Modulation of Breast Cancer Risk by Nonsteroidal Anti-inflammatory Drugs

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Nonsteroidal anti-inflammatory drugs (NSAIDs) clearly reduce the risk of human colorectal neoplasia in epidemiological and prospective randomized clinical studies of aspirin and nonaspirin NSAIDs, including selective cyclooxygenase-2 (COX-2) inhibitors, or coxibs (1–3). In contrast, the epidemiological and clinical data on NSAIDs in reducing breast cancer risk are not consistent. This inconsistency is likely attributable to contrasting expression patterns of COX-2, a key target of NSAIDs, in breast and colon neoplasia (4,5), and to differing activities of individual NSAIDs (which have varying selectivity for COX-2 vs COX-1), including a potentially selective impact of certain NSAIDs on hormone receptor–positive breast tumors.

In this issue of the Journal, Takkouche et al. (6) report an extensive meta-analysis (involving 38 studies) supporting an inverse association between NSAID use and risk of breast cancer. They found a statistically significant reduction in breast cancer risk associated with use of any NSAID (relative risk [RR] = 0.88, 95% confidence interval [CI] = 0.84 to 0.93) and similar associations for aspirin (RR = 0.87, 95% CI = 0.82 to 0.92) and ibuprofen (RR = 0.79, 95% CI = 0.64 to 0.97). They found no evidence of a dose–response relationship, and some studies indicated that coxibs were also associated with a lower risk of breast cancer (7,8).

This large-scale meta-analysis is consistent with several smaller meta-analyses (9–12). Furthermore, NSAIDs can prevent experimental breast cancer in numerous rodent models (4,5). Why then do individual observational and clinical studies vary substantially in their findings on NSAID use and breast cancer risk? The answer lies in an appreciation of the likely mechanisms of NSAID-mediated breast cancer suppression.

COX enzymes, the primary molecular targets of NSAIDs, synthesize prostaglandins (PGs) from arachidonic acid (13,14). *COX-1* is normally expressed constitutively, whereas *COX-2* is an early-response gene whose expression is increased in response to growth factors, oncogenes, and cytokines and is a key component of the inflammatory response (5,14,15). Transgenic overexpression of *COX-2* induces mammary tumor formation in mice (16); activation of COX/PG signaling has multiple procarcinogenic consequences, including regulation of proliferation, apoptosis, angiogenesis, invasion, and immune responsiveness (5,14). Patterns of COX-2 overexpression differ substantially between breast and colorectal neoplasia.

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The frequency of overexpression is approximately 40% in invasive breast cancer vs approximately 80% in colorectal cancer (4,17) and approximately 80% in breast precancers vs approximately 50% in colorectal adenomas (4,5,18). The magnitude of COX-2 overexpression also is much higher in colorectal than breast cancer. In breast cancer, COX-2 overexpression is associated with overexpression of human epidermal growth factor receptor 2 (HER2) (17,19–21), also called c-erbB2 and neu, which (like COX-2) is expressed at a higher frequency in ductal carcinoma in situ than in invasive breast cancer. HER2 signaling can induce *COX-2* transcription in vitro (22). Therefore, it is conceivable that coxibs may selectively target breast tumors that overexpress HER2 (and thus COX-2). HER2 overexpression is associated with hormone receptor–negative breast cancer, which can be prevented in mouse models by targeting HER2 (23,24). Coxibs can inhibit the development of hormone receptor–positive and –negative breast cancer in rodent models (4,5); either pharmacologic inhibition (coxib mediated) or genetic ablation of COX-2 can suppress HER2-driven, hormone receptor–negative mammary tumorigenesis in transgenic mouse strains (25,26). Perhaps surprisingly in light of the COX-2/HER2 relationship, to our knowledge no epidemiological studies to date have stratified NSAID responsiveness according to HER2 expression status. However, a selective effect of NSAIDs on HER2-overexpressing cancers (due to the coupled expression of HER2 and COX-2) may be obscured by procarcinogenic contributions of constitutive COX-1.

COX-1–derived PGs can contribute to tumorigenesis, as demonstrated most clearly by decreased rodent skin and intestinal neoplasia after genetic deletion of *COX-1* (27–29). Therefore, the sum of COX-1 and COX-2 activity may be a key determinant in breast carcinogenesis. Consistent with this notion, tissue levels of the protumorigenic eicosanoid PGE_2 are only halved by knocking out *COX-2* in HER2-overexpressing mouse mammary glands, with a parallel 50% decrease in mammary tumor multiplicity (25). In aggregate, these preclinical data suggest that inhibiting COX-1 could be important for the anticancer activity of NSAIDs in the setting of human breast cancer, in which COX-2 overexpression is not particularly prevalent (4,17). Furthermore, all NSAIDs are not equal in relative potency toward COX-1 and COX-2, ranging from greater than 150-fold selectivity of aspirin for COX-1 (vs COX-2) to greater than 100-fold selectivity of coxibs (such as celecoxib) for COX-2 (vs COX-1). Between these extremes are ibuprofen and naproxen, which are relatively nonselective. Perhaps the association between NSAID use and breast cancer risk could be clarified by evaluating individual NSAIDs or NSAID classes in the subset of breast cancers that are most likely to be sensitive to each one. This paradigm is well illustrated by the available datasets concerning aspirin.

Data on the association between aspirin use and breast cancer risk are mixed—an inverse association in some studies (7,8,30–39) but no apparent benefit in others, including several large cohort studies and one randomized clinical trial (40–48). However, subset analysis with stratification according to hormone receptor status revealed a selective inverse association of aspirin use with risk of hormone receptor–positive breast cancer in some but not all studies (35,43–46,49,50). The apparent relationship between hormone receptor expression and aspirin sensitivity may reflect the link between COX/PG signaling and estrogen biosynthesis (51). COX-derived PGs can activate a signaling cascade leading to increased transcription of the *CYP19* gene that encodes the estrogen synthetase aromatase, and thus to increased estrogen biosynthesis (52–55). (Estradiol can then increase PG levels in a positive feedback loop.) This PG-dependent pathway is thought to contribute predominantly to regulation of peripheral, rather than ovarian, estrogen synthesis and thus assumes greater importance in the postmenopausal setting. Elucidation of this molecular pathway provides a potential mechanistic explanation for the selective suppression of hormone receptor–positive breast tumors by aspirin and other NSAIDs (35,43,44,49) and may help to explain why the receptor-positive–NSAID sensitivity relationship has been identified only in certain studies. An aspirin-mediated reduction in peripheral estrogen synthesis is likely to be more evident in postmenopausal than premenopausal women, in whom ovarian estrogen production far outweighs peripheral production. Furthermore, a model of NSAID suppression of estrogen synthesis and breast tumorigenesis suggests that hormone replacement therapy (HRT) could abrogate any protective effects of aspirin or other NSAIDs.

COX-independent effects also may contribute to potentially protective NSAID effects (56), particularly apoptosis. These effects may be mediated in part through 15-lipoxygenase-1 (15-LOX-1), decreased expression of which in human breast cancer is associated with a poor prognosis (57). NSAIDs can restore 15-LOX-1 expression, leading to apoptosis in other systems (58).

The findings of Takkouche et al. (6) support targeting the COX/PG signaling axis to prevent breast cancer. The cardiovascular side effects associated with coxibs (well described elsewhere) and potentially other NSAIDs necessitate refocusing COX-directed cancer prevention strategies to avoid this danger (3,4). Current directions include agents that target other components of the COX/PG signaling pathway and combination approaches that should allow increased efficacy and diminished toxicity with lower doses of the individual agents (59). For example, low-dose celecoxib plus the rexinoid bexarotene has synergistic preventive efficacy in an animal model of breast cancer (60).

Moving forward, analyses of associations between NSAID use and breast cancer risk will likely gain clarity from stratification based on the biology of NSAID action. Responsiveness to an individual NSAID may be predicated on hormone receptor expression, menopausal status and HRT use, or HER2 status (a routinely examined clinical marker that may be a surrogate for COX-2 overexpression in the breast). Risk modeling, eg, for hormone receptor–positive or –negative cancer, is also likely to be important to future NSAID chemoprevention of breast cancer (61). Adding to the complexity, genetic polymorphisms in *COX-2* (and likely other components of the pathway) are also associated with breast cancer risk, potentially through modulation of NSAID responsiveness (62–64). Elucidating the contribution of such variant alleles will advance us toward personalized use of NSAIDs for reducing breast cancer risk.

References

1. Dube C, Rostom A, Lewin G, 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(5):365–375.

2. Rostom A, Dube C, Lewin G, 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(5):376–389.
3. Lippman SM. The future of molecular-targeted cancer chemoprevention. *Gastroenterology*. In press.
4. Howe LR. Inflammation and breast cancer. Cyclooxygenase/prostaglandin signaling and breast cancer. *Breast Cancer Res.* 2007;9(4):210.
5. Howe LR, Subbaramaiah K, Brown AMC, Dannenberg AJ. Cyclooxygenase-2: a target for the prevention and treatment of breast cancer. *Endocr Relat Cancer*. 2001;8(2):97–114.
6. Takkouche B, Regueira-Méndez C, Etminan M. Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *J Natl Cancer Inst*. 2008;100(20):1439–1447.
7. Rahme E, Ghosn J, Dasgupta K, Rajan R, Hudson M. Association between frequent use of nonsteroidal anti-inflammatory drugs and breast cancer. *BMC Cancer*. 2005;5:159.
8. Harris RE, Beebe-Donk J, Alshafie GA. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. *BMC Cancer*. 2006;6:27.
9. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. *Cancer Causes Control*. 2006;17(7):871–888.
10. Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. *BMC Cancer*. 2003;3(1):28.
11. Khuder SA, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. *Br J Cancer*. 2001;84(9):1188–1192.
12. Mangiapane S, Blettner M, Schlattmann P. Aspirin use and breast cancer risk: a meta-analysis and meta-regression of observational studies from 2001 to 2005. *Pharmacoepidemiol Drug Saf*. 2008;17(2):115–124.
13. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol*. 1971;231(25):232–235.
14. Wang D, Dubois RN. Prostaglandins and cancer. *Gut*. 2006;55(1):115–122.
15. Herschman HR. Prostaglandin synthase 2. *Biochim Biophys Acta*. 1996;1299(1):125–140.
16. Liu CH, Chang SH, Narko K, et al. Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. *J Biol Chem*. 2001;276(21):18563–18569.
17. Ristimaki A, Sivula A, Lundin J, et al. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. *Cancer Res.* 2002;62(3):632–635.
18. Perrone G, Zagami M, Santini D, et al. COX-2 expression in lobular in situ neoplasia of the breast: correlation with histopathological grading system according to the Tavassoli classification. *Histopathology*. 2007;51(1):33–39.
19. Boland GP, Butt IS, Prasad R, Knox WF, Bundred NJ. COX-2 expression is associated with an aggressive phenotype in ductal carcinoma in situ. *Br J Cancer*. 2004;90(2):423–429.
20. Subbaramaiah K, Norton L, Gerald W, Dannenberg AJ. Cyclooxygenase-2 is overexpressed in HER-2/neu-positive breast cancer. Evidence for involvement of AP-1 and PEA3. *J Biol Chem*. 2002;277(21):18649–18657.
21. Wulfing P, Diallo R, Muller C, et al. Analysis of cyclooxygenase-2 expression in human breast cancer: high throughput tissue microarray analysis. *J Cancer Res Clin Oncol*. 2003;129(7):375–382.
22. Vadlamudi R, Mandal M, Adam L, Steinbach G, Mendelsohn J, Kumar R. Regulation of cyclooxygenase-2 pathway by HER2 receptor. *Oncogene*. 1999;18(2):305–314.
23. Piechocki MP, Dibbley SK, Lonardo F, Yoo GH. Gefitinib prevents cancer progression in mice expressing the activated rat HER2/neu. *Int J Cancer*. 2008;122(8):1722–1729.
24. Strecker T, Zhang Y, Hill J, et al. The dual tyrosine kinase inhibitor, lapatinib, prevents estrogen receptor-negative breast cancer in mice by suppressing the development of pre-malignant lesions. *J Natl Cancer Inst*. In press.
25. Howe LR, Chang SH, Tolle KC, et al. HER2/neu-induced mammary tumorigenesis and angiogenesis are reduced in cyclooxygenase-2 knockout mice. *Cancer Res.* 2005;65(21):10113–10119.
26. Howe LR, Subbaramaiah K, Patel J, et al. Celecoxib, a selective cyclooxygenase-2 inhibitor, protects against human epidermal growth factor receptor 2 (HER-2)/neu-induced breast cancer. *Cancer Res.* 2002;62(19):5405–5407.
27. Chulada PC, Thompson MB, Mahler JF, et al. Genetic disruption of Ptgs-1, as well as Ptgs-2, reduces intestinal tumorigenesis in Min mice. *Cancer Res.* 2000;60(17):4705–4708.
28. Takeda H, Sonoshita M, Oshima H, et al. Cooperation of cyclooxygenase 1 and cyclooxygenase 2 in intestinal polyposis. *Cancer Res.* 2003;63(16):4872–4877.
29. Tiano HF, Loftin CD, Akunda J, et al. Deficiency of either cyclooxygenase (COX)-1 or COX-2 alters epidermal differentiation and reduces mouse skin tumorigenesis. *Cancer Res.* 2002;62(12):3395–3401.
30. Coogan PF, Rao SR, Rosenberg L, et al. The relationship of nonsteroidal anti-inflammatory drug use to the risk of breast cancer. *Prev Med.* 1999;29(2):72–76.
31. Cotterchio M, Kreiger N, Sloan M, Steingart A. Nonsteroidal anti-inflammatory drug use and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2001;10(11):1213–1217.
32. Garcia Rodriguez LA, Gonzalez-Perez A. Risk of breast cancer among users of aspirin and other anti-inflammatory drugs. *Br J Cancer*. 2004;91(3):525–529.
33. Harris RE, Namboodiri KK, Farrar WB. Nonsteroidal antiinflammatory drugs and breast cancer. *Epidemiology*. 1996;7(2):203–205.
34. Swede H, Mirand AL, Menezes RJ, Moysich KB. Association of regular aspirin use and breast cancer risk. *Oncology*. 2005;68(1):40–47.
35. Terry MB, Gammon MD, Zhang FF, et al. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. *JAMA*. 2004;291(20):2433–2440.
36. Friedman GD, Ury HK. Initial screening for carcinogenicity of commonly used drugs. *J Natl Cancer Inst*. 1980;65(4):723–733.
37. Harris RE, Kasbari S, Farrar WB. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. *Oncol Rep*. 1999;6(1):71–73.
38. Johnson TW, Anderson KE, Lazovich D, Folsom AR. Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2002;11(12):1586–1591.
39. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology*. 1994;5(2):138–146.
40. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294(1):47–55.
41. Egan KM, Stampfer MJ, Giovannucci E, Rosner BA, Colditz GA. Prospective study of regular aspirin use and the risk of breast cancer. *J Natl Cancer Inst*. 1996;88(14):988–993.
42. Friis S, Thomassen L, Sorensen HT, et al. Nonsteroidal anti-inflammatory drug use and breast cancer risk: a Danish cohort study. *Eur J Cancer Prev*. 2008;17(2):88–96.
43. Gierach GL, Lacey JV Jr, Schatzkin A, et al. Nonsteroidal anti-inflammatory drugs and breast cancer risk in the National Institutes of Health-AARP Diet and Health Study. *Breast Cancer Res*. 2008;10(2):R38.
44. Gill JK, Maskarinec G, Wilkens LR, Pike MC, Henderson BE, Kolonel LN. Nonsteroidal antiinflammatory drugs and breast cancer risk: the multiethnic cohort. *Am J Epidemiol*. 2007;166(10):1150–1158.
45. Jacobs EJ, Thun MJ, Connell CJ, et al. Aspirin and other nonsteroidal anti-inflammatory drugs and breast cancer incidence in a large U.S. cohort. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):261–264.
46. Marshall SF, Bernstein L, Anton-Culver H, et al. Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status. *J Natl Cancer Inst*. 2005;97(11):805–812.
47. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. *Br Med J*. 1989;299(6710):1247–1250.
48. Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med*. 1991;325(23):1593–1596.
49. Kirsh VA, Kreiger N, Cotterchio M, Sloan M, Theis B. Nonsteroidal antiinflammatory drug use and breast cancer risk: subgroup findings. *Am J Epidemiol*. 2007;166(6):709–716.

50. Zhang SM, Cook NR, Manson JE, Lee IM, Buring JE. Low-dose aspirin and breast cancer risk: results by tumour characteristics from a randomised trial. *Br J Cancer.* 2008;98(5):989–991.
51. DuBois RN. Aspirin and breast cancer prevention: the estrogen connection. *JAMA.* 2004;291(20):2488–2489.
52. Agarwal VR, Bulun SE, Leitch M, Rohrich R, Simpson ER. Use of alternative promoters to express the aromatase cytochrome P450 (CYP19) gene in breast adipose tissues of cancer-free and breast cancer patients. *J Clin Endocrinol Metab.* 1996;81(11):3843–3849.
53. Chen S, Zhou D, Okubo T, Kao YC, Yang C. Breast tumor aromatase: functional role and transcriptional regulation. *Endocr Relat Cancer.* 1999; 6(2):149–156.
54. Subbaramaiah K, Howe LR, Port ER, et al. HER-2/neu status is a determinant of mammary aromatase activity in vivo: evidence for a cyclooxygenase-2-dependent mechanism. *Cancer Res.* 2006;66(10): 5504–5511.
55. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE_2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. *Endocrinology.* 1996;137(12):5739–5742.
56. Grosch S, Maier TJ, Schiffmann S, Geisslinger G. Cyclooxygenase-2 (COX-2)-independent anticarcinogenic effects of selective COX-2 inhibitors. *J Natl Cancer Inst.* 2006;98(11):736–747.
57. Jiang WG, Watkins G, Douglas-Jones A, Mansel RE. Reduction of isoforms of 15-lipoxygenase (15-LOX)-1 and 15-LOX-2 in human breast cancer. *Prostaglandins Leukot Essent Fatty Acids.* 2006;74(4): 235–245.
58. Shureiqi I, Chen D, Lee JJ, et al. 15-LOX-1: a novel molecular target of nonsteroidal anti-inflammatory drug-induced apoptosis in colorectal cancer cells. *J Natl Cancer Inst.* 2000;92(14):1136–1142.
59. Dannenberg AJ, Lippman SM, Mann JR, Subbaramaiah K, DuBois RN. Cyclooxygenase-2 and epidermal growth factor receptor: pharmacologic targets for chemoprevention. *J Clin Oncol.* 2005;23(2):254–266.
60. Brown PH, Subbaramaiah K, Salmon AP, et al. Combination chemoprevention of HER2/neu-induced breast cancer using a COX-2 inhibitor and an RXR-selective retinoid. *Cancer Prev Res.* 2008;1(3):208–214.
61. Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst.* 2007;99(22):1695–1705.
62. Cox DG, Buring J, Hankinson SE, Hunter DJ. A polymorphism in the 3' untranslated region of the gene encoding prostaglandin endoperoxide synthase 2 is not associated with an increase in breast cancer risk: a nested case-control study. *Breast Cancer Res..* 2007;9(1):R3.
63. Langsenlehner U, Yazdani-Biuki B, Eder T, et al. The cyclooxygenase-2 (PTGS2) 8473T>C polymorphism is associated with breast cancer risk. *Clin Cancer Res.* 2006;12(4):1392–1394.
64. Shen J, Gammon MD, Terry MB, Teitelbaum SL, Neugut AI, Santella RM. Genetic polymorphisms in the cyclooxygenase-2 gene, use of nonsteroidal anti-inflammatory drugs, and breast cancer risk. *Breast Cancer Res.* 2006;8(6):R71.

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