REVIEW

Non-steroidal anti-inflammatory drugs and colorectal cancer prevention

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Colorectal cancer is the second leading cause of cancer deaths in the United States. Currently, the most effective strategy available for colon cancer prevention is endoscopic screening, with polypectomy or surgical resection for advanced lesions. This intervention carries with it many concerns regarding cost, patient acceptance, and the growing burden of surveillance colonoscopies for patients with polyps. Further improvements in the understanding of the multistep model of colorectal carcinogenesis will probably lead to the development of other primary and secondary prevention strategies. Data obtained from animal and epidemiological studies and most recently from randomised, placebo controlled trials, suggest that non-steroidal anti-inflammatory drugs may prove effective chemopreventive agents in different groups of people, from patients with familial adenomatous polyposis to those with sporadic adenomas.

both in patients with hereditary colon cancer syndromes, as well as those with sporadic colorectal cancer. Although not the focus of this review, other agents that have been considered in CRC chemoprevention include folate, calcium, hormone replacement therapy, vitamins, antioxidants, and fibre. Of these, folate has been studied most extensively and shows significant benefit. In a prospective cohort study, following up 25 474 patients, Giovannucci *et al* showed a relative risk reduction of 0.71 (95% confidence intervals, 0.56 to 0.89), with the greatest benefit in those taking folate supplementation.³

MECHANISMS OF NSAID INHIBITION IN COLON CARCINOGENESIS

NSAIDs are known potent inhibitors of cyclooxygenase (COX) enzymes, resulting in decreased prostaglandin synthesis, which, in turn, induces tumour cell apoptosis. Other studies have shown that NSAIDs also promote apoptosis through COX independent pathways. A combination of these effects is the probable source of the antineoplastic effect of NSAIDs, which continues to be an area of intense research.

The mechanism of inhibition of COX activity by aspirin and NSAIDs was first described by Vane in 1971.⁴ In the early 1990s, several groups reported the discovery of two COX isoforms.^{5–6} COX-1, the constitutively expressed form, seems to function as a physiological regulatory enzyme in most tissues. COX-2, however, is strongly inducible and plays an integral part in several physiological and pathological processes, including cell proliferation and inflammatory responses. COX-2 mRNA expression and protein were found to be increased in human colorectal adenomas and adenocarcinomas.^{7–8} Conversely, specific COX-2 inhibition, either by targeted knockout of the COX-2 gene or by pharmacological intervention, has been shown to effectively decrease the growth of murine intestinal adenomas.^{9–11} In a rat model of chemically induced colorectal cancer, the COX-2 selective inhibitor celecoxib suppressed the formation of aberrant crypt foci, precursors of adenomas.¹² Celecoxib also inhibited the incidence and multiplicity of colon tumours by 93% and 97%, respectively.¹³

As noted above COX-2 overexpression is important during colorectal carcinogenesis, however it is unclear exactly where in the multistep process COX-2 deregulation occurs (fig 1).^{14–15}

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; CRC, colorectal cancer; COX, cyclooxygenase; FAP, familial adenomatous polyposis; HNPCC, hereditary non-polyposis colorectal cancer

Last year 148 000 new cases of colorectal cancer (CRC) were diagnosed in the United States, and 57 000 people died from complications of their disease.¹ Overall, about one half of patients diagnosed with CRC ultimately die from the disease. This poor outcome is related to inadequate screening of the population, resulting in detection of the disease at an advanced stage when curative resection is no longer possible. Our understanding of the development of colon cancer has progressed rapidly over the past decades, and it is now well established that most colorectal cancer develops from neoplastic precursor lesions. The multistep progression of an adenomatous polyp to invasive cancer is now well explicated and offers opportunities for targeted chemoprevention. In a prospective necropsy study involving the colon, adenomas were found in 36.9% of male cases and 28.7% of female cases, with the prevalence and multiplicity of polyps increasing with advancing age.² The subgroup of people with adenomas offers an excellent opportunity for specific chemoprevention with various agents, such as non-steroidal anti-inflammatory drugs (NSAIDs), which are known to inhibit tumorigenesis based upon animal and epidemiological studies and, more recently, upon prospective trials. In this review, we will discuss the molecular basis for the chemopreventive effect of NSAIDs, as well as the numerous epidemiological and prospective studies that have assessed the effect of NSAIDs

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Because COX-2 overexpression occurs even in small adenomas, it is thought to represent an early event, promoting tumour proliferation and suppression of apoptosis. In vitro, many NSAIDs including sulindac, indomethacin, naproxen, piroxicam, aspirin, and COX-2 specific inhibitors are known to cause apoptosis in colon cancer cells. Thus, a growing body of experimental data supports the hypothesis that NSAIDs exert their chemopreventive effect by restoring to normal the frequency of apoptosis in colonic mucosa.¹⁵

CHEMOPREVENTION IN HEREDITARY COLON CANCER

Hereditary colorectal cancer, best defined in the familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) syndromes, has been estimated to account for 15% of all colon cancers occurring in the general population.¹⁶ Chemoprevention is of special interest in patients with germline mutations resulting in FAP or HNPCC as these patients are at risk for the development of tumours in multiple organs. Most of the studies to date have concentrated on the role on NSAIDs in FAP.

In brief, FAP results from mutations in the *APC* gene (chromosome 5q), and pedigree analysis shows an autosomal dominant pattern with nearly complete penetrance. Typically, patients with FAP develop diffuse colorectal polyposis by their adolescent years, and, if untreated, will be diagnosed with colorectal cancer by 40 years of age. Currently, the most effective management is initial intensive endoscopic surveillance starting at age 10–12. Once the number of polyps increases to a level that eliminates the possibility of safe endoscopic treatment, prophylactic total colectomy or subtotal colectomy followed by annual endoscopy of the remaining rectum is recommended. Patients with FAP are also at an increased risk for other malignancies, particularly small bowel, stomach, and extraintestinal neoplasia such as desmoid tumours, papillary thyroid carcinoma, sarcomas, hepatoblastoma, pancreatic carcinoma, and medulloblastoma. Although it is recommended that FAP patients be screened for duodenal adenomas with upper endoscopy,

Figure 1 Multistep progression of colon cancer and sites of NSAID action.

screening for other extracolonic tumours is not routinely performed.

Chemoprevention in FAP has been studied intensively both in animals and humans, using agents such as ascorbic acid, calcium, and, most promisingly, NSAIDs. FAP research has benefited from a mutant mouse model with multiple intestinal neoplasias (Min), which harbours mutations of the *APC* gene.^{17–19} Multiple studies using the Min mouse model have provided encouraging results with both non-selective and selective NSAIDs, reducing tumour burden, size, and multiplicity.²⁰ In humans, numerous uncontrolled and controlled studies have evaluated the effects of NSAIDs, particularly sulindac, and now the more selective COX-2 inhibitor celecoxib, on polyp size and number (table 1). The data are encouraging, and celecoxib was shown in one study to cause regression of polyps in patients with FAP.²¹ However, studies have additionally shown that withdrawal of treatment results in the recurrence of polyps, and patients receiving sulindac therapy have been reported to develop CRC.²⁰ Therefore, because of concerns regarding the length of treatment required, the development of CRC in patients receiving treatment, chemoprevention with NSAIDs has not replaced conventional endoscopic surveillance and colectomy recommendations in FAP patients.

Of particular interest in FAP are common extracolonic malignancies such as desmoid tumours and duodenal adenocarcinomas, which represent important targets for chemoprevention agents. Studies have shown that sulindac may be effective in the treatment of early duodenal adenomas in FAP.²² Celecoxib at a dose of 400 mg twice daily has been shown to decrease duodenal polyposis in patients with clinically significant disease at baseline (greater than 5% covered by polyps), a 31% reduction in involved areas compared with 8% taking placebo ($p = 0.049$).²³ No studies have shown the utility of NSAIDs in treating desmoid tumours.

Currently, no definitive recommendations have been formulated regarding the use of NSAIDs in patients with FAP. Based upon the studies mentioned above, some centres are increasingly using NSAIDs to delay the necessity for colectomy, and thereafter to decrease polyp formation in the retained rectum after subtotal colectomy. Celecoxib was approved recently by the US Food and Drug Administration for use in this setting. Additionally, the use of NSAIDs, particularly celecoxib, seems to be a useful adjunct in patients with duodenal polyposis.

Chemoprevention with NSAIDs in HNPCC has not been as vigorously evaluated either in animal models or in human trials. Interestingly, COX-2 is overexpressed less commonly in HNPCC than in sporadic CRC.²⁴ Conversely, aspirin and sulindac have been shown to reduce the microsatellite instability (MSI) phenotype of CRC cell lines caused by mutations in the *hMLH1*, *hMSH2*, and *hMSH6* genes.²⁴ Further studies are required, and an ongoing trial, concerted action polyp prevention (CAPP II), will shed further light on the role of NSAIDs in HNPCC.

CHEMOPREVENTION IN SPORADIC COLON CANCER

Studies showing the efficacy of NSAIDs in hereditary CRC have provided a basis for investigating the role of NSAIDs in primary and secondary prevention of sporadic CRC. Several large prospective cohort and randomised, placebo controlled trials have examined aspirin as a chemopreventive agent, both in preventing CRC and the development of polyps. Table 2 provides an overview of the trials.

Three major prospective cohort studies addressed the effect of primary prophylaxis with aspirin on CRC. In the cancer prevention study II, 662 424 people answered questionnaires regarding their aspirin use, with death from CRC the primary

Table 1 Randomised, placebo controlled trials of colorectal cancer chemoprevention in familial adenomatous polyposis

Study	Patients (n)	Agent	Dose	Outcome
Labayle <i>et al</i> ³	9	Sulindac	100 mg thrice daily	Decrease in polyp number compared with placebo (p<0.01)
Nugent <i>et al</i> ⁴	14	Sulindac	200 mg twice daily	Decrease in polyp number compared with placebo (p=0.01)
Giardiello <i>et al</i> ⁵	22	Celecoxib	100 mg twice daily	44% decrease in polyp number (p=0.014)
Steinbach <i>et al</i> ¹	77	Celecoxib Celecoxib	100 mg twice daily 400 mg twice daily	12% decrease in polyp number 28% decrease in polyp number (p=0.33 and p=0.003 respectively)

end point of the study.²⁵ More frequent use of aspirin, at least 16 times a month, was associated with a noticeable decrease in the relative risk, 0.60 for men and 0.58 for women (95% confidence intervals, 0.40 to 0.89 and 0.37 to 0.90, respectively). Similarly, two other cohort studies, the health professionals follow-up study and the nurses' health study, found a decrease in the relative risk for developing CRC with regular aspirin use.^{26, 27} Interestingly, in the second study, minimal risk reduction with aspirin use was detected during the initial nine years, but the relative risk declined to 0.56 after 20 years of use.²⁷ Although these studies found a protective benefit among aspirin users, the duration and frequency of dosing has yet to be established.

Only one randomised, placebo controlled trial has addressed the effect of aspirin on the development of CRC. The physicians' health study followed up 22 071 male physicians, primarily to assess the effect of aspirin on the risk of developing coronary artery disease.²⁸ Analysis of the data with respect to CRC showed no significant difference between the treatment and control groups. Notably, the treatment was 325 mg every other day, continuously for five years, and the patients were followed up for 12 years thereafter. It is possible that the treatment and follow up periods were of insufficient duration to show significant differences, as the development of CRC from the precursor lesion averages 10 or more years.

Perhaps a more viable end point in evaluating the efficacy of aspirin treatment would be the development of adenomatous polyps. Two recent, well designed trials have been published addressing this very issue. Sandler *et al* randomised 635 patients with previous CRC, definitively cured, to receive either 325 mg of aspirin daily or a placebo.²⁹ The study was

terminated after a median treatment period of 31 months, at which time one or more adenomas were found in 17% of patients taking aspirin and 27% of patients taking placebo (p = 0.004). Another study, published at the same time, randomised 1121 patients with history of recent adenomas to receive placebo, 81 mg of aspirin, or 325 mg of aspirin daily.³⁰ A follow up colonoscopy was performed about one year after randomisation in 1084 of the patients. The incidence of one or more adenomas was 47% in the placebo group, 38% in the 81 mg aspirin group, and 45% in the 325 mg aspirin group (global p = 0.04). More importantly, for the larger adenomas, measuring at least 1 cm or with tubulovillous or villous features, the relative risks were as follows: 0.59 (95% confidence intervals, 0.38 to 0.92) for the 81 mg treatment arm, and 0.83 (95% confidence intervals, 0.55 to 1.23) for the 325 mg treatment arm. The authors did not provide a clear explanation for the greater risk reduction with the lower aspirin dose. They speculated that the most probable reason for the difference was chance, as both the 81 mg and the 325 mg dose seem to suppress prostaglandin values to similar extents. There was no significant difference in the incidence of adverse events among the various patient groups, including gastrointestinal haemorrhage and haemorrhagic stroke, which might be attributable to the short duration of aspirin treatment.

Once again, these trials provide encouraging data regarding aspirin use, especially in secondary prophylaxis for patients with a history of adenomas or CRC. The duration and dose are, however, not well established (one trial curiously found the 81 mg dose to be more effective than the 325 mg dose³⁰), and the cumulative safety profile must be weighed against the benefit of the treatment. Furthermore, additional studies need

Table 2 Chemoprevention trials in non-hereditary colon cancer

Study	Design	Number	Agent	Outcome
Thun <i>et al</i> ²⁵ (cancer prevention study II)	Prospective cohort	662424	Aspirin	Relative risk reduction of death from colorectal cancer 0.60 for men and 0.58 for women
Giovannucci <i>et al</i> ⁶⁶ (health professionals study)	Prospective cohort	47900	Aspirin	Relative risk of colon cancer decreased to 0.35 with continuous, regular use
Giovannucci <i>et al</i> ⁶⁷ (nurses' health study)	Prospective cohort	89446	Aspirin	Relative risk of colon cancer decreased to 0.56 with 20 years of regular use
Gann <i>et al</i> ⁶⁸ , Sturmer <i>et al</i> ⁶⁹ (physicians' health study)	Randomised, placebo controlled, then prospective cohort	22071	Aspirin	No significant difference in colon cancer even after 12 years of follow up
Baron <i>et al</i> ⁷⁰ (polyp prevention study)	Randomised, placebo controlled	1121	Aspirin	Relative risk of large adenoma (at least 1 cm) decreased to 0.59 in patients receiving 81 mg aspirin daily
Sandler <i>et al</i> ²⁹ (colorectal adenoma prevention study)	Randomised, placebo	635	Aspirin	Relative risk of recurrent adenoma in patients with prior colorectal cancer was decreased to 0.65

to be done to assess if secondary prophylaxis can actually be helpful in reducing the frequency of surveillance colonoscopy. Cost effectiveness and safety of aspirin for primary prophylaxis are even less clear, because such an approach would require long term use, greater than 10 years, in a large segment of the population only at average risk for CRC. Chemoprevention would also require a comparison with successful screening strategies already in place.

DISCUSSION

In summary, several recent experimental, epidemiological, and controlled trials have investigated the usefulness of NSAIDs in CRC chemoprevention. The major cohort studies and placebo controlled trials in FAP and sporadic CRC prevention are summarised in tables 1 and 2. At this stage, no definitive recommendations have been established regarding the use of any NSAIDs or aspirin in primary or secondary prophylaxis, or as a substitute for screening or surveillance protocols.

The most promising arena for NSAID use is secondary prophylaxis in patients who have had CRC or adenomas in the past. These patients are at an increased risk for developing further lesions, and the benefit of prophylaxis may thus outweigh the risks of major gastrointestinal bleeding or haemorrhagic stroke associated with the use of these agents. Further studies need to investigate whether NSAID prophylaxis can reduce current endoscopic surveillance recommendations. In addition, long term studies evaluating the use of selective COX-2 inhibitors, which seem to carry a lower risk for the development of gastrointestinal haemorrhage,³¹ will be necessary before recommending their use for not only secondary, but also primary, CRC prophylaxis.

The use of NSAIDs or aspirin in primary prevention of CRC has not been validated. Chemoprophylaxis in average risk patients would require regular aspirin use for at least 10 to 20 years, and the cumulative risk of major adverse events may outweigh any reduction in CRC risk. Interestingly, although the benefit of aspirin in coronary artery disease has been established, the US Preventive Services Task Force does not recommend aspirin unless the five year risk for coronary

artery disease is at least three 3%.³² In fact, cost effectiveness analyses of aspirin for primary prophylaxis have shown an increase in cost per life saved when compared with any of the current screening recommendations.³²

In conclusion, to better appreciate the cost and side effects of aspirin in primary and secondary CRC chemoprophylaxis, it is useful to compare the number of people needed to be treated to achieve particular end points. For primary prevention of CRC or death from CRC, the numbers needed to treat are 471 962 and 1250, respectively. Because primary prophylaxis requires treatment for at least 10 years or more, toxicity related to aspirin becomes an additional concern. This point is further highlighted upon reviewing the numbers needed to treat for adverse effects: 100 for gastrointestinal haemorrhage, 300–800 for major gastrointestinal haemorrhage, and 800 for haemorrhagic stroke. In contrast, for secondary prevention of adenoma of any size or prevention of advanced neoplasm, the number of people needed to achieve significance are 10 and 19, respectively.³² These data seem to support the usefulness of aspirin for secondary CRC prophylaxis, but not necessarily primary prevention.

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Key points

- NSAIDs are potent inhibitors of cyclooxygenase (COX) enzymes. Studies have shown NSAIDs produce their antineoplastic effect through COX dependent and independent pathways.
- NSAIDs were first studied intensively in hereditary CRC, particularly FAP. Currently, certain centres use NSAIDs to delay the time to colectomy, as prophylaxis in patients with retained rectum after subtotal colectomy, and also as chemoprevention for duodenal polyposis. This approach does not presently affect recommendations for surveillance.
- In sporadic CRC, the most promising arena for NSAID use is secondary prophylaxis in patients who have had either CRC or adenomas in the past.
- Use of NSAIDs or aspirin in primary prevention of CRC has not been validated. Chemoprophylaxis in average risk patients would require regular medication use for at least 10–20 years, and the cumulative risk of major adverse events may outweigh any reduction in CRC risk.
- Chemoprophylaxis with NSAIDs/aspirin does not replace or change current recommendations for CRC screening or surveillance.

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FILLER.....

SMON, clioquinol, and copper

In addition to being an antimicrobial, clioquinol is a copper-zinc (Cu-Zn) chelator. Recent understanding of the metallobiology of Alzheimer's disease (AD) has led to renewed interest in clioquinol. Knowledge regarding metal-ion metabolism in the brain has suggested that A β precipitation and toxicity in AD is caused by abnormal interaction with metal ions like Cu and Zn.¹ Cu and Zn are found at high levels in neocortical regions prone to AD abnormality. Clioquinol has been shown to increase solubilisation of A β in the AD plaque from postmortem human brain tissue and to reduce brain A β deposition in a transgenic mouse model of AD.² These bench findings led to a pilot clinical trial of clioquinol in AD that showed the drug to be well tolerated.³ Plasma A β ₄₂ concentrations decreased in the clioquinol group, plasma Zn concentrations increased, and there was no effect on plasma Cu. The authors felt that metal protein attenuating compound drugs like clioquinol are not gross tissue chelators, but facilitate dissociation of Cu and Zn from the lowest affinity metal binding sites on A β . Alternatively, the clioquinol dose might have been too low to have an impact on serum Cu concentrations.

Subacute myelo-optico-neuropathy (SMON) is characterised by paraparesis, sensory deficits, and visual impairment. The pathological findings include symmetrical demyelination of the lateral and posterior columns of the spinal cord with optic nerve and peripheral nerve involvement. Extensive epidemiological studies in Japan confirmed that SMON was attributable to ingestion of the antibacterial clioquinol. There were nearly 10 000 cases of SMON in Japan by the end of 1970. This led to banning of clioquinol in 1970. Subsequently new cases of SMON disappeared.

Before clioquinol can be studied on a large scale basis as a treatment for AD, its relation to SMON must be resolved. The mechanism of clioquinol induced SMON was never definitively established. Hypotheses include mitochondrial toxicity of the clioquinol-Zn chelate and vitamin B12 deficiency. We propose a mechanism in which Cu is the mediator. Cu deficiency myelopathy bears striking similarities to the subacute combined degeneration seen in vitamin B12 deficiency⁴ and to SMON. Optic neuritis has been reported in association with Cu deficiency.⁵ Cu deficiency in ruminants is known to cause an ataxic myelopathy characterised by demyelination of the spinal cord white matter. We believe that a plausible mechanism of SMON is clioquinol induced Cu deficiency. The re-emergence of interest in clioquinol makes testing this hypothesis in available animal models an important issue.

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