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Prospective Study of Urinary Prostaglandin E2 Metabolite and Pancreatic Cancer Risk

Yong Cui[1], **Xiao-Ou Shu**[1], **Hong-Lan Li**[2], **Gong Yang**[1], **Wanqing Wen**[1], **Yu-Tang Gao**[2], **Qiuyin Cai**[1], **Nathaniel Rothman**[4], **Hui-Yong Yin**[3], **Qing Lan**[2], **Yong-Bing Xiang**[2], and **Wei Zheng**[1]

[1]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, 2525 West End Avenue, 8th floor, Nashville, TN 37203-1738, USA

[2]Department of Epidemiology, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[3]Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

[4]Division of Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, USA

Abstract

The cyclooxygenase 2 (COX-2) pathway is upregulated in many pancreatic cancer cells, and it is believed that carcinogenetic effects of COX2 upregulation are largely through prostaglandin E2 (PGE2) overproduction. We tested this hypothesis by evaluating the association between urinary PGE2 metabolites (PGE-M), a biomarker of *in vivo* PGE2 overproduction, and pancreatic cancer risk. We conducted a case-control study with 722 subjects (239 cases and 483 controls) nested within two prospective cohort studies, the Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS). Pre-diagnosis urine samples were measured for PGE-M using a liquid chromatography/tandem mass spectrometric method. Conditional logistic regression was used to estimate odds ratio (OR) and 95% confidence intervals (95%CI), with adjustment for potential confounders. Compared to those with the lowest urine level of PGE-M (the first quartile), individuals with higher urine levels of PGE-M had an increased risk of developing pancreatic cancer, with adjusted ORs (95%CI) of 1.63 (0.98–2.73), 1.55 (0.90–2.69), and 1.94 (1.07–3.51), for the second to the fourth quartile groups, respectively (*P* for trend=0.054). This dose-response positive association was more evident among those who had BMI < 25 kg/m^2 than overweight individuals (*P* for interaction=0.058). After excluding cases diagnosed in the first year of follow-up and their matched controls, this positive association persisted (*P* for trend=0.037) and the interaction became statistically significant (*P* for interaction=0.017). This study adds additional evidence that the COX-2 pathway is involved in pancreatic carcinogenesis and suggests that urinary PGE-M may serve as a biomarker for predicting pancreatic cancer risk.

Address correspondence to: Wei Zheng, MD, PhD., Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, 2525 West End Avenue, 8th floor, Nashville, TN 37203-1738, USA, Phone: 615-936-0682, Fax: 615-343-0719, wei.zheng@vanderbilt.edu.

Keywords

pancreatic cancer; prostaglandin E2 metabolite; biomarkers; cancer risk; body mass index

Introduction

Pancreatic cancer is one of the most lethal malignancies. Worldwide, it is the eighth leading cause of cancer death in men and the ninth leading cause of cancer death in women (1). In the United States, pancreatic cancer ranks as the fourth leading cause of cancer death, with an overall 5-year survival rate of approximately 7.0% (2, 3). In China, pancreatic cancer is the seventh leading cause of cancer death (4). Over the past decade, the incidence of pancreatic cancer has been rising continuously but the survival rate remains very low (4–6). It has been predicted that pancreatic cancer will be the second leading cause of cancer death by 2030 in the United States (7).

Cumulative evidence suggests that the cyclooxygenase 2 (COX-2) pathway may play an important role in the pathogenesis of pancreatic cancer. COX-2 is the rate-limiting enzyme of prostaglandin synthesis, and overexpression of the *COX-2* gene can lead to increased prostaglandin-E2 (PGE2) production. PGE2 is a key mediator of inflammation and plays an important role in carcinogenesis (8–10). Experimental and animal model studies have found that overproduction of PGE2 can induce epithelial cell proliferation and angiogenesis and inhibit immunosurveillance and cell apoptosis (11–14). In humans, COX-2 expression has been found to be significantly increased in pancreatic tumor tissue compared with adjacent non-tumorous tissue or normal pancreatic tissue, and increased COX-2 overexpression correlated with the prognosis of disease (15–19). Several epidemiologic studies have shown that use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with reduced pancreatic cancer risk (20–27). The postulated protective effects of NSAIDs are thought to be mediated largely through their roles in inhibiting COX-2, and in turn reducing PGE2 production. Although multiple lines of evidence suggest a possible link between COX-2-derived PGE2 and pancreatic cancer risk, epidemiological evidence directly linking PGE2 and pancreatic cancer risk is lacking. To our knowledge, there is only one publication, based on a retrospective case-control study, which evaluated the relationship between urinary PGE2 metabolites (PGE-M) and pancreatic cancer risk. This study found that levels of PGE-M in post-diagnosis urine samples taken from cases were significantly higher than in control urine samples (28). Because cancer progression and cancer-associated treatments can substantially increase tissue inflammation, resulting in a higher level of PGE-M, results of that study need to be confirmed by prospective epidemiological studies in which the association of PGE2 with pancreatic cancer risk can be prospectively evaluated.

Measurement of excreted urinary PGE-M has been accepted as the best way to quantify endogenous PGE2 production (29, 30). We have previously shown that urinary PGE-M level is positively associated with the risk of developing colorectal adenoma and cancer (31–34), gastric cancer (35) and breast cancer (36). The objective of this study is to examine whether urinary PGE-M levels may be associated with pancreatic cancer risk using samples and data

collected in two large population-based, prospective cohort studies, the Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS).

Materials and Methods

Study population

The Shanghai Women's Health Study (SWHS) and Shanghai Men's Health Study (SMHS) are two large population-based prospective cohort studies conducted in Shanghai, China. The studies were approved by the institutional review boards of all participating institutions. Detailed descriptions of study design and methods have been published elsewhere (27, 38). Briefly, participants were recruited from typical urban communities in Shanghai, China. The SWHS recruited 74,941 women aged 40–70 years from 1996 to 2000 with a 92.7% participation rate in the baseline survey. The SMHS recruited 61,480 men aged 40–74 years from 2002 to 2006 with a 74.0% participation rate in the baseline survey. At the time of enrollment, each participant signed consent and completed an in-person survey conducted by trained interviewers. The baseline information collected included demographic characteristics, medical history and medication use, menstrual and reproductive history, physical activities, and other lifestyle factors. Body measurements were also taken. Of the study participants, 65,754 (88%) women and 54,769 (89%) men provided a spot urine sample. Urine samples were collected into a sterilized cup containing 125 mg ascorbic acid to prevent oxidation of labile metabolites. After collection, the samples were kept in a portable Styrofoam box with ice packs (at approximately 0 to 4°C) and processed within 6 hours for long-term storage at −70°C. Each participant also filled out a biospecimen collection form at the time of sample collection, which included the date and time of sample collection, time of last meal, and day of last menstruation (for premenopausal women), as well as intake of selected foods, cigarette smoking, and use of any medications over the previous 24 hours and during the previous week.

Cases for this study were selected from cohort members who were diagnosed with a primary, incident pancreatic cancer (ICD-9 codes 157) after urine collection. Included in this nested case-control study are 239 incident pancreatic cancer cases and 483 matched controls that provided a urine sample at the baseline survey. Incident pancreatic cancer cases were identified through in-person follow-up interviews and by linking to the Shanghai Cancer Registry and the Shanghai Vital Statistics Unit. Two controls were randomly selected from cohort members and individually matched to each case by age at sample collection (≤ 2 years), sex, menopausal status (for women), time of sample collection (morning or afternoon), date of sample collection (≤ 1 month), time interval since last meal (≤ 2 hours), and availability of urine and plasma sample. Controls were also free of any cancer at the time of cancer diagnosis for their corresponding case.

Urinary PGE-M measurement

Measurement of urinary PGE-M (11 alpha-hydroxy-9,15-dioxo-2,3,4,5-tetranorprostane-1,20-dioic acid) concentration using a liquid chromatography/tandem mass spectrometric method was described previously (29, 30). Briefly, to 0.75 mL urine was added D6-PGEM internal standard (2 ng) and acidified to pH 3 with HCl; endogenous PGE-

M was then converted to the O-methyloxime derivative by treatment with methoxyamine HCl. The methoximated PGE-M was extracted, applied to a C-18 Sep-Pak, and eluted with ethyl acetate. Liquid chromatography was performed on a Phenomenex Kinetix-C18 column (2.6 μm, 2.1 × 50.0 mm) attached to a CTC-HTS autosampler and Shimadzu LC-10A VP system (Kyoto, Japan). For endogenous PGE-M, m/z 395 to 336 and the analogous ion, m/z 391.2 to 341, for the deuterated internal standard, were monitored in the selected reaction monitoring (SRM) mode. Quantification of endogenous PGE-M utilized the ratio of the mass chromatogram peak areas of the m/z 336 and m/z342 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 coefficient of variation for samples analyzed in intra batch was 10.8%. Urinary creatinine levels were measured using a test kit from Sigma Company (St Louis, MO). Urine samples for each case-control set were analyzed in the same batch and adjacently to eliminate between-assay variability. Laboratory staff was blinded to the case-control status of urine samples and the identity of quality control samples included in the study.

Statistical Analyses

Urinary PGE-M levels in each sample were standardized using the urinary creatinine level of the sample and measured as ratios in ng/mg creatinine (ng/mg Cr). The distribution of PGE-M levels was skewed to the high values and thus log-transformation was used to improve the normality. Median and geometric means of the PGE-M levels were estimated. Case-control differences in PGE-M levels were evaluated using the t test. Cases and controls were categorized based on the quartile distribution of PGE-M levels among controls. Conditional logistic regression models were used to estimate odds ratios (OR) of pancreatic cancer risk associated with urinary PGE-M levels and 95% confidence intervals (95%CI). *P* values for linear trends were estimated by modeling the log-transformed urinary PGE-M levels into the regression. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). All statistical tests were based on 2-sided probability.

Results

Baseline characteristics of pancreatic cancer cases and their matched controls are presented in Table 1. Due to matching, the distributions of age and sex are similar in cases and controls. The distribution on other matching variables, including date and time of urine collection, interval since last meal, menopausal status (for women), and antibiotic use in the past week, are also similar (data not shown). Compared with controls, cases were more likely to be ever smokers (29.4 vs. 23.2). Cases and controls were comparable in educational level, family history of cancer, body mass index (BMI), regular exercise, regular alcohol consumption, and NSAIDs use within 7 days before urine collection. The median time interval between urine sample collection and pancreatic cancer diagnosis was 5.8 years with a range from 2 months to 14 years (data not shown).

Table 2 shows the association between baseline urinary PGE-M levels and subsequent risk of pancreatic cancer. Compared to those who had the lowest urine level of PGE-M (the first quartile as a reference), individuals with higher urine level of PGE-M (the second, third and fourth quartiles) had an increased risk for pancreatic cancer with adjusted ORs (95%CI) at

1.63 (0.98–2.73), 1.55 (0.90–2.69), and 1.94 (1.07–3.51), respectively; *P* for linear trend = 0.054). To evaluate the potential effect of undiagnosed subclinical pancreatic cancer on observed association, we excluded cases diagnosed in the first year of follow-up, as well as their matched controls. The analyses showed that this association pattern persisted (Table 2), suggesting that it is unlikely that the elevated baseline urinary PGE-M level among pancreatic cancer patients can be attributed to PGE-M produced by a subclinical malignancy.

Stratified analyses by sex showed a positive association of PGE-M levels with pancreatic cancer risk in both males and females. Compared with the lowest PGE-M quartile group, adjusted ORs (95%CI) for pancreatic cancer risk in the second to the fourth quartile groups were at 3,52 (1.18–10.5), 1.88 (0.60–5.90), and 2.46 (0.81–7.49) for men and at 1.35 (0.71–2.54), 1.98 (0.97–4.07), and 2.15 (0.94–4.90) for women, respectively (data not shown in tables). No interaction between PGE-M and sex was detected in analyses including all subjects (*P* for interaction = 0.201) nor in analyzes after excluding cases diagnosed within the first year of follow-up as well as their matched controls (*P* for interaction = 0.216). However, a borderline significant interaction between PGE-M and BMI were seen for all subjects (P = 0.058). After excluding cases diagnosed in the first year of follow-up and their matched controls, this interaction was statistically significant (*P* for interaction=0.017).

We further conducted an analysis to evaluate pancreatic cancer risk by time interval between urine collection and cancer diagnosis (Table 3). Case subjects were grouped into two strata based on the median cutoff point (5.8 years) between urine collection and cancer diagnosis. Compared to those with the lowest urine levels of PGE-M (the first quartile), an increased risk for pancreatic cancer was observed among individuals with the highest urine level of PGE-M (the fourth quartile), and the positive association was stronger for cancer diagnosed within 5.8 years (adjusted OR = 2.36, 95%CI = 1.01–5.55) than for cancer diagnosed after 5.8 years (OR=1.65, 95%CI = 0.71–3.84).

Due to the suggestive interaction between PGE-M and BMI, we evaluated the association of urinary PGE-M levels with subsequent risk of pancreatic cancer, stratified by BMI (< 25 kg/m^2 or ≥ 25 kg/m^2). As shown in table 4, the positive association between urinary level of PGE-M and pancreatic cancer risk was more evident among individuals who had BMI < 25 kg/m^2. Adjusted ORs (95%CI) increased from 1.00 (reference) to 1.42 (0.77–2.60), 1.64 (0.85–3.13), and 2.18 (1.09–4.35) with increasing quartiles of urinary PGE-M (P for trend = 0.031). This dose-response association pattern was not observed among those with BMI ≥ 25 kg/m^2.

Discussion

In the present study, we showed that pre-diagnosis urinary PGE-M levels were significantly associated with a subsequent risk of developing pancreatic cancer in a dose-response manner. This positive association persisted after adjusting for multiple potential confounders and after excluding cases diagnosed in the first year of follow-up as well as their matched controls. Furthermore, we found that this association with PGE-M was more evident among individuals of normal weight than those who were overweight or obese. This is the first prospective epidemiological study to demonstrate a positive association of urinary PGE-M

with the development of pancreatic cancer and a potential modifying effect of body weight on this association.

The etiology of pancreatic cancer remains largely unclear, but cumulative evidence has suggested that multiple biologic pathways, including the COX-2 pathway, are involved in the development of the disease (8–10). Both *in vitro* experiments and animal model studies have linked the COX-2 pathway to pancreatic carcinogenesis (11–14). Overexpression of the *COX-2* gene has been found in pancreatic tumor tissues and is correlated with poor prognosis of the disease (15–19). Epidemiological studies have also shown an inverse association between pancreatic cancer risk and use of NSAIDs that inhibit COX-2 (20–27). Intake of COX-2 inhibitors has been found to reduce the level of urinary PGE-M (29). Thus, our finding of a positive association between urinary PGE-M and pancreatic cancer is consistent with the role of *COX-2* overexpression and excessive prostaglandin production in pancreatic carcinogenesis. Our study provides additional evidence supporting an important role of the COX-2 pathway in the etiology of pancreatic cancer.

Our finding is also in line with a recent report from a retrospective case-control study that found urinary level of PGE-M was significantly higher among pancreatic cancer cases than in controls (28). The potential influence of body weight on the association was not evaluated in that study. Similar to findings from our previous study on urinary PGE-M and breast cancer risk (36), we found in this study that body weight may modify the association between urinary PGE-M and pancreatic cancer risk. The mechanism for such potential modification, however, is unclear. Obesity is a risk factor for pancreatic cancer (39) and creates a chronic inflammatory status, which has also been linked to various types of cancer (40, 41). It has been well documented that both tumor cells and adipose tissue can produce inflammatory cytokines and PGE_2 (41, 42). Overweight or obese individuals have an increased PGE_2 production by adipose tissue and thus a higher level of urinary PGE-M (36). In addition, multiple obesity-related pathways may also be involved in and/or interact with COX2/PGE2 signaling (43, 44). We speculate that the relationship between PGE-M and pancreatic cancer among overweight or obese individuals may be masked by an excessive background level of PEG_2. This may explain the clearer dose-response association between PGE-M and pancreatic cancer we observed among normal weight individuals in our study.

Pancreatic cancer is one of the most fatal cancers. Besides the aggressive nature of this malignancy, multiple factors have been attributed to the poor outcome of the disease, including a lack of biomarkers for predicting pancreatic cancer risk. It is generally accepted that the most accurate index of endogenous eicosanoid production in humans is the measurement of excreted urinary metabolites. The measurement of excreted urinary PGE-M has been accepted as the best way to quantify systemic PGE2 production *in vivo* (29, 30). Thus, the positive association found in our study for urinary PGE-M levels and pancreatic cancer risk reflects the relationship between *in vivo* level of COX-2 pathway activity and development of pancreatic cancer and suggests that urinary PGE-M may serve as a promising cancer biomarker to predict pancreatic cancer risk, particularly in normal weight individuals.

The most important strength of the present study is our prospective study design. In contrast with the retrospective study, our study used urine samples collected before cancer diagnosis and treatment, and thus minimized potential reverse causality and avoided influence of cancer treatments. Other strengths of the present study include the population-based cohort, high follow-up rates, and high response rates for urine collection at baseline, which reduced the selection bias. In addition, a broad range of potential confounding factors were adjusted for during data analysis. These strengths have largely minimized potential selection and confounding biases. A number of limitations, however, should be acknowledged. First, as with most cohort studies, the SWHS and SMHS participants were not screened for cancer at baseline. Thus, there is a concern that undiagnosed, asymptomatic cancer could explain part of the association observed in the early years of follow-up. Our sensitivity analyses, however, showed that the significant association persisted after excluding cases diagnosed in the first year of follow-up. Nevertheless, we are most interested in evaluating a biomarker for predicting cancer risk, and therefore a biomarker that is capable of identifying undiagnosed, asymptomatic cancer could be highly valuable. Second, the misclassification of cases into the control group would falsely increase the mean urinary PGE-M levels and attenuate the true association. This bias is unlikely to be large because pancreatic cancer is a relatively uncommon cancer in China, and thus the possibility of undiagnosed cases in the control group is likely to be very small. In fact, based on the most recent follow-up, no controls included in the analysis were found to have any cancer diagnoses.

In summary, using data from two prospective cohort studies, we have shown that urinary level of PGE-M was positively associated with pancreatic cancer risk in a dose-response fashion. Such an association was more evident among normal weight than overweight or obese individuals. Our findings are consistent with the biological role of COX-2 and PGE2 in carcinogenesis and suggest that urinary PGE-M may serve as a promising cancer biomarker to predict pancreatic cancer risk. Further studies are warranted to verify our findings in other racial and ethnic populations.

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Abbreviations

BMI	body mass index
CI	confidence interval
COX-2	cyclooxygenase 2
NSAIDs	nonsteroidal anti-inflammatory drugs
PGE2	prostaglandin E2
PGE-M	metabolite of PGE2

OR	odds ratio
SWHS	Shanghai Women's Health Study
SMHS	Shanghai Men's Health Study

References

1. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. 2014; 371:1039–49. [PubMed: 25207767]
2. Cancer, A-Z. Key statistics for pancreatic cancer. Atlanta, (GA): American Cancer Society; c2017. http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-key-statistics [accessed April 2, 2017]
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013; 63:11–30. [PubMed: 23335087]
4. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016:115–32. [PubMed: 26808342]
5. Luo J, Xiao L, Wu C, Zheng Y, Zhao N. The Incidence and Survival Rate of Population-Based Pancreatic Cancer Patients: Shanghai Cancer Registry 2004–2009. PLoS One. 2013; 8:e76052. [PubMed: 24130758]
6. Cancer Statistics. SEER Stat Fact Sheets. Cancer of the Pancreas. Bethesda (MD): National Cancer Institute; http://seer.cancer.gov/statfacts/html/pancreas.html [accessed April 2, 2017]
7. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian Lm. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014; 74:291–321.
8. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002; 420:860–67. [PubMed: 12490959]
9. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008; 454:436–44. [PubMed: 18650914]
10. Hanahan D, Weinberg PA. Hallmarks of cancer: the next generation. Cell. 2011; 140:646–74.
11. Taketo MM. Cyclooxygenase-2 inhibit tumorigenesis. J Natl Cancer Inst. 1988; 90:1529–1536. 1609–20.
12. Elwood PC, Gallagher AM, Duthie GG, Mur LA, Morgan G. Aspirin, salicylates, and cancer. Lancet. 2009; 373:1301–9. [PubMed: 19328542]
13. Thun MJ, Blackard B. Pharmacologic effects of NSAIDs and implications for the risks and benefits of long-term prophylactic use of aspirin to prevent cancer. Recent Results Cancer Res. 2009; 181:215–21. [PubMed: 19213571]
14. Wang D, DuBois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010; 10:181–93. [PubMed: 20168319]
15. Matsubayashi H, Infante JR, Winter J, et al. Tumor COX-2 expression and prognosis of patients with resectable pancreatic cancer. Cancer Biol Ther. 2007; 6:1569–75. [PubMed: 18000398]
16. Juuti A, Louhimo J, Nordling S, Ristimaki A, Haglund C. Cyclooxygenase-2 expression correlates with poor prognosis in pancreatic cancer. J Clin Pathol. 2006; 59:382–6. [PubMed: 16467169]
17. Merati K, Said SM, Andea A, et al. Expression of inflammatory modulator COX-2 in pancreatic ductal adenocarcinoma and its relationship to pathologic and clinical parameters. Am J Clin Oncol. 2001; 24:447–52. [PubMed: 11586094]
18. Yip-Schneider MT, Barnard DS, Billings SD, et al. Cyclooxygenase-2 expression in human pancreatic adenocarcinomas. Carcinogenesis. 2000; 21:139–46. [PubMed: 10657949]
19. Tucker ON, Dannenberg AJ, Yang EK, et al. Cyclooxygenase-2 expression is up-regulated in human pancreatic cancer. Cancer Res. 1999; 59:987–90. [PubMed: 10070951]
20. Risch HA, Lu L, Streicher SA, et al. Aspirin Use and Reduced Risk of Pancreatic Cancer. Cancer Epidemiol Biomarkers Prev. 2017; 26:68–74. [PubMed: 27999143]

21. Kho PF, Fawcett J, Fritschi L, et al. Nonsteroidal anti-inflammatory drugs, statins, and pancreatic cancer risk: a population-based case-control study. Cancer Causes Control. 2016; 27:1457–64. [PubMed: 27817122]
22. Vaughan LE, Prizment A, Blair CK, Thomas W, Anderson KE. Aspirin use and the incidence of breast, colon, ovarian, and pancreatic cancers in elderly women in the Iowa Women's Health Study. Cancer Causes Control. 2016; 27:1395–402. [PubMed: 27677628]
23. Cui XJ, He Q, Zhang JM, Fan HJ, Wen ZF, Qin YR. High-dose aspirin consumption contributes to decreased risk for pancreatic cancer in a systematic review and meta-analysis. Pancreas. 2014; 43:135–40. [PubMed: 24263109]
24. Streicher SA, Yu H, Lu L, et al. Case-control study of aspirin use and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2014; 23:1254–63. [PubMed: 24969230]
25. Bonifazi M, Gallus S, Bosetti C, et al. Aspirin use and pancreatic cancer risk. Eur J Cancer Prev. 2010; 19:352–4. [PubMed: 20502343]
26. Tan XL, Reid Lombardo KM, Bamlet WR, et al. Aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen, and pancreatic cancer risk: a clinic-based case-control study. Cancer Prev Res. 2011; 4:1835–41.
27. Anderson KE, Johnson TW, Lazovich D, Folsom Ar. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. J Natl Cancer Inst. 2002; 94:1168–71. [PubMed: 12165642]
28. Zhao J, Wang J, Du J, et al. Urinary Prostaglandin E2 Metabolite and Pancreatic Cancer Risk: Case-Control Study in Urban Shanghai. PLoS One. 2015; 10:e0118004. [PubMed: 25679523]
29. Wang D, DuBois RN. Urinary PGE-M: a promising cancer biomarker. Cancer Prev Res. 2013; 6:507–10.
30. Murphey LJ, Williams MK, Sanchez SC, 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; 334:266–7531. [PubMed: 15494133]
31. Cai Q, Gao YT, Chow WH, et al. Prospective study of urinary prostaglandin E2 metabolite and colorectal cancer risk. J Clin Oncol. 2006; 24:5010–6. [PubMed: 17075120]
32. Johnson JC, Schmidt CR, Shrubsole MJ, 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. [PubMed: 16996805]
33. Shrubsole MJ, Cai Q, Wen W, et al. Urinary prostaglandin E2 metabolite and risk for colorectal adenoma. Cancer Prev Res. 2012; 5:336–42.
34. Davenport JR, Cai Q, Ness RM, et al. Evaluation of pro-inflammatory markers plasma C-reactive protein and urinary prostaglandin-E2 metabolite in colorectal adenoma risk. Mol Carcinog. 2016; 55:1251–61. [PubMed: 26333108]
35. Dong LM, Shu XO, Gao YT, 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. [PubMed: 19861525]
36. Cui Y, Shu XO, Gao YT, et al. Urinary prostaglandin E2 metabolite and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2014; 23:2866–73. [PubMed: 25214156]
37. Zheng W, Chow WH, Yang G, et al. The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol. 2005; 162:1123–31. [PubMed: 16236996]
38. Shu XO, Li H, Yang G, Gao J, Cai H, Takata Y. Cohort Profile: The Shanghai Men's Health Study. Int J Epidemiol. 2015; 44:810–18. [PubMed: 25733578]
39. Cancer, A-Z. Pancreatic cancer risk factors. Atlanta, (GA): American Cancer Society; www.cancer.org/cancer/pancreaticcancer/…/pancreatic-cancer-risk-factors [Accessed March 8, 2017]
40. Wellen KE, Hotamisligil GS. Obesity-induced inflammatory changes in adipose tissue. J Clin Invest. 2003; 112:1785–8. [PubMed: 14679172]
41. Ramos-Nino ME. The role of chronic inflammation in obesity-associated cancers. ISRN Oncol. 2013; 2013:697521. [PubMed: 23819063]

42. Simpson ER, Brown KA. Obesity and breast cancer: role of inflammation and aromatase. J Mol Endocrinol. 2013; 51:T51–9. [PubMed: 24163427]

43. Tian J, Lambertz I, Berton TR, et al. Transgenic insulin-like growth factor-1 stimulates activation of COX-2 signaling in mammary glands. Mol Carcinog. 2012; 51:973–83. [PubMed: 22006370]

44. Prueitt RL, Boersma BJ, Howe TM, et al. Inflammation and IGF-I activate the Akt pathway in breast cancer. Int J Cancer. 2007; 120:796–805. [PubMed: 17096325]

Novelty and Impact

Experimental and animal model studies suggest that overproduction of prostaglandin-E2 (PGE2) may promote the development pancreatic and other cancers. In this prospective study, we demonstrated, for the first time, that individuals with a high level of urinary PGE2 metabolites (PGE-M) were at an elevated risk of developing pancreatic cancer, and this risk may be modified by body weight. Our findings suggest that urinary PGE-M may serve as a biomarker in predicting pancreatic cancer risk.

Table 1

Baseline Characteristics of Pancreatic Cancer Cases and Matched Controls from the Shanghai Men's Health Study and Shanghai Women's Study

Baseline Characteristics	Case (n = 239)	Control (n = 483)	* P for difference
Age, mean ± sd (years)	61.5 ± 8.6	61.6 ± 8.6	0.88
Sex, male (%)	45.2	44.3	0.82
Education, < high school (%)	63.0	57.2	0.16
Positive family history of cancer (%)	27.2	29.0	0.66
Body mass index, mean ± sd (kg/m^2)	23.9 ± 3.1	24.1 ± 3.4	0.32
Never smoking (%)	68.2	74.6	0.20
Drank alcohol regularly (%)	13.8	17.0	0.33
Exercised regularly (%)	49.8	50.7	0.87
Regular use of aspirin (%)	5.4	7.0	0.52
Use of NSAIDs within past 7 days (%)	11.7	12.2	0.90

* P-values were derived from t-tests for continuous variables or Chi-squared tests for categorical variables

Table 2

Association between baseline urinary PGE-M levels and subsequent risk of pancreatic cancer

Urinary PGE-M levels	Cases	Controls	* OR (95%CI)	** Adjusted OR (95%CI)
All subjects (by quartile)	239	483		
Q1 (low)	47	121	1.00 (ref.)	1.00 (ref.)
Q2	65	121	1.54 (0.93–2.55)	1.63 (0.98–2.73)
Q3	58	121	1.42 (0.83–2.42)	1.55 (0.90–2.69)
Q4	69	120	1.80 (1.02–3.19)	1.94 (1.07–3.51)
P for trend			0.084	0.054
P for interaction between PGE-M and BMI			0.077	0.058
P for interaction between PGE-M and sex			0.446	0.201
Excluding cases diagnosed <1st year of follow-up (by quartile)	222	450		
Q1 (low)	43	115	1.00 (ref.)	1.00 (ref.)
Q2	62	117	1.63 (0.96–2.76)	1.74 (1.02–2.98)
Q3	54	108	1.62 (0.91–2.87)	1.78 (0.98–3.21)
Q4	63	110	1.96 (1.06–3.58)	2.11 (1.13–3.94)
P for trend			0.056	0.037
P for interaction between PGE-M and BMI			0.022	0.017
P for interaction between PGE-M and sex			0.4086	0.216

* ORs and 95 CIs were derived from conditional logistic models.

** ORs and 95 CIs were derived from conditional logistic models, with adjustment for BMI, family history of cancer, smoking status, alcohol consumption, regular exercise, regular aspirin use, and NSAIDs use in 7 days before blood collection.

Table 3

Association between baseline urinary PGE-M levels and subsequent risk of pancreatic cancer by follow-up time

Urinary PGE-M levels by median of follow-up years	Cases	Controls	* OR (95%CI)	** Adjusted OR (95%CI)
Cases diagnosed ≤ 5.8 years (by quartile)	120	240		
Q1 (low)	25	63	1.00 (ref.)	1.00 (ref.)
Q2	30	53	1.83 (0.85–2.53)	1.79 (0.79–4.06)
Q3	24	60	1.34 (1.04–3.45)	1.47 (0.66–3.30)
Q4	41	64	2.31 (1.00–5.35)	2.36 (1.01–5.55)
P for trend			0.114	0.093
Cases diagnosed > 5.8 years (by quartile)	119	243		
Q1 (low)	22	58	1.00 (ref.)	1.00 (ref.)
Q2	35	68	1.39 (0.73–2.65)	1.58 (0.82–3.08)
Q3	34	61	1.55 (0.74–3.24)	1.62 (0.75–3.49)
Q4	28	56	1.43 (0.64–3.18)	1.65 (0.71–3.84)
P for trend			0.392	0.277

* ORs and 95 CIs were derived from conditional logistic models.

** ORs and 95 CIs were derived from conditional logistic models, with adjustment for BMI, family history of cancer, smoking status, alcohol consumption, regular exercise, regular aspirin use, and NSAIDs use in 7 days before blood collection.

Table 4

Association between baseline urinary PGE-M levels and subsequent risk of pancreatic cancer by BMI

Urinary PGE-M levels by BMI	Cases	Controls	* OR (95%CI)	** Adjusted OR (95%CI)
Subjects with BMI < 25 (by quartile)	163	301		
Q1 (low)	35	82	1.00 (ref.)	1.00 (ref.)
Q2	43	83	1.30 (0.72–2.35)	1.42 (0.77–2.60)
Q3	37	64	1.52 (0.81–2.88)	1.64 (0.85–3.13)
Q4	48	72	2.00 (1.02–3.91)	2.18 (1.09–4.35)
P for trend			0.046	0.031
Subjects with BMI ≥ 25 (by quartile)	76	182		
Q1 (low)	12	39	1.00 (ref.)	1.00 (ref.)
Q2	22	38	2.10 (0.90–4.92)	2.19 (0.92–5.21)
Q3	21	57	1.38 (0.58–3.28)	1.44 (0.60–3.48)
Q4	21	48	1.77 (0.71–4.15)	1.72 (0.70–4.77)
P for trend			0.488	0.506

*ORs and 95 CIs were derived from conditional logistic models.

**ORs and 95 CIs were derived from conditional logistic models, with adjustment for BMI, family history of cancer, smoking status, alcohol consumption, regular exercise, regular aspirin use, and NSAIDs use in 7 days before blood collection.