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Association Between Systemic Inflammatory Markers and Serum Prostate-Specific Antigen in Men without Prostatic Disease—The 2001–2008 National Health and Nutrition Examination Survey

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Abstract

BACKGROUND—Serum prostate specific antigen (PSA) may be elevated in otherwise healthy men; systemic inflammation has been associated with cancer. The study of systemic inflammatory markers in men without clinical prostate disease, but with elevated PSA may characterize the subgroup of men at higher risk for subsequent prostate cancer.

METHODS—We investigated the associations between systemic inflammatory markers and serum PSA in 3,164 healthy men without prostatic disease, aged >40 years, from the 2001 to 2008 U.S. National Health and Nutrition Examination Survey (NHANES). Serum total PSA levels and concentrations of serum C-reactive protein (CRP) and plasma fibrinogen, neutrophil count, lymphocyte count, and platelet count were recorded. Neutrophil-lymphocyte ratio (NLR) ratio and platelet-lymphocyte (PLR) ratio were calculated. PSA elevation was defined as levels equal or greater than 4 ng/ml.

RESULTS—Elevated serum PSA (194 men, 6.1% of the total), was significantly associated with plasma fibrinogen (OR_{multiv}=1.88; 95% CI, 1.09–3.25), and NLR (OR_{multiv}=1.14; 95% CI, 1.03–1.26), after adjustment for age, smoking, body mass index, education, race, co-morbidities, and use of medications.

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CONCLUSIONS—Markers of systemic inflammation were associated with elevated PSA in men without known prostatic disease. Future studies are needed to examine these markers' relationship with prostate cancer occurrence and progression.

Keywords

prostate cancer; systemic inflammation; screening; NHANES

INTRODUCTION

Serum prostate-specific antigen (PSA) is the most widely used screening test for prostate cancer (PC), though its use remains controversial. Although PSA has a good sensitivity, the test suffers from low specificity due to the difficulty in distinguishing patients with PC versus benign prostatic diseases [1]. Common urologic conditions, such as benign prostatic hyperplasia (BPH), acute/chronic prostatitis, or urinary tract infection can be associated with an elevated serum PSA. However, men with serum PSA levels ≥4.0 ng/ml are typically considered to be at risk for occult PC, and are often referred for further evaluation and a potential biopsy. As a result of the low specificity of PSA, a significant percentage of men who undergo an invasive prostate biopsy do not have PC. Furthermore, an invasive biopsy may miss cancer in some men, given that up to 20% of men will have PC on a repeat biopsy [2] Other data show that men with a false positive PSA at screening are more likely to develop PC during the follow-up [3]. The complexities of PC screening highlight the potential clinical value of additional serum biomarker(s) which, among men with elevated PSA, distinguishes those who may develop PC during the follow-up versus those with benign prostate conditions.

In an attempt to understand the biological meaning of a high PSA value, local and systemic inflammation has been studied. Local prostate inflammation infiltrates have been found in asymptomatic men with elevated PSA levels [4–8]; however, the evidence of an association between histological inflammation and PC is inconsistent. In addition, local inflammation was recently defined a non useful risk indicator in PC screening [9].

Systemic inflammation may play a role in the development and progression of cancer; epidemiologic evidence has linked PC to infectious agents, chronic and persistent infections, and pro-inflammatory hormonal or dietary factors [10,11]. Elevated C-reactive protein (CRP) and fibrinogen levels have been found to be associated with an increased risk of developing colorectal and lung cancer [12,13]; markers such as CRP, platelet counts, neutrophil counts, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) were reported to be associated with progression and poorer prognosis for multiple different cancers including lung, colorectal, pancreatic, ovarian, and PC [14–19]. However, there is no information on how systemic inflammation links to PSA levels in asymptomatic men. This is relevant, because if markers can be identified which track with PSA levels, it is possible that they may correlate with PC risk, thus becoming a useful additional tool to assess individual PC risk in men with elevated PSA.

To address this, we performed a cross-sectional study to test the association between serum PSA and markers of systemic inflammation in men without clinical prostate diseases; we

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hypothesized that systemic inflammatory markers would be positively associated with elevated serum PSA.

MATERIALS AND METHODS

Study Design and Population

The National Health and Nutrition Examination Survey (NHANES) is a population-based survey that uses a complex, multistage design to collect health and nutritional information from a nationally representative sample of non-institutionalized U.S. adults and children. In this cross-sectional study, we aggregated all available data from 2001 to 2008 to examine whether markers of systemic inflammation (CRP, fibrinogen, neutrophil count, platelet count, lymphocyte count, and NLR and PLR) were associated with elevated serum PSA (≥4 ng/ml) in men, aged >40 years, with no known evidence of prostatic disease.

Sample Selection

There were 6,832 men, aged >40 years, who participated in NHANES from 2001 to 2008. Of these men, 1,180 were missing serum PSA data and were not screened for PC, therefore were excluded; 2,488 men had various prostatic diseases including BPH, infection or inflammation of the prostate, self reported history of malignancy including PC, self-reported diagnosis of diabetes, taking 5-alpha-reductase inhibitors, and were therefore excluded from the analyses, leaving 3,164 men (~46% of the original sample) included in the present analysis. All study participants signed informed consent forms; and, the 2001–2008 NHANES was approved by the Research Ethics Review Board of the National Center for Health Statistics.

Data Collection

Demographic information (age, race, marital status, and educational status), current and past medical conditions, medication use (beta-blockers, statins, and nonsteroidal anti-inflammatory drugs), and lifestyle behaviors (i.e., alcohol drinking and smoking) were collected through questionnaires administered by trained interviewers. Meanwhile, medical examinations were conducted and participants' body mass index (BMI) (kg/m^2) was measured. Blood specimens were collected and laboratory tests were performed to examine the following: serum total PSA levels (ng/ml), serum CRP levels (mg/dl), plasma fibrinogen levels (g/L), neutrophil count (1,000 cells/μl), lymphocyte count (1,000 cells/μl), and platelet count (1,000 cells/μl). NLR was calculated as neutrophil cell count divided by lymphocyte cell count; and PLR was calculated as platelet count divided by lymphocyte cell count. Not all laboratory tests were performed throughout the 2001–2008 NHANES time period; as a result, sample size for the analysis of each marker was slightly different.

Laboratory Analysis

Latex-enhanced nephelometry was used to measure the quantification of high-sensitivity CRP in serum [20]. Plasma fibrinogen was determined by using the Clauss clotting method [21]. Complete blood count of platelets and white blood cells which include neutrophils and lymphocytes were determined by using the Beckman Coulter method [22]. Total PSA levels

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in serum were determined using the Access Hybritech PSA assay (Beckman Coulter, Inc.) [23].

Data Analysis

Men were categorized as having either normal (<4 ng/ml) or elevated (≥4 ng/ml) serum PSA; study characteristics were compared between the two PSA groups using a chi-square test for categorical variables and a Student's *t*-test for continuous variables. The geometric mean and standard error were calculated for these markers of systemic inflammation due to their skewed frequency distribution. Univariate, age-adjusted, and multivariable logistic regression models were used to examine whether markers of systemic inflammation, considered one at a time, were associated with elevated serum PSA by calculating the odds ratios (OR) and 95% confidence intervals (CI). In these analyses, markers of systemic inflammation (independent variables) were entered as a continuous variable in the regression models. Multivariable logistic regression analyses that examined the relationship between markers of systemic inflammation and elevated serum PSA were adjusted for the following variables due to their possible influence on serum PSA: age (continuous), ever smoker (yes or no), BMI (continuous), education (<high school, high school graduate, or >high school), race (Black, White, or other), medications (beta blockers, statins, and nonsteroidal anti-inflammatory drugs), and co-morbid conditions (heart disease, asthma, arthritis, chronic bronchitis, and emphysema).

All data analyses used the appropriate survey sample weights to provide nationally representative estimates. Statistical significance was determined at alpha level of 0.05. Data analysis was conducted in SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Of the 3,164 study participants, there were 2,970 (93.9%) and 194 (6.1%) men who had a normal and elevated serum PSA, respectively. On average, men with elevated PSA were significantly older, less likely to report drinking alcohol, and had a significantly lower BMI compared to men with normal PSA (Table I). Men with elevated PSA were also less educated, more likely to take beta blockers and statin, and less likely to take NASIDs in comparison to men with normal PSA; however, these differences were not statistically significant (Table I).

Men with elevated PSA had significantly higher geometric mean for serum CRP, plasma fibrinogen, NLR, and PLR compared to men with normal PSA. Lymphocytes were significantly lower in men with elevated PSA in comparison to men with normal PSA (Table II).

In univariate logistic regression analyses, serum CRP levels (OR_{crude}=1.19; 95% CI. 1.06–1.33), plasma fibrinogen levels (OR_{crude}=2.12; 95% CI, 1.56–2.87), and NLR (OR_{crude}=1.34; 95% CI, 1.21–1.48) were significantly associated with elevated PSA (Table III). When the analyses were age-adjusted, only plasma fibrinogen ($OR_{age\text{-}adj}$=1.79; 95% CI, 1.29–2.50) and NLR ($OR_{age\text{-}adj}$=1.15; 95% CI, 1.06–1.25) remained significantly associated with elevated PSA. After further adjustment for smoking, BMI, education, race,

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medications, and co-morbidities, plasma fibrinogen (OR_{multiv}=1.88; 95% CI, 1.09–3.25), and NLR (OR_{multiv} =1.14; 95% CI, 1.04–1.26) remained significantly and positively associated with elevated PSA (Table III).

DISCUSSION

To our knowledge, the current study is the first to date to examine the relationship between several systemic inflammatory markers and serum PSA levels among men without clinical signs of prostate disease. A previous study [24], and has shown that CRP and PSA are significantly associated. The study re-analyzed a data set from a clinical laboratory on an unselected population of 300 men who underwent PSA screening, whose clinical profile was unknown, thus some current and/or previously treated PC patients could have been included.

We found that NLR and plasma fibrinogen were positively associated with elevated serum PSA. These findings suggest that certain markers of systemic inflammation/immune system activation are associated with an elevated serum PSA. Whether the high serum PSA levels stem from unreported prostatic inflammation or BPH, undiagnosed PC, or some other source is not known in the present study. Appropriately designed prospective studies are needed to examine the source of the elevated PSA associated with increased markers of systemic inflammation in healthy men. If the source is unrecognized PC, then this not only provides further support for the link between inflammation and PC, but suggests that inflammatory markers may be useful in PC detection.

In this study, men with elevated serum PSA had a higher NLR in comparison to men with normal PSA levels. Since NLR is believed to reflect the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses, its association with higher serum PSA levels may indicate impairment in the adaptive host's ability to control inflammation. Studies have shown that elevated NLR is associated with increased concentration of various pro-inflammatory cytokines in patients with recurrent liver cancer and with colorectal cancer [15,25,26]. These pro-inflammatory cytokines may cause cellular DNA damage that could increase cancer risk. Whether elevated NLR is associated with increased concentration of pro-inflammatory cytokines in patients with elevated serum PSA is not known in the present study. A study conducted among PC patients in Glasgow, United Kingdom found a significant association between NLR and poor PC prognosis; however, the relationship between NLR and PC risk was not examined [14]. Further studies that examine interrelationships among NLR, pro-inflammatory cytokines, and PC risk are warranted.

A positive relationship between plasma fibrinogen and elevated serum PSA was also reported in the present study. Epidemiologic studies found higher fibrinogen levels in patients with cancer compared to patients with benign tumors or healthy individuals [27,28]. Based on previous studies, fibrinogen has been found to be positively associated with overall risk for smoking-associated cancers [13,29]; but its relationship with PC has been less investigated. A recent study reported a null association between fibrinogen and PC risk among Finnish men, aged ≥42 years [30]; however, the relationship between fibrinogen and serum PSA was not examined in this or previous studies.

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In the present study, serum CRP levels were higher for men with elevated serum PSA compared to men with normal serum PSA, although the association was not significant after age and multivariable adjustments. This finding is consistent with a study that found serum CRP positively associated with PSA in men (n=302), aged >35 years, who were referred for PC screening, and in men with PSA levels of >2.5 ng/ml [24]. However a study conducted among a random sample of men, aged 40–79 years, in the Olmstead County, Minnesota cohort reported no association between elevated CRP levels and a rapid increase in PSA levels [31]. Two studies, one conducted among a small sample of French men (n=156) [32], the another within the Physicians' Health Study, reported an association between PC and serum CRP [33]. Whether men with elevated CRP and elevated PSA are at higher risk of PC is a topic for future studies.

The present study is unique because it used a large sample of the US general population with PSA testing performed, where several biological markers were measured in a standardized fashion. The database contains a wealth of individual clinical information on medical history, hospital admissions, and pharmacological treatment, which allowed the exclusion of subjects with history of PC or of other malignancy, as well as with conditions/medications linked to inflammation and to PSA levels. Limitations of the study are the cross-sectional nature of the survey which lacks follow-up information on the subjects interviewed, the presence of missing data for parts of the sample, and the lack of details on some of the demographic variables collected. Another limitation is that not all laboratory tests were performed throughout the 2001–2008 time period, therefore the association of each systemic marker with PSA was performed one at a time, and combined associations and interactions could not be examined. Finally, the outcome was elevated PSA, not PC occurrence or PC mortality as these data were not available in the present study. Despite these limitations, we presented solid evidence that NLR and plasma fibrinogen are positively associated with elevated serum PSA levels among a large sample of asymptomatic U.S. men. This is the first study to comprehensively test inflammatory markers for their association with elevated PSA.

Since an elevated PSA is indicative of increased PC risk [3], there is a need to further understand if men with elevated inflammatory markers and elevated PSA are a distinct sub-group at increased risk of future PC during the follow-up.

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TABLE I

Baseline Characteristics of Study Participants Stratified by Serum PSA Levels

	PSA < 4 ng/ml		PSA ≥ 4 ng/ml		*P*-value
	N	Mean (SD) or percent	N	Mean (SD) or percent	
Age (years)	2,970	51.8 (0.20)	194	63.6 (1.16)	<0.0001
BMI (kg/m^2)	2,938	28.7 (0.13)	188	27.6 (0.44)	0.02
Race or ethnic origin	2,970		194		0.2
Black	553	18.6%	50	25.8%	
White	1,589	53.5%	105	54.1%	
Other	828	27.9%	39	20.1%	
Marital status	2,968		193		0.14
Currently married or live with partner	2,205	74.3%	122	63.2%	
Ever been married	532	17.9%	57	29.5%	
Never been married	231	7.8%	14	7.3%	
Educational Status	2,968		194		0.07
Less than high school	868	29.3%	75	38.7%	
High school graduate	728	24.5%	51	26.3%	
More than high school	1,372	46.2%	68	35.1%	
Alcohol drinker	2,506/2,970	84.4%	151/194	77.8%	0.03
Ever smoker	1,846/2,968	62.2%	110/193	57.0%	0.4
Ever medication use	2,970		194		
Beta blockers	300	10.1%	23	11.9%	0.08
Statin	412	13.9%	31	16.0%	0.42
NSAIDs	142	4.8%	7	3.6%	0.07
Intake of any of the 3 medications combined	692	23.3%	49	25.3%	0.56

N, number; PSA, prostate specific antigen; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drugs; SD, standard deviation.

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TABLE II

Comparison of Systemic Inflammatory Markers According to Serum PSA Levels

	PSA < 4 ng/ml		PSA : 4 ng/ml		
Variable	**N**	**Geometric mean (SE)**	**N**	**Geometric mean (SE)**	***P*-value**
Serum C-reactive protein (mg/dl)	2,969	0.17 (0.00)	194	0.22 (0.03)	0.02
Plasma Fibrinogen (g/L)	747	3.41 (0.07)	48	3.93 (0.14)	0.0006
Neutrophils (1,000 cells/μl)	2,262	3.94 (0.05)	145	4.09 (0.14)	0.36
Lymphocytes (1,000 cells/μl)	2,262	1.97 (0.02)	145	1.76 (0.07)	0.007
Platelets (1,000 cells/μl)	2,267	245.53 (1.58)	146	241.48 (6.99)	0.55
Neutrophil-Lymphocyte ratio	2,262	2.00 (0.02)	145	2.32 (0.11)	0.002
Platelet-lymphocyte ratio	2,262	124.82 (1.11)	145	136.90 (5.48)	0.03

N, number; PSA, prostate specific antigen; and SE, standard error.

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TABLE III

Associations Between Systemic Inflammatory Markers and Serum PSA Levels

Variable	Elevated/normal PSA N of men	Crude odds ratio (95% CI)	Age-adjusted odds ratio (95% CI)	Elevated/normal PSA N of men	Multivariable[a] odds ratio (95% CI)
Serum C-reactive protein (mg/dl)	194/2,969	1.19 (1.06–1.33)	1.11 (0.99–1.25)	187/2,933	1.11 (0.98–1.27)
Plasma fibrinogen (g/L)	48/747	2.12 (1.56–2.87)	1.79 (1.29–2.50)	45/729	1.88 (1.09–3.25)
Neutrophils (1,000 cells/μl)	145/2,262	1.06 (0.93–1.20)	1.03 (0.90–1.17)	140/2,232	1.03 (0.91–1.17)
Lymphocytes (1,000 cells/μl)	145/2,262	1.03 (0.95–1.11)	1.03 (0.99–1.07)	140/2,232	1.03 (0.99–1.07)
Platelets (1,000 cells/μl)	146/2,267	1.0 (1.0–1.0)	1.0 (1.0–1.01)	41/2,237	1.0 (1.0–1.01)
Neutrophil-lymphocyte ratio	145/2,262	1.34 (1.21–1.48)	1.15 (1.06–1.25)	140/2,232	1.14 (1.04–1.26)
Platelet-lymphocyte ratio	145/2,262	1.01 (1.0–1.01)	1.0 (1.0–1.01)	140/2,232	1.0 (1.0–1.01)

N, number; PSA, prostate specific antigen; CI, confidence interval.

[a]Multivariate model includes age (continuous), ever smoker (yes/no), body mass index (continuous), education (<high school, high school graduate, >high school), race (Black, White, other), medications (beta blockers, statins, nonsteroidal anti-inflammatory drugs), and co-morbid conditions (heart disease, asthma, arthritis, chronic bronchitis, and emphysema).