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Review Article

A meta-analysis of the correlation between non-steroidal anti-inflammatory drugs and recurrent colorectal adenomatous polyps

Yuanyuan Zhang, Lisha Chen, Huixin Chen

Department of Gastroenterology, Huizhou Municipal Center Hospital, Huizhou 516001, Guangdong Province, China

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Abstract: Aim: The purpose of this study was to evaluate the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on the recurrence risk of colorectal adenomas through a meta-analysis of published studies. Methods: A meta-analysis was performed to evaluate the effect of NSAIDs on the incidence rates of colorectal adenomatous polyps, using PubMed, Ovid, Elsevier, and other journal databases. Data were processed using Review Manager 5.3 and random errors were calculated using trial sequential analysis (TSA). Results: A total of 8 studies published between 2003 and 2014 were selected. In the data collected, the patients on long-term usage of low-dose NSAIDs were shown to have significantly lower risk of colorectal adenoma compared with those on placebos (RR=0.80, 95% CI=0.70-0.92), with relatively low random errors. Long-term usage of low-dose NSAIDs was also found to have inhibitory effects on advanced adenomas (RR=0.66, 95% CI=0.44-0.99), but with relatively high random errors. Besides, high-dose NSAIDs were also shown to have inhibitory but inconsistent effects on adenomas and advanced adenomas (RR=0.66, 95% CI=0.59-0.72), and the withdrawal was associated with increased risks of the disease. Conclusion: These results suggest that low-dose NSAIDs have an inhibitory effect on recurrent adenomas, but the efficacy for late-stage adenomas remain inconclusive. The withdrawal of the drug might be associated with increased risks of the disease.

Keywords: Non-steroidal anti-inflammatory drugs, colorectal adenomatous polyps, meta-analysis

Introduction

Colorectal adenoma is a prominent precursor lesion of colorectal cancer [1]. Most colorectal cancers develop from colorectal adenomatous polyps, which involve long-term genetic mutations [2]. In patients with histories of colorectal cancers or adenomas, recurrence rates were higher in patients with adenomatous polyps than in the normal population [2]. Currently, many studies have shown that NSAIDs have beneficial effects on recurrent colorectal adenomas [3, 4].

Recent studies have focused on the effect of aspirin on the recurrence risks of colorectal adenomas, which have shown that all aspirins reduce the risks of colorectal adenomas, but high doses increase the risks of gastrointestinal complications [5, 6]. As a result, low dosages are mostly recommended in clinics for cardiovascular protection. The previous meta-analysis studies have shown that low-dose aspirin has a moderately beneficial effect on recurrent adenomas, but has no protective effect on recurrent advanced adenomas [7, 8]. However, most of the previous studies have not effectively eliminated random bias, which may lead to inaccurate conclusions. The trial sequential analysis (TSA), which takes random errors into consideration, uses required sample sizes and boundaries to determine whether the results are conclusive [9].

In addition, some observational studies have indicated that the protective effects of NSAIDs on recurrent adenomas may disappear after withdrawal of the drug [10]. Another study showed that COX-2 inhibitors were not effective in preventing recurrent adenomas after drug

withdrawal. Besides, a study indicated that the risks of adenomas significantly increased 1 year after discontinued treatment [11]. These results are mainly concerned with the preventative and withdrawal effects of NSAIDs on recurrent adenomas. This study aimed to systematically analyze the effects of varied doses of NSAIDs on recurrent colorectal adenomas.

Materials and methods

Document retrieval methods

In PubMed, Scopus (Elsevier), Embase, Ovid, CNKI and Wanfang database (included in Cochrane), studies during the period of August 20, 2008 to August 20, 2019 were included for the retrieval. Retrieval methods: 'Polyps', 'adenoma', or 'NSAID' were used as the keywords, in combination with 'adenomas', 'aspirin', 'ibuprofen', 'naproxen', 'sulindac', 'ketoprofen', 'ketorolac', 'flurbiprofen', 'diclofenac', 'indomethacin', 'piroxicam', 'eodolac', 'nabumetone', 'meloxicam', 'rofecoxib', 'celecoxib', 'etoricoxib', or 'valdecoxib'. Studies with full text and accessible data were included. Besides, the references were also retrieved.

Literature selection criteria

The studies included in the meta-analysis needed to meet the following criteria: (1) papers were published in English; (2) studies had randomized controlled trials; (3) follow-up period was longer than 1 year; (4) patients were adults with history of colorectal cancer or adenomas; (5) NSAIDs were used as interventions, and placebos or non-treatment were used in the control groups; (6) the outcome was the recurrence rates for adenomas; (7) the data could be extracted. Exclusion criteria: (1) data could not be extracted; (2) review or case studies; (3) randomized controlled trials of combined use of NSAIDs with other drugs; (4) patients had history of familial cancer syndromes (such as Lynch syndrome).

Data extraction and quality evaluation

Two proctologists independently examined the studies, extracted data and assessed the risk of bias. The assessment included: research cohort, double-blind method, data integrity, data selection, and other sources of bias. The opinion of a third researcher was included when disagreements were encountered. GRADEpro was adopted to grade the quality of evidence (high, medium, low, and very low) from the meta-analysis.

Statistical analysis

Data analysis was performed by Review Manager 5.3. The included studies were used as inputs for random effect summaries. Logarithmic standard errors were only present in subgroup comparison analysis, in which I^2 values of < 25%, 25-50%, and > 50% indicated low, medium, and high heterogeneity respectively. The precisions in the funnel plot were used to evaluate the publication bias. The results were then represented by a forest plot. Tests for funnel chart asymmetry and the Egger's regression test were used to evaluate the publication bias.

Results

Characteristics of studies included

A total of 5252 studies were retrieved from the databases. 4014 studies were then obtained after the exclusion of duplicates. 151 studies were excluded after reading the abstract as well as 76 studies that did not meet the inclusion criteria. 67 studies were further excluded based on quality evaluations. 8 studies were eventually acquired [5, 6, 11-16] (**Table 1**). 5 randomized controlled trials (RCT) [5, 6, 12-14] were studies of aspirin and placebos, and the remaining 3 were studies of non-aspirin and placebos, with a total of 9431 patients included [11, 15, 16] (**Figure 1**).

The effects of aspirin on the incidence rates of recreant colorectal adenomas

5 studies [5, 6, 12-14] of RCT indicated the effect of varied doses of aspirin on recurrent colorectal adenomas compared to placebos. A total of 2950 patients undergoing colonoscopy during follow-ups were included in the study. The results indicated that 540 (32%) out of 1668 patients treated with aspirin had recurrent adenomas, while of 1282 patients in the placebo group, 468 (37%) had recurrent adenomas. The results of statistical analysis showed that aspirin intake could reduce the relative risks of recurrent adenomas by 17% over a period of 2-4 years (RR, 0.83 [95% CI 0.73-0.83], I^2=29.8%) (**Figure 2**). In addition, 125 patients (7.5%) on aspirin interventions and 128 pa-

Table 1. Summary of included randomized controlled trials of the effect of NSAIDs on recurrent colorectal cancers

Study, year	Types of NSAIDs	Duration of treatment	Population	Interventions NSAIDs/placebo
Baron 2003	Aspirin	3 years	169/175 (Age-range, 21-81 years; % male: 64)	81 mg/day (n=169); aspirin 325 mg/day (n=167); aspirin 81 mg/day and folic acid 1 mg/day (n=175); 325 mg/day and folic acid 1 mg/day (n=171); folic acid 1 mg/day (n=170); placebo (n=169).
Sandler 2003	Aspirin	3 years	317/318 (Ages-range, 30-80 years; % male: 52)	Aspirin 325 mg/day (n=317); placebo (n=318).
Logan 2008	Aspirin	3 years	236/233 (Age = mean, 58 years; range, 28-75 years; % male: 56)	Aspirin 300 mg/day (n=236); folic acid 0.5 mg/day (n=234); aspirin 300 mg/day and folic acid 0.5 mg/day (n=236); placebo (n=233).
Benamouzig 2012	Aspirin	4 years		Aspirin 160 mg/day (n=73); aspirin 300 mg/day (n=67); placebo (n=132).
Ishikawa 2014	Aspirin	2 years		Aspirin (enteric-coated) 100 mg/day (n=191); placebo (n=198).
Arber 2006	Celecoxib	3 years	Age-median, 61 years; range, 30-92 years; % male: 66	Celecoxib 400 mg/day (n=933); placebo (n=628).
Bertagnolli 2006	Celecoxib	3 years	Age-median, 59 years; range, 31-88 years; % male: 68	Celecoxib 400 mg/day (n=685); Celecoxib 800 mg/day (n=671); Placebo (n=679).
Baron 2006	Rofecoxib	3 years	Age-mean, 59.4 years; range, 40-86 years; % male: 62.3%	Rofecoxib 25 mg/day (n=1277); placebo (n=1293).

Note: Not available: stated "no significant difference between the two groups in compliance rates"; Interventions NSAIDs/placebo: the description of interventions in the non-steroidal and placebo groups introduced in the study; Population: general information about the subjects studied in both groups.

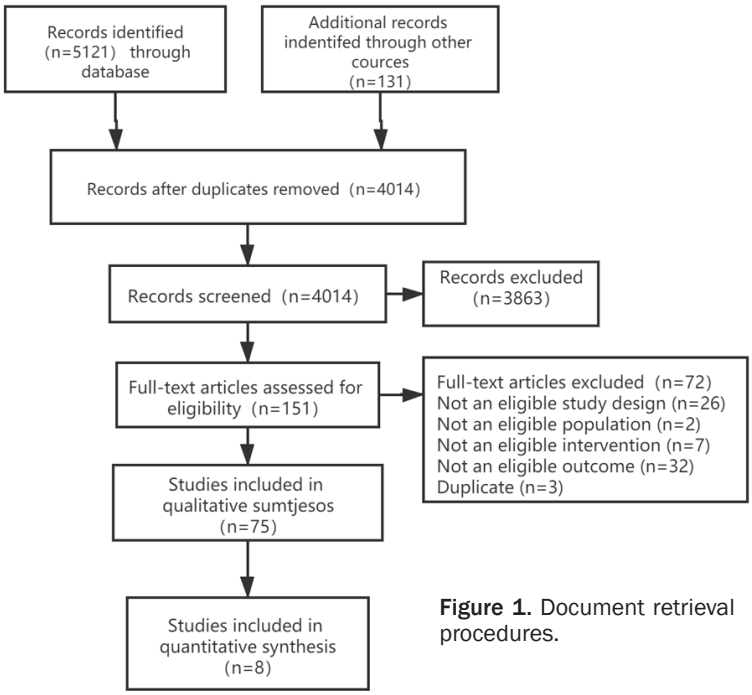

Figure 1. Document retrieval procedures.

tients (10%) on placebos developed advanced adenomas (RR, 0.70 [95% CI 0.55-0.88], I^2= 0%) (**Figure 3**).

Analysis of the effect of varied doses on patients

Three studies [5, 6, 12] analyzed the effect of varied doses. The results showed no heterogeneity at low doses (80-160 mg/day) (RR, 0.80 [95% CI 0.70-0.92], I^2=0%) (**Figure 4**). Low doses were also shown to have 34% relative risk reduction (RRR) (RR, 0.66 [95% CI 0.44-0.99], I^2=0%) in the prevention of advanced adenoma, with no heterogeneity (**Figure 5**). The intervention effects of high-dose aspirin had relatively high heterogeneity in different studies (I^2=78.2%), and the relative risk reduction was not statistically significant (RR, 0.90 [95% CI 0.68-1.18]) (**Figure 6**). However, it was shown to have a 27% risk reduction in preventing advanced adenomas (RR, 0.73 [95% CI 0.56], I^2=0%) (**Figure 7**).

The effect of other NSAIDs on the recurrence of colorectal cancers

3 studies of RCT were involved in this analysis. The incidence rates of recurrent adenomas and advanced adenomas were significantly reduced (RR, 0.66 [95% CI 0.59-0.72]). However, there was an increased risk of adverse cardiovascular events associated with COX inhibitors.

Publication bias

In a meta-analysis of fewer studies (less than 10), the asymmetry test was unable to distinguish random bias from true asymmetry. Therefore, our analysis cannot assess publication bias due to the insufficient number of included studies.

Discussion

In this study, 5 studies of RCT on aspirin [5, 6, 12-14] and 3 studies of RCT on non-aspirin NSAIDs [11, 15, 16] were selected to explore their effects on incidence rates of recurrent adenomatous polyps. From the current studies, all the RCTs on aspirin interventions were of high quality, while studies on other NSAIDs were shown to have limitations such as systemic errors. Recent studies on aspirin indicated that long-term usage of any dose could reduce the recurrence rates of colorectal adenomas, especially in advanced adenomas. These studies provide strong evidence for the beneficial effects of aspirin in preventing the recurrence of these adenomas.

The aspirin is widely known as a chemopreventive agent against adenomas. Since it also provides cardiovascular protection, a low dosage is recommended to balance the risks and benefits. In colorectal cancer or adenoma patients on long-term usage of NSAIDs, severe adverse events such as myocardial infarction, gastrointestinal bleeding, peptic ulcer, dyspepsia, and colorectal cancer were not reported. Some studies have indicated a higher incidence of stroke in patients taking aspirin, but no explanation or further study has been included [17]. In addition, high-quality evidence indicated that aspirin could increase incidence rates of adverse events in patients with cardiovascular diseases [18]. At the same time, studies of the

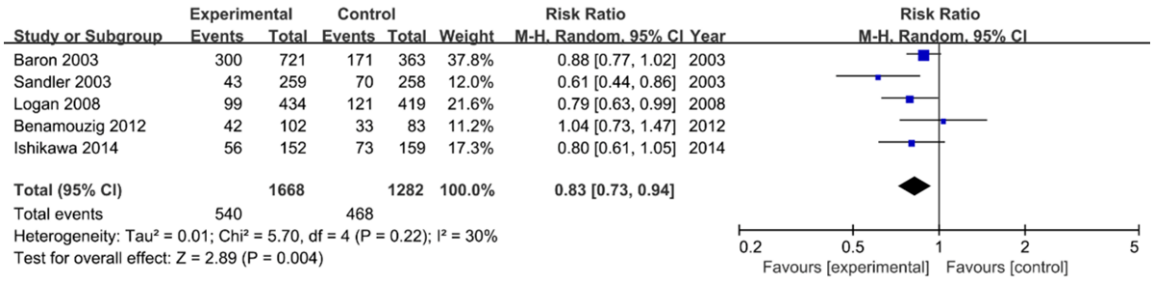

Figure 2. Forest plot for the effect of aspirin on the recurrence rates of colorectal adenomas.

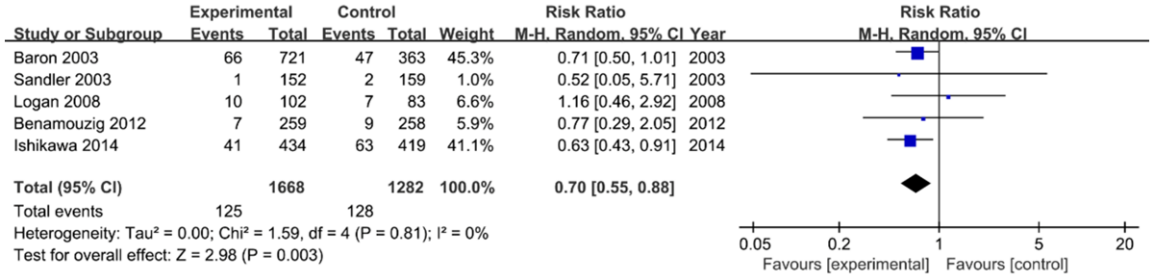

Figure 3. Forest plot for the effect of aspirin on the incidence rates of advanced adenomas.

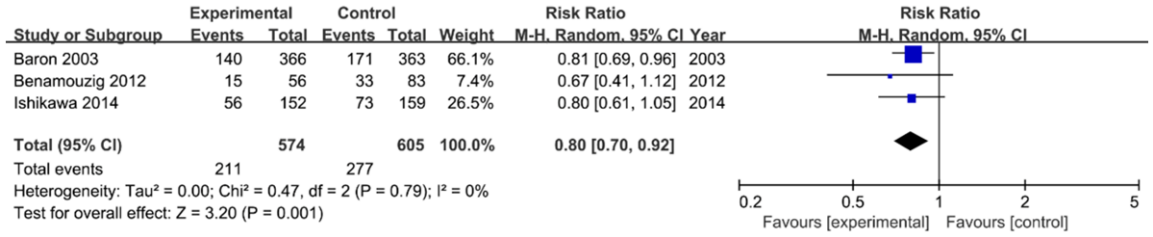

Figure 4. Forest plot for the effect of low-dose aspirin on the recurrence rates of colorectal adenomas.

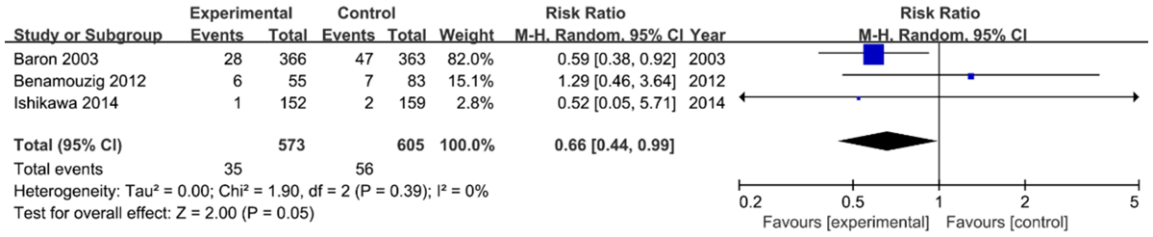

Figure 5. Forest plot for the effect of low-dose aspirin on the incidence rates of advanced adenomas.

effect of varied doses of aspirin also indicated the presence of such risk.

Therefore, the effect of varied doses of aspirin was further analysed. The results indicated that low doses had significant preventive effects against recurrent adenomas by reducing the recurrence risks of 20%. In addition, the results also showed that low doses of aspirin reduced the incidence risks of advanced adenomas. However, the sample numbers were found to be limited, resulting in low quality. A 20-year long-term study has found that the treatment results show increased benefits as the time of aspirin treatment increases, and aspirin treatment for 5 years or longer can

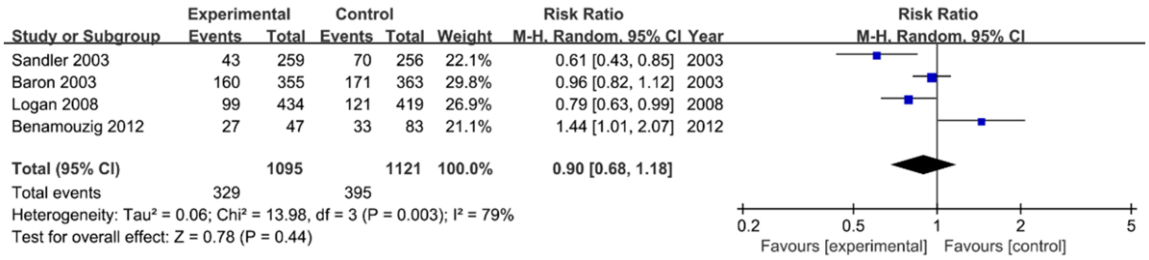

Figure 6. Forest plot for the effect of high-dose aspirin on the recurrence rates of colorectal adenomas.

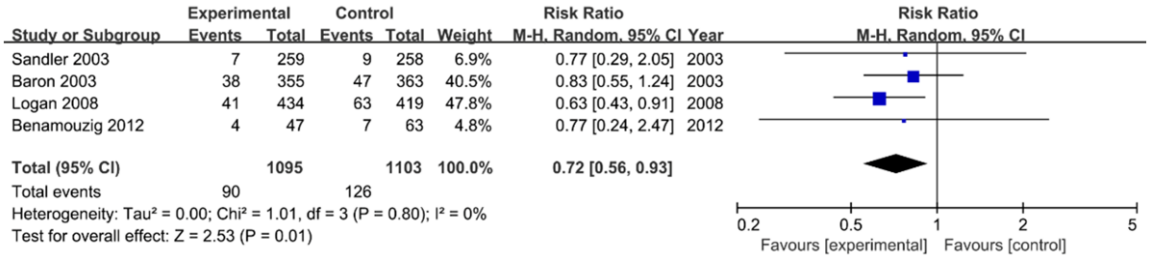

Figure 7. Forest plot for the effect of high-dose aspirin on the recurrence rates of advanced adenomas.

reduce the risk of recurrence of colon cancer by 70% [19], which is consistent with other studies [20, 21].

COX-2 inhibitors are efficacious in preventing recurrent colorectal adenomatous polyps and advanced adenomas. However long-term use may lead to increased risks of gastrointestinal or cardiovascular adverse events, which should be considered in the administration of these drugs [4, 22-24].

In conclusion, the results of current RCTs show that all NSAIDs could reduce risks of recurrent adenomas, but NSAIDs other than aspirin could also lead to risks of adverse events. As a result, aspirin has a greater clinical significance as the chemopreventive agent. The evidence suggested that low doses of aspirin should be used in clinics for the balance of benefits and risks. Even though high-quality RCTs were adopted to evaluate the intervention effects of NSAIDs including aspirin on the incidence rates of recurrent adenomas, this analysis also has some limitations. First, the varied doses of aspirin were similar but not the same in different studies. Besides, the analysis of the long-term effect of aspirin was limited by the follow-up durations. Furthermore, the relevant sample size was small and the studies on NSAIDs other than aspirin were limited. Hence, new evidence is expected for further analysis.

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Disclosure of conflict of interest

None.

Address correspondence to: Huixin Chen, Department of Gastroenterology, Huizhou Municipal Center Hospital, No. 41, Eling North Road, Huicheng District, Huizhou 516001, Guangdong Province, China. Tel: +86-752-2260027; E-mail: jiangtttaot@163.com

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