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Systematic review with meta-analysis: use of 5-aminosalicylates and risk of colorectal neoplasia in patients with inflammatory bowel disease

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SUMMARY

Background
The relationship of 5-aminosalicylates' use with the risk of colorectal neoplasia in patients with inflammatory bowel disease (IBD) has been the focus of a growing body of research.

Aim
To investigate this association through an updated meta-analysis of observational studies.

Methods
PubMed, Scopus and major conference proceedings were searched up to December 2016. The identified studies were evaluated for publication bias and heterogeneity. Pooled relative risk (RR) estimates were calculated using random-effect models. Detailed subgroup analyses were performed. The GRADE approach was used to assess the quality of evidence.

Results
Thirty-one independent observational studies including 2137 cases of colorectal neoplasia (of which 76% were cancers) were incorporated. Between-study heterogeneity was moderate, while strong suspicion of small-study effects was raised. The overall analysis revealed a protective association between 5-aminosalicylates' use and colorectal neoplasia (RR = 0.57, 95% CI: 0.45–0.71). When the analysis was stratified according to study design and setting, the association was significant in cohort (RR = 0.65, 95% CI: 0.43–0.99; n = 10) and case–control studies (RR = 0.53, 95% CI: 0.40–0.70; n = 21), population-based (RR = 0.70, 95% CI: 0.52–0.94; n = 12) and hospital-based studies (RR = 0.46, 95% CI: 0.34–0.61; n = 19). Exposure to 5-aminosalicylates was protective against cancer (RR = 0.58, 95% CI: 0.45–0.74) and dysplasia (RR = 0.54, 95% CI: 0.35–0.84). The reduction in colorectal neoplasia risk was strong in ulcerative colitis (RR = 0.50, 95% CI: 0.38–0.64), but nonsignificant in Crohn's disease (RR = 0.76, 95% CI: 0.43–1.33). Mesalazine (mesalamine) use was protective (RR = 0.70, 95% CI: 0.51–0.94) with evidence of a dose-effect. The effect of sulfasalazine was marginally nonsignificant (RR = 0.72, 95% CI: 0.51–1.01).

Conclusions
Our findings support a potential chemopreventive role of 5-aminosalicylates in IBD. Further, high-quality prospective research is warranted.

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INTRODUCTION

Patients with long-standing inflammatory bowel disease (IBD) – either ulcerative colitis (UC) or Crohn's disease (CD) – have an increased risk of developing colorectal cancer (CRC) due to chronic inflammation and other mechanisms promoting the neoplastic transformation of colonic mucosa.[1] As a result, CRC accounts for approximately 15% of all deaths in IBD patients.[2]

Current CRC prevention strategies rely on active surveillance: performance of colonoscopy at regular intervals, detection of pre-cancerous dysplastic lesions on mucosal biopsies, and endoscopic removal or proctocolectomy, when dysplasia is detected.[3–6] However, strategies based on colonoscopy have certain limitations: precursor dysplastic lesions may be difficult to detect, and transformation from dysplasia to cancer may be rapid. Accordingly, the research on chemoprevention of CRC has received considerable attention, and 5-aminosalicylic acid (5-ASA) has been identified as a potential chemopreventive agent. 5-ASA has demonstrated antineoplastic properties in preclinical studies,[7] and a protective effect against CRC in early clinical studies of patients with IBD.[8]

The relationship between 5-ASA and colorectal neoplasia (i.e, cancer or dysplasia; CRN) has been the focus of a growing body of epidemiological research, with often conflicting results ranging from very protective to harmful. Similarly, the results from recent meta-analyses on the subject have been inconsistent.[9–11] Thus, the effect of 5-ASA use on CRN risk in IBD patients remains to be determined. To address this issue, we sought to perform an updated systematic review and meta-analysis to reflect the current totality of evidence on the subject.

METHODS

Our study protocol[12] is registered with the International Prospective Register of Systematic Reviews (PROSPERO – http://www.crd.york.ac.uk/prospero). The current study was performed in accordance with the Cochrane Handbook,[13] the MOOSE proposal,[14] and the PRISMA statement.[15]

Data sources and searches

We systematically searched PubMed and Scopus, up to 31 December 2016, using the terms: {aminosalicylic acid, aminosalicylate, 5-aminosalicylic acid, 5-aminosalicylate, 5ASA, 5-ASA, pentasa, mesalamine, mesalazine salicylazosulfapyridine, salicylazosulphapyridine, sulfasalazine, sulphasalazine, olsalazine, or balsalazide} combined with {cancer(s), carcinoma(s), malignancy(ies), neoplasm(s), neoplasia(s), tumor(s), dysplasia(s), adenocarcinoma(s) or adenoma(s)} and {inflammatory bowel disease, ulcerative colitis or Crohn's disease}. Language or age restrictions were not imposed.

Two authors (SB, GN) independently read titles and abstracts of the studies identified in the search, and excluded those that were clearly irrelevant. The full text of the selected articles was carefully read to determine whether it contained information on the topic of interest. Their reference lists, as well as those of relevant systematic reviews,[8–11] were inspected to identify any eligible studies missed by the electronic database search. Finally, recent international conference proceedings were investigated (European Crohn's and Colitis Organisation, 2011–2016; Digestive Disease Week, 2010–2016; and United European Gastroenterology Week, 2010–2016).

Selection criteria

Prospective or retrospective epidemiological studies (case–control or cohort) evaluating any exposure to 5-aminosalicylates and risk of colorectal neoplasia in patients with IBD were eligible for inclusion. We considered all articles irrespective of publication type; we did not exclude articles published as short reports or conference abstracts, even though critical appraisal of such publications is limited. Studies were included if they investigated patients with IBD; evaluated 5-ASA use as a risk factor for colorectal neoplasia (cancer and/or dysplasia); and reported (or provided sufficient data to determine) an effect estimate and a confidence interval. Studies conducted in populations with IBD and primary sclerosing cholangitis were excluded. In the case of multiple studies involving the same population, data from the most recent or most comprehensive one (higher number of cases/complete information) were included. Finally, studies reporting different effect measures (risk ratio, odds ratio, hazard ratio) were incorporated. In practice, these measures of effect yield similar estimates of relative risk, because the absolute risk of colorectal neoplasia is low.[16]

Data extraction and quality assessment

Two authors (SB, GN) independently abstracted the following information from each study in a form: citation data, first author's last name, time period of study and geographical setting; study design; setting (population- or hospital-based); number of participants; population characteristics (age, sex); underlying condition (UC, CD); exposure definition (medication type, dose and frequency of use); outcomes reported (colorectal cancer and/or

dysplasia); estimated measures of effect with 95% CIs; and control for confounding factors by matching or adjustments. In studies where more than one effect estimate was reported, we extracted the "most adjusted" estimate, i.e. the estimate controlled for the largest number of potential confounders. When relative risk was reported separately for different types of medication, doses or durations of exposure, we calculated the study's combined effect estimate before inclusion in the overall meta-analysis. Any differences in data extraction were settled by consensus, referring back to the original article.

We assessed the potential risk of bias in included studies using the Newcastle–Ottawa scale,[17] which addresses the following three domains: selection of the study groups; comparability of the groups; and ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. Studies could get a total of four stars for selection, 2 two for comparability, and three 3 for assessment of the outcome or exposure for a total of nine stars per study. Studies scoring six stars or higher were considered as of low risk of bias (i.e, high quality). Discrepancies among reviewers were discussed and agreement was reached by consensus.

Quantitative data synthesis

Pooled effect estimates and 95% CIs were calculated under the assumption of a random-effect model (DerSimonian–Laird approach).[18] Publication bias was assessed using the Begg's test[19] and the Egger's test,[20] as well as the funnel plot. To examine whether the results of the studies were homogeneous, we employed the Cochran's Q test,[21] with a 0.10 level of significance. We also calculated the *I*-squared statistic,[22] which quantifies the proportion of total variation across studies that is due to heterogeneity rather than chance; we used cut-offs of <30%, 30–59%, 60–75% and >75% to suggest low, moderate, substantial and considerable heterogeneity respectively.[23]

To examine the stability of results and explore heterogeneity, the studies were grouped on the basis of study design (cohort vs. case–control), study setting (population-based or geographically representative registries or databases vs. hospital-based studies that included populations from IBD referral clinics or surveillance centres), quality score, control for confounding, publication type, underlying condition, medication and dose, and outcome studied (dysplasia, cancer) and separate analyses were conducted. Pooled effect estimates derived from subgroup analyses were compared with tests of interaction.[24]

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.[25] GRADE assessment begins with the study design (observational studies start as low-quality evidence) and then addresses five reasons to possibly rate down the quality of evidence (risk of bias, imprecision, indirectness, inconsistency, publication bias) and three to possibly rate up the quality (large magnitude of effect, dose–response gradient, and effect of plausible residual confounding). It results in an assessment of the quality of a body of evidence in one of four grades: high, moderate, low or very low.

For statistical analysis, we used the R software,[26] version 3.3.2, and the "meta" package for R,[27] version 4.6-0. All *P*-values are two-tailed. For all tests (except for heterogeneity), a $P < 0.05$ indicates statistical significance.

RESULTS

Search results

After duplicates' removal, the database search yielded 2302 literature citations (Figure 1, flow chart). Records clearly not eligible or irrelevant to the topic were excluded. We retrieved 74 publications for detailed evaluation. The full text was read and the reference lists were carefully investigated. Finally, we identified and included 31 independent studies, which met the predefined eligibility criteria;[28–58] three of them had been published solely as conference abstracts.[56–58] Five additional studies were excluded due to the rule for multiple publications involving the same population.[59–63] The full list of excluded studies, with reasons for exclusion, is given in the Appendix S1. There was full agreement between reviewers regarding study selection.

Thirty-one studies selected for inclusion[28–58] analysed exposure to 5-ASA and risk of developing CRN, and reported (or provided sufficient data to determine) an effect estimate and a confidence interval. Among them, 10 were cohort studies,[29, 31, 35, 39, 40, 44, 51, 53, 54, 57] and the remaining 21 were case–control studies.[28, 30, 32–34, 36–38, 41–43, 45–50, 52, 55, 56, 58] Twelve were population-based,[28–30, 35, 39–41, 45, 46, 49, 54, 55] while 19 were hospital-based studies.[31–34, 36–38, 42–44, 47, 48, 50–53, 56–58] Seventeen studies analysed patients with UC,[30–33, 36–38, 44, 47, 50–55, 57, 58] two studies had patients with CD,[43, 48] and 12 studies included both UC and CD patients.[28, 29, 34, 35, 39–42, 45, 46, 49, 56]

The number of CRN cases ranged between 4 and 364 among the studies, for a total of 2137 cases (of which 76% were colorectal cancers), while the mean age of patients ranged between 40 and 75 years. Fourteen of 31

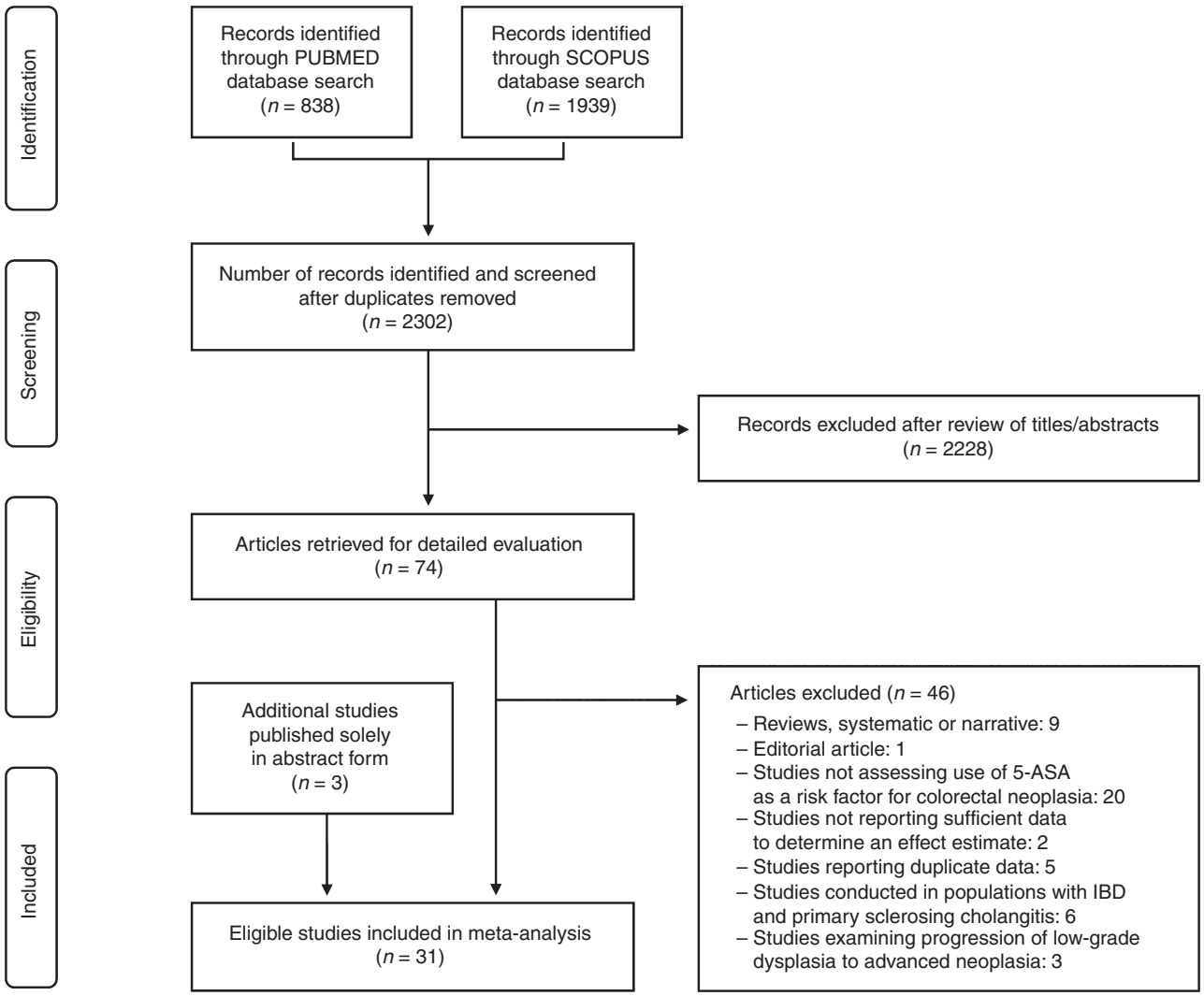

Figure 1 | Summary of the evidence search and selection process (flow chart). *Abbreviations:* 5-ASA, 5-aminosalicylates; IBD, inflammatory bowel disease.

studies also included patients with dysplasia. The vast majority[30, 33, 34, 37, 39, 44, 45, 50, 51, 53, 57] were cases positive for dysplasia. Only one study[36] included six cases indefinite for dysplasia (together with 38 cases positive for dysplasia), while two studies, published as abstracts,[56, 58] did not report details.

Twenty-one studies were controlled for potential confounding factors by matching or adjustments (eight of them at least for age, disease extent and disease duration). The majority of the studies were conducted in Europe (n = 18), but some were carried out in the USA (n = 8), Europe and the USA (n = 1), Canada (n = 1) and Asia (n = 3). Publication dates ranged between 1994 and 2017. A summary of the study characteristics is given in Table 1.

Risk of bias assessment using the Newcastle–Ottawa scale

Twenty-four studies[28–30, 32–36, 38–40, 42–50, 52–55] scored six stars or higher, and were rated as of high quality (Table S1). Four studies published as short reports,[37] or conference abstracts,[56–58] were not assessed for quality, as critical appraisal of such publications is limited.

Results of meta-analyses

Use of 5-aminosalicylates and risk of colorectal neoplasia. Data from 31 studies[28–58] were synthesised. Exposure to 5-ASA was significantly associated with a 43% decrease in the risk of developing CRN (RR = 0.57, 95% CI: 0.45–0.71; Figure 2, forest plot). The P-values for the Begg's and the Egger's test were P = 0.39 and

Table 1 | Studies included in the meta-analysis

Study, publication year	Country	Time period	Design	Setting	Condition	Exposure	Outcomes	No. of subjects	CRN cases	RR (95% CI)	Control for potential confounding factors †
Carrat *et al.* [28], 2017	France	2004–2007	C-C	Population	UC, CD	Any 5-ASA; any use during the year of cancer diagnosis	Cancer	430	144	0.59 (0.37–0.94)	1–6
Cheddani *et al.* [29], 2016	France	1988–2006	Cohort	Population	UC, CD	Any 5-ASA; any use	Cancer	844	15	0.7 (0.2–2.6)	–
Gordillo *et al.* [30], 2015	Spain	2006–2009	C-C	Population	UC	Any 5-ASA; any use	Cancer/ dysplasia	831	45	0.49 (0.21–1.26)	–
Nowacki *et al.* [31], 2015	Germany	2002–2013	Cohort	Hospital	UC	Any 5-ASA; NR	Cancer	434	27	0.9 (0.2–3.6)	–
Zhang *et al.* [32], 2015	China	2000–2012	C-C	Hospital	UC	Any 5-ASA; NR	Cancer	624	4	0.17 (0.02–1.72)	2–4,7,8
Freire *et al.* [33], 2014	Portugal	2011–2013	C-C	Hospital	UC	Any 5-ASA; NR	Dysplasia	76	7	0.33 (0.04–4.06)	–
Nieminen *et al.* [34], 2014	Finland	1996–2008	C-C	Hospital	UC, CD	Any 5-ASA; NR	Cancer/ dysplasia	553	183	0.46 (0.13–1.57)	2–6,9–11
Jess *et al.* [35], 2013	Denmark	1978–2010	Cohort	Population	UC, CD	Any 5-ASA; any use	Cancer	2,211	27	0.82 (0.28–2.42)	1,4,5
Rubin *et al.* [36], 2013	USA	1994–2005	C-C	Hospital	UC	Mesa/Sulfa; any use	Cancer/ dysplasia	200	59	0.08 (0.01–0.68)	2,3,9
Bessissow *et al.* [37], 2013	Belgium	2008–2011	C-C	Hospital	UC	Any 5-ASA; NR	Cancer/ dysplasia	126	28	0.54 (0.21–1.38)	3,9
Gong *et al.* [38], 2012	China	1998–2009	C-C	Hospital	UC	Any 5-ASA; NR	Cancer	3,922	34	0.28 (0.13–0.60)	2,3
Van Schaik *et al.* [39], 2012	Netherlands	2001–2009	Cohort	Population	UC, CD	Any 5-ASA; minimum 6 mo	Cancer/ dysplasia	2,578	28	0.56 (0.22–1.40)	1–5,10,12–15
Bernstein *et al.* [40], 2011	Canada	1995–2008	Cohort	Population	UC, CD	Any 5-ASA; any use	Cancer	8,744	108	1.17 (0.80–1.72)	1,3,4
Baars *et al.* [41], 2011	Netherlands	1990–2006	C-C	Population	UC, CD	Any 5-ASA; any use	Cancer	565	173	0.73 (0.42–1.27)	–
Tang *et al.* [42], 2010	USA	1970–2005	C-C	Hospital	UC, CD	Any 5-ASA; any use	Cancer	48	18	0.17 (0.003–2.45)	2–5,9,16
Sobala *et al.* [43], 2010	Austria	1997–2006	C-C	Hospital	CD	Any 5-ASA; any use	Cancer	28	7	11.0 (0.00–433 $\times 10^3$)	1
Gupta *et al.* [44], 2007	USA	1996–2006	Cohort	Hospital	UC	Mesa; NR	Cancer/ dysplasia	418	65	0.6 (0.3–1.2)	–
Jess *et al.* [45], 2007	Denmark, USA	1940–2002	C-C	Population	UC, CD	Mesa/Sulfa; any use	Cancer/ dysplasia	145	43	2.3 (0.9–6.0)	2–5,9,17,18
Terdiman *et al.* [46], 2007	USA	2000–2003	C-C	Population	UC, CD	Any 5-ASA; any use 1 yr before cancer diagnosis	Cancer	1,536	364	0.97 (0.77–1.23)	1, 4
Velayos *et al.* [47], 2006	USA	1976–2002	C-C	Hospital	UC	Any 5-ASA; minimum 1 yr	Cancer	376	188	0.59 (0.38–0.92)	2–4,18
Siegel *et al.* [48], 2006	USA	1990–2004	C-C	Hospital	CD	Any 5-ASA; any use	Cancer	54	27	0.50 (0.11–1.87)	4,9

Table 1 | (Continued)

Study, publication year	Country	Time period	Design	Setting	Condition	Exposure	Outcomes	No. of subjects	CRN cases	RR (95% CI)	Control for potential confounding factors †
Van Staa *et al.* [49], 2005	UK	1987–2001	C-C	Population	UC, CD	Any 5-ASA; any use in 6 mo before cancer diagnosis	Cancer	700	100	0.60 (0.38–0.96)	1,3,4,19–26
Rutter *et al.* [50], 2004	UK	1988–2002	C-C	Hospital	UC	Any 5-ASA; minimum 3 mo	Cancer/ dysplasia	204	68	2.31 (0.60–13.0)	2–4,9,27
Lindberg *et al.* [51], 2001	Sweden	1974–1993	Cohort	Hospital	UC	Sulfa; minimum 6 mo	Cancer/ dysplasia	142	50	0.64 (0.21–2.02)	–
Eaden *et al.* [52], 2000	UK	1980s	C-C	Hospital	UC	Any 5-ASA; 5–10 yr	Cancer	204	102	0.47 (0.22–1.00)	1–4,28–30
Lashner *et al.* [53], 1997	USA	1986–1992	Cohort	Hospital	UC	Mesa/Sulfa; minimum 6 mo	Cancer/ dysplasia	98	29	0.95 (0.34–2.70)	1,18
Moody *et al.* [54], 1996	UK	1972–1992	Cohort	Population	UC	Sulfa; long-term, up to 20 yr	Cancer	168	10	0.08 (0.02–0.39)	–
Pinczowski *et al.* [55], 1994	Sweden	1965–1983	C-C	Population	UC	Sulfa; minimum 3 mo	Cancer	298	102	0.38 (0.20–0.69)	1,2,4,18,31
Kirchgesner *et al.* [56], 2016	France	1996–2015	C-C	Hospital	UC, CD	Any 5-ASA; NR	Cancer/ dysplasia	130	38	0.27 (0.08–0.88)	6,10,32,33
Soon *et al.* [57], 2011	Singapore	NR	Cohort	Hospital	UC	Mesa/Sulfa; NR	Cancer/ dysplasia	138	8	0.25 (0.06–1.02)	–
Nourani *et al.* [58], 2008	USA	NR	C-C	Hospital	UC	Any 5-ASA; minimum 6 mo	Cancer/ dysplasia	182	36	0.10 (0.03–0.32)	–

CRN, colorectal neoplasia; C-C, case–control study; UC, ulcerative colitis; CD, Crohn's disease; 5-ASA, 5-aminosalicylates; Mesa, mesalazine; Sulfa, sulfasalazine; NR, not reported; RR, relative risk; CI, confidence interval.

†1, age; 2, disease extent; 3, disease duration; 4, sex; 5, IBD type; 6, primary sclerosing cholangitis; 7, disease severity; 8, use of corticosteroids; 9, age at diagnosis; 10, use of thiopurines; 11, inflammation activity; 12, history of dysplasia; 13, history of colon resection; 14, use of folic acid; 15, use of calcium; 16, race; 17, nationality; 18, year of diagnosis; 19, medical practice; 20, calendar time; 21, body mass index; 22, history of colorectal polyps; 23, use of NSAIDs, paracetamol, aspirin, immunosuppressants, and glucocorticoids; 24, prior gastrointestinal hospitalisation; 25, recorded colonoscopy; 26, number of GP visits; 27, year of index surveillance colonoscopy; 28, frequency of contacts with hospital doctor; 29, family history of colorectal cancer; 30, frequency of colonoscopies; 31, number of exacerbations per year; 32, presence of excess neutrophils or crypt abscess; 33, glandular distortion.

$P = 0.01$, respectively, posing a strong suspicion of small-study effects; however, inspection of the funnel plot (Figure S1) did not reveal any clearly asymmetrical pattern. In contrast, the Cochran's Q test had a $P < 0.001$ and the corresponding I-squared was 55%, indicating moderate heterogeneity among the studies (Table 2).

When the analysis was restricted to studies judged to be at low risk of bias (i.e. those scoring ≥6 stars at Newcastle–Ottawa scale; $n = 24$),[28–30, 32–36, 38–40, 42–50, 52–55] 5-ASA use was again associated with a significant reduction in the risk of developing CRN (RR = 0.61, 95% CI: 0.48–0.78; Table 2). Similarly, when only studies published in full-text form were included,[28–36, 38–55] the results did not materially change (RR = 0.63, 95% CI: 0.51–0.79; $n = 27$). Finally, when the analysis was restricted to studies adequately controlled for potential confounders (at least for age, disease extent and duration), the number of eligible studies[28, 34, 36, 39, 42, 45, 50, 52] was rather limited ($n = 8$), and the association became nonsignificant (RR = 0.66, 95% CI: 0.38–1.14; Table 2).

Analysis by study design and setting. To examine the consistency of our meta-analytic findings across varying study designs and settings with different potential biases,

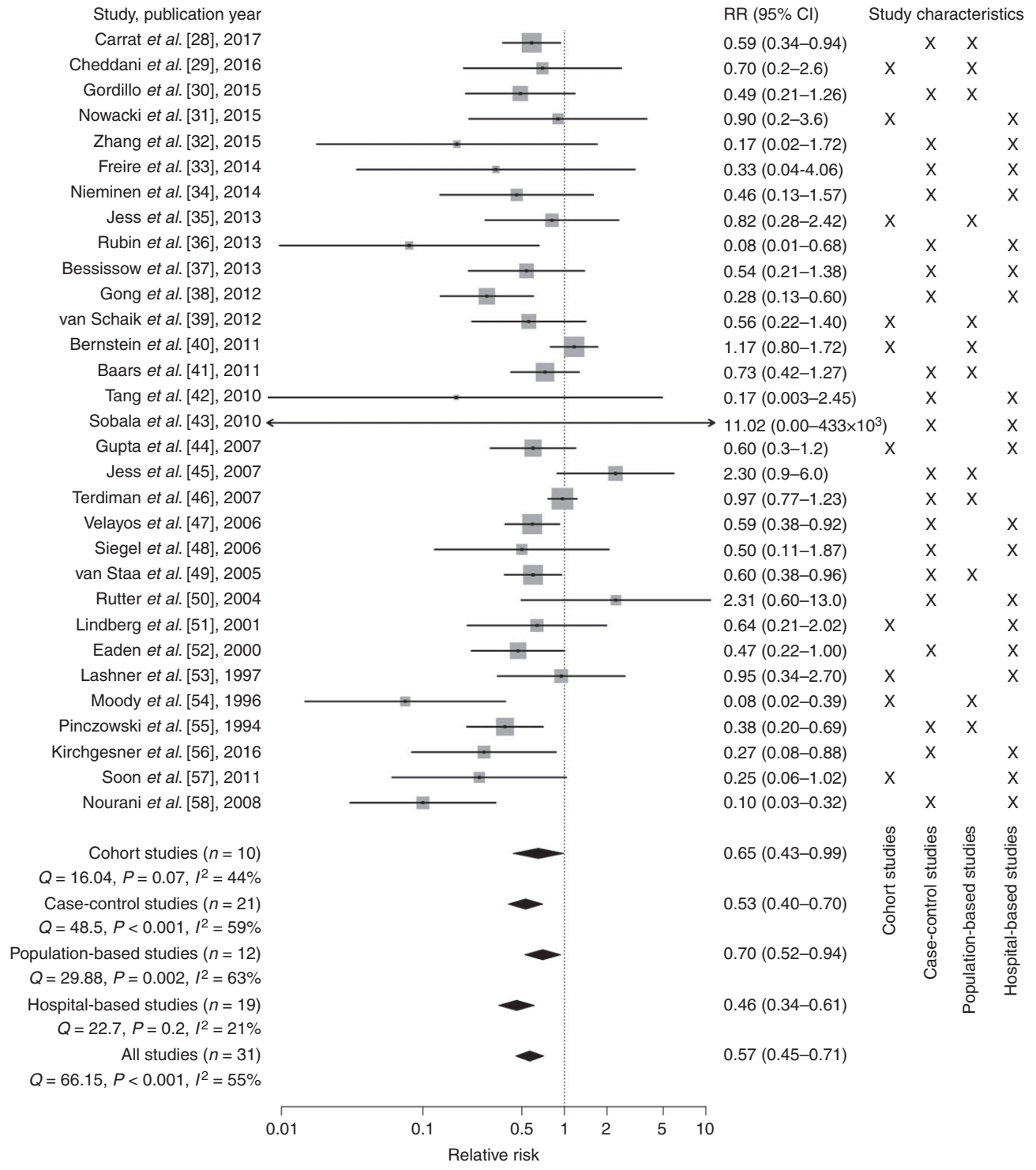

Figure 2 | Forest plot for colorectal neoplasia: results from individual studies and meta-analyses. *Footnote:* The RR and 95% CI for each study are displayed on a logarithmic scale. Pooled effect estimates are from random-effect models.

we stratified the data into subgroups. The inverse association between the exposure to 5-ASA and the risk of CRN was significant among both the cohort[29, 31, 35, 39, 40, 44, 51, 53, 54, 57] (RR = 0.65, 95% CI: 0.43–0.99; n = 10), and the case–control studies[28, 30, 32–34, 36–38, 41–43, 45–50, 52, 55, 56, 58] (RR = 0.53, 95% CI: 0.40–0.70; n = 21) (Table 2; Figure 2). Furthermore, we compared these RR estimates with a test of interaction.

Table 2 | Meta-analysis results

	No. of studies	Pooled effect estimate‡ RR (95% CI)	Tests of homogeneity Q value (d.f.)	P-value	I-squared	Tests of publication bias Begg's P-value	Egger's P-value
All studies	31	0.57 (0.45–0.71)	66.2 (30)	<0.001	55%	0.39	0.01
Cohort studies	10	0.65 (0.43–0.99)	16.0 (9)	0.07	44%	0.28	0.02
Case–control studies	21	0.53 (0.40–0.70)	48.5 (20)	<0.001	59%	0.57	0.02
Population-based studies	12	0.70 (0.52–0.94)	29.9 (11)	0.002	63%	0.73	0.12
Hospital-based studies	19	0.46 (0.34–0.61)	22.7 (18)	0.20	21%	0.55	0.37
Studies rated as low risk of bias (i.e, high-quality)*	24	0.61 (0.48–0.78)	50.5 (23)	<0.001	54%	0.82	0.03
Studies rated as high risk of bias, or not assessed	7	0.42 (0.24–0.74)	11.7 (6)	0.07	49%	0.55	0.21
Studies adequately controlled for confounding†	8	0.66 (0.38–1.14)	15.1 (7)	0.035	54%	0.71	0.82
Studies not adequately controlled for confounding	23	0.54 (0.42–0.70)	50.8 (22)	<0.001	57%	0.41	<0.01
Studies published in full-text form	27	0.63 (0.51–0.79)	50.6 (26)	0.003	49%	0.83	0.03
Studies published as short reports or abstracts	4	0.26 (0.13–0.54)	4.8 (3)	0.19	37%	0.31	0.39
Data for ulcerative colitis	21	0.50 (0.38–0.64)	32.8 (20)	0.035	39%	0.22	0.13
Data for Crohn's disease	5	0.76 (0.43–1.33)	1.4 (4)	0.85	0%	0.46	0.38
Data for colorectal cancer	21	0.58 (0.45–0.74)	40.4 (20)	0.005	50%	0.53	<0.01
Data for colorectal dysplasia	5	0.54 (0.35–0.84)	1.0 (4)	0.91	0%	0.81	0.66
Data for mesalamine	9	0.70 (0.51–0.94)	14.6 (8)	0.07	45%	0.47	0.13
Data for sulfasalazine	11	0.72 (0.51–1.01)	21.2 (10)	0.020	53%	0.99	0.12

RR, relative risk; CI, confidence interval; d.f., degrees-of-freedom.

Tests of interaction: Cohort vs. Case–control studies, $P = 0.41$; Population- vs. Hospital-based studies, $P = 0.04$; Low vs. High risk of bias, $P = 0.23$; Studies adequately controlled vs. not adequately controlled for confounding, $P = 0.52$; Studies published in full-text form vs. Short reports or abstracts, $P = 0.02$; Ulcerative colitis vs. Crohn's disease, $P = 0.19$.

*Studies scoring ≥6 stars at Newcastle–Ottawa scale were rated as low risk of bias (i.e, high-quality).

†Studies controlled at least for age, disease extent and duration.

‡Pooled effect estimates are derived from random-effect models.

We found no significant difference (cohort vs. case–control studies, $P = 0.41$).

Similarly, when we analysed by study setting, the inverse association between 5-ASA and CRN risk was significant among population-based,[28–30, 35, 39–41, 45, 46, 49, 54, 55] (RR = 0.70, 95% CI: 0.52–0.94; $n = 12$) and hospital-based studies[31–34, 36–38, 42–44, 47, 48, 50–53, 56–58] (RR = 0.46, 95% CI: 0.34–0.61; $n = 19$) (Table 2; Figure 2). However, the pooled estimates were significantly different (population- vs. hospital-based, test of interaction: $P = 0.04$). It is worth noting that population-based studies are less susceptible to selection biases; indeed, they scored higher at Newcastle–Ottawa scale (population- vs. hospital-based studies: 8 vs. 7, median values).

Analysis by underlying condition. Twenty-one studies contributed data specific for UC,[28, 30–33, 35–38, 40, 44, 47, 49–55, 57, 58] while only five studies for CD.[28, 35, 43, 48, 49] The reduction in CRN risk associated with 5-ASA use was 50% among UC patients (RR = 0.50, 95% CI: 0.38–0.64), but weaker and nonsignificant among patients with CD (RR = 0.76, 95% CI: 0.43–1.33) (Table 2).

Analysis by outcome studied. Twenty-one studies[28–32, 34–36, 38, 40–43, 46–49, 51, 52, 54, 55] evaluated the association of 5-ASA with CRC risk, while five studies[33, 34, 36, 37, 51] reported data for dysplasia. Exposure to 5-ASA was significantly associated with a protective effect against both outcomes (cancer: RR = 0.58, 95% CI: 0.45–0.74, Figure 3; dysplasia: RR = 0.54, 95% CI: 0.35–0.84, Figure 4) (Table 2).

Analysis by medication and dose. Nine studies[28, 36, 44–46, 49, 50, 52, 53] reported data for the CRN risk in IBD

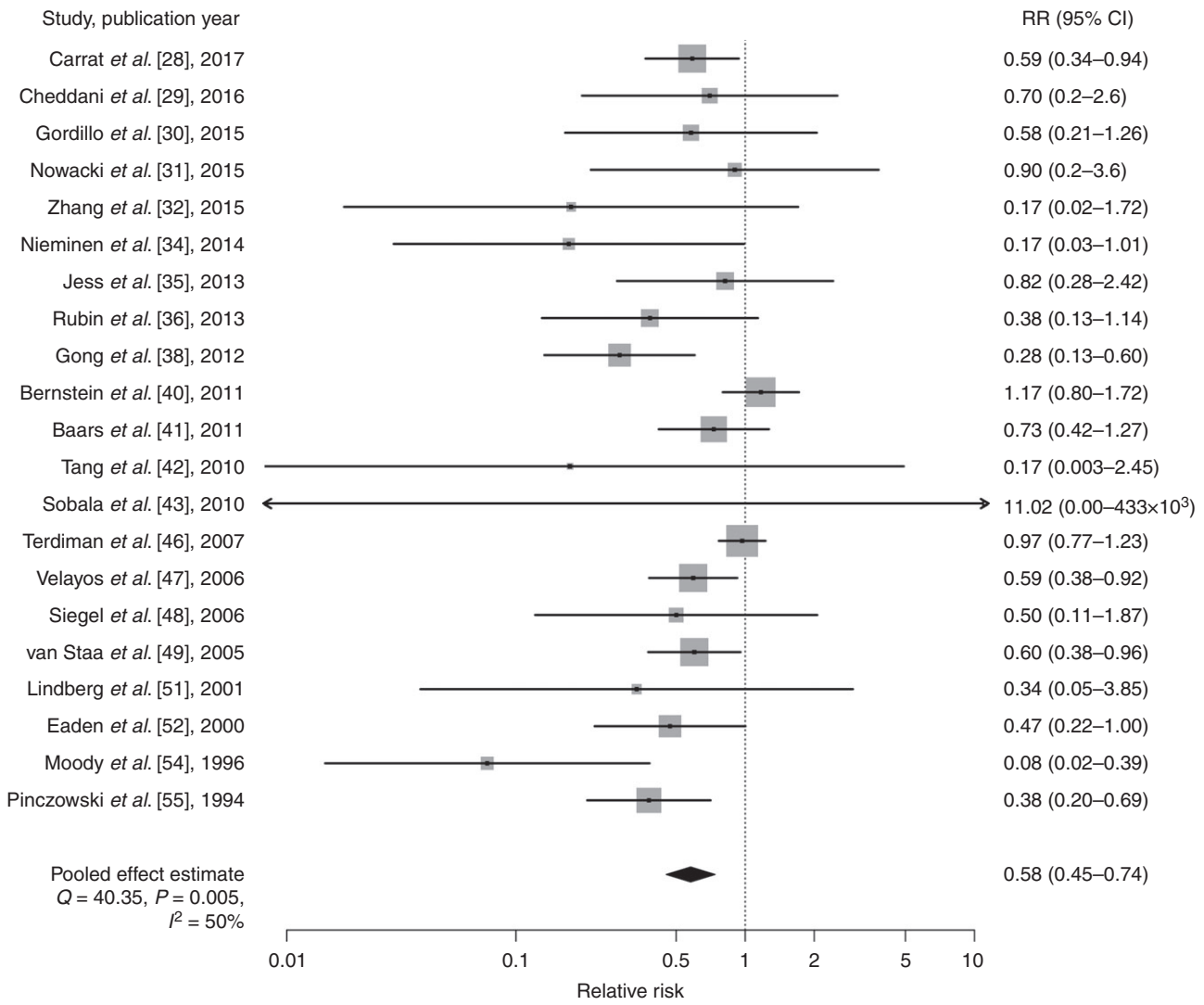

Figure 3 | Forest plot for colorectal cancer: results from individual studies and meta-analysis. *Footnote:* The RR and 95% CI for each study are displayed on a logarithmic scale. Pooled effect estimate is from a random-effect model.

patients prescribed mesalazine, while 11 studies[28, 36, 45, 46, 49–55] reported relevant data for patients receiving sulfasalazine treatment.

Exposure to mesalazine was significantly associated with a 30% reduction in the risk of neoplasia (RR=0.70, 95% CI: 0.51–0.94; Table 2). To determine whether there is a dose-effect associated with mesalazine use, we pooled data from four studies[36, 45, 49, 52] exploring the association in patients receiving mesalazine at doses higher than 1.2 g per day; colonic neoplasia risk reduction was more profound (RR=0.51, 95% CI: 0.29–0.88; I-squared = 39%). On the other hand, only two studies[49, 52] reported the association in patients receiving mesalazine at doses lower than 1.2 g per day; the pooled effect estimate was not significant (RR=0.23, 95% CI: 0.05–1.09; I-squared = 0%).

In contrast, the sulfasalazine-specific effect on CRN risk was marginally nonsignificant (RR=0.72, 95% CI: 0.51–1.01; Table 2). Sulfasalazine was not effective either at doses higher than 2.0 g per day (RR=0.99, 95% CI: 0.66–1.49) or at doses lower than 2.0 g per day (RR=0.87, 95% CI: 0.37–2.05), based on data from four studies,[36, 45, 49, 52] and two studies,[49, 52] respectively.

GRADE ASSESSMENT OF QUALITY OF THE BODY OF EVIDENCE

The overall analysis showed that 5-ASA use is associated with a 43% reduction in the risk of CRN (RR=0.57, 95% CI: 0.45–0.71). Quality of evidence, assessed using the GRADE criteria, is *"very low"* because the result is relied on observational studies, and presence of small-study

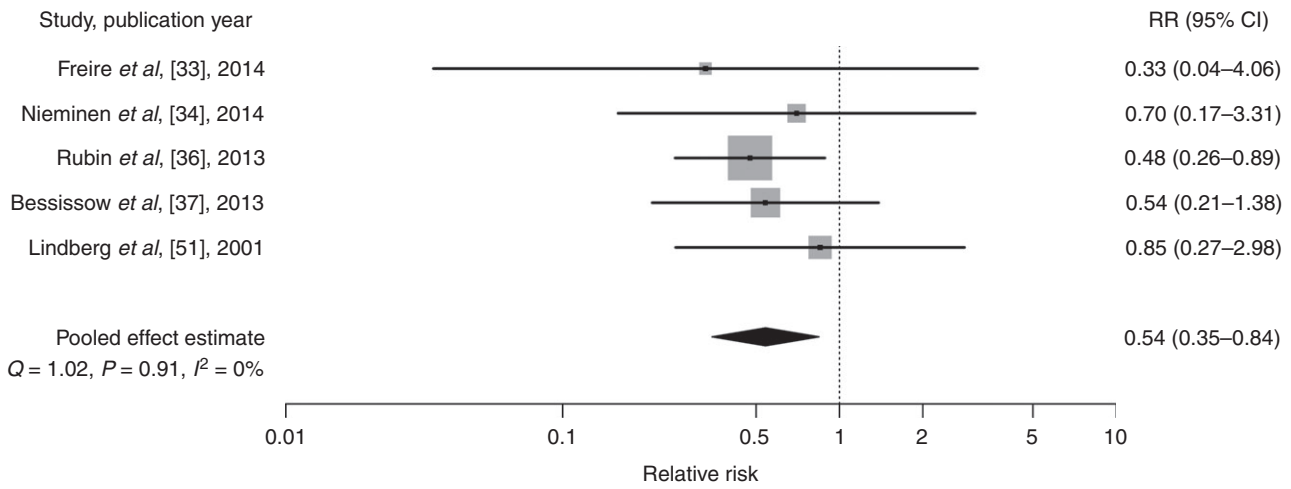

Figure 4 | Forest plot for colorectal dysplasia: results from individual studies and meta-analysis. Footnote: The RR and 95% CI for each study are displayed on a logarithmic scale. Pooled effect estimate is from a random-effect model.

effects is suspected. On the other hand, the reduction in CRN risk associated with 5-ASA is strong among UC patients (RR = 0.50, 95% CI: 0.38–0.64) and quality of this evidence was considered *"moderate"* because the data is derived solely from observational studies, but the magnitude of the effect is relatively large. Similarly, the quality of evidence for the mesalazine-specific effect (RR = 0.70, 95% CI: 0.51–0.94) was considered *"moderate"* because the result is relied on observational studies, but we identified a possible dose–response relation lending support to a causal explanation[64] of the mesalazine-CRN association. Quality assessment of the evidence, and summary of findings, are given in Table S3.

DISCUSSION

In this updated systematic review and meta-analysis of observational studies, we synthesised the current totality of evidence on the association of 5-ASA use with colorectal neoplasia in IBD patients. Overall, synthesis of 31 independent studies identified a large (on the order of 40–45% risk reduction) protective effect of 5-ASA use, at therapeutic doses, against colorectal neoplasia in patients with IBD. The findings were almost identical for both outcomes (colorectal cancer and dysplasia) and remained strongly significant when the data were analysed by study design, study setting and quality score.

Moderate between-study heterogeneity was detected; thus, differences in the underlying treatment effect are likely, due to differences in the populations studied, medications used and study methods. Indeed, inconsistency of results was partly explained in subgroup analyses: (i) the reduction in CRN risk associated with 5-ASA use was 50% among UC patients, but nonsignificant among CD patients; (ii) exposure to mesalazine significantly decreased neoplasia risk, while there was no significant sulfasalazine-specific effect and (iii) the findings were statistically significant in both population-based and clinic-based studies, but much stronger in the latter category (30% vs. 54% risk reduction).

To the best of our knowledge, the current work is the most comprehensive meta-analysis on the topic. In 2005, Velayos *et al.*[8] published a meta-analysis of nine observational studies (474 CRN cases) examining the effect of 5-ASA on colorectal neoplasia in UC patients. They identified a significant reduction in the risk of CRN, but not of dysplasia; however, only two studies evaluated this outcome. Since then, several meta-analyses have been published with often conflicting results. In 2012, Nguyen *et al.*[9] reported a meta-analysis of four studies conducted in nonreferral populations; they failed to identify any protective effect of 5-ASA on CRC in IBD. Then, O'Connor *et al.*[10] synthesised data from eight studies (867 CRN cases) and reported a mesalazine-specific protective effect against CRN. Finally, Zhao *et al.*[11] published in 2014 the most comprehensive work (17 studies, 1508 CRN cases) showing a 37% reduction in CRN among UC patients using 5-ASA.

As compared to these studies, our meta-analysis uses a much broader evidence base, includes a much larger number of studies (n = 31) and CRN cases (n = 2137), identifies associations not previously shown (protective effect also for dysplasia, significant reduction in CRN risk in population-based studies), and provides updated evidence that can inform patients and clinicians.

Nevertheless, several limitations should be considered in interpreting the results of this meta-analysis: First, though a rigorous and extensive literature search was conducted to retrieve all eligible studies (i.e. PubMed, Scopus, major conference proceedings and relevant review articles were investigated), Embase – that is considered as a standard for many systematic reviews – was not searched; however, recent research has shown that for systematic reviews of the effects of therapeutic interventions, gains from searching sources beyond PubMed, and from searching Embase in particular, may be modest.[65] Second, the included studies were variable in terms of study designs, and definitions of 5-ASA exposure. We investigated sources of heterogeneity conducting detailed subgroup analyses; however, the pooled effect estimates are still based on rather heterogeneous data and should be interpreted cautiously. Third, bias and confounding may always constitute an alternative explanation for the results. Twenty-one of the primary studies were controlled for confounders by matching or adjustments; however, control for different factors among the studies may also explain the heterogeneity observed. In any event, the possibility of residual confounding cannot be excluded, either from unknown or unmeasured factors, or from imperfectly controlled confounders. Finally, small-study effects or publication bias is another issue that may affect a meta-analysis. Our literature search was as inclusive as possible, and we did not exclude any study because of methodological characteristics or any subjective quality criteria. Nevertheless, we did not search for unpublished studies or for original data. Though visual inspection of the funnel plot did not reveal any clearly asymmetric pattern, the Begg's and the Egger's tests posed a strong suspicion of small-study effects. Thus, selective publication of smaller studies with statistically significant results may have occurred to some extent.

Although our knowledge of the possible biological mechanisms underlying this association is rather incomplete, our results may be biologically plausible. A body of experimental data has demonstrated the ability of 5-ASA to inhibit pathways that sustain colon carcinogenesis;[66] thus, the potential protective effect of 5-ASA may extend beyond simply reducing colonic inflammation. For instance, mesalazine has been shown to interfere with colon cancer cell growth and survival, through negatively regulating the COX-2/PGE2 axis,[67, 68] inhibiting the EGFR, NF-κB and Wnt/β-catenin signalling,[69–73] activating PPAR-γ in colorectal cancer cells,[74, 75] modulating cell cycle-related proteins,[76] and improving replication fidelity.[77]

In conclusion, synthesis of the existing epidemiologic evidence supports the hypothesis that exposure to 5-ASA, at therapeutic doses, may significantly reduce the risk of developing colorectal neoplasia. This finding was confirmed particularly for UC patients, and for exposure to mesalazine; in contrast, we found no such evidence for CD patients, or any sulfasalazine-specific effect. Nevertheless, further research is warranted to confirm or refute these findings, and explore the association for critical issues, such as the dose and duration of drug exposure, or the extent and severity of the disease over time. Until further high-quality prospective research is available, this class of medications remains a strong, but as yet unproven, candidate for colorectal cancer chemoprevention.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Contour-enhanced funnel plot of observed relative risk against standard error (as a surrogate of study size) for all studies analysed.

Table S1. Risk of bias assessment for the studies included in the meta-analysis.

Table S2. GRADE assessment of quality of the body of evidence, and summary of findings.

Appendix S1. Studies not found eligible for this systematic review (n = 46), with reasons for exclusion.

AUTHORSHIP

Guarantor of the article: Dr. Stefanos Bonovas.

Author contributions: SB, GF, TL, GN, LPB, SD: conception and design; SB, GN: literature search and data collection; SB, TL: statistical analysis; SB, GF, TL, GN, LPB, SD: data interpretation; SB: drafting of the manuscript; SB, GF, TL, GN, LPB, SD: critical revision of the manuscript for important intellectual content; SB, GF, TL, GN, LPB, SD: final approval of the version to be published, including the authorship list.

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