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Review

Current Concepts in Colorectal Cancer Prevention with Cyclooxygenase Inhibitors

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Abstract. *Colorectal cancer is one of the commonest malignancies worldwide. Recently, there has been much speculation regarding the role of cyclooxygenase-2 (COX-2) suppression in chemoprevention. Drugs with the ability to inhibit COX-2 expression include aspirin, nonsteroidal anti-inflammatory drugs (NSAID) and selective COX-2 inhibitors. Any strategy for chemoprevention must be able to quantify how effective the potential treatment is likely to be and which drugs will be most useful. We would also need to know for how long the agent could be taken safely and if any side-effects could preclude long-term use. Evidence from observational studies and recent updates of randomised controlled trials have been very encouraging – at least indicating benefit from the long term use of aspirin, even at low dose, with greatest impact on prevention of proximal colon cancers and adenomas. Most studies do, however, also warn that risks of gastrointestinal bleeding increase with long-term use of aspirin and related drugs. The risk-to-benefit ratio of a chemoprevention regimen using these medications needs to be carefully examined.*

Colorectal cancer is one of the most common cancers in developing countries. Around 1 million new cases occur per year with nearly 600,000 deaths, globally (1).

It is well accepted that most colorectal cancers develop from adenomas *via* the adenoma-carcinoma sequence. Initially a small adenoma develops, becomes dysplastic and, eventually, accumulates enough genomic injury to become an invasive malignancy. This process may occur over a considerable number of years (2) and is probably linked, in part, to abnormal prostaglandin synthesis.

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COX-2-Driven Carcinogenesis

It is thought prostaglandins have a key role in the evolution of many types of epithelial cancer from precursor lesions (3-5).

Benign polyps and invasive colorectal cancers both contain increased levels of prostaglandins compared to normal tissues (6). Prostaglandin E2 is considered to be the major contributor to carcinogenesis compared to other prostaglandins – its levels are elevated in human tumors (7, 8) and increase in a size-dependent manner in the adenomas of patients with polyposis syndromes (9).

The key step in prostaglandin synthesis is catalyzed by the cyclooxygenase (COX) group of enzymes on cell membrane phospholipids - COX-1 and COX-2.

Although the isoenzymes are approximately 60% identical, COX-2 has a larger active site. This allows "substrate promiscuity" metabolisation of molecules structurally similar to prostaglandins (10, 11).

COX-1, is a "housekeeping gene" driving stable prostaglandin expression by most cells in almost all tissues (12). COX-2 in contrast, is most of the time only induced in response to growth factors, tumor promoters, hormones, bacterial endotoxins, cytokines and shear stress (13, 14) but is, however, also expressed constitutively in some tissues (15-19).

Expression of COX-2 drives unregulated expression of prostaglandins, which has key effects in promoting tumor cell division and spread (20), and can lead to the induction of angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF-1), platelet-derived growth factor (PDGF) and endothelin (21-23). Elevated expression of COX-2 also depletes arachidonic acid, which in itself might lead to reduced cellular apoptosis (24). Substrate promiscuity and co-oxidation can allow the formation of potent carcinogenic molecules (25).

COX-Inhibition as a Strategy for Cancer Prevention

Simple medications such as aspirin can effectively suppress COX activity (26).

The lag time for development of cancer from adenoma is appealing for a strategy of chemoprevention with long-term regular dosing.

Over the last fifteen years, a number of studies have examined the effect of aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors in the chemoprevention of colorectal cancer.

Two well-known major randomised controlled trials (RCTs) examined the role of low dose aspirin in colorectal cancer prevention but failed to find a significant reduction in incidence or mortality on short term follow-up. These trials were similar in design, using low dose aspirin on alternate days for 5 years (Physicians' Health Study; PHS) and 10 years (Women's Health Study; WHS, 27, 28).

Longer-term follow-up has recently been published for the WHS, which reported a reduction in cancer incidence appearing after 10 years of study in the aspirin group, primarily with proximal colon cancers (29).

In support of this, Rothwell and colleagues recently published a 20-year follow-up of 5 smaller RCTs and concluded that aspirin, taken at a dose of at least 75 mg daily, reduced colorectal cancer incidence and mortality, again with most benefit for proximal colon cancers (30).

The results of cohort and case-control studies support these findings; with statistically significant reductions in colorectal cancer mortality and incidence (31-36) with non-significant trends, however, in favour of aspirin use (37-39, Table I).

A reduction in cancer incidence and mortality suggests that these drugs interfere in the adenoma-carcinoma sequence in some way but the very nature of all of these studies makes it hard to exclude uncontrolled factors, which might be associated with aspirin use, for example, healthier lifestyle choices.

Key supportive evidence for a role in terminating adenoma progression or formation comes from RCTs looking specifically at adenoma prevention and some observational studies.These indicate that daily low dose aspirin (81-325 mg/d) confers significant risk reduction in adenoma incidence in patients with a previous history of these lesions (27, 40, 41) (Table II), while the observational studies generally confirm a reduction in the incidence of colorectal adenomas with regular aspirin use for over 5 years (35, 36, 42).

There are few well-designed controlled prospective studies looking at non-aspirin NSAIDs and COX-2 inhibitors, however, simple observational studies seem to conclude that there is a statistically significant protective effect of non-aspirin NSAIDs on colorectal cancer incidence with a risk reduction of around 30% (33-35) (Table III).

Recent good quality RCTs have examined the effects of COX-2 inhibitors in patients with a history of colorectal adenomas (43-45). As with the case for aspirin, long term seems to lead to a statistically significant reduction in incidence of all adenomas and advanced adenomas (Table II).

Other main findings are a trend to greater relative risk reduction in advanced adenomas with celecoxib, a reduced protective effect or perhaps even slightly higher risk over time with rofecoxib and no significant effect with sulindac (46).

Observational studies also suggest that regular use of any NSAID for more than 5 years significantly reduces colorectal adenoma incidence in patients with a previous history of these lesions, or in average-risk individuals (47-50).

Adverse Effects

It has been known for some time that long term use of aspirin and related drugs is associated with increased risks of gastrointestinal bleeding and haemorrhagic stroke. Recent data from systematic reviews has given good insight into the potential harms of long term aspirin administration (51-54). In general, although protective for the risk of acute myocardial infarction and ischaemic stroke, there is an elevated risk of haemorrhagic stroke, which appears to be dose-dependent increasing with higher doses of aspirin (Table IV)

Furthermore, there is a well-described risk of gastrointestinal bleeding across all studies. Although the actual risk of death from aspirin-induced bleeding is rare, these events are associated with hospital admission and surgery (55, 56). The WHS recent update also revealed a higher rate of self-reported gastrointestinal haemorrhage in the aspirin group. The five trials update by the Rothwell's group did not examine the overall risks of long term aspirin use in patients.

A number of good quality-systematic reviews have also reported on adverse effects with the use of COX-2 inhibitors and non-ASA NSAIDs (57-63). These studies appear to indicate an increase in overall cardiovascular events, highest in those already at high risk, and a significantly increased risk of myocardial infarction with the use of COX-2 inhibitors. The adenomatous polyp prevention on vioxx(APPROVe) study demonstrated an increased risk of cardiovascular events with rofecoxib. This effect is similar across the class of these agents and has led to the withdrawal of most of these agents from the market. These risks are also present for higher doses of non-ASA NSAIDs, except naproxen.

With non-ASA NSAIDs, there is an approximate risk of perforation and bleeding (*i.e.* complications from peptic ulcers) of around 2% per year rising to 10% per year in patients with a past history of peptic ulcers and other comorbidities.

Table I. *Observational studies with aspirin and colorectal cancer prevention.*

Study (reference)	Design	Participants	Aspirin	Duration	Relative risk
Cancer Prevention Study II (31)	Cohort	1,083, 531	Various	>15 years	0.58-0.61 (mortality)
Nurses' Health Study (35)	Cohort	89, 446	>2/week	10 years	0.62 (incidence)
Slattery *et al*. (34)	Case-control	3,051	>3/week	>5 years	0.7 (incidence)
Health Professionals'Follow-up Study (36)	Cohort	47, 900	>2/week	4 years	0.54 (incidence)

Table II. *Risk reduction - adenomas.*

Trial (reference)	Drug	Duration	Risk reduction
Baron *et al*. (40)	Aspirin 81 mg/d, OR 325 mg/ d	1 year	0.96
Benamouzig *et al*. (41)	Aspirin 160 mg/d, OR 300 mg/d	1 year	0.61
PreSAP (45)	Celecoxib, 400 mg/d	3 years	0.64
APC (44)	Celecoxib, 400 mg/d, OR 800 mg/d	3 years	0.67 (0.43 for higher dose celecoxib)
APPROVe (43)	Rofecoxib 25 mg/d	3 years	0.76

APPROVe, Adenomatous polyp prevention on vioxx; APC, antrochoanal polyp; PreSAP, prevention of sporadic adenomatous polyps.

Table III. *Risk reduction with non-ASA NSAIDs.*

Study (reference)	Medication	Duration	Design	Relative risk
Nurses' Health Study (35)	More than 2 tablets per week of non-ASA NSAID	20 years	Cohort	0.71
Kune *et al*. (33)	Aspirin or non-ASA NSAID, dose unspecified	At least 1 year	Case control	0.77
Slattery *et al*. (34)	Any NSAID	At least 1 year	Case control	0.80

ASA, Acetylsalicylic acid (aspirin); NSAIDs, nonsteroidal anti-inflammatory drugs.

Discussion

A number of studies over the last fifteen years have reported on the effectiveness of chemoprevention of colorectal cancer and adenomas with aspirin, non-ASA NSAIDs and COX-2 inhibitors. The initial disparity that was seen between the results from RCTs and observational studies was probably due to inadequate long term follow-up of relatively healthy individuals from these trials; the WHS comprised healthy females with a mean age of 54.6 years. A small proportion of patients had a family history of malignancy (18%) or were smokers (13%). The PHS had a follow-up period of only 5 years.

Recently published longer-term data from these and other RCTs not only support findings from case-control and cohort studies but also, interestingly, pave the way for the attractive idea of aspirin-led chemoprevention at low doses.

It was initially thought that termination of COX-2 formation by nucleated cells required large doses of aspirin and NSAIDs, for example, more than 1 g of aspirin daily (64). Observational epidemiological studies in the general population persistently suggested that sustained low-dose NSAID/aspirin administration was associated with a 30-50% reduction in polyp formation, cancer incidence and mortality.

Table IV. *Adverse events with aspirin.*

Aspirin	Stroke % (Ci)	Gastrointestinal Bleeding % (Ci)	Ulcer Bleeding/ Perforation (%)
<100 mg	0.3 (0.2-0.4)	1.1 (0.9-1.3)	n/a
100-325 mg	0.3 (0.2-0.3)	2.5 (2.2-2.6)	
>325 mg	1.1 (0.7-1.5)		
325 mg every 2 days	n/a	n/a	0.34
>2.5g/d			0.86

There has been some recent evidence that COX-1 activity in activated platelets may act as an induction signal for COX-2 expression (65). This may partly explain the chemopreventitive effect seen with aspirin and NSAIDs in observational studies at dose regimens not feasible to suppress COX-2 expression in nucleated cells and may, finally, have been unmasked in the longer-term follow-up

from various RCTs. Permanent inactivation of platelet COX-1 may inhibit COX-2 up-regulation in adjacent cell types in the intestinal mucosa at sites of mucosal injury. It is also possible that aspirin might have effects *via* COX-2 independent pathways, for example, phosphatidylinositol 3-kinase (PI3KCA)-related pathways (66). Recent work has suggested that tumours with mutant PI3KCA could be more responsive to chemoprevention with aspirin; intake in this group after colorectal cancer resection was associated with a significant improvement in survival (67).

The general consensus of opinion suggests that even low-dose aspirin, taken regularly, could prevent colon cancer.

Future studies should allow us to determine with clarity the precise risk:benefit ratio of this strategy.

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