

Reduction in cancer risk by selective and nonselective cyclooxygenase-2 (COX-2) inhibitors

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Abstract: We conducted a series of epidemiologic studies to evaluate the chemopreventive effects of aspirin, ibuprofen, and selective cyclooxygenase-2 (COX-2) inhibitors (coxibs) against cancers of the breast, colon, prostate, and lung. Composite results across all four cancer sites revealed that regular intake of 325 mg aspirin, 200 mg ibuprofen, or standard dosages of coxibs (200 mg celecoxib or 25 mg rofecoxib) produced risk reductions of 49%, 59%, and 64%, respectively. Use of coxibs for at least 2 years was associated with risk reductions of 71%, 70%, 55%, and 60% for breast cancer, colon cancer, prostate cancer and lung cancer, respectively. Effects of ibuprofen were similar to selective coxibs, and slightly stronger than aspirin. These observed effects are consistent with the relative COX-2 selectivity of ibuprofen, coxibs, and aspirin. Acetaminophen, an analgesic without COX-2 activity, had no effect. Overexpression of COX-2 and increased prostaglandin biosynthesis correlates with carcinogenesis and metastasis at most anatomic sites. These results indicate that regular intake of nonselective or selective COX-2 inhibiting agents protects against the development of major forms of cancer.

Keywords: inflammation, breast cancer, colon cancer, prostate cancer, lung cancer, chemoprevention

Introduction

Vane discovered that the anti-inflammatory effects of aspirin-like drugs are primarily due to their inhibition of cyclooxygenase (COX), the rate-limiting enzyme of the prostaglandin cascade.¹ Metabolism of the essential fatty acid, arachidonic acid, via the cyclooxygenase pathway produces various prostaglandins that have a diverse array of physiologic activities throughout the human system. These shortlived molecules appear not only to control the inflammatory response, but also to help regulate constriction of blood vessels, constriction of smooth muscle, aggregation of platelets, sensitization of neurons to pain, regulation of intracellular calcium, cell division, apoptosis, and many other molecular events that are critical to the maintenance of physiologic homeostasis.²

Two genes regulate cyclooxygenase expression, a constitutive gene (*COX-1*) and its inducible isoform (*COX-2*).³⁻⁵ The inducible *COX-2* gene is the master switch that activates the inflammatory response. Induction of *COX-2* by any inflammatory stimulus (eg, tobacco, alcohol, ischemia, trauma, pressure, foreign bodies, toxins, bacteria, viruses, lipopolysaccharides, etc) quickly results in the biosynthesis of prostaglandins of the E-series, particularly PGE-2, and these prostaglandins in turn orchestrate the inflammatory response.

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The discovery of the inducible *COX-2* gene and the impact of *COX-2* overexpression on mechanisms of cancer development, have rekindled interest in the theorized inflammogenesis of cancer.^{6,7} This hypothesis was originally proposed by Rudolph Virchow more than 150 years ago.^{8–10} Current models of *COX-2* and the inflammogenesis of cancer are based upon consistent evidence linking constitutive *COX-2* expression with key elements of carcinogenesis: mutagenesis, mitogenesis, angiogenesis, dysfunctional apoptosis, immune suppression, and metastasis.^{11–13}

Under normal conditions, acute inflammation is a tightly controlled, self-limited response to the offending stimulus. The process involves the integration of multiple cell types of the vascular and immune systems for the purpose of targeting, capturing, degrading, and removing the offending agent from the tissue under attack. Concurrent with inflammation, *COX-2* expression by endothelial cells, epithelial cells, stromal cells, monocytes, and lymphocytes increases basal levels up to 100-fold.¹⁴

In contrast to self-limited inflammatory responses, constitutive overexpression of the inducible *COX-2* gene and resulting heightened prostaglandin E2 (PGE2) biosynthesis play a significant role in carcinogenesis of many cancers, and blockade of this process has strong potential for intervention and chemoprevention.^{15–19}

Over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen inhibit both *COX-1* and *COX-2* and are thus called nonselective *COX-2* inhibitors (coxibs). Since these agents are widely used for relief of pain, fever, and inflammation in the general population, they have recently come under intensive investigation in epidemiologic studies that aim to determine the extent and nature of their anticancer properties.^{20,21}

Prescription compounds such as rofecoxib and celecoxib are called selective *COX-2* blockers since they primarily inhibit *COX-2* and have relatively little activity against *COX-1*.

This review synthesizes and interprets a series of investigations of the role of aspirin, ibuprofen, and selective coxibs in human cancer prevention. Our investigations have focused specifically on cancers of the colon, breast, prostate, and lung that, collectively, account for more than half of all cancer deaths in the United States and the United Kingdom.^{22,23} Here, we generalize previous findings, provide a review of molecular mechanisms of carcinogenesis, and share perspectives discussed on *COX-2* blockade in cancer prevention and therapy.

Methods and populations

From 1987 to 2008, we conducted a series of epidemiologic studies of the relationships between NSAIDs, selective coxibs, and cancers of the breast, prostate, colon, and lung. In each investigation, information was obtained about the entire profile of NSAID and coxib use for each participant, including both over-the-counter and prescription drugs. All studies were designed to specifically evaluate and compare the effects of the two major over-the-counter compounds, aspirin and ibuprofen.

Two selective coxibs, celecoxib and rofecoxib, were approved for the treatment of arthritis by the United States Food and Drug Administration in 1999. Until the recall of rofecoxib in September 2004 (due to its association with cardiovascular events), these two compounds, plus other selective coxibs, valdecoxib and meloxicam, were widely utilized in the US for pain relief and the treatment of osteoarthritis and rheumatoid arthritis.²⁴ The time period between the approval of celecoxib and the recall of rofecoxib provided an approximate 6-year window for evaluation of exposure to such compounds by a case control approach. Studies conducted from 1999 to 2004 therefore included examination of the two available coxibs during this period, rofecoxib and celecoxib.

We also collected data on the use of acetaminophen, a commonly used analgesic that has little or no activity against either *COX-1* or *COX-2*. Acetaminophen therefore served as a comparator (control) drug that was not expected to have anticancer effects.

Methods of analysis

Effects of specific agents were quantified by estimating relative risks (or odds ratios [ORs]) adjusted for cancer risk factors with standard errors and 95% confidence intervals (CIs). In each study, estimates for specific NSAIDs or coxibs were derived by comparison with a reference group that reported nonuse of any type of NSAID or coxib.

Methods developed by Schlesselman²⁵ and Greenland²⁶ were adapted for combined analysis of the data from these studies. For each cancer site and level of NSAID exposure, estimates of RR and 95% CI were converted to $\ln(RR)$ with a corresponding variance estimate (v). Combined estimates of $\ln(RR^*) = \sum \ln(RR)w$ were obtained by weighting individual estimates by $w = 1/v$. Chi-square tests of heterogeneity were utilized to test for differences among studies of each type of cancer and to check the consistency of estimates across cancer sites. Estimates of relative risk were contrasted for dosages of 325 mg aspirin or 200 mg ibuprofen taken at least two times

per week for at least 5 years. Results for coxibs pertain to median (standard) daily dosages of 200 mg for celecoxib and 25 mg for rofecoxib for at least 2 years.

Results

Altogether, we conducted ten separate epidemiologic investigations of cancer comparing the effects of selective and nonselective coxibs: five for breast cancer, two for lung cancer, two for prostate cancer, and one for colon cancer.^{15–19,27–32} Results of these studies are summarized in Table 1.

Coxib use reduced the overall risk of cancer development by 64% (71%, 70%, 55%, and 60% for cancers of the breast, colon, prostate, and lung, respectively). Similar reductions in cancer risk were noted for ibuprofen with slightly lower reductions for aspirin. Overall, ibuprofen reduced the risk of cancer development by 59%, compared with 49% for aspirin. The declining pattern of risk for aspirin, ibuprofen, and coxibs was significant by a linear trend test ($P < 0.05$), suggesting that chemopreventive effects become progressively stronger with greater selective COX-2 inhibition. These risk reductions are consistent with the relative levels of COX-2 inhibition that have been observed for therapeutic concentrations of aspirin, ibuprofen and celecoxib or rofecoxib.³³

Discussion

Selective coxibs (celecoxib and rofecoxib) were approved for use in 1999, and rofecoxib (Vioxx) was withdrawn from the marketplace in 2004. Nevertheless, even in the short

window of exposure to these compounds, intake of selective coxibs produced significant reductions in the risk of the four major human cancers (breast, prostate, colon, and lung). It is important to note that ibuprofen use produced risk reductions similar in magnitude to the coxibs which is consistent with its high activity against COX-2. Risk reductions noted for aspirin were significant of slightly less magnitude. These results tend to substantiate the important role of COX-2 in carcinogenesis, and reciprocally, the strong potential for selective COX-2 blockade in cancer chemoprevention.⁷

COX-2 blockade of molecular carcinogenesis

Inhibition of cyclooxygenase and blockade of the prostaglandin cascade may have an impact upon neoplastic growth and development by reducing key features of carcinogenesis, including mutagenesis, mitogenesis, angiogenesis, and metastasis, as well as by stimulating apoptosis of malignant cells and enhancing immunosurveillance and antineoplastic activity of T and B lymphocytes.^{7,12,13,34–36} Continuous overexpression of COX-2 could initiate and promote carcinogenesis by: (1) increasing production of malondialdehyde and other reactive oxygen species that are carcinogenic (mutagenesis); (2) increasing production of PGE-2 and other factors that strongly promote cell proliferation, such as correlative up-regulation of CYP19, and estrogen biosynthesis in stromal cells (mitogenesis); (3) stimulation of VEGF and PDGF by PGE-2 resulting

Table 1 Relative risks and odds ratios for aspirin, ibuprofen, and selective COX-2 inhibitors (coxibs) from epidemiologic studies of cancers of the breast, colon, prostate, and lung

Reference	Type	Aspirin	Ibuprofen	Coxibs
Breast cancer				
Harris et al ^{27,28}	Case control	0.69 (0.46–0.99)	0.57 (0.36–0.91)	0.29 (0.14–0.59)
Harris et al ^{15,18}	Case control	0.49 (0.26–0.94)	0.36 (0.18–0.72)	
Harris et al ²⁹	Cohort	0.64 (0.45–0.90)	0.49 (0.30–0.80)	
Harris et al ³²	Cohort	0.79 (0.66–1.04)	0.51 (0.28–0.96)	
	(Pooled data)	0.61 (0.51–0.78)	0.45 (0.34–0.61)	
Colon cancer				
Harris et al ¹⁷	Case control	0.33 (0.20–0.56)	0.28 (0.15–0.54)	0.30 (0.16–0.55)
Prostate cancer				
Nelson and Harris ³⁰	Case control	0.55 (0.31–0.85)	0.25 (0.10–0.49)	0.45 (0.26–0.99)
Harris ¹⁹	Case control	0.52 (0.29–0.93)	0.62 (0.27–1.42)	
	(Pooled data)	0.54 (0.40–0.75)	0.49 (0.35–0.82)	
Lung cancer				
Harris et al ³¹	Case control	0.68 (0.35–0.88)	0.58 (0.40–0.80)	0.40 (0.19–0.81)
Harris et al ¹⁶	Case control	0.53 (0.34–0.82)	0.40 (0.23–0.73)	
	(Pooled data)	0.57 (0.45–0.70)	0.38 (0.27–0.62)	
All cancer sites	(Pooled data)	0.51 (0.43–0.60)	0.41 (0.33–0.54)	0.36 (0.28–0.50)

Notes: Estimates are for 325 mg aspirin or 200 mg ibuprofen taken at least two times per week for at least 5 years. The median daily dosages of coxib were 200 mg for celecoxib and 25 mg for rofecoxib.

Abbreviation: COX-2, cyclooxygenase-2.

in de novo formation of blood vessels (angiogenesis); (4) increasing production of metalloproteinases via coexpression of COX-2 and Her-2/Neu, thus enhancing invasive potential (metastasis); (5) decreasing bioavailable arachidonic acid pools necessary for conversion of sphingomyelin to ceramide, and stimulation of Bcl-2 and PPAR γ by PGE-2, thereby reducing cell differentiation and apoptosis (anti-apoptosis); and (6) inhibiting proliferation of B and T lymphocytes, particularly natural killer T cells, thus limiting antineoplastic activity (immunosuppression). Notably, it has recently been discovered that COX-2 overexpression is correlated with heightened intracellular telomerase, an important reverse transcriptase enzyme associated with increased cell proliferation, diminished apoptosis and cellular immortality.^{37,38}

A key event in the carcinogenic process is the induction of constitutive expression of COX-2. It is indeed striking that many important risk factors linked to cancer causation have been found capable of inducing COX-2. These include nicotine and its metabolites, nitrosamines, heterocyclic amines, polycyclic aromatic hydrocarbons, and many other inflammatory elements of tobacco smoke; certain essential dietary fatty acids, such as unconjugated linoleic acid; ultraviolet B; free radicals; oncogenic proteins; growth factors; infectious agents such as helicobacter pylori, human papilloma viruses, hepatitis viruses, and the Epstein–Barr virus; hypoxia; hormones; neurotransmitters; shear stress; and endotoxins.^{39–58}

Induction of constitutive COX-2 expression may also involve other microenvironmental stimuli such as bacterial lipopolysaccharides, tumor necrosis factor, and byproducts of protein synthesis and degradation. Since the *COX-2* gene contains multiple promoter binding sites, nuclear transcription factors such as NF κ B and NF-IL6 and signal transduction by cyclic adenosine monophosphate response elements may also be important mediators of its induction and up-regulation.

Genetic induction and upregulation of COX-2 in breast cancer cells has been shown to induce local constitutive estrogen biosynthesis by activation of the promoter II region of the aromatase gene (*CYP-19*) in contiguous fat and muscle cells.⁵⁹ Terry et al observed a significant reduction in the risk of estrogen receptor positive breast cancer with daily intake of aspirin (OR = 0.72, 95% CI: 0.58–0.90), but there was no effect for estrogen receptor negative tumors.⁶⁰ These findings demonstrate an important link between COX-2 overexpression and the promotion of mammary carcinogenesis by estrogen. Thus, COX-2 carcinogenesis appears to involve synergistic interactions between a number of microenvironmental and genetic cofactors.

Recent studies of cancer patients have demonstrated that regular intake of aspirin or other nonselective coxibs have significant therapeutic impact. In a follow-up study of 4164 breast cancer patients, regular intake of aspirin reduced the risk of death from breast cancer by more than 70%; in a study of 1279 colon cancer patients, regular intake of aspirin initiated after diagnosis was associated with a 46% reduction in the risk of death from colon cancer.^{61,62}

The *sine qua non*s of an effective chemopreventive agent are efficacy in prevention of disease, safety to the population, low cost, and acceptability to the general public. The epidemiologic data on aspirin and aspirin-like agents suggest that regular intake at a low dosage (one standard 200 mg ibuprofen tablet or one standard 325 mg aspirin tablet, taken two or more times per week) significantly reduces cancer risk. It is important to note that these dosages are well below the therapeutic window for the standard treatment of inflammatory conditions, and while there is a small risk of gastrointestinal and other side effects associated with NSAID use, the vast majority of individuals who take them, even at therapeutic doses, do not appear to suffer serious side effects or complications. Since adverse effects of NSAIDs are dose-dependent, recommendations for chemoprevention should be based upon the lowest possible (subtherapeutic) doses with preventive efficacy, that is, no more than one standard tablet a few times per week.

In view of the available evidence, continued exploration of both nonselective and selective coxibs should be considered a top cancer research priority. Selective and nonselective coxibs are already dispensed on a regular basis to a large population of patients, for the treatment of inflammatory conditions. Comparative studies should therefore be designed to determine the appropriate dose, duration, adverse effects (particularly *vis a vis* the gastrointestinal, renal, and cardiovascular systems), and costeffectiveness of individual compounds. As was initially pointed out more than a decade ago, “there is an urgent need for human clinical trials of these compounds in order to expedite their efficacious application in the chemoprevention and therapy of cancer.”⁶

Conclusion

In summary, in a series of epidemiologic studies, we found chemopreventive effects of aspirin, ibuprofen, and selective coxibs against cancers of the breast, colon, prostate, and lung. The main findings were:

1. Regular intake of aspirin (325 mg) produced risk reductions of 39% for breast cancer, 67% for colon cancer, 46% for prostate cancer, and 43% for lung cancer.

2. Regular intake of ibuprofen (200 mg) produced risk reductions of 72% for breast cancer, 51% for colon cancer, 62% for prostate cancer, and 59% for lung cancer.
3. Regular intake of coxibs (200 mg celecoxib or 25 mg rofecoxib) produced risk reductions of 71% for breast cancer, 70% for colon cancer, 55% for prostate cancer, and 64% for lung cancer.
4. Risk reductions became apparent after 5 or more years of NSAID use or 2 or more years of coxib use and appeared to increase with longer duration.

These observed chemopreventive effects are consistent with relative levels of COX-2 inhibition achieved with standard dosages of aspirin, ibuprofen, and celecoxib. Overexpression of COX-2 and dysregulation of prostaglandin biosynthesis correlates with carcinogenesis and metastasis of cancers of the breast, colon, prostate, and lung. Our results indicate that regular intake of nonselective or selective COX-2 inhibiting agents protects against the development of these major forms of cancer.

Disclosure

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