Aspirin as a chemoprevention agent for Colorectal cancer

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Abstract

Colorectal cancer (CRC) is one of the leading causes of mortality in the western world. It is widely accepted that neoplasms such as colonic polyps are precursors to CRC formation; with the polyp-adenoma-carcinoma sequences well described in medical literature.[1,2] It has been shown that Aspirin and other non-steroid anti-inflammatory drugs (NSAID) have a negative effect on polyp and cancer formation. This review aims to describe some of the mechanism behind the chemoprotective properties of aspirin; COX 2 inhibition, regulation of proliferation and apoptosis and effects on the immune system and also the current evidence that supports its use as a chemoprevention agent against CRC. We will also aim to explore the side effects with the use of aspirin and the pitfalls of using aspirin routinely for primary prophylaxis against CRC.

Introduction

Colorectal cancer(CRC) is one of the most commonly diagnosed malignancies both in men and women.[3] It is one of the leading causes of mortality in developed countries; and in Europe it is estimated to account for 212,000 deaths per year with more than 400,000 new cases diagnosed each year.[4] Though its incidence seems to have peaked in developed countries, rapidly developing countries such as China and India are seeing a surge in the incidence of CRC.[3,5,6] The continual rise in the cost of cancer treatment and cancer related care means CRC places a significant burden to the healthcare resources and is a major public health issue.[7-9]

Collectively healthcare professionals have worked aggressively to address the impact of CRC on human health. Over the past few decades, life expectancy has improved due to medical advances and better care.[10] Earlier detection of CRC by screening has helped to improve prognosis through detection of earlier stage disease.[11] Indeed with CRC screening that uses colonoscopy as the primary or secondary tool, colonic polyps, precursors of CRC; can be detected and removed which in turn prevents the development of CRC itself.[12,13] There are currently a number of screening strategies available for the detection of CRC. There are however limitations to screening strategies and primary prevention by identifying and reducing the risk of CRC and polyp formation would be ideal in a large population both in terms of clinical efficacy and cost effectiveness.[14]

Epidemiological studies have demonstrated that environmental factors play a big part in the pathogenesis of CRC.[15] Observations from a number of these studies have shown a significant reduction in CRC incidence and mortality among people who use aspirin and/or non steroidal anti-inflammatory drugs (NSAIDs) regularly compared to non-

users.[16-18] This has generated much interest in utilizing aspirin as a chemoprevention drug for primary prevention of CRC in the general population and research into its interaction with polyp formation and carcinogenesis. Herein we review the pharmacology of aspirin and the mechanisms that are proposed to be behind its ability to reduce CRC incidence and therefore mortality. We also look at the current evidence for its use as a chemoprevention agent and the challenges with advocating it for primary prevention against CRC in the general population.

Pharmacologic properties of Aspirin

Aspirin, first developed in 1853 by Charles Gerhardt and later refined by Felix Hoffman in 1899, is produced by modifying the structure of salicylic acid with acetylation of its phenol group.[19] Since its inception aspirin was very quickly adopted into medical practice for its anti-inflammatory and analgesic properties but little was known of the mechanism of action until the later part of the 20th century. The arachidonate-prostaglandin synthesis pathway was then discovered along with the inhibitory properties of aspirin and NSAIDs on the enzyme cyclooxygenase (COX).[20] COX is a membrane bound hemoprotein and glycoprotein of a molecular weight of 72 KDa.[20,21] Existing as 3 isoforms (COX-1, -2 and -3) naturally, COX is the rate limiting enzyme involved in the metabolism of arachidonic acid by adding the 15-hydroperoxy group to form Prostaglandin G_2 (PGG_2). PGG_2 is then converted by the additional peroxidase activity of COX to from PGH_2 which in turn is a substrate for the synthesis of a variety of prostaglandins that serve as important mediators in major physiological functions including; inflammation, vasoconstriction, platelet aggregation and gastric mucosal integrity. Figure 1. The two

clinically significant isoenzymes of COX (COX-1 and COX-2) exhibit different prostaglandin synthesis profiles. COX-1, which is expressed ubiquitously and constitutively, produces prostaglandins that are involved in physiological homeostasis such as gastric mucosa protection and platelet aggregation. In contrast, COX-2 expression is mainly found in inflammatory cells and could be induced by mitogens, growth factors, tumour promoters and liposaccharide.[22] Induction of COX-2 leads to the production of potent inflammatory mediators, particularly Prostaglandin E_2 (PGE_2). [20] Aspirin, as well as other NSAIDs, act on both COX I and II and it is generally thought that the desirable anti-inflammatory properties are attributed to COX-2 inhibition while the unwanted side-effects are COX-I mediated.[20-22] The likelihood of generating side effects at a given therapeutic dose is different for each NSAIDs and is in part explained by their differential inhibitory potency to each COX isoform (I and II).[23] Using whole blood assays the concentration needed to inhibit 50% of COX-I or -II activity (IC_{50}) can be measured for each given compound. The ratio of IC_{50} of COX-2 to IC_{50} of COX-1; also called the selectivity index, can then be derived for each individual NSAIDs. Table 1. A high selectivity index denotes high COX-I selectivity and is associated with increased side effects such as GI toxicity.[23]

Aspirin acts on COX by acetylation of the hydroxyl group of one serine residue. This results in irreversible inhibition of the enzyme as the acetylated group prevents the substrate arachidonic acid from binding to the active site. This reaction occurs on a competitive basis and new COX enzyme synthesis is required for further production of more prostaglandins. The peroxidase activity of the COX enzyme remains unaffected by this acetylation.[19,20,22]

In terms of pharmacokinetics aspirin is readily absorbed in the stomach and small intestines once ingested.[24,25] Aspirin is then rapidly metabolized by esterases into its active metabolite salicylic acid which persists at a high concentration for up to 6 hours.[26]

The half life of aspirin itself is estimated to be around 15 to 20 minutes.[24] Aspirin is essentially not excreted unchanged but rather through further metabolism of salicylic acid. The elimination pathways of salicylic acid are complex, mainly through conjugation with glycine to form salicyluric acid prior to renal excretion.[27] This pathway can be saturable with high doses of salicyclic acid (usually at doses of 600mg) and other pathways such as cytochrome P450 hydroxylation to gentisic acid become more important.[28] All metabolites are renally excreted and have no COX properties. There are significant inter-subject variations in terms of the clearance of salicylic acid; with sex and age differences having an influence as well. Salicyclic acid clearance was noted to be 61% higher in males than females while metabolite levels of salicyuric acid and gentisic acid were found to be raised in chronic users of aspirin above the age of 60.[29,30] Hence due consideration will have to be given when prescribing aspirin in the setting of the elderly population and in hepatic or renal impairment.

Proposed Chemoprevention Mechanisms of Aspirin

The chemopreventive properties of aspirin and NSAIDs were first proposed after it was reported that various animal and human tumour tissues contain high concentrations of prostaglandins.[31-35] Since then there has been an increasing body of evidence to support this. Experimental models for various tumours ,including colon adenocarcinoma, have shown that aspirin and NSAIDs reduce tumour growth.[36-38] Furthermore this effect was noted to behave in a dose dependent manner.[39] Subsequent translational studies looking at the effects of sulindac in patients with familial adenomatous polyposis (FAP) demonstrated the effectiveness of COX inhibition in the reduction of the size and number of colonic polyps which are precursors of colorectal cancer.[40-42] It was also noted that

this phenomenon was reversible, with recurrence of the polyps on cessation of the drug.[43,44]

Further studies looking into the relationship of NSAIDs and tumorigenesis have implicated COX-2 inhibition as one of the major mechanisms underpinning the anti-carcinogenic properties of aspirin. The data on the effect of COX-2 in cancer formation since the discovery of the isoenzyme COX-2 in the 1990s has been reviewed succinctly by Taketo (1998) with considerable evidence to support a key anti-carcinogenic role.[22,45] Several studies have shown an increase in COX-2 expression in colorectal cancer tissue and cells compared to controls while COX-1 expression remained unchanged.[46,47] COX-2 expression has also been shown to be associated with the size and the grade of dysplasia in colorectal polyps.[48] Greater COX-2 expression correlated with more advanced stage of CRC, larger tumour size, differentiation, metastasis and lympho-vascular invasion.[49][50-52] Using adenomatous polyposis coli (APC) gene knockout mice, Oshima et al were able to demonstrate that knocking out the COX-2 gene in these mice resulted in a significant reduction of polyps both in the colon and small intestine.[53] Furthermore this effect can be mimicked by administering a COX-2 inhibitor in this animal model of FAP.[53] Recently it has also been shown that single nucleotide polymorphisms of COX-2 (rs5277 and rs4648310) are associated with increased risk of adenoma recurrence in a colorectal polyp prevention trial; lending further support for the role of COX-2 in the etiology of CRC.[54]

The exact nature by which COX-2 inhibition helps with tumour suppression is complex and not as yet fully understood. Inhibition of COX-2 reduces PGE2, itself an inflammatory mediator implicated in the inflammation carcinogenesis pathway.[55,56] Increased cellular arachidonic acid levels due to COX-2 inhibition can also induce apoptosis.[57,58] Apoptosis has a central role in cell turnover and its dysregulation is a

major component of carcinogenesis.[59] In a inflammation-related CRC mouse model it has been shown that aspirin promotes apoptosis of CRC cells by suppressing the IL-6-STAT3 signaling pathway as well as its downstream anti-apoptotic genes *Bcl-2* and *Bcl-xl*.[60]

Additionally it is proposed that aspirin could have anti-proliferative and apopotic effects that are independent of COX-2.[59] This is due to observations that aspirin and NSAIDs can still inhibit colon cancer cell lines that do not express COX-1 or COX-2.[61,62] Bousserouel et al investigated the role of long term aspirin administration on a rodent model and showed that aspirin treatment for 10 months was associated with reduction of aberrant crypt foci, a surrogate marker for neoplasia by 50% and suppressed colonic tumour formation by 80%. The group also found an increase in expression of α-defensin-5 and lipocalin-2 in aspirin treated mice while *Bcl-2* level was decreased. [63] This shows that the innate immune system could also be upregulated by aspirin which may help defend against mucosal inflammation and inhibit tumour growth.

Furthermore Secondary analysis of the Aspirin/Folate Polyp Prevention Trial suggested that another mechanism other than inflammation may be involved in the inhibition of carcinogenesis.[64] Aspirin has been shown to have the ability to downregulate NF-kB which regulates the transcription of many genes involved in immune responses and promotes apoptosis.[56,65] Aspirin could also target the Wnt/β-catenin signalling pathway through phosphorylation and inactivation of β-catenin which is a key mediator of colon tumorigenesis.[66] A study looking at cancer cell lines and its interaction with peripheral blood mononuclear cells (PBMC) found that they reacted differently in the presence of aspirin regarding their ability to produce pro- and anti-inflammatory cytokines when they are cultured together, suggesting that on top of its anti-inflammatory properties aspirin may have an additional effect on direct cell-to-cell interactions between cancer and immune

cells which in turn modulates cytokine production and inflammation-driven tumorigenesis.[67]

Evidence for Aspirin as a chemoprevention agent in clinical studies

Primary Prevention for Colorectal Cancer

Epidemiological studies provided the initial body of evidence that highlighted aspirin and NSAIDs as potential agents in primary prevention against CRC. Kune et al published the first case control study showing a reduced incidence of CRC in frequent users of aspirin (RR= 0.63; P < 0.001; 95% CI= 0.50-0.78) in an Australian population.[16] This generated much interest and subsequent case-control studies have shown a similar protective effect.[16,18,68-73]. Table 2. Observational studies from other ethnic populations support the findings and suggest the effect is similar among different populations.[74] Similar results were also noted for users of NSAIDs, reaffirming that common protective pathways were at work.[75] Cohort studies however have shown heterogenous results, with some reporting a relative risk reduction by up to 50% while others observed no benefit from aspirin.[76-86] Recently further analysis of the Nurses' Health Study involving 83,767 participants identified among other things that regular aspirin taking reduced the risk of CRC by 29%.[83,87] Data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) in America showed that regular aspirin use in the past year was associated with a reduction of left sided adenomatous and hyperplastic polyps. This is interesting as hyperplastic polyps are increasingly being associated with CRC formation via the serrated polyp pathway.[72,88]

Important insights gained among these observational studies include the facts that the chemopreventive effect is probably dose dependent; that benefit is only observed after an extended duration of using aspirin and that the effect is nullified on cessation of the drug for at least one year.[80,82,83,86]

Controversies remain regarding the minimum dose of aspirin required to see a chemopreventive effect. A case control study involving 5,186 patients showed that even the lowest dose of aspirin (75mg) conferred a protective effect against CRC evident after 1 year and increasing with duration use.[73] There is however conflicting evidence that suggests that doses below 300mg are unhelpful.[82] On foot of these findings randomised controlled trials were developed to further assess the relationship between aspirin and CRC. The first published randomised controlled trial came from the physicians health study (PHS) involving 22,071 male physicians. At a dose of 325mg of Aspirin every other day the study did not detect an association with reduced risk of colorectal cancer after a median follow up of 5 years. [89] In the Women's Health Study (WHS), a large scale randomised control trial with an average of 10 years follow up; aspirin dose of 100mg on alternate day similarly did not show any benefit in terms of lowering the risk of colorectal cancer.[90] However pooled analysis of two randomised trials; the British Doctors Aspirin Trial (BDAT) and the UK-TIA Aspirin Trial (UK-TIA); were able to demonstrate a significant reduction in the incidence of CRC with aspirin use of 5 years or more [pooled Relative Risk(RR)=0.74, 95% Confidence Interval(CI)=0.56-0.97) though there was a latency period of 10 years before the effect becomes apparent.[91] It is also interesting to note that the aspirin doses for these two trials were considerably higher than the WHS and PHS. In the BDAT doctors randomised to the treatment arm were taking 500mg of soluble aspirin daily (or 300mg enteric coated) while subjects in the UK-TIA were assigned either 300mg or 1200mg of aspirin daily.[92,93] While the above data seems to indicate the necessity to

prescribe an aspirin dose in excess of those associated with cardio protective properties, for a chemopreventive effect, there is also an increasing body of literature to support the efficacy of a lower dose of daily aspirin, which is more likely to be tolerated by patients due to side effects. Long term follow up, 20 years, of four trials of daily low-dose aspirin (75-300mg) in prevention of vascular events showed that with prolonged treatment, more than 5 years there is an absolute reduction in CRC of 1.75% overall. It is of significant interest that this effect is most prominent for proximal colon cancer where a risk reduction of up to 70% was observed with aspirin users.[94]. Table 3..

Prevention of CRC in at Risk Groups

There is also an increasing body of evidence to support the use of aspirin in secondary prevention and in patients who are at a higher risk of developing CRC. Baron et al investigated the effect of aspirin on patients with a recent history of colorectal adenomas in the Aspirin/Folate Polyp Prevention Study (AFPPS). In this randomised controlled trial with 1121 subjects, users of low dose aspirin (81mg daily) had a relative risk of 0.81 for adenomas and 0.59 for advanced neoplasms on follow up colonoscopy after 3 years.[95] The subject group taking 325mg of aspirin daily did not have a reduction in adenoma or advanced adenoma risk in this study. The United Kingdom Colorectal Adenoma Prevention Study (UK CAP); a randomised double blinded multi-center trial of aspirin (300mg daily) and folate supplements to prevent colorectal adenoma recurrence, in contrast showed a relative risk reduction of 21% and 37% for adenomas and advanced adenomas respectively when compared to placebo controls after 3 years follow up.[96] The Association pour la Prevention par l'Aspirine du Cancer Colorectal (APACC) study group in France looked at the effect of long term aspirin (160mg and 300mg daily versus

placebo) on adenoma recurrence. They reported a protective effect at 1year's follow up but after a follow up of 4 years there was no statistical difference in adenoma recurrence rate between users and non-users of aspirin. This finding, however, has to be interpreted with caution due to a lack of statistical power of the final analysis due to excessive drop outs.[48,97] Meta-analysis of four clinical trials, including the three above, determined an absolute risk reduction of 6.7% in adenoma recurrence with aspirin use in individuals with a history of colorectal polyps.[98]

The role of aspirin in individuals predisposed to inherited forms of CRC and polyposis is less clear. FAP is an autosomal dominant genetic disorder characterised by the presence by multiple polyps throughout the colon. Patients with FAP carry a significant risk for CRC, with 95% chance of developing cancer by the age of 50. There is already strong evidence to show that sulindac and COX-II inhibitors help to reduce the burden of disease in FAP.[42,99-101] In contrast, the effect of aspirin is modest in FAP. A recent multi-center randomized placebo controlled trial involving 206 patients with FAP found that patients treated with aspirin 600mg/day for at least a year showed a trend towards reduced polyp numbers in the sigmoid and rectum though it did not reach statistical significance. They did however discover that there was a significant reduction in the size of the largest polyp noted on endoscopy for aspirin users of more than 1 year.[102] Burn et al also conducted a similar trial on a cohort of patients with Lynch syndrome; an autosomal dominant genetic defect in mismatch repair genes predisposing to the development of CRC. This trial in which 693 patients were randomly assigned to using aspirin 600mg daily or placebo failed to detect any difference in the incidence of colorectal adenoma or carcinoma after an average follow up of 29 months.[103] The reason for the seemingly lack of efficacy of aspirin in these two hereditary forms of CRC is unknown but one explanation could be the lesser potency of aspirin against COX-II activity compared to

other NSAIDs. Nevertheless this underscores the notion that chemopreventive properties noted in a particular NSAID are not always generalisable to other NSAIDs and further research is needed to advocate the use of aspirin for chemoprevention in the setting of FAP and HNPCC.

Prevention of CRC Recurrence

Tertiary prevention of CRC; that is the prevention of recurrence of CRC or its precursors in a patient with previous history of treated CRC, is also an area that aspirin is seen to be useful. Chan et al conducted a prospective cohort study of 1279 patients who were diagnosed with stage I, II or III CRC. When compared to non users of aspirin post diagnosis with CRC, aspirin users has a reduced risk of CRC related mortality (RR= 0.71) on median follow up of 11.8 years.[104] On further analysing for COX-2 expression in the tumour tissue, aspirin use was only associated with decreased mortality in patients whose primary tumour expressed high levels of COX-2. There was no reduction in risk in aspirin users whose tumour expressed weak or absent levels of COX-2.[104] Interestingly in this study, CRC mortality was not seen to be reduced in patients who used aspirin regularly prior to the diagnosis of CRC nor was a reduction in mortality observed on continuation of aspirin post diagnosis. This is certainly in contrast to the observations found in an extension of the California Teachers Study (CTS) where the authors found a reduction of CRC related mortality with aspirin and NSAIDs use pre diagnosis of CRC[105] but intriguingly this effect was only noted in patients with low meat consumption.[106] Finally, a randomised controlled trial investigated the effect of daily aspirin (325mg) on patients with a history of non-metastatic CRC who had undergone curative resection and reported a significant reduction in the risk of recurrent adenoma in the aspirin group as compared to

placebo (RR= 0.65, 95%CI= 0.46 to 0.91) over a median follow up of 12.8 months. This study was terminated early due to positive results shown during a planned interim analysis.[107]

Limitations of Aspirin as chemoprevention for CRC

While aspirin has shown promising chemopreventive properties, there are limitations to advocating the routine use of aspirin solely for this purpose. The main issue stems from its side effect profile. Its inadvertent interaction with COX-1 results in the loss of production of protective prostaglandin functions and the consequent side effects can render the therapy hazardous for the user.[20,23] Aspirin is known to have significant gastrointestinal (GI) related side effects.[108] Minor GI side effects such as nausea, vomiting and dyspepsia occur more frequently. Aspirin is also ulcerogenic and is associated with increased risk of upper GI bleeding, potentially precipitating major bleeds requiring transfusion.[109] A meta-analysis of 21 randomised controlled trials comparing aspirin and placebo found an increased risk of GI bleeding with aspirin; pooled odds ratio 1.5 to 2.0. The risk of peptic ulcers and upper GI symptoms were increased at 1.3 and 1.7 respectively.[110] Also importantly this GI side effect seemed to be dose related.[110] While some studies have suggested that low daily doses of aspirin (75mg) are sufficient to confer a chemopreventive benefit; such doses are still associated with increased GI bleeding.[111]

Aspirin therapy has also been shown to be associated with increased risk of haemorrhagic stroke due to its anti-platelet effects. A met-analysis of 16 randomised controlled trials with 55,462 participants reported an absolute increase of 12 events per 10,000 persons treated with aspirin.[112]

Other aspirin related side effects include renal insufficiency, but this is usually encountered at doses much higher than that used in cardiovascular or for chemopreventive purposes.[109] Aspirin could also worsen the respiratory status in a small percentage of asthmatic patients due to aspirin sensitivity.[113]

In light of the current evidence the US Preventive Services Task Force (USPSTF) recommended against the routine use of aspirin for the prevention of CRC in individuals at average risk for CRC as it was felt that the harms outweigh the benefits.[114] All patients older than 50 who are at average risk for CRC should be screened for CRC regardless of their aspirin or NSAID status according to the USPSTF.

Cost Effectiveness and Added Value

Given the work that has been done to show the chemopreventive properties of aspirin, cost effective analyses have been carried out to determine if routine aspirin chemoprevention is a cost effective strategy against the development of CRC. A study based on data from the U.S. population found that adding aspirin (325mg daily) to patients who adhere to CRC screening was not cost effective. They also concluded that aspirin chemoprophylaxis alone cannot be a substitute for CRC screening.[115] Another U.S. study compared the cost effectiveness of chemoprevention with aspirin (325mg daily) against the strategies of no intervention; screening colonoscopy and lastly a combination of both aspirin and colonoscopy strategy in the prevention of CRC. They reported an incremental cost-effectiveness ratio (ICER) of $47,249 per life-year saved for aspirin compared to no intervention while the ICER for colonoscopy was calculated at $10,983 per life-year saved compared to no intervention. This implied screening colonoscopy is a more cost effective measure to prevent CRC than chemoprevention with aspirin. On combining both strategies, the ICER was $227,607 per life-year saved compared with screening

colonoscopy alone; suggesting that such a strategy is unlikely to be cost effective when applied to the general U.S. population.[116] While these studies were disappointing it should be noted that economic evaluation based on the U.S healthcare delivery system may not be generalisable to healthcare systems in other countries. Cooper et al conducted a cost effective analysis applicable to the National Health Service in the U.K and found that the use of aspirin as an adjunct to CRC screening was a cost effective strategy when administered to the general population from age 50 to 60 years.[117]

Furthermore the use of aspirin in individuals with increased risk of CRC seems promising. A cost effective analysis by DuPont et al focused on subjects with a history of endoscopic polypectomy. In this U.S. based study the ICER for aspirin versus no intervention was $87,609 per life-year saved while colonoscopic surveillance yield an ICER of $78,226 per life-year saved. Interestingly the strategy of combined aspirin and colonoscopic surveillance against CRC was most cost effective, with an ICER of $60,942 per life-year gained.[118] Similar results were also noted on cost effectiveness analysis on patients with intermediate risk for CRC in the NHS setting.[117]

It should be noted that the evidence and economic evaluation of aspirin presented thus far only home in on its chemopreventive effect on CRC. Aspirin also has other added benefits that can be of value to the target population. Its anti-platelet properties are known to be effective in the chemoprevention of cardiovascular disease.[19,109] Aspirin use has also been associated with reduced risk of other cancers, including gastric, endometrial, pancreatic, oesophageal and lung cancer.[119-123] In fact, a met-analysis of 8 randomized trials involving 25,570 patients looking at the effect of aspirin on cancer deaths demonstrated a reduction in the overall risk of cancer deaths in the aspirin group compared to controls (RR= 0.80, 95%CI=0.72-0.88); with an absolute reduction in 20-year risk of cancer death reaching 7.08% at age 65 and older. This observed protective effect

was noted to be greatest for adenocarcinomas (RR= 0.66, 95%CI=0.56-0.77). Importantly, this benefit was only apparent after 5 years of aspirin use and did not appear to increase at aspirin dose greater than 75mg.[124]

Finally it could also be useful in augmenting the effectiveness of some modalities of CRC screening. One study found that low dose aspirin enhanced the performance of faecal immunochemical test (FIT) in the detection of CRC and polyps in a screening population by inducing microbleeding in the lesions, thereby increasing the amount of haemoglobin present in the faecal sample.[125]

Future direction and Conclusion

Despite the fact that it was first developed over 150 years ago, aspirin has continued to remain relevant through the history of medicine. From its first use as an anti-pyretic and anti-inflammatory agent; it has evolved into an important therapeutic agent both in the treatment and prevention of cardiovascular disease. Now its role in the prevention of cancer; the leading cause of death worldwide, is being explored. While there are encouraging results to support aspirin as a chemoprevention drug in CRC; conflicting data from clinical trials mandate that further research will be needed prior to prescribing this medication to the general population solely for this indication. It is likely that further research will concentrate on selecting out the population that would benefit most from such intervention. In particular, those in whom aspirin imparts the most risk reduction in CRC incidence and mortality while avoiding complications associated with its usage in the long term. Although aspirin chemoprophylaxis cannot be recommended for use in the general population, in certain at risk groups in particular patients with a history of CRC or advanced adenomas its use could be considered on a case by case basis.

Further research into the development of novel compounds with better efficacy and safety profile is also in progress.[126] One such compound; Nitric oxide-donating aspirin

(NO-ASA), is currently being investigated for its efficacy in inhibiting tumourigenesis.

[127,128].

In conclusion, the discovery of aspirin and the prostaglandin synthesis pathway have led to enhanced understanding of CRC pathogenesis. Future work into factors influencing this pathway and its interaction with tumour biology will certainly add towards the armamentarium against the occurrence, and not least the recurrence of this common but deadly disease.

Figure 1: Arachidonate-Prostaglandin synthesis pathway
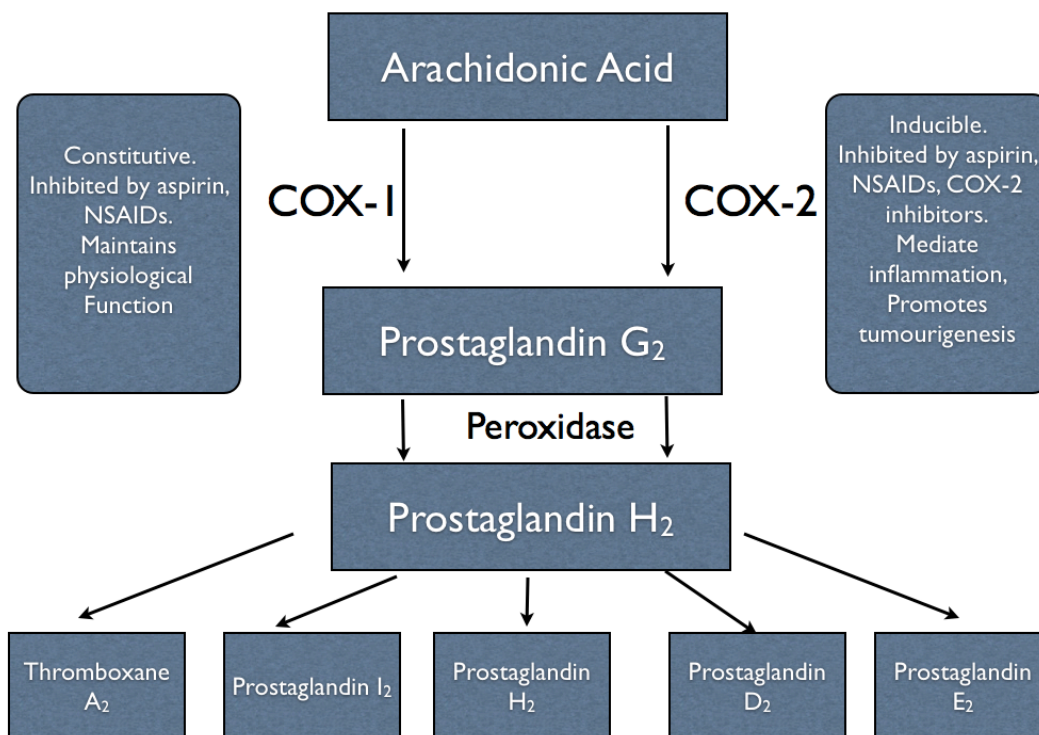
Compound	IC_{50} (μM) for COX-1	IC_{50} (μM) for COX-2	Selectivity Index
Aspirin	1.7	7.5	4.4
Diclofenac	0.075	0.020	0.3
Ibuprofen	7.6	20	2.6
Indomethacin	0.013	0.13	10
Mefenamic Acid	25	1.3	0.049
Sulindac Sulphide	1.9	1.21	0.64
Celecoxib	1.2	0.34	0.3
Rofecoxib	63	0.31	0.0049

Table 1: Inhibition potencies of aspirin and selected NSAIDs and their selectivity index.

Table 2: List of case controlled and cohort studies reporting estimates of relative risk of colorectal cancer(CRC)/polyps associated with aspirin.
*Study estimated relative risk for colorectal polyps only.
[b]Estimate of relative risk for CRC in users of aspirin 300mg daily only. Aspirin doses of 150mg and 75mg daily was not associated with reduced risk.

Study	Study Location	Study Design	StudyPopulation	Relative Risk for CRC/ Polyps*	95% CI
Kune et al, 1988	Australia	Case controlled	Cases 715;Controls 727	0.53	0.40-0.71
Rosenberg et al, 1991	USA	Case controlled	Cases1,326; Controls 4,891	0.5	0.4-0.8
Suh et al, 1993	USA	Case controlled	Cases 830; Controls 1,662	0.38	0.15-0.93
La Vecchia et al, 1997	Italy	Case controlled	Cases 1,357; Controls 1,891	0.7	0.5-1.0
Friedman et al, 1998	USA	Case controlled	Cases 1,993; Controls 2,410	0.7	0.6-0.8
Hoffmeister et al, 2007	Germany	Case controlled	Cases 540; Controls 614	0.77	0.55-1.07
Johnson et al, 2010	USA	Case controlled	Cases 5,663; Controls 38,396	0.8*	0.7-0.9
Din et al, 2010	UK	Case controlled	Cases 354; Controls 526	0.78	0.65-0.92
Paganini-Hill et al, 1989	USA	Cohort	13,987	1.5	1.1-2.2
Thun et al, 1993	USA	Cohort	635,031	0.6	0.34-1.01
Giovanucci et al, 1994	USA	Cohort	47,900	0.68	0.52-0.92
Schreinemachers and Everson, 1994	USA	Cohort	12,668	0.85	0.63-1.15
Giovanucci et al, 1995	USA	Cohort	89,446	0.56	0.36-0.90
Stürmer et al, 1998	USA	Cohort	22,071	1.03	0.83-1.28
García-Rodríguez et al, 2001	UK	Cohort	94,903	0.6[b]	0.4-0.9
Chan et al, 2005	USA	Cohort	82,911	0.77	0.67-0.88
Allison et al, 2006	USA	Cohort	91,534	0.96	0.8-1.2
Larsson et al, 2006	Sweden	Cohort	74,250	0.65	0.45-0.94
Chan et al, 2008	USA	Cohort	47,363	0.79	0.69-0.90

Table 3: List of randomized controlled trials and met-analysis reporting estimates of relative risk of colorectal cancer(CRC)/polyps associated with aspirin.
*Study estimated relative risk for colorectal polyps only.

Study	Location	Study Population	Study Design	Risk for CRC in study population	Aspirin Dose	Median Follow up	Relative Risk for CRC/ Polyps*	95%CI
Gann et al, 1993	USA	22,071, males only	RCT	Average risk	325mg alternate days	5 years	1.15	0.80-1.65
Cook et al, 2005	USA	39,876, females only	RCT	Average risk	100mg alternate days	10 years	0.97	0.77-1.24
Flossmann et al, 2007	UK	7,588	Pooled Analysis,2 trials	Average risk	300-1200mg daily	23 years	0.74	0.56-0.97
Rothwell et al, 2010	UK, Sweden, Holland	14,033	Met-Analysis, 4 trials	Average risk	75-1200mg daily	18.3 years	0.76	0.60-0.96
Baron et al, 2003	USA	1,121	RCT	History of polyps	81mg daily/ 325mg daily	32 months	0.81*/0.96*	0.69-0.96/0.81 -1.13
Logan et al, 2008	UK	945	RCT	History of polyps	300mg daily	3 years	0.79*	0.63-0.99
Cole et al, 2009	International	2,967	Met-Analysis, 4 RCTs	History of polyps, early stage CRC	81-325mg daily	33 months	0.83*	0.72-0.96
Benamouzig et al, 2010	France	272	RCT	History of polyps	160mg daily/ 300mg daily	4 years	Pooled 0.72*	0.45-1.16
Burn et al, 2008	International	1071	RCT	HNPCC	600mg daily	29 months	1.0*	0.7-1.4
Burn et al, 2011	Europe	206	RCT	FAP	600mg daily	1 year	0.77*	0.54-1.10
Sandler et al, 2003	USA	635	RCT	History of CRC	325mg daily	12.8 months	0.65*	0.46-0.94

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