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Association between Non-Steroidal Anti-Inflammatory Drugs, PSA, and Prostate Volume

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Abstract

Purpose—NSAIDs such as aspirin prevent CVD, and several prior studies suggest NSAIDs also reduce prostate inflammation and prostate cancer risk. We investigated the association between NSAID use, PSA, and prostate volume, hypothesizing lower PSA and volume levels with NSAID use.

Methods—The Nashville Men's Health Study utilizes a multi-centered, rapid-recruitment protocol to collect clinical, biological, behavioral, and body measurement data from 1,277 men over age 40 years and scheduled for diagnostic prostate biopsy. NSAID use was ascertained by survey and clinical interview, and medical charts were reviewed to ascertain current PSA levels, prostate volume, and clinical diagnoses following biopsy.

Results—Approximately 46% of subjects reported taking NSAIDs, primarily aspirin (37%). After adjusting for age, race, and other factors; prostate volume was similar between aspirin users and non-users (47.6 vs. 46.0 mls, $p=0.16$). In contrast, PSA was significantly lower among aspirin users (7.3 vs. 8.0 ng/ml, $p=0.01$). The association between PSA and aspirin was significant among men with latent prostate cancer (6.1 vs. 7.3 ng/ml, $p<0.01$), marginal among PIN patients (5.0 vs. 5.9 ng/ml, $p=0.09$), while nonsignificant with a negative biopsy (5.6 vs. 5.7 ng/ml, $p=0.64$). The strongest PSA-aspirin association was among cancer cases with a prostate volume of 60 mls or more (7.3 vs. 12.7 ng/ml, $p<0.01$).

Conclusions—PSA levels were significantly lower among aspirin users with latent cancer. Prostate volume was not associated with NSAID use. Results suggest aspirin may affect prostate cancer detection, and suggests a potential detection bias in address in future studies of NSAIDs and prostate cancer prevention.

Keywords

prostate cancer; PSA; NSAID; aspirin; BPH

Introduction

Prostate histology consistent with prostate inflammation is common. Inflammatory infiltrates may be found in 43% of benign prostatic hyperplasia (BPH) cases¹, and chronic inflammation is associated with lower urinary tract symptoms and a larger prostate volume^{1,2}. Free radicals

induce, and derive from, inflammatory and immune responses, and trigger prostaglandin (PG) synthesis via the cyclooxygenase (COX) pathway³. The COX-1 and inducible COX-2 isoforms are rate limiting in the conversion of arachidonic acid to PGE₂ and other PGs known to increase cell proliferation in prostate and other tissues³. Several endogenous or exogenous factors may induce prostate tissue inflammation and PG synthesis, such as infection, trauma from urine reflux and prostatic calculi, sex hormone imbalance, and obesity. To varying degrees, these factors are also associated with prostate cancer risk and progression⁴. Similarly, COX-2 expression and PGE₂ levels are higher in prostate cancer and high-grade prostatic intraepithelial neoplasia (PIN) compared to benign tissue^{5,6}, and genetic variants in *COX-2* have been associated with prostate cancer risk⁷.

To the extent that inflammation generates an environment conducive to prostate tumor growth, non-steroidal anti-inflammatory drugs (NSAIDs) may reduce prostate cancer risk. NSAIDs, such as aspirin, inhibit COX activity and arachidonic acid metabolism, and a recent meta-analysis estimated NSAID use was associated with a 10% to 30% reduction in prostate cancer risk⁸. Subsequent investigations from the Baltimore Longitudinal Study of Aging (BLSA)⁹, the American Cancer Society's Cancer Prevention Study II¹⁰, and administrative data for pharmaceutical claims¹¹ also report protective associations between NSAID use and prostate cancer risk. However, several prior studies found no association, little dose-response effect, or inconsistent associations with stage or grade of disease⁸⁻¹⁰.

Inconsistencies as these across studies may derive from any relationship between NSAID use and the clinical methods used to detect early-stage prostate cancer within a population. Any decrease in prostate inflammation or infiltration into the glandular epithelium with NSAID use may decrease PSA levels below the level of clinical suspicion. NSAID administration decreased PSA velocity in two small trials of patients with biochemical failure following prostate cancer treatment^{12,13}. In contrast, PSA levels were slightly but significantly higher with non-aspirin-NSAID use among healthy men over 70 years of age and participating in the BLSA⁹. In addition, decreased prostate inflammation with NSAID use also may decrease prostate volume. Aside from the potential benefits in reducing the severity of lower urinary tract symptoms, volume reduction may improve PSA as a marker of cancer or increase the efficacy to sample cancer at prostate biopsy¹⁴.

This study investigates the association between NSAID use, PSA levels, and prostate volume, hypothesizing that NSAID users have lower PSA and volume levels. Results may have implications for prostate cancer detection, clinical decision-making following cancer diagnosis, and research investigating prostate cancer chemoprevention.

Materials and Methods

Study Population

All participants provided written informed consent with guarantees of confidentiality prior to data collection in accordance with the Vanderbilt University IRB. Men scheduled for a diagnostic prostate biopsy between 2002 and 2008 at a Vanderbilt University Medical Center (Nashville, TN), the Tennessee Valley Veteran's Administration Hospital (Nashville, TN), or Urology Associates, a private urology clinic in Nashville, were approached for recruitment. Eligible participants were 40 years of age or older and had no prior prostate cancer diagnosis. Approximately 95% of eligible men approached for recruitment agree to participate, and the study population included 1,372 eligible consenting subjects.

Data Collection

Measures of body size and weight were collected by a trained research staff member at the time of recruitment using standardized protocols. Participants wore a hospital gown or other light clothing, and did not wear shoes. Chart review included age, race, PSA history, and prostate needle-biopsy result (cancer, high-grade prostatic intraepithelial neoplasia (PIN), negative, or a suspicious, atypical, or other lesion). Gleason scores at biopsy were also ascertained for subjects diagnosed with cancer following pathology review of the biopsy specimen. Prostate volume (cm³) was measured by transrectal ultrasound (TRUS) during the prostate biopsy procedure. Family history of prostate cancer was ascertained from the surgical chart and by a structured research questionnaire administered to each participant upon recruitment. Subjects with a family history recorded on the chart or reporting a family history by questionnaire were considered positive for a family history. The analytic study population includes 1,277 (93%) subjects with data on PSA levels and prostate volume.

As a part of the pre-biopsy clinic visit, all subjects record all current medications on a medication record form. Subjects are instructed to make a list of all current medications at home or to bring their medications to this clinic visit. Medications reported on the medication record form were entered into the subject's computerized medical record. Prior to biopsy, the surgeon reviews all survey responses with the subject to confirm that the subject has been taking the listed drugs. Additionally, the surgeon makes specific queries to the subject for drugs such as aspirin or Coumadin that might affect bleeding or clotting during the biopsy procedure.

All prescription and non-prescription NSAIDs were abstracted from the medical record following consent from the subject. We also collected from the chart all data on prescription and non-prescription medications to treat cardiovascular disease (CVD), diabetes, hyperlipidemia, and BPH. Frequency and duration of use for these drugs were not systematically recorded and therefore were not included in this analysis. Drugs formulated as a combination of two or more active drugs were classified by the component drugs.

Data Analysis

Descriptive analyses included Chi-square tests between population characteristics and NSAID use, and Spearman correlation coefficients between PSA and prostate volume. The primary analytic approach compared mean PSA levels or prostate volume between men using vs. men not using aspirin, a selective COX-2 inhibitor, or another NSAID. The distributions of PSA level and prostate volume data were natural log transformed prior to analysis. In a linear model, mean PSA and volume scores across NSAID categories were adjusted for age; race (black/white); family history (Yes/No); number of prior PSA tests (1, 2, 3 or more); BMI; WHR; height; use of finasteride/dutasteride (Yes/No); other treatment for BPH (Yes/No), diabetes (Yes/No), CVD (Yes/No), hyperlipidemia (Yes/No); and the diagnosis of PIN, atypical findings suspicious for cancer, low-grade cancer, or high-grade cancer following biopsy. High-grade cancer was defined by a biopsy Gleason sum score of 7 or higher. PSA and prostate volume scores were back-transformed and geometric mean values are reported. Tests for trend in adjusted PSA or prostate volume were determined by the significance of a continuous variable for each categorization in a multivariable linear regression model. Tests for interaction were determined by cross-product term with NSAID use in the presence of each main-effect and other covariates.

Results

NSAID use was reported from 45.9% (n=586) of subjects (Table 1). Aspirin was the most common NSAID reported (36.7%, n=468), while only 3.5% (n=45) reported using celecoxib and other selective COX-2 inhibitors. Other NSAIDs reported by subjects included diclofenac

(n=5), etodolac (n=8), ibuprofen (n=40), indomethacin (n=12), meloxicam (n=17), nabumetone (n=2), naproxen (n=38), oxaprozin (n=1), piroxicam (n=1), sulindac (n=1), and leflunomide (n=1).

Several demographic and health-related factors were associated with NSAID use, including increasing age (< 50 yrs (18.8%), 80 yrs or more (56.0%); $p<0.01$), a higher BMI (<25 (40.4%), 35 or more (49.5%); $p<0.01$), and Caucasian race (Caucasian (47.4%), African-American (35.4%); $p=0.03$). NSAID use was significantly associated with taking medication for hyperlipidemia (Yes (61.9%), No (34.8%); $p<0.01$) or CVD (Yes (53.3%), No (36.1%); $p<0.01$) and marginally associated with taking medication for diabetes (Yes (54.1%), No (44.6%); $p=0.06$). NSAID use was not significantly associated with taking a steroid reductase inhibitor ($p=0.93$) or cancer grade at biopsy ($p=0.84$).

PSA levels were approximately 9% lower among aspirin users vs. non-aspirin users (7.3 vs. 8.0 ng/ml, $p=0.01$, adjusted for age, race, family history, biopsy outcome, and BPH treatment) (Table 2). Differences in PSA with aspirin use persisted after controlling for obesity and treatment for other conditions (7.1 vs. 7.8 ng/ml, $p=0.05$), and also with further adjustment for prostate volume (6.8 vs. 7.5 ng/ml, $p=0.01$). Results were similar when we repeated analyses after excluding any subject using an NSAID other than the one in question (aspirin: $n=450$: PSA=7.2 vs. 8.1; $p=0.01$; Cox-2 inhibitor: $n=27$: PSA=9.9 vs. 9.0; $p=0.51$; other: $n=91$: PSA=8.7 vs. 8.9; $p=0.69$). In contrast, prostate volume was not significantly associated with NSAID use.

Table 3 summarizes the association between PSA and aspirin by age, prostate volume, and diagnostic biopsy outcome. PSA levels were lower with aspirin use regardless of age (p -interaction = 0.82). However, differences in PSA associated with aspirin were significant among men with latent cancer ($p=0.02$), marginal among PIN patients ($p=0.09$), while negligible among men with a negative biopsy ($p=0.64$). Furthermore, PSA was lower among aspirin users with a prostate volume greater than 60 mls (8.6 vs. 9.7 ng/ml, $p=0.06$), but not among men with a volume between 40 and 60 mls (p -interaction<0.01).

We looked at the PSA and aspirin association within prostate volume and diagnostic categories (Table 4). PSA levels were somewhat lower among aspirin users within each category. Differences in PSA with aspirin use were statistically significant among cancer cases with a prostate volume of 60 mls or more (7.3 vs. 12.7 ng/ml, $p<0.01$).

Discussion

We found that men taking aspirin had approximately 9% lower PSA levels. Two prior small trials targeting prostate cancer patients with biochemical failure found PSA velocity decreased with selective COX-2 inhibitor administration^{12,13}. However, a prior cross-sectional analysis found PSA levels were slightly higher with NSAID use among healthy older men with low PSA levels⁹. Our results are, in part, consistent with these prior studies, as aspirin was associated with lower PSA levels among men with concurrent prostate cancer or PIN but less so among men with a negative biopsy. However, the association between aspirin use and PSA among biopsy-negative subjects was not modified by age (not shown), and we did not find an association between selective COX-2 inhibitors and PSA levels.

Aspirin is widely recommended to reduce CVD risk. Similarly, we found aspirin use significantly associated with age, BMI, and treatment for CVD and hyperlipidemia. PSA and prostate volume are also associated with obesity¹⁵, and medications used to treat these chronic conditions may affect PSA expression¹⁶. However, controlling for BMI, WHR, and the use of medications to treat CVD, hyperlipidemia, and diabetes had little effect on the association

between aspirin use and PSA levels, suggesting aspirin was not simply a proxy for these comorbid conditions or their associated treatments.

Prostate enlargement and histologic BPH are among the most common conditions associated with aging, and are often seen with concurrent acute or chronic inflammation. However, the effect of aspirin on PSA appears to be separated from the clinical parameters associated with BPH. For example, PSA levels were lower among aspirin users regardless of age. Furthermore, prostate volume was not associated with aspirin use, and although prostate volume and PSA levels were moderately correlated (NSAID user: $r_s=0.24$, $p<0.01$; NSAID non-user: $r_s=0.25$, $p<0.01$), aspirin remained associated with lower PSA levels after controlling for volume. Finally, aspirin was not associated with PSA levels among men without latent prostate cancer. Inflammation in the prostate tissue comprises multiple cellular and tissue phenotypes, and our results suggest that the effect of aspirin on PSA may be independent of the cellular or inflammatory processes associated with prostate enlargement.

In contrast, PSA levels were significantly lower with aspirin use among men with latent cancer. COX enzymes may be induced with conversion to cancer^{5,6}, perhaps providing a target for aspirin to reduce PG synthesis and the inflammatory response. Any decrease in PGs or inflammatory infiltration into the glandular epithelium with aspirin use may be sufficient to reduce PSA levels without affecting overall volume. A stronger association between aspirin and PSA among men with a larger prostate volume may reflect a larger tumor volume, or perhaps the effect of aspirin on PSA is more evident when prostate tissue is in a hyperproliferative or hyperinflammatory state⁵. Furthermore, these potential mechanisms do not exclude the possibility that aspirin also more directly effects carcinogenesis, perhaps through inhibiting testosterone secretion, inducing apoptosis in prostate cancer cells, or inhibiting VEGF expression associated with angiogenesis^{17,18}.

To the extent that aspirin lowers PSA levels, men with latent prostate cancer may not be referred for a diagnostic biopsy. An overall difference of approximately 1 ng/ml PSA with aspirin use may have the greatest impact on men with borderline PSA levels (e.g., >2.5 ng/ml). Cancer detected in these patients is often localized and may be most responsive to early treatment. Furthermore, several prior studies report a small risk reduction associated with NSAID use⁸. However, our data suggest such a protective association could also be caused by differential prostate cancer detection with respect to aspirin use. While our study could not determine whether aspirin affects referral patterns, we found among men referred for biopsy aspirin was not associated with cancer grading at biopsy. Finally, aspirin use could potentially affect treatment decisions, as PSA levels at diagnosis are included in predictive models of pathological stage¹⁹ used to inform treatment decision-making. Thus, our results may have broad clinical and research implications that will require further investigation to characterize.

Strengths of this study include evaluation of PSA levels and volume in the ranges of clinical relevance. Furthermore, evaluation of subjects seeking a diagnostic biopsy allowed us to identify PIN cases and subjects without latent cancer or PIN at biopsy. BMI and WHR were measured by trained staff and standardized protocols. NSAIDs and other ascertained drugs included non-prescription drugs that would not be captured through prescription or billing records, and medication assessment occurs prior to biopsy or subject's knowledge of disease status, removing the potential for recall bias. All analyses controlled for finasteride/dutasteride use and other treatment for BPH or CVD. Surgeons routinely query patients specifically for drugs such as NSAIDs to avoid complications during the biopsy procedure, greatly increasing our ability to identify current NSAID users and the type of NSAID.

Study limitations include the cross-sectional design, and we were not able to capture with confidence data regarding duration or dose of NSAID use. However, aspirin use was clearly

the most common NSAID, consistent with the prevention of CVD. Indeed, aspirin was significantly associated with CVD and hyperlipidemia treatment, and it may be reasonable to assume that most subjects were taking aspirin on a regular basis consistent with guidelines to prevent CVD or other chronic conditions. Results from prior studies have been inconsistent regarding prostate cancer risk and duration or dose of NSAID use^{9–11}. The frequency of selective COX-2 inhibitors or other non-aspirin NSAID use was insufficient to analyze thoroughly and we cannot exclude the possibility of an association with non-aspirin NSAIDs.

In summary, PSA levels were significantly lower among men with latent cancer and taking aspirin. Contrary to hypothesis, prostate volume was not associated with NSAID use. Our results suggest aspirin use may affect prostate cancer detection and suggest a potential detection bias to address in future studies of NSAID use and prostate cancer prevention.

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References

1. Roehrborn CG. Definition of at-risk patients: baseline variables. *BJU Int* 2006;97 (Suppl 2):7. [PubMed: 16507046]
2. Nickel JC, Roehrborn CG, O'Leary MP, Bostwick DG, Somerville MC, Rittmaster RS. The Relationship between Prostate Inflammation and Lower Urinary Tract Symptoms: Examination of Baseline Data from the REDUCE Trial. *Eur Urol*. 2007
3. Lucia MS, Torkko KC. Inflammation as a target for prostate cancer chemoprevention: pathological and laboratory rationale. *J Urol* 2004;171:S30. [PubMed: 14713750]
4. Palapattu GS, Sutcliffe S, Bastian PJ, Platz EA, De Marzo AM, Isaacs WB, et al. Prostate carcinogenesis and inflammation: emerging insights. *Carcinogenesis* 2005;26:1170. [PubMed: 15498784]
5. Wang W, Bergh A, Damber JE. Cyclooxygenase-2 expression correlates with local chronic inflammation and tumor neovascularization in human prostate cancer. *Clin Cancer Res* 2005;11:3250. [PubMed: 15867220]
6. Denkert C, Thoma A, Niesporek S, Weichert W, Koch I, Noske A, et al. Overexpression of cyclooxygenase-2 in human prostate carcinoma and prostatic intraepithelial neoplasia-association with increased expression of Polo-like kinase-1. *Prostate* 2007;67:361. [PubMed: 17265445]
7. Shahedi K, Lindstrom S, Zheng SL, Wiklund F, Adolfsson J, Sun J, et al. Genetic variation in the COX-2 gene and the association with prostate cancer risk. *Int J Cancer* 2006;119:668. [PubMed: 16506214]
8. Mahmud S, Franco E, Aprikian A. Prostate cancer and use of nonsteroidal anti-inflammatory drugs: systematic review and meta-analysis. *Br J Cancer* 2004;90:93. [PubMed: 14710213]
9. Platz EA, Rohrmann S, Pearson JD, Corrada MM, Watson DJ, De Marzo AM, et al. Nonsteroidal anti-inflammatory drugs and risk of prostate cancer in the Baltimore Longitudinal Study of Aging. *Cancer Epidemiol Biomarkers Prev* 2005;14:390. [PubMed: 15734963]
10. Jacobs EJ, Rodriguez C, Mondul AM, Connell CJ, Henley SJ, Calle EE, et al. A large cohort study of aspirin and other nonsteroidal anti-inflammatory drugs and prostate cancer incidence. *J Natl Cancer Inst* 2005;97:975. [PubMed: 15998950]
11. Garcia Rodriguez LA, Gonzalez-Perez A. Inverse association between nonsteroidal anti-inflammatory drugs and prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13:649. [PubMed: 15066932]
12. Smith MR, Manola J, Kaufman DS, Oh WK, Bubley GJ, Kantoff PW. Celecoxib versus placebo for men with prostate cancer and a rising serum prostate-specific antigen after radical prostatectomy and/or radiation therapy. *J Clin Oncol* 2006;24:2723. [PubMed: 16782912]

13. Pruthi RS, Derksen JE, Moore D, Carson CC, Grigson G, Watkins C, et al. Phase II Trial of Celecoxib in Prostate-Specific Antigen Recurrent Prostate Cancer after Definitive Radiation Therapy or Radical Prostatectomy. *Clin Cancer Res* 2006;12:2172. [PubMed: 16609031]
14. Kulkarni GS, Al-Azab R, Lockwood G, Toi A, Evans A, Trachtenberg J, et al. Evidence for a Biopsy Derived Grade Artifact Among Larger Prostate Glands. *The Journal of Urology* 2006;175:505. [PubMed: 16406982]
15. Fowke JH, Signorello LB, Chang SS, Matthews CE, Buchowski MS, Cookson MS, et al. Effects of Obesity and Height on PSA and Percent Free PSA Levels Among African-American and Caucasian Men. *Cancer* 2006;107:2361. [PubMed: 17031814]
16. Yang CC, Ku CY, Wei S, Shiau CW, Chen CS, Pinzone JJ, et al. Peroxisome Proliferator-Activated Receptor γ -Independent Repression of Prostate-Specific Antigen Expression by Thiazolidinediones in Prostate Cancer Cells. *Mol Pharmacol* 2006;69:1564. [PubMed: 16452400]
17. Conte D, Romanelli F, Fillo S, Guidetti L, Isidori A, Franceschi F, et al. Aspirin inhibits androgen response to chorionic gonadotropin in humans. *Am J Physiol Endocrinol Metab* 1999;277:E1032.
18. Liu XH, Kirschenbaum A, Yu K, Yao S, Levine AC. Cyclooxygenase-2 suppresses hypoxia-induced apoptosis via a combination of direct and indirect inhibition of p53 activity in a human prostate cancer cell line. *J Biol Chem* 2005;280:3817. [PubMed: 15550400]
19. Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, Epstein JI, et al. Updated Nomogram to Predict Pathologic Stage of Prostate Cancer Given Prostate-Specific Antigen Level, Clinical Stage, and Biopsy Gleason Score (Partin Tables) Based on Cases from 2000 to 2005. *Urology* 2007;69:1095. [PubMed: 17572194]

Table 1

Study Population Characteristics

		n	%
Age (years)	40 – <50	48	3.8%
	50 – <60	292	22.9%
	60 – <70	518	40.6%
	70 – <80	344	26.9%
	80 – ≤90	75	5.9%
Race	African American	144	11.4%
	Caucasian	1125	88.6%
Family	Yes	258	20.2%
History	No/Unsure	1019	79.8%
# Prior	1	498	39.0%
PSA tests	2	402	31.5%
	3 or more	377	29.5%
NSAIDs	Yes	586	45.9%
	No	691	54.1%
	Aspirin *	468	36.7%
	Cox-2 inhibitors	45	3.5%
	Other	91	7.1%
Finasteride/Dutasteride	Yes	63	4.9%
	No	1214	95.1%
Other BPH Treatment	Yes	309	24.2%
	No	968	75.8%
Diabetes Treatment	Yes	172	13.5%
	No	1105	86.5%
Lipid Treatment	Yes	520	40.7%
	No	757	59.3%
CVD Treatment	Yes	726	56.9%
	No	551	43.2%
Biopsy Outcome	Gleason = 8–10	82	6.4%
	Gleason = 7	123	9.6%
	Gleason = 6	259	20.3%
	Atypia/suspicious	27	2.1%
	PIN	148	11.6%
	Negative	638	50.0%
Volume(mls)	Less than 40	545	42.7%
	40-< 60	409	32.0%
	60 or more	323	25.3%
PSA (ng/ml)	Less than 4.0	229	17.9%
	4.0 - <6.0	491	38.5%
	6.0 - <8.0	248	19.4%
	8.0 - <10	112	8.8%

	n	%
10 or more	197	15.4%

Frequencies may not total to 1,277 due to missing data.

* Use of Aspirin, selective COX-2 inhibitors (celecoxib, rofecoxib, valdecoxib) and Other NSAIDs are not mutually exclusive.

Table 2

Adjusted Mean PSA and Prostate Volume by NSAID Use

Drug Class	Use	n	Volume		PSA	
			mls [*]	mls ^{***}	ng/ml [*]	ng/ml ^{***}
NSAID	Yes	586	48.5	47.6	7.4	7.3
	No	691	47.0	46.0	8.1	7.8
Aspirin	Yes	468	0.21	0.17	0.04	0.09
	No	809	48.4	47.7	7.3	7.1
COX-2 Inhibitor	Yes	45	47.2	46.1	8.0	7.8
	No	1232	0.35	0.21	0.01	0.05
Other	Yes	91	48.0	45.4	8.7	8.3
	No	1186	47.6	46.7	7.8	7.5
	Yes	91	0.90	0.67	0.29	0.34
	No	1186	49.3	48.0	7.9	7.5
	Yes	91	47.4	46.6	7.8	7.5
	No	1186	0.33	0.53	0.88	0.98

* Adjusted for age, race, family history of prostate cancer, number of prior PSA tests, biopsy outcome, finasteride/dutasteride use, and treatment with other BPH medications.

** Additionally adjusted for BMI, WHR, height, and treatment for diabetes, hyperlipidemia, and CVD.

*** p-value for difference in PSA or volume scores by NSAID use.

Table 3
PSA and aspirin association across age, biopsy outcome, and prostate volume.

	Aspirin		No Aspirin		p-diff**
	n	PSA*	n	PSA	
Age (years)					
40 - <50	3	14.9	45	15.1	0.98
50 - <60	72	7.9	220	8.1	0.77
60 - <70	209	6.6	309	7.4	0.07
70 - <80	148	7.5	196	8.5	0.11
80 - ≤90	36	8.1	39	8.7	0.76
		*** = 0.82			
Biopsy Status ^{&}					
Negative	233	5.6	405	5.7	0.64
PIN	53	5.0	95	5.9	0.09
Cancer	173	6.1	291	7.3	0.02
Gleason 6	99	4.8	160	5.7	0.01
Gleason 7-10	74	14.9	131	16.2	0.56
		p-int = 0.09			
Volume (mls)					
Less than 40	175	6.5	370	7.2	0.13
40 - <60	160	7.5	249	7.6	0.87
60 or more	133	8.6	190	9.7	0.06
		p-int = <0.01			

* Adjusted for age, race family history, biopsy outcome, prostate volume, BMI, WHR, number of prior PSA tests, and treatment for BPH, CVD, hyperlipidemia, and diabetes. Excluded 24 subjects with atypia or other suspicious findings from analysis.

** p-value for difference in PSA levels between aspirin users and aspirin non-use within each stratum.

*** p-value for interaction to evaluate if the association between aspirin and PSA is similar across strata.

Table 4
PSA and aspirin association stratified by prostate volume and biopsy outcome.

Volume	Biopsy Status	Aspirin		No Aspirin		p-diff**
		n	PSA*	n	PSA	
less than 40ml [§]	Negative	71	3.9	154	4.2	0.45
	PIN	20	4.3	34	5.7	0.17
	Cancer	81	6.5	172	6.9	0.56
	Gleason 6	41	5.5	94	6.0	0.46
	Gleason 7-10	40	7.9	78	8.1	0.84
40 - <60 mls	Negative	82	5.6	142	5.4	0.45
	PIN	16	5.4	31	6.4	0.41
	Cancer	58	7.5	71	8.9	0.15
	Gleason 6	34	6.3	38	6.7	0.69
	Gleason 7-10	24	9.8	33	12.8	0.14
60 mls or more	Negative	80	6.4	109	6.7	0.71
	PIN	17	6.0	30	8.2	0.15
	Cancer	34	7.3	48	12.7	<0.01
	Gleason 6	24	5.5	28	7.5	0.09
	Gleason 7-10	10	15.5	20	27.9	0.02

* Adjusted for age, race family history, biopsy outcome, prostate volume, BMI, WHR, number of prior PSA tests, and treatment for BPH, CVD, hyperlipidemia, and diabetes. Excluded 24 subjects with atypia or other suspicious findings from analysis.

** p-value for difference in PSA levels between aspirin users and aspirin non-use within each stratum.