Published in final edited form as:
Cancer Prev Res (Phila). 2011 November ; 4(11): 1728–1735. doi:10.1158/1940-6207.CAPR-11-0166.

Non-steroidal Anti-inflammatory Drugs and Coxibs In Chemoprevention: A Commentary Based Primarily on Animal Studies

Susan M. Fischer[1], **Ernest Hawk**[2], and **Ronald A. Lubet**[3]

[1]Department of Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Science Park, Smithville, TX

[2]Vice President, Cancer Prevention Research, University of Texas MD Anderson Cancer Center, Houston, TX

[3]Chemoprevention Agent Development Group, National Cancer Institute, Bethesda, MD

Abstract

This article endeavors to evaluate the data on the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) and Coxibs in preclinical studies on cancer prevention carried out by the authors. The overall objective was to address questions that we see as significant for the field. The preclinical studies evaluated here are restricted to our rodent studies on colon/intestinal, bladder and non-melanoma skin cancer in which NSAIDs or celecoxib were administered as either prevention agents or therapeutic agents. These studies may shed light on several questions. Should human use of NSAIDs/Coxibs consider not only efficacy but also whether celecoxib is unique compared to other NSAIDs? Are standard NSAIDs as effective as celecoxib in animal studies? Is the efficacy of celecoxib in particular or NSAIDs in general due to their off-target effects or to their effects on COX-1 and COX-2? What is the likely efficacy of low dose aspirin? Some questions raised by human trials and human epidemiology are discussed and related to our observations in animal models. We also considered the problem with cardiovascular (CV) events and whether animal models are predictive of efficacy in humans. Based on human epidemiological studies and its CV profile, it appears that aspirin is the most promising NSAID for the prevention of human colon, bladder and skin cancer, although the animal data for aspirin is less conclusive. We hope that this discussion of the results in animal studies may help inform and shape human trials of these commonly employed, relatively inexpensive and highly effective classes of compounds.

Keywords

chemoprevention; prostaglandins; COX-2; NSAIDs

Introduction

This commentary is based primarily upon preclinical studies performed by the authors that we feel sheds some light on questions regarding the use of nonsteroidal anti-inflammatory drugs (NSAIDs)/Coxibs in chemoprevention of cancer in humans. The commentary is not

Corresponding Author: Susan M. Fischer, Department of Molecular Carcinogenesis, University of Texas MD Anderson Cancer Center, Science Park, PO Box 389, Smithville, TX 78957. Phone: 512-237-9482; Fax: 512-237-9566; smfischer@mdanderson.org.

There are no potential conflicts of interest

all-inclusive and examines results only in models of colon/intestine, urinary bladder and squamous cell cancer of the skin. Nevertheless, the studies presented contribute to an understanding of certain generalized questions including: Is COX-2 the primary prevention target when employing (NSAIDs) and Coxibs? Is there something unique about celecoxib as contrasted with other NSAIDs? Are NSAIDS/Coxibs effective when taken later in tumor progression? Can one achieve a safe and effective NSAID/Coxib regimen for human use?

Prostaglandin Synthesis: Multiple Levels of Regulation

Prostaglandins (PGs) are one of the most abundant members of the eicosanoid family of arachidonic acid-derived autacoids. Arachidonic acid, a 20-carbon, 4-double bond fatty acid, is either obtained from the diet or, to a much lesser extent, synthesized from linoleic acid, an 18-carbon, 2-double bond dietary fatty acid. Arachidonic acid is normally stored esterified to the glycerol backbone of membrane phospholipids; in this form it cannot be metabolized to PGs. Following hydrolysis by phospholipase A_2, which is one of the rate limiting steps for PG synthesis, arachidonic acid is available as a substrate for enzymatic oxidation by several different enzyme systems, including cyclooxygenases, lipoxygenases, and cytochrome P450s. Prostaglandin synthesis is thus regulated at several levels including substrate abundance and availability, the level of expression of the cyclooxygenases (COX), of which there are two isoforms, COX-1 and COX-2, and the level of expression of the PG synthases. COX-1 is a constitutively expressed gene while COX-2, which is nearly undetectable in most epithelial tissues, is highly upregulated by a wide variety of physical irritants, growth factors, cytokines, etc. The biological activities, particularly those related to inflammation, of the three major PG products of COX-1 and COX-2, namely PGE_2, $PGF_{2\alpha}$, and PGD_2 were not understood until Vane et al, showed that aspirin inhibited PG synthesis as well as inflammation [1,2]. Other drugs, e.g., indomethacin, that inhibit PG synthesis were subsequently developed and are collectively referred to as NSAIDs. NSAIDs are a heterogeneous group of compounds that are often chemically unrelated, but have similar mechanisms of action and typically similar side effects (Figure 1).

Recognition of two isoforms of cyclooxygenase suggested different biological activities [2]. The PGs derived from COX-1 are responsible for homeostatic maintenance of the GI mucosa and for smooth muscle contraction. COX-2, on the other hand, is induced during inflammation, including arthritis, and is over-expressed in many epithelial tumors. These observations led pharmaceutical companies to develop selective COX-2 inhibitors, referred to as Coxibs, which reduced inflammation with a decreased propensity for GI complications. Based on the observed upregulation of COX-2 in many cancers, the chemopreventive activity of Coxibs was examined in animal models.

Colorectal Cancer (CRC)

The hypothesis that NSAIDs might prevent the occurrence or severity of CRC arose from studies showing that PGE_2 levels were higher in CRC than surrounding normal tissue [3–5]. Additionally, many epidemiologic studies showed that long-term use of aspirin and other NSAIDs was associated with a significant reduction in risk of CRC [3,6], including a very recent prospective study on >300,000 men and women that showed a significant reduction in risk of CRC with aspirin and non-aspirin NSAIDs [7]. The two models of gastrointestinal neoplasia most commonly used in identifying preventive activity are the rodent azoxymethane (AOM) carcinogen model and the genetically modified Min mouse model. The adenomatous polyps and carcinomas induced by AOM are similar to those observed in humans [8]. AOM induces minimally invasive colon cancer in rats and mice, which have mutations in the Wnt pathway, e.g., APC, beta-catenin. The Min mouse has a germline

mutation in the APC gene and primarily develops spontaneous small intestinal neoplasias [9].

The first uses of NSAIDs in models of colon cancer showed that indomethacin was highly effective when treatment was initiated prior to AOM treatment [10]. These initial studies led to a series of studies with enolic acids [e.g., piroxicam] and the propionic acid derivatives [e.g., ibuprofen] [11]. In most early studies, treatment was initiated when no carcinogen-initiated cells were present suggesting that indomethacin, piroxicam or other NSAIDs may either inhibit activation of AOM or inhibit the earliest stages of carcinogenesis. Many of these NSAIDs decreased colon tumor multiplicity by 65–80% in the AOM model [10,11], which showed that NSAIDs of varied structures (Figure 1) were effective in preventing colon cancer. We have recently undertaken studies with naproxen, a 2-arylpropionic acid derivative, which appears to be associated with minimal cardiovascular (CV) effects [12]. This agent is highly effective in preventing both aberrant crypt foci (ACFs) and colon tumors at various doses [13]. Subsequent to the studies showing NSAIDS were effective when initiated early, it was shown that piroxicam was also highly effective when initiated later in tumor progression when ACFs and even adenomas already existed [14,15].

The first study using dietary celecoxib found that a dose of 1500 ppm decreased CRC multiplicity by 95% in the AOM rat model, which appeared more effective than most NSAIDs [16]. A second study testing doses of 500, 1000 and 1500 ppm in the diet showed a dose-dependent decrease in colon cancer incidence (55, 62 and 77% reduction, respectively), and multiplicity (67, 73, and 84% reduction, respectively) [17]. Additionally, we found that administering celecoxib starting at 14 weeks after the second AOM treatment was still able to reduce incidence and multiplicity by ~60% [17], which confirmed prior findings with piroxicam. These studies (see Table 1) suggested that celecoxib could be an effective preventive agent for the secondary prevention of colon cancer in patients with familial adenomatous polyposis (FAP) or sporadic polyps. In the APC trial, celecoxib at doses of 400 mg bid significantly reduced the development of advanced adenomas by 55 to 65% [18], although this efficacy was achieved at doses that increased serious adverse CV events 2–3 fold. In the PreSAP trial, celecoxib administered at 400 mg once a day significantly reduced advanced adenomas by roughly 50%, without increasing CV events [19]. A subsequent pooled analysis of safety data arising from six placebo-controlled trials showed that celecoxib was associated with an increased risk of serious adverse CV events, but that these risks were strongly associated with baseline CV risk, suggesting there may be individuals who could be treated safely [20]. However, this hypothesis needs to be prospectively tested in order to be confirmed.

Even though aspirin is one of the most commonly consumed NSAIDs by humans, few prevention studies have been carried out in animal models of colon cancer. Our own studies in rats indicated that a relatively high dose of aspirin (1800 ppm) was required to achieve a significant decrease in colon tumors [21]. In contrast, efficacy was achieved at a dose of 600 ppm for prevention of ACFs. There have been some reports of efficacy with aspirin at lower doses (400 ppm), but typically those results show somewhat lower effectiveness and are still substantially above the dose equivalent of low dose aspirin in humans based on normal FDA scaling factors [22].

Intestinal Tumors in the Min Mouse

FAP is an autosomal dominantly inherited syndrome characterized by the development of multiple colorectal adenomas, some of which progress to malignancy. Groden et al, [23] were among the first to show that the disease is due to heritable mutations in the APC gene. APC mutations have also been shown to be common in sporadic colon cancers as well [24].

The Min mouse, which carries a mutation in the APC gene, mimics the rapid development of numerous polyps that affect individuals with FAP [9]. In an early study, piroxicam (200 ppm) significantly reduced tumor multiplicity in the Min model [25]. Furthermore, sulindac, which inhibits polyp development in FAP patients [26] significantly decreased average tumor load in Min mice, further validating this model [27]. When started early, celecoxib (1500 ppm) reduced tumor multiplicity and tumor load 70 and 83%, respectively, in the Min model, while starting treatment late, after most adenomas were established, still reduced tumor multiplicity and size by ~50% [28]. Based in part on these preclinical studies a double-blind, placebo-controlled clinical trial with celecoxib in FAP patients was performed. After 6 months, patients receiving 400 mg bid had a 28% reduction in the number of colorectal polyps while the 100 mg bid group showed a ~12% reduction. Although significant, and the basis for an FDA approval for celecoxib as an adjunct to usual standard of care in FAP patients, these results were not as dramatic as those from the animal studies. However, in the animal model the endpoint has routinely been preventing the development of new polyps, i.e., tumor multiplicity, whereas in the human FAP trial the primary endpoint was polyp regression although the endpoint included assessment of the overall polyp burden in an area, expressed as the sum of the diameter of the polyps, which includes both regression of existing polyps and prevention of new polyps in a defined area of the colon [29].

Several studies have been carried out in the Min model with aspirin [30]. A review of these studies showed that a small reduction was seen in tumors of the small intestine but no effect was observed on colonic polyps. In one early study, however, Min mice fed 250 or 500 ppm aspirin had a ~55% reduction in the number of intestinal tumors [31]. In human clinical trials, aspirin consistently reduced colonic adenoma recurrence by 15–25% [32]. However, this is markedly lower than that obtained in either celecoxib [40–45% reduction] [18] or the combined sulindac-difluoromethylornithine (DFMO) trials [70% reduction] [33]; it is recognized, however, that comparing the efficacy of different agents used in unrelated trials can be misleading.

Bladder Tumors

In both rats and mice N-butyl-N-(4-hydroxybutyl)-nitrosamine (OH-BBN) induces invasive urinary bladder cancers that are histologically similar to human transitional cell carcinomas. Early studies showed that ketoprofen and sulindac have strong preventive activity when administered beginning one week before 8–10 weeks of treatment with OH-BBN [34]. Studies with aspirin have been more problematic with a number of groups showing minimal efficacy at a ~300 ppm dose, but substantial activity at 3000 ppm [35]. On the other hand, celecoxib at doses of 200, 400, or 1500 ppm reduced palpable and microscopic tumors by 43, 57, and 77%, respectively [36]. We also found that celecoxib decreased bladder cancer in rats when treatment was initiated either following the last dose of OH-BBN or even 3 months later [35]. Recently, we have explored the use of naproxen, which has the least CV problems of any of the traditional NSAIDs, and nitric oxide (NO)-naproxen, based on the finding that adding a NO group to NSAIDs (see Figure 1) may help alleviate GI tract toxicity. At doses significantly below the standard human dose, naproxen and NO-naproxen reduced the development of large urinary tract tumors by ~80% [13], comparable to the effects of high dose celecoxib [36]. These agents were also highly effective in preventing the development of large palpable tumors when treatment was initiated after microscopic carcinomas of the bladder already existed [35].

A recently published pre-surgical study of celecoxib (400 mg bid) given for at least 14 days to 13 patients with invasive transitional cell carcinoma of the bladder demonstrated a lack of residual cancer at resection in 3 patients and induction of apoptosis in an additional 7

patients [37]. These short-term data suggest the efficacy of celecoxib/NSAIDs for bladder cancer intervention and justify further investigation.

Non-melanoma skin cancer (NMSC)

NMSC in mice can be elicited with either the classical two-stage initiation-promotion protocol or by repetitive exposure to ultraviolet (UV) light. Both models induce a marked inflammatory response. This observation triggered the earliest study on the ability of NSAIDs to prevent NMSC, i.e., topical indomethacin reduced skin tumor development by ~30% in the initiation/promotion model [38]. More recently, we found that mice fed 150 or 500 ppm celecoxib showed a dose-dependent reduction (60% and 89%, respectively) in tumor multiplicity in the UV carcinogenesis model. Indomethacin (4 ppm) reduced tumor multiplicity 78% [39], suggesting that celecoxib is not markedly more effective. Subsequently, we found that celecoxib was relatively effective in causing the regression of preexisting skin cancers in the UV model [40]. We also found that piroxicam and naproxen are highly effective in preventing UV induced skin cancer (unpublished data). We have also shown that the NSAIDs and celecoxib that are effective in preventing NMSC also inhibit PGE_2 production in UV- exposed epidermis ([39] and unpublished data). Thus, there is a strong correlation between short-term inhibition of PGE_2 and long-term efficacy in preventing NMSC.

To further examine whether the inhibition of COX-2 was responsible for the dramatic reduction in skin tumors seen in the UV studies, we took a genetic approach. While the loss of one allele of COX-1 had no effect on skin tumor development, the loss of only one allele of COX-2 significantly reduced tumor development in response to UV exposure [41]. In humans, topical diclofenac, a FDA approved NSAID with selectivity for COX-2 inhibition, is efficacious in treating actinic keratoses [42]. A recent clinical trial showed that celecoxib significantly reduced the development of NMSC in individuals with actinic keratoses [43]. Collectively, these studies strongly suggest that COX-2 is a critical target for preventing skin cancer in humans as well as mice.

Considerations and Conclusions

Finally, we will address certain controversies that have arisen in the field and offer our perspective and speculation based in large part, but not exclusively, on the *in vivo* preclinical studies in which we have been directly involved.

Is There Something Unique About Celecoxib?

One of the questions raised is whether celecoxib has some unique prevention efficacy as compared with most NSAIDs. The first study achieved a 95% reduction in colon cancer in the AOM model [16] in contrast to traditional NSAIDs, which reduced colon cancer by 70–80% [11,13]. However, in a subsequent study a similar dose achieved roughly an 85% effect similar to traditional NSAIDs [17] and the dose used, 1500 ppm, is in excess of the standard human dose (250 ppm), based on scaling factors. A lower dose of celecoxib is somewhat effective in colon, bladder and skin models, but no more effective than a wide variety of NSAIDs at their own human equivalent doses (Table 1). In humans, celecoxib at 400 mg bid [18] was more effective at polyp prevention than aspirin [32], but less effective than the combination of sulindac and DFMO [33]. However, data in FAP patients implies that celecoxib even at these supraoptimal doses is no more effective than even a relatively low dose of sulindac alone [26]. It is recognized, however, that the comparisons between celecoxib and NSAIDs needs to also take into consideration that there is variability in outcome between studies. Side-by-side comparisons of celecoxib and NSAIDs are needed to address this issue.

Is COX-2 the Primary Target of NSAIDS/Coxibs? Are There Substantial Off-Target Effects of NSAIDs/Coxibs?

Another issue that has been raised is whether the preventive effects of the NSAIDs or Coxibs are really due to inhibition of PG synthesis or are due, at least in part, to off-target effects. Celecoxib was observed to inhibit Akt activation and this COX-2-independent activity is associated with its apoptotic activity in some cell types [44]. The off-target effects of aspirin also appear to be cell type dependent. For example, aspirin induces apoptosis in cervical cancer cells through reduction of ErbB2 expression [45]. In the case of sulindac, it produces a major metabolite (sulindac sulfone) with substantially different properties and targets (it does not inhibit COX-2). However, there are significant caveats. These off-target effects are routinely seen in cell culture, e.g., celecoxib >25 uM, at concentrations far higher than are achieved clinically in serum (4–5 uM after 400 mg twice daily oral dosing) [46]. In the case of sulindac, although sulindac sulfone is not a COX-2 inhibitor, the other major metabolite, sulindac sulfide, is.

As shown in Figure 1 and Table 1, a wide variety of NSAIDS and celecoxib are highly effective at preventing colon, bladder and skin tumors. It is hard to imagine that such a structurally varied group of agents can have similar off-target effects, although it is possible that NSAID-specific off-target effects may contribute to the preventive action of any particular NSAID. Furthermore, the finding that knocking out the COX-2 gene can inhibit tumor formation in colon and skin would be compatible with prostaglandin production being the primary target. In addition, Chan et al [1] recently reported that aspirin reduced the risk of developing COX-2-expressing, but not other, colorectal cancers. Given these results, the COX-2 hypothesis would appear to be consistent with the widest variety of data. In addition, the data in the UV-induced skin model showing that local inhibition of COX-2-induced PGE_2 is predictive of preventive efficacy is similarly compatible with a COX-2 target. If indeed inhibition of prostaglandin production is the primary target, then a non-specific NSAID that would inhibit prostaglandin production by COX-1 and COX-2 should be effective because most tumors express COX-1 as well as COX-2.

What About Aspirin?

Aspirin, a salicylate, is the most commonly consumed NSAID. Multiple population-based case control studies and several randomized, controlled trials demonstrate a significantly reduced risk of CRC in regular aspirin users [47], although efficacy depends on the dose and duration of exposure. For example, alternate day use of low dose aspirin was reported to be ineffective in reducing the risk of CRC in the Women's Health Study [48] as well as in the Physicians' Health Study, although the study was terminated after 5 years [49]. A recent compilation of data, however, demonstrated that doses as low as 75 mg/day are effective in reducing colorectal cancer risk after extended dosing [50]. The long duration of aspirin use required to prevent CRC may reflect the time required for cancer to develop for precursor lesions. By contrast, animal data imply that high doses of aspirin are required for efficacy, which may be based on inter-species differences in metabolism. However, the finding that celecoxib was equally effective in inhibiting adenoma formation in individuals taking low doses of aspirin as in those not taking aspirin argues that low dose aspirin is unlikely to be highly effective [18]. These controversies make aspirin dosing decisions quite difficult and are further complicated since many potential participants in trials may already be taking low dose aspirin for prevention of CV events. This positive attribute of low dose aspirin was summarized in a recent meta-analysis of nine randomized trials that concluded that aspirin decreased the risk for CV events and nonfatal myocardial infarctions [51]. However, the effects of lower doses of aspirin required extended exposures often of 10 years or greater.

How Late in Tumor Progression Can You Wait?

One might imagine that NSAIDs and Coxibs, which were first proposed for use in a preventive setting, might be effective only in early cancer development. Thus, some of the epidemiologic data with colon cancer implied that striking efficacy was observed only after extended exposure of >10 years [52], which would be most compatible with efficacy early in tumor development. Furthermore, early animal studies support this view because most studies administered agents early in tumor development and continually. However, other studies showed that these agents were effective in later stages of colon cancer development when adenomas already existed [14,15]. Similarly, we found in skin and bladder that NSAIDs and Coxibs are effective even when tumors are present [35,39]. This greater efficacy at later stages is consistent with the finding in various adenoma studies that NSAIDs appear more effective in prevention of advanced adenomas as contrasted with earlier adenomas. Human data on celecoxib effects on early stage ACFs are equivocal [53] and sulindac was found to be ineffective in reducing the number of ACFs in patients with multiple/advanced colorectal adenomas [54]. Additionally, recent data in skin shows that while celecoxib was ineffective in blocking the formation of early stage actinic keratosis, it reduced the formation of NMSC by 50% [43], arguing that NSAIDs/Coxibs work further along in tumor progression. Finally, recent epidemiologic studies find that NSAIDs are effective even in patients being treated with standard therapies for advanced colon and breast cancers [1,55]. In another study, regular aspirin use after diagnosis of CRC reduced the risk of both CRC specific and overall mortality [56].

Can Animal Models Predict the Efficacy of NSAIDs in Human Trials?

In the present commentary, we have discussed colon/intestine, NMSC and bladder cancer for the effects of NSAIDs/Coxibs. Multiple clinical efficacy trials employing NSAIDs/Coxibs for blocking the development of colon adenomas have shown that these agents are effective; with aspirin showing more limited activity than celecoxib [18,19,47]. However, the relative contribution of each agent is not known and there are caveats when comparing trials using different agents. Recently, a clinical trial of oral celecoxib showed that this agent could inhibit the formation of squamous and basal cell skin cancers by roughly 60% [43]. Furthermore, there is clinical data showing that topical application of diclofinac is partially effective in preventing actinic keratoses and may be more effective in blocking SCCs of the skin [42]. Thus, the clinical results appear to be in line with the high efficacy observed in animals.

Can We Identify a (Relatively) Non-Toxic NSAID?

Given the striking animal data, significant epidemiologic data in colon and esophagus, and clinical trials particularly in colon (but more recently in skin cancer), the identification of an NSAID/Coxib that can be used safely in a prevention setting is a high priority. The initial concerns with regards to the NSAIDs were ulcers and potentially life-threatening bleeding. Although the incidence of these events is probably <1/10,000 for most NSAID users, these are serious concerns for individuals who might consider NSAIDs for colorectal cancer prevention, given the rarity of the disease in the general population as well as competing preventive strategies, such as endoscopic polypectomy. It appears that the COX-2 inhibitors are associated with significantly less upper GI toxicity [57]. Thus, there was no significant increase in GI toxicity in the celecoxib trial [18,19]. However, rofecoxib and valdecoxib (at standard doses) appear to increase CV events. While celecoxib at the standard dose does not significantly increase CV events, the higher doses used in adenoma prevention trials did. This led to an examination of most NSAIDs, and agents like diclofenac clearly increase CV events and has led to a black-box warning. One NSAID that has consistently proven to have minimal CV effects, and potentially even to be cardioprotective, has been naproxen [12], although the data from the Alzheimer's Disease Anti-inflammatory Prevention Trial

(ADAPT) is suggestive of increased cardiovascular risk [58]. In addition, low dose aspirin, as mentioned above, is both cardioprotective and chemopreventive when taken over an extended duration [18,19]. This raises the question of whether it is “better” to take 1) low dose celecoxib, which probably has low gastric toxicity and limited CV effects but for which the prevention data are not as clear, or 2) aspirin over an extended time period, which has a cardioprotective effect and for which there is the strongest epidemiologic evidence of prevention; however, questions arise regarding an effective dose, or 3) naproxen, which appears to have a good CV profile along with the potential use of a proton pump inhibitor to decrease GI events. At the moment, aspirin would appear to be the choice with the most epidemiologic evidence behind it. As with all prevention studies the real question is the risk to benefit ratio and whether one can define a “high risk” group who has more to gain than lose through interventions of this nature.

REFERENCES

1. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med. 2007; 356:2131–2142. [PubMed: 17522398]
2. Vane JR, Bakhle YS, Botting RM. Cyclooxygenases 1 and 2. Annu Rev Pharmacol Toxicol. 1998; 38:97–120. [PubMed: 9597150]
3. Arber N, Levin B. Chemoprevention of colorectal neoplasia: the potential for personalized medicine. Gastroenterology. 2008; 134:1224–1237. [PubMed: 18395100]
4. Bennett A, Del Tacca M. Proceedings: Prostaglandins in human colonic carcinoma. Gut. 1975; 16:409. [PubMed: 1140693]
5. Jaffe BM. Prostaglandins and cancer: an update. Prostaglandins. 1974; 6:453–461. [PubMed: 4366016]
6. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst. 2002; 94:252–266. [PubMed: 11854387]
7. Ruder EH, Laiyemo AO, Graubard BI, Hollenbeck AR, Schatzkin A, Cross AJ. Non-Steroidal Anti-Inflammatory Drugs and Colorectal Cancer Risk in a Large, Prospective Cohort. Am J Gastroenterol. 2011
8. Ward JM, Yamamoto RS, Brown CA. Pathology of intestinal neoplasms and other lesions in rats exposed to azoxymethane. J Natl Cancer Inst. 1973; 51:1029–1039. [PubMed: 4355212]
9. Su LK, Kinzler KW, Vogelstein B, Preisinger AC, Moser AR, Luongo C, Gould KA, Dove WF. Multiple intestinal neoplasia caused by a mutation in the murine homolog of the APC gene. Science. 1992; 256:668–670. [PubMed: 1350108]
10. Narisawa T, Sato M, Tani M, Kudo T, Takahashi T, Goto A. Inhibition of development of methylnitrosourea-induced rat colon tumors by indomethacin treatment. Cancer Res. 1981; 41:1954–1957. [PubMed: 7214363]
11. Reddy BS, Tokumo K, Kulkarni N, Aligia C, Kelloff G. Inhibition of colon carcinogenesis by prostaglandin synthesis inhibitors and related compounds. Carcinogenesis. 1992; 13:1019–1023. [PubMed: 1600605]
12. Fosbol EL, Folke F, Jacobsen S, Rasmussen JN, Sorensen R, Schramm TK, Andersen SS, Rasmussen S, Poulsen HE, Kober L, Torp-Pedersen C, Gislason GH. Cause-specific cardiovascular risk associated with nonsteroidal antiinflammatory drugs among healthy individuals. Circ Cardiovasc Qual Outcomes. 2010; 3:395–405. [PubMed: 20530789]
13. Steele VE, Rao CV, Zhang Y, Patlolla J, Boring D, Kopelovich L, Juliana MM, Grubbs CJ, Lubet RA. Chemopreventive efficacy of naproxen and nitric oxide-naproxen in rodent models of colon, urinary bladder, and mammary cancers. Cancer Prev Res (Phila Pa). 2009; 2:951–956.
14. Li H, Kramer PM, Lubet RA, Steele VE, Kelloff GJ, Pereira MA. Termination of piroxicam treatment and the occurrence of azoxymethane-induced colon cancer in rats. Cancer Lett. 1999; 147:187–193. [PubMed: 10660105]

15. Reddy BS, Maruyama H, Kelloff G. Dose-related inhibition of colon carcinogenesis by dietary piroxicam, a nonsteroidal antiinflammatory drug, during different stages of rat colon tumor development. Cancer Res. 1987; 47:5340–5346. [PubMed: 3652039]
16. Kawamori T, Rao CV, Seibert K, Reddy BS. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, against colon carcinogenesis. Cancer Res. 1998; 58:409–412. [PubMed: 9458081]
17. Reddy BS, Hirose Y, Lubet R, Steele V, Kelloff G, Paulson S, Seibert K, Rao CV. Chemoprevention of colon cancer by specific cyclooxygenase-2 inhibitor, celecoxib, administered during different stages of carcinogenesis. Cancer Res. 2000; 60:293–297. [PubMed: 10667579]
18. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET. Investigators, A.P.C.S. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med. 2006; 355:873–884. [PubMed: 16943400]
19. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, Zavoral M, Lechuga MJ, Gerletti P, Tang J, Rosenstein RB, Macdonald K, Bhadra P, Fowler R, Wittes J, Zauber AG, Solomon SD, Levin B. Pre, S.A.P.T.I. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med. 2006; 355:885–895. [PubMed: 16943401]
20. Solomon SD, Pfeffer MA, McMurray JJ, Fowler R, Finn P, Levin B, Eagle C, Hawk E, Lechuga M, Zauber AG, Bertagnolli MM, Arber N, Wittes J. Apc and Pre, S.A.P.T.I. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation. 2006; 114:1028–1035. [PubMed: 16943394]
21. Li H, Schut HA, Conran P, Kramer PM, Lubet RA, Steele VE, Hawk EE, Kelloff GJ, Pereira MA. Prevention by aspirin and its combination with alpha-difluoromethylornithine of azoxymethane-induced tumors, aberrant crypt foci and prostaglandin E2 levels in rat colon. Carcinogenesis. 1999; 20:425–430. [PubMed: 10190557]
22. Reddy BS, Wang CX, Kong AN, Khor TO, Zheng X, Steele VE, Kopelovich L, Rao CV. Prevention of azoxymethane-induced colon cancer by combination of low doses of atorvastatin, aspirin, and celecoxib in F 344 rats. Cancer Res. 2006; 66:4542–4546. [PubMed: 16618783]
23. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, Albertsen H, Joslyn G, Stevens J, Spirio L, Robertson M, et al. Identification and characterization of the familial adenomatous polyposis coli gene. Cell. 1991; 66:589–600. [PubMed: 1651174]
24. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell. 1996; 87:159–170. [PubMed: 8861899]
25. Jacoby RF, Marshall DJ, Newton MA, Novakovic K, Tutsch K, Cole CE, Lubet RA, Kelloff GJ, Verma A, Moser AR, Dove WF. Chemoprevention of spontaneous intestinal adenomas in the Apc Min mouse model by the nonsteroidal anti-inflammatory drug piroxicam. Cancer Res. 1996; 56:710–714. [PubMed: 8631000]
26. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, Booker SV, Robinson CR, Offerhaus GJ. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993; 328:1313–1316. [PubMed: 8385741]
27. Beazer-Barclay Y, Levy DB, Moser AR, Dove WF, Hamilton SR, Vogelstein B, Kinzler KW. Sulindac suppresses tumorigenesis in the Min mouse. Carcinogenesis. 1996; 17:1757–1760. [PubMed: 8761438]
28. Jacoby RF, Seibert K, Cole CE, Kelloff G, Lubet RA. The cyclooxygenase-2 inhibitor celecoxib is a potent preventive and therapeutic agent in the min mouse model of adenomatous polyposis. Cancer Res. 2000; 60:5040–5044. [PubMed: 11016626]
29. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000; 342:1946–1952. [PubMed: 10874062]
30. Corpet DE, Pierre F. How good are rodent models of carcinogenesis in predicting efficacy in humans? A systematic review and meta-analysis of colon chemoprevention in rats, mice and men. Eur J Cancer. 2005; 41:1911–1922. [PubMed: 16084718]

31. Barnes CJ, Lee M. Chemoprevention of spontaneous intestinal adenomas in the adenomatous polyposis coli Min mouse model with aspirin. Gastroenterology. 1998; 114:873–877. [PubMed: 9558273]
32. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med. 2003; 348:891–899. [PubMed: 12621133]
33. Meyskens FL Jr, McLaren CE, Pelot D, Fujikawa-Brooks S, Carpenter PM, Hawk E, Kelloff G, Lawson MJ, Kidao J, McCracken J, Albers CG, Ahnen DJ, Turgeon DK, Goldschmid S, Lance P, Hagedorn CH, Gillen DL, Gerner EW. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res (Phila). 2008; 1:32–38. [PubMed: 18841250]
34. Rao KV, Detrisac CJ, Steele VE, Hawk ET, Kelloff GJ, McCormick DL. Differential activity of aspirin, ketoprofen and sulindac as cancer chemopreventive agents in the mouse urinary bladder. Carcinogenesis. 1996; 17:1435–1438. [PubMed: 8706245]
35. Lubet RA, Steele VE, Juliana MM, Grubbs CJ. Screening agents for preventive efficacy in a bladder cancer model: study design, end points, and gefitinib and naproxen efficacy. J Urol. 2010; 183:1598–1603. [PubMed: 20172542]
36. Grubbs CJ, Lubet RA, Koki AT, Leahy KM, Masferrer JL, Steele VE, Kelloff GJ, Hill DL, Seibert K. Celecoxib inhibits N-butyl-N-(4-hydroxybutyl)-nitrosamine-induced urinary bladder cancers in male B6D2F1 mice and female Fischer-344 rats. Cancer Res. 2000; 60:5599–5602. [PubMed: 11059745]
37. Dhawan D, Craig BA, Cheng L, Snyder PW, Mohammed SI, Stewart JC, Zheng R, Loman RA, Foster RS, Knapp DW. Effects of short-term celecoxib treatment in patients with invasive transitional cell carcinoma of the urinary bladder. Mol Cancer Ther. 2010; 9:1371–1377. [PubMed: 20423998]
38. Slaga, TJ.; Fischer, SM.; Viaje, A.; Berry, DL.; Bracken, WM.; LeClerc, S.; Miller, DR. Inhibition of tumor promotion by anti-inflammatory agents. In: Slaga, TJ.; Sirak, A.; Boutwell, RK., editors. Mechanisms of Tumor Promotion and Carcinogenesis. Vol. vol. 2. New York: Raven Press; 1978. p. 173-195.
39. Fischer SM, Lo HH, Gordon GB, Seibert K, Kelloff G, Lubet RA, Conti CJ. Chemopreventive activity of celecoxib, a specific cyclooxygenase-2 inhibitor, and indomethacin against ultraviolet light-induced skin carcinogenesis. Mol Carcinog. 1999; 25:231–240. [PubMed: 10449029]
40. Fischer SM, Conti CJ, Viner J, Aldaz CM, Lubet RA. Celecoxib and difluoromethylornithine in combination have strong therapeutic activity against UV-induced skin tumors in mice. Carcinogenesis. 2003; 24:945–952. [PubMed: 12771040]
41. Rundhaug JE, Mikulec C, Pavone A, Fischer SM. A role for cyclooxygenase-2 in ultraviolet light-induced skin carcinogenesis. Mol Carcinog. 2007; 46:692–698. [PubMed: 17443745]
42. Ulrich C, Johannsen A, Rowert-Huber J, Ulrich M, Sterry W, Stockfleth E. Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratoses. Eur J Dermatol. 2010; 20:482–488. [PubMed: 20507841]
43. Elmets CA, Viner JL, Pentland AP, Cantrell W, Lin HY, Bailey H, Kang S, Linden KG, Heffernan M, Duvic M, Richmond E, Elewski BE, Umar A, Bell W, Gordon GB. Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. J Natl Cancer Inst. 2010; 102:1835–1844. [PubMed: 21115882]
44. Lin HP, Kulp SK, Tseng PH, Yang YT, Yang CC, Chen CS. Growth inhibitory effects of celecoxib in human umbilical vein endothelial cells are mediated through G1 arrest via multiple signaling mechanisms. Mol Cancer Ther. 2004; 3:1671–1680. [PubMed: 15634661]
45. Xiang S, Sun Z, He Q, Yan F, Wang Y, Zhang J. Aspirin inhibits ErbB2 to induce apoptosis in cervical cancer cells. Med Oncol. 2010; 27:379–387. [PubMed: 19424877]
46. Grossman SA, Olson J, Batchelor T, Peereboom D, Lesser G, Desideri S, Ye X, Hammour T, Supko JG. New Approaches to Brain Tumor Therapy, C.N.S.C. Effect of phenytoin on celecoxib

pharmacokinetics in patients with glioblastoma. Neuro Oncol. 2008; 10:190–198. [PubMed: 18287342]

47. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, Chaussade S, Baron JA. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst. 2009; 101:256–266. [PubMed: 19211452]
48. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005; 294:47–55. [PubMed: 15998890]
49. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. J Natl Cancer Inst. 1993; 85:1220–1224. [PubMed: 8331682]
50. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010; 376:1741–1750. [PubMed: 20970847]
51. Bartolucci AA, Tendera M, Howard G. Meta-Analysis of Multiple Primary Prevention Trials of Cardiovascular Events Using Aspirin. Am J Cardiol. 2011
52. Flossmann E, Rothwell PM, Aspirin Trial BD, Aspirin Trial UK-TIA. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet. 2007; vol. 369:1603–1613. [PubMed: 17499602]
53. Cho NL, Redston M, Zauber AG, Carothers AM, Hornick J, Wilton A, Sontag S, Nishioka N, Giardiello FM, Saltzman JR, Gostout C, Eagle CJ, Hawk ET, Bertagnolli MM. Aberrant crypt foci in the adenoma prevention with celecoxib trial. Cancer Prev Res (Phila). 2008; 1:21–31. [PubMed: 19138933]
54. Limburg PJ, Mahoney MR, Ziegler KL, Sontag SJ, Schoen RE, Benya R, Lawson MJ, Weinberg DS, Stoffel E, Chiorean M, Heigh R, Levine J, Della'Zanna G, Rodriguez L, Richmond E, Gostout C, Mandrekar SJ, Smyrk TC. Cancer Prevention, N. Randomized phase II trial of sulindac, atorvastatin, and prebiotic dietary fiber for colorectal cancer chemoprevention. Cancer Prev Res (Phila). 2011; 4:259–269. [PubMed: 21209397]
55. Holmes MD, Chen WY, Li L, Hertzmark E, Spiegelman D, Hankinson SE. Aspirin intake and survival after breast cancer. J Clin Oncol. 2010; 28:1467–1472. [PubMed: 20159825]
56. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009; 302:649–658. [PubMed: 19671906]
57. Rostom A, Muir K, Dube C, Jolicoeur E, Boucher M, Joyce J, Tugwell P, Wells GW. Gastrointestinal safety of cyclooxygenase-2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol. 2007; 5:818–828. [PubMed: 17556027]
58. ADAPT. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). PLoS Clin Trials. 2006; 1:e33. [PubMed: 17111043]

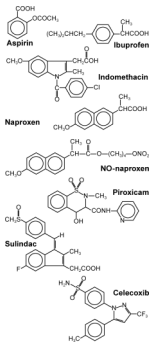

Figure 1.
Chemical structure of common non-steroidal anti-inflammatory drugs and the selective COX-2 inhibitor celecoxib.

Cancer Prev Res (Phila). Author manuscript; available in PMC 2012 November 1.

Table 1

Effects of NSAIDs or Celecoxib In Animal Models

Model	Species	NSAID (ppm)	Relative Efficacy (%↓)	HED	Ref.
AOM Colon	rats	Naproxen (400 ppm)	++ (60%)	320 mg	13
AOM Colon	rats	Aspirin (200 ppm)	+ (20%)	160 mg	21
AOM Colon	rats	Aspirin (1800 ppm)	++ (60%)	1440 mg	21
AOM Colon	rats	Celecoxib (1500 ppm)	++++ (96%)	1200 mg	16
AOM Colon	rats	Celecoxib (1500 ppm)	+++ (84%)	1200 mg	17
AOM Colon	rats	Celecoxib (500 ppm)	++ (67%)	400 mg	17
Min Intestine	mice	Aspirin (250 ppm)	++ (55%)	265 mg	31
Min Intestine	mice	Celecoxib (1500 ppm)	+++ (70%)	1590 mg	28
UV Skin	mice	Celecoxib (500 ppm)	+++ (70%)	533 mg	39
UV Skin	mice	Celecoxib (150 ppm)	++ (60%)	160 mg	39
UV Skin	mice	Indomethacin (4 ppm)	+++ (70%)	4.3 mg	39
UV Skin	mice	Naproxen (400 ppm)	+++ (70)	427 mg	Unpublished data
OHBBN Bladder	rats	Celecoxib (1000 ppm)	++++ (90%)	800 mg	36
OHBBN Bladder	mice	Celecoxib (1250 ppm)	++++ (90%)	1333 mg	36
OHBBN Bladder	rats	Naproxen (400 ppm)	++++ (87%)	320 mg	35
OHBBN Bladder	rats	Aspirin (300 ppm)	0	240 mg	35
OHBBN Bladder	rats	Aspirin (3000 ppm)	++ (65%)	2400 mg	35

* HED, human equivalent dose

The calculations below are standard scaling factors that would be used for the FDA. They do not take into account specific pharmacokinetics of individual agents which can only properly be performed after gavage dosing.

HED's were calculated as follows, using 100 ppm (100 μg/g diet) as an example. Rats, which eat 15 g food daily, would consume 1.5 mg drug; for a 250 g rat, the daily weight-based dose would be 6 mg drug/Kg body weight. Dividing by the rat-to-human scaling factor of 6, the HED is 1 mg/Kg body weight; for an 80 Kg human this is 80 mg. Mice, which eat 4 g food daily, would consume 0.4 mg drug; for a 25 g mouse, the daily weight-based dose would be 16 mg drug/Kg body weight. Dividing by the mouse-to-human scaling factor of 12, the HED is 1.33 mg/Kg body weight; for an 80 Kg human this is 106 mg.