META-ANALYSIS

Does aspirin or non-aspirin non-steroidal anti-inflammatory drug use prevent colorectal cancer in inflammatory bowel disease?

Nick E Burr, Mark A Hull, Venkataraman Subramanian

Nick E Burr, Mark A Hull, Venkataraman Subramanian, Leeds Institute for Biomedical and Clinical Sciences, St James's University Hospital, University of Leeds, LS9 7TF Leeds, United Kingdom

Correspondence to: Dr. Venkataraman Subramanian, MD, DM, MRCP, Leeds Institute for Biomedical and Clinical Sciences, St James's University Hospital, University of Leeds, LS9 7TF Leeds, United Kingdom. nick.burr@nhs.net
Telephone: +44-113-2068691
Fax: +44-113-2068688

Abstract

AIM: To determine whether aspirin or non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs) prevent colorectal cancer (CRC) in patients with inflammatory bowel disease (IBD).

METHODS: We performed a systematic review and meta-analysis. We searched for articles reporting the risk of CRC in patients with IBD related to aspirin or NA-NSAID use. Pooled odds ratios (OR) and 95%CIs were determined using a random-effects model. Publication bias was assessed using Funnel plots and Egger's test. Heterogeneity was assessed using Cochran's Q and the I^2 statistic.

RESULTS: Eight studies involving 14917 patients and 3 studies involving 1282 patients provided data on the risk of CRC in patients with IBD taking NA-NSAIDs and aspirin respectively. The pooled OR of developing CRC after exposure to NA-NSAIDs in patients with IBD was 0.80 (95%CI: 0.39-1.21) and after exposure to aspirin it was 0.66 (95%CI: 0.06-1.39). There was significant heterogeneity ($I^2 > 50\%$) between the studies. There was no change in the effect estimates on subgroup analyses of the population studied or whether adjustment or matching was performed.

CONCLUSION: There is a lack of high quality evidence on this important clinical topic. From the available evidence NA-NSAID or aspirin use does not appear to be chemopreventative for CRC in patients with IBD.

Core tip: Colorectal cancer (CRC) remains a serious complication of inflammatory bowel disease (IBD) and chemoprevention is an attractive alternative to prophylactic surgery or intensive surveillance programs. Aspirin and non-steroidal anti-inflammatory drugs have chemopreventative activity against "sporadic" CRC. We have synthesized the available data for the prevention of IBD associated CRC and found no potential protective effect for either medication. There is a lack of available data on the potential effects of these medications in preventing CRC in patients with IBD and there is a need for high quality, focused studies on this topic.

INTRODUCTION

One of the most serious complications of inflammatory bowel disease (IBD) is the development of colorectal cancer (CRC). Worldwide, the risk of developing CRC ranges between 5-40/100000 people depending on location, with a marked increase in Western populations[1,2], this is increased to 300/100000 in patients with longstanding ulcerative colitis (UC)[3]. The cumulative probability of developing CRC in patients with UC increases from 2%, 8% and 18% after 10, 20 and 30 years of disease respectively[3]. In patients with CD, a meta-analysis of population-based studies has demonstrated an increased risk of CRC, with a standardized incidence ratio of 1.9 (95%CI: 1.4-2.5)[4]. Whilst the risk of CRC in CD appears to be stable, a recent study from Denmark[5] has reported a decrease in CRC incidence in patients with UC over the past 30 years. It is currently unclear why there may be a reduction in incidence, but a plausible hypothesis is that increased use of IBD medications may reduce inflammation-driven colorectal carcinogenesis.

Identified risk factors for developing CRC in patients with IBD include primary sclerosing cholangitis[6], degree of inflammation[7-9], duration of disease, extent of colonic involvement[10], as well as family history of colorectal cancer[10,11]. International society guidelines advocate regular surveillance colonoscopy examinations to identify malignant and pre-malignant lesions[12]. These are resource intensive and not without risk. As such primary prevention of CRC in these patients is an attractive alternative. Several treatment modalities have been proposed as potential chemopreventative agents and studied mainly *via* retrospective case-control and cohort studies[13]. These include 5-aminosalicylic acid preparations[14-16], ursodeoxycholic acid (in patients with concomitant PSC)[17,18], thiopurine analogues[19], aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NA-NSAIDs), and statins[20].

There are plausible biological mechanisms for how NA-NSAIDs, and aspirin, may prevent CRC development in patients with IBD. In epidemiological, laboratory and clinical studies aspirin has consistently been shown to reduce the incidence of several tumors, including "sporadic" CRC not related to a defined genetic predisposition or IBD[21]. The exact anti-neoplastic mechanism(s) of aspirin and NA-NSAIDs is not yet clear but several cell signaling pathways have been implicated as targets for COX-dependent and COX-independent mechanisms of action[22,23]. Aspirin use also appears to prevent CRC metastasis, as well as the risk of primary CRC[24].

As well as the potential benefits for chemoprevention there are concerns about negative effects of aspirin and the NA-NSAIDs on the lower gastrointestinal tract. Adverse effects of NA-NSAIDs on the colon include a NSAID colonopathy with diaphragm-like stricturing and mucosal inflammation and ulceration, complicated diverticular disease including bleeding[25], and microscopic colitis[26,27]. A possible association between the use of NSAIDs including aspirin and the onset or relapse of IBD has been repeatedly suggested. However, lack of controlled prospective trials make it difficult to draw definite conclusions[28,29].

Aspirin use is associated with several side effects. The main concern is the risk of upper gastrointestinal bleeding and hemorrhagic stroke. Most studies using aspirin have not shown increased death rates from gastrointestinal bleeding suggesting that any bleeds related to aspirin are small and relatively insignificant[30].

There are currently conflicting data on the putative role of NA-NSAIDs and aspirin in the prevention of CRC in IBD. We therefore performed a systematic review and meta-analysis in order to identify if there is evidence that aspirin and NA-NSAIDs have chemopreventative activity against CRC in patients with IBD.

MATERIALS AND METHODS

We followed a pre-specified and peer-reviewed protocol; the PRISMA statement, a 27 item checklist deemed essential for reporting systematic reviews and meta-analyses of randomized controlled trials and observational studies[31].

Search strategy
We searched multiple electronic databases including

MEDLINE (1965 to July 2015), EMBASE (1974 to July 2015), ISI Web of Science (1945-July 2015) and the Cochrane Register of Controlled Trials. The MeSH search terms included were Inflammatory Bowel Disease AND CRC AND Aspirin OR NSAIDs. Free text terms and variations were used. No limits or language restrictions were applied. We performed a recursive search of the bibliographies of relevant review articles and of the included studies. Articles were assessed by two independent reviews (Burr NE and Subramanian V) to assess eligibility for inclusion. Any disagreements were resolved by consensus decision.

Study selection

Studies were eligible for inclusion if they reported on risk of developing CRC in patients with IBD on either NA-NSAIDs or aspirin compared to a control population. Studies published only in abstract form were not included. Two reviewers (Burr NE and Subramanian V) independently screened titles and abstracts identified by the preliminary searches to identity potentially eligible studies. Both reviewers independently assessed the full text articles of potentially relevant studies for inclusion in the pooled analysis. Data from included studies were independently extracted by two investigators (Burr NE and Subramanian V). Information was collected on characteristics of the study (population studied, country of origin, study design, definition of drug exposure) and medication use including NA-NSAIDs, aspirin and development of CRC. Agreement between the reviewers was greater than 95% and differences between the datasets were resolved by consensus decision.

Statistical analysis

The odds ratio (OR) with 95% confidence interval (CI) of developing CRC in patients with IBD on aspirin or NA-NSAIDs compared with controls was extracted from the study. When insufficient (no information on odds ratio or drug exposure) data had been published, we contacted the study authors. As randomization and blinding is not possible in observational studies and baseline differences between the groups can confound the results we used the authors' ORs with adjustment for potential confounding factors wherever available. The pooled OR estimate was calculated from an inverse-variance-weighted average of the individual studies[32]. A DerSimonian-Laird random effects model was used a priori[33]. As a further sensitivity analysis a fixed effects model was used for comparison. Stata version 12 (StataCorp, College Station, Texas, United States), was used for all of the data analysis.

We used the Cochran's Q statistic to test hete-rogeneity among pooled estimates[34]. Statistical heterogeneity was also measured by the I^2 statistic, which quantifies the proportion of inconsistency in individual studies that cannot be explained by chance[35]. Values of I^2 equal to 25%, 50%, and 75% represent low, moderate, and high heterogeneity,

respectively. To test for publication bias, we used a test for asymmetry of the funnel plot proposed by Egger *et al*[36]. This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the normalized effect estimate (estimate divided by the standard error) against precision (reciprocal of the standard error of the estimate) weighted by the reciprocal of the variance of the estimate.

The quality of the primary studies assessing the risk of bias was evaluated using the Newcastle-Ottawa Scale for non-randomized studies (NOS)[37]. Studies score for a maximum of 4 for selection, 2 for comparability and 3 for outcomes (cohort) or exposures (case-control). We regarded scores of 0-3 as low, 4-6 as medium and 7-9 as high methodological quality.

We performed pre-planned subgroup analyses to assess the following factors on the trial outcome and on the heterogeneity of the analyses: (1) matching or adjustment for confounders (any or none); and (2) the population studied (population-based or other).

RESULTS

Our searches retrieved 9 potentially relevant articles, of which 3[14,38,39] provided data on aspirin exposure and risk of CRC and 8[14,39-45] on NA-NSAID exposure and risk of CRC in patients with IBD. Figure 1 outlines the fate of the selected articles. The studies were either retrospective case-control, nested case-control or cohort studies by design and 5[14,40-42,44] included population-based analysis. Table 1 lists all the included studies and their characteristics. We contacted authors of papers for missing data but did not obtain any extra information. The quality assessment of the studies using the Newcastle Ottawa scale is also detailed in Table 1. Only 3 studies[39,41,42] provided multivariate analysis of data for risk of developing CRC in IBD patients exposed to aspirin or NA-NSAIDs.

Cumulative risk of developing CRC in IBD patients exposed to NA-NSAIDs

Eight studies, including 14917 patients with IBD provided data on the risk of developing CRC after exposure to NA-NSAIDs. Using a random effects model, the pooled adjusted OR of developing CRC after exposure to NA-NSAIDs in patients with IBD was 0.80 (95%CI: 0.39-1.21) (Figure 2). The heterogeneity between the studies was high (Cochran's Q = 38.15, P = 0.00 and I^2 = 81.6%).

Sensitivity analysis and publication bias

Pre-planned subgroup analyses showed that there was no difference in the overall effect estimate when comparing the population studied or whe-ther adjustment or matching for confounders was performed (Table 2). There was no heterogeneity among population-based studies (Cochran's Q = 2.39,

Table 1 Characteristics of studies included in the analysis

Author	Design	Population	Definition of IBD	Drug exposure	Exclusion criteria	No. of patients	OR (95%CI)[1]	Adjustment/matching	NOS quality assessment
Bansal *et al*[42], 1996	Case-control	US veterans affairs	Clinical database	NSAID associated diagnosis	Not specified	11446	0.84 (0.65-1.09)	Adjusted for age, sex and ethnicity	6
Eaden *et al*[38], 2000	Case-control	UK Hospital	Clinical, pathological and radiological records	Prescribed 5-10 years before diagnosis	Colorectal surgery, IBD diagnosed at time of cancer diagnosis	206	0.80 (0.21-2.98) Aspirin	Non-adjusted	4
Van Staal *et al*[14], 2005	Nested case-control	UK general practice	Clinical records	Prescribed in the 6 mo prior to diagnosis	Colorectal surgery, previous history of CRC	700	1.52 (0.7-3.25) (Aspirin) 0.80 (0.38-1.66) (NA-NSAID's)	Non-adjusted	5
Velayos *et al*[39], 2006	Case-control	US Hospital	Clinical, pathological and endoscopic records	2 records of use in notes	Previous CRC, IBD diagnosed at same time as CRC, incomplete data	376	0.3 (0.1-0.8) (Aspirin) 0.1 (0.03-0.5) (NA-NSAID)	Matched on gender, duration of disease and extent of disease	8
Terdiman *et al*[40], 2007	Case-control	US insurance claims	Clinical records	Prescribed in the year before diagnosis	Colorectal surgery	1536	0.97 (0.74-1.28)	Non-adjusted	5
Tang *et al*[43], 2010	Retrospective cohort	US Hospital	Clinical database	Ever used	No colonic involvement of IBD	48	0.29 (0.03-2.75)	Non-adjusted	5
Samadder *et al*[41], 2011	Case-control	N. Israel community	Patient questionnaires	Weekly for > 3 yr	Previous history of CRC	60	0.49 (0.07-3.32)	Matched for age, gender and ethnicity	6
Baars *et al*[44], 2011	Case-control	Netherlands nationwide pathology	Pathology reports	Ever used	IBD diagnosed at the same time as CRC	551	1.96 (0.72-5.36)	Non-adjusted	6
Rubin *et al*[45], 2013	Case-control	US Hospital	Pathology reports	Not specified	Incomplete records	200	1.84 (0.75-2.5)	Non-adjusted	5

[1]OR for colorectal cancer (CRC) chemoprotective effect of non-aspirin non-steroidal (NA-NSAID) use in patients in inflammatory bowel disease (IBD) unless otherwise stated. For cohort studies was used only for the Tang *et al*[43] study. The scale for case-control studies was used for the other studies. NOS: Newcastle-Ottawa Score.
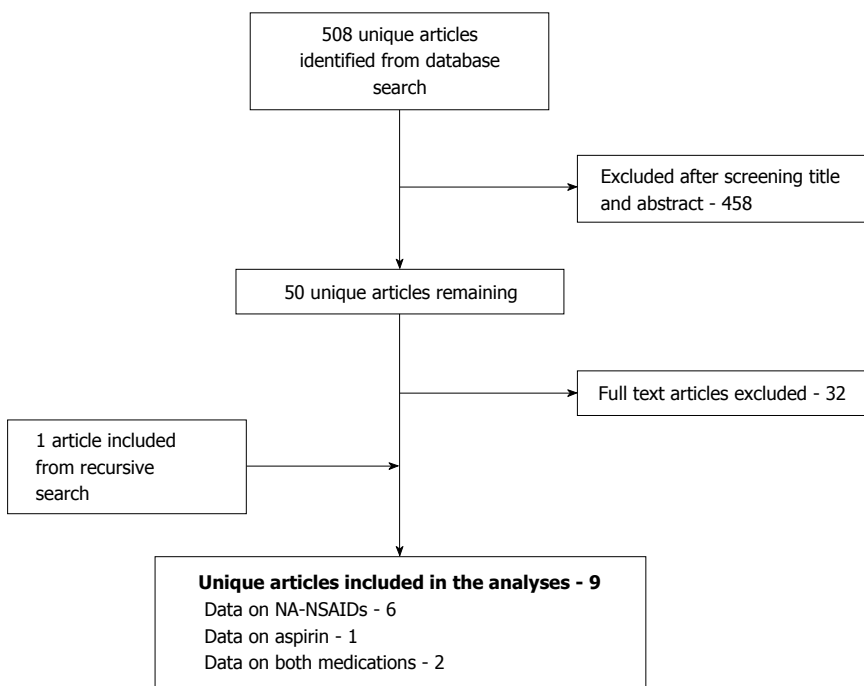
Figure 1 Flow chart showing the results from the search strategy. NA-NSAIDs: Non-aspirin non-steroidal anti-inflammatory drugs.

Study ID	ES (95%CI)	% Weight
NA-NSAID		
Bansal (1996)	0.84 (0.65, 1.09)	16.11
Van Staal (2005)	0.80 (0.38, 1.66)	10.64
Velayos (2006)	0.10 (0.03, 0.50)	15.95
Terdiman (2007)	0.97 (0.74, 1.28)	15.56
Tang (2010)	0.29 (0.03, 2.75)	4.52
Sammader (2011)	0.49 (0.07, 3.32)	3.44
Baars (2011)	1.96 (0.72, 5.36)	1.87
Rubin (2013)	1.84 (0.75, 2.50)	7.97
Subtotal (I^2 = 81.6%, P = 0.000)	0.80 (0.39, 1.21)	76.07
Aspirin		
Eaden (2000)	0.80 (0.21, 2.98)	4.40
Van Staal (2005)	1.52 (0.70, 3.25)	4.96
Velayos (2006)	0.30 (0.10, 0.80)	14.57
Subtotal (I^2 = 44.4%, P = 0.166)	0.66 (-0.06, 1.39)	23.93
Overall (I^2 = 77.1%, P = 0.000)	0.76 (0.42, 1.09)	100.00
NOTE: Weights are from random effects analysis		

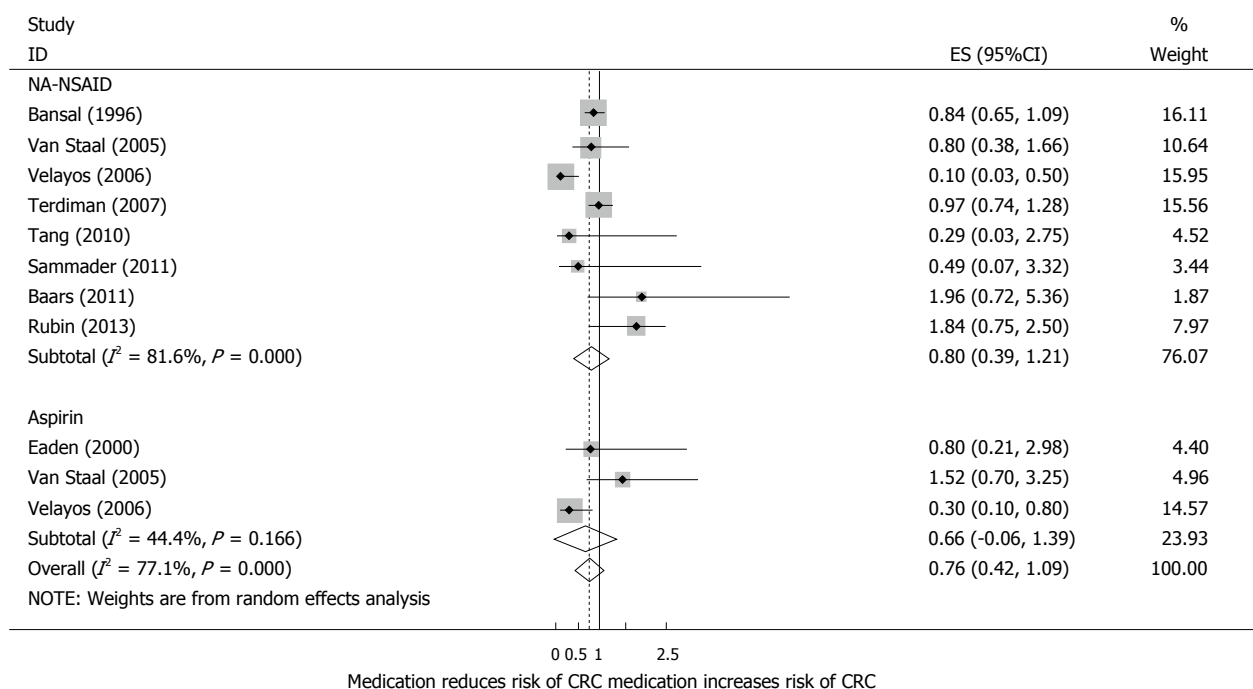Medication reduces risk of CRC medication increases risk of CRC

Figure 2 Forest plot of odds ratios and 95%CI for effect of non-aspirin non-steroids anti-inflammatory drugs or aspirin on colorectal cancer development in patients with inflammatory bowel disease. Random effects model.

Table 2 Subgroup analyses for studies reporting on risk of colorectal cancer in patients with inflammatory bowel disease taking non-aspirin non-steroidal anti-inflammatory drugs

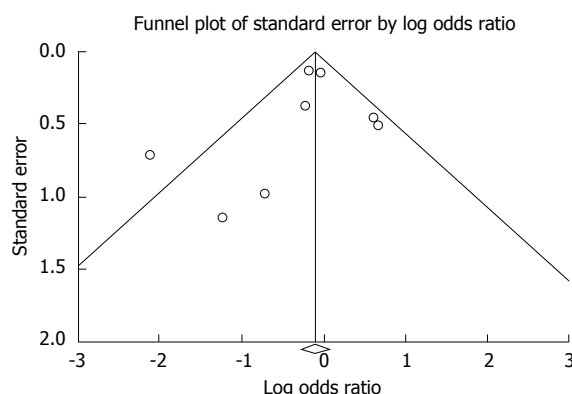|	No. of studies	Pooled OR (95%CI)
Matched y/n		
Matched/adjusted	3	0.47 (0.18-1.13)
None	5	1.04 (0.65-1.43)
Study location		
Hospital	6	0.92 (0.78-2.62)
Population	2	0.88 (0.72-1.04)

Figure 3 Funnel plot for publication bias for studies looking at the odds ratio of developing colorectal cancer in patients with inflammatory bowel disease on non-aspirin non-steroids anti-inflammatory drugs.

P = 0.79 and I^2 = 0%) but high heterogeneity between hospital-based studies (Cochran's Q = 14.17, P < 0.005 and I^2 = 92%)). There was some funnel plot asymmetry compatible with publication bias (Figure 3). However Egger's regression asymmetry test was non-significant (P = 0.56). The regression asymmetry test is probably underpowered as there are only 8 studies included in this meta-analysis[46].

Cumulative risk of developing CRC in IBD patients exposed to aspirin

Three studies, including 1282 patients with IBD, provided data on risks of developing CRC after exposure to aspirin. The pooled adjusted OR of developing CRC after exposure to aspirin in patients with IBD was 0.66 (95%CI: 0.06-1.39) (Figure 2). A random effects model was chosen a priori. The heterogeneity between the studies was high (Cochran's Q = 0.166. and I^2 = 44.4%). A fixed effects model was performed as a sensitivity test which changed the pooled adjusted OR to 0.41 (95%CI: 0.08-0.74). We

did not attempt to do an analysis of publication bias or subgroup analyses as there were only 3 studies included in the final analysis.

DISCUSSION

We present the first systematic review and meta-analysis of the effects of NA-NSAIDs and aspirin for CRC chemoprevention in patients with IBD to our knowledge. It is important to synthesize the available literature on this subject as CRC remains an important complication of IBD and NA-NSAIDs including aspirin have been consistently shown to have a protective effect in sporadic colorectal cancer[47,48]. We found 9 retrospective studies fitting the inclusion criteria, but unfortunately there have been no prospective randomized trials.

There were only 3 studies that reported on aspirin use in patients with IBD associated cancer. We found no significant potential protective effect for NA-NSAIDs or aspirin against the development of CRC in IBD patients.

There are several limitations to this meta-analysis. All the included studies are retrospective and are therefore subject to inherent biases and confounding. Publication bias is another possible limitation as negative studies are less likely to be published and therefore not included in the analyses. However we have attempted to reduce the possibility of publication bias by conducting an exhaustive search of the literature and did not limit inclusion of studies based on language. Most of the studies included in our analysis reported NA-NSAID and aspirin use as a secondary outcome measure and results from a multivariate analysis was provided only by 3 studies[39,41,42]. The study with the most robust methodology from Velayos *et al*[39] reported a significant chemopreventative role for both NA-NSAIDs and aspirin. There were differences in the studies related to the definition of drug exposure and as these studies were all retrospective it was not possible to check compliance with the medication. A further limitation with studies of this type is confounding by indication. Aspirin and NA-NSAID use could be associated with another factor, such as another medical condition, that is associated with colorectal cancer. It is not possible to adjust or correct for all such factors so this always must be born in mind when interpreting such studies.

The dose and duration of medication exposure was not consistently recorded. An important consideration of chemoprevention against colorectal cancer is the duration of exposure to the medication. In the evidence for aspirin protecting against sporadic CRC a duration of > 5 years conferred a 34% reduction in CRC risk[49]. The only study included here which took this into consideration was Eaden *et al*[38] where a prescription in the preceding 5-10 years before diagnosis was required for inclusion as positive exposure (Table 1). The dose of aspirin used was not stated in most of the studies but it is likely to have been low dose as used in routine clinical practice in patients with cardiovascular risk factors, 75 mg in the United Kingdom and 81 mg in the United States. It is possible that a higher dose may be needed for chemoprevention of colitis-associated CRC. For example, a recent trial in patients with Lynch syndrome, a hereditary condition associated with high risk of CRC, demonstrated that high dose (600 mg daily) aspirin conferred protection against CRC[50]. Little information was provided about the timing and duration of exposure to aspirin and NA-NSAID's in any of the included studies. Aspirin and NA-NSAIDs may be unable to prevent the progression from dysplasia to cancer and could therefore be chemopreventative only in those with exposure to the drug from soon after onset of IBD and those with longer duration of exposure to the medication. Unfortunately none of the studies included in this meta-analysis provided data on the timing of exposure to NA-NSAID/aspirin and duration of IBD, to determine if early or long-term exposure was chemopreventative. The main outcome of interest was the development of CRC and not dysplasia which could support the argument that in some of the patients, CRC may have developed in those exposed to aspirin or NA-NSAIDs only after they had already developed colorectal neoplasia.

Adverse effects of NSAIDs on the gastrointestinal tract need to be considered in future studies as there is a potential increased incidence of disease flares with the use of NSAIDs, including aspirin[51]. This issue is still under debate as NSAIDs are often used for treatment of arthralgia and abdominal pain and it may be that NSAIDs are used after the flare develops rather than being the potential cause of the flare.

Colorectal cancer remains a serious complication of IBD. Current methods to reduce CRC in IBD are the use of colonoscopic surveillance or by prophylactic proctocolectomy. British Society of Gastroenterology guidelines advocate screening and surveillance colonoscopy which can result in annual tests for high risk patients[52]. Chemoprevention is therefore an attractive proposition for these patients. NA-NSAIDs and aspirin remain biologically plausible targets for chemoprevention in IBD. As we have shown the clinical evidence is limited. The available data is hampered as most of the studies include small numbers of patients and do not include adequate information on medication dose and duration. Potential chemoprevention agents are likely to take several years to display a protective effect as in the sporadic CRC population and this should be borne in mind in future studies. Prospective randomized chemoprevention trials are unlikely to be done as the sample size required would be too large and therefore well-conducted epidemiological studies using prospective databases are needed to clarify the true effect of aspirin and/or NA-NSAIDs on the risk of CRC in patients with IBD.

ACKNOWLEDGMENTS

COMMENTS

Background
Colorectal cancer is an important complication of inflammatory bowel disease (IBD). Primary prevention is an attractive strategy and aspirin and non-aspirin anti-inflammatory drugs are plausible options. Several studies have investigated the possible use of these medications but the data has not been synthesized.

Research frontiers
These medications have shown promise in preventing colorectal cancer in a non IBD population. It is important to examine this potential effects in the IBD population who are at greater risk of colorectal cancer.

Innovations and breakthroughs
This is the first meta-analysis to investigate this potential effect. From the

available evidence there is no data to support the use of these medications in chemoprevention against colorectal cancer but the study has highlighted the lack of high quality data.

Applications
The study highlights the need for focused studies into the potential protective effect of these medications.

Peer-review
This systematic review and meta-analysis gives useful information to clinicians and patients on the role of these medications. It highlights the lack of data in this area and the need for high quality focused studies.

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