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Urinary PGE-M: A Promising Cancer Biomarker

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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 pro-inflammatory COX-2-derived prostaglandin E_2 (PGE_2) in inflammation and cancers, Morris and colleagues found that urinary PGE-M is positively associated with obesity, smoking, and lung metastases in breast cancer patients (beginning on page **XXX**). 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 **XXX**). 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.

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 (CRC). 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 this issue of the journal, Morris and colleagues report 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, Kim and colleagues present the first evidence

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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 five structurally related prostanoids generated from arachidonic acid by prostaglandin G/H synthases (also referred to as COX enzymes). COX enzymes exist in two 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 pro-inflammatory gene *COX-2* and CRC (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 CRC patients (11). In addition to CRC, COX-2 overexpression is also an indicator of poor prognosis in multiple cancer types, including breast, gastric, and head and neck squamous cell carcinoma (12, 13). The biological 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 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 1) directly inducing tumor epithelial cell proliferation, survival, and migration/invasion and 2) 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 demonstrate 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’s disease, CRC, or large adenomas (greater than 1 cm in size) were significantly elevated compared to 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 are positively associated with disease progression and death in head and neck squamous cell carcinomas (24). The work reported by Kim *et al.* 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 (NSAIDs) (5). Along the same lines, Morris *et al.* showed that urinary PGE-M levels are significantly elevated in breast cancer patients with lung metastases and/or liver metastases compared to patients with only primary tumors in a cross-sectional study

(4). Both studies reported by Kim et al. and Morris et al. indicate that urinary PGE-M is positively associated with the risk of developing breast cancer and metastasis. Based on 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 to never smokers (27–29). Kim *et al.* further reveals 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 *et al.* shows for the first time that elevated urinary PGE-M levels are 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 breast cancer patients 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 demonstrated 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 (COXIBs). NSAIDs have been reported to have beneficial effects on reducing the risk of developing some solid tumors including the four 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 (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 CRC but also for other cancers as well (32). Moreover, an analysis of five 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 CRC (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 CRC 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 CRC depend on COX-2. Taken together, these results indicate that aspirin and/or other non-selective NSAIDs exert their antitumor effects by primarily targeting COX-2.

Based on both studies reported in this issue of the journal (4, 5) and previously published results (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 anti-tumor 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 pharmacological activity of NSAIDs in cancer prevention and adjuvant treatment. Indeed, a single-institution phase II study revealed that non-small cell lung cancer (NSCLC) patients 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, recurrent NSCLC patients with the greatest proportional decline in urinary PGE-M levels experienced a longer survival compared to 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. Since 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 *et al.* also show that breast cancer patients who had received cytotoxic chemotherapy have significantly higher levels of urinary PGE-M compared to patients without chemotherapy (4). It will be important to determine whether patients treated with combinations of chemotherapy or/and radiation therapy with NSAIDs respond better than those not treated with NSAIDs.

In conclusion, these novel findings reported in this 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.

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