RESEARCH ARTICLE

The Efficacy of Aspirin in Preventing the Recurrence of Colorectal Adenoma: a Renewed Meta-Analysis of Randomized Trials

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Abstract

Background: Through search the possible randomized control trials, we make a renewed meta-analysis in order to assess the impact of aspirin in preventing the recurrence of colorectal adenoma. Materials and Methods: The Medicine/PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese biomedical literature service system (SinoMed) databases were searched for the related randomized controlled trials until to the April 2016. Three different authors respectively evaluated the quality of studies and extracted data, and we used the STATA software to analyze, investigate heterogeneity between the data, using the fixed-effects model to calculate and merge data. Results: 7 papers were included the renewed meta-analysis, among these studies, two pairs were identified as representing the same study population, with the only difference being the duration of follow-up. Thus there were only five papers included our meta-analysis, and one Chinese paper were also included the work. Results were categorized by the length of follow-up, different kinds of people, varied dose of oral aspirin. The relative of adenoma in patients taking aspirin vs placebo were 0.73 (95% CI 0.55-0.98, *P*=0.039) with 1 year follow up; 0.84 (95% CI 0.72-0.98, *P*=0.484) with greater than 1 year follow up; for the advanced adenoma, the RR 0.68 (95% CI 0.49-0.94, *P*=0.582),for one year; RR=0.75 (95% CI 0.52-1.07, *P*=0.552) for greater one year. Furthermore the white population could divided into two subgroups according to the different length of follow-up time. When the length of follow-up time less than 3-year, The RR of two subgroups respective were RR=0.86 (95% CI 0.76-0.98, *P*=0.332), I^2=0%, RR=0.68 (95% CI 0.47-0.98, *P*=0.552), I^2=64.6%, But with the extension of follow-up time greater than 2-year, with the white, oral aspirin without considering dose had no efficacy on preventing the recurrence of any adenoma, the RR was 0.86 (95% CI 0.71-1.05, *P*=0.302), I^2=16.4%. Conclusions: This meta-analysis indicated that oral aspirin is associated with a remarkable decrease in the recurrence of any adenoma and advanced adenomas in patients follow-up for 1 year without concerning the dose of aspirin, but with the extension of follow-up time for greater than 1 year, oral aspirin can be effective on preventing the recurrence of any adenoma, but for the advanced adenoma, the result indicated that oral aspirin had no efficacy, According to the inclusion of ethnic groups, we also divided relevant papers into two subgroups as the yellow and white group. Then the follow-up time was less than 3 years, oral aspirin without considering the dose, had an significant efficacy on preventing the recurrence of any adenoma. But with the follow-up greater than 2 years, oral aspirin had no effect in the white.

Keywords: Colorectal adenoma - aspirin - recurrence - meta-analysis

Asian Pac J Cancer Prev, **17 (5)**, 2711-2717

Introduction

The colorectal cancer is the second most common cancer of deaths in the western countries (Ferlay et al., 2004), Colorectal adenomas-the precursors to most colorectal Cancers (Neugut et al., 1993; Peipins et al., 1994), Colorectal adenomas have been estimated to develop in 70-90% of all colorectal cancers (Cotton et al., 1996; Itzkowitz et al., 1996). According to some report, the incidence of colorectal cancer would be reduced by as much as 90% following endoscopic removal of pre-cancerous adenomas (Winawer et al., 1993). But unfortunately, this procedure may be uncomfortable and expensive, this may limit the application of this operation extensively.

Aspirin has been associated with reduced risk for colorectal adenomas in randomized clinical trials (Baron et al., 2003; Sandler et al., 2003). Aspirin is a synthetic medicine based on the structure of salicylates, which are commonly found in fruits and vegetables. Aspirin's

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antineoplastic effects have been mechanistically explained by its cyclooxygenase (COX) inhibitory activity. The use of aspirin as a cancer chemo-preventive agent is advantageous because it has a long history of clinical use and its adverse effects are well known. Moreover, the cost effectiveness of aspirin administration to prevent other diseases, such as cardiovascular disease, has also been demonstrated (Greving et al., 2008). Cyclooxygenease-2 (COX-2), an inducible form of cyclooxygenase, is a well-studied pharmacological target of aspirin (Zha et al., 2004). COX-2 is overexpressed in colon cancer cells and is known to be implicated in carcinogenesis through several mechanisms including inhibition of apoptosis, modulation of cellular adhesion and motility, promotion of angiogenesis, and immunosuppression, Adipose-driven inflammatory cytokines are involved in many of these mechanisms possibly via NF-jB, a transcription factor regulating various inflammatory, apoptotic and oncogenic genes (Macarthur et al., 2004).

Three mate-analysis have been reported before (Gao et al., 2008; Bernard et al., 2009; Wang et al., 2014), among this meta-analysis, they found that aspirin was effective for the prevention of colorectal adenomas in individuals with a history of these lesions. But these studies also had many defects, for instance, the different inclusion criteria among these groups may cause obviously heterogeneity, the No. of experiments of these meta-analysis was too small, the type of experimental drug was not uniform, the distribution of the sample was too single, and so on.

Thus it is necessary for us to make an updated meta-analysis to further clarify the association between aspirin and colorectal adenomas by trying our best to searching the detail papers meeting the conditions of the Chinese and English literature.

Materials and Methods

We identified all randomized controlled trials that tested the impact and safety of NSAIDs, in any dose, on the recurrence of colorectal adenomas, by searching the Medicine/PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese biomedical literature service system (SinoMed) databases up to April 2016 with the following MeSH terms and keywords: 'adenoma*', 'aspirin', 'non-steroidal anti-inflammatory drugs', '' NSAIDS' and 'random*'. We restricted the language to papers published in English and Chinese.

Two authors (Tai-Yun Zhao, Jing Tu) reviewed the search results to reduce the possibility of missing additional reports. Where key data were not included in the published report, authors were contacted directly to obtain the relevant information. All studies included in the meta-analysis were required to satisfy the following inclusion criteria: 1) the study followed a randomized, controlled trial format; 2) participants had undergone a colonoscopy and had adenomas detected and removed before enrolment; 3) a treatment arm included exposure to aspirin in any dose, and a control arm included treatment with placebo; 4) the primary endpoint was recurrent incidence of colorectal adenomas; 5) there was colonscopic follow-up to at least 1 year following treatment. The following were excluded from the meta-analysis: 1) reviews, letters, comments and case reports; and 2) any subjects with a history of familial adenomatous polyposis, hereditary non-polyposis colorectal cancer or inflammatory bowel disease, Lynch syndrome or colorectal resection; 3) patients with a known aspirin allergy; 4) patients currently taking an anticancer drug; 5) pregnant patients or those who planned to become pregnant during the trial period; 6) patients taking non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief more than thrice weekly; 7) patients with IBD, haemorrhagic diverticulitis or haemorrhagic tendency; 8) patients with a platelet count of ≤100 000/mm3 or abnormal prothrombin time.

Data extraction

Three reviewers (Tai-Yun Zhao, Jing Tu and Yin Wang) independently extracted the following data for each eligible study: first author, year of publication, geographical location of the study and number of participants (male/female), their age in years (mean and range), the choice of Aspirin used, quality assessment by Jadad score (Table 1), First author, length of follow up, and number of patients completing the follow-up examination. We documented the number of patients with at least one colorectal adenoma and also specifically documented those with advanced adenomas (ie, tubulovillous adenomas, villous adenomas, adenomas ≥ 1 cm in diameter, adenomas with high-grade dysplasia, or invasive cancer with invisions confined to the mucosa) after randomization. Serious adverse events were noted. The quality of each study was formally assessed using the Jadad score. The data were extracted and registered independently by two investigators (Tai-Yun Zhao, Jing Tu) and any disagreement was resolved by discussion with a third investigator (Yao-Jun Wang).

Quality assessment

Two reviewers independently assessed study quality using the Jadad composite scale (Jadad et al., 1996; Kjaergard et al., 2001), which consists of three parameters: random sequence production, blind method, and withdrawals. The Jadad tool assigns a maximum of two points for random sequence production, two for the methods of blinding and one for withdrawals, with a total score of five reflecting the highest quality. Points were awarded as follows: *i*). Random sequence production: adequate (two points), computer generated random data or parallel approach; unclear (one point), randomized experiment but with no description of the randomization methods; inadequate (0 points), use of the method of alternative distribution. *ii*). Blinding method: adequate (two points), double blinded, with a description of the correct methodology; unclear (one point), stated to be double-blinded but without reference to the blinding methodology; inadequate (0 points), not using double-blind, or false double-blind. *iii*). Withdrawals: adequate (one point), detailed description of the number of withdrawn or lost cases with reasons; inadequate (0 points), not mentioned.

Studies with a total score of 2 were ranked as low

quality; those with a score of 3 were ranked as high quality. Where the study report was unclear, uncertainty in scoring was resolved by the third assessor (Moher et al., 1998; Kjaergard et al., 2001).

Statistical analysis

The data included were summarized as relative risk (RR) with 95% confidence intervals (CI) to enable an assessment of the efficacy and safety of NSAIDs in preventing the recurrence of colorectal adenomas. Heterogeneity was evaluated using the Q statistic and the I^2 statistic. The I^2 value ranges from 0 to 100% (where a value of 0-25% is taken as representing no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2=50-75%, extensive heterogeneity; and I^2= 75-100%, extreme heterogeneity). Where heterogeneity was identified, the fixed-effects model was used to merge the data. All analyses were performed with STATA software (version 12.0; Stata Corp, College Station, Texas, USA).

Results

There were about 160 studies included the meta-analysis, after excluding the unrelated meta-analysis, system reviews and other papers by reading their title and abstract. 23 remained, and of these, only seven studies (Figure 1) were found to be suitable following review of the full text (Baron et al., 2003; Benamouzig et al., 2003; Logan et al., 2008; Grau et al., 2009; Li et al., 2011; Benamouzig et al., 2012; Ishikawa et al., 2014). Among these seven studies, two pairs (Baron et al., 2003; Benamouzig et al., 2003) were identified as representing the same study population, with the only difference being the duration of follow-up (Grau et al., 2009; Benamouzig et al., 2012). Thus, there were five study (Baron et al., 2003; Benamouzig et al., 2003; Logan et al., 2008; Li et al., 2011; Ishikawa et al., 2014) population in the seven reports included in our analysis, all in randomized control trials. 6 studies are in English (Baron et al., 2003; Benamouzig et al., 2003; Logan et al., 2008; Grau et al., 2009; Li et al., 2011; Ishikawa et al., 2014), the other one is in Chinese (Li et al., 2011), According to geographical position, of the five studies, one (Baron et al., 2003) from the North America, two (Benamouzig et al., 2003; Logan et al., 2008) from the European countries, one (Li et al., 2011) from china, and the last one (Ishikawa et al., 2014) from Japan. The dose of aspirin in the 8 studies ranged from 81mg to 325mg per day, when the oral dose is less than 200 mg, we define that it is a low dose, and vice versa. The duration of follow-up time from recruitment to the meta-analysis varied, and included 1-year follow (Baron et al., 2003; Benamouzig et al., 2003; Li et al., 2011), 2 year (Ishikawa et al., 2014), 3 years (Logan et al., 2008), 4 years (Grau et al., 2009; Benamouzig et al., 2012), The selected study characteristics and quality assessment by Jadad score are summarized in Table 1. The follow-up time, the number of patients completing the follow-up examination, the number of patients with recurrence of any adenoma or advanced adenomas and serious adverse events are all given in Table 2.

Quality assessment of the trials

The quality of the studies included in this meta-analysis was assessed by the Jadad score. The quality assessments are shown in Table 2 and suggested that all studies. Were high quality.

Recurrence of adenomas or advanced adenomas

For the subjects, according to the length of follow-up time, we took the patients into two subgroups, the follow-up time with 1-year, equal or greater than 2-year.

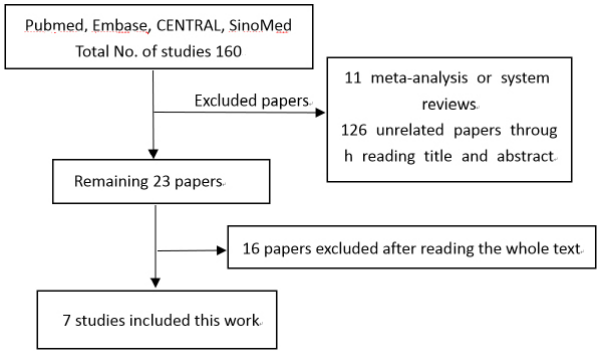

Figure 1. Summary of Study Selection Process

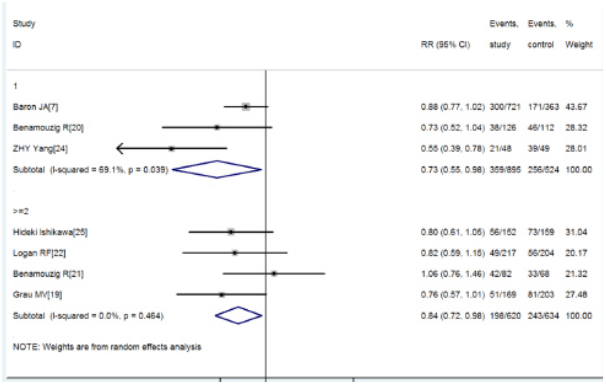

Figure 2. Randomized-Effects model of RR Recurrence of any adenome with Duration of Follow-up 1, ≥2 yeat

Table 1. Basic Characteristics of the Randomized Controlled Trials Included in the Meta-analysis

First author	Year	Region	NO.of participant: male/female	Mean-age (year/range)	Drug type	Quality assessment by Jadad score
Baron JA [7]	2003	The North America	1121: 712/409	47.83-67.1	81 or 325mg/day aspirin	5
Benamouzig R [20]	2003	France	272:190/82	56.15-56.35	160 or 300mg/day aspirin	5
Logan RF [22]	2008	The UK	939:534/405	48.4-67.13	300mg/day aspirin	5
ZHY Yang [23]	2011	China	100:74/26	61.31-80.18	100mg/day aspirin 10mg/ day Omeprazole	3
Hideki Ishikawa [24]	2014	Japan	311:246/65	53.3-67.2	100mg/day aspirin	5

Table 2. Characteristics of the Randomized Controlled Trials Included in the Meta-analysis

First Author	Length of follow up	No.of patientscompleting the follow-up examination	patients with least one adenoma	patients with advanced adenoma	Serious adverse events*
Baron JA[7]	1	PA:1084 P:363 A 81mg:366 A 325mg:355	P:171/363 A 81mg:140/366 A 325mg:160/355	P:47/363 A 81mg:28/366 A 325mg:38/355	P:20/372 A 81mg:34/377 A 325mg:37/372
Grau MV[19]	4	PA:372 P:203 A:169 A 81mg:84 A 325mg:85	P:81/203 &1 A:51/169 &2 A 81mg:23/84 A 325mg 28/85	P:25/203 $1 A:14/169 $2 A 81mg:3/84 A 325mg:11/85	No Report
Benamouzig R	1[20]	PA:238 P:112 A 160mg:66 A 300mg:60	P:46/112 A 160mg:23/66 A 300mg:15/60	P:13/112 A:8/126	P:24/132 A:25/140
	4[21]	PA:150 P:68 A 160mg:42 A 300mg:40	P:33/68 A 160mg:15/42 A 300mg:27/40	P:7/68 A 160mg:6/42 A 300mg:4/40	P:22/83 A:25/102
Logan RF[22]	3	PA:421 P:204 A 300mg:217	P:56/204 A 300mg:49/217	P:30/204 A 300mg:22/217	P:30/419 A 300mg:30/434
ZHY Yang[23]	1	PA:97;P:49;A 100mg:48	P:39/49; A 100mg:21/48	No Report	P:1/50; A 100mg:2/50
Hideki Ishikawa[24]	2	PA:311; P:159; A 100mg: 152	P:73/159; A 100mg: 56/152	No Report	P:2/159; A 100mg: 2/152

PA:placebo and aspirin;P:placebo;A:aspirin; &1:patients with least one adenoma,all placebo use NSAIDS must be less than 2 days per week. &2:All aspirin use NSAIDS must be equal or greater than 2 days per week. $1:patients with advanced adenoma,all placebo use NSAIDS must be less than 2 days per week. $2:patients with advanced adenoma,all placebo use NSAIDS must be equal or greater than 2 days per week.* Death, myocardial infarction, stroke, major bleeding, invasive cancer, colorectal cancer, vascular events requiring NSAIDS.

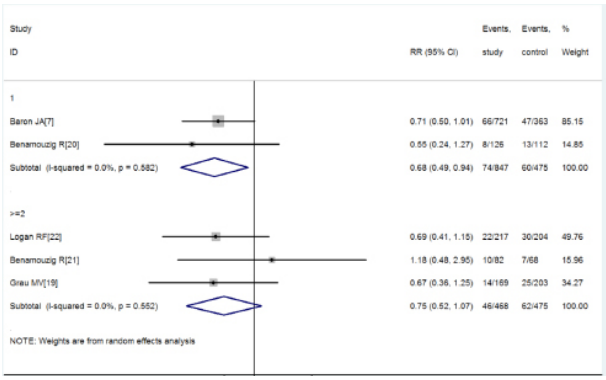

Figure 3. Randomized-effects Model of RR Tecurrence of Advanced Adenoma with Duration of Follow-up 1, ≥2 yeat

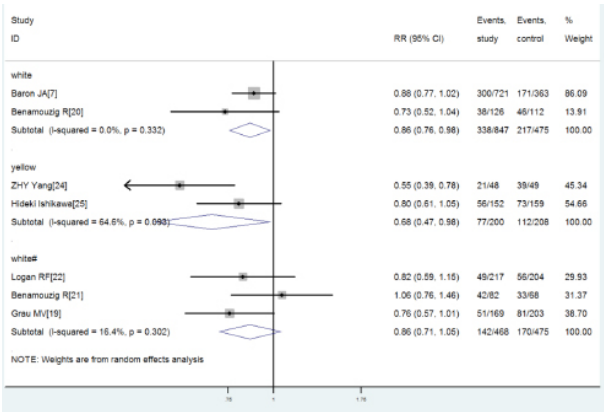

Figure 4. Randomized-effects Model of RR Recurrence of any Adenoma with White and yellow population for the follow-up with less than 3-year (# RR Recrrence of any Adenoma with white population with the Follow-up 2-year)

We use the randomized-effects model to calculate the likelihood of any adenoma recurrence for patients treated with aspirin, without concerning the dose of aspirin. Data were pooled from three studies for 1-year and four studies with the follow-up time equal or greater than 2-year, the two subgroups demonstrated a significant decrease in the risk of any adenomas (Figure 2), the RR for recurrence of any adenoma with 1-year and equal or greater the 2-year respectively were 0.73 (95% CI 0.55-0.98, P=0.039), I^2=69.1%; 0.84 (95% CI 0.72-0.98, P=0.484), I^2=0; the heterogencity among the first subgroup was significant, it may originated from the study with ZHY Li (Li et al., 2011), for its No. of population was a little, for the another thing, it was short of the detailed base-line characteristics of the patients, last but not the list , the dose of oral aspirin were significant difference. All above may cause the obvious heterogencity. While the same follow-up, with the advanced adenoma (Figure 3), without considering the dose of aspirin. From the forest test, we concluded that two studies[Baron et al., 2003; Benamouzig et al., 2003] demonstrated a significant decrease in the risk of advanced adenoma with the length of follow-up 1-year, the RR = 0.68 (95% CI 0.49-0.94, P=0.582), I^2=0%; but when the follow-up time lengthened from 1-year to greater than 1-year, the three studies (Logan et al., 2008; Grau

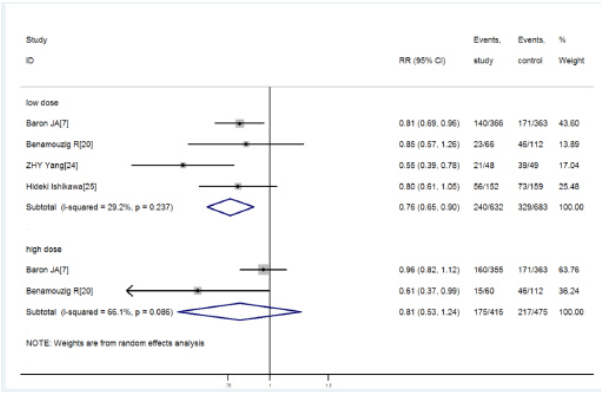

Figure 5. Randomized-effects Model of RR Recurrence of Any Adenoma with Lose and High Dose Aspirin for the Follow-up with Less than 3-year

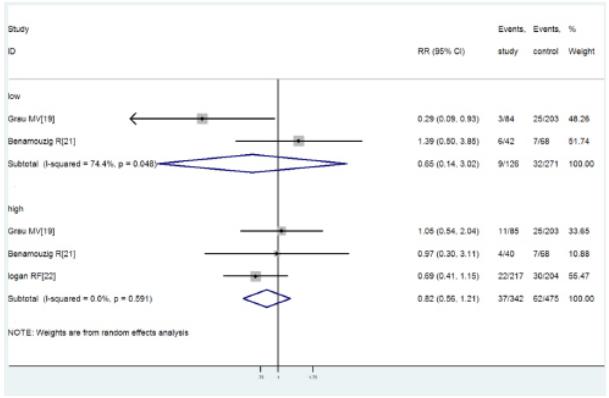

Figure 7. Randomized-effects Model of RR Recurrence of Advanced Adenoma with Lose and High Dose Aspirin for the Follow-up with Grater than 3-year

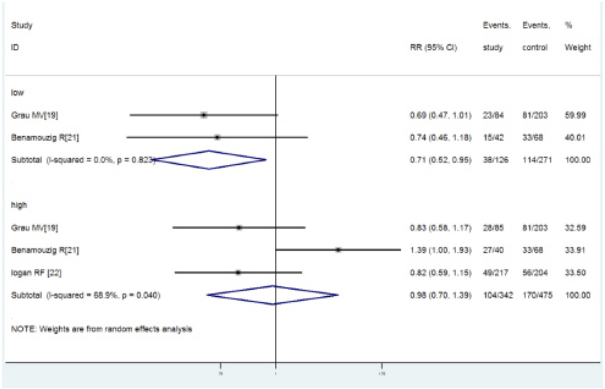

Figure 6. Randomized-effects Model of RR Recurrence of Any Adenoma with Low and High Dose Aspirin for the Follow-up with Greater than 2 -year

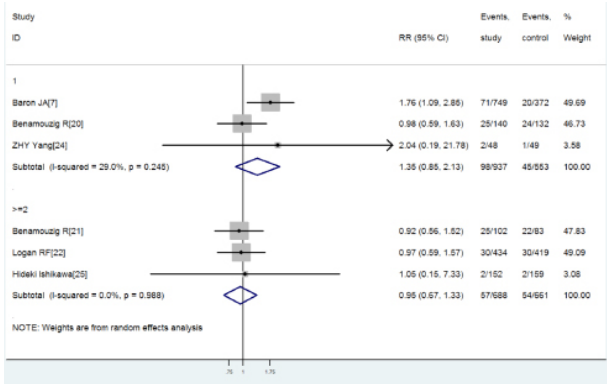

Figure 8. Randomized-effects Model of RR Recurrence of Adverse Events with the Length of Follow-up 1-year and Greater than 1-year

et al., 2009; Benamouzig et al., 2012) indicated that oral aspirin without concerning the dose did not have obviously efficacy on preventing the recurrence of advanced adenoma, RR=0.75 (95% CI 0.52-1.07, *P*=0.552), I^2=0%.

According to the studies, population distribution were from East Asia, European and the North American counties. Thus we could take the studies into two subgroups, as the yellow population and the white population. Furthermore the white population could divided into two subgroups according to the different length of follow-up time. When the length of follow-up time less than 3-year, both the yellow and the white indicated that oral aspirin without concerning the dose could demonstrate significant decrease in the risk of any recurrent adenomas (Figure 4). The RR of two subgroups respective were RR=0.86 (95% CI 0.76-0.98, *P*=0.332), I^2=0%, RR=0.68 (95% CI 0.47-0.98, *P*=0.552), I^2=64.6%, the significant heterogencity might come from the little sample and the low Jadad score. But with the extension of follow-up time greater than 2-year, with the white, oral aspirin without considering dose had no efficacy on preventing the recurrence of any adenoma, the RR was 0.86 (95% CI 0.71-1.05, *P*=0.302), I^2=16.4%, due to the lack of data from the yellow with the follow-up greater than 2-year, we did not judge the efficacy on the recurrence of any adenoma in yellow.

We also reviewed the effect of dose of aspirin and the length of follow-up less than 3-year. For aspirin at low dose (81mg-160mg) the overall RR for recurrence of any adenoma was 0.76 (95% CI 0.65-0.90, *P*=0.237), I^2=29.2%, there was no insignificant heterogeneity among the studies. It indicated that oral low-dose aspirin had an effective on preventing the recurrence of any adenoma. With regard to high dose aspirin (300-325mg), the overall RR was 0.81 (95% CI 0.53-1.24, *P*=0.086), I^2=66.1%, but among these studies the heterogeneity was obvious. It may be from the different doses. The forest test as the Figure 5, it concluded that high-dose aspirin did not have efficacy the recurrence of any adenoma. While with the extension of follow-up time greater than 2-year, when the RR from low-dose aspirin was 0.71 (95% CI 0.52-0.95, *P*=0.823), I^2=0 %, and the RR from high-dose was 0.98 (95% CI 0.70-1.39, *P*=0.995), I^2=0%. Through the up results, we could include that low-dose had obvious efficacy on the recurrence of any adenoma, but the high-dose could not (Figure 6).

And for the advanced adenoma, we also divided into two subgroups as the low and high dose aspirin, because of the shortage of the data from the length of follow-up less than 3-year. We only calculated and analyzed the length for greater than 2 years. The RR from the low and high dose were 0.65 (95% CI 0.14-3.02, *P*=0.048), I^2=74.4%, 0.82 (95% CI 0.56-1.21, *P*=0.591), I^2=0% (Figure 7), and the heterogenecity from low dose was obvious, it may be originated from the dose of two studies and a huge gap in the sample size among the studies. From the results,

we can indicated that no matter how much the dose, there was no influence on the recurrence of advanced adenomas.

Several adverse effects were reported in the studies included in the meta-analysis, including death, myocardial infarction, stroke, major bleeding, invasive malignancy and colorectal cancer. For oral aspirin, compared with placebo with concerning the dose of aspirin, but taking these studies into two subgroups according to the length of follow-up as 1-year and greater than 1-year, we calculated a pooled RR for all adverse events of 1.35 (95% CI 0.85-2.13, P=0.245), I^2=29%, 0.95 (95% CI 0.67-1.33, P=0.988), I^2=0%. From the results, we could conclude that with longer follow-up, oral aspirin did not increase the incidence of adverse effects (Figure 8).

Discussion

From this meta-analysis, we searched all related papers in Chinese and English to test oral aspirin in preventing the recurrence of adenoma. To this end we have developed a strict inclusion and exclusion criteria. In the end about 7 studies in our work. In these studies, two pairs were from the same population, the only difference was the length of follow-up time. The results indicated that oral aspirin is associated with a remarkable decrease in the recurrence of any adenoma and advanced adenomas in patients follow-up for 1 year without concerning the dose of aspirin, but with the extension of follow-up time for greater than 1 year, oral aspirin can be effective on preventing the recurrence of any adenoma, but for the advanced adenoma, the result indicated that oral aspirin had no efficacy.

According to the inclusion of ethnic groups, we also divided relevant papers into two subgroups as the yellow and white group. Then the follow-up time was less than 3 years, oral aspirin without considering the dose, had significant efficacy on preventing the recurrence of any adenoma. But with the follow-up greater than 2 years, oral aspirin had no effect in the white. Due to the lack of effective data support, we had not carried out the efficacy in the yellow population with the follow-up time greater than 2 years.

We also analyzed the dose of aspirin on the recurrence of any adenoma and advanced adenoma. When the follow-up time less than 3 years and greater than 2 years, oral low-dose aspirin could remarkable decrease the recurrence of any adenoma, but oral high-dose aspirin had no efficacy. While when we took the dose of aspirin on the efficacy into consideration, we found that whether to take a high dose or low dose of aspirin with the follow-up time greater than 2 years, there was no effect on preventing the recurrence of advanced adenoma.

For the adverse events, with the extension of follow-up time without concerning the dose of aspirin, oral aspirin could not increase the incidence of adverse events.

Three other meta-analysis and system review have previously summarized the relationship between NSAIDs and the recurrence of colorectal adenoma (Gao et al., 2008; Bernard et al 2009; Wang et al., 2014). Compared with the previous analysis, our analysis presents several advantages. First and for the most, in all the studies, we have demonstrated for the first time, whether there is a difference in the effectiveness of oral aspirin for the prevention of colorectal adenomas in different populations and regions between the yellow and the white . Second the No. subjects of the sample was relative large, and we only analyze a drug aspirin that can effectively avoid the unnecessary heterogeneity of different kinds of non-steroidal anti-inflammatory drugs. Last but not the least, all the studies are randomized, placebo-controlled trials, increasing the credibility of the article.

Despite the up advantages, our studies also had some disadvantages. First, with regard to the consolidation of data and calculation, we used the original data without correction, this may increase the heterogeneity among the studies. Second, although we were the first time to calculate the yellow and the white population in the reaction of aspirin on preventing of recurrence of colorectal adenoma, the No. of subjects included the two subgroups was too small, this may influence on the accuracy of the results. Third, retrieval of language is limited to both English and Chinese, which may bring retrieval bias.

To sum up, the effect of aspirin on the prevention of colorectal adenoma was first discovered in different regions and populations. But the results were imprecise. Thus, in future research, we needs to be more Perfect experimental design, multicenter, large sample, randomized controlled trials to further validate and improve our conclusions.

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