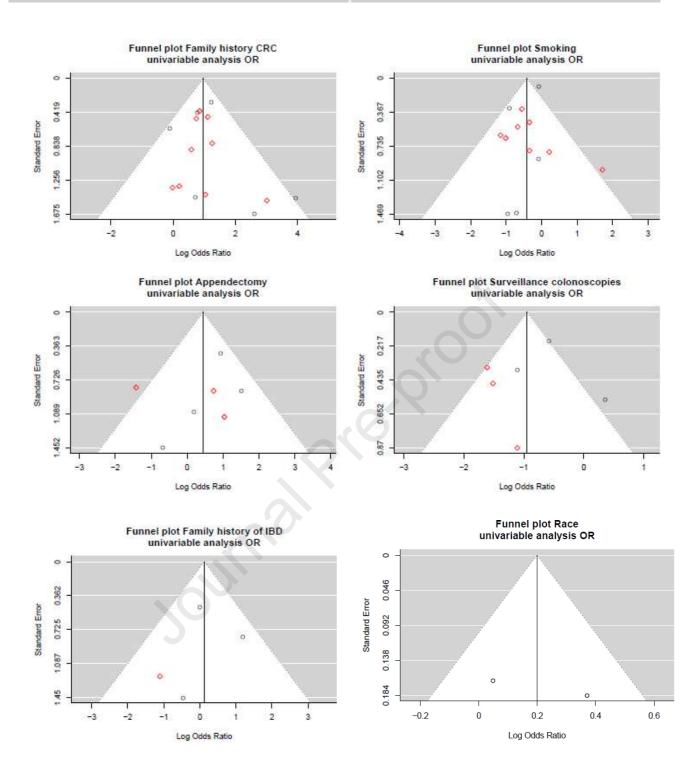


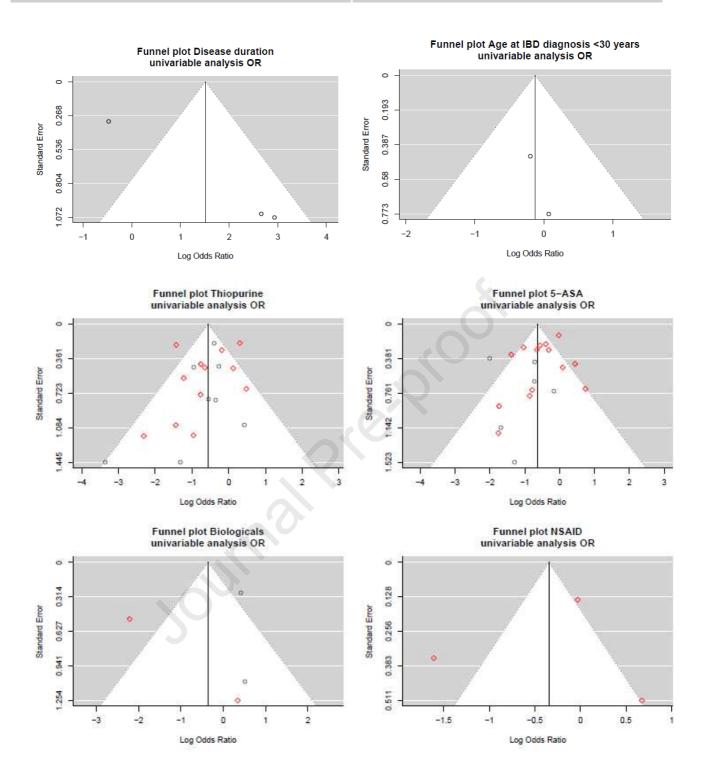


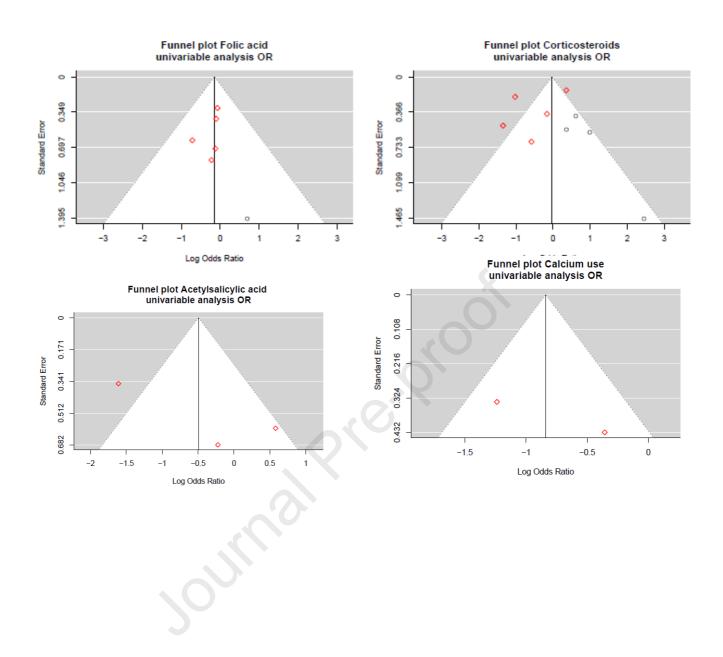
Supplementary file 43: Funnel plot univariable OR analyses











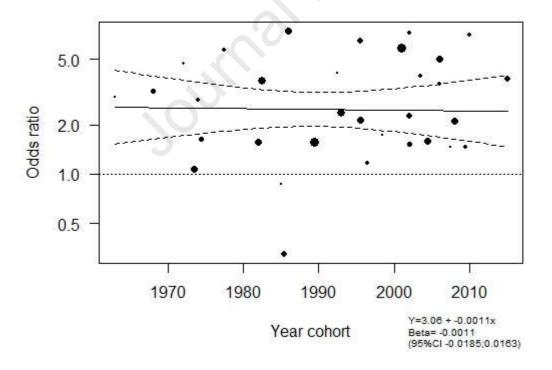
Supplementary file 44A-C: Meta-regression (univariable OR analyses)

Prognostic factor	Test of moderators	Test for residual heterogeneity	Z-value meta-regression model (p- value, 95% Cl)
Disease extent	p .90	p .52	-0.12 (p .90, 95%CI -0.019-0.016)
Thiopurines	p .46	p < .01	-0.75 (p .46, 95%CI -0.046-0.021)
5-ASA	р.95	p < .01	-0.06 (p .95, 95%CI -0.049-0.046)

Supplementary Table 44A: Results meta-regression of calendar time

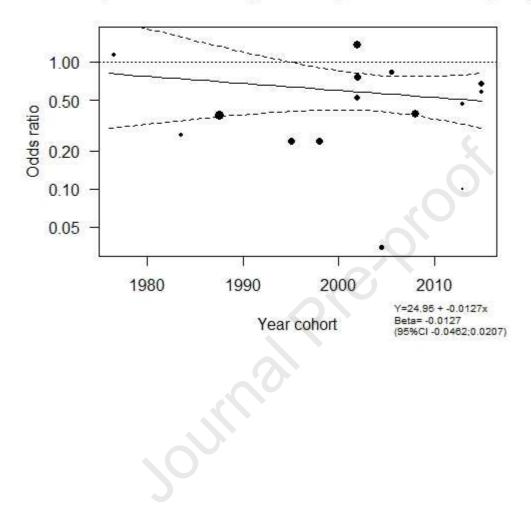
Based on the test of moderators (omnibus test) and meta-regression analyses, we conclude that none of the evaluated prognostic factors displayed statistically significant temporal changes in effect size (supplementary table 44A). Scatterplots in which each study was proportionally sized to the precision of the study indicated a possible reduced risk over time for thiopurines (supplementary figure 44B). The test for residual heterogeneity was significant for thiopurines and 5-ASA, indicating a role for other moderator variables influencing the effect sizes of these prognostic factors.

Supplementary Figure 44A: Disease extent meta-regression (extensive versus limited extent), moderator variable 'year cohort'



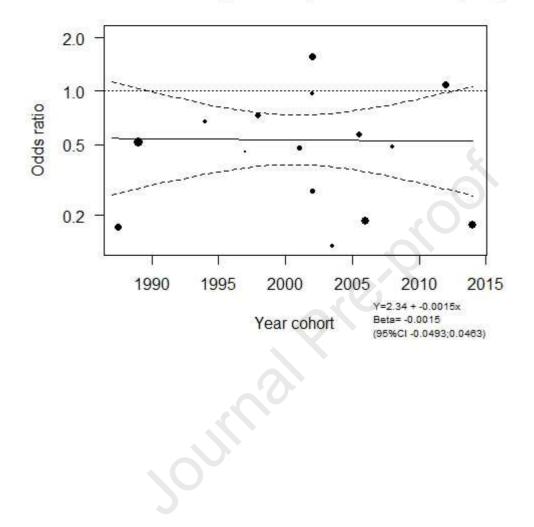
Disease extent meta-regression (univariable data, OR)

Supplementary Figure 44B: Thiopurines meta-regression (yes versus no), moderator variable 'year cohort'



Thiopurines meta-regression (univariable data, OR)

Supplementary Figure 44C: 5-ASA meta-regression (yes versus no), moderator variable 'year cohort'



5-ASA meta-regression (univariable data, OR)

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Supplementary file 45: Summary of identified protective factors for aCRN

We observed that thiopurines protected against the development of aCRN in univariable pooled analyses (OR and HR). This association was not observed in our pooled multivariable analyses (OR and HR). Two^{1,2} out of 3 ¹⁻³ previous metaanalyses on the impact of thiopurines showed similar results as our study. Also, the use of 5-ASA has a protective effect in both pooled univariable and multivariable analyses (OR), in line with two previous meta-analyses. ^{4,5} However, this effect was not observed in univariable and multivariable HR analyses. No previous metaanalysis evaluated the effect of TNF-alpha inhibitors on aCRN or CRC. Our pooled univariable OR analysis did not show a protective effect (OR 0.71, 95% CI 0.14-3.67). One study reported a protective effect in multivariable analysis (HR 0.22, 95% CI 0.10-0.50) ⁶ and one study did not find an association (OR 1.01, 95% CI 0.62-1.65). ⁷ The anti-inflammatory mechanisms of these medications may underlie the lower risk of aCRN. One can speculate that no protective effect was found for TNFalpha inhibitors as a result of selection bias, as patients who use anti-TNF are generally the patients with a more severe disease.

One can speculate that the protective effect of smoking in the pooled univariable OR analysis (0.66, 95% CI 0.49-0.91) is related to the anti-inflammatory effect of smoking in UC patients.⁸ In our pooled multivariable analysis we did not observe any association (OR 1.27, 95% CI 0.75-2.13).

In accordance with a recent meta-analysis reporting a lower CRC risk in IBD patients undergoing surveillance (OR 0.58, 95% CI 0.42-0.80)⁹, we found surveillance colonoscopies to be protective for the development of aCRN (univariable OR 0.39,

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95% CI 0.23-0.66). It should be noted that the definitions used in the included studies varied widely (supplementary file 15E).

In contrast to a previous meta-analysis (pooled OR 3.97, 95% CI 1.35-11.70)¹⁰, we did not observe an association between appendectomy and subsequent development of aCRN in 7 studies (6 studies in UC patients). This difference may be explained by the different selection of studies. We identified additional studies and we excluded cohorts that included only patients who had received a proctocolectomy. We excluded 'proctocolectomy only' cohorts since these cohorts do not represent the general IBD population, but generally patients with more severe disease or patients who had severe dysplasia.

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Supplementary file 46: References from included studies (from supplementary file 3 and 5)

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