Commentary

Cancer Prevention Research

Urinary PGE-M in Colorectal Cancer: Predicting More than Risk?

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Abstract

Progress in cancer chemoprevention has been hindered by a lack of validated biomarkers of risk and interventive response. The identification of accurate, reliable, and easily measurable risk and response biomarkers within the field of cancer prevention could dramatically alter our approach to the disease. Colorectal cancer is associated with substantial morbidity and a limited 5-year survival rate for late-stage disease. The identification of biomarkers to predict (i) those most at risk of clinically significant colorectal neoplasia in conjunction with or building upon current risk models and/or (ii) those most likely to respond to potential colorectal chemopreventive agents, such as aspirin and NSAIDs, would significantly advance colorectal cancer risk management. Urinary PGE-M is an established indicator of systemic prostaglandin E_2 production and has previously been demonstrated to predict risk of advanced colorectal neoplasia in a handful of studies. In the July 2014 issue, Bezawada and colleagues confirmed those earlier risk associations and demonstrated that PGE-M can also predict responsiveness to aspirin/NSAIDs in a small subset of women undergoing lower endoscopy in the Nurse's Health Study. PGE-M has the potential to define subsets of the population that may derive greater chemopreventive benefit from NSAIDs, as well as the potential to optimize the use of expensive and/or invasive screening tests. Additional larger and more diverse prospective studies meeting the criteria for phase IV biomarker studies are needed to advance the development of PGE-M as a noninvasive biomarker of both risk and chemopreventive response in populations at risk for colorectal cancer. *Cancer Prev Res; 7(10); 969–72. ©2014 AACR.*

Cancer prevention has advanced tremendously in the past few decades, driven primarily by greater insights into the mechanisms of early stages of neoplastic development as well as progress in the screening, early detection, and surgical removal of precancerous lesions and cancer. The area of chemoprevention, however, has seen slower and less steady progress. Though we now have refined insights into disease pathogenesis, successful risk assessments and new risk models, as well as the established efficacy of 13 agents approved for the treatment of precancerous lesions and cancer risk reduction (1), progress has been hindered by a lack of validated biomarkers of risk and interventive response. The identification and development of accurate, reliable, and easily measurable risk and response biomarkers within the field of cancer prevention could dramatically alter our approach to the disease. Confirmed risk biomarkers would allow us to more precisely predict who will develop cancer and, therefore, who is most likely to benefit from chemopreventive or surgical interventions. In addition, validated risk biomarkers that can also serve as measures of chemopreventive response would allow us to not only estimate risk, but also to tailor interventions based on potential benefits or risks—important considerations given that chemoprevention often involves asymptomatic, if not entirely healthy, individuals.

The potential of accessible validated biomarkers to improve our ability to reduce risk and prevent more cancers is neatly illustrated by the use of cholesterol and blood pressure measurements to guide risk factor management and therapy and thereby reduce the risk of cardiovascular events. These serve as markers of risk and response, allowing cardiologists and primary care physicians to identify those at higher risk of developing coronary artery disease and life-threatening cardiac events and to then tailor risk-reducing interventions (e.g., statins, β-blockers) in those higher risk subsets. Such risk stratification and tailoring of medical therapy before advanced stages of disease have become a dominant theme in standard cardiovascular risk management. In effect, such biomarkers led to the evolution of cardiology from a predominantly treatment-oriented subspecialty to a discipline with much more of a preventive focus, paving the way for an approximate 60% reduction in the U.S. mortality

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rate of heart diseases between the years 1950 and 2008 (2, 3). The identification of similar biomarkers for cancer risk stratification and prevention would significantly advance the field of chemoprevention and catalyze a much needed similar evolution in oncology—away from a dominant or exclusive focus on treatment of those with symptomatic disease and toward a greater appreciation of risk factors, screening/early detection, and preventive management through the behavioral adoption of healthy lifestyles, as well as surgical and medical preventive interventions. In addition, recent data from the sequencing of cancer genomes highlight the extreme genetic heterogeneity of advanced cancers, challenging the ultimate potential of an exclusive focus on treatment of advanced disease and underscoring the urgent need for such an evolution (4).

Colorectal cancer represents a significant public health burden in the United States. It is the third most common cancer among both men and women and the second most fatal cancer, associated with substantial morbidity and a limited 5-year survival rate for late-stage disease (5). A variety of evidence-based screening tests proved to reduce cancer-associated mortality exist, but none are ideal, as they all represent various trade-offs between performance, invasiveness, affordability, patient acceptance, convenience, and efficacy. Lifestyle alterations and chemopreventive strategies, as used so effectively in cardiovascular risk reduction, may significantly reduce colorectal cancer morbidity and mortality in conjunction with effective screening programs. The identification of biomarkers to predict those most at risk of clinically significant colorectal neoplasia (i.e., advanced adenomas and cancer) in conjunction with or building upon current risk models (6) and/or those most likely to respond to potential colorectal chemopreventive agents, such as aspirin and NSAIDs, would significantly advance colorectal cancer risk management.

Urinary PGE-M, an established indicator of systemic prostaglandin E_2 (PGE_2) production (7, 8), is one such promising biomarker. As the primary metabolite of PGE_2, it demonstrates strong biologic plausibility in predicting risk of colorectal advanced neoplasia and cancer, given that the tumor-promoting effects of the COX-2 enzyme in colorectal neoplasia are largely thought to follow from the generation of PGE_2 in settings of chronic inflammation. PGE-M has been previously demonstrated to predict risk of advanced colorectal neoplasia in a handful of innovative studies (9–11). Cai and colleagues (9) used a nested case–control design ($N = 300$) in the prospective Shanghai Women's Health Study and demonstrated that baseline urinary PGE-M levels were 50% higher in colorectal cancer cases than in controls and associated with as much as a 5.6-fold significantly increased risk of colorectal cancer. Johnson and colleagues (10) reported that PGE-M was significantly elevated in men and women ($N = 228$) with colorectal cancer and with large (>1 cm) adenomas when compared with patients with small or no adenomas. Sensitivity and specificity of urinary PGE-M concentrations for colorectal cancer or large adenomas versus small or no adenomas were 88% and 53%, respectively (10). More recently, Shrubsole and colleagues (11) assessed urinary PGE-M in patients with any of various forms of colorectal adenomas (i.e., 3 categories of cases were included: individuals with any advanced adenoma, multiple small tubular adenomas, or single small tubular adenomas) versus those who underwent complete colonoscopy without evidence of colorectal neoplasia (i.e., controls) from the Tennessee Colorectal Polyp Study. They found that cases with either an advanced adenoma or multiple small adenomas had PGE-M levels 25% higher than controls, and those in the highest quartile of PGE-M levels were 2.5-fold more likely to have advanced or multiple small adenomas than were those in the lowest quartile (11). On the basis of these studies, PGE-M has the potential to identify patients with the highest risk of clinically concerning colorectal neoplasia (8). However, important unresolved questions arising from these studies included PGE-M's utility in both genders (preliminary data suggest that it may be more useful in women), as well as its specificity for advanced colorectal neoplasia versus other potential states of chronic inflammation (e.g., obesity, inflammatory bowel disease, or even tobacco use) or noncolorectal cancers. Recent commentators have recommended replication in larger and more diverse populations as well as validation in prospective studies (8).

In the July 2014 issue, Bezawada and colleagues (12) partially answered that call by evaluating urinary PGE-M in another prospective, nested case–control study ($N = 840$) as a possible marker of colorectal adenoma risk and responsiveness to aspirin chemoprevention in women from the population-based Nurses' Health Study (NHS. The authors found that women with the highest levels of urinary PGE-M had a 65% increased risk of advanced adenoma, a 69% increased risk of large adenoma, and more than twice the risk for multiple adenomas. A statistically significant association between urinary PGE-M and the risk of low-risk adenomas was not identified. These findings confirm the results of the smaller and/or retrospective studies by Cai and colleagues (9), Johnson and colleagues (10), and Shrubsole and colleagues (11) and, more generally, add to the growing body of literature supporting PGE-M as a potential biomarker for cancer risk and prognostication for colorectal neoplasia, and possibly more broadly across other cancers (e.g., lung, breast, pancreas; refs. 13–16). Interestingly, PGE-M seems to be relatively specific for predicting high-risk adenomas across three published studies—Johnson and colleagues (10), Shrubsole and colleagues (11), and Bezawada and colleagues (12). This suggests the possibility of using PGE-M to target the use of invasive, inconvenient, or expensive screening tests such as colonoscopy (17) or stool-based molecular tests (18) to those at greatest risk of developing colorectal cancer.

Furthermore, Bezawada and colleagues (12) broaden the previous work in this area by suggesting a strong chemopreventive benefit from the regular use of aspirin or NSAIDs in women with elevated levels of PGE-M but not in women with lower levels of urinary PGE-M. Could assessments of urinary PGE-M help to define population subsets most

likely to benefit from chemopreventive agents, thus improving *a priori* risk:benefit considerations to better target preventive interventions? Alternatively, PGE-M could serve as a marker not only of risk but also of therapeutic response to aspirin or NSAIDs, as well. The authors demonstrated NSAID/aspirin use to be associated with a 39% reduction in adenoma risk among women with elevated baseline levels of PGE-M at baseline. Of note, the authors tested the ability of acetaminophen to reduce adenoma risk among those with elevated PGE-M but did not see an effect, highlighting the specificity of their findings and strengthening the hypothesis that aspirin and NSAIDs reduce the risk of colorectal neoplasia through anti-inflammatory pathways involving COX-2 and PGE_2. However, the study could not assess a direct effect of NSAID/aspirin use in women with less elevated urinary levels of PGE-M. Furthermore, over half the study sample were regular users of aspirin/NSAIDs at the time of urine collection. Theoretically, these individuals should already have reduced levels of PGE-M, since exposure to anti-inflammatory agents has been shown to induce a reduction in the levels of prostaglandin metabolites in the urine (19). Yet, the majority of these regular users were considered to have high levels of PGE-M and were shown to derive the most chemopreventive benefit. Consequently, there is a need to better understand the variation and overall dynamics of PGE-M as a biomarker in populations of regular users of aspirin and other NSAIDs. Larger prospective studies are needed to define the levels that will predict a benefit of the intervention, when the biomarker should be assessed in populations that are already users of NSAIDs, and the inter- and intrapatient variation over time, among other variables. Finally, given the high percentage of Americans with underlying cardiovascular disease or type II diabetes, which seems to have a strong component of chronic inflammation as a part of their pathogenesis, or other less common disorders involving chronic inflammation (e.g., Crohn, ulcerative colitis, arthritis, other cancers), as well as the risks associated with NSAID use (20), it may be beneficial for future studies to assess the levels of urinary PGE-M and their response to treatments across a wider spectrum of the population.

In 2001, Pepe and colleagues (21) proposed a five-phase framework for developing cancer screening biomarkers. These guidelines provide recommended aims, outcomes, selection criteria, and sample sizes for each phase. With the exception of its prospective foundation, the Bezawada and colleagues study most closely aligns with criteria for phase III studies, which are typically retrospective in nature and draw upon clinical specimens collected and stored from cohorts of apparently healthy individuals where cancer cases are identified from the cohort along with an appropriate set of controls, with the sample ideally reflecting the target population for screening in relation to both cancer and biomarker processes (21). An important limitation of the Bezawada and colleagues study is its limited sample, both in size and composition. Although prospective in nature, the sample represents a small (involving 840 women from the cohort of more than 115,000), selected subset of women from the NHS meeting various inclusion criteria; therefore, it is unclear how closely the sample reflects all aspects of the target population for colorectal cancer screening. Additional larger and more diverse prospective studies meeting the criteria for phase IV biomarker studies are needed to advance the development of PGE-M as a noninvasive biomarker of both risk and chemopreventive response in colorectal neoplasia.

Despite the many recent advances in cancer screening and prevention, a lack of validated risk and response biomarkers hinders progress in chemoprevention. The identification of a noninvasive biomarker that can potentially serve as both a risk and response marker in patients with colorectal adenoma would be a significant advance in the screening and prevention of colorectal cancer and for the field of chemoprevention more broadly. The potential of PGE-M to optimize the use of expensive screening tests is suggested by its strong biologic plausibility, as well as the consistency and specificity of its association with clinically significant adenomas. Although previous studies had documented the potential of urinary PGE-M to serve as a marker of risk for advanced colorectal neoplasia and colorectal cancer itself, the study from Bezawada and colleagues (12) suggests that its utility may go beyond risk estimation and allow for the tailoring of preventive interventions before cancer's development, much as in cardiovascular risk reduction.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: E. Vilar, E. Hawk
Development of methodology: E. Hawk
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Hawk
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Vilar, E. Hawk
Writing, review, and/or revision of the manuscript: K.C. Maresso, E. Vilar, E. Hawk
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E. Hawk
Study supervision: E. Hawk

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