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# Current Status of Nonsteroidal Anti-inflammatory Drugs in Colorectal Cancer Prevention

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## Introduction

To date, lifestyle modification and screening are the main tools of the CRC preventive strategy. *Chemoprevention*, i.e. the use of specific agents (natural or chemical) with suggested antineoplastic effect, has been also proposed for the same purpose. Belonging to this category, *NSAIDs* have been widely investigated within the last two decades, with promising although not (yet) definitive results.[1-3] These agents possibly act through the *inhibition of the COX-1 and COX-2* enzymes - both involved in the conversion of arachidonic acid into prostaglandins, metabolites affecting inflammation and multiple potentially tumorigenic cellular processes (proliferation, apoptosis, angiogenesis etc).[4,5] The chemopreventive effect is exerted through retardment, regression or prevention of the development of adenomas (i.e. CRC precursors) resulting in the reduction in both number and size of existing lesions along with protection against new adenoma formation[1-3,5-8], whereas antitumor effect has been also reported in established carcinomas.[3,7]

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**Chemopreventive Mechanism**

Both COX-2 (albeit not COX-1) overexpression and $P_GE_2$ increase have been observed in colorectal tumors (polyps and cancers).[4] Their carcinogenic role is probably mediated through several complex molecular pathways including -besides COX-2 induction- activation of oncogenes and cytokines and growth factor signaling, such as the Wnt (APC/b-catenin) and Ras pathways (both representing major tumorigenic steps).[2,3,5] Nevertheless, COX-2 upregulation and the subsequent $P_GE_2$ accumulation results in the activation of particular genes with specific tumorigenic activities, such as cyclin-D proliferative factor, Bcl-2 anti-apoptotic oncogene and VEGF.[3]

Thus, the COX-derived $P_GE_2$ promotes tumor growth by increasing cell proliferation, migration and invasiveness, blocking apoptosis, impairing humoral and cellular immunity and inducing angiogenesis.[3,4,5,7]

In this context the chemopreventive effect of NSAIDs is primarily attributed to their well known pharmacological activity to inhibit either COX-2 (selective inhibitors) or both COX-1 and COX-2 (conventional NSAIDs), resulting in suppression of prostaglandin synthesis. However, NSAID antineoplastic effect may be also exerted through COX independent mechanisms, including other specific drug targets such as NF-KB, caspases, PDEs, survinin, protein kinases etc.[5,7,8,10] Indirect effect on COX has been also reported specifically for aspirin (besides inhibitory action) through the anti-platelet activity of the drug.[7]

Therefore, NSAID chemopreventive mechanism is likely dual: some effects derived from the fundamental anti-inflammatory activity (through COX inhibition), while others appear to be unrelated to this property - suppressing neoplasia through different pathways.[10]

**Supportive Arguments**

Several arguments advocate for NSAID chemoprevention in CRC: **1)** the considerable burden of adenomas among Western populations (40-50% possibility of developing adenoma by the age of 70 [4,5]), combined with a 5-6% lifetime risk of CRC[2,3,5] **2)** the long duration of the progressive multi-step carcinogenic process (10-20 years) allowing intervention at early steps[1,5,8] **3)** the existing limitations (mostly economical) in wide screening implementation, leading to a frequently late clinical presentation of CRC necessitates the consideration of alternative preventive strategies[5,8] **4)** the existence of well-defined and detectable hereditary CRC forms consisting a high risk group warranting such intervention[1,2,7-9] **5)** the extensive regular use of NSAIDs for various conditions (chronic inflammation, pain, cardioprotection) providing sufficient clinical experience[1,2,5] **6)** the potentially coexisting additional NSAID preventive effect against other common cancers (e.g. breast, prostate, lung, esophageal, gastric).[2,4]

Epidemiological (cohort and case-control) studies and randomized-controlled trials reported a *CRC risk reduction with NSAID use* ranging between 20 and 40%, in both general population and particular risk groups (family history of CRC, personal history of polyps).[1-3,6-9] The effect appears to be stronger for advanced adenomas and cases with family history (including Lynch syndrome).[1,2,6-9] It may also vary by anatomical segment (colon vs. rectum, proximal vs. distal colon), although data supporting this association are rather contradictory.[6,7] Notably, for all categories, chemopreventive result appears to be depended on the administered specific drug, the dose, frequency and duration of treatment[1,2,6,7] and -possibly- COX-2 expression status[3,7] (~40-50% of adenomas and 80-85% of carcinomas overexpress COX-2[4,5]).

**Contrasting Arguments**

The main argument against routine NSAID use for CRC prevention is their *serious side-effects* (attributable to the diminution of physiologically important prostagladins[10]); *gastrointestinal* - especially bleeding and peptic ulcer (for all NSAIDs) - and *cardiovascular* (for selective COX-2 inhibitors - coxibes).[1,2,5] Notably, these toxicities are age and dose-depended, discouraging NSAID chemoprevention in older individuals as well as their long-term use in high doses.[1,2,7,8,10] Coadministration of NSAIDs with proton-pump inhibitors provides satisfactory protection against peptic ulcer - thus minimizing a relatively common adverse effect.[1,2,8] However, the possibility of *bleeding from other anatomic areas* (e.g. haemorrhagic stroke), specifically caused by aspirin use, remains unaffected - representing a severe, although rather rare (1-2 bleeds / 10.000 person-years) toxicity.[2,7] Regarding cardiovascular toxicity from selective COX-2 inhibitors, shorter treatment duration appears as a relatively safe (specifically for celecoxib administration in individuals with low cardiovascular risk) and potentially effective option[1,3,5] (although the antineoplastic effect may attenuate and vanish soon after interruption of this particular treatment[7,8], likely being rather cytostatic than cytotoxic[5]).

**Research Issues**

In this context, the current research challenge is the definition of: **1)** *optimal drug* (effective and safe) **2)** *appropriate dosage and duration* of NSAID administration **3)** *particular target groups* for this intervention. Regarding the first goal, there is no ideal drug so far, although aspirin (extensively and sufficiently investigated) emerges as the more attractive candidate for chemoprevention, combining "very probable antitumor effect"[2] (lasting long after drug withdrawal) with cardioprotection.[1-3,7] Moreover, the optimum dose, duration and administration schedule (daily or other) remain unclear[1,2,7] -probably depending on the specific target group(1) (see below)- although daily

aspirin dose <100 mg for 5-10 years is likely adequate for both CRC prevention and cardioprotection.[7] Finally, potential targets of chemoprevention (albeit with varying doses, increasing with the risk level)[1] include high risk group (hereditary cases with ~80-100% lifetime risk[1]), intermediate (moderate) risk individuals (with family history -other than hereditary disease- or history of polyps exhibiting ~10-20% lifetime CRC risk[1]) and -perhaps- the 50-60 years age group of the general population (a proposal combining the possible -at this age- initiation of CRC tumorigenesis with a relatively satisfactory treatment tolerance, concurrently appearing as economically viable[2,11]). However, the existing evidence is convincing only for the first category (for which the benefits overweigh the harms), possible for the intermediate risk group and insufficient for the last category (Table 1).[1-3,7,9]

Admittedly, further *treatment personalization* is necessary; for instance, among individuals with previous history of polyps only those with advanced adenomas are at high recurrence risk (~50%) - justifying chemoprevention (with probably higher dose and for longer period).[1] Also, cases of low cardiovascular risk (not demanding aspirin prevention) could be eligible for chemoprevention with other conventional (e.g. sulindac) or selective (celecoxib) NSAID.[1,3] In addition, confirmation of COX-2 expression status role, may orientate therapy preferentially to COX-2 (+) cases.[3,7] Furthermore, ongoing investigation of potential NSAID antineoplastic effect unrelated to COX pathway, may allow identification of particular individuals eligible for chemoprevention with NSAID derivatives (modified forms) targeting other tumorigenesis-related molecules (although currently available data for such intervention are only experimental, Table 1).[1,2,7,10] Also, elucidation of the conflicting states regarding segmental predilection of NSAID effect may generate chemopreventive strategies adjusted to the expected site-specific risk; individuals being at higher risk for proximal cancer (females, African Americans, cholecystectomized)[12] could be treated differently -with probably disparate drugs (aspirin/nonaspirin)[6] -than those with reported higher risk for distal or rectal cancer (males, middle-aged and likely smokers and drinkers).[3,12] Finally, potential interactions of NSAIDs with other CRC risk/protective factors (e.g. obesity, hormonal treatment) concurrently existing and possibly modifying their effect, should be also taken into account.[3,13]

An alternative option regarding NSAID chemoprevention is the "*combination treatment*", i.e. the coadministration of two NSAIDs (e.g. aspirin / celecoxib) or the use of single NSAID plus another agent (e.g. calcium, statins or DFMO). Such strategy results in potentially synergistic and multi-pathway actions with lower doses and fewer toxicities.[1,7,8] Similarly, the clinical development of NSAID derivatives, may offer another effective and less toxic option.[10]

**Table 1. Research issues and existing evidence for NSAID use in CRC prevention**

| Research issues | Comments | Evidence (for CRC prevention)* |
|---|---|---|
| *Optimal drugs* | *Effect / Complications* | |
| Aspirin | CRC prevention - cardioprotection / gastro-intestinal, haemorragic stroke | Very probable |
| Other non - selective NSAIDs (e.g. Sulindac) | CRC prevention / gastrointestinal | Possible (probable for Sulindac) |
| Selective COX-2 inhibitors (Celecoxib) | CRC prevention / gastrointestinal, cardio-vascular | Possible |
| NSAID derivatives | CRC prevention / lower complications rate | Unclear (only preclinical) |
| *Dosing schedule* | | |
| Dose | Daily aspirin ≤100mg is likely effective alt-hough higher doses may be needed | Unclear** |
| Duration | 5-10 years for aspirin, lower duration for Celecoxib | Probable<br>Possible |
| Frequency | Daily administration is likely required (for all agents), although other schedules (e.g. every other day) are under investigation | Unclear |
| *Target groups* | | |
| High risk | Hereditary cases | Convincing |
| Intermediate risk | Family history (one first-degree relative with CRC)<br>Personal history of CRC or polyps | Possible |
| Low risk | General population (eligible only the 50-60 years age group) | Insufficient |
| *Potential molecular targets* | | |
| COX-2 | COX-2 (+) cases exhibit better response to NSAID treatment in established carcinomas | Suggestive |
| *Other* | | |
| CGMP-PDEs | Only experimental data from laboratory (in vitro and animal) studies | Insufficient |
| Survinin | | |
| NF-kb | | |
| PPARδ, b-catenin, caspases 8 and 9 | | |

* Evidence characterization is based on the prevailing literature opinions.[2,3,7-10]

** Trials examining the preventive efficacy of 100mg daily aspirin dose in various populations are underway.[7,8]

**Abbreviations:** NSAID, nonsteroidal anti-inflammatory drug; CRC, colorectal cancer; COX-2, cyclooxygenase-2; CGMP-PDEs, cyclic guanosine monophosphate-phosphodiesterases; NF-kb, nuclear factor - kappa b; PPARδ, peroxisome proliferator activated receptor δ.

Recent data suggested a considerable survival benefit from *post-diagnosis NSAID administration in established carcinomas.*[3,7] Current research is underway to determine the appropriate therapeutic schedule and the specific patient categories (clinicopathological and molecular) expected to respond to this treatment, particularly among those receiving standard chemotherapy (e.g. the CALGB/SWOG80702 trial, examining celecoxib effect on survival in stage III CRC).[14]

## Conclusion

NSAID use potentially represents an alternative considerable preventive intervention in CRC. However, adverse effects limit administration of these drugs to specific populations of increased risk (mostly hereditary cases). In future, novel drugs (or combination of drugs) along with treatment personalization (a particularly complicated issue) may allow a larger and more safe use of these agents.

## Abbrevations

CRC - Colorectal cancer

NSAIDs - Nonsteroidal anti-inflammatory drugs

COX-1 - Cyclooxygenase-1

COX-2 - Cyclooxygenase-2

$P_GE_2$ - Prostagladine $E_2$

VEGF - Vascular endothelial growth factor

NF-KB - Nuclear factor Kappa-B

PDEs - phosphodiesterases

DFMO - Difluoromethyloornithine

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