Curr Pharmacol Rep (2015) 1:295–301
DOI 10.1007/s40495-015-0042-x

CANCER CHEMOPREVENTION (R AGARWAL, SECTION EDITOR)

NSAIDs and Colorectal Cancer Control: Promise and Challenges

George J. Tsioulias[1] · **Mae F. Go**[2] · **Basil Rigas**[3]

Published online: 14 May 2015

Abstract The chemoprevention of colorectal cancer (CRC) is a realistic option given the low acceptance and cost of screening colonoscopy. Nonsteroidal anti-inflammatory drugs (NSAIDs), currently not recommended for CRC prevention, are the most promising agents. Here, we review relevant work and assess the chemopreventive potential of NSAIDs. The chemopreventive efficacy of NSAIDs is established by epidemiological and interventional studies as well as analyses of cardiovascular prevention randomized clinical trials. The modest chemopreventive efficacy of NSAIDs is compounded by their significant toxicity that can be cumulative. Efforts to overcome these limitations include the use of drug combinations; the emphasis on the early stages of colon carcinogenesis such as aberrant crypt foci, which may require shorter periods of drug administration; and the development of several families of chemically modified NSAIDs such as derivatives of sulindac, nitro-NSAIDs, and phospho-NSAIDs, with some of them appearing to have higher safety and efficacy than conventional NSAIDs and thus to be better candidate agents. The successful development of NSAIDs as chemopreventive agents will likely require a combination of the following: identification of subjects at high risk and/or those most likely to benefit from chemoprevention; optimization of the timing, dose, and duration of administration of the chemopreventive agent; novel NSAID derivatives and/or combinations of agents; and agents that may prevent other diseases in addition to CRC. Ultimately, the clinical implementation of NSAIDs for the prevention of CRC will depend on a strategy that drastically shifts the currently unacceptable risk/benefit ratio in favor of chemoprevention.

Keywords Chemoprevention · Colon cancer · NSAIDs · Aspirin · Sulindac · Phospho-sulindac

This article is part of the Topical Collection on *Cancer Chemoprevention*

✉ Basil Rigas
basil.rigas@stonybrookmedicine.edu

George J. Tsioulias
george.tsioulias@va.gov

Mae F. Go
mae.go@va.gov

[1] Department of Surgery, Rutgers Medical School of New Jersey, Medical Sciences Building G530, 185 South Orange Avenue, Newark, NJ 07103, USA

[2] Gastroenterology Section, VA Southern Nevada Healthcare System, 6900 N. Pecos Rd, North Las Vegas, NV 89086, USA

[3] Department of Medicine, Stony Brook University, HSC, L4, Room 169, Stony Brook, NY 11794-8430, USA

Introduction

Colorectal cancer (CRC) represents a major medical challenge. Despite significant progress, the mortality of advanced CRC has remained unchanged for decades [1]. Although screening colonoscopy can prevent CRC, it is not widely employed because of poor patient acceptance and cost [2]. Virtual colonoscopy has its own limitations, and its application to CRC screening is even more limited [3]. These considerations provide renewed impetus for the development of CRC chemoprevention. Nonsteroidal anti-inflammatory drugs (NSAIDs) are currently the most promising class of compounds for the prevention of CRC. Here, we review salient points of their efficacy and safety and assess their prospects as the agents of choice for the chemoprevention of CRC.

NSAIDs Old and New

NSAIDs have been in development for over 100 years, beginning with the synthesis of acetylsalicylic acid or aspirin in 1897 [4]. This seminal event was the culmination of over two centuries of efforts beginning with the 1763 letter by the Reverend Edward Stone to the Earl of Macclesfield describing the use of powder derived from willow bark for treating fever in 50 patients. *Salicin*, the Latin word for *willow*, served as the basis for the term salicylic and its derivatives.

Conventional NSAIDs are classified based on their structural features or on their ability to inhibit cyclooxygenase (COX), with their selectivity for COX-2 inhibition considered a defining characteristic, e.g., COX-2 selective inhibitors [5]. The structural similarities between them are few, with the exception of a carboxylic moiety that is present in nearly all of them. There are currently at least 20 approved NSAIDs in the USA and more elsewhere.

Seemingly incessant efforts to generate improved NSAIDs have led to several new (non-FDA approved yet) compounds, all chemically modified NSAIDs. Nitro-NSAIDs are NSAID derivatives in which a nitric oxide releasing moiety ($-ONO_2$) is attached covalently to NSAIDs via an aromatic or aliphatic linker [6]. Several novel sulindac derivatives have been generated [7] including sulindac benzylamine [8, 9] and *des*-methyl-sulindac sulfide and its pro-drug *des*-methyl-sulindac that fail to inhibit COX-2 activity [10]. Esterification/amidation of the carboxylic acid moiety in various NSAIDs, e.g., indomethacin [11], has been pursued to obtain selective COX-2 inhibitors [12]. Phosphatidylcholine (PC) NSAIDs have been synthesized to remove the gastrointestinal (GI) toxicity of conventional NSAIDs by capitalizing on the ability of PC to protect the gastrointestinal mucosa without diminishing their pharmacological efficacy [13]. Finally, phospho-NSAIDs are derived by a fairly simple chemical modification of existing NSAIDs. In particular, their carboxylic moiety is often esterified to a dialcohol spacer moiety; the second –OH of the spacer is linked to a diethylphosphate moiety, which enhances cellular uptake [14]. Recently, one of the phospho-NSAIDs was pegylated to improve its pharmacokinetics and bioavailability [15].

Chemopreventive Efficacy

That NSAIDs can prevent CRC is now well established thanks to an extensive and fairly consistent body of work by many investigators around the world. Such work includes huge epidemiologic studies with hundreds of thousands of subjects in the aggregate. The clear conclusion is that the prolonged use of NSAIDs reduces adenomatous polyps, incident disease, and death from CRC by 30–50 % [16–18]. Most of the interventional studies have focused on aspirin and sulindac.

Studies with Aspirin and its Derivatives

Randomized clinical trials (RCTs) using the development of colon adenomas as surrogate endpoints for CRC prevention demonstrated the ability of aspirin to prevent CRC. The results of three such trials were congruent, but the effect was modest and somewhat disappointing, as the risk of recurrent adenoma was reduced at most by one third [19–21].

Rothwell et al. [22] examined the cancer outcomes of four randomized trials originally designed to evaluate the effect of aspirin 75–1200 mg/day on the prevention of cardiovascular events in populations including subjects at low and high risk. Treatment with aspirin 75–500 mg/day reduced the 20-year risk of CRC by 24 % and the CRC-associated mortality by 35 %. The same group examined data from eight cardiovascular prevention RCTs of daily aspirin included in a study that pooled individual patient data and examined the effects of randomized aspirin treatment on all cancer mortality [23••]. Aspirin 75–1200 mg/day was associated with 21 % lower risk of death from any cancer. What was rather surprising was the 5-year lag until the benefit became evident. This lag also applied to the risk of death due to CRC (HR=0.41; p=0.05), whose reduction began 5 years after the initiation of aspirin treatment. Analysis of 51 RCTs of daily low-dose aspirin for primary prevention revealed that aspirin reduced cancer incidence beginning on the third year of administration [24••]. Although these data are compelling, the reservation has been raised that these trials were not originally designed to examine CRC incidence or mortality [17, 25].

Sosters et al. [25] have recently argued that the antiplatelet action of aspirin plays a central role in its antitumor effect, since daily low-dose aspirin given for the prevention of cardiovascular disease events prevents adenoma recurrence and decreases the incidence of CRC and attributable mortality. We have speculated similarly in the past, based on the profile of eicosanoids in human colon cancers [26].

NO-aspirin administered for CRC prevention was both efficacious and safe, at least in terms of gastric toxicity [6, 27]. All three positional isomers of NO-aspirin showed promise as anticancer agents [28], but the clinical evaluation of their role in CRC prevention was not pursued because of concerns regarding potential genotoxicity.

Both aspirin-PC and ibuprofen-PC showed in vitro and in vivo properties suggesting their potential utility in patients at risk for CRC [29]. For example, both inhibited the growth of colon cancer cells in vitro and the development of colonic aberrant crypt foci (ACF) in the azoxymethane rat model of CRC. Clinical studies with these compounds are apparently in progress.

Studies with Sulindac and Related Compounds

In a well-reasoned effort to overcome the limited chemopreventive efficacy of conventional NSAIDs, Gerner and

Meyskins have developed a combination approach [30]. Their biochemical goal was to reduce the intracellular levels of polyamines, which control, at least in part, colonocyte proliferation. To this end, they used a combination of difluoromethylornithine (DFMO) and sulindac. DFMO is a suicide inhibitor of ornithine decarboxylase, which catalyzes the rate-limiting step in polyamine synthesis. Sulindac, on the other hand, increases cellular export of polyamines by activating the spermidine/spermine acetyltransferase. This combination produced impressive results both in preclinical studies and in a phase III trial in patients with prior colon polyps, reducing total metachronous colorectal adenomas by 70 % and advanced and/or multiple adenomas by >90 % [31]. This regimen was well tolerated; in particular, there were no auditory side effects induced by DFMO. The combination of aspirin and folate produced no benefit from folate [32].

Takayama and Niitsu have for years pursued assiduously as chemoprevention targeting ACF, aggregates of colonic crypts, considered precursors of polyps. Their reasoning was that the low complexity of ACF would make easier their elimination by chemopreventive agents [33–35]. A 12-month interim analysis of a RCT of sulindac 300 mg or etodolac 400 mg given daily for the first two months showed that sulindac was able to reduce aberrant crypt foci by 41 % at 2 months and the number of polyps by 51 % at 12 months [36••]. Of note, the COX-2-specific inhibitor etodolac showed no such effect. They also observed that this effect of sulindac was similar in magnitude to that obtained after long-term administration of NSAIDs with polyp recurrence as the endpoint. Responsiveness of ACF to the chemopreventive agent may predict its effect on polyps. Thus, short-term or even discontinuous administration of NSAIDs such as sulindac may prevent CRC. The newer, more efficacious derivatives of sulindac, e.g., phospho-sulindac [14], may have a role in such an approach.

Sulindac benzylamine, a novel sulindac derivative, does not inhibit COX-1 or COX-2, yet potently inhibits the growth and induces the apoptosis of human colon tumor cells [9]. The basis for this activity appears to involve cyclic guanosine 3′,5′, -monophosphate phosphodiesterase (PDE); the PDE5 isoform is essential for colon tumor cell growth. Other sulindac derivatives such as *des*-methyl-sulindac sulfide and its pro-drug *des*-methyl-sulindac failed to significantly inhibit tumor formation in APC/Min mice [10], a result attributed to limited activation to their active forms in vivo.

The last group of chemically modified NSAIDs that has been studied in the prevention of CRC is that of phospho-NSAIDs, with phospho-sulindac (PS) being the one most extensively studied. PS is >10-fold more potent than sulindac in inhibiting the growth of cultured CRC cells and more efficacious in the prevention of CRC [14, 37••]. Like sulindac, PS synergized with DFMO to prevent CRC; in *Apc*/*Min* mice, the PS/DFMO combination reduced tumor multiplicity by 90 %. The mechanism of action of PS/DFMO appears complex. Two prominent effects are the induction of oxidative stress and the suppression of polyamine levels. A very interesting aspect of the effect of PS/DFMO is the strong suppression of the thioredoxin system [37••], an emerging regulator of chemoprevention [38].

PS was studied extensively for its safety, a critical parameter for any candidate chemopreventive agent. Multiple studies have shown its safety to be equivalent to that of placebo and far superior to that of sulindac [14]. Although not fully understood, the safety of PS is partly attributed to its unique pharmacokinetic properties: the blood $AUC_{0-24\ h}$ of PS is around 40 % of that produced by an equimolar amount of sulindac, while in the stomach, the main site of NSAID toxicity, PS is mainly intact and its two gastrotoxic metabolites, sulindac and sulindac sulfide, are present in miniscule amounts [39]. PS's more rapid detoxification by cytochrome P450s and flavin monooxygenases seems to contribute to its safety [40].

Genetic Syndromes: Familial Adenomatous Polyposis and Lynch Syndrome

The chemoprevention efficacy of NSAIDs has been evaluated in familial adenomatous polyposis (FAP) and Lynch syndrome (hereditary non-polyposis colorectal cancer). These syndromes not only constitute a pressing clinical need but also provide the opportunity to conduct expedited studies on CRC chemoprevention. Sulindac and the COX-2 selective inhibitors celecoxib and rofecoxib reduced the size and number of colorectal polyps after 6–9 months of treatment in FAP patients [41–43]. Aspirin 600 mg/day, however, failed to significantly reduce the number of polyps in the sigmoid colon and rectum [44••]. Similarly, aspirin 100 mg/day showed limited efficacy in another trial that was largely inconclusive due to small subgroup size [45]. In Lynch syndrome, aspirin 600 mg/day for up to 4 years was effective in preventing CRC [46••]. For those taking aspirin for 2 years or longer, the hazard ratio was 0.41 ($p=0.02$). This trial was the first RCT of aspirin with CRC as the primary endpoint. The evidence is strong that aspirin is an effective chemopreventive agent in hereditary cancer with an effect equivalent to that achieved with surveillance colonoscopy.

Mechanistic Aspects of NSAIDs

The mechanistic effects of NSAIDs in cancer have been conceptualized as COX dependent and COX independent. Initially, the anticancer activity of NSAIDs was considered to derive solely from its COX inhibitory effect [47]. This speculation was based primarily on the well-recognized ability of aspirin and NSAIDs to inhibit COX, the enzyme catalyzing the

synthesis of prostaglandins, and on the increased PGE_2 levels in CRC [26]; PGE_2 stimulates the proliferation of CRC cells [48], an effect blocked by NSAIDs [49]. However, additional work pointed out that COX-independent effects may also contribute greatly to the chemopreventive effect of NSAIDs [50]. Multiple signaling pathways have been implicated, both COX dependent and COX independent. Key players seem to be NF-κB, the Wnt pathway, the DNA mismatch repair system, NAG-1 (NSAID-induced gene) [51], and sphingosine-1 kinase [52]. Induction of oxidative stress may play a role, at least where it is the initial event that activates redox-responsive signaling cascades culminating in apoptotic cell death [38, 53]. The modified NSAIDs seem to work both via COX-dependent and COX-independent pathways, but redox effects are prominent [54••]. Recent work is exploring whether epigenetic regulation by NSAIDs may contribute to their chemopreventive effects [55, 56]. Despite decades of work, no unifying mechanism has been obtained [47, 57, 58], indicating either that different mechanisms may operate in particular instances [59] or that the actual mechanism awaits discovery.

The Safety of NSAIDs

Safety, important for any medication, is critical in chemoprevention as the NSAID will likely be taken for years when its side effects may be compounded. Of note, the side effects of NSAIDs are broad and can be lethal [18, 60]. The most consequential of them are GI and renal toxicity and, to a lesser extent, cardiovascular, CNS, and platelet side effects. There is no safe NSAID.

Aspirin, the oldest and most extensively used, has the greatest safety database of all NSAIDs. A close parallel to the chemoprevention use of aspirin is its long-term administration for the prevention of cardiovascular events, a standard clinical practice for many years. The GI side effects of aspirin have been the subject of numerous studies [61]. Compared to those who did not use it, aspirin not only increased by 1.6–3.1 times the RR for GI bleeding but also increased the risk for adverse GI symptoms (OR=1.7), such as nausea and dyspepsia [62]. The GI toxicity of aspirin increased with increasing dose and with advancing patient age. For example, 2.5 % of those taking more than 100 mg of aspirin per day had GI bleeding compared with 1.1 % of those taking fewer than 100 mg/day [63].

The cardiovascular complications of NSAIDs and COX-2 selective inhibitors are a topic of major concern and significant complexity [64–66]. Suffice it to mention here that most nonselective NSAIDs and COX-2 selective NSAIDs (coxibs) increase the risk of adverse cardiovascular events, including death, myocardial infarction, heart failure, and stroke. The risk varies depending upon the baseline cardiovascular event risk of the patient, the NSAID used, and its dose. Naproxen is generally preferred over other nonselective NSAIDs as it appears to be an exception in terms of significant cardiovascular toxicity. Of note, the beneficial effect of aspirin may be attenuated by prior or ongoing administration of some nonselective NSAIDs, including ibuprofen and naproxen. It is currently uncertain how the cardiovascular toxicity of NSAIDs will affect their chemoprevention application, if any. Interestingly, cardiac toxicity during CRC chemoprevention trials was the main reason for withdrawing COX-2-specific inhibitors [67].

Conclusions

The data reviewed above strongly indicate the following: the chemoprevention of CRC by NSAIDs is feasible; conventional NSAIDs alone are not suitable for CRC chemoprevention due to low efficacy and high toxicity; certain subpopulations at risk for CRC may be better candidates for NSAID-based chemoprevention; targeting early stages of carcinogenesis such as ACF holds promise; and some of the newer modified NSAIDs may turn out to be far superior to their parent compounds, thus being appropriate for chemoprevention.

These conclusions raise a multitude of issues. As perhaps in all of medicine, the common element in trying to deal with them is that one must weigh the risk and benefit of each contemplated intervention. Chemoprevention requires administration of an agent for prolonged periods of time. The higher the risk of CRC in a given individual and the lower the cumulative side effects of the chemopreventive agent, the clearer is the justification for prescribing it. Conventional NSAIDs have side effects that increase with prolonged administration, especially in older patients who, because of comorbidities, take medications that interact with the chemopreventive agent. Thus, to justify the lifetime administration of a conventional NSAID, the CRC risk must be much higher than the <5 % probability that an individual at average risk has to develop CRC [68].

These and similar considerations suggest the need to focus on the transition of chemoprevention from its current investigational stage to that of clinical application. Relevant to it would be the following:

- *Identification of subjects at high risk and those most likely to benefit from the chemopreventive agent*. The development of approaches to reliably estimate risk and of predictive biomarkers would be extremely helpful in this context.
- *Optimization of the administration of the chemopreventive agent*. The work of Takayama and Niitsu has opened an important window into this aspect, as it suggests that attempting to arrest colon carcinogenesis at a very early stage may require relatively short periods of agent

administration. Thus, the timing, dose, and duration of NSAID administration could be fine-tuned so that the lowest possible NSAID dose is used for the shortest period of time. Furthermore, in those at risk, it may be helpful such an intervention to commence at a relatively young age.

- *New agents or combinations of agents*. The promise of higher efficacy and safety of the modified NSAIDs, such as PS, indicates that their further exploration may have merit. The efficacy of sulindac/DFMO supports the argument for combination approaches that will increase efficacy beyond the currently low levels of single agents.
- *Agents that may prevent other diseases in addition to CRC* would shift dramatically the risk/benefit ratio in favor of the intervention. For example, preventing both colon cancer and heart attacks, as conventional aspirin does albeit weakly, is altogether different than only preventing one of these two diseases.

The enormous accomplishments of the last two decades have provided proof-of-concept for NSAID prevention of CRC and moved the field to its current exciting stage where rationally targeted implementation strategies can be contemplated. Although significant work lies ahead, there is ample reason for serious optimism.

Acknowledgments The research reported in this publication was supported by the National Institutes of Health under award number R01CA139454 (National Cancer Institute). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance with Ethics Guidelines

Conflict of Interest George J. Tsioulias and Mae F. Go declare no conflict of interest.

Basil Rigas has an equity position in Medicon Pharmaceuticals, Inc., which is developing phospho-NSAIDs.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors that have not been published previously.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clin Colon Rectal Surg. 2009;22:191–7.
2. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369:1095–105.
3. Yee J, Weinstein S, Morgan T, Alore P, Aslam R. Advances in CT colonography for colorectal cancer screening and diagnosis. J Cancer. 2013;4:200–9.
4. Miner J, Hoffhines A. The discovery of aspirin's antithrombotic effects. Tex Heart Inst J. 2007;34:179–86.
5. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst. 2002;94:252–66.
6. Rigas B. Novel agents for cancer prevention based on nitric oxide. Biochem Soc Trans. 2007;35:1364–8.
7. Haanen C. Sulindac and its derivatives: a novel class of anticancer agents. Curr Opin Investig Drugs. 2001;2:677–83.
8. Tinsley HN, Piazza GA. Novel therapeutics: NSAIDs, derivatives, and phosphodiesterases. Current Color Cancer Rep. 2012;8:325–30.
9. Whitt JD, Li N, Tinsley HN, Chen X, Zhang W, Li Y, et al. A novel sulindac derivative that potently suppresses colon tumor cell growth by inhibiting cGMP phosphodiesterase and beta-catenin transcriptional activity. Cancer Prev Res (Phila). 2012;5:822–33.
10. Wang X, Kingsley PJ, Marnett LJ, Eling TE. The role of NAG-1/GDF15 in the inhibition of intestinal polyps in APC/Min mice by sulindac. Cancer Prev Res (Phila). 2011;4:150–60.
11. Kalgutkar AS, Crews BC, Saleh S, Prudhomme D, Marnett LJ. Indolyl esters and amides related to indomethacin are selective COX-2 inhibitors. Bioorg Med Chem. 2005;13:6810–22.
12. Kalgutkar AS, Crews BC, Rowlinson SW, Marnett AB, Kozak KR, Remmel RP, et al. Biochemically based design of cyclooxygenase-2 (COX-2) inhibitors: facile conversion of nonsteroidal antiinflammatory drugs to potent and highly selective COX-2 inhibitors. Proc Natl Acad Sci U S A. 2000;97:925–30.
13. Lim YJ, Dial EJ, Lichtenberger LM. Advent of novel phosphatidylcholine-associated nonsteroidal anti-inflammatory drugs with improved gastrointestinal safety. Gut Liver. 2013;7:7–15.
14. Mackenzie GG, Sun Y, Huang L, Xie G, Ouyang N, Gupta RC, et al. Phospho-sulindac (OXT-328), a novel sulindac derivative, is safe and effective in colon cancer prevention in mice. Gastroenterology. 2010;139:1320–32.
15. Mattheolabakis G, Wong CC, Sun Y, Amella CA, Richards R, Constantinides PP, et al. Pegylation improves the pharmacokinetics and bioavailability of small-molecule drugs hydrolyzable by esterases: a study of phospho-ibuprofen. J Pharmacol Exp Ther. 2014;351:61–6.
16. Rostom A, Dube C, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146:376–89.
17. Garcia-Albeniz X, Chan AT. Aspirin for the prevention of colorectal cancer. Best Pract Res Clin Gastroenterol. 2011;25:461–72.
18. Thun MJ, Blackard B. Pharmacologic effects of NSAIDs and implications for the risks and benefits of long-term prophylactic use of aspirin to prevent cancer. Recent Results Cancer Res. 2009;181:215–21.
19. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med. 2003;348:891–9.
20. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med. 2003;348:883–90.
21. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, et al. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology. 2003;125:328–36.

22. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010;376:1741–50.
23.•• Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377:31–41. **Provides the first proof in man that aspirin reduces deaths due to several common cancers. Benefit was consistent across the different trial populations, suggesting that the findings are likely to be generalizable**.
24.•• Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 2012;379:1602–12. **Extensive study addressing a gap in the literature in that previous systematic reviews did not consider the effects of aspirin on cancer incidence, mortality, or non-vascular death or the effect of the duration of use. Their findings suggest that the extended use of aspirin will be safer than previously supposed and will be of value in the prevention of cancer**.
25. Sostres C, Gargallo CJ, Lanas A. Aspirin, cyclooxygenase inhibition and colorectal cancer. World Journal Gastrointestin Pharmacol Ther. 2014;5:40–9.
26. Rigas B, Goldman IS, Levine L. Altered eicosanoid levels in human colon cancer. J Lab Clin Med. 1993;122:518–23.
27. Williams JL, Kashfi K, Ouyang N, del Soldato P, Kopelovich L, Rigas B. NO-donating aspirin inhibits intestinal carcinogenesis in Min (APC(Min/+)) mice. Biochem Biophys Res Commun. 2004;313:784–8.
28. Kashfi K, Borgo S, Williams JL, Chen J, Gao J, Glekas A, et al. Positional isomerism markedly affects the growth inhibition of colon cancer cells by nitric oxide-donating aspirin in vitro and in vivo. J Pharmacol Exp Ther. 2005;312:978–88.
29. Lichtenberger L, Waters D, Phan T, Dial E. GI-safe NSAIDs and the suppression of colon cancer. FASEB J. 2014;26:840.5.
30. Laukaitis CM, Gerner EW. DFMO: targeted risk reduction therapy for colorectal neoplasia. Best Pract Res Clin Gastroenterol. 2011;25:495–506.
31. Meyskens FL, McLaren CE, Pelot D, Fujikawa-Brooks S, Carpenter PM, Hawk E, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. Cancer Prev Res Phila Pa. 2008;1:9–11.
32. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR, uk CAPTG. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology. 2008;134:29–38.
33. Takayama T, Katsuki S, Takahashi Y, Ohi M, Nojiri S, Sakamaki S, et al. Aberrant crypt foci of the colon as precursors of adenoma and cancer. N Engl J Med. 1998;339:1277–84.
34. Takayama T, Miyanishi K, Hayashi T, Kukitsu T, Takanashi K, Ishiwatari H, et al. Aberrant crypt foci: detection, gene abnormalities, and clinical usefulness. Clin Gastroenterol Hepatol. 2005;3: S42–5.
35. Rasheed S, Rigas B. Screening for colorectal cancer: does it all start with aberrant crypt foci? Gastrointest Endosc. 2008;67:1103–5.
36.•• Takayama T, Nagashima H, Maeda M, Nojiri S, Hirayama M, Nakano Y, et al. Randomized double-blind trial of sulindac and etodolac to eradicate aberrant crypt foci and to prevent sporadic colorectal polyps. Clin Cancer Res. 2011;17:3803–11. **This 1-year study shows that a 2-month administration of sulindac to eradicate aberrant crypt foci was as effective in reducing polyps as long-term administration of similar drugs in previously reported trials. The intriguing and potentially big point here is that short-term and discontinuous administration of drugs may be chemopreventive and is worth exploring further. Responsiveness of aberrant crypt foci to the chemopreventive agent may predict its effect on polyps**.
37.•• Mackenzie GG, Ouyang N, Xie G, Vrankova K, Huang L, Sun Y, et al. Phospho-sulindac (OXT-328) combined with difluoromethylornithine prevents colon cancer in mice. Cancer Prev Res (Phila). 2011;4:1052–60. **The first study of a phospho-NSAID in chemoprevention demonstrating the strong effect of phospho-sulindac in CRC prevention, its extraordinary safety (no side effects), and its synergy with DFMO. It also provides phospho-sulindac's mechanism of action**.
38. Sun Y, Rigas B. The thioredoxin system mediates redox-induced cell death in human colon cancer cells: implications for the mechanism of action of anticancer agents. Cancer Res. 2008;68:8269–77.
39. Xie G, Nie T, Mackenzie GG, Sun Y, Huang L, Ouyang N, et al. The metabolism and pharmacokinetics of phospho-sulindac (OXT-328) and the effect of difluoromethylornithine. Brit J Pharmacol. 2012;165:2152–66.
40. Xie G, Wong CC, Cheng KW, Huang L, Constantinides PP, Rigas B. Regioselective oxidation of phospho-NSAIDs by human cytochrome P450 and flavin monooxygenase isoforms: implications for their pharmacokinetic properties and safety. Br J Pharmacol. 2012;167:222–32.
41. Giardiello FM, Hamilton SR, Krush AJ, Piantadosi S, Hylind LM, Celano P, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. N Engl J Med. 1993;328:1313–6.
42. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med. 2000;342:1946–52.
43. Hallak A, Alon-Baron L, Shamir R, Moshkowitz M, Bulvik B, Brazowski E, et al. Rofecoxib reduces polyp recurrence in familial polyposis. Dig Dis Sci. 2003;48:1998–2002.
44.•• Burn J, Bishop DT, Chapman PD, Elliott F, Bertario L, Dunlop MG, et al. A randomized placebo-controlled prevention trial of aspirin and/or resistant starch in young people with familial adenomatous polyposis. Cancer Prev Res (Phila). 2011;4:655–65. **The largest clinical trial ever, conducted in the setting of FAP, found a trend of reduced polyp load**.
45. Ishikawa H, Wakabayashi K, Suzuki S, Mutoh M, Hirata K, Nakamura T, et al. Preventive effects of low-dose aspirin on colorectal adenoma growth in patients with familial adenomatous polyposis: double-blind, randomized clinical trial. Cancer Med. 2013;2:50–6.
46.•• Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet. 2011;378:2081–7. **The first randomized trial of aspirin as a chemopreventive agent with cancer as the primary endpoint. In the context of the published literature, the trial provides clear evidence that aspirin is an effective chemopreventive agent in hereditary cancer with an effect equivalent to that achieved with surveillance colonoscopy**.
47. Schror K. Pharmacology and cellular/molecular mechanisms of action of aspirin and non-aspirin NSAIDs in colorectal cancer. Best Pract Res Clin Gastroenterol. 2011;25:473–84.
48. Qiao L, Kozoni V, Tsioulias GJ, Koutsos MI, Hanif R, Shiff SJ, et al. Selected eicosanoids increase the proliferation rate of human colon carcinoma cell lines and mouse colonocytes in vivo. Biochim Biophys Acta. 1995;1258:215–23.
49. Shiff SJ, Koutsos MI, Qiao L, Rigas B. Nonsteroidal antiinflammatory drugs inhibit the proliferation of colon adenocarcinoma cells: effects on cell cycle and apoptosis. Exp Cell Res. 1996;222:179–88.

50. Hanif R, Pittas A, Feng Y, Koutsos MI, Qiao L, Staiano-Coico L, et al. Effects of nonsteroidal anti-inflammatory drugs on proliferation and on induction of apoptosis in colon cancer cells by a prostaglandin-independent pathway. Biochem Pharmacol. 1996;52:237–45.
51. Iguchi G, Chrysovergis K, Lee SH, Baek SJ, Langenbach R, Eling TE. A reciprocal relationship exists between non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1) and cyclooxygenase-2. Cancer Lett. 2009;282:152–8.
52. Ponnusamy S, Meyers-Needham M, Senkal CE, Saddoughi SA, Sentelle D, Selvam SP, et al. Sphingolipids and cancer: ceramide and sphingosine-1-phosphate in the regulation of cell death and drug resistance. Future Oncol. 2010;6:1603–24.
53. Rigas B, Sun Y. Induction of oxidative stress as a mechanism of action of chemopreventive agents against cancer. Br J Cancer. 2008;98:1157–60.
54.•• Sun Y, Huang L, Mackenzie GG, Rigas B. Oxidative stress mediates through apoptosis the anticancer effect of phosphononsteroidal anti-inflammatory drugs: implications for the role of oxidative stress in the action of anticancer agents. J Pharmacol Exp Ther. 2011;338:775–83. **Definitive demonstration of the critical role of oxidative stress in the mechanism of action of phospho-NSAIDs. It has wider mechanistic implications for the role of redox chemistry in anticancer drug action**.
55. Tahara T, Shibata T, Yamashita H, Nakamura M, Yoshioka D, Okubo M, et al. Chronic nonsteroidal anti-inflammatory drug (NSAID) use suppresses multiple CpG islands hyper methylation (CIHM) of tumor suppressor genes in the human gastric mucosa. Cancer Sci. 2009;100:1192–7.
56. Yiannakopoulou E. Targeting epigenetic mechanisms and microRNAs by aspirin and other non steroidal anti-inflammatory agents—implications for cancer treatment and chemoprevention. Cell Oncol (Dordrecht). 2014;37:167–78.
57. Stolfi C, De Simone V, Pallone F, Monteleone G. Mechanisms of action of non-steroidal anti-inflammatory drugs (NSAIDs) and mesalazine in the chemoprevention of colorectal cancer. Int J Mol Sci. 2013;14:17972–85.
58. Tinsley HN, Grizzle WE, Abadi A, Keeton A, Zhu B, Xi Y, et al. New NSAID targets and derivatives for colorectal cancer chemoprevention. Recent Results Cancer Res. 2013;191:105–20.
59. Shiff SJ, Rigas B. The role of cyclooxygenase inhibition in the antineoplastic effects of nonsteroidal antiinflammatory drugs (NSAIDs) [comment]. J Exp Med. 1999;190:445–50.
60. Salvo F, Fourrier-Reglat A, Bazin F, Robinson P, Riera-Guardia N, Haag M, et al. Cardiovascular and gastrointestinal safety of NSAIDs: a systematic review of meta-analyses of randomized clinical trials. Clin Pharmacol Ther. 2011;89:855–66.
61. Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146:365–75.
62. Roderick PJ, Wilkes HC, Meade TW. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. Br J Clin Pharmacol. 1993;35:219–26.
63. Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. Am J Hematol. 2004;75:40–7.
64. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med. 2011;8, e1001098.
65. Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011;342:c7086.
66. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013;382:769–79.
67. Solomon SD, Pfeffer MA, McMurray JJ, Fowler R, Finn P, Levin B, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. Circulation. 2006;114:1028–35.
68. Burt RW, DiSario JA, Cannon-Albright L. Genetics of colon cancer: impact of inheritance on colon cancer risk. Annu Rev Med. 1995;46:371–9.