Published in final edited form as:
J Urol. 2011 June ; 185(6): 2102–2107. doi:10.1016/j.juro.2011.02.020.

Oxidative Stress Measured by Urine F2-Isoprostane Level Is Associated With Prostate Cancer

Daniel A. Barocas, MD, MPH[1,2], **Saundra Motley, RN**[3], **Michael S. Cookson, MD, MMHC**[1], **Sam S. Chang, MD**[1], **David F. Penson, MD, MPH**[1,2,4], **Qi Dai, MD, PhD**[3], **Ginger Milne, PhD**[5], **L. Jackson Roberts II, MD**[5], **Jason Morrow, MD**[5], **Raoul S. Concepcion, MD**[1,6], **Joseph A. Smith Jr., MD**[1], and **Jay H. Fowke, PhD, MPH**[3]

[1]Vanderbilt University Medical Center, Department of Urologic Surgery, Nashville, TN

[2]Vanderbilt University Medical Center, Center for Surgical Quality and Outcomes Research, Nashville, TN

[3]Vanderbilt University Medical Center, Division of Epidemiology, Nashville, TN

[4]VA Tennessee Valley Healthcare System, Nashville, TN

[5]Vanderbilt University Medical Center, Division of Clinical Pharmacology, Nashville, TN

[6]Urology Associates, Nashville, TN

Abstract

Background—Oxidative stress is implicated in prostate cancer (PCa) by several lines of evidence. We studied the relationship between the level of F2-Isoprostanes (F2IP), a validated biomarker of oxidative stress, and PCa and high-grade prostatic intraepithelial neoplasia (HGPIN).

Methods—This case-control analysis within the Nashville Men's Health Study (NMHS) included men recruited at prostate biopsy. Body morphometrics, health history and urine were collected on over 2000 men prior to biopsy. F2-isoprostanes were measured by gas chromatography/mass spectrometry within an age-matched sample of NMHS participants that included 140 patients with HGPIN, 160 biopsy-negative controls, and 200 PCa cases. Multivariable linear and logistic regression were used to determine the associations between F2IP level and HGPIN and PCa.

Results—Mean age was 66.9 (SD 7.2) and 10.1% were non-white. Adjusted geometric mean F2IP levels were higher in patients with PCa (1.82, 95% CI[1.66-2.00]) or HGPIN (1.82, 95% CI[1.68-1.96]) than in controls (1.63, 95% CI[1.49-1.78]), $p<0.001$, but were similar across Gleason scores ($p=0.511$). The adjusted odds of HGPIN and PCa increased with increasing F2IP quartile (p-trend = 0.015 and 0.047, respectively) and the highest F2IP quartile was associated with a significantly increased odds of PCa (OR 2.44, 95% CI [1.17-5.09], $p=0.017$).

Conclusions—Pre-diagnosis urine F2IP level is elevated in men with HGPIN or PCa, suggesting urinary F2IP provides a biomarker for the role for oxidative stress in prostate carcinogenesis. F2IP may also serve to estimate the efficacy of interventions targeting oxidative stress mechanisms in prostate cancer prevention or treatment.

Corresponding Author: Daniel A. Barocas, MD, MPH, Vanderbilt University Medical Center, 2525 West End Avenue, Suite 600, Nashville, TN 37203, Dan.barocas@vanderbilt.edu, Telephone: 615-936-8322, Facsimile: 615-322-8990.

Supplemental Material URL: https://www.mc.vanderbilt.edu/root/vumc.php?site=urologicsurgery&doc=32446

Financial Disclosures: None to report

Keywords

prostate cancer; oxidative stress; isoprostanes; high-grade prostatic intraepithelial neoplasia; biopsy

Introduction

The mechanism of prostate carcinogenesis is not completely understood, but evidence suggests that oxidative stress (OxS) plays a role. Most cells in healthy individuals have adequate antioxidant defenses to protect them from reactive oxygen species (ROS)2. However, this capacity diminishes with aging and can be overwhelmed by an abundance of ROS from exogenous or endogenous sources, or by enzymatic deficiencies due to polymorphisms and mutations.

Chronic inflammation and OxS have been linked to carcinogenesis including stomach, liver and colon.3 The relevance of OxS in prostate carcinogenesis is suggested by associations between prostate cancer (PCa) and conditions associated with OxS, such as inflammation3, obesity4, GSTP1 methylation5 and the metabolic syndrome6; as well as medications and nutrients that affect oxidative stress level, such as vitamin E7, lycopene8, selenium9, non-steroidal anti-inflammatory medicines (NSAIDs)10, and HMG-CoA reductase inhibitor medications (statins)11. However, there have been few studies of systemic OxS indices and PCa risk, and no prior study has investigated the association between OxS biomarkers and high-grade prostatic intraephithelial neoplasia (HGPIN).

Thus, our goals were: 1) to determine whether chronic levels of systemic OxS, as measured by urine F2-isoprostane (F2IP) metabolite levels, are elevated in men with HGPIN and PCa compared to controls; 2) to characterize F2IP levels across the spectrum of prostate biopsy findings and; 3) to assess whether obesity influences the relationship between F2IP and diagnosis.

Methods

Parent Study Design

Protocols regarding the Nashville Men's Health Study (NMHS) have been published12. The NMHS is a prospective cohort study of men scheduled for transrectal ultrasound-guided (TRUS) biopsy of the prostate. It is designed to investigate markers of PCa risk and progression, and to explore gene-environment interactions involving obesity, diet, and other lifestyle-related risk factors. NMHS recruitment is ongoing, and recruitment efficacy is 96% of eligible subjects.

Participants were identified through the leading urologic clinics in Nashville, TN, including Vanderbilt University Hospital, the Nashville Veterans Administration Hospital and Urology Associates Clinic in Nashville. Men age 40 and older, with no prior history of PCa and with the ability to give consent were approached for enrollment on the day of their biopsy. All protocols were approved by the VUMC IRB, and all subjects signed consent.

Data Collection

A urine sample was collected prior to biopsy, processed and stored at -80° C. Research staff took body measurements and body mass index (BMI) was calculated. A structured questionnaire was used to assess socioeconomic status, race, health history, family history and other risk factors. The questionnaire return rate was approximately 70%. Medical charts were reviewed systematically to determine the results of the biopsy, digital rectal exam

(DRE) results, prostate-specific antigen (PSA) level, family history, current use of NSAIDs and statins, and TRUS prostate volume.

Biomarker Sub-Study

We created a biomarker sub-study of 500 NMHS participants recruited between 2003 and December 2008 to investigate the associations between cancer and candidate urine biomarkers. The sub-study included two case groups (HGPIN and PCa) and a control group without PCa or HGPIN or other suspicious findings at biopsy. Since the inclusion of patients with HGPIN is unique to this study, we selected all 140 available HGPIN patients. We then selected 100 low-grade cancer cases (Gleason = 6), 100 high-grade cancer cases (Gleason = 4+3=7, 8, 9, 10), and 160 biopsy-negative controls. Cancer case and control groups were frequency-matched by 5-year age categories according to the distribution of patients in the HGPIN group by random selection. 498 of the 500 selected patients (99.6%) had a urine specimen available.

Our primary aim was to determine whether men in the highest quartile of urine F2IP level had a detectable increase in the odds of HGPIN or PCa compared to controls. With a fixed sample size of 498 men, we calculated a minimum detectable difference (odds ratio) of 2.0 for HGPIN and 1.9 for cancer, assuming an alpha level of 0.05 and a power of 80% (PS DuPont Software, http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize.)

F2IP Assay

The major urinary metabolite of 15-F2t-Isoprostane was measured by gas chromatography/ negative ion chemical ionization mass spectrometry (GC/NICI MS), as reported in detail previously13. In brief, GC uses a 15-m, 0.25-mm-diameter, 0.25-μm-film thickness, DB1701 fused silica capillary column (Fisons, Folsom, CA). The column temperature is programmed from 190° to 300°C at 15°C /min. The metabolite is chemically synthesized and converted to an $^{18}O2$-labeled derivative for use as an internal standard. After purification, the compound is analyzed as a pentafluorobenzyl ester trimethylsilyl ether. Precision of the assay is ±4% and accuracy is 97%13. The lower limit of sensitivity is approximately 20pg13. The laboratory was unable to calculate F2IP level for one cancer case due to an inadequate urine aliquot volume, and one with a low urine creatinine.

Statistical Analysis

F2IP levels were normalized to urinary creatinine. Median F2IP level was compared across categorized baseline characteristics using Kruskal-Wallis and Wilcoxon tests. We calculated adjusted geometric mean F2IP levels with 95% confidence intervals across participant characteristic by regression of log F2IP level on each baseline characteristic or case-control status, while adjusting for all covariates in the final multinomial model (below). F2IP levels were then back-transformed and geometric means with 95% confidence intervals are reported.

We evaluated the association between F2IP level and diagnostic group using multinomial logistic regression. Covariates were determined *a priori* including age (continuous and categorized) and those factors believed to influence OxS or associated with cancer detection on biopsy. We conducted analyses with and without PSA because it may be associated with F2IP level (thus, a potential confounder), but we also recognize that F2IP level and PSA could measure similar processes (i.e., OxS could lead to increases in both F2IP levels and PSA), or be directly causally related. Continuous measures were entered into the model using restricted cubic splines in order to avoid assumptions of linearity. F2IP level was categorized according to quartile in order to facilitate interpretation of the results. The final model included age, race (white/non-white), PSA level prior to biopsy, prostate volume,

DRE result (positive / negative), waist-to-hip ratio (WHR), BMI and current NSAID use (yes/no). The assumptions of each model were tested using the likelihood ratio test of goodness of fit. The two patients with incalculable F2IP level and patients with missing one or more covariates were excluded from the multivariate analysis (n=23), leaving 475 patients in the model.

In order to test the hypothesis that obesity was an effect modifier of the association between F2IP and diagnosis, the basic multinomial model (including only F2IP as the independent variable and age, to account for the study design) was stratified by BMI and WHR in separate analyses. In addition, the basic model was run with cross-product interaction terms for obesity ([F2IP X BMI] and [F2IP X WHR]). For each of the multinomial models, trend tests were performed by assigning consecutive integer values to each F2IP quartile and running the regression with F2IP quartile as a continuous variable.

In all analysis, a two-tailed p-value <0.05 was considered significant. No adjustments were made for multiple comparisons. Analysis was performed with STATA/SE 10.1 (Stata Corporation, College Station, TX).

Results

Mean age was 66.9 (SD 7.2) and 10.1% were non-white. Patients differed across diagnostic groups (control, HGPIN, PCa) with respect to PSA, positive DRE and prostate volume. The groups were similar in terms of age (through the study design), race, family history of PCa, smoking history, NSAID use and BMI (Table 1).

Median F2IP levels varied across strata of some baseline variables, such as race, BMI and PSA categories. Adjusted geometric mean F2IP level varied by age group, NSAID use, DRE result and prostate volume quartile (S. Table 1).

Median F2IP levels were significantly higher in patients with PCa or HGPIN than in biopsy-negative controls (median F2IP = 1.89 vs. 1.83 vs. 1.54, respectively, p=0.032; Table 2). F2IP levels did not differ significantly between HGPIN cases and PCa cases (p=0.855) or between low-grade and high-grade cancer cases (1.80 vs. 1.94, respectively, p = 0.691). Adjusted geometric means showed a similar pattern, with elevated levels among men with HGPIN or cancer, but no statistically significant differences between HGPIN and cancer or between low- and high-grade cancer (Table 2).

The basic multinomial regression model, including only F2IP quartile and age demonstrated that men in the highest quartile of F2IP level had significantly higher odds of PCa (OR= 1.99, 95% confidence interval [1.07, 3.72], p=0.030). The relationship between F2IP and diagnosis was relatively constant across strata of WHR and BMI, although the association between F2IP and PCa was significant only among men with a larger WHR circumference (S. Table 2). Cross-product interaction terms for [F2IP X WHR] and [F2IP X BMI] were not statistically significant.

In the final multivariate model (Table 3), higher F2IP levels were significantly associated with PCa on biopsy (Q4 vs. Q1: OR=2.44 [1.17 - 5.09], p-trend = 0.015). Similarly, the risk of HGPIN was associated with F2IP levels (p-trend = 0.047.) A one-level increase in F2IP quartile was associated with a 27% increased odds of HGPIN and a 33% increased odds of PCa. These results upheld the relationship seen in the basic model, demonstrating that the relationship between F2IP and diagnosis is independent of other factors, including PSA. Exploratory models including family history of PCa and smoking history did not alter the relationship between F2IP level and diagnosis (data not shown).

Discussion

We found that urine F2IP levels were higher in men with HGPIN or PCa than in controls, whereas differences between HGPIN and cancer patients were small and non-significant. There was a statistically significant trend of increasing odds of PCa or HGPIN with higher quartile F2IP levels, even after adjusting for covariates that influence OxS levels, PCa risk, or PCa detection. The highest quartile of F2IP level was associated with a statistically significant increase in the odds of PCa. Obesity did not modify this relationship, suggesting that the influence of obesity on PCa may not be mediated by OxS level.

OxS occurs when the load of ROS exceeds the cell's capacity to quench the ROS, leading to DNA damage, mutagenesis and, ultimately, cancer2. Numerous factors may influence both the ROS/detoxification balance and the development of PCa, including inactivation of GST-Pi, an important detoxification enzyme14, inflammation3, androgen and estrogen metabolism15, intake of exogenous anti-oxidants7, use of certain medications10, 11, and diet/obesity. Although recent clinical trials of Vitamin E, C and Selenium have shown no decrease in PCa incidence16, 17, animal and human studies support the concept that the OxS pathway can be modified, with resultant changes in PSA kinetics and disease progression10, 11, 18.

A number of studies have identified a link between OxS and PCa, using *tissue-level* markers such as 8-hydroxydeoxyguanosine (8-OHdG)2, 19-21. However, few studies have compared the level of *systemic* OxS biomarkers between men with PCa and men with negative biopsies, and none have done so in men with HGPIN22, 23. Although the results are not completely consistent, most studies of C-reactive protein (CRP) levels, a copper-induced peroxidation assay, and MDA have demonstrated an association with disease status21, 22, 24, 25.

Isoprostanes are prostaglandin (PG)-like compounds, formed from the free-radical-catalyzed peroxidation of arachidonic acid. F2IP measured by GC/MS has impressive performance characteristics26: levels remain relatively constant over long periods of time; are not subject to collection-related oxidation artifact; are not influenced by the lipid content of the diet; and do not degrade over time in -80 C conditions13. As such, F2IP measurement has supplanted other methods of measuring systemic OxS, such as measuring levels of MDA, 8-hydroxydeoxyguanosine (8-OHdG), or measuring serum levels of antioxidant micronutrients. Urine F2IP has been measured in only one prior PCa study, with no observed difference between men with PCa compared to healthy controls23. However, F2IP levels were measured by radio-immunoassay, which is far less accurate, presumably due to cross-reactivity of the antibody27. In contrast, we found F2IP levels were significantly higher among men with PCa when F2IP was measured by GC/MS. While the magnitude of the difference in F2IP levels between cases and controls was not sufficient to warrant further study of F2IP as a clinical biomarker, it does suggest that men with HGPIN and PCa have higher levels of systemic OxS than men without cancer or HGPIN. Thus, these findings implicate OxS as an important process in prostate carcinogenesis.

Obesity induces a state of chronic inflammation via pro-inflammatory cytokines such as IL-6 and TNF-alpha, and may result in downstream pathology through OxS mechanisms28. Obesity also increases the risk of aggressive PCa and is consistently associated with poorer prognosis after detection and disease progression after treatment4. While systemic OxS levels are generally elevated in obese people and those with metabolic syndrome, the difference is far more pronounced in women than men and may, in fact, be negligible in men29. This suggests that susceptibility to the effects of OxS may be more at issue than its

absolute level and may explain why we did not see an effect of obesity on the relationship between F2IP and diagnosis.

There are several strengths with this investigation. The NMHS provides a very well-characterized study population with pre-diagnostic biospecimen and data collection, preventing any influence of post-diagnostic behavioral changes to affect F2IP levels and allowing for adjustment for a wide range of covariates. We included biopsy-negative controls, which is important due to the high prevalence of occult PCa in the community. In addition, we included a large number of patients with HGPIN, which is entirely novel. Lastly, although we elected not to include other OxS biomarkers, we utilized the gold-standard marker of systemic OxS (urine F2IP) and the most precise assay available (GC/MS), making this the first study to use this assay for the evaluation of OxS in men undergoing prostate biopsy and the first to evaluate F2IP levels in HGPIN patients.

While urine F2IP level is a validated marker of systemic OxS, the extent to which levels may be influenced by local conditions in the prostate remains unclear. The study is limited by the fact that the exposure (F2IP) and the outcome (diagnosis) are ascertained at nearly the same point in time, and the temporal sequence between OxS and PCa cannot be firmly established. However, past analyses have found urinary F2IP levels are stable over time and represent chronic level of OxS30, leaving open the possibility that the F2IP elevation predates the presence of HGPIN or cancer. The only way to address the ‘reverse causality’ question would be to collect urine in a large prospective cohort of men without cancer and follow patients over a long period of time, awaiting the accumulation of cases. Thus, our results require confirmation in a large, long-term prospective study or randomized trial in which biospecimens were collected at enrollment.

Conclusions

The current study confirms that OxS levels are elevated in men with HGPIN and PCa, and this association was independent of central adiposity or obesity. These results suggest that OxS may play a role in the initiation and/or progression of PCa and may position F2IP as an important surrogate marker in studies aimed at manipulating the OxS pathway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: Grant R01 CA121060 from the National Cancer Institute (PI: JHF)and UL1 RR024975 from NCRR/NIH; Grant K12 ES015855 from the National Institute of Environmental Health Sciences (K12 Scholar: DAB); Grant GM42056 from NIH (PI: LJR); Vanderbilt University Department of Urologic Surgery.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA: a cancer journal for clinicians. 2009; 59:225. [PubMed: 19474385]
2. Pathak SK, Sharma RA, Steward WP, et al. Oxidative stress and cyclooxygenase activity in prostate carcinogenesis: targets for chemopreventive strategies. Eur J Cancer. 2005; 41:61. [PubMed: 15617991]
3. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. Nat Rev Cancer. 2007; 7:256. [PubMed: 17384581]

4. Freedland SJ, Aronson WJ, Kane CJ, et al. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. J Clin Oncol. 2004; 22:446. [PubMed: 14691122]
5. Nelson WG, De Marzo AM, Isaacs WB. Prostate cancer. N Engl J Med. 2003; 349:366. [PubMed: 12878745]
6. Gong Z, Neuhouser ML, Goodman PJ, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006; 15:1977. [PubMed: 17035408]
7. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med. 1994; 330:1029. [PubMed: 8127329]
8. Etminan M, Takkouche B, Caamaño-Isorna F. The role of tomato products and lycopene in the prevention of prostate cancer: a meta-analysis of observational studies. Cancer Epidemiol Biomarkers Prev. 2004; 13:340. [PubMed: 15006906]
9. Clark LC, Combs GF, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. JAMA. 1996; 276:1957. [PubMed: 8971064]
10. Smith M. Celecoxib Versus Placebo for Men With Prostate Cancer and a Rising Serum Prostate-Specific Antigen After Radical Prostatectomy and/or Radiation Therapy. Journal of Clinical Oncology. 2006; 24:2723. [PubMed: 16782912]
11. Hamilton RJ, Goldberg KC, Platz EA, et al. The influence of statin medications on prostate-specific antigen levels. J Natl Cancer Inst. 2008; 100:1511. [PubMed: 18957682]
12. Fowke JH, Motley SS, Wills M, et al. Prostate volume modifies the association between obesity and prostate cancer or high-grade prostatic intraepithelial neoplasia. Cancer Causes Control. 2007; 18:375. [PubMed: 17334811]
13. Morrow JD, Zackert WE, Yang JP, et al. Quantification of the major urinary metabolite of 15-F2t-isoprostane (8-iso-PGF2alpha) by a stable isotope dilution mass spectrometric assay. Anal Biochem. 1999; 269:326. [PubMed: 10222005]
14. Brooks JD, Weinstein M, Lin X, et al. CG island methylation changes near the GSTP1 gene in prostatic intraepithelial neoplasia. Cancer Epidemiol Biomarkers Prev. 1998; 7:531. [PubMed: 9641498]
15. Tam NN, Leav I, Ho SM. Sex hormones induce direct epithelial and inflammation-mediated oxidative/nitrosative stress that favors prostatic carcinogenesis in the noble rat. Am J Pathol. 2007; 171:1334. [PubMed: 17717140]
16. Lippman S, Klein E, Goodman P, et al. Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2009; 301:39. [PubMed: 19066370]
17. Gaziano J, Glynn R, Christen W, et al. Vitamins E and C in the Prevention of Prostate and Total Cancer in Men: The Physicians' Health Study II Randomized Controlled Trial. JAMA. 2009; 301:52. [PubMed: 19066368]
18. Basu H, Thompson T, Church D, et al. A Small Molecule Polyamine Oxidase Inhibitor Blocks Androgen-Induced Oxidative Stress and Delays Prostate Cancer Progression in the Transgenic Adenocarcinoma of the Mouse Prostate Model. Cancer Res. 2009; 69:7689. [PubMed: 19773450]
19. Bostwick DG, Alexander EE, Singh R, et al. Antioxidant enzyme expression and reactive oxygen species damage in prostatic intraepithelial neoplasia and cancer. Cancer. 2000; 89:123. [PubMed: 10897009]
20. Chiou CC, Chang PY, Chan EC, et al. Urinary 8-hydroxydeoxyguanosine and its analogs as DNA marker of oxidative stress: development of an ELISA and measurement in both bladder and prostate cancers. Clin Chim Acta. 2003; 334:87. [PubMed: 12867278]
21. Arsova-Sarafinovska Z, Eken A, Matevska N, et al. Increased oxidative/nitrosative stress and decreased antioxidant enzyme activities in prostate cancer. Clinical Biochemistry. 2009; 42:1228. [PubMed: 19465015]
22. Yossepowitch O, Pinchuk I, Gur U, et al. Advanced but not localized prostate cancer is associated with increased oxidative stress. J Urol. 2007; 178:1238. [PubMed: 17698111]

23. Gill J, Franke A, Steven Morris J, et al. Association of selenium, tocopherols, carotenoids, retinol, and 15-isoprostane F2t in serum or urine with prostate cancer risk: the multiethnic cohort. Cancer Causes Control. 2009; 20:1161. [PubMed: 19212706]

24. Latif Z, McMillan DC, Wallace AM, et al. The relationship of circulating insulin-like growth factor 1, its binding protein-3, prostate-specific antigen and C-reactive protein with disease stage in prostate cancer. BJU Int. 2002; 89:396. [PubMed: 11872031]

25. McMillan DC, Talwar D, Sattar N, et al. The relationship between reduced vitamin antioxidant concentrations and the systemic inflammatory response in patients with common solid tumours. Clinical nutrition (Edinburgh, Scotland). 2002; 21:161.

26. Kadiiska M, Gladen B, Baird D, et al. Biomarkers of Oxidative Stress Study II: Are oxidation products of lipids, proteins, and DNA markers of CCl4 poisoning? Free Radical Biology and Medicine. 2005; 38:698. [PubMed: 15721980]

27. Il'yasova D, Morrow JD, Ivanova A, et al. Epidemiological marker for oxidant status: comparison of the ELISA and the gas chromatography/mass spectrometry assay for urine 2,3-dinor-5,6-dihydro-15-F2t-isoprostane. Ann Epidemiol. 2004; 14:793. [PubMed: 15519902]

28. Cottam DR, Mattar SG, Barinas-Mitchell E, et al. The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obesity surgery. 2004; 14:589. [PubMed: 15186624]

29. Tsai IJ, Croft KD, Mori TA, et al. 20-HETE and F2-isoprostanes in the metabolic syndrome: the effect of weight reduction. Free Radic Biol Med. 2009; 46:263. [PubMed: 19013235]

30. Basu S. F2-isoprostanes in human health and diseases: from molecular mechanisms to clinical implications. Antioxid Redox Signal. 2008; 10:1405. [PubMed: 18522490]

Table 1

Patient characteristics and urine F2 isoprostane levels compared across diagnostic category.

	Control N=160 (%)	HGPIN N=140 (%)	Cancer N=196 (%)
Age in years, mean (SD)	67.0 (7.7)	65.9 (6.7)	67.5 (7.0)
Racial group			
White	144 (90.6)	125 (89.3)	177 (89.9)
Non-white	15 (9.4)	15 (10.7)	20 (10.1)
Body Mass Index			
≤ 25	20 (12.5)	27 (19.3)	32 (16.2)
> 25-30	88 (55.0)	71 (50.7)	96 (48.5)
>30	52 (32.5)	42 (30.0)	70 (35.3)
Waist-to-Hip Ratio, mean (SD)	1.02 (0.06)	1.01 (0.06)	1.03 (0.07)
NSAID use	76 (47.5)	61 (43.6)	89 (44.9)
PSA			
<= 4	51 (32.3)	16 (11.6)	23 (11.7)
>4 to 10	91 (57.6)	103 (74.6)	122 (61.9)
>10	16 (10.1)	19 (13.8)	52 (26.4)
Suspicious DRE	5 (3.1)	1 (0.7)	17 (8.6)
Family History	29 (25.4)	30 (28.3)	28 (20.9)
Ever smoked	67 (59.3)	67 (64.4)	93 (70.5)
Smoke now	11 (9.8)	15 (14.3)	18 (13.5)
Prostate Volume in cc, median (IQR)	46.8 (36.0-68.0)	47.0 (34.0-64.5)	40.0 (28.0-51.5)

HGPIN = High-grade prostatic intraepithelial neoplasia; NSAID = non-steroidal anti-inflammatory drug; PSA = prostate-specific antigen; DRE = digital rectal exam; F2IP = Urine F2-isprostane level, normalized to creatinine.

Table 2

F2-isoprostane levels across diagnostic categories

	Median F2IP	IQR	p value*	Adjusted Geometric Mean†	95% CI	p value*
Diagnostic Group						
Control	1.54	1.21 – 2.15	0.032	1.63	1.49 – 1.78	<0.001
HGPIN	1.83	1.23 – 2.56		1.82	1.66 – 2.00	
Cancer	1.89	1.26 – 2.56		1.82	1.68 – 1.96	
Grade of Cancer						
Gleason 6	1.80	1.27 – 2.44	0.691	1.82	1.68 – 1.98	0.511
Gleason 7 and above	1.94	1.27 – 2.71		1.81	1.66 – 1.96	

*Kruskal-Wallis test and Wilcoxon rank-sum test.

†Adjusted for age, race, DRE result, WHR quartile, BMI, NSAID use, prostate volume quartile, PSA category.

HGPIN = high-grade prostatic intraepithelial neoplasia.

p value for HGPIN vs. Cancer was 0.855 in the unadjusted analysis and 0.864 in the adjusted analysis.

Table 3

Fully adjusted multinomial logistic regression predicting HGPIN or prostate cancer on biopsy

	HGPIN			Prostate Cancer		
F2IP Quartile	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Q1	1			1		
Q2	0.87	0.42 – 1.77	0.696	1.41	0.71 – 2.82	0.325
Q3	1.56	0.76 – 3.17	0.223	1.72	0.84 – 3.55	0.139
Q4	1.82	0.87 – 3.80	0.113	2.44	1.17 – 5.09	0.017
p-trend			0.047			0.015

Controlled for age,5-year age category,race, PSA, prostate volume, DRE, WHR, BMI, and NSAID use.

F2IP = Urine F2-isprostane level, normalized to creatinine; HGPIN = high-grade prostatic intraepithelial neoplasia.