TITLE PAGE

Title: 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.

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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

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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.

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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

202 therapy for the management of UC [3]. In addition, these organizations also recommend against
203 the use of 5-ASAs for induction or maintenance therapy in moderate to severe CD [20 21]. A
204 current research gap is whether 5-ASAs have an additional chemopreventive effect when used
205 in combination with advanced therapies in UC or CD. A previous systematic review assessed
206 the association of tumour necrosis factor-α inhibitors in seven studies, containing around
207 27,000 patients [4]. It did not demonstrate any associated chemoprevention with these drugs and
208 in the intervening 3 years more observational studies have been published. It is crucial to
209 understand if advanced therapies also reduce the risk of CRC to inform current practice as to
210 whether to continue 5-ASAs in combination with these drugs or not.

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

217

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).

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Data analysis: Alexander C. Ford (ACF).

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

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Competing interest statement

This is no conflict of interest to declare.

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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
B	**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%

[n]**:** Number of pooled studies

* 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.

- : means no study for this parameter.

Note: Data in **bold font** are statistically significant.

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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%	- -	- -

[n]**:** Number of studies

* 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.

- : no study was for this parameter.

Note: Data in **bold font** are statistically significant.

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**	**I²**	**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**
Biologics	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.