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Original Article

Association between systemic inflammation and serum prostate-specific antigen in a healthy Korean population

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ABSTRACT

Objective: Serum prostate-specific antigen (PSA) may be elevated in healthy men with systemic inflammation. We aimed to investigate the association between systemic inflammation markers and serum PSA in a healthy Korean population.

Material and methods: A cohort of 20,151 healthy native Korean men without prostate disease between the ages of 40 and 65 years who underwent medical checkups were studied from January 2007 to December 2013. Serum total PSA and serum C-reactive protein concentrations, neutrophil, lymphocyte, and platelet counts were determined. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated. We checked the correlation between systemic inflammation markers and PSA.

Results: Data obtained from 18,800 healthy men were analyzed. The mean age of the study subjects was 50.72±7.62 years and the mean NLR was 1.764±0.804. Correlation analysis after adjustment for age and body mass index (BMI) revealed that neutrophil count (coefficient = 0.028, p value <0.001), and NLR (coefficient = 0.027, p value <0.001) correlated with PSA. Multivariate analysis using the full model revealed that age, neutrophil count and NLR were positively correlated with PSA (p<0.001, 0.001, and 0.043 respectively). Multivariate analysis using a stepwise model revealed that age, neutrophil count and NLR were positively correlated with PSA (p<0.001, 0.001, and 0.040, respectively) and BMI was negatively correlated with PSA (p<0.001).

Conclusion: Systemic inflammation markers are useful with a serum PSA in a healthy Korean population. NLR in particular is significantly associated with serum PSA.

Keywords: Prostatic hyperplasia; screening; systemic inflammation.

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Introduction

The incidence of metabolic syndrome, obesity, and inflammation increase in old age. Prostate cancer (PCa) becomes much more prevalent with age. Serum prostate-specific antigen (PSA) was assessed for its usefulness in PCa screening and was found to be a highly sensitive marker.[1] However, other prostate diseases, such as prostatitis, benign prostatic hyperplasia (BPH), and other prostate-related procedures can result in elevated serum PSA levels. A high serum PSA level is generally considered as an indication for prostate biopsy, and it can be associated with PCa. Serum PSA level has low specificity, so unnecessary biopsies are often taken, patients who need to undergo biopsies may be missed, and only repeated biopsies can reveal PCa.[2] PSA screening is not easy because it is difficult to discriminate between true PCa and other prostate diseases.

In consideration of the features of PSA, systemic inflammation has been studied. Systemic inflammation is related to various conditions associated with elevated PSA levels.[3] However, PCa is not clearly accompanied by local inflammation histologically.[4] Many kinds of cancer are associated with systemic inflammation, such as chronic inflammation and other factors.[5]

High levels of circulating C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are associated with an increased risk of

developing colorectal cancer.[6] The levels of CRP and ESR are associated with an increased risk of lung cancer.[7] CRP, neutrophil count, neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) are associated with development of PCa.[8] Recently, some articles have linked inflammation with PSA levels in subclinical conditions.[9] So, asymptomatic patients with elevated PSA levels are well served by checking systemic inflammation. Several other studies have addressed markers of systemic inflammation. However, those papers have mostly focused on PSA levels of 4.0 ng/mL or above. Serum PSA levels ≥4.0 ng/mL are associated with an increased risk of PCa. Recently, serum PSA levels ≥2.5 ng/mL have been shown to increase the risk of PCa, rather than PSA ≥4.0 ng/mL.[10] Because PCa may be missed in patients with PSA levels between 2.5 ng/mL and 4.0 ng/mL, we studied the association between systemic inflammation markers and serum PSA using a cut-off value of 2.5 ng/mL in a healthy Korean population who underwent medical checkups and did not have prostate diseases.

Material and methods

Study sample

We enrolled patients between the ages of 40 and 89 years who voluntarily underwent medical checkups at the health promotion center of Soonchunhyang Hospital from January 2007 to December 2013, after our study was approved by Ethics Committee. A total of 20,151 healthy native Korean men were enrolled in this study. All participants were assessed for inflammatory markers and we collected the information indicated on Informed Consent forms. A total of 1,351 men were excluded from the study because they had prostate diseases such as prostatitis, BPH, confirmed malignancy, diabetes, conditions requiring treatment with 5-alpha-reductase inhibitors, abnormal findings on DRE, pyuria, neurogenic bladder dysfunction, or previous surgery for a prostate condition.

Biochemical analyses

C-reactive protein was checked using the particle- enhanced immunoturbidimetric assay (Roche C-Reactive protein Latex, COBAS). Complete blood cell count with differential count was assessed using automated analysers (fluorescence flow cytometry, electrical impedance, Sysmex 2100). Serum total PSA was measured using immunochemical methods (Robotic sample handler, Architect i2000 sr). ESR was checked using the capillary photometry method (Test-1 Bcl).

Statistical analysis

Partial correlation analyses were conducted after adjustment for age and body mass index (BMI) to investigate the association between systemic inflammation markers and PSA. Multivariate regression analysis was conducted to investigate the association between systemic inflammation markers and PSA after adjustment for age and BMI. All analyses were 2 tailed, and $p<0.05$ was considered statistically significant. Multivariate logistic regression analysis after adjustment for age and BMI was used to study the association between systemic inflammation markers and elevated serum PSA by calculating the odds ratios (ORs) and 95% confidence intervals (CIs). $P<0.05$ was considered statistically significant. All statistical analyses were done using IBM Statistical Package for the Social Sciences (IBM SPSS Statistics; Armonk, NY, USA) version 20.0 for Windows.

Results

Patient characteristics

The mean age of the 18,800 participants was 50.72±7.62 years. The mean values for some important parametres were as follows: PSA, 1.253±1.148 ng/mL; BMI, 24.565±2.702 kg/m²; CRP, 0.160±0.422 mg/dL, ESR, 16.35±11.562 mm/hr; neutrophil count, 3.445±1.28 x 10^3/mm^3; Lymphocyte count, 2.060±0.562 x 10^3/mm^3; NLR, 1.764±0.804 and PLR, 124.061±40.202 (Table 1).

Correlation Analysis Between systemic inflammation markers and PSA after Adjustment for Age and BMI

Correlation analyses were conducted after adjustment for age and BMI to investigate the association between systemic inflammation markers and PSA. Serum PSA levels were positively correlated with neutrophil (coefficient=0.028, $p<0.001$), and platelet counts (coefficient=0.023, $p=0.002$), NLR (coefficient=0.027, $p<0.001$), PLR (coefficient=0.022, $p=0.003$), and ESR (coefficient=0.017, $p=0.029$) (Table 2). Serum CRP levels and lymphocyte counts were not correlated with PSA.

Multiple regression analysis of systemic markers and PSA

Multiple regression analysis using the full model revealed that age, neutrophil counts and NLR were positively correlated with PSA (unstandardized coefficients=0.027, 0.053, 0.059, respectively, and $p<0.001$, 0.001, and 0.043, respectively; Table 3).

Table 1. Demographic characteristics of the study participants (n=18,800)

Variables	Mean±SD
Age (y)	50.72±7.62
PSA (ng/mL)	1.25±1.15
BMI (kg/m^2)	24.56±2.70
CRP (mg/dL)	0.16±0.422
Neutrophil count (1,000 cells/μL)	3.445±1.28
Lymphocyte count (1,000 cells/μL)	2.060±0.562
Platelet count (1,000 cells/μL)	241±55.85
NLR	1.764±0.804
PLR	124.061±40.202
ESR (mm/hr)	16.35±11.562

N: number; PSA: prostate-specific antigen; BMI: body mass index; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; ESR: erythrocyte sedimentation rate

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Table 2. Correlation analysis after adjustment for age and BMI

	PSA	CRP	Neutr	Lympho	Plt	NLR	PLR	ESR
PSA								
Correlation	1.000							
Significance								
CRP								
Correlation	-0.002	1.000						
Significance	0.833							
Neutrophil counts								
Correlation	0.028	0.221	1.000					
Significance	0.000	0.000						
Lymphocyte counts								
Correlation	-0.012	-0.007	0.244	1.000				
Significance	0.099	0.344	0.000					
Platelet counts								
Correlation	0.022	0.070	0.283	0.248	1.000			
Significance	0.002	0.000	0.000	0.000				
NLR								
Correlation	0.027	0.228	0.700	-0.416	0.078	1.000		
Significance	0.000	0.000	0.000	0.000	0.000			
PLR								
Correlation	0.022	0.077	0.033	-0.632	0.504	0.506	1.000	
Significance	0.003	0.000	0.000	0.000	0.000	0.000		
ESR								
Correlation	0.017	0.317	0.148	0.057	0.154	0.099	0.071	1.000
Significance	0.029	0.000	0.000	0.000	0.000	0.000	0.000	

Significance: 2-tailed; Neutrophil, neutrophil count; lymphocyte, lymphocyte count; Platelet, platelet count; N: number; PSA: prostate-specific antigen; BMI: body mass index; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; ESR: erythrocyte sedimentation rate

Multiple regression analysis using a stepwise model revealed that age, neutrophil counts, and NLR were positively correlated with PSA (unstandardized coefficients=0.027, 0.053, 0.060, respectively, and p<0.001, 0.001, and 0.040, respectively) and BMI was negatively correlated with PSA (unstandardized coefficients=-0.020, p<0.001; Table 4).

Serum CRP (OR_{crude}=1.048; 95% CI 0.939-1.169), neutrophil counts (OR_{crude}=1.017; 95% CI 0.976-1.059), NLR (OR_{crude}=1.117; 95% CI 1.054-1.184), and serum ESR (OR_{crude}=1.014; 95% Cl 1.010-1.018) were significantly associated with high PSA (≥2.5 ng/mL) levels in crude univariate logistic regression analysis (Table 5). Neutrophil counts (OR_{age}=1.074; 95% CI 1.067-1.080) and NLR (OR_{age}=1.066; 95% CI 1.003-1.134) were significantly associated with high

Table 3. Mutiple regression analysis with dependent variables by full model

	Unstandardized coefficients		Standardized coefficients	
Variables	**B**	**Std. error**	**Beta**	**p**
Age	0.027	0.001	0.178	0.000
BMI	-0.020	0.003	-0.047	0.000
CRP	0.015	0.011	0.012	0.165
Neutrophil counts	0.053	0.017	0.059	0.001
Lymphocyte counts	-0.069	0.031	-0.033	0.062
NLR	0.059	0.029	0.041	0.043
PLR	0.001	0.000	0.019	0.067
ESR	0.001	0.001	0.007	0.378

Std.: standard; BMI: body mass index; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; ESR: erythrocyte sedimentation rate

Table 4. Mutiple regression analysis with dependent variables by stepwise model

	Unstandardized coefficients		Standardized coefficients	
Variables	**B**	**Std. error**	**Beta**	**p**
Age (yrs)	0.027	0.001	0.180	0.000
BMI, kg/m^2	-0.020	0.003	-0.047	0.000
Neutrophil counts	0.053	0.017	0.060	0.001
NLR	0.060	0.029	0.042	0.040

BMI: body mass index; NLR: Neutrophil-lymphocyte ratio

Table 5. Correlation analysis between systemic inflammatory markers and PSA

	High/normal PSA N of men	Crude odds ratio (95% CI)	Age-adjusted odds ratio (95% CI)
CRP	1484/17316	1.048 (0.939-1.169)	0.974 (0.856-1.109)
Neutrophil count	1484/17316	1.017 (0.976-1.059)	1.074 (1.067-1.080)
Lymphocyte count	1484/17316	0.777 (0.704-0.858)	0.877 (0.795-0.968)
Platelet count	1484/17316	0.999 (0.998-1.000)	1.001 (1.000-1.002)
NLR	1484/17316	1.117 (1.054-1.184)	1.066 (1.003-1.134)
PLR	1484/17316	1.002 (1.001-1.003)	1.002 (1.000-1.003)
ESR	1387/16177	1.014 (1.010-1.018)	1.003 (0.999-1.007)

N: number; PSA: prostate-specific antigen; CRP: C-reactive protein; NLR: Neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; ESR: erythrocyte sedimentation rate

PSA values in univariate logistic regression analysis performed among age-adjusted patients.

Discussion

Prostate is an immunoregulatory organ with inflammatory cells. Various factors are related to prostate Inflammation. Several possible factors that contribute to the development and progression of PCa have recently been elucidated.

This study investigated the association between systemic inflammatory markers and serum PSA levels using a PSA cut-off value of 2.5 ng/mL. The previous study revealed that CRP and PSA are significantly associated.[11] But our study has revealed that CRP isn't associated with PSA. This study has revealed that increased NLR and neutrophil counts are associated with high serum PSA levels. There may be an association between some systemic inflammatory markers and high serum PSA levels. In healthy men, CRP levels are correlated with lower urinary tract symptoms.[12] It is known that high serum PSA levels are associated with prostatitis, PCa, ejaculation, endoscopic procedures, prostate massage, and acute urinary retention. Systemic inflammation is especially prevalent in cases of prostate inflammation and PCa. Therefore, systemic inflammatory markers can be used to detect PCa. If patients have high serum PSA levels with elevated inflammation markers, this condition may increase the risk of PCa. So may be we should strongly recommend a prostate biopsy for the diagnosis.

Previous studies revealed that high NLR is associated with high serum PSA.[13-15] Neutrophils have a role in innate immunity and lymphocytes play a role in adaptive immunity. NLR is a marker that reveals the balance between neutrophils and lymphocytes. In many cancers, high NLR is correlated with poor overall survival.[16] In recurrent liver cancer and colorectal cancer, high NLR is correlated with the level of pro-inflammatory cytokines. Cytokines can cause cell damage, and injured DNA can cause cancer. In PCa, elevated NLR is clearly associated with poor overall survival, progression-free survival, and recurrence-free suvival.[17,18] Other studies reported that NLR is useful in the early detection of PCa.[19,20] NLR has been more strongly and positively correlated with PSA than ESR or CRP in BPH.[21] Our study reveals that NLR is significantly associated with high serum PSA levels. Our results in healthy Korean men are similar to those of other papers.

However, this study has several limitations regarding its retrospective design, selection bias in the long time period from January 2007 to December 2013. So our data may not be generalized. Systemic inflammation markers are not organ- specific markers. Therefore we can not determine whether prostatic inflammation is present based on these markers.

In conclusion, systemic inflammation markers were associated with high serum PSA levels. NLR in particular was significantly associated with high serum PSA levels. Future studies are needed where prostate biopsies should be performed to determine if the risk of cancer is likely to increase when a patient has both higher PSA value increased NLR.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Soonchunhyang University Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – W.Y.; Design - J.Y., H.L.; Supervision – J.Y.; Resources – W.Y.; Materials – J.Y.; Data Collection and/or Processing – J.Y., H.L.; Analysis and/or Interpretation – J.Y.; Literature Search – J.Y.; Writing Manuscript – J.Y.; Critical Review – J.Y.; Other – J.Y.

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