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MINIREVIEWS

Aspirin, cyclooxygenase inhibition and colorectal cancer

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Abstract

Colorectal cancer (CRC) is the third most common type of cancer worldwide. Screening measures are far from adequate and not widely available in resource-poor settings. Primary prevention strategies therefore remain necessary to reduce the risk of developing CRC. Increasing evidence from epidemiological studies, randomized clinical trials and basic science supports the effectiveness of aspirin, as well as other non-steroidal anti-inflammatory drugs, for chemoprevention of several types of cancer, including CRC. This includes the prevention of adenoma recurrence and reduction of CRC incidence and mortality. The detectable benefit of daily low-dose aspirin (at least 75 mg), as used to prevent cardiovascular disease events, strongly suggests that its antiplatelet action is central to explaining its antitumor efficacy. Daily low-dose aspirin achieves complete and persistent inhibition of cyclooxygenase (COX)-1 in platelets (in pre-systemic circulation) while causing a limited and rapidly reversible inhibitory effect on COX-2 and/or COX-1 expressed in nucleated cells. Aspirin has a short half-life in human circulation (about 20 minutes); nucleated cells have the ability to resynthesize acetylated COX isozymes within a few hours, while platelets do not. COX-independent mechanisms of aspirin have been suggested to explain its chemopreventive effects but this concept remains to be demonstrated *in vivo* at clinical doses.

Key words: Aspirin; Colorectal cancer; Cyclooxygenase inhibition; Mechanisms; Risk; Benefits

Core tip: Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide. Currently, CRC screening programs are not widely available and need to be improved. New prevention strategies are therefore necessary. Daily low-dose aspirin, as given for the prevention of cardiovascular disease events, has demonstrated benefits in clinical and basic studies in terms of preventing adenoma recurrence and decreasing the incidence of CRC and attributable mortality. These findings indicate that the antiplatelet action of aspirin plays a central role in its antitumor effect. Cyclooxygenase-dependent and independent mechanisms have been suggested to explain this effect. Extensive translational medical research is mandatory for future progress in CRC prevention.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common can-

cer worldwide, accounting for an estimated 9.8% of all new cancers (1.2 million cases annually) and 8.1% of all cancer mortality[1]. It arises through the cumulative effects of inherited genetic predisposition and environmental factors. Genomic instability is an integral part of the transformation of normal colonic or rectal mucosa into carcinoma. Three molecular pathways have been identified: chromosomal instability, microsatellite instability and CpG island methylator phenotype pathways. These pathways are not mutually exclusive, with some tumors exhibiting features of multiple pathways. Germline mutations are responsible for hereditary CRC syndromes (accounting for less than 5% of all CRC), while a stepwise accumulation of genetic and epigenetic alterations results in sporadic CRC.

Today it is well known that screening reduces CRC mortality and is recommended, beginning at age 50, for average risk individuals, although compliance is far from adequate and screening is not widely available in resource-poor settings[2,3]. Primary prevention strategies are therefore still necessary to reduce the risk of CRC, especially because of the limitations of population-based secondary prevention programs that rely on detection and removal of adenomas.

Aspirin has demonstrated its efficacy in the prevention of adverse events related to cardiovascular disease (CVD). It is one of the most widely used drugs in the world. One survey suggested that over one-third of the United States adult population use low-dose aspirin (LDA) regularly[4]. In England in 2007, over 30 million primary care prescriptions were issued for aspirin[5]. Hence, both physicians and patients are largely familiar with the long-term use of aspirin for chronic disease management. In addition, CRC and CVD share the same risk factors, such as older age, being overweight/obesity and physical inactivity.

Today, a large body of clinical and experimental evidence indicates that aspirin can protect against different types of cancer, in particular CRC[6]. A role of the anti-platelet effect of aspirin in its anti-cancer effect is also supported by several studies.

In this review we will discuss clinical results related to the impact of aspirin on the risk of CRC. Then, we will explain the pharmacology of aspirin at low doses in order to provide a mechanistic interpretation of aspirin action as a chemopreventive agent for CRC, in particular the selective inhibition of platelet cyclooxygenase (COX)-1 activity.

CLINICAL EFFECTS OF ASPIRIN ON SPORADIC CRC

Evidence from epidemiological studies

Most case-control and cohort studies have found that regular aspirin use was associated with reduced risk of CRC[7]. A systematic review of case-control studies published in 2012 showed a statistically significant reduction of long-term risk of developing CRC (OR = 0.62, 95%CI: 0.58-0.67) in regular aspirin users compared with non-users, as well as a significant reduction in the proportion of cancers with distant metastasis at diagnosis (OR = 0.69, 95%CI: 0.57-0.83)[8] (Table 1). An analysis of 662424 men and women enrolled in the Cancer Prevention Study Ⅱ cohort showed that daily use of aspirin for at least 5 years was associated with a 32% reduction in risk of CRC[9]. Two cohort studies of United States health professionals (47363 men and 82911 women) showed that regular aspirin users (≥ 2 times/wk) had 21% and 23% lower risk of CRC, respectively, during follow-up periods of 18 and 20 years respectively[10,11]. Moreover, in a separate analysis of a Nurses Health Study cohort, regular aspirin use also reduced the risk of death from CRC by 28% and risk of death from any type of cancer by 12%[12].

Table 1 Summary of the associations between regular use of aspirin and risk of colorectal cancer in case-control and cohort studies

Study type	*n*	Aspirin	Controls	OR (95%CI)	*P* value
Case-control					
Any ASA	26	10464/25618	28300/47834	0.67 (0.60-0.74)	< 0.0001
Maximum reported ASA	17	1551/12659	2664/18153	0.62 (0.58-0.67)	< 0.0001
ASA ≥ 5 yr	10	971/7682	1534/10029	0.68 (0.63-0.75)	< 0.0001
Daily ASA	4	165/1254	349/1523	0.49 (0.40-0.60)	< 0.0001
Daily ASA ≥ 5 yr	1	66/1668	121/1973	0.63 (0.46-0.86)	0.004
Standard cohort					
Any Aspirin	11	3791/2764414	3623/2514652	0.85 (0.82-0.89)	< 0.0001
Maximum reported ASA	8	661/664475	1858/1374905	0.78 (0.71-0.84)	< 0.0001
ASA ≥ 5 yr	4	889/1 022192	1311/1304760	0.76 (0.70-0.82)	< 0.0001
Daily ASA	5	741/658536	1115/819288	0.80 (0.73-0.88)	< 0.0001
Daily ASA ≥ 5 yr	1	60/38302	420/232116	0.68 (0.52-0.90)	0.0060
Nested case-control					
Any ASA	6	2215/8926	65 099/109526	0.87 (0.75-1.00)	0.0700
Maximum reported ASA	5	206/4457	8302/40948	0.67 (0.58-0.77)	< 0.0001
ASA ≥ 5 yr	1	116/228	23704/37935	0.62 (0.48-0.81)	< 0.0001
Daily ASA	1	53/165	8744/22975	0.77 (0.55-1.07)	0.1400
Daily ASA ≥ 5 yr	1	29/141	7274/21505	0.51 (0.34-0.76)	0.0120

Modified from Algra *et al*[8]. Estimates from standard cohort studies are based on results adjusted for age and other baseline clinical characteristics. ASA: Aspirin.

Evidence from clinical trials

In 2010, Rothwell *et al*[13] obtained long-term follow-up data on cancer outcomes from four randomised trials that were originally designed to evaluate the effect of aspirin on the prevention of CVD events (Table 2). These trials studied diverse populations with CVD, including men at low risk (n = 10,224) and men and women at high risk (n = 3809). Dosage ranged from 75-1200 mg/d, median treatment duration was 6 years and median follow-up was 18.3 years. Treatment with aspirin (75-500 mg/d) reduced the 20-year risk of CRC by 24% and CRC-associated

Table 2 Characteristics of trials included in Rothwell *et al* study and details of post-trial follow-up

	Thromobosis prevention trial	Swedish aspirin low dose trial	UK-TIA aspirin trial	British doctors aspirin trial
ASA comparison	75 mg/d *vs* placebo	75 mg/d *vs* placebo	300 mg *vs* 1200 mg/d *vs* placebo	500 mg/d *vs* placebo
Recruitment period	1989-1992	1984-1989	1979-1985	1978-7199
Median duration of scheduled treatment in original trial (yr)	6.9	2.7	4.4	6
Year post-trial follow up extended to	2009	2007	2006	2002

Modified from Algra *et al*[8]. ASA: Aspirin.

Table 3 Clinical effects of aspirin on sporadic colorectal cancer (clinical trials)

	Rothwell *et al* meta analysis	Physician's health study	Women's health study
ASA dosage	75-1200 mg/d	325 mg per every other day	100 mg per every other day
Duration of follow up (yr)	⩾ 20	10	10
Relative risk of CRC over follow up (HR)	0.76 (95%CI: 0.60-0.96)	1.03 (95%CI: 0.83-1.28)	0.97 (95%CI: 0.77-0.24)

Comparison of findings from meta-analysis performed by Rothwell *et al*[13] and incidence data of Physician's Health Study and Women's Health Study studies[13,15,16]. CRC: Colorectal cancer; ASA: Aspirin.

mortality by 35%. The benefit increased with longer duration of treatment and seemed to be higher for proximal CRC compared to distal CRC. An absolute reduction of 1.76% (P = 0.001) in 20-year risk of any fatal CRC after 5 years of daily treatment with aspirin (75-300 mg) was observed. Subsequently, the same authors published a study that examined the effects of daily aspirin on long-term risk of death due to all cancers. They included data from eight randomised trials (25570 patients, 674 cancer deaths) and concluded that aspirin use reduced the risk of death due to cancer (pooled OR = 0.79, P = 0.003), but the benefit was only apparent after 5 years of treatment. Absolute reduction reached 7% in 20-year risk of death due to cancer for patients aged ⩾ 65 years. In the 3 trials reporting data on the specific site of cancer occurrence with treatment duration of 5 years or longer and long-term follow-up, patients randomized to aspirin showed a statistically significant 20 year risk reduction of death due to CRC of 40% (HR = 0.60; 95%CI: 0.45-0.81, P = 0.0007)[14].

Although these data are compelling, it should be taken into account that these studies were secondary analyses of CVD prevention trials and therefore they were not originally designed to examine CRC incidence or mortality. In addition, there are two large randomized trials of alternate-day aspirin treatment in healthy subjects: the Physician's Health Study (PHS)[15] and Women's Health Study (WHS), which showed no effect of aspirin on the incidence of CRC over a 10-year follow-up period[16]. The PHS determined the effect of aspirin 325 mg every other day on CVD in 22,071 healthy male physicians. In this study, the relative risk of CRC over a 10-year follow up was 1.03 (95%CI: 0.83-1.28). The WHS examined the effect of 100 mg every other day in 39876 healthy women. The relative risk of CRC was 0.97 (95%CI: 0.77-1.24). There are several plausible explanations for the discrepancy in results between the meta-analyses performed by Rothwell and incidence data of the PHS and WHS trials. Firstly, both trials used alternate-day dosing regimens in contrast to daily dosing used in the studies included in both meta-analyses. Secondly, in the PHS and WHS trials, the duration of follow-up was shorter and may have been insufficient to detect the aspirin effect. Finally, in the WHS trial, the equivalent daily dose of aspirin was 50 mg, lower than the 75 mg/d shown to be the minimum effective dose in the Rothwell meta-analyses[13] (Table 3).

The precursors of CRC are colorectal adenomas in most cases. It would be expected that the chemopreventive effects of aspirin should begin before the development of CRC. The long duration of aspirin treatment required to show a preventive effect against invasive CRC probably reflects the time required for the development of cancer from precursor lesions (5-10 years). To date, four randomized double-blind placebo-controlled trials with 2967 participants have evaluated aspirin versus placebo for the secondary prevention of colorectal adenomas (in patients who had had colorectal adenomas or CRC)[17-20]. Doses ranged from 81 to 325 mg/d and median follow-up was 33 mo. The meta-analysis of these randomized trials[21] showed a statistically significant 17% reduction of the risk of developing adenoma with any dose of aspirin vs placebo (RR = 0.83; 95%CI: 0.72-0.96). This corresponded to a significant absolute risk reduction of 6.7%. For any advanced lesion, a significant relative risk reduction of 28% for aspirin at any dose was observed. This preventive effect emerged rather quickly (1 year) after the initiation of aspirin use (Table 4).

CLINICAL EFFECTS OF ASPIRIN IN HIGH-RISK POPULATIONS: FAMILIAL ADENOMATOUS POLYPOSIS AND LYNCH SYNDROME

To date, there are two controlled randomized trials that primarily evaluated the efficacy of aspirin in high-risk CRC patients: the Colorectal Adenoma/Carcinoma Programme (CAPP)1[22], which included 206 young individuals with a diagnosis of familial adenomatous polyposis (FAP), and CAPP2[23], which studied 1009 patients with Lynch syndrome. Both studies compared aspirin (600 mg/d), with or without resistant starch or resistant starch placebo. Data from CAPP1 patients were only analyzed

Table 4 Clinical effects of aspirin in incidence of sporadic colorectal adenomas (clinical trials)

Study	Patients	Treatment	RR (95%CI)	Ref.
AFPPS trial	Patients with a recent history of histologically documented (removed) adenomas	ASA (81 or 325 mg/d) or folic acid (1 mg/d) or placebo for 2.7 years	Any adenoma 0.81 (0.69-0.96), ASA 81mg *vs* non ASA 0.96 (0.81-1.13), ASA 325 mg *vs* non ASA Advanced lesion 0.59 (0.38-0.92), ASA 81 mg *vs* non ASA 0.83 (0.55–1.23), ASA 325 mg vs non ASA	[17]
CAPS trial	Patients with a histologically documented colon or rectal cancer with a low risk of recurrent disease	ASA 325 mg/d or placebo for 2.6 years	0.65 (0.46-0.91)	[18]
APACC trial	Patients with a history of colorectal adenomas	ASA 160 or 300 mg/d or placebo for 1 and 4 years	0.73 (0.52-1.04) for both doses, after 1 year 0.96 (0.75-1.22), for both doses, after 4 years	[20]
ukCAP trial	Patients with an adenoma removed in the 6 mo before recruitment	ASA (300 mg/d) plus placebo or ASA plus folic acid (0.5 mg/d) or folic acid plus placebo or double placebo for about 2.6 years	Any adenoma 0.79 (0.63-0.99), ASA *vs* non ASA, Advanced adenoma 0.63 (0.43-0.91), ASA *vs* non ASA	[19]
J-CAPP trial	Patients with previous sporadic colorectal tumors	ASA 100 mg/d or placebo for 2 years	Ongoing	

ASA: Aspirin.

Table 5 Clinical effects of aspirin in high risk population (clinical trials)

Study	Patients	Treatment	RR or HR (95%CI)	Ref.
CAPP1 trial	FAP young patients (10 to 21 years of age)	ASA (600 mg/d) plus placebo or resistant starch (30 g daily) plus placebo or double placebo for 17 years	RR = 0.77 (0.54-1.10), ASA *vs* non ASA	[22]
CAPP2 trial	Hereditary non-polyposis colon cancer or HNPCC	ASA (600 mg/d) or ASA placebo or resistant starch (30 g daily) or starch placebo for up to 4 years	HR = 0.63 (0.35-1.13), for the entire post-randomization period (ASA *vs* placebo) HR = 0.41 (0.19-0.86), for ≥ 2 years of treatment (ASA *vs* placebo)	[23]
J-FAPP Ⅱ trial	FAP patients (≥ 16 years of age)	Placebo *vs* enteric coated ASA (100 mg/d) for 6-10 mo	Ongoing	[25]

ASA: Aspirin; FAP: Familial adenomatous polyposis.

if they had received treatment for at least 1 year. CAPP2 patients received aspirin for a mean of 29 mo.

The CAPP1 trial showed that the mean size of the largest polyps was significantly reduced in aspirin users. Despite a trend to fewer polyps in the rectum and sigmoid colon in aspirin versus non-aspirin users at the end of intervention (from 1 to 12 years), the difference was not significant.

CAPP2 was the first clinical trial that had cancer prevention as a primary endpoint. At the end of the intervention phase, analysis showed that aspirin treatment did not reduce the risk of developing new adenomas (RR = 1.03; 95%CI: 0.7-1.4) or CRC. The study design involved post-intervention follow-up[24]. Over a mean follow-up of 55.7 mo, 48 aspirin users had developed 53 primary CRC, whereas in intention-to-treat analysis of time to first CRC there were no differences (HR = 0.63; $P = 0.12$) and the per-protocol analysis of patients completing 2 years of intervention yielded a HR of 0.41 (0.19-0.86, $P = 0.02$) (Table 5).

In Japan, two chemoprevention studies are currently being performed: one in patients with previous sporadic colorectal tumors [Japan Colorectal Aspirin Polyps Prevention (J-CAPP study)] and the second in patients with familial adenomatous polyposis (J-FAPP study Ⅱ). Both are double-blind randomized controlled trials with low-dose aspirin (100 mg/d) and study the effect of aspirin in colorectal carcinogenesis[25].

CLINICAL EFFECTS OF ASPIRIN IN PATIENTS WITH PREVIOUS CRC

It has been suggested that aspirin may prevent recurrence or death in CRC patients. In a placebo-controlled randomized trial of patients with a history of non-metastatic CRC after resection, daily treatment with LDA was associated with a 35% reduction in risk of recurrent adenoma or carcinoma at 36 mo[18]. In a cohort study of health professionals diagnosed with stage Ⅰ-Ⅲ CRC, regular use of aspirin after diagnosis was associated with higher CRC specific survival compared with non-users[26].

DOSING FOR CHEMOPREVENTION

Because most aspirin-related adverse effects are dose-dependent, to find the minimum effective dose required for CRC prevention remains a critically important issue.

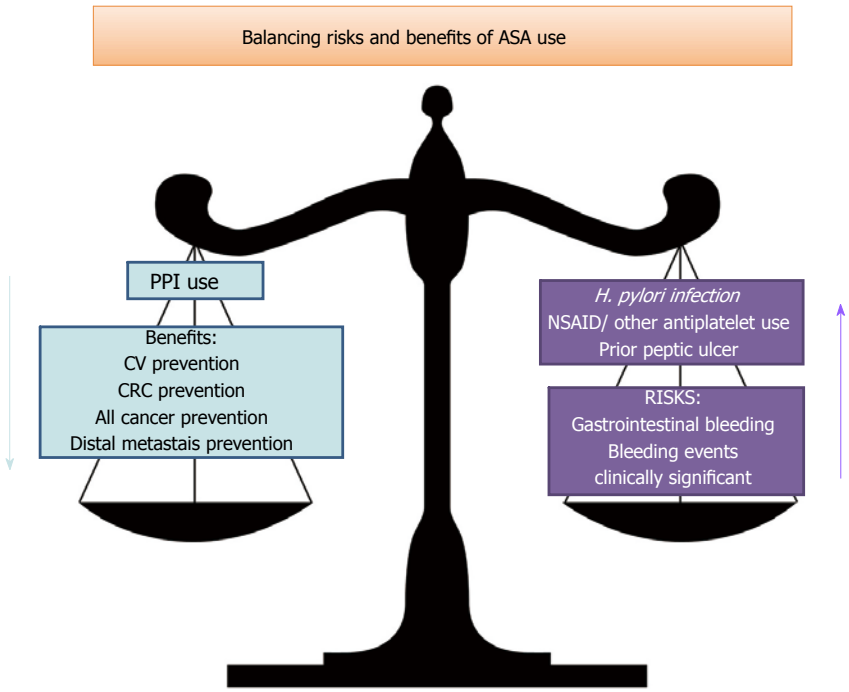

Figure 1 Balancing risk-benefits for the use of low dose aspirin. CRC: Colorectal cancer; NSAID: Nonsteroidal anti-inflammatory drug; CV: Cardiovascular; PPI: Proton pump inhibitor; ASA: Aspirin.

The Rothwell meta-analysis found that daily LDA regimens for the prevention of CVD-related events (75-325 mg) were as effective as daily high-dose aspirin[13]. However, the short-term follow up data from the PHS[15] (aspirin 325 mg every other day) and the WHS[16] (aspirin 100 mg every other day) did not show a reduction in risk of CRC. These negative findings could be attributed to alternate day dosage and/or short follow up and/or the lower dose, especially in the WHS trial. The adenoma trials (REFS) also indicate that LDA (81-325 mg/d) reduces the risk of developing adenomas and advanced adenomas.

Although follow-up of the randomized trial of daily aspirin in CVD prevention and adenoma prevention trials demonstrated that daily LDA of 75-81 mg may be sufficient for CRC prevention, the results of observational studies are controversial. Some suggested that 300-325 mg may be necessary for CRC prevention but most provided incomplete information regarding the dose and duration of aspirin treatment[7,8,10,11,27].

Therefore, taking the clinical trial and observational information together, there is very strong evidence that long-term LDA (75-325 mg/d) reduces the risk of CRC. Importantly, for the prevention of CVD-related events, LDA (75-81 mg/d) seems to be as effective as high-dose aspirin (300-325 mg/d) and, moreover, LDA has a better safety profile. However, daily aspirin at any dose may show greater benefit in patients with CVD than in those at risk of CRC.

BALANCING RISKS AND BENEFITS

Based on current evidence, treatment with LDA for 5 years in patients at risk of CVD-related events will probably prevent between 12 and 40 myocardial infarctions per 1000 patients treated, assuming an overall 10% risk of CVD-related events in this population[28]. Unfortunately, LDA use is also associated with 2-4 upper gastrointestinal bleeding events per 1000 patients[28]. However, the risk of adverse events differs according to patient characteristics (gender, age, history of ulcer, *etc.*). It is of course possible to reduce gastrointestinal risk with proton pump inhibitors, but we cannot reduce the risk of intracranial bleeding. Given the risk of bleeding, clinical guidelines (2007) recommended against the routine use of aspirin for CRC prevention in average-risk individuals[29]. However, the accumulating evidence from randomized clinical trials provides an exciting opportunity to reconsider the potential role of aspirin in cancer prevention; therefore, future practice guidelines recommendation for primary prevention in average-risk individuals for aspirin prophylaxis may also consider the prevention of cancer and not only the benefits of aspirin for the prevention of CVD-related events (Figure 1).

MECHANISM OF ACTION OF ASPIRIN

Aspirin, like other nonsteroidal anti-inflammatory drugs (NSAIDs), has the capacity to reduce prostanoid generation by inhibiting the activity of COX isozymes. Prostanoids are biologically active derivatives of arachidonic acid (AA) released from membrane phospholipids through the activity of different phospholipases[30,31]. There are two isoforms of COX, named COX-1 and COX-2[32]. Both COX isozymes are differently regulated catalytically, transcriptionally and post-transcriptionally, but they share the same catalytic activities.

COX-1 gene is considered a "housekeeping gene" and the protein is highly expressed in platelets where it is responsible for the generation of thromboxane A2 (*TXA2*), which promotes platelet activation and aggregation, vasoconstriction and proliferation of vascular smooth muscle

cells[31,33]. In addition, COX-1 is highly expressed in gastric epithelial cells where it plays an important role in cytoprotection through the generation of prostanoids, such as prostaglandin E2 (PGE2)[31,33]. In contrast, *COX-2* gene, a primary response one with many regulatory sites[34], is constitutively expressed in some tissues in physiological conditions, such as the endothelium, kidney and brain, and in pathological conditions, such as in cancer[35]. In cancer cells, the major prostanoid produced through COX-2 is PGE2, which plays important roles in modulating motility, proliferation and resistance to apoptosis[36,37].

Unlike other NSAIDs, aspirin is able to produce an irreversible inactivation of COX isozymes through the acetylation of a specific serine moiety (Ser529 of COX-1 and Ser516 of COX-2)[38]. Acetylation of the allosteric subunit of COX-1 by aspirin causes an irreversible inhibition of COX activity and, in turn, of the generation of PGG2 from AA. Acetylated COX-2 is not able to form PGG_2 but it generates 15R-hydroxyeicosapentaenoic acid (15R-HETE) from AA[39]. However, there is no convincing evidence that these lipid mediators triggered by aspirin are generated *in vivo* in humans.

ASPIRIN PHARMACOLOGY

Aspirin has a short half-life when administered *in vivo* and it is rapidly inactivated by plasma and tissue esterases into salicylic acid, which is a weak inhibitor of COXs (in the millimolar range)[40-42]. The inhibitory effects of aspirin have been found to be > 100-fold more potent in inhibiting platelet COX-1 than monocyte COX-2[17-20]. Aspirin at low doses (75-100 mg daily) is able to cause nearly complete inhibition of the capacity of platelet COX-1 to generate TXA_2[43,44]. Due to irreversible inhibition of COX-1 and the limited capacity of platelets for *de novo* protein synthesis[45], the profound inhibitory effect of platelet function by aspirin persists throughout the dose interval (*i.e.*, 24 h).

The major part of the inhibitory effect of platelet COX-1 by the oral administration of low-dose aspirin occurs in the presystemic circulation where the drug reaches higher concentrations[46,47]. The impact of low-dose aspirin, administered once daily, on COX-2 activity *in vivo* is marginal. In summary, the pharmacokinetics and pharmacodynamics of low-dose aspirin support the fact that the drug acts mainly by modifying platelet function as a consequence of COX-1 inhibition. At higher doses, aspirin may affect COX-2 in a dose-dependent fashion.

COX-DEPENDENT MECHANISMS FOR ANTITUMOR EFFECTS

Randomised clinical trials have shown that once daily LDA provides a chemopreventive effect against atherothrombosis[24] and CRC[13,14]. This finding suggests that enhanced platelet activation is involved in the development of these two pathological conditions. In fact, these aspirin doses and dosing intervals are consistent with a selective inhibitory effect of aspirin on platelet COX-1 activity and on TXA2-dependent platelet function.

Transcriptional upregulation of the *COX-2* gene has been observed in nearly half of human colorectal adenomas and 80%-90% of CRC, probably related to the disturbed function of the *APC* gene. However, *COX-1* gene and protein expression are not affected[48-52] and the role of this enzyme in CRC carcinogenesis remains unclear. In colonic mucosa, COX-2 is localized predominantly in tumor tissue, including epithelial cells, mononuclear cells, endothelial and stromal cells, but not in nearby normal tissue. Upregulation of COX-2 is associated with increased cell adhesion, phenotypic changes, resistance to apoptosis and tumor angiogenesis[53-57]. COX-2 expression does not always correlate with survival and/or with Duke's stage of the disease[58-60]. This suggests a role of upregulated COX-2 for the initial stages of colon carcinogenesis but not for clinical outcome at advanced stages. The best studied consequence of upregulated COX-2 in CRC is enhanced prostaglandin production[48]. Prostaglandin levels in CRC tissue are 3-4 fold higher than in healthy tissue in the vicinity, with PGE2 being the predominant product[61]. PGE2 inhibits apoptosis and stimulates tumor growth and angiogenesis via stimulation of b-catenin/T-cell factor dependent transcription[62]. In addition, PGE2 acts as an immunosuppressant in patients with CRC[53,63]. The clearest clinical evidence for COX-2 as a pharmacological target for the chemopreventive action of aspirin was the finding that aspirin reduced the risk of CRC exclusively in individuals with elevated COX-2 expression but not in those without[64]. This was associated with a reduction in mortality[65]. Although these findings were from observational studies, they confirmed experimental data that prostaglandins and non-prostaglandin COX-2 products are central to the pathogenesis of CRC. The vast majority of published experimental studies have reported beneficial antitumor effects for aspirin, celecoxib and non-aspirin NSAIDs in a variety of experimental models[65-67]. These data strongly suggest a central role of COX-2 in CRC and its inhibition is an effective chemopreventive measure (Figure 2).

The generation of TXA2, a major product of platelet COX-1 which promotes platelet aggregation and vasoconstriction[68], represents another important mechanism by which platelets can affect tumorigenesis. One study has shown that enhanced TXA2 generation into murine colon-26 adenocarcinoma cell line (C26) stimulated tumor angiogenesis, tumor growth *in vivo*[69] and promoted the interaction between metastasizing tumor cells and the host hemostatic system[69], thus suggesting a role of TXA2 in promoting angiogenesis and the development of tumor metastasis[70].

In one study, the authors demonstrated PGE2 inhibition in rectal biopsies performed 1 mo after treatment with three different doses of aspirin (81, 325 and 650 mg) versus placebo[71]. Unexpectedly, the 81 mg daily aspirin dose suppressed PGE2 levels to the same extent as the 650 mg dose. In another study, treatment with 81 mg of aspirin per day for 3 mo reduced mucosal PGE2

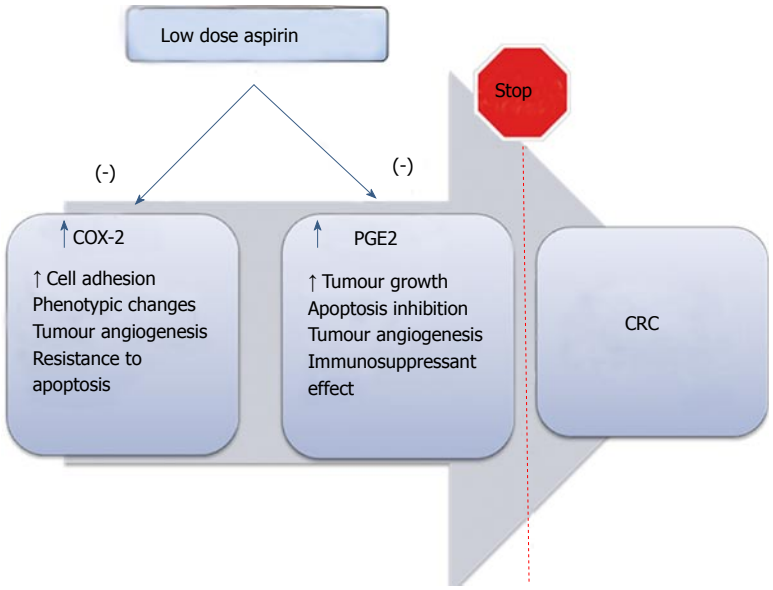

Figure 2 Cyclooxygenase-dependent mechanisms for antitumoral effects of low dose aspirin. CRC: Colorectal cancer; COX: Cyclooxygenase; PGE2: Prostaglandin E2.

and transforming growth factor-α expression in apparently normal rectal mucosa of individuals with a history of adenomatous polyps[72]. Further studies using more appropriate methodologies are required to definitively clarify whether LDA affects COX-1 activity in the gastrointestinal tract.

Some investigators have proposed that both COX-1 and COX-2 pathways are involved in intestinal tumorigenesis and that they operate sequentially. This is strongly supported by the findings of experimental animal studies in which the loss of either *COX-1* or *COX-2* genes blocks intestinal polyposis in mouse models of FAP by about 90%[66,67].

COX-INDEPENDENT MECHANISMS OF ANTITUMOR EFFECTS

Evidence from different lines of research indicates that COX-2 independent mechanisms may also affect apoptosis and cell proliferation in CRC and are sensitive to both aspirin and non-aspirin NSAIDs. Nearly but not all human colon cancer cells express COX-2 and produce prostaglandins[53,73]. Today, several COX-independent mechanisms of aspirin have been reported that might contribute to its chemopreventive effects in tumorigenesis[73]. Most of these effects have been found *in vitro* using supra-therapeutic concentrations of aspirin which cannot be obtained in systemic circulation with low doses of the drug. However, no convincing evidence has been obtained to demonstrate that these mechanisms are operative *in vivo*, particularly with low doses of aspirin which have been associated with chemopreventive benefits in randomised clinical trials. In any case, currently available evidence clearly points to the existence of further cellular targets of NSAIDs, in addition to COX-2 inhibition, which may contribute to their antitumor effects. Further studies are needed to completely understand the mechanisms involved.

CONCLUSION

A large body of clinical evidence supports the protective action of aspirin as a chemopreventive agent for different types of cancer, in particular CRC[6]. Also, increasing indirect evidence has led to the hypothesis that the antiplatelet effect of aspirin is a central mechanism for its antitumor effect[34,41]. The finding of an apparent maximum chemopreventive efficacy against cancer and atherothrombosis by low-dose aspirin lends support to this hypothesis[6]. At low doses every 24 h, aspirin acts as a complete and persistent inhibitor of COX-1 in platelets (in pre-systemic circulation)[47], while causing a limited and rapidly reversible inhibitory effect on COX-2 and/or COX-1 expressed in nucleated cells[39]. Despite uncertainty about the precise mechanisms that underlie aspirin's anticancer benefit, the evidence supporting its effectiveness for the prevention of CRC is substantial; daily aspirin for at least 5 years has been shown to reduce the 20-year risk of CRC by 32% and 20-year mortality by 43%[13]. Therefore, the potential benefit of aspirin in both CVD and prevention of cancer at multiple sites may favor its use for broader chronic disease prevention. It is likely that the benefits in terms of morbidity and mortality will outweigh concerns about gastrointestinal bleeding, which is rarely life threatening, and cerebral bleeding, which is extremely uncommon. Health authorities should consider the possibility of extending recommendations on the routine use of aspirin, taking into account its beneficial effects in cardiovascular disease and cancer prevention.

Extensive translational medical research is required to confirm the hypothesis of platelet-mediated colon tumorigenesis. Importantly, these studies will need to address the current uncertainty concerning the optimal aspirin dose, the dosing regimen for cancer prevention, the possible contribution of individual genetic cancer susceptibility to aspirin response[74] and also the target

population most likely to benefit from daily aspirin use.

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