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Racial differences in the relationship between clinical prostatitis, presence of inflammation in benign prostate and subsequent risk of prostate cancer

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Abstract

BACKGROUND—Epidemiologic studies, primarily done in white men, suggest that a history of clinically-diagnosed prostatitis increases prostate cancer risk, but that histological prostate inflammation decreases risk. The relationship between a clinical history of prostatitis and histologic inflammation in terms of how these two manifestations of prostatic inflammation jointly contribute to prostate cancer risk and whether racial differences exist in this relationship is uncertain.

METHODS—Using a nested design within a cohort of men with benign prostate tissue specimens, we analyzed the data on both clinically-diagnosed prostatitis (NIH categories I–III) and histological inflammation in 574 prostate cancer case-control pairs (345 white, 229 African American).

RESULTS—Clinical prostatitis was not associated with increased prostate cancer risk in the full sample, but showed a suggestive inverse association with prostate cancer in African Americans (odds ratio (OR) = 0.47; 95% confidence interval (CI) = 0.27–0.81). In whites, clinical prostatitis increased risk by 40%, but was only associated with a significant increased prostate cancer risk in the absence of evidence of histological inflammation (OR = 3.56; 95% CI = 1.15–10.99). Moreover, PSA velocity ($P = 0.008$) and frequency of PSA testing ($P = 0.003$) were significant modifiers of risk. Clinical prostatitis increased risk of prostate cancer almost three-fold (OR = 2.97; 95% CI = 1.40–6.30) in white men with low PSA velocity and about twofold in white men with more frequent PSA testing (OR = 1.91; 95% CI = 1.09–3.35).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONCLUSIONS—In our cohort of men with benign prostate specimens, race, and histological inflammation were important cofactors in the relationship between clinical prostatitis and prostate cancer. Clinical prostatitis was associated with a slightly decreased risk for prostate cancer in African American men. In white men, the relationship between clinical prostatitis and prostate cancer risk was modified by histological prostatic inflammation, PSA velocity, and frequency of PSA testing—suggesting a complex interplay between these indications of prostatic inflammation and prostate cancer detection.

INTRODUCTION

Inflammation of the prostate gland—prostatitis—is a complex and heterogeneous condition.[1] The National Institutes of Health (NIH) classifies prostatitis into four categories:[2] Types I–III are symptomatic; in contrast, Type IV is asymptomatic and detected only upon histological examination of a prostate specimen.[3] Acute prostatitis (Type I) is more common in younger men,[4] whereas chronic prostatitis (Types II–IV) is associated with increasing age.[5] Two separate meta-analyses have estimated about a 60% increased risk of prostate cancer associated with prostatitis[6,7] and larger case-control studies have reported similar increased positive associations between prostatitis and prostate cancer.[8,9] Prevalence estimates of symptomatic prostatitis range between 9 and 12% in men between 20 and 79 years of age.[4,10,11] Acute prostatitis makes up < 1% of all prostatitis cases[12] and the most common type of prostatitis—asymptomatic (NIH Type IV)—is not fully captured in prevalence surveys. In fact, over 50% of surgical prostate specimens demonstrate some histological evidence of chronic inflammation.[13,14] Cross-sectional studies have found that histologic prostatic inflammation is 4–5 times more common in men without prostate cancer than those with cancer.[15–17] Although a recent prospective study examining histologic inflammation in benign prostate at time of cancer diagnosis found a strong association between inflammation and high-grade cancer,[18] most studies have found that inflammation in benign prostate is inversely associated with future prostate cancer risk.[14,17,19–22]

Associations between inflammation and prostate cancer may also vary by race. African American men are at greater risk for prostate cancer[23] and demonstrate higher levels of circulating PSA,[24,25] which can confound the relationship between inflammation and prostate cancer.[26] Even after adjusting for gland volume, benign prostatic tissue of African American men appears to contribute more PSA to circulating blood than that of white men.[27] One study has shown that histologic inflammation and higher PSA are more common in African American men with prostate cancer.[28] Another study of African American men found that prostatitis increased the risk for prostate cancer almost fivefold,[29] but a more recent study found no association in the African American case-control subset.[8] Our own study of inflammation and prostate carcinogenesis found no racial differences in prevalence of histologic inflammation.[14]

Although most histologic inflammation of the prostate is asymptomatic, previous prostate cancer risk studies have not considered histologic findings in the context of clinical presentation of prostatitis. In the present study, we first determined how the presence of histologic inflammation in the prostate is related to the subsequent clinical presentation of prostatitis, and whether this association differed by race. We hypothesized that the prostate

cancer risk associated with clinical prostatitis would differ according the presence or absence of histologic prostatic inflammation. To test this hypothesis, we conducted a nested case-control study to investigate the race-specific prostate cancer risk associated with clinically-reported prostatitis taking into account systematically acquired data on histologic prostatic inflammation as well as other factors that may have a role in inflammation-mediated prostate carcinogenesis.

MATERIALS AND METHODS

Study sample

After obtaining approval from the Henry Ford Health System Institutional Review Board, we selected a sample comprised of 574 case-control pairs matched on age at entry into cohort (±2 years), date of entry into cohort (±2 years), race (African American or white), and type of specimen (biopsy or TURP) from a historical cohort of 6692 men with a benign prostate specimen collected between January 1990 and December 2002.[14] An additional potential 228 pairs were excluded owing to: lack of analyzable prostate tissue (55%); lack of a PSA test within 1 year of cohort entry (16%); evidence of malignancy upon review of a previously classified benign specimen (13%); a benign specimen collected outside the window of cohort eligibility (5%); and incomplete medical records (10%). When we compared the 574 analytic cases with the 228 excluded cases we found no statistically significant differences in race, PSA level or time from cohort entry to diagnosis. Excluded cases were on average 1.3 years older ($P = 0.03$) and entered the cohort on average 13 months earlier ($P < 0.0001$). These two differences are likely owing to higher percentages of missing PSA data and availability of matching prostate specimens for the earliest years of the cohort.

Medical record and pathologic review

Clinical, demographic and comorbidity data were abstracted from patients' medical records, from 5 years before the date of cohort entry through the date of diagnosis (for prostate cancer cases) or reference date (for controls). Initially, medical records were scanned for any clinical note of 'prostatitis' during the reference period. Next, clinical information necessary to assign a NIH prostatitis diagnostic category[2] was obtained from additional chart review. Men with clinical notes of acute prostatitis (Type I) that later progressed to chronic prostatitis (Types II or III) were coded as having chronic prostatitis for analytic purposes. Diagnoses of prostatitis that appeared to be based primarily upon histology underwent a second medical chart review to confirm whether the prostatitis diagnosis could be classified as (a) chronic bacterial prostatitis (Type II) based on a history of bacteriuria or pyuria, or (b) chronic inflammatory prostatitis (Type IIIa) based on a history of inflammatory symptoms such as hematuria or dysuria, or (c) in absence of inflammatory symptoms, chronic noninflammatory prostatitis (Type IIIb) if specific pain-related symptoms, such as suprapubic discomfort, were reported.

Data on all PSA tests were recorded and the PSA test value immediately prior to the initial benign biopsy was used as the baseline. Data on lower urinary tract symptoms such as dysuria, frequent urination and hesitancy in urination were also recorded. Screening

intensity was measured as the number of PSA tests during follow-up. All surgical specimens were reviewed for the presence of inflammation and high-grade prostatic intraepithelial neoplasia by a single urological pathologist (ONK) blinded to outcomes.[14] Inflammation in biopsy specimens was classified by grade (mild, moderate or severe), extent (focal, multifocal or diffuse), and compartmental location (stromal, periglandular or glandular).[3] The latter definitions were used for analyses where we related presentation of clinical prostatitis (chronic or acute) with histologic location (stromal or glandular). Prostate size was estimated primarily from radiology reports as (dimension 1 × dimension 2 × dimension 3) × (3.14/6). In the absence of the dimensional data, recorded prostate volume or weight was used (based on the estimated density of 1 g cm^{-3} for prostate tissue).

Statistical analysis

Chi-squared tests were used to investigate associations between histological prostate inflammation and clinically-diagnosed prostatitis in all patients, and race and clinically-diagnosed prostatitis in patients with evidence of histological prostatic inflammation. A Cochran–Armitage Trend Test was used to test for a linear relationship between increased extent and grade of histological inflammation and a subsequent diagnosis of clinical prostatitis. Overall and race-specific percent agreements between clinical prostatitis and histologic inflammation were calculated, as was the sensitivity and specificity of histological inflammation of the prostate being a predictor of subsequent clinical prostatitis.

PSA density was calculated by dividing the PSA level at cohort entry by prostate volume. PSA velocity was the regression slope of the annual rate of PSA change from the time of cohort entry to the reference date. Conditional logistic regression analyses were used to estimate both unadjusted and adjusted odds ratios (ORs) and confidence interval (CI) for prostate cancer risk and to account for the one-to-one matched design that controlled for age, race and specimen type and to investigate any effect modification. Comparisons between the stratified models were assessed using a conditional logistic regression model that included interaction terms with the stratified variable. All tests were two sided.

RESULTS

Relationship between clinical and histological prostatitis

Our study sample of 574 case-control pairs comprised 968 unique individuals in which we first examined the association between presence of histologic inflammation and a subsequent manifestation of clinical prostatitis (Table 1). Overall, the proportion of men with histological prostate inflammation who subsequently had clinically-diagnosed prostatitis varied significantly by race (28.0% in African Americans versus 17.0% in whites; $P = 0.002$). Evidence of histological inflammation at baseline predicted subsequent clinical prostatitis with a sensitivity of 71%, but had low specificity (42.8%), and the overall agreement between the two manifestations of prostatic inflammation was low (47.8%). When we limited the analysis to agreement between chronic prostatitis and stromal inflammation, sensitivity dropped (58%) but specificity improved to (54.9%). Race-stratified analyses demonstrated that stromal inflammation was a more sensitive predictor of chronic prostatitis in African Americans than in whites (sensitivity 63.2% versus 52.6%), whereas

glandular inflammation was a slightly more sensitive predictor of acute prostatitis in whites (37.9% versus 20.0%).

We next examined whether increasing grade and/or extent of inflammation at cohort entry was associated with the development of clinical prostatitis (Table 2). Grade of inflammation was not associated with acute prostatitis to any significant degree, but the prevalence of chronic prostatitis increased steadily with increasing grade ($P_{trend} = 0.0005$). This association was observed more prominently in African Americans than in whites. Increasing extent of inflammation showed a positive association with both acute ($P_{trend} < 0.003$) and chronic ($P_{trend} < 0.0001$) prostatitis. In race-stratified analyses, acute prostatitis showed a stronger positive relationship with extent of histological inflammation in whites ($P_{trend} = 0.004$), whereas chronic prostatitis had a stronger positive relationship with increasing extent of histologic inflammation in African Americans ($P_{trend} = 0.0002$).

Clinical prostatitis and prostate cancer risk

We found no evidence of an association between history of clinical prostatitis and prostate cancer risk in unadjusted or adjusted analyses (Table 3). Separate analyses of acute and chronic prostatitis produced similar results. However, in race-stratified analyses, we found marked differences in the association between chronic prostatitis and prostate cancer. In whites, the risk was elevated (adjusted OR = 1.45; 95% CI = 0.79–2.64), but did not reach statistical significance. In African Americans, the adjusted odds ratio for chronic prostatitis showed a significant decreased risk (OR = 0.47; 95% CI = 0.27–0.81). Among the three categories of chronic prostatitis we analyzed, the main race-specific differences were observed for type II (2.0% in cases versus 0.9% in controls for whites and 2.2% in cases versus 3.9% in controls in African Americans) and type IIIb (1.7% in cases versus 0.6% in controls for whites and 0.9% in cases versus 3.9% controls in African Americans), the two least frequent forms of chronic prostatitis.

To better examine the observed racial difference in the association between clinical prostatitis and prostate cancer risk, we modeled histological inflammation and clinical prostatitis as separate covariates, both for the full sample as well as in a race-stratified manner (Table 4). In the full sample, history of clinical prostatitis was positively associated with prostate cancer in the absence of histological inflammation (OR = 1.50); this was reversed in the presence of histological inflammation (OR = 0.72). In race-stratified analyses, this difference became greater and statistically significant ($P = 0.04$). In whites, clinical prostatitis in the absence of histological inflammation increased risk of prostate cancer over 3-fold (OR = 3.56; 95%CI = 1.15–10.99). This difference in odds ratios for clinical prostatitis in the presence or absence of histological inflammation was less striking for African Americans.

Elevated PSA is an establish risk factor for prostate cancer—but it is also associated with prostatic inflammation, and therefore a potential confounder and/or effect modifier of the relationship between prostatitis and prostate cancer. In our sample, men whose PSA level was > 10 ng/ml at time of cohort entry had a 68% increased risk of prostate cancer ($P < 0.0001$). In addition, PSA levels were higher in men with histological prostatic inflammation versus those without (7.1 ± 7.2 versus 6.4 ± 5.5 ng/ml) and higher in men with a history of

clinical prostatitis versus those without (7.4 ± 8.1 versus 6.7 ± 6.2 ng/ml). Therefore, we tested whether PSA-related variables modified the prostate cancer risk associated with clinical prostatitis (Table 5). Stratifying on the median PSA level in our study sample (4.8 ng/ml), we found a significant difference between the low and high PSA strata ($P = 0.01$). In similar analyses for PSA density and PSA velocity, we found the latter was the strongest PSA-related effect modifier ($P = 0.008$) of the risk associated with clinical prostatitis in white men; men with low PSA velocity and a history of clinical prostatitis demonstrated almost 3-fold increased risk for prostate cancer (OR = 2.97; 95% CI = 1.40–6.30). In both the full sample and in white men, number of PSA tests was a significant modifier of risk ($P = 0.003$); the OR for prostate cancer associated with clinical prostatitis was 1.91 (95% CI = 1.09–3.35) in white men receiving ≥ 5 PSA tests.

DISCUSSION

In our large historical cohort of men with benign prostate specimens, men with histological inflammation of the prostate were more likely to also have clinical prostatitis with a greater concordance between the two in African American compared with white men. In the full sample and in white men, we found no evidence of an increased risk of prostate cancer associated with clinical prostatitis. However, in African American men, there was a weak inverse association between prostate cancer risk and prostatitis. In whites, a history of clinical prostatitis in the absence of histological inflammation increased risk for prostate cancer over threefold. This risk estimate was adjusted for number of PSA tests between cohort entry and diagnosis, and further adjustments for number of digital rectal exams and prostate biopsies did not diminish this risk estimate. As indicators of medical surveillance could not account for this paradoxical finding, it would seem that a more in-depth dissection of how clinically-diagnosed prostatitis relates to inflammation-driven prostate carcinogenesis in whites is needed.

Although we observed race-specific patterns in the association between clinical prostatitis and prostate cancer, most studies of prostatitis and prostate cancer have under-represented African Americans. A few studies with sizable African American samples have reported elevated prostate cancer risk associated with self-reported prostatitis in African American men.[29–31] Interestingly, both published meta-analyses of prostatitis have found significantly lower estimates of prostate cancer risk associated with prostatitis in clinic-based study populations where the diagnosis of prostatitis is likely more accurate.[6,7] The largest case-control study of prostatitis to date, not reviewed in either of these meta-analyses, found a modest 30% increased risk associated with prostatitis in whites and an inverse non-significant risk in African Americans.[8]

Extent and grade of prostatic inflammation are positively correlated with circulating PSA levels.[14,26,32,33] In our study, clinical prostatitis only increased prostate cancer risk among white men with lower PSA density and velocity. Although PSA level showed some suggestive modifying effect of the prostate cancer risk associated with clinical prostatitis in African Americans, neither PSA density nor velocity modified the prostate cancer risk associated with clinical prostatitis in African American men to the same extent that was observed in white men. Racial differences exist in PSA production after accounting for

prostate size,[24,27] which may account for racial differences we observed in the association between PSA levels and inflammatory-mediated prostate carcinogenesis.

Patients presenting with symptoms of prostatitis may be more likely followed by their urologist and thus more often screened for prostate cancer. Because of the overlap of lower urinary tract symptoms (LUTS) related to benign prostatic hypertrophy and chronic prostatitis,[34] clinicians may be more likely to label a patient with LUTS as having clinical prostatitis when evidence for histological inflammation is present. However, when we examined the association of LUTS with a diagnosis of clinical prostatitis by presence or absence of histological inflammation based on our systematic biospecimen review, 86.1% of men with histological inflammation and LUTS were diagnosed with clinical prostatitis, whereas 84.6% of men without histological inflammation but with LUTS were diagnosed with clinical prostatitis. Therefore, based on our definition of clinical prostatitis, over diagnosis does not appear to occur when LUTS and histological inflammation occur together. Retrospective studies of prostatitis are vulnerable to misclassification bias, as clinical signs and symptoms are variable and diagnoses are often uncertain.[1,35] Detection bias also appears to be an issue; in our study, clinical prostatitis was only associated with prostate cancer risk in white men with a high frequency of PSA testing. Interestingly, PSA testing frequency did not show a similar effect in African Americans, which may be explained in part by the racial differences in PSA production, perhaps amplified in the presence of prostatic inflammation.

Our assessment of clinical prostatitis was restricted to medical chart review at a single institution. Although this reduces recall bias, prostatitis diagnoses could have been missed if they occurred at another medical facility. We limited our analyses to ‘clinical prostatitis’ that could be classified as acute (Type I) or ‘chronic’ prostatitis (Types II and III) under the NIH prostatitis classification scheme[2]—essentially those cases with some symptomatic presentation. Even with this definition, the prevalence of prostatitis in our study sample was generally higher than previously reported,[8,36] reflecting our high-risk cohort. Our cohort was biased toward higher PSA levels, more inflammation and increased medical surveillance, but the extensive medical follow-up allowed us to test how PSA levels and testing can influence clinical associations in a race-specific manner. To that end, our results are generalizable to the ~ 700 000 US men who annually undergo a prostate biopsy and receive a negative result.[37]

Prostatitis is a biologically and clinically heterogeneous condition; as a result, determining its role in prostate carcinogenesis is challenging. As clinically-reported prostatitis is more likely when the underlying prostatic inflammation is extensive, the factors that influence the spread of prostatic inflammation, and how these factors may promote carcinogenesis need to be better understood. Epidemiologic studies of prostatitis must also consider detection bias and how to best correct for it given the link between prostatic inflammation and elevated PSA, which increases screening intensity for prostate cancer. Further dissection of inflammatory phenotypes—perhaps on the molecular level[38,39]—may ultimately be necessary to determine which inflammatory conditions of the prostate increase cancer risk.

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Table 1

Agreement between prostatic histological inflammation and presentation of clinical prostatitis

Type of histological inflammation	Prevalence of histologic inflammation by prostatitis status			Measures of agreement		
	Overall	Present	Absent	% Agreement	Sensitivity	Specificity
Full sample (n = 968)						
Any inflammation	59.6	70.7	57.2	47.8	70.7	42.8
Stromal inflammation	46.8	58.4	45.1	55.4	58.4	54.9
Glandular inflammation	18.5	30.6	17.9	79.6	30.6	82.2
Whites (n = 593)						
Any inflammation	58.7	68.6	57.0	46.7	68.6	43.0
Stromal inflammation	45.9	52.6	45.2	54.6	52.6	54.9
Glandular inflammation	20.4	37.9	19.3	78.6	37.9	80.7
African Americans (n = 375)						
Any inflammation	61.1	72.7	57.5	49.6	72.7	42.5
Stromal inflammation	48.3	63.2	45.0	56.5	63.2	55.1
Glandular inflammation	15.7	20.0	15.5	81.1	20.0	84.5

Table 2

Prevalence of clinical prostatitis (acute and chronic) by grade and extent of histological inflammation

Histological inflammation	*Full sample* (n = 968)				*Whites* (n = 593)				*African Americans* (n = 375)			
	% AP	P_{trend}	*% CP*	P_{trend}	*% AP*	P_{trend}	*% CP*	P_{trend}	*% AP*	P_{trend}	*% CP*	P_{trend}
Grade												
Absent	3.6	0.18	9.5	0.0005	2.9	0.12	8.2	0.10	4.8	0.82	11.6	0.0005
Mild	6.4		12.8		6.9		8.6		5.8		18.3	
Moderate	4.3		14.7		3.9		11.5		5.3		21.1	
Severe	6.7		20.8		7.4		13.7		5.6		33.3	
Extent												
Absent	3.6	0.003	9.5	< 0.0001	2.9	0.004	8.2	0.02	4.8	0.23	11.7	0.0002
Focal	4.4		11.7		4.9		8.3		3.7		16.8	
Multifocal	7.4		18.1		6.6		10.7		8.5		29.3	
Diffuse	16.7		36.7		20.0		35.0		10.0		40.0	

Abbreviations: AP, Acute prostatitis (NIH type I) prevalence; CP, Chronic prostatitis (NIH types II and III) prevalence.

Table 3

Distribution of prostatitis by case/control status and associated prostate cancer risk in full sample and stratified by race

Type of prostatitis		*Cases*		*Controls*		*Crude*		*Adjusted* [a]	
		Number	*Percent*	*Number*	*Percent*	*Odds ratio (95% CI)*	P-*value*	*Odds ratio (95% CI)*	P-*value*
Full sample (n = 574 pairs)									
None		472	82.2	469	81.7	Reference		Reference	
All prostatitis		102	17.8	105	18.3	0.96 (0.71–1.31)	0.81	0.82 (0.58–1.15)	0.24
Acute	I	30	5.2	28	4.9	1.07 (0.64–1.81)	0.79	0.92 (0.51–1.67)	0.79
Chronic	II	12	2.1	12	2.4	0.92 (0.65–1.31)	0.65	0.79 (0.53–1.17)	0.24
	IIIa/IIIb	60	10.5	6	11.3				
Whites (n = 345 pairs)									
None		293	84.9	303	87.8	Reference		Reference	
All prostatitis		52	15.1	42	12.2	1.29 (0.83–2.00)	0.26	1.20 (0.76–1.99)	0.40
Acute	I	16	4.6	16	4.6	1.00 (0.50–2.00)	1.00	0.92 (0.43–1.99)	0.84
Chronic	II	7	2.0	3	0.9	1.48 (0.85–2.57)	0.17	1.45 (0.79–2.64)	0.23
	IIIa/IIIb	29	8.4	23	6.7				
African Americans (n = 229 pairs)									
None		179	78.2	166	72.5	Reference		Reference	
All prostatitis		50	21.8	63	27.5	0.73 (0.47–1.13)	0.16	0.51 (0.30–0.85)	0.01
Acute	I	14	6.1	12	5.2	1.18 (0.53–2.64)	0.68	0.93 (0.37–2.40)	0.88
Chronic	II	5	2.2	9	3.9	0.65 (0.41–1.05)	0.08	0.47 (0.27–0.81)	0.007
	IIIa/IIIb	31	13.5	42	18.3				

Abbreviations: CI, confidence interval; HGPIN, high-grade prostatic intraepithelial neoplasia.

[a] Adjusted for PSA level, presence of HGPIN and number of PSA tests.

Table 4

Effect modification of histological prostate inflammation on risk of prostate cancer associated with clinical prostatitis[a]

Histologic inflammation	*Full sample* (n = 574 pairs)			*Whites* (n = 335 pairs)			*African Americans* (n = 229 pairs)		
	Odds ratio	*95% CI*	P-*value*	*Odds ratio*	*95% CI*	P-*value*	*Odds ratio*	*95% CI*	P-*value*
Any									
Absent	1.50	0.76–2.93	0.07	3.56	1.15–10.99	0.04	0.76	0.31–1.87	0.42
Present	0.72	0.47–1.09		0.92	0.52–1.65		0.49	0.26–0.92	
Stromal[b]									
Absent	1.18	0.64–2.17	0.12	3.00	1.06–8.47	0.08	0.58	0.25–1.32	0.58
Present	0.62	0.36–1.06		0.93	0.41–2.10		0.42	0.20–0.90	
Glandular[c]									
Absent	1.05	0.51–2.18	0.56	1.05	0.38–2.89	0.73	1.03	0.35–3.02	0.67
Present	0.72	0.26–2.02		0.79	0.24–2.66		0.63	0.09–4.65	

Abbreviations: CI, confidence interval; HGPIN, high-grade prostatic intraepithelial neoplasia.

[a]Adjusted for PSA level, number of PSA tests, and presence of HGPIN.

[b]Odds ratio is for risk associated with clinical chronic prostatitis.

[c]Odds ratio is for risk associated with clinical acute prostatitis.

Table 5

Effect modification of PSA variables on risk of prostate cancer associated with clinical prostatitis

PSA variable	*Full sample*			*Whites*			*African Americans*		
	Odds ratio	*95% CI*	P *value*	*Odds ratio*	*95% CI*	P *value*	*Odds ratio*	*95% CI*	P *value*
PSA level[a]	(*n* = 574 pairs)			(*n* = 345 pairs)			(*n* = 229 pairs)		
Low (< 4.8 ng/ml)	1.38	0.81–2.35	0.01	1.85	0.90–3.80	0.16	0.83	0.35–1.95	0.13
High (≥ 4.8 ng/ml)	0.58	0.37–0.89		0.94	0.50–1.77		0.37	0.19–0.69	
PSA density[a]	(*n* = 415 pairs)			(*n* = 241 pairs)			(*n* = 174 pairs)		
Low (< 0.12 ng/ml/ml)	0.97	0.57–1.64	0.55	2.11	1.00–4.45	0.15	0.39	0.15–0.94	0.49
High (≥ 0.12 ng/ml/ml)	0.75	0.41–1.37		0.85	0.33–2.19		0.60	0.26–1.39	
PSA velocity[a]	(*n* = 517 pairs)			(*n* = 312 pairs)			(*n* = 205 pairs)		
Low (< 0.36 ng/ml/year)	1.24	0.73–2.10	0.23	2.97	1.40–6.30	0.008	0.40	0.16–1.00	0.23
High (≥ 0.36 ng/ml/year)	0.78	0.45–1.33		0.65	0.30–1.41		0.84	0.38–1.86	
Number of PSA tests[b]	(*n* = 574 pairs)			(*n* = 345 pairs)			(*n* = 229 pairs)		
< 5	0.18	0.06–0.55	0.002	0.07	0.01–0.57	0.003	0.37	0.09–1.42	0.37
5 or more	1.12	0.78–1.61		1.91	1.09–3.35		0.70	0.42–1.16	

Abbreviations: CI, confidence interval; HGPIN, high-grade prostatic intraepithelial neoplasia.

[a]Adjusted for number of PSA tests and presence of HGPIN.

[b]Adjusted for PSA level and presence of HGPIN.