Cancer Prevention Research

Commentary

See related article by Kim et al., p. 511 and Cancer Prev Res 6(5):428–36

Urinary PGE-M: A Promising Cancer Biomarker

Dingzhi Wang[1] and Raymond N. DuBois[1,2]

Abstract

Cancer prevention, early diagnosis, and targeted therapies are the keys to success in better cancer control and treatment. A big challenge remains to identify biomarkers for predicting who may have higher cancer risk and are able to respond to certain chemopreventive agents as well as for assessing a patient's response during treatment. Although a large body of evidence indicates that chronic inflammation is a risk factor for cancer, it is unclear whether inflammatory biomarkers can be used to predict cancer risk, progression, and death. Considering the importance of the proinflammatory COX-2–derived prostaglandin E_2 (PGE_2) in inflammation and cancer, Morris and colleagues found that urinary PGE-M is positively associated with obesity, smoking, and lung metastases in patients with breast cancer (4). Along the same lines, Kim and colleagues showed a potential association between urinary PGE-M and breast cancer risk in postmenopausal women (beginning on page 511). In agreement with previous reports, their findings indicate that urinary PGE-M may serve as a promising biomarker for prognosticating cancer risk and disease progression. *Cancer Prev Res; 6(6); 507–10. ©2013 AACR.*

It is widely accepted that chronic inflammation caused by infectious or immune diseases is associated with increased cancer risk for a number of malignancies, including esophageal, gastric, hepatic, pancreatic and colorectal cancer. For example, it has long been known that patients with persistent hepatitis B, *Helicobacter pylori* infections, or immune disorders such as inflammatory bowel disease have a higher risk for the development of liver or gastrointestinal tract cancer. The emerging evidence shows that obesity is also associated with increased risk of many cancers. For example, recent cohort studies indicate that obesity is also a risk factor for multiple types of cancers, including breast cancer, and is associated with a poor prognosis of breast and colon cancer (1–3). Several mechanisms have been proposed to explain the association of obesity with cancer risk. Obesity-associated inflammation is postulated to be one of most important factors connecting obesity to cancer. In addition, several specific obesity-associated factors correlate with an increased risk of organ-specific cancers. For example, obesity-induced esophageal reflux, hypertension, insulin resistance, and hormone alternations could contribute to an increased risk in esophageal, kidney, colorectal, pancreatic, breast, and endometrial cancers. In the previous issue of the journal, Morris and colleagues reported for the first time that urinary PGE-M, a biomarker of inflammation, is associated with obesity and lung metastases in breast cancer patients, suggesting that obesity-associated inflammation may contribute to the spread of breast cancer cells to the lung (4). Moreover, in this issue of the journal, Kim and colleagues present the first evidence showing that urinary PGE-M is potentially associated with postmenopausal breast cancer risk (5).

Urinary PGE-M, a major urinary metabolite of PGE_2, can be used as an index of systemic PGE_2 production (6, 7). PGE_2 is one of 5 structurally related prostanoids generated from arachidonic acid by prostaglandin G/H synthases (also referred to as COX enzymes). COX enzymes exist in 2 isoforms: COX-1 (PGHS-1) and COX-2 (PGHS-2). In general, COX-1 is thought to be a housekeeping enzyme responsible for maintaining basal prostanoid levels that are important for tissue homeostasis and platelet function. In contrast, COX-2 is an immediate-early response gene that is normally absent from most cells but is highly induced at sites of inflammation and during tumor progression (8). Our group was first to establish a correlation between a proinflammatory gene *COX-2* and colorectal cancer (9). Subsequent studies reveal that COX-2 expression is elevated in up to 90% of colorectal carcinomas and 50% of adenomas (10), and its expression is associated with a lower survival rate among patients with colorectal cancer (11). In addition to colorectal cancer, COX-2 overexpression is also an indicator of poor prognosis in multiple cancer types, including breast, gastric, and head and neck squamous cell carcinomas (12, 13). The biologic functions of COX-2 depend on which COX-2–derived prostanoids are produced in cancers.

PGE_2 is the most abundant prostaglandin found in various types of human malignancies including colorectal, lung, breast, head and neck cancer and is often associated with a poor prognosis (14–17). Significant progress has

Authors' Affiliations: [1]Center for Inflammation and Cancer, Biodesign Institute of Arizona State University, and [2]Department of Chemistry and Biology, Arizona State University, Tempe, Arizona

Corresponding Author: Raymond N. DuBois, Center of Inflammation and Cancer, Biodesign Institute of Arizona State University, 727 E. Tyler Street, Tempe, AZ 85287. Phone: 480-965-1228; Fax: 480-727-9550; E-mail: duboisrn@asu.edu

doi: 10.1158/1940-6207.CAPR-13-0153

been made in elucidating the mechanisms underlying PGE_2 acceleration of tumor progression in *in vitro* and animal studies. PGE_2 has been shown to promote tumor formation, growth, and metastasis through (i) directly inducing tumor epithelial cell proliferation, survival, and migration/invasion and (ii) switching the tumor microenvironment from "normal" to one supporting tumor growth and metastatic spread by inhibiting immunosurveillance and inducing angiogenesis (18). Recent evidence uncovered a previously unrecognized role of PGE_2 in promoting intestinal tumor growth by silencing certain tumor suppressor and DNA repair genes via DNA methylation (19). These findings show that COX-2–derived PGE_2 plays a key role in cancer formation and progression. However, PGE_2 is an unstable compound that is rapidly metabolized *in vivo* to a stable PGE-M by the enzyme 15-hydroxy prostaglandin dehydrogenase, and therefore, the direct quantitation of PGE_2 levels is an unreliable indicator in humans. Thus, measurement of excreted urinary PGE-M is the best way to quantify systemic PGE_2 production *in vivo*.

A great effort has been made to evaluate whether levels of urinary PGE-M are associated with cancer risk and disease progression. Indeed, a nested case–control study within a large population-based prospective cohort study revealed that increasing quartiles of urinary PGE-M levels were associated with the relative risks of developing colorectal (20) and gastric cancer (21). Interestingly, urinary PGE-M levels among patients with Crohn disease, colorectal cancer, or large adenomas (more than 1 cm in size) were significantly elevated compared with patients who had either small adenomas (less than 1 cm in size), or no adenomas (22). A recent case–control study further confirmed that the levels of urinary PGE-M were associated with increased risk for multiple or advanced adenoma but not single small adenoma (23). A phase II biomarker study showed that urinary PGE-M levels were positively associated with disease progression and death in head and neck squamous cell carcinomas (24). The work reported by Kim and colleagues provides case-cohort data showing that increasing quartiles of urinary PGE-M levels are potentially associated with the risk of developing breast cancer among postmenopausal women who did not regularly use nonsteroidal anti-inflammatory drugs (NSAID; ref. 5). Along the same lines, Morris and colleagues showed that urinary PGE-M levels were significantly elevated in breast cancer patients with lung metastases and/or liver metastases compared with patients with only primary tumors in a cross-sectional study (4). Both studies reported by Kim and colleagues and Morris and colleagues indicate that urinary PGE-M is positively associated with the risk of developing breast cancer and metastasis. On the basis of previously published results mentioned above and the findings reported in this issue of the journal, urinary PGE-M might serve as a promising biomarker for predicting cancer risk and prognosis, including breast cancer.

In addition to genetic mutations and epigenetic changes, a large body of evidence indicates that chronic inflammation, diet, aging, and lifestyle are risk factors for development of many cancers. For example, high dietary fat intake is not only associated with obesity, diabetes, and heart disease but also cancers, especially with colorectal, liver, breast, pancreatic, and prostate cancer (25). As mentioned earlier, arachidonic acid, a major ingredient in animal fats, is the substrate of COX enzymes. As expected, urinary PGE-M is correlated with dietary fat intake in adult health men (26). In addition, urinary levels of PGE-M were significantly higher in healthy ever smokers compared with never smokers (27–29). Kim and colleagues further reveal that urinary PGE-M levels are positively associated with high saturated fat intake, obesity, current smoking, and poor self-reported health status in postmenopausal women (5). Moreover, Morris and colleagues showed for the first time that elevated urinary PGE-M levels were positively associated with obesity, aging, and pack-year smoking history in patients with breast cancer. In particular, they found that ever smokers with lung metastases had the highest urinary PGE-M levels in patients with breast cancer who were not users of NSAIDs (4). Collectively, these results indicate that these risk factors may contribute to elevation of COX-2 expression and/or PGE_2 production in the human body. Further studies with larger populations are necessary to determine whether urinary PGE-M can be used as a promising indicator for these risk factors.

COX-2–derived PGE_2 has been shown to play an important role in cancer (18). Currently, the best agents for targeting the COX-2 enzyme are NSAIDs, including nonselective NSAIDs and selective COX-2 inhibitors (COXIB). NSAIDs have been reported to have beneficial effects on reducing the risk of developing some solid tumors including the 4 most prevalent cancers worldwide: colorectal, breast, lung, and prostate cancer (30). Unlike COXIBs and other nonselective NSAIDs, long-term daily aspirin use is beneficial for prevention of both cancer and cardiovascular disease. A recent systematic review for case–control and cohort studies indicates that regular use of aspirin is associated with a reduced risk of many cancers with distant metastasis, including colorectal, esophageal, gastric, breast, and lung cancers (31). A recent analysis of 51 randomized trials of aspirin for prevention of vascular disease also revealed that daily use of aspirin reduced the incidence and mortality of not only colorectal cancer but also for other cancers as well (32). Moreover, an analysis of 5 large randomized trials revealed that daily aspirin use reduced the spread of primary tumor cells to other organs of the body after the diagnosis of localized diseases in many cancers, particularly in colorectal cancer (33). Epidemiologic studies showed that regular use of aspirin specifically reduced risk for development of cancer in the subgroup of patients whose colon tumors expressed COX-2 at higher levels (34) and its use after the diagnosis of colorectal cancer at stage I, II and III prolonged overall survival, especially among individuals whose tumors overexpress COX-2 (35). These results suggest that the preventive and inhibitory effects of aspirin on colorectal cancer depend on COX-2. Taken together, these results indicate that aspirin and/or

other nonselective NSAIDs exert their antitumor effects by primarily targeting COX-2.

On the basis of the study reported in this issue of the journal (5) and previously published results (4, 28), levels of urinary PGE-M in healthy humans or patients are suppressed significantly not only by the nonselective COX inhibitors, including aspirin, but also by the COX-2–selective inhibitors, suggesting that the majority of PGE_2 formed *in vivo* is derived from COX-2. Given that the antitumor effects of NSAIDs depend on reduction of PGE_2 production via targeting COX-2, urinary PGE-M may serve a valuable intermediate marker for the pharmacologic activity of NSAIDs in cancer prevention and adjuvant treatment. Indeed, a single-institution phase II study revealed that patients with non–small cell lung cancer (NSCLC) with complete and partial responses to adjuvant therapy with paclitaxel, carboplatin, and celecoxib had a significant decrease in the level of urinary PGE-M (36). In another phase II trial of combined treatment with celecoxib and docetaxel, patients with recurrent NSCLC with the greatest proportional decline in urinary PGE-M levels experienced a longer survival compared with those with no change or an increase in PGE-M (37). These findings indicate that urinary PGE-M is a potential biomarker for predicting efficacy of COX-2 inhibitors in adjuvant therapies. Because cytotoxic chemotherapy and radiation therapy enhance COX-2 protein expression as well as PGE_2 synthesis in human cancer cells, elevated PGE_2 production may increase resistance to therapy by giving cells a survival advantage. As expected, Morris and colleagues also showed that patients with breast cancer who had received cytotoxic chemotherapy have significantly higher levels of urinary PGE-M compared with patients without chemotherapy (4). It will be important to determine whether patients treated with combinations of chemotherapy and/or radiation therapy with NSAIDs respond better than those not treated with NSAIDs.

In conclusion, these novel findings reported in this and the previous issue of the journal support the hypothesis that urinary PGE-M may be used as not only a promising biomarker for determining breast cancer risk and disease progression but also an indicator for cancer-related risk factors such as saturated fat intake, obesity, smoking, and aging. Moreover, if this can be carefully validated, urinary PGE-M may also serve as a potential biomarker for predicting efficacy of COX-2 inhibitors in adjuvant therapies. Additional studies with larger patient populations are needed to evaluate urinary PGE-M as a cancer biomarker and/or an indicator of risk factors. Clearly, identifying new biomarkers will lead to novel strategies for cancer prevention, early diagnosis, and targeted therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: D. Wang, R.N. DuBois
Writing, review, and/or revision of the manuscript: D. Wang, R.N. DuBois
Study supervision: R.N. DuBois

Acknowledgments

The authors also thank the National Colorectal Cancer Research Alliance (NCCRA) for its generous support (RND)

Grant Support

The work is supported in part by funding from the NIH MERIT award R37 DK47297, RO1 DK 62112, and NCI P01 CA77839.

Received April 25, 2013; accepted April 25, 2013; published OnlineFirst May 1, 2013.

References

1. Majed B, Moreau T, Senouci K, Salmon RJ, Fourquet A, Asselain B. Is obesity an independent prognosis factor in woman breast cancer? Breast Cancer Res Treat 2008;111:329–42.
2. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 2011;11:886–95.
3. Sinicrope FA, Foster NR, Sargent DJ, O'Connell MJ, Rankin C. Obesity is an independent prognostic variable in colon cancer survivors. Clin Cancer Res 2010;16:1884–93.
4. Morris PG, Zhou X, Milne GL, Goldstein D, Hawks L, Dang CT, et al. Increased levels of urinary PGE-M, a biomarker of inflammation, occur in association with obesity, aging and lung metastases in patients with breast cancer. Cancer Prev Res 2013;6:428–36.
5. Kim S, Taylor JA, Milne GL, Sandler DP. Association between urinary prostaglandin E2 metabolite and breast cancer risk: a prospective, case-cohort study of postmenopausal women. Cancer Prev Res 2013;6:511–18.
6. Ferretti A, Flanagan VP, Roman JM. Quantitative analysis of 11 alpha-hydroxy-9,15-dioxo-2,3,4,5,20-pentanor-19-carboxyprostanoic acid, the major urinary metabolite of E prostaglandins in man. Anal Biochem 1983;128:351–8.
7. Seyberth HW, Sweetman BJ, Frolich JC, Oates JA. Quantifications of the major urinary metabolite of the E prostaglandins by mass spectrometry: evaluation of the method's application to clinical studies. Prostaglandins 1976;11:381–97.
8. Dubois RN, Abramson SB, Crofford L, Gupta RA, Simon LS, Van De Putte LB, et al. Cyclooxygenase in biology and disease. FASEB J 1998;12:1063–73.
9. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up–regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 1994;107:1183–8.
10. Newcomb PA, Baron J, Cotterchio M, Gallinger S, Grove J, Haile R, et al. Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev 2007;16:2331–43.
11. Ogino S, Kirkner GJ, Nosho K, Irahara N, Kure S, Shima K, et al. Cyclooxygenase-2 expression is an independent predictor of poor prognosis in colon cancer. Clin Cancer Res 2008;14:8221–7.
12. Koki A, Khan NK, Woerner BM, Dannenberg AJ, Olson L, Seibert K, et al. Cyclooxygenase-2 in human pathological disease. Adv Exp Med Biol 2002;507:177–84.
13. Gallo O, Masini E, Bianchi B, Bruschini L, Paglierani M, Franchi A. Prognostic significance of cyclooxygenase-2 pathway and angiogenesis in head and neck squamous cell carcinoma. Hum Pathol 2002;33:708–14.
14. Rigas B, Goldman IS, Levine L. Altered eicosanoid levels in human colon cancer. J Lab Clin Med 1993;122:518–23.
15. Wang D, Dubois RN. Cyclooxygenase-2: a potential target in breast cancer. Semin Oncol 2004;31:64–73.

16. McLemore TL, Hubbard WC, Litterst CL, Liu MC, Miller S, McMahon NA, et al. Profiles of prostaglandin biosynthesis in normal lung and tumor tissue from lung cancer patients. Cancer Res 1988;48: 3140–7.
17. Hambek M, Baghi M, Wagenblast J, Schmitt J, Baumann H, Knecht R. Inverse correlation between serum PGE2 and T classification in head and neck cancer. Head Neck 2007;29:244–8.
18. Wang D, DuBois RN. Eicosanoids and cancer. Nat Rev Cancer 2010; 10:181–93.
19. Xia D, Wang D, Kim SH, Katoh H, DuBois RN. Prostaglandin E2 promotes intestinal tumor growth via DNA methylation. Nat Med 2012;18:224–6.
20. Cai Q, Gao YT, Chow WH, Shu XO, Yang G, Ji BT, et al. Prospective study of urinary prostaglandin E2 metabolite and colorectal cancer risk. J Clin Oncol 2006;24:5010–6.
21. Dong LM, Shu XO, Gao YT, Milne G, Ji BT, Yang G, et al. Urinary prostaglandin E2 metabolite and gastric cancer risk in the Shanghai women's health study. Cancer Epidemiol Biomarkers Prev 2009;18: 3075–8.
22. Johnson JC, Schmidt CR, Shrubsole MJ, Billheimer DD, Joshi PR, Morrow JD, et al. Urine PGE-M: A metabolite of prostaglandin E2 as a potential biomarker of advanced colorectal neoplasia. Clin Gastroenterol Hepatol 2006;4:1358–65.
23. Shrubsole MJ, Cai Q, Wen W, Milne G, Smalley WE, Chen Z, et al. Urinary prostaglandin E2 metabolite and risk for colorectal adenoma. Cancer Prev Res 2012;5:336–42.
24. Kekatpure VD, Boyle JO, Zhou XK, Duffield-Lillico AJ, Gross ND, Lee NY, et al. Elevated levels of urinary prostaglandin E metabolite indicate a poor prognosis in ever smoker head and neck squamous cell carcinoma patients. Cancer Prev Res 2009;2: 957–65.
25. Woutersen RA, Appel MJ, van Garderen-Hoetmer A, Wijnands MV. Dietary fat and carcinogenesis. Mutat Res 1999;443:111–27.
26. Ferretti A, Judd JT, Taylor PR, Schatzkin A, Brown C. Modulating influence of dietary lipid intake on the prostaglandin system in adult men. Lipids 1989;24:419–22.
27. Duffield-Lillico AJ, Boyle JO, Zhou XK, Ghosh A, Butala GS, Subbaramaiah K, et al. Levels of prostaglandin E metabolite and leukotriene E (4) are increased in the urine of smokers: evidence that celecoxib shunts arachidonic acid into the 5-lipoxygenase pathway. Cancer Prev Res 2009;2:322–9.
28. Murphey LJ, Williams MK, Sanchez SC, Byrne LM, Csiki I, Oates JA, et al. Quantification of the major urinary metabolite of PGE2 by a liquid chromatographic/mass spectrometric assay: determination of cyclooxygenase-specific PGE2 synthesis in healthy humans and those with lung cancer. Anal Biochem 2004;334:266–75.
29. Gross ND, Boyle JO, Morrow JD, Williams MK, Moskowitz CS, Subbaramaiah K, et al. Levels of prostaglandin E metabolite, the major urinary metabolite of prostaglandin E2, are increased in smokers. Clin Cancer Res 2005;11:6087–93.
30. Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. Inflammopharmacology 2009;17:55–67.
31. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012; 13:518–27.
32. 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.
33. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012;379:1591–1601.
34. 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; 356:2131–42.
35. Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. JAMA 2009;302:649–58.
36. Mutter R, Lu B, Carbone DP, Csiki I, Moretti L, Johnson DH, et al. A phase II study of celecoxib in combination with paclitaxel, carboplatin, and radiotherapy for patients with inoperable stage IIIA/B non-small cell lung cancer. Clin Cancer Res 2009;15:2158–65.
37. Csiki I, Morrow JD, Sandler A, Shyr Y, Oates J, Williams MK, et al. Targeting cyclooxygenase-2 in recurrent non-small cell lung cancer: a phase II trial of celecoxib and docetaxel. Clin Cancer Res 2005;11: 6634–40.