Research Article

Cancer Prevention Research

Urinary Prostaglandin E2 Metabolite and Risk for Colorectal Adenoma

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Abstract

COX-2 is upregulated in most colorectal cancers. Most of the COX-2 tumor–inducing effects are believed to be mediated through overproduction of prostaglandin E_2 (PGE_2), which can be measured using a urinary metabolite of PGE_2, PGE-M. Urinary PGE-M was assessed in a case–control study of colorectal adenoma. Included in the analysis were 224 cases with at least one advanced adenoma, 152 cases with multiple small tubular adenomas, 300 cases with only a single small tubular adenoma, and 364 polyp-free controls. There were no statistical differences in PGE-M levels between controls and cases with a single small tubular adenoma. However, cases with either an advanced adenoma or multiple small tubular adenomas had more than 25% higher levels of PGE-M than controls. Participants with the highest quartile level of PGE-M were approximately 2.5-fold more likely to have advanced or multiple small tubular adenoma in comparison with those with the lowest level of PGE-M [OR = 2.53; 95% confidence interval (CI), 1.54–4.14; $P_{trend} < 0.001$]. The association was strongest among women. PGE-M level was associated with increased risk for multiple or advanced adenoma but not single small adenoma. Our study suggests that PGE-M may be a useful risk marker for assessing the risk of harboring clinically more important versus less important colorectal neoplasia. *Cancer Prev Res; 5(2); 336–42. ©2011 AACR.*

Introduction

Colorectal cancer is the fourth most common incident cancer and the second most common cause of cancer death in the United States, with approximately 150,000 new cases and 51,000 deaths per year (1). About 1 in 18 individuals will develop colorectal cancer over their lifetime and 40% will die within 5 years of diagnosis (1). Because most colorectal cancers arise from adenomatous polyps, identification of markers for adenoma risk will be highly significant for risk assessment and primary and secondary prevention of colorectal cancer (2).

COX-2 is a key enzyme responsible for the conversion of arachidonic acid to prostaglandins. COX-2 expression is elevated in more than 50% of colorectal adenoma and carcinomas (3, 4). Furthermore, nonsteroidal anti-inflammatory drug (NSAID) use, a proven chemopreventive for colorectal neoplasia (5–10), targets COX enzymes and may be most effective in reducing risk among tumors which overexpress COX-2 (4) and reducing mortality among patients with COX-2 overexpression in primary tumors (11). Of the prostaglandins, PGE_2 is also likely to be the primary mediator of the effects of COX-2 in colorectal carcinogenesis. PGE_2 is the most abundant prostaglandin detected in colorectal neoplasia (12) and has been shown to inhibit apoptosis (13), stimulate angiogenesis (14, 15), and increase cellular proliferation (16, 17), cycling (18), and migration (19).

Given the critical role of the COX-2 pathway in colorectal carcinogenesis, it is conceivable that biomarkers in the COX-2 pathway may be useful to assess risk of colorectal cancer. A noninvasive method to quantify the major urinary metabolite of PGE_2, PGE-M, was developed recently (20) and has been associated with colorectal and gastric cancer risks in Chinese women (21, 22). In this study, we analyzed data and urine samples collected from approximately 1,040 participants recruited in a large colonoscopy-based case–control study to evaluate the association of urinary PGE-M with colorectal adenomas.

Materials and Methods

The Tennessee Colorectal Polyp Study

Participants were part of the Tennessee Colorectal Polyp Study, a colonoscopy-based case–control study conducted in Nashville, TN. Study methods have been published elsewhere (23). Briefly, eligible participants aged 40 to 75

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years were identified from patients scheduled for colonoscopy at the Vanderbilt Gastroenterology Clinic and the Veterans Affairs Tennessee Valley Health System Nashville campus between February 1, 2003, and October 29, 2010. Excluded from our study were participants who had a prior history of genetic colorectal cancer syndromes (e.g., hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis), inflammatory bowel disease, adenomatous polyps, or any cancer other than nonmelanoma skin cancer. The study was approved by relevant committees for the use of human subjects in research.

Among 12,585 eligible persons, 7,621 (61%) provided written informed consent and participated in at least one component of the study. Participants and nonparticipants were similar with respect to age, gender, and study location. On the basis of the colonoscopy and pathology findings, participants were assigned as polyp-free controls, cases with adenomatous polyps, or persons with other diagnoses. An adenoma was classified as advanced if it met one of the following 3 criteria: (i) size greater than or equal to 1.0 cm, (ii) greater than 25% villous component, or (iii) containing high-grade dysplasia. To be diagnosed as a control, the participant must have had a complete colonoscopy reaching the cecum and have been polyp-free at colonoscopy.

Urine samples were collected from participants between April 16, 2004, and October 10, 2008, prior to colonoscopy. A total of 4,404 of eligible participants (77.0%) donated a spot fasting urine sample during this time. At the time of urine collection, a questionnaire about medication use and other activities in the 48 hours prior to colonoscopy was collected from participants. Most patients are routinely advised to stop NSAID use for at least 48 hours prior to colonoscopy. Because recent NSAID use affects PGE-M level, 274 participants who had used an NSAID within this time frame (6.2%) were not eligible for this analysis. For the purposes of sample selection, adenoma cases were further classified into case groups: cases with any advanced adenoma, cases with multiple ($\geq$2) small (<1 cm) tubular adenomas, and cases with only a single small tubular adenoma. Controls were matched to one or more case groups in a 1:1 ratio on age (mostly within 5 years), gender, race (white/non-white) and on the basis of at least one of the following additional criteria: NSAID use of at least 3 times per week for 1 year or more duration (current; former or never), sample collection date ($\pm$90 days; season), and/or study site (academic medial center/VA hospital). Included in the analysis were 224 cases with at least one advanced adenoma, 152 cases with multiple small tubular adenomas, 300 cases with only a single small tubular adenoma, and 364 polyp-free controls.

Laboratory measurements

Urinary PGE-M (11-α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid) level was measured using a liquid chromatography/tandem mass spectrometric method as described previously (20). Briefly, 0.75 mL urine was acidified to pH 3 with HCl and endogenous PGE-M was then converted to the *O*-methyloxime derivative by treatment with methyloxime HCl. The methoximated PGE-M was extracted, applied to a C-18 Sep-Pak, and eluted with ethyl acetate. An [$^2H_6$]*O*-methyloxime PGE-M internal standard was then added. Liquid chromatography was conducted on a Zorbax Eclipse XDB-C18 column attached to a ThermoFinnigan Surveyor MS Pump (Thermo Finnigan). For endogenous PGE-M, the predominant product ion m/z 336 representing $[M\text{-}(OCH_3 + H_2O)]^-$ and the analogous ion, m/z 339 ($M\text{-}OC[^2H_3 + H_2O)$, for the deuterated internal standard, was monitored in the selected reaction monitoring (SRM) mode. Quantification of endogenous PGE-M used the ratio of the mass chromatogram peak areas of the m/z 336 and m/z 339 ions. The lower limit of detection of PGE-M was in the range of 40 pg, approximately 100-fold below levels in normal human urine. The coefficients of variation were 6.1% for between batches and 7.8% for within batches. Urinary creatinine levels were measured using a test kit from Sigma Company. Laboratory staff was blinded to the case–control status of urine samples and the identity of quality control samples included in the study. Urine creatinine levels also were measured and values of PGE-M were reported as ng PGE-M/mg creatinine.

Statistical analyses

Frequencies, means, SDs, medians, and interquartile ranges were calculated for select characteristics of cases and controls. *P* values for case–control differences were evaluated using χ^2 tests for categorical variables, ANOVA for age and body mass index (BMI), and Kruskal–Wallis test for other continuous measures. *P* values of $\leq$0.05 (2-sided probability) were interpreted as being statistically significant for all analyses.

Urine PGE-M level was right-skewed, thus, medians and interquartile ranges, and geometric means were used for descriptive statistics. Case–control differences in PGE-M levels were evaluated using the Wilcoxon rank-sum test and linear regression models of log-transformed PGE-M level after adjustment for age, gender, race, educational attainment, and the study site.

Quartile cutoff points were determined using the distribution of PGE-M level among the controls. Logistic regression models were used to estimate the ORs and 95% confidence intervals (95% CI) for the association between PGE-M level and risk of colorectal adenoma after adjustment for other factors. Tests for linear trend were conducted by entering the categorical variables as continuous parameters in the models Statistical analyses were conducted by using SAS statistical software (version 9.2; SAS Institute).

Results

Characteristics of cases and controls are presented in Table 1. Although not statistically significant, adenoma cases were more likely to have a family history of colorectal neoplasia and advanced adenoma cases were more likely to have a colonoscopy for diagnostic purposes.

In comparison to controls, cases with an advanced adenoma or multiple small tubular adenomas were more

Table 1. Comparison of select characteristics of adenoma case groups and polyp-free controls, Tennessee Colorectal Polyp Study

		Adenoma case type			
Characteristic	**Control**	**Any advanced**	**Multiple small tubular**	**Single small tubular**	***P*[a]**
N	364	224	152	300	
Age, mean (SD)[c], y	57.6 (7.1)	59.2 (7.1)	58.9 (6.7)	57.8 (7.3)	0.02
Male (%)[c]	64.8	71.0	79.0	69.7	0.02
Educational attainment (%)					
High school graduate or less	20.5	36.6	38.9	25.2	
Some college	30.8	24.9	25.2	27.9	
College graduate	22.4	18.3	19.9	21.8	
Graduate or professional school	26.3	20.3	16.0	25.2	0.001
White (%)[c]	85.2	86.6	86.2	95.0	<0.001
Academic medical center (%)[c]	71.7	67.9	59.2	72.3	0.02
Indication for colonoscopy (%)					
Screening	62.9	61.2	63.2	61.7	
Family history of colorectal neoplasia	10.4	7.1	7.9	12.0	
Diagnostic	18.1	26.3	19.1	17.7	
Other	8.5	5.4	9.9	8.7	0.17
NSAID use (%)[c]					
Never	36.9	51.3	42.4	37.3	
Former	9.4	6.1	8.3	7.3	
Current	53.6	42.6	49.2	55.3	0.03
Regular alcohol drinking (%)					
Never	59.0	50.8	46.2	50.0	
Former	20.5	30.6	32.6	21.7	
Current	20.5	18.6	21.2	28.3	0.002
Cigarette smoking (%)					
Never	51.0	33.0	31.8	45.3	
Former	31.6	38.5	38.6	38.0	
Current	17.4	28.5	29.6	16.7	<0.001
Physically active within past 10 y, (%)	59.4	51.5	40.8	56.2	0.002
BMI, mean (SD), kg/m^2	28.0 (5.8)	29.4 (6.1)	29.2 (5.8)	28.7 (5.6)	0.03
Red meat intake, mean (SD), g/d	46.7 (18.9–81.2)	59.4 (30.2–98.0)	72.1 (34.0–115.2)	48.3 (18.9–90.7)	<0.001
Postmenopausal (%)[b]	75.4	80.3	81.5	78.0	0.84

[a]*P* value derived from χ^2 test for categorical variables, ANOVA for age and BMI, and Kruskal–Wallis test for other continuous variables.
[b]Among females only.
[c]Matching factor.

likely to be older, male, a current cigarette smoker, to have lower educational attainment and a higher BMI, and to consume more red meat. Cases with a single small tubular adenoma were more likely to be white than controls. Advanced adenoma cases were less likely to have used NSAIDs.

PGE-M levels were not statistically significantly higher in cases with a single small tubular adenoma than in controls (Table 2). However, among cases with either an advanced adenoma or multiple small tubular adenomas, PGE-M level was statistically significantly higher than controls. Advanced adenoma cases had 25% (median) or 28% (geometric mean) higher PGE-M level than controls. Multiple small tubular adenoma cases had 31% (median) or 25% (geometric mean) higher PGE-M level than controls. PGE-M levels for multiple small tubular cases with only 2 adenomas and multiple small tubular cases with more than 2 adenomas were similarly elevated (data not shown in table).

There was no evidence that PGE-M level was associated with risk for a single small tubular adenoma (Table 3). Higher levels of PGE-M were associated with an increased risk for both advanced adenoma and multiple small tubular adenoma ($P_{trend} = 0.04$ and 0.03, respectively). Compared with those in the lowest quartile of PGE-M, participants with the upper 3 quartile levels of PGE-M were approximately 2-fold more likely to have advanced or multiple small tubular adenoma.

Table 2. Urinary PGE-M levels (ng/mg creatinine) by study group, Tennessee Colorectal Polyp Study

Study group	*n*	Median (Q1–Q3)	Difference (%)	*P*[a]	Geometric mean (95% CI)	Difference (%)	*P*[b]
Polyp-free controls	358	10.1 (5.7–17.1)			10.2 (9.3–11.1)		
Adenoma cases							
Any advanced	222	12.6 (8.4–21.4)	25	<0.001	13.1 (12.0–14.3)	28	0.001
Multiple small tubular	148	13.2 (7.9–21.9)	31	<0.001	12.8 (11.4–14.4)	25	0.34
Single small tubular	298	10.1 (5.7–17.1)	0	0.39	10.4 (9.5–11.4)	2	0.88

[a]The difference and *P* value were derived from Wilcoxon rank-sum test.

[b]The difference between the log (geometric mean) and *P* value were derived from linear regression model for log-transformed PGE-M levels, adjusted for age, gender, race, educational attainment, and study site.

The relationship between PGE-M level and risk of advanced or multiple small tubular adenoma did not substantially vary by use of NSAIDs or by smoking status (Table 4). Among males, higher PGE-M levels were associated with a moderately increased risk of advanced or multiple small tubular adenoma. Among females, however, a very strong relationship was observed between PGE-M level and risk (OR = 5.40; 95% CI, 1.78–16.41; $P_{trend} = 0.006$). No statistically significant interaction between gender and PGE-M level on risk for advanced or multiple small tubular adenomas was observed ($P_{interaction} = 0.96$). Results were similar when gender-specific quartiles were used.

Discussion

We found that high PGE-M urinary level was significantly associated with an increased risk of advanced or multiple adenomas, particularly among females. Conversely, PGE-M level was not associated with risk for a simple small single tubular adenoma. These findings suggest that urinary PGE-M may be useful to classify patients into groups with either clinically significant or less significant adenomas.

PGE-M is the primary urinary metabolite of PGE_2 and a role for high levels of PGE_2 in colorectal tumorigenesis has been established on the basis of previous studies. COX-2 is

Table 3. Association of urinary PGE-M levels and colorectal adenoma risk, Tennessee Colorectal Polyp Study

	PGE-M (quartile)				
Study group	Q1 (low)	Q2	Q3	Q4	P_{trend}
Polyp-free controls					
n	90	89	90	89	
Any advanced adenoma					
n	26	51	76	69	
OR (95% CI)[a]	1.00 (reference)	1.64 (0.90–2.95)	2.42 (1.37–4.28)	2.17 (1.20–3.92)	0.006
OR (95% CI)[b]	1.00 (reference)	1.56 (0.84–2.90)	2.25 (1.23–4.09)	1.84 (0.97–3.48)	0.04
Multiple small tubular adenoma					
n	16	36	44	52	
OR (95% CI)[a]	1.00 (reference)	2.13 (1.02–4.44)	2.13 (1.03–4.40)	2.57 (1.24–5.34)	0.03
OR (95% CI)[b]	1.00 (reference)	2.59 (1.20–5.60)	2.31 (1.07–5.00)	2.88 (1.32–6.24)	0.03
Single small tubular adenoma					
n	66	80	73	79	
OR (95% CI)[a]	1.00 (reference)	1.14 (0.72–1.82)	0.99 (0.61–1.61)	1.11 (0.67–1.82)	0.87
OR (95% CI)[b]	1.00 (reference)	1.16 (0.72–1.86)	0.93 (0.56–1.53)	1.04 (0.62–1.74)	0.88
Advanced or multiple adenoma					
n	42	87	120	121	
OR (95% CI)[a]	1.00 (reference)	1.84 (1.11–3.05)	2.32 (1.41–3.81)	2.34 (1.41–3.87)	0.001
OR (95% CI)[b]	1.00 (reference)	1.95 (1.15–3.30)	2.31 (1.37–3.89)	2.19 (1.28–3.76)	0.008

[a]Adjusted for age, gender, race, educational attainment, and study site.

[b]Additionally adjusted for cigarette smoking, alcohol consumption, BMI, red meat intake, and NSAID use.

Table 4. Associations of urinary PGE-M levels and advanced or multiple small tubular colorectal adenoma risk stratified by NSAID use, smoking status, and gender, Tennessee Colorectal Polyp Study

	PGE-M (quartile)					
	Q1 (low)	Q2	Q3	Q4	P_{trend}	$P_{interaction}$
Males						
Case/controls	24/34	59/55	97/68	95/76	0.24	0.96
OR (95% CI)[a]	1.00 (reference)	1.52 (0.75–3.09)	1.96 (1.01–3.83)	1.58 (0.81–3.10)		
Females						
Case/controls	18/56	28/34	23/22	26/13	0.006	
OR (95% CI)[a]	1.00 (reference)	2.71 (1.14–6.42)	2.33 (0.87–6.23)	5.40 (1.78–16.41)		
Never or former NSAID users						
Case/controls	23/46	42/41	50/39	62/39	0.06	0.80
OR (95% CI)[a]	1.00 (reference)	1.91 (0.90–4.04)	2.19 (1.01–4.75)	2.29 (1.03–5.09)		
Current NSAID users						
Case/controls	15/43	34/47	53/50	46/49	0.04	
OR (95% CI)[a]	1.00 (reference)	2.36 (1.06–5.28)	2.96 (1.38–6.36)	2.51 (1.14–5.54)		
Never smokers						
Case/controls	15/55	32/50	30/42	30/33	0.03	0.88
OR (95% CI)[a]	1.00 (reference)	1.90 (0.86–4.20)	1.91 (0.83–4.38)	2.44 (1.01–5.89)		
Former/current smokers						
Case/controls	23/34	45/38	73/47	80/56	0.06	
OR (95% CI)[a]	1.00 (reference)	1.98 (0.94–4.16)	2.74 (1.36–5.54)	2.09 (1.04–4.20)		

[a]Adjusted for age, race, educational attainment, study site, alcohol consumption, BMI, red meat intake, and cigarette smoking or gender or NSAID use.

aberrantly expressed in the majority of colorectal cancers and adenoma (24). In addition, use of NSAIDs, such as COX-2 inhibitors, decreases the recurrence or increases the regression of colorectal adenoma (6–9, 25). Thus, a role of the COX-2–related pathway in colorectal carcinogenesis is well established. COX-2 catalyzes the conversion of arachidonic acid to prostaglandin H_2 (PGH_2) which is the precursor for several prostaglandins including PGE_2. Most of the effects of COX-2 on tumorigenesis are presumed to be through overproduction of PGE_2, which is a mediator of inflammatory response (26) and has many other physiologic effects (13–17, 19). PGE_2 levels are elevated in colorectal neoplasia (12, 27) and loss of expression of 15-PGDH, which degrades PGE_2, is common in colorectal cancer (28, 29). In addition, PGE_2 enhanced carcinogen-induced tumor incidence and multiplicity in rats (30, 31) and adenoma growth in mice (28). We also previously found in a prospective cohort study of Chinese women that baseline PGE-M level was associated with a strong risk for subsequent diagnosis of colorectal cancer (21). The stronger association observed in that study is consistent with findings from our study that suggest PGE_2 is either more detectable in larger tumors or more likely to have its effects in later tumorigenesis. In a small pilot study, we found that, in comparison to controls, urinary PGE-M levels were elevated in individuals with colorectal cancers or multiple or advanced adenomas (32). We also found among patients with rectal cancer that PGE-M levels decreased after treatment with a selective COX-2 inhibitor (32).

Individuals with multiple or advanced adenoma are at an increased risk for adenoma recurrence in comparison to individuals with single small tubular adenoma (33, 34). The finding that PGE-M was related to multiple or advanced adenoma and not simple adenoma may reflect a more substantial effect of PGE_2 on tumor progression than on tumor initiation. Although nearly 100% of colorectal cancers have elevated PGE_2, only a subset of adenoma have elevated levels (27, 35). Tissue levels of PGE_2 have also been reported to be related to increased size of adenoma (35, 36). PGE_2 exerts its cellular effects by binding to its cognate receptors (EP1-4; ref. 37) and a study found that overexpression of EP4 was present in all colorectal cancer tissues and cell lines, but only a little more than a third of adenoma or adenoma cell lines (16). Many of the described mechanisms of PGE_2 are also relevant to progression. These include cell proliferation (16, 17), inhibition of apoptosis (13), increased cell motility (19), and increased angiogenesis (14, 15).

Similar to previous studies, we observed higher PGE-M levels among men (32) and among smokers (38). However, the association between PGE-M level and risk of advanced or multiple small tubular adenoma did not vary substantially by smoking status. Conversely, the association was more apparent among women than among men. It is possible that a moderate change in PGE-M level among

women who have generally lower levels may have a larger effect than a similar change among men with generally higher levels. However, a mechanism for the potential difference is not clear, and future studies are needed to address this issue. Nonetheless, higher PGE-M level was also, in general, associated with increased risk among men even though the association was not always statistically significant. We also found that similar to PGE-M, BMI and red meat intake were higher among adenoma cases, particularly in advanced or multiple small tubular cases, compared with controls. It is unclear whether the effects of high BMI and red meat intake are through PGE_2 effects.

In this study, we used a spot urine sample. It is possible that a single spot urine may not adequately reflect long-term PGE-M status which, because of random within-person variation, may attenuate the true association between this biomarker and adenoma risk. However, in a study of 23 participants, we collected a spot urine sample 2 to 3 days prior to colonoscopy and a second sample on the day of colonoscopy. The correlation between the 2 samples was very high ($r = 0.91$) and the mean levels were virtually identical. PGE-M levels were also virtually identical between screening and diagnostic colonoscopies within either controls or cases which provides some assurance that the observed differences were not because of selection bias.

This study has several strengths. All participants underwent a complete colonoscopy which decreases the likelihood of misclassification of disease status. Although it is still possible that some controls may have been misclassified, this would have led to attenuation of results and, thus, the true association could be potentially stronger than what was observed in this study. Participants were recruited prior to diagnosis, and a high proportion of participants provided a urine sample (77%) which decreases the likelihood of selection bias affecting the observed results. To our best knowledge, this is the first large study to evaluate PGE-M, a specific marker reflecting COX-2 pathway activity, and colorectal adenoma risk.

In summary, PGE-M level was associated with increased risk for multiple or advanced adenoma, particularly among women. This finding is consistent with a role of PGE_2 in colorectal carcinogenesis. Our study suggests that PGE-M may be a useful risk marker for significant colorectal neoplasia.

Disclosure of Potential Conflicts of Interest

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the NIH. No potential conflicts of interest were disclosed.

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