This article has been accepted for publication in FLGASTRO following peer review.
The definitive copyedited, typeset version is available online at
10.1136/flgastro-2025-103409

Reduced Risk of Colorectal Cancer with non-sulfasalazine 5-ASAs in ulcerative colitis and Crohn's disease and Anti-TNF therapy in ulcerative colitis: A Systematic Review and Meta-analysis**.**

Short title: Association of IBD medications on colorectal cancer risk in patients with IBD.

Authors: Amirhosein Kefayat[1,2], Ross J. Porter[3,4], Antonia M.D. Churchhouse[1,2], Jonathan Blackwell[2], Eleanor F. Watson[2], A. John Morris[4], Morris Gordon[5], Gaurav B. Nigam[6], James E. East[6], Matthew D. Rutter[7,8], Christopher A. Lamb[9,10], Tim Raine[11], Alexander C. Ford[12,13], Shahida Din[1,2]

[1]Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, United Kingdom.

[2]Edinburgh Inflammatory Bowel Diseases Unit, Western General Hospital, Edinburgh, United Kingdom.

[3]School of Cancer Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, United Kingdom.

[4]Department of Gastroenterology, Queen Elizabeth University Hospital, Glasgow UK.

[5]School of Medicine, University of Central Lancashire, Preston, Lancashire, UK.

[6]Translational Gastroenterology Unit, Nuffield Department of Medicine, John Radcliffe Hospital, University of Oxford, Oxford, UK.

[7]Department of Gastroenterology, North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees, UK

[8]Faculty of Medical Sciences, Newcastle University, Newcastle-upon-Tyne, UK

[9]Translational & Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK.

[10]Gastroenterology, Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, UK.

[11]Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Trust, Cambridge, UK.

[12]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, United Kingdom.

[13]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, United Kingdom.

Grant Support: None.

Abbreviations:

5-ASAs	5-Aminosalicylates
CD	Crohn's disease
CI	confidence intervals
CRC	colorectal cancer
IBD	inflammatory bowel disease
IBD-U	inflammatory bowel disease-unclassified
NOS	Newcastle-Ottawa scale
RCT	randomised controlled trial

RR	relative risk
UC	ulcerative colitis

Correspondence: Dr Shahida Din

Edinburgh Inflammatory Bowel Diseases Unit

Level 1 Anne Ferguson Building

Western General Hospital

Crewe Road South

Edinburgh

United Kingdom

Email: sdin@ed.ac.uk

Telephone +44 (0) 131 537 1758

ORCID ID: 0000-0003-2855-3400

X: @ShahidaDin1

Disclosures:

Amirhosein Kefayat nothing to disclose

Ross J. Porter is funded by a Cancer Research UK Fellowship and reports travel and meeting support from Dr Falk and Janssen.

Antonia MD. Churchhouse reports funding by Wellcome Trust, Royalties from Elsevier, and reports travel and meeting support from Takeda.

Jonathan M. Blackwell reports honoraria or speaker fees from Ferring, Dr Falk, Pfizer and consulting, travel, and meeting support from Takeda.

Eleanor F. Watson reports meeting and travel support from Galapagos and Ferring.

A.John Morris reports honoraria or speaker fees from Astrazeneca and travel and meeting support from Tillotts.

Morris Gordon nothing to disclose

Gaurav B, Nigam is funded by an NIHR Fellowship.

James E. East is Chair of the BSG IBD colorectal surveillance guideline update 2024 working group and reports honoraria or speaker fees from Dr Falk and Janssen.

Matthew D. Rutter is Chair, Joint Advisory Group for Gastrointestinal Endoscopy and Member, British Society of Gastroenterology Endoscopy committee.

Christopher A. Lamb was Secretary of the Inflammatory Bowel Disease Section Committee of the British Society of Gastroenterology 2021 to 2024; sits on the Steering Committee and Board of IBD UK, acknowledges research support from the NIHR Newcastle Biomedical Research Centre, Medical Research Council, The Leona M. and Harry B. Helmsley Charitable Trust, Crohn's & Colitis UK, EU Innovative Medicines Initiative, Wellcome Trust, Open Targets, European Bioinformatics Institute (EMBL-EBI), Janssen, Takeda, Abbvie, AstraZeneca, Eli Lilly, Orion, Pfizer, Roche, Sanofi Aventis, UCB, Biogen, Genentech, Bristol Myers Squibb (BMS), GSK and Merck Sharp and Dohme (MSD); has undertaken consultancy for Janssen and BMS; has received honoraria for development and / or delivery of education from Takeda, Ferring, Janssen, Dr Falk, and Nordic Pharma; and

has received conference attendance support from Tillotts Pharma UK, Janssen, British Society of Gastroenterology (BSG), International Organisation of IBD (IOIBD) and the European Crohn's & Colitis Organisation (ECCO).

Tim Raine is on the ECCO and UEG scientific committee board, reports grants from Abbvie, personal consulting fees from Abbvie, Alfasigma, Arena, Aslan, AstraZeneca, Boehringer-Ingelheim, BMS, Eli Lilly, Ferring, Galapagos, Gilead, GSK, Heptares, LabGenius, MonteRosa, Novartis, Numab, Janssen, Pfizer, Roche, Takeda, UCB and XAP therapeutics, and participation in UCB data safety monitoring board.

Alexander C. Ford reports grants from Tillotts Pharma.

Shahida Din is Chair of British Society of Gastroenterology Inflammatory Bowel Disease Committee; Scottish Government Lead for Inflammatory Bowel Disease Cancer Surveillance,

The Royal College of Physicians of Edinburgh Gastroenterology Specialty Advisor and MHRA Gastroenterology, Rheumatology, Immunology & Dermatology Expert Advisory Group. Reports grants from The Helmsley Charitable Trust, Edinburgh and Lothians Health Foundation, Pathological Society of Great Britain and Northern Ireland, and Lord Leonard and Lady Estelle Wolfson Foundation; consultant to Abbvie, honoraria or speaker fees from Janssen, Takeda, Ferring, and Abbvie and meeting and travel grants from Abbvie, Janssen, Takeda, Lilly, and Dr Falk.

Writing assistance: None

Specific Authorship Statements:

SD, ACF and AK conceived and drafted the study. AK and SD literature search and all data collection. ACF analysed the data; AK, ACF and SD, interpreted the data. AK & SD and ACF drafted the manuscript. All authors critically reviewed and approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data Sharing Statement

Study level data are already in the public domain, but we would consider reasonable requests to share the trial level data we extracted with others. No other data are available. The protocol for this systematic review and meta-analysis is available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024559501 and was update on 15 March 2025.

Guarantor: SD is guarantor.

Word count: 4344

ABSTRACT

Objective: The incidence of colorectal cancer remains elevated in the inflammatory bowel disease population. We aimed to examine the association of biologics, 5-aminosalicylates, and immunomodulators with the risk of colorectal cancer and/ or dysplasia (CRC/Dys) in different IBD phenotypes.

Methods: We searched Web of Science, PubMed, MEDLINE, and EMBASE from inception to 15th March 2025 for all studies assessing the association of biologics, 5-aminosalicylates and immunomodulators on the occurrence of CRC/Dys in adults (≥16years) with IBD. No RCTs were identified. Data were pooled using a random effects model generating relative risk (RR) estimates. The protocol was registered on PROSPERO (CRD42024559501).

Results: Fifty observational studies containing 29,325 cases of CRC/Dys in 1,434,939 patients with IBD were included. Biologic therapies (RR 0.74; 95% CI 0.64-0.85, I^2=56.8%) and 5-ASAs (RR 0.78; 95% CI 0.70-0.86, I^2=52.1%) were associated with a reduced risk of CRC/Dys in patients with IBD. Immunomodulators were not associated with a reduced risk (RR 0.92; 95% CI 0.82-1.02, I^2=82.7%). After stratification for IBD phenotypes, medication subgroups, and CRC outcome, anti-TNF therapies were associated with a reduced risk of CRC in patients with ulcerative colitis (RR 0.78; 95% CI 0.73-0.83, I^2=0%) but not in Crohn's disease. Non-sulfasalazine 5-ASAs were associated with a reduced risk of CRC in ulcerative colitis (RR: 0.66; 95% CI 0.45-0.96, I^2=75.4%) and Crohn's disease (RR: 0.84; 95% CI: 0.81-0.87, I^2=41.9%).

Conclusion: Use of anti-TNF biologics or non-sulfasalazine 5-ASAs are associated with a reduction in colorectal cancer risk in IBD, with differential effects by IBD phenotype.

Key words: Inflammatory bowel disease, 5-Aminosalicylates, Biologics, Immunomodulators Colorectal cancer.

Key Messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Patients with inflammatory bowel disease (IBD) have a higher risk of colorectal cancer (CRC), but the chemopreventive effects of commonly used IBD therapies remain uncertain.

WHAT THIS STUDY ADDS

- This study shows that anti-TNF biologics and non-sulfasalazine 5-ASAs are associated with a significantly reduced risk of CRC in ulcerative colitis and non-sulfasalazine 5-ASAs are associated with reduced risk of CRC in Crohn's disease. Immunomodulators were not associated with CRC risk reduction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These findings may guide evidence-based treatment strategies, inform cost-effective care, and highlight the need for randomised trials assessing impact of IBD therapies on the risk of CRC.

INTRODUCTION

Patients with colonic inflammatory bowel disease (IBD) have an increased relative risk of colorectal cancer (CRC), estimated to be 1.4 to 1.7 times higher than the general population [1]. This risk has steadily decreased over time, which may reflect better cancer surveillance strategies and / or more effective disease modifying therapies. CRC screening programmes in IBD remain suboptimal, and several key areas for improvement have been proposed recently [2 3]. The cumulative impact of chronic active inflammation is a predictable risk factor associated with the development of colorectal cancer [4]. Durable control of

inflammation is associated with improved quality of life, fewer hospitalisations, and reduced need for surgery [5] and the reduction in colorectal cancer remains uncertain.

The direct impact of specific immunosuppressive therapies on cancer pathways and risk will remain an evolving field due to the high attrition rate of individual therapies [6], novel discoveries in immune pathogenesis [7 8], the dynamic mutational landscape, and the absence of an accurate multimodal cancer risk prediction models for IBD [9]. The absolute cancer risk is low and, therefore, conventional short term randomised controlled trials (RCTs), long-term extension studies, or observational registries insufficiently powered to determine cancer occurrence [10 11]. Large scale population-based studies describe time dependent trends [12], although these are limited by restrictive data validation at an individual patient level. Moreover, cancer risk increases independently with age and, with an ageing population of patients with IBD [13], the interaction of other risk factors is unknown. CRC risk is unevenly distributed in patients with IBD and patients with more severe and extensive disease have greater risk, whereas others may have no increased risk compared with the general non-IBD population [2].

Chemoprevention refers to the use of a drug or substance to lower individual cancer risk or prevent future cancer reoccurrence. However, no RCTs have been conducted in patients with IBD to assess the impact of chemopreventive medications. The impact of 75 mg of aspirin daily on cancer risk is currently being tested in a placebo-controlled trial in patients with IBD with concomitant primary sclerosing cholangitis over a 5-year period [https://www.isrctn.com/ISRCTN12358813].

The chemoprevention of 5-aminosalicylates (5-ASAs) is well-established. However, there has been an exponential rise in the use of advanced therapies. The American Gastroenterology Association [18] and the British Society of Gastroenterology guidelines [19]

suggest discontinuation of 5-ASAs therapy in patients with moderate to severe ulcerative colitis once remission has been achieved using advanced therapies, but this is based on the risk of flare, and any association of advanced therapies and CRC has not been established. The BSG IBD CRC surveillance guidelines suggest a protective effect of 5-ASAs when used as the sole therapy for the management of UC [3]. In addition, these organizations also recommend against the use of 5-ASAs for induction or maintenance therapy in moderate to severe CD [20] [21]. A current research gap is whether 5-ASAs have an additional chemopreventive effect when used in combination with advanced therapies in UC or CD. A previous systematic review assessed the association of tumour necrosis factor-α inhibitors in seven studies, containing around 27,000 patients [4]. It did not demonstrate any associated chemoprevention with these drugs and in the intervening 3 years more observational studies have been published. It is crucial to understand if advanced therapies also reduce the risk of CRC to inform current practice as to whether to continue 5-ASAs in combination with these drugs or not.

In this study, we examined the association between biologics, 5-ASAs, and immunomodulators and risk of CRC and/or dysplasia in patients with IBD in a contemporaneous systematic review and meta-analysis. The comprehensive stratification demonstrates a differential cancer risk reduction in patients with IBD and defining the cohort who may benefit from potential chemopreventive approaches is an unmet need in IBD-CRC management.

METHODS

Data Sources and Search Strategy

An electronic search of the literature was performed using Web of Science, PubMed, MEDLINE, and EMBASE from inception to 15th March 2025, to assess the association of treatment with 5-ASAs, immunomodulators (azathioprine, mercaptopurine and methotrexate only) or biologics on the risk of developing CRC and/ or colonic dysplasia (CRC/Dys) among patients with IBD. The applied medical subject headings or free text terms used in the research are included in the supplementary material.

The primary outcome was the occurrence of CRC and dysplasia in patients with IBD stratified by medication type (biologics, 5-ASA, and immunomodulators). Secondary analyses included subgroup comparisons evaluating the association of different medication classes (e.g., anti-TNFs, non-sulfasalazine 5-ASAs, immunomodulators) and different outcomes including CRC or CRC and/or dysplasia, stratified by IBD phenotype (UC or CD), study design, quality, and adjustment for confounders.

The primary outcome was defined as the occurrence of colorectal cancer (CRC) and/or colonic dysplasia. For consistency, we refer to this composite outcome throughout as 'CRC/Dys.' Studies reporting CRC alone, dysplasia alone, or a combined endpoint (CRC with dysplasia) were all included under this definition. In pooled analyses (Table 1), these outcomes were grouped together as 'CRC/Dys.' To explore whether outcome definition influenced results, we conducted stratified analyses (Table 2) where studies reporting CRC alone or combined CRC/dysplasia were analysed separately. Thus, the term 'CRC/Dys' always refers to the composite endpoint unless otherwise specified, while 'CRC' or 'dysplasia' denote studies reporting these outcomes individually.

The study protocol was registered with the International Prospective Register of Systematic Reviews (CRD42024559501) on 26/09/2024 date for the BSG colorectal cancer guidelines [3] and the search was updated on 15th March 2025. The meta-analysis was performed in accordance with the MOOSE and PRISMA checklists [22].

Study Selection

Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia; www.covidence.org) was used and two investigators (SD and AK) evaluated all titles and abstracts of studies identified in the search independently. Duplicate records were identified and removed using Covidence's automated duplicate detection algorithm. Studies that did not meet inclusion criteria were excluded (Supplemental Figure S1). A recursive search of eligible articles' bibliographies and previously published systemic reviews was also performed (Table 3) [4]. No RCTs were identified in this search. Observational studies, including case-control or cohort studies investigating any exposure to 5-ASAs, immunomodulators, or biologics and reporting risk estimates (odds ratio (OR), relative risk (RR), or hazard ratio (HR)) for the occurrence of CRC and / or colonic dysplasia according to whether or not there had been exposure to these drugs were included. If more than one article was published using the same institution and/or registry, only data from the most recent article was included. Any disagreements between investigators were resolved by discussion.

Data Extraction and Quality Assessment

Two investigators (SD and AK) extracted all data from fully published eligible studies independently onto a Microsoft Excel spreadsheet. We extracted the adjusted OR, RR, or HR, with 95% CIs for the occurrence of CRC or dysplasia, wherever possible. For studies where the adjusted OR, RR, or HR were not reported, we used the unadjusted OR, RR, or HR, depending on study reporting, with 95% CIs. If risk estimates were unavailable, these were calculated by the investigators using the raw data extracted from the individual study. Given that the absolute risk of CRC or dysplasia in the included populations was generally low (i.e., <10%), we applied the rare disease assumption, which permits the approximation of ORs,

RRs, or HR due to their convergence under low event rates [23]. This approach allowed us to pool these effect measures as comparable estimates. If the risk of the event were >10%, this approximation would no longer be valid. Additional data fields extracted are included in the supplementary material.

The Newcastle-Ottawa scale (NOS) was utilised to assess the quality of included studies (please see the supplementary data 2), with a score of ≥6 considered to represent higher quality [24]. Discrepancies in data extraction were resolved by discussion among investigators.

Data Synthesis and Statistical Analysis

A DerSimonian and Laird inverse variance random effects model was utilised to pool risk estimates with 95% CIs from individual studies, which was done using StatsDirect version 3.3.6 (StatsDirect Ltd, Sale, Cheshire, England). The association between biologics, 5-ASAs, or immunomodulators and CRC or dysplasia were expressed as RRs with 95% CIs, where if the RR was less than 1 and the 95% CIs did not cross 1, there was a significantly reduced risk of CRC or dysplasia. Additional subgroup analysis undertaken are included in supplementary material.

The Cochrane Q and I^2 statistics were utilised to assess statistical heterogeneity between studies. A *P* value <0.10 was used to define a significant degree of heterogeneity. The I^2 statistic ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and ≥75% high heterogeneity [25]. The Egger test was applied to funnel plots to assess for possible publication bias, or other small study effects, with a *P* value <0.05 used to indicate statistically significance, where there were sufficient studies (≥10) [26 27].

3. RESULTS

Fifty studies containing 29,325 cases of CRC/Dys in 1,434,939 patients with IBD met the predefined eligibility criteria and were included (Figure S1) [28-77]. The data from 11, 32, and 34 studies were pooled for biologics, 5-ASAs, and immunomodulators, respectively including 43 case-control and 34 cohort studies. Detailed characteristics of the pooled studies for each medication group are provided in the Supplementary Tables 2, 3, and 4. Overall, 38 out of 50 studies were high-quality according to the NOS scoring system. Nineteen, sixteen, and eight studies provided an adjusted OR, RR, or HR (controlling for different confounding variables including age, disease extent, drug type and dosage, degree of inflammation, and disease duration) for 5-ASAs, immunomodulators, and biologics, respectively.

Association of medications and IBD Phenotype on risk of CRC and/or Dysplasia

Biologics

In the pooled analysis of 11 IBD studies with 8,721 cases of CRC/Dys in 447,637 patients with IBD (Supplementary Table 2), biologics (infliximab, adalimumab, certolizumab, golimumab & anti-integrins) were associated with a reduced risk of CRC/Dys in patients with IBD (RR 0.74; 95% CI 0.64 to 0.85, I^2=56.8%) (Table 1). There was moderate heterogeneity between these studies (I^2=56.8%, P =0.005) but no evidence of publication bias (Egger test P=0.99). When separated by type of biologic (Table 1) in the pooled analysis anti-TNF alone demonstrated a reduction in risk (RR 0.72; 95% CI 0.62 to 0.84, I^2=66.8%); while studies reporting combined data for anti-TNF and anti-integrin (RR 1.00; 95% CI 0.53 to 1.89, I^2=0%) did not. Data was then analysed by IBD phenotype. In the UC studies with 4,254 cases of CRC/Dys in 212,522 patients the reduction in CRC/Dys risk was retained (RR 0.78; 95% CI 0.74 to 0.84, I^2=0%) with a similar reduction (RR 0.69; 95%

CI 0.66 to 0.72, I^2=0%) in the CD studies with 3,769 cases of CRC/Dys in 235,637 patients (Table 1). For the subgroup analysis by IBD phenotype and biologic type, only the studies reporting UC and anti-TNFs had a reduction in CRC/Dys risk (RR 0.78; 95% CI 0.73 to 0.83, I^2=0%) with low heterogeneity and no evidence of publication bias (Egger test P=0.12), or other small study effects.

5-ASAs

Overall, in the pooled analysis of 32 IBD 5-ASAs studies containing 9,847 cases of CRC/Dys in 462,408 patients with IBD (Supplementary Table 3), 5-ASAs were associated with a reduced risk of CRC/Dys in patients with IBD (RR 0.78; 95% CI 0.70 to 0.86; Table 1). There was moderate heterogeneity between studies (I^2=52.1%, P=0.0002), but no evidence of publication bias (Egger test, P=0.11) or other small study effects. When separated by type of 5-ASAs (studies that reported mixed sulfasalazine and non-sulfasalazine 5-ASA data were excluded) in the pooled IBD analysis only those with non-sulfasalazine 5-ASAs demonstrated a reduction in CRC/Dys risk (RR 0.80; 95% CI 0.74 to 0.88, I^2=41.9%); while studies reporting data for sulfasalazine (RR 0.52; 95% CI 0.21 to 1.29, I^2=74.7%) did not. Data was then analysed separately for IBD phenotypes and the reduction in CRC/Dys risk was retained for both UC studies with 8,551 cases of CRC/Dys in 446,032 IBD patients (RR 0.59; 95% CI 0.45 to 0.78, I^2=65.9%) and CD studies with 3,741 cases of CRC/Dys in 240,435 IBD patients (RR 0.84; 95% CI 0.81 to 0.87, I^2=0%) (Table 1). For the subgroup analysis by IBD phenotype and 5-ASAs type, non-sulfasalazine 5-ASAs reduced risk of CRC/Dys for both UC (RR 0.64; 95% CI 0.48 to 0.84, I^2=58.6%) and CD (RR 0.84; 95% CI 0.81 to 0.87 I^2=0%) with no evidence of publication bias or other small study effects.

Immunomodulators

For the 34 immunomodulators studies containing 10,757 cases of CRC in 524,894 patients with IBD (Supplementary Table 4) in the pooled IBD analysis, immunomodulators were not associated with a reduction in risk of CRC/Dys in patients with IBD (RR 0.92; 95% CI 0.82 to 1.02; Table 1). There was high heterogeneity between studies (I^2= 83.1%. P<0.0001), but no evidence of publication bias, or other small study effects (Egger test, P=0.33). Separating the pooled IBD studies by only thiopurines (RR 0.89; 95% CI 0.89 to 1.18, I^2=0%) and other immunomodulators (data combined with methotrexate: RR 0.92; 95% CI 0.82 to 1.04, I^2=87.2%) reduced the heterogeneity; however, no reduction in CRC/Dys risk was seen. Additional subgroup analysis by IBD and IMM type decreased the heterogeneity in between studies while the risk of CRC/Dys was still not significant (Table 1). In the Thiopurine + Methotrexate immunomodulators subgroup (This group represents pooled monotherapy immunomodulator exposure groups rather than simultaneous combination therapy.) composed of two studies included CRC only outcome, the pooled estimated effect showed increased risk of CRC for 28% (RR 1.28; 95% CI 1.16 to 1.43, I^2=8.9%) in UC.

Association of different medications subtypes and IBD phenotypes on risk of CRC alone

Some of the studies in this meta-analysis enrolled only IBD patients with CRC, while others combined CRC and dysplasia (CRC/Dys) as their primary outcome. Given the low concordance in the histopathological interpretation of dysplasia between experts and clinical uncertainty surrounding dysplasia [78], we evaluated how different outcomes (CRC alone vs CRC/Dys) influenced the pooled risk estimates (Table 2). When the pooled estimates for CRC alone, the studies reporting UC and anti-TNFs had a reduction in risk (RR 0.78; 95% CI 0.73 to 0.83, I^2=0%) (Table 2).

For 5-ASAs analysis, studies that reported only data for each medication subgroup were included. There was a reduction in CRC risk in UC studies with sulfasalazine (RR 0.18; 95% CI 0.04 to 0.94, I^2=79.8%) with high heterogeneity. When subcategosizing by non-sulfasalazine 5-ASAs, there was a reduction in CRC risk in UC studies (RR 0.66; 95% CI 0.45 to 0.96, I^2=75.4%) and CD studies (RR 0.84; 95% CI 0.81 to 0.87, I^2=41.9%). For UC studies there was also a reduction in the combined CRC/Dys risk (RR 0.55; 95% CI 0.37 to 0.82, I^2=0%).

The primary analysis by IMM and IBD phenotypes did not demonstrate a reduced risk in the composite outcome of CRC/Dys (Table 1) and similar results were observed for further subgroup analysis (Table 2). Of note, UC studies which reported data for IBD patients taking thiopurines or methotrexate as a subgroup had an increase in CRC risk (RR 1.28; 95% CI 1.16 to 1.43, I^2=8.9%) with low heterogeneity and no evidence of publication bias or other small study effects.

Association of other variables on composite CRC and/or dysplasia risk in UC and CD

Previous meta-analysis' have suggested that other variables such as study setting, study type, adjustment status, quality of studies according to NOS scoring. We further subdivided each medication class for these factors in UC and CD.

For biologics most of the UC and CD data was derived from similar populations this means the overall reduction in overall CRC/Dys risk was the same/similar when separating the data for these variables as evidenced by the low level of heterogeneity (Supplementary Table 5).

In both UC and CD, non-sulfasalzine 5-ASAs have demonstrated a reduction in CRC risk (Table 2) and the reduction in CRC/Dys risk holds when the data are further restricted by

adjustment for other variables (Supplementary Table 6), high quality studies and non-surveillance populations. For UC, there is also a reduced CRC/Dys risk in cohort or hospital-based studies and for CD in population-based studies.

IMM studies as anticipated (Supplementary Table 7) , did not show a reduction in CRC/Dys risk regardless of how the UC or CD studies were separated.

DISCUSSION

Although the occurrence of colorectal cancer in patients with IBD has declined over time, it remains a significant concern committing some patients to long-term surveillance programmes [3]. To date, it has not been possible for the chemoprotective effect of inflammatory bowel disease therapies to be tested in randomised controlled trials and therefore this systematic review and meta-analysis of observational studies assessing the association of biologics, 5-ASAs, or immunomodulators and the occurrence of CRC and dysplasia in patients with IBD is the highest quality evidence to inform modern clinical practice. Cancer risk is not uniformly distributed across the IBD population and this comprehensive stratification revealed important distinctions in chemopreventive association with medication subtypes and IBD phenotypes, reinforcing the need for personalised chemoprevention strategies in IBD.

We found the pooled RR of developing CRC was lower in patients prescribed biologics or 5-ASAs in UC and only non-sulfasalazine 5-ASAs in CD but not in those prescribed immunomodulators. The biologic studies included patients exposed to anti-TNF (infliximab, adalimumab, certolizumab, or golimumab) or other biologics (anti-integrins), and no studies included Janus kinase inhibitors or Ustekinumab. We assessed long-term extension studies for cancer occurrence and only the NCT02118584 trial in patients with UC

previously enrolled in Etrolizumab Phase II/III Studies [11] reported the outcome of 0.06% (1/1773) colon cancer, 0.06% (1/1773) rectal cancer and 0.011% (2/1773) for colonic dysplasia. Biologics are recommended for the induction and maintenance of remission [79 80] and as chronic inflammation is a predictor of cancer risk [4 79 80], it is reasonable to assume that effective control of inflammation is the driver for the reduction in CRC. Conversely, although there is no evidence of an overall increased risk of CRC in patients with IBD treated with biologics, the risk of lymphoma and melanoma remains uncertain [81 82].

The pooled analysis of studies of 5-ASAs is consistent with previous meta-analyses (Table 3). 5-ASAs are recommended for the induction and maintenance of remission for mild to moderate UC [21], but not for CD [83 84]. The reduction in cancer risk with 5-ASAs was lower in both patients with UC and CD (disease location was not specified in the studies) when strict case definition criteria where applied. Gupta *et al.*[46] utilized a histologic activity index to quantify microscopic inflammation over time, demonstrating that increased inflammation scores were associated with a higher risk of advanced neoplasia. However, 5-ASAs chemopreventive effects was neither independently significant, nor did it alter the relationship between inflammation and any neoplasia. Multivariate analysis by Nieminen *et al.* [58] using the same inflammation scoring system as Gupta *et al*, demonstrated independent effect of inflammation to increase risk of CRC but the inter-association with 5-ASAs was not tested. Rubin *et al.*[62] employed a 6-point histologic inflammatory activity scale to evaluate biopsy samples, finding a strong correlation between higher inflammation scores and CRC risk and after adjusting for inflammation, the protective effect of immunomodulators remained significant, while that of 5-ASAs was no longer observed. This suggests that the reduced CRC risk may primarily reflect control of mucosal inflammation rather than a direct chemopreventive effect of the drug itself. The reduction in cancer risk of 5-ASAs may be explained by similar structural homology to aspirin [85]. Although, preclinical studies have

demonstrated that 5-ASAs can directly affect CRC-associated cellular pathways, such as inhibiting COX-2/PGE2 [86], NF-kB, Wnt/β-catenin [87] [88], or EGFR signalling with anti-neoplastic effects [89], similar to aspirin, however this has not been confirmed in human clinical studies

The immunomodulator studies predominantly reported on thiopurine use. The overall association is close to statistical significance and there was a reduced RR in some subgroups, consistent with previous meta-analyses (Table 3). Moreover, moderate to high heterogeneity was detected between studies and, therefore, it is uncertain if the true result demonstrates a chemopreventive benefit or not. Immunomodulators are judiciously recommended in IBD [21] [90] and are also associated with malignancies. The primary objective of many studies included in this meta-analysis was to capture overall malignancy rates and, therefore, they may not have been optimally designed to evaluate CRC risk. It has also not been resolved whether thiopurines can promote CRC which may negate any potential benefits [82]. For these reasons it is not surprising that immunomodulators appear to have no consistent reduction in cancer risk in IBD-CRC.

The therapeutic strategy in IBD is now that of "treat to target" [91], with an escalation to modern, effective therapy earlier in the disease course to minimise long-term complications [92]. When patients with UC have achieved prolonged remission and mucosal healing with immunomodulators, biologics, or Janus kinase inhibitors 5-ASAs can be discontinued without an increase in disease-related adverse events [93-95]. This has led to some societies recommending 5-ASAs withdrawal when on an another more potent IBD therapy is controlling disease activity with a reduced risk of flare [18] [96]. However, these recommendations have not previously accounted for, or considered, any potential chemotherapeutic effects of 5-ASAs independent of disease control, which may be a significant reason to continue them, particularly in higher risk patient populations. While

modern guidelines do not recommend 5-ASAs for the treatment of CD, they appear to be frequently prescribed. The reduction in cancer risk may reflect mild disease activity or that cancer risk is not increased within these groups. The STATIC (Stopping Aminosalicyte Therapy In Inactive Crohn's Disease) Study: A randomised, open label, non-inferiority trial (https://www.static-trial.com/) aims to understand the role of 5-ASAs in the management of CD. Although cancer and dyspepsia are not included as outcomes the occurrence of flares will be recorded which can help to estimate the inflammatory burden.

The current data are, unfortunately, unable to distinguish between an independent chemopreventive association of these drugs and effective control of active inflammation. The included studies examined the medications separately and therefore the combination of medications on cancer risk could not be determined. A similar reduction in risk is demonstrated with biologics or 5-ASAs suggesting this is mediated through a general anti-inflammatory action rather than any additional chemopreventive benefit. The “perfect” RCT for determining the impact of any cancer prevention strategy, including medications or colonoscopic surveillance in the context of effective control of inflammation, is challenged by the low event rate, need for a large number of participants, long duration of follow-up, and potentially unethical approach to withholding active treatment in a population at risk of cancer. The gold standard of CRC colonoscopic surveillance was analysed retrospectively in a Cochrane review of five observational studies with 7,199 patients [97]. The studies found a significantly higher rate of cancer in the no surveillance group compared to the colonoscopy surveillance group. The estimate of the protective effect of colonoscopic surveillance for cancer prevention was greater than the pooled estimates for 5-ASAs or biologics reported in our study. Until a RCT assessing the additional benefit of chemoprevention alongside colonoscopic surveillance in IBD is undertaken, chemoprevention remains an adjunct to, rather than a substitute for, effective cancer surveillance. Additionally, the lack of a

prospective accurate IBD-specific CRC prediction tool limits the ability to understand the interaction of multiple dynamic risk factors. This ambitious model has been achieved for sporadic CRC. The increasing investment in prospective IBD disease-specific registries [98 99], integrating longitudinal data collection with linkage to cancer registries and medication prescriptions, is a major step towards personalised CRC risk assessment in IBD. A risk model for IBD-CRC derived from historic datasets demonstrates the possibilities, but needs to be matched with an effective implementation plan to support clinical utility [100]. Individualised CRC risk assessment could allow all patients to benefit from personalised mitigation strategies, while also accommodating increasing comorbidity and frailty [101]. The UC-care tool is an example of an online algorithm that estimates the progression to high grade dysplasia and / or CRC in patients with IBD who have low grade dysplasia and can be used to personalise shared decision making [102].

There are limitations in interpreting the results of this meta-analysis. All included studies were observational studies, and several confounding variables will be inevitable by the nature of study design and source data including lack of reporting data for mortality, disease location, key confounders associated with CRC risk in IBD patients, such as smoking history, concurrent use of aspirin or statins, family history of CRC, participation in regular surveillance programs, and variability of disease extension report across the studies. Disease extent influences colorectal cancer risk in IBD. However, the included studies did not stratified outcomes by disease extent or provide sufficient quantitative data to allow subgroup analysis by disease extent. As such, a formal analysis was not feasible. The data included in this meta-analysis were derived from studies reporting monotherapy exposure to biologics, 5-ASAs, or immunomodulators. Although combination therapy is increasingly common in clinical practice, the available studies did not provide sufficient data to evaluate the combined use of these agents. As such, our results reflect the effect of individual drug classes used as

monotherapy. Future studies with stratified analyses by treatment combination are warranted to better delineate independent drug-specific effects. Some studies were likely underpowered with greater risk estimate size, and wide CIs, suggesting imprecision and this may explain the differences seen between different geographical regions. For the primary outcome of IBD-CRC and / or dysplasia it was uncertain if this was verified at an individual patient level (i.e., whether cancer or dysplasia was considered to be IBD-related or not). Additionally, the grade of dysplasia was not specified-and as low-grade dysplasia has a lower concordance between expert pathologists this may have influenced the differing RR when cancer cases were reported separately from cancer and dysplasia outcomes. Patient compliance and duration of medication at the individual patient-level was not ascertained in these studies, although it is likely to be more reliable for some biologics, as this is recorded as a hospital episode where an infusion is administered. It was also not possible to segregate data by timing and more expanded use of biologics as these will have been adopted at different rates in each country[103]. Moreover, the outcome of CRC/dysplasia was reported by both case-control and cohort studies, thereby combining prevalence and incidence data. While case-control studies primarily capture the prevalence of existing cases at the time of study enrolment, cohort studies evaluate the incidence of new cases over time. These two measures are not strictly interchangeable, as prevalence is influenced by both disease incidence and survival, as well as by surveillance intensity and diagnostic practices [104]. By pooling these study designs, our estimates may reflect a mixture of risk of developing CRC/dysplasia and probability of detecting existing cases. Although this approach increases statistical power and reflects the available evidence base, it introduces heterogeneity and should be considered when interpreting the findings.

Many of these limitations will only be addressed once RCTs are completed to determine the impact of IBD therapies on cancer risk. Equally, acknowledging that an RCT is

nearly impossible in this context we must apply the available methodologies to synthesise and analyse the current data to inform modern clinical practice.

CONCLUSION

In conclusion, these new data show that use of anti-TNFs in UC and 5-ASAs in both UC and CD, but not immunomodulators, are associated with a reduced risk of cancer in patients with IBD in the observational studies. However, whether 5-ASAs has any additional chemopreventive benefit, when used in combination with biologics or immunomodulators, will only be addressed in well-designed randomised controlled trials. Ultimately, the optimal integration of chemoprevention into IBD care will require validated, individualized CRC risk prediction tools, greater understanding of drug-specific effects on carcinogenic pathways, and well-designed studies. Until such data are available, clinicians should tailor decisions regarding maintenance therapy with chemopreventive potential based on individual risk profiles and ensure close adherence to surveillance recommendations to mitigate the long-term burden of IBD-associated colorectal cancer.

Contributorship statement

Concept and design: Shahida Din (SD), Alexander C. Ford (ACF), Amirhosein Kefayat (AK).

Literature search and data collection: Amirhosein Kefayat (AK), Shahida Din (SD).

Data analysis: Alexander C. Ford (ACF).

Data interpretation: Amirhosein Kefayat (AK), Alexander C. Ford (ACF), Shahida Din (SD).

Manuscript drafting: Amirhosein Kefayat (AK), Alexander C. Ford (ACF), Shahida Din (SD).

Critical revision of the manuscript for important intellectual content: All authors.

Final approval of the version to be published: All authors.

Guarantor: Shahida Din (SD).

Funding Statement

The funders did not influence any part of this study despite author affiliations with their respective funders.

GBN is funded by National Institute for Health and Care Research (Grant number 302607) for a doctoral research fellowship.

JEE is funded by the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre.

CAL acknowledges support from the NIHR Newcastle Biomedical Research Centre.

SD acknowledges funding from NHS Lothian RD.

The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Competing interest statement

This is no conflict of interest to declare.

References

1. Wan Q, Zhao R, Xia L, et al. Inflammatory bowel disease and risk of gastric, small bowel and colorectal cancer: a meta-analysis of 26 observational studies. *Journal of cancer research and clinical oncology* 2021;147:1077-87.
2. Porter RJ, Song M, Gillespie S-L, et al. Real-world retrospective cohort study of inflammatory bowel disease colorectal cancer surveillance. *Frontline Gastroenterology* 2025
3. East JE, Gordon M, Nigam GB, et al. British Society of Gastroenterology guidelines on colorectal surveillance in inflammatory bowel disease. *Gut* 2025
4. Wijnands AM, de Jong ME, Lutgens MW, et al. Prognostic factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis. *Gastroenterology* 2021;160(5):1584-98.
5. Noor NM, Lee JC, Bond S, et al. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. *The Lancet Gastroenterology & Hepatology* 2024;9(5):415-27.
6. Kapizioni C, Desoki R, Lam D, et al. Biologic therapy for inflammatory bowel disease: Real-world comparative effectiveness and impact of drug sequencing in 13 222 patients within the UK IBD BioResource. *Journal of Crohn's and Colitis* 2024;18(6):790-800.
7. Stankey C, Bourges C, Haag L, et al. A disease-associated gene desert directs macrophage inflammation through ETS2. *Nature* 2024:1-10.
8. Dart RJ, Zlatareva I, Vantourout P, et al. Conserved γδ T cell selection by BTNL proteins limits progression of human inflammatory bowel disease. *Science* 2023;381(6663):eadh0301.
9. Porter RJ, Arends MJ, Churchhouse AM, Din S. Inflammatory bowel disease-associated colorectal cancer: translational risks from mechanisms to medicines. *Journal of Crohn's and Colitis* 2021;15(12):2131-41.
10. Peyrin-Biroulet L, Rahier J-F, Kirchgesner J, et al. I-CARE, a European prospective cohort study assessing safety and effectiveness of biologics in inflammatory bowel disease. *Clinical Gastroenterology and Hepatology* 2023;21(3):771-88. e10.
11. Study for Participants With Ulcerative Colitis Previously Enrolled in Etrolizumab Phase II/III Studies. https://clinicaltrials.gov/search?cond=NCT02118584 [
12. Murthy SK, Tandon P, Matthews P, et al. A Population-Based Matched Cohort Study of Digestive System Cancer Incidence and Mortality in Individuals With and Without Inflammatory Bowel Disease. *Official journal of the American College of Gastroenterology| ACG* 2022:10.14309.
13. Jones G-R, Lyons M, Plevris N, et al. IBD prevalence in Lothian, Scotland, derived by capture–recapture methodology. *Gut* 2019;68(11):1953-60.
14. Ishikawa H, Mutoh M, Suzuki S, et al. The preventive effects of low-dose enteric-coated aspirin tablets on the development of colorectal tumours in Asian patients: a randomised trial. *Gut* 2014;63(11):1755-59.
15. Hull MA, Sprange K, Hepburn T, et al. Eicosapentaenoic acid and aspirin, alone and in combination, for the prevention of colorectal adenomas (seAFOod Polyp Prevention trial): a multicentre, randomised, double-blind, placebo-controlled, 2× 2 factorial trial. *The Lancet* 2018;392(10164):2583-94.
16. Burn J, Gerdes A-M, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *The Lancet* 2011;378(9809):2081-87.
17. Grancher A, Michel P, Di Fiore F, Sefrioui D. Colorectal cancer chemoprevention: is aspirin still in the game? *Cancer Biology & Therapy* 2022;23(1):446-61.
18. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology* 2020;158(5):1450-61.
19. Moran GW, Gordon M, Sinopolou V, et al. British Society of Gastroenterology guidelines on inflammatory bowel disease in adults: 2025. *Gut* 2025;74(Suppl 2):s1-s101.

20. Feuerstein JD, Ho EY, Shmidt E, et al. AGA clinical practice guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology* 2021;160(7):2496-508.
21. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut* 2019;68(Suppl 3):s1-s106.
22. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama* 2000;283(15):2008-12.
23. VanderWeele TJ. Optimal approximate conversions of odds ratios and hazard ratios to risk ratios. *Biometrics* 2020;76(3):746-52.
24. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000
25. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
26. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994:1088-101.
27. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *bmj* 1997;315(7109):629-34.
28. Alkhayyat M, Abureesh M, Gill A, et al. Lower Rates of Colorectal Cancer in Patients With Inflammatory Bowel Disease Using Anti-TNF Therapy. *INFLAMMATORY BOWEL DISEASES* 2021;27(7):1052-60. doi: 10.1093/ibd/izaa252
29. Ananthakrishnan AN, Cagan A, Cai TX, et al. Statin Use Is Associated With Reduced Risk of Colorectal Cancer in Patients With Inflammatory Bowel Diseases. *CLINICAL GASTROENTEROLOGY AND HEPATOLOGY* 2016;14(7):973-79. doi: 10.1016/j.cgh.2016.02.017
30. Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. *Am J Gastroenterol* 2010;105(7):1604-9. doi: 10.1038/ajg.2009.745
31. Baars JE, Looman CWN, Steyerberg EW, et al. The risk of inflammatory bowel disease-related colorectal carcinoma is limited: results from a nationwide nested case-control study. *The American journal of gastroenterology* 2011;106(2):319-28. doi: https://dx.doi.org/10.1038/ajg.2010.428
32. Bergeron V, Vienne A, Sokol H, et al. Risk factors for neoplasia in inflammatory bowel disease patients with pancolitis. *Am J Gastroenterol* 2010;105(11):2405-11. doi: 10.1038/ajg.2010.248
33. Bernstein CN, Blanchard JF, Metge C, Yogendran M. Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal cancer? *Am J Gastroenterol* 2003;98(12):2784-8. doi: 10.1111/j.1572-0241.2003.08718.x
34. Bernstein CN, Nugent Z, Blanchard JF. 5-aminosalicylate is not chemoprophylactic for colorectal cancer in IBD: a population based study. *Am J Gastroenterol* 2011;106(4):731-6. doi: 10.1038/ajg.2011.50
35. Biancone L, Orlando A, Kohn A, et al. Infliximab and newly diagnosed neoplasia in Crohn's disease: a multicentre matched pair study. *Gut* 2006;55(2):228-33. doi: 10.1136/gut.2005.075937
36. Camus M, Seksik P, Bourrier A, et al. Long-term outcome of patients with Crohn's disease who respond to azathioprine. *Clin Gastroenterol Hepatol* 2013;11(4):389-94. doi: 10.1016/j.cgh.2012.10.038
37. Carrat F, Seksik P, Colombel JF, et al. The effects of aminosalicylates or thiopurines on the risk of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017;45(4):533-41. doi: 10.1111/apt.13897
38. Charkaoui M, Hajage D, Tubach F, et al. Impact of Anti-tumour Necrosis Factor Agents on the Risk of Colorectal Cancer in Patients with Ulcerative Colitis: Nationwide French Cohort Study. *J Crohns Colitis* 2022;16(6):893-99. doi: 10.1093/ecco-jcc/jjab184
39. Cheddani H, Dauchet L, Fumery M, et al. Cancer in Elderly Onset Inflammatory Bowel Disease: A Population-Based Study. *Am J Gastroenterol* 2016;111(10):1428-36. doi: 10.1038/ajg.2016.304

40. Connell WR, Kamm MA, Dickson M, et al. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. *Lancet* 1994;343(8908):1249-52. doi: 10.1016/s0140-6736(94)92150-4
41. Desai D, Shah S, Deshmukh A, et al. Colorectal cancers in ulcerative colitis from a low-prevalence area for colon cancer. *World J Gastroenterol* 2015;21(12):3644-9. doi: 10.3748/wjg.v21.i12.3644
42. Eaden J, Abrams K, Ekbom A, et al. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther* 2000;14(2):145-53. doi: 10.1046/j.1365-2036.2000.00698.x
43. Fraser AG, Orchard TR, Robinson EM, Jewell DP. Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine. *Aliment Pharmacol Ther* 2002;16(7):1225-32. doi: 10.1046/j.1365-2036.2002.01297.x
44. Gong W, Lv N, Wang B, et al. Risk of ulcerative colitis-associated colorectal cancer in China: a multi-center retrospective study. *Dig Dis Sci* 2012;57(2):503-7. doi: 10.1007/s10620-011-1890-9
45. Gordillo J, Cabré E, Garcia-Planella E, et al. Thiopurine Therapy Reduces the Incidence of Colorectal Neoplasia in Patients with Ulcerative Colitis. Data from the ENEIDA Registry. *J Crohns Colitis* 2015;9(12):1063-70. doi: 10.1093/ecco-jcc/jjv145
46. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007;133(4):1099-105; quiz 340. doi: 10.1053/j.gastro.2007.08.001
47. Jess T, Loftus EV, Jr., Velayos FS, et al. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterol* 2007;102(4):829-36. doi: 10.1111/j.1572-0241.2007.01070.x
48. Jung YS, Han M, Park S, et al. Cancer Risk in the Early Stages of Inflammatory Bowel Disease in Korean Patients: A Nationwide Population-based Study. *JOURNAL OF CROHNS & COLITIS* 2017;11(8):954-62. doi: 10.1093/ecco-jcc/jjx040
49. Kopylov U, Vutcovici M, Kezouh A, et al. Risk of Lymphoma, Colorectal and Skin Cancer in Patients with IBD Treated with Immunomodulators and Biologics: A Quebec Claims Database Study. *Inflamm Bowel Dis* 2015;21(8):1847-53. doi: 10.1097/MIB.0000000000000457
50. Lakatos L, Mester G, Erdelyi Z, et al. Risk factors for ulcerative colitis-associated colorectal cancer in a Hungarian cohort of patients with ulcerative colitis: Results of a population-based study. *INFLAMMATORY BOWEL DISEASES* 2006;12(3):205-11. doi: 10.1097/01.MIB.0000217770.21261.ce
51. Lashner BA, Provencher KS, Seidner DL, et al. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. *Gastroenterology* 1997;112(1):29-32. doi: 10.1016/s0016-5085(97)70215-4
52. Lindberg BU, Broomé U, Persson B. Proximal colorectal dysplasia or cancer in ulcerative colitis. The impact of primary sclerosing cholangitis and sulfasalazine: results from a 20-year surveillance study. *Dis Colon Rectum* 2001;44(1):77-85. doi: 10.1007/BF02234825
53. Lutgens M, Vermeire S, Van Oijen M, et al. A rule for determining risk of colorectal cancer in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2015;13(1):148-54.e1. doi: 10.1016/j.cgh.2014.06.032
54. Mak JWY, So J, Tang W, et al. Cancer risk and chemoprevention in Chinese inflammatory bowel disease patients: a population-based cohort study. *Scand J Gastroenterol* 2020;55(3):279-86. doi: 10.1080/00365521.2020.1731760
55. Matula S, Croog V, Itzkowitz S, et al. Chemoprevention of colorectal neoplasia in ulcerative colitis: the effect of 6-mercaptopurine. *Clin Gastroenterol Hepatol* 2005;3(10):1015-21. doi: 10.1016/s1542-3565(05)00738-x
56. Moody GA, Jayanthi V, Probert CS, et al. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur J Gastroenterol Hepatol* 1996;8(12):1179-83. doi: 10.1097/00042737-199612000-00009

57. Navaneethan U, Rai T, Venkatesh PGK, Kiran RP. Primary sclerosing cholangitis and the risk of colon neoplasia in patients with Crohn's colitis. *GASTROENTEROLOGY REPORT* 2016;4(3):226-31. doi: 10.1093/gastro/gov007
58. Nieminen U, Jussila A, Nordling S, et al. Inflammation and disease duration have a cumulative effect on the risk of dysplasia and carcinoma in IBD: a case-control observational study based on registry data. *Int J Cancer* 2014;134(1):189-96. doi: 10.1002/ijc.28346
59. Nowacki TM, Brückner M, Eveslage M, et al. The risk of colorectal cancer in patients with ulcerative colitis. *Dig Dis Sci* 2015;60(2):492-501. doi: 10.1007/s10620-014-3373-2
60. Pasternak B, Svanström H, Schmiegelow K, et al. Use of azathioprine and the risk of cancer in inflammatory bowel disease. *Am J Epidemiol* 2013;177(11):1296-305. doi: 10.1093/aje/kws375
61. Pinczowski D, Ekbom A, Baron J, et al. Risk factors for colorectal cancer in patients with ulcerative colitis: a case-control study. *Gastroenterology* 1994;107(1):117-20. doi: 10.1016/0016-5085(94)90068-x
62. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. *Clin Gastroenterol Hepatol* 2013;11(12):1601-8.e1. doi: 10.1016/j.cgh.2013.06.023
63. Rubin DT, LoSavio A, Yadron N, et al. Aminosalicylate therapy in the prevention of dysplasia and colorectal cancer in ulcerative colitis. *Clin Gastroenterol Hepatol* 2006;4(11):1346-50. doi: 10.1016/j.cgh.2006.08.014
64. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126(2):451-9. doi: 10.1053/j.gastro.2003.11.010
65. Satchi M, Korelitz BI, Panagopoulos G, et al. Is treatment with 6-mercaptopurine for colitis associated with the development of colorectal cancer? *Inflamm Bowel Dis* 2013;19(4):785-8. doi: 10.1097/MIB.0b013e318289664c
66. Setshedi M, Epstein D, Winter TA, et al. Use of thiopurines in the treatment of inflammatory bowel disease is associated with an increased risk of non-melanoma skin cancer in an at-risk population: a cohort study. *J Gastroenterol Hepatol* 2012;27(2):385-9. doi: 10.1111/j.1440-1746.2011.06865.x
67. Shah SC, Ten Hove JR, Castaneda D, et al. High Risk of Advanced Colorectal Neoplasia in Patients With Primary Sclerosing Cholangitis Associated With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* 2018;16(7):1106-13.e3. doi: 10.1016/j.cgh.2018.01.023
68. Siegel CA, Sands BE. Risk factors for colorectal cancer in Crohn's colitis: a case-control study. *Inflamm Bowel Dis* 2006;12(6):491-6. doi: 10.1097/00054725-200606000-00008
69. Terdiman JP, Steinbuch M, Blumentals WA, et al. 5-Aminosalicylic acid therapy and the risk of colorectal cancer among patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2007;13(4):367-71. doi: 10.1002/ibd.20074
70. Tung BY, Emond MJ, Haggitt RC, et al. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med* 2001;134(2):89-95. doi: 10.7326/0003-4819-134-2-200101160-00008
71. Ullman T, Croog V, Harpaz N, et al. Progression to colorectal neoplasia in ulcerative colitis: effect of mesalamine. *Clin Gastroenterol Hepatol* 2008;6(11):1225-30; quiz 177. doi: 10.1016/j.cgh.2008.05.020
72. van Schaik FD, van Oijen MG, Smeets HM, et al. Thiopurines prevent advanced colorectal neoplasia in patients with inflammatory bowel disease. *Gut* 2012;61(2):235-40. doi: 10.1136/gut.2011.237412
73. van Staa TP, Card T, Logan RF, Leufkens HG. 5-Aminosalicylate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut* 2005;54(11):1573-8. doi: 10.1136/gut.2005.070896
74. Velayos FS, Loftus EV, Jr., Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: A case-control study. *Gastroenterology* 2006;130(7):1941-9. doi: 10.1053/j.gastro.2006.03.028
75. Weimers P, Ankersen DV, Lokkegaard ECL, et al. Occurrence of Colorectal Cancer and the Influence of Medical Treatment in Patients With Inflammatory Bowel Disease: A Danish

Nationwide Cohort Study, 1997 to 2015. *INFLAMMATORY BOWEL DISEASES* 2021;27(11):1795-803. doi: 10.1093/ibd/izaa340
76. Zhang Q, Sha S, Xu B, et al. Prevalence of colorectal cancer in patients with ulcerative colitis: A retrospective, monocenter study in China. *J Cancer Res Ther* 2015;11(4):899-903. doi: 10.4103/0973-1482.143345
77. Gomez-Garcia M, Cabello-Tapia MJ, Sanchez-Capilla AD, et al. Thiopurines related malignancies in inflammatory bowel disease: local experience in Granada, Spain. *World journal of gastroenterology* 2013;19(30):4877-86. doi: https://dx.doi.org/10.3748/wjg.v19.i30.4877
78. Odze R. Diagnostic problems and advances in inflammatory bowel disease. *Modern pathology* 2003;16(4):347-58.
79. Gordon H, Minozzi S, Kopylov U, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *Journal of Crohn's and Colitis* 2024:jjae091.
80. Raine T, Bonovas S, Burisch J, et al. ECCO guidelines on therapeutics in ulcerative colitis: medical treatment. *Journal of Crohn's and Colitis* 2022;16(1):2-17.
81. Minnis-Lyons SE, Aiken Z, Chow S, Din S. Managing IBD in patients with previous cancers. *Frontline Gastroenterology* 2022;13(e1):e44-e50.
82. Gordon H, Biancone L, Fiorino G, et al. ECCO guidelines on inflammatory bowel disease and malignancies. *Journal of Crohn's and Colitis* 2023;17(6):827-54.
83. Lim WC, Wang Y, MacDonald JK, Hanauer S. Aminosalicylates for induction of remission or response in Crohn's disease. *Cochrane Database of Systematic Reviews* 2016(7)
84. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane database of systematic reviews* 2016(9)
85. Allgayer H. Mechanisms of action of mesalazine in preventing colorectal carcinoma in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2003;18:10-14.
86. Collier H, Francis AA, McDonald-Gibson WJ, Saeed S. Inhibition of prostaglandin biosynthesis by sulphasalazine and its metabolites. *Prostaglandins* 1976;11(2):219-25.
87. Monteleone G, Franchi L, Fina D, et al. Silencing of SH-PTP2 defines a crucial role in the inactivation of epidermal growth factor receptor by 5-aminosalicylic acid in colon cancer cells. *Cell Death & Differentiation* 2006;13(2):202-11.
88. Kaiser GC, Yan F, Polk DB. Mesalamine blocks tumor necrosis factor growth inhibition and nuclear factor κB activation in mouse colonocytes. *Gastroenterology* 1999;116(3):602-09.
89. Egan LJ, Mays DC, Huntoon CJ, et al. Inhibition of interleukin-1-stimulated NF-κB RelA/p65 phosphorylation by mesalamine is accompanied by decreased transcriptional activity. *Journal of Biological Chemistry* 1999;274(37):26448-53.
90. Stournaras E, Qian W, Pappas A, et al. Thiopurine monotherapy is effective in ulcerative colitis but significantly less so in Crohn's disease: long-term outcomes for 11 928 patients in the UK inflammatory bowel disease bioresource. *Gut* 2021;70(4):677-86.
91. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021;160(5):1570-83.
92. Gonczi L, Bessissow T, Lakatos PL. Disease monitoring strategies in inflammatory bowel diseases: What do we mean by "tight control"? *World journal of gastroenterology* 2019;25(41):6172.
93. Ungaro RC, Limketkai BN, Jensen CB, et al. Stopping 5-aminosalicylates in patients with ulcerative colitis starting biologic therapy does not increase the risk of adverse clinical outcomes: analysis of two nationwide population-based cohorts. *Gut* 2019;68(6):977-84.
94. Chapman TP, Frias Gomes C, Louis E, et al. withdrawal of 5-aminosalicylates in inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2020;52(1):73-84.
95. Seo J, Kim S, Hong SW, et al. Continuing or stopping 5-aminosalicylates in patients with inflammatory bowel disease on anti-TNF therapy: A nationwide population-based study. *Alimentary Pharmacology & Therapeutics* 2024

96. Ko CW, Singh S, Feuerstein JD, et al. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology* 2019;156(3):748-64.
97. Bye WA, Nguyen TM, Parker CE, et al. Strategies for detecting colon cancer in patients with inflammatory bowel disease. *Cochrane Database of Systematic Reviews* 2017(9)
98. IBD BioResource https://www.ibdbioresource.nihr.ac.uk/ [
99. Gut Reaction https://www.hdruk.ac.uk/helping-with-health-data/health-data-research-hubs/gut-reaction/ [
100. Wijnands AM, de Vries BBP, Lutgens MW, et al. Dynamic Prediction of Advanced Colorectal Neoplasia in Inflammatory Bowel Disease. *Clinical Gastroenterology and Hepatology* 2024
101. Taleban S, Toosizadeh N, Junna S, et al. Frailty assessment predicts acute outcomes in patients undergoing screening colonoscopy. *Digestive diseases and sciences* 2018;63:3272-80.
102. Curtius K, Kabir M, Al Bakir I, et al. Multicentre derivation and validation of a colitis-associated colorectal cancer risk prediction web tool. *Gut* 2022;71(4):705-15.
103. Targownik LE, Suissa S. Understanding and avoiding immortal-time bias in gastrointestinal observational research. *Official journal of the American College of Gastroenterology| ACG* 2015;110(12):1647-50.
104. Noordzij M, Dekker FW, Zoccali C, Jager KJ. Measures of disease frequency: prevalence and incidence. *Nephron Clinical Practice* 2010;115(1):c17-c20.
105. Nguyen GC, Gulamhusein A, Bernstein CN. 5-aminosalicylic acid is not protective against colorectal cancer in inflammatory bowel disease: a meta-analysis of non-referral populations. *Official journal of the American College of Gastroenterology| ACG* 2012;107(9):1298-304.
106. Zhao L-N, Li J-Y, Yu T, et al. 5-Aminosalicylates reduce the risk of colorectal neoplasia in patients with ulcerative colitis: an updated meta-analysis. *PloS one* 2014;9(4):e94208.
107. O'Connor A, Packey CD, Akbari M, Moss AC. Mesalamine, but not sulfasalazine, reduces the risk of colorectal neoplasia in patients with inflammatory bowel disease: an agent-specific systematic review and meta-analysis. *Inflammatory bowel diseases* 2015;21(11):2562-69.
108. Qiu X, Ma J, Wang K, Zhang H. Chemopreventive effects of 5-aminosalicylic acid on inflammatory bowel disease-associated colorectal cancer and dysplasia: a systematic review with meta-analysis. *Oncotarget* 2017;8(1):1031.
109. Bonovas S, Fiorino G, Lytras T, et al. Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2017;45(9):1179-92.
110. Gong J, Zhu L, Guo Z, et al. Use of thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel diseases: a meta-analysis. *PloS one* 2013;8(11):e81487.
111. Jess T, Lopez A, Andersson M, et al. Thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel disease: a meta-analysis. *Clinical Gastroenterology and Hepatology* 2014;12(11):1793-800. e1.
112. Lu M, Qiu X, Mao X, et al. Systematic review with meta-analysis: thiopurines decrease the risk of colorectal neoplasia in patients with inflammatory bowel disease. *Alimentary pharmacology & therapeutics* 2018;47(3):318-31.
113. Zhu Z, Mei Z, Guo Y, et al. Reduced risk of inflammatory bowel disease-associated colorectal neoplasia with use of thiopurines: a systematic review and meta-analysis. *Journal of Crohn's and Colitis* 2018;12(5):546-58.

Table 1. Pooled analysis of studies examining biologics*, 5-ASAs, and immunomodulators for risk of CRC or dysplasia outcomes in all the studies and after subcategorizing by IBD phenotypes

Medications	Subgroups	Pooled risk estimates in different IBD phenotypes		
		All IBD phenotypes	UC	CD

		RR (95% CI) [n]	I^2	RR (95% CI) [n]	I^2	RR (95% CI) [n]	I^2
Biologics	All	**0.74 (0.64 - 0.85)** [11]	56.8%	**0.78 (0.74 - 0.84)** [5]	0%	**0.69 (0.66 - 0.72)** [3]	0%
	Anti-TNF	**0.72 (0.62 - 0.84)** [10]	66.8%	**0.78 (0.73 - 0.83)** [4]	0%	0.64 (0.34 - 1.21) [2]	8.5%
	Anti-TNF + Anti-Integrins	1.00 (0.53 - 1.89) [3]	0%	1.38 (0.56 - 3.44) [1]	0%	0.55 (0.19-1.57) [1]	0%
5-ASAs	All	**0.78 (0.70 - 0.86)** [32]	52.1%	**0.59 (0.45 - 0.78)** [18]	65.9%	**0.84 (0.81 - 0.87)** [4]	0%
	Sulfasalazine	0.52 (0.21 - 1.29) [5]	74.7%	0.52 (0.21 - 1.29) [5]	74.9%	-	-
	Non-Sulfasalazine	**0.80 (0.74 - 0.88)** [17]	41.9%	**0.64 (0.48 - 0.84)** [13]	58.6%	**0.84 (0.81 - 0.87)** [4]	0%
IMM	All	0.92 (0.82 - 1.02) [34]	83.1%	0.97 (0.73 - 1.30) [15]	57.1%	0.79 (0.50 - 1.27) [5]	58.8%
	Thiopurines	0.89 (0.67 - 1.18) [10]	0%	0.83 (0.57 - 1.22) [13]	44.9%	0.56 (0.20 - 1.54) [3]	54.6%
	Other IMM**	0.92 (0.82 - 1.04) [24]	87.2%	**1.28 (1.16 - 1.43)** [2]	8.9%	1.02 (0.98 - 1.06) [2]	0%

* Biologics: Anti-TNF (infliximab, adalimumab, certolizumab, golimumab) & anti-Integrins

** Thiopurine plus methotrexate which represents pooled immunomodulator monotherapy exposure groups rather than simultaneous combination therapy.

IBD; Inflammatory bowel disease, N/A; RR; relative risk, not applicable, NOS; Newcastle-Ottawa scale.

Note: Data in **bold font** are statistically significant. [n]**:** Number of pooled studies. - : means no study for this parameter.

Table 2. Stratified analysis of the studies examining biologics*, 5-ASA, and immunomodulators in patients with IBD for CRC chemoprevention according to outcome definition and IBD phenotypes

Subgroups		Pooled risk estimates in studies reported different outcomes					
		All (CRC + CRC/Dys)		CRC		CRC/Dys	
		RR (95% CI) [n]	I^2	RR (95% CI) [n]	I^2	RR (95% CI) [n]	I^2
Biologics	Anti-TNF	UC: **0.78 (0.73 - 0.83)** [4] CD: 0.64 (0.34 - 1.21) [2]	0% 8.5%	UC: **0.78 (0.73 - 0.83)** [3] CD: 0.64 (0.34 - 1.21) [2]	0% 8.5%	UC: 1.6 (0.2 -13.8) [1] -	0% -
	Anti-TNF + Anti-Integrins	UC: 1.38 (0.56 - 3.44) [1] CD: 0.55 (0.19-1.57) [1]	0% 0%	UC: 1.38 (0.56 - 3.44) [1] CD: 0.55 (0.19-1.57) [1]	0% 0%	- -	- -
5-ASAs	Sulfasalazine	UC: 0.52 (0.21 - 1.29) [5] -	74.9% -	UC: **0.18 (0.04 - 0.94)** [2] -	79.8% -	UC: 1.01 (0.51 - 2.01) [3] -	15.7%
	Non-Sulfasalazine	UC: **0.64 (0.48 - 0.84)** [13] CD: **0.84 (0.81 - 0.87)** [4]	58.6% 41.9%	UC: **0.66 (0.45 - 0.96)** [7] CD: **0.84 (0.81 - 0.87)** [4]	75.4% 41.9%	UC: **0.55 (0.37 - 0.82)** [6] -	0% -
IMM	Thiopurines	UC: 0.83 (0.57 - 1.22) [13] CD: 0.56 (0.20 - 1.54) [3]	44.9% 54.6%	UC:1.52 (0.86 - 2.67) [5] CD: 0.90 (0.27 - 3.00) [2]	0% 34.3%	UC: 0.65 (0.42 - 1.00) [8] CD: **0.30 (0.13 - 0.7)** [1]	44.4% 0%
	Other IMM**	UC: **1.28 (1.16 - 1.43)** [2] CD: 1.02 (0.98 - 1.06) [2]	8.9% 0%	UC: :**1.28 (1.16 -1.43)** [2] CD: 1.02 (0.98 - 1.07) [2]	8.9% 0%	- -	- -

* Biologics: Anti-TNF (infliximab, adalimumab, certolizumab, golimumab) & anti-Integrins.

** Thiopurine plus methotrexate.

IBD; Inflammatory bowel disease, N/A; RR; relative risk, not applicable, NOS; Newcastle-Ottawa scale.

Note: Data in **bold font** are statistically significant. [n]**:** Number of studies. - : no study was for this parameter.

Table 3. Previously published systematic reviews and meta-analyses in comparison with the current study

	Authors & publication year [ref]	No. of studies	Pooled estimate (95% CI)	*P*-value	I^2	IBD patients	CRC cases
5-ASAs	Nguyen et al. 2012 [105]	4	0.95 (0.66 to 1.38)	0.07	58.2%	NR	NR
	Zhao et al. 2014 [106]	17	0.63 (0.48 to 0.84)	<0.001	64.8%	20,193	1,508
	O'Connor et al. 2015 [107]	8	0.6 (0.4 to 0.9)	0.04	60%	NR	867
	Qui et al. 2017 [108]	26	0.58 (0.45 to 0.75)	0.000	58.3%	13,492	1,958
	Bonovas et al. 2017 [109]	31	0.57 (0.45 to 0.71)	<0.001	55%	NR	2,137
	Wijnands et al. 2021 [4]	20	0.53 (0.39 to 0.72)	<0.00001	67%	NR	NR
	Kefayat *et al* 2024	**32**	**0.78 (0.70 to 0.86)**	**< 0.0001**	**52.1%**	**462,408**	**9,847**
Immunomodulators	Gong et al. 2013 [110]	19	0.71 (0.54 to 0.94)	<0.001	68.0%	NR	NR
	Jess et al. 2014 [111]	15	0.87 (0.71 to 1.06)	0.01	51.8%	NR	NR
	Lu et al. 2017 [112]	24	0.63 (0.46 to 0.86)	< 0.001	65.5%	76,999	NR
	Zhu et al. 2018 (Cohort studies)* [113]	11	0.96 (0.94 to 0.98)	0.67	0.0%	95,397	NR
	Zhu et al. 2018 (Case-control)* [113]	16	0.49 (0.34 to 0.70)	< 0.001	65.2%	95,397	NR
	Wijnands et al. 2021 [4]	19	0.55 (0.37 to 0.82)	<0.00001	66%	NR	NR
	Kefayat *et al* 2024	**35**	**0.91 (0.82 to 1.02)**	**0.092**	**82.7%**	**544,380**	**10,794**
ogic	Wijnands et al. 2021 [4]	4	0.71(0.14 to 3.67)	<0.00001	86%	NR	NR

	Kefayat *et al* 2024	**11**	**0.74 (0.64 to 0.85)**	**< 0.0001**	**56.8%**	**447,637**	**8,721**

NR, not reported; CRC, colorectal cancer; IBD, inflammatory bowel disease.

*The authors did not report the overall pooled estimates and just reported meta-analyses of case-control and cohort studies separately.