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Association between the Systemic Immune-Inflammation Index and Prostate Cancer

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ABSTRACT

The systemic immune-inflammation index (SII) is a novel and integrated marker that has not been studied with prostate cancer. We aimed to ascertain the association between SII levels and prostate cancer. We utilized data from the 1999–2010 cycles of the National Health and Nutrition Examination Survey (NHANES). Multivariate logistic regression analyses were conducted to evaluate the relationship between SII and prostate cancer. Additionally, subgroup analyses stratified by age, BMI, history of hypertension and diabetes were performed. A total of 8,020 participants were included in our analysis. After full adjustment, SII was associated with a 7% increased risk of prostate cancer (OR 1.07, 95% CI 0.99–1.15, $p=0.094$). We further categorized SII values into three segments and found that individuals in the highest SII group had a 33% increased risk of prostate cancer than those in the tertile 1 group (OR 1.33; 95% CI 1.01–1.81; $p=0.044$; P for trend = 0.046). In addition, a higher SII level was associated with a 137% increased risk of prostate cancer in the diabetes subgroup (OR 2.37; 95% CI 1.08–5.21; $p=0.031$). The current study suggested that SII was positively associated with increased risks of prostate cancer. The SII might be an easily accessible indicator for identifying prostate cancer.

Abbreviations: SII: Systemic immune-inflammation index; NHANES: National Health and Nutrition Examination Survey; NCHS: National Center for Health Statistics; PIR: ratio of family income to poverty; BMI: body mass index; SD: standard deviation

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Introduction

Prostate cancer is the most common non-skin cancer among men worldwide, with an estimated >1,200,000 new diagnoses and 350,000 deaths annually (1). Bell et al. performed a systematic review of autopsy studies and found that the prevalence of prostate cancer increased from 5% at age < 30 years to 59% by age >79 years (2). The etiology of prostate cancer is complex, including ethnic background (3), germline mutations (4), dietary factors (5), obesity (6), old age (2) and smoking (7). Furthermore, growing evidence reveals that chronic inflammation might contribute to prostate tumorigenesis (8). Circulating inflammatory marker C–C motif chemokine ligands 21 and 11, C-reactive protein, and elevated leukocyte counts were positively associated with an increased risk of prostate cancer (9–11). Additionally, the neutrophil-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were well-known inexpensive markers that can be easily obtained from routine blood counts. Higher NLR and PLR values were associated with the development of metastatic prostate cancer (12). However, many of these biomarkers involve only one or two type of inflammatory cytokines or cells, and might not accurately reflect host inflammatory and immune status.

The systemic immune-inflammation index (SII) is a novel and integrated marker calculated based on peripheral lymphocyte, neutrophil, and platelet counts. The SII index was first developed by Hu et al. to predict prognosis in hepatocellular carcinoma (13). Then, it was confirmed that this index was a promising tool for predicting prognosis in patients with colorectal cancer (14), bladder cancer (15),

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endometrial cancer (16) and non-small cell lung cancer (17). However, the impact of SII on prostate cancer is not fully elucidated, and whether SII acts as an independent risk factor for developing prostate cancer remains unclear. Therefore, we utilized data from the 1999 – 2010 cycles of the National Health and Nutrition Examination Survey (NHANES), for the first time, to ascertain the association between SII levels and prostate cancer.

Methods

Data and Sample Sources

NHANES is a population-based national survey undertaken by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention in the U.S. The Centers for Disease Control and Prevention collected a wide variety of health and nutritional statistics on the non-institutionalized, civilian population utilizing a multistage probability sampling design. The Institutional Review Board of NCHS approved the survey protocol and each recruited participant had signed informed consent. Six cycles of the NHANES (1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008 and 2009–2010) were selected as data simultaneously recording SII and prostate cancer was only available in these years. The exclusion criteria were: (I) female participants ($N = 31,575$); (II) age < 18 years ($N = 13,576$); (III) incomplete data of dietary, demographic and socioeconomic ($N = 4,276$); (IV) incomplete data of SII ($N = 1,834$); (V) missing data of prostate cancer ($N = 2,879$). Eventually, 8,020 individuals were enrolled in the final analysis (Figure 1).

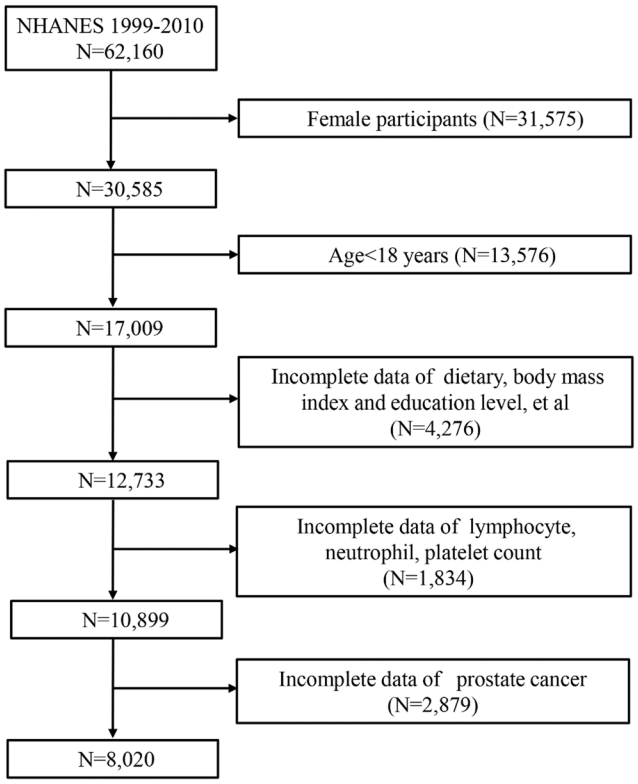

Figure 1. Flowchart of the study population from NHANES 1999–2010.

Exposure and Outcome Assessment

Lymphocyte, neutrophil, and platelet counts (present by $\times 10^3$ cells/μl) were obtained utilizing automated hematology analyzing devices. The SII value was designed as the exposure variable and measured as (platelet count × neutrophils count)/lymphocytes (13). The endpoint of this study was the history of prostate cancer, which was assessed by the question "Have you ever been told by a doctor or health professional that you had prostate cancer".

Covariates

This investigation included the following covariates based on previous studies (18, 19): age, race (Mexican American, other Hispanic, Non-Hispanic white, Non-Hispanic black, and other race), the ratio of family income to poverty (PIR) (< 1.3, 1.3–3.5 and > 3.5) (20, 21), an education level (less than high school, high school and above high school), body mass index (BMI) (< 25, 25–30 and > 30), smoking status (nonsmoker, former smoker and current smoker), diabetes (Yes and no), hypertension (Yes and no), total energy intake, protein intake, carbohydrate intake, total fat intake, total polyunsaturated fatty acids intake, cholesterol intake, calcium intake, magnesium intake and C-reactive protein. Current smokers were defined as participants who answered "Yes" to the question "Have you smoked at least 100 cigarettes in your entire life?" and "Yes" to "Do you now smoke cigarettes?"; Former smokers were defined as those who answered "Yes" to the first question and "No" to the second question; Individuals who responded "No" to the first question were classified as nonsmokers (22, 23). Hypertension and diabetes are defined as a prior diagnosis of hypertension or diabetes.

Statistical Analysis

The current study analysis was adjusted for sampling weights, strata, and primary sampling units. As all continuous variables had nonnormal distributions, the

comparison between non-prostate-cancer and prostate cancer groups was conducted by Kruskal Wallis Rank Test for continuous variables and chi-square test for categorical variables. Continuous and categorical variables were presented as median (Quartile 1 – Quartile 3) and percentage values, respectively. Multivariate logistic regression analyses were established to evaluate the independent relationship between SII and prostate cancer. The crude model was adjusted for no confounders. The model I simply adjusted for age, race and BMI, while Model II adjust for age, race, ratio of family income to poverty, education level, BMI, smoking, diabetes, hypertension total energy, protein, carbohydrate, total fat, total polyunsaturated fatty acids, cholesterol, calcium, magnesium and C-reactive protein. We utilized the Box-Tidwell method to assess a linear relationship between continuous independent variables and dependent variable logit conversion values (24). There was no multicollinearity among independent variables in the model.

Additional sensitivity analyses were also performed to test the robustness of our results: we categorized SII values into three segments to examine whether there existed a dose-response association. To investigate the relationship between SII and prostate cancer in different subgroups, subgroup analysis was carried out. Potential effect modifiers included age (<60 and ≥60 years), BMI (< 25, 25–30 and > 30), history of hypertension (Yes and no) and diabetes (Yes and no). Interaction analysis was performed as well to evaluate the heterogeneity of the correlation between the subgroups. All analyses were conducted with R software (version 4.1.2) and Empower (www.empowerstats.com). Results were regarded as statistically significant for $p < 0.05$ (double-sided).

Results

A total of 8,020 participants were included in our analysis, with 4.0% having a history of prostate cancer. The baseline characteristics of respondents by prostate cancer status were illustrated in Table 1. Compared with the non-prostate-cancer group, participants in the prostate cancer group were more likely to be older [75.0 (68.0–80.0) vs. 59.0 (48.0–69.0), $p < 0.001$], Non-Hispanic Black (25.9% vs. 18.4%, $p < 0.001$), with a PIR from 1.3 to 3.5 (51.0% vs. 38.3%, $p < 0.001$), former smoker (53.0% vs. 39.2%, $p < 0.001$), with a history of hypertension (36.8% vs. 28.3%, $p < 0.001$), a lower total energy intake [1905.5 (1452.3–2403.5) vs. 2137.0 (1576.8–2801.3), $p < 0.001$], a lower protein intake [74.5 (53.4–98.1) vs. 81.7 (58.8–109.9), $p < 0.001$], a lower carbohydrate intake [227.2 (169.2–292.0) vs. 251.8 (183.3–338.4), $p < 0.001$], a lower total fat intake [69.1 (50.0–98.9) vs. 78.2 (52.1–109.4), $p < 0.001$], a lower total polyunsaturated fatty acids intake [14.5 (9.3–21.5) vs. 15.7 (9.9–23.6), $p = 0.048$], a lower cholesterol intake (236.6 (140.0–426.3) vs. 258.0 (151.0–457.4), $p = 0.038$), a lower magnesium intake (265.5 (200.8–354.0) vs. 290.0 (209.0–388.9), $p = 0.006$), a lower lymphocyte counts [1.6 (1.2–2.1) vs. 1.9 (1.5–2.4), $p < 0.001$], a lower platelet counts [228.0 (187.0–266.0) vs. 234.0 (200.0–275.0), $p = 0.012$] and a higher SSI value [526.8 (373.5–772.9) vs. 484.2 (343.3–684.0), $p < 0.001$] (Table 1).

The baseline characteristics of participants by tertile of SII were presented in Table 2.

Compared with men in the lowest SII group, men in the highest SII group were more likely to be older, Non-Hispanic White, with a PIR from 1.3 to 3.5, with a BMI less than 25, former or current smoker, with a history of diabetes, with a lower level of lymphocyte counts, with a higher level of C-reactive protein, higher neutrophil counts, higher platelet counts and with a history of prostate cancer (all $p < 0.05$) (Table 2).

Table 3 demonstrates the associations between SII and prostate cancer. Our results indicated that SII was associated with higher risks of prostate cancer (Crude Model, OR 1.15, 95% CI 1.08–1.22, $p < 0.001$; Model I, OR 1.09, 95% CI 1.02–1.14, $p = 0.045$). After full adjustment, SII was associated with a 7% increased risk of prostate cancer (Model II, OR 1.07, 95% CI 0.99–1.15, $p = 0.094$) (Table 3). We further categorized SII values into three segments to examine the robustness of our results. Our results demonstrated a dose-response correlation between SII and prostate cancer after adjusting for all covariates. Individuals in the highest SII group had a 33% increased risk of prostate cancer than those in the tertile 1 group (Model II, OR 1.33; 95% CI 1.01–1.81; $p = 0.044$; P for trend = 0.046) (Table 3).

There was no significant interaction in each subgroup in the association between SII and prostate cancer, except for stratifying by a history of diabetes (P for interaction = 0.026) (Figure 2). After adjusting for all the potential covariates, our results revealed that higher SII level was associated with a 137% increased risk of prostate cancer in the diabetes subgroup (Model II, OR 2.37; 95% CI 1.08–5.21; $p = 0.031$) (Figure 2).

Discussion

The current study is the first large cross-sectional study to evaluate the correlation between SII and

Table 1. Baseline characteristics of participants by prostate cancer status in NHANES 1999–2010.

	No prostate cancer	Has prostate cancer	*P* value
Number	7699	321	
Age, years	59.0 (48.0–69.0)	75.0 (68.0–80.0)	< 0.001
Race, n (%)			< 0.001
Mexican American	1481 (19.2%)	20 (6.2%)	
Other Hispanic	478 (6.2%)	11 (3.4%)	
Non-Hispanic White	4074 (52.9%)	198 (61.7%)	
Non-Hispanic Black	1413 (18.4%)	83 (25.9%)	
Other race	253 (3.3%)	9 (2.8%)	
Ratio of family income to poverty, n (%)			< 0.001
Less than 1.3	1854 (26.2%)	48 (16.4%)	
1.3 – 3.5	2708 (38.3%)	149 (51.0%)	
Over 3.5	2512 (35.5%)	95 (32.5%)	
Education level, n (%)			0.056
Less than high school	2453 (32.1%)	92 (28.7%)	
High school	1796 (23.5%)	67 (20.9%)	
Above high school	3374 (44.1%)	159 (49.5%)	
Missing	22 (0.3%)	3 (0.9%)	
BMI, kg/m^2, n (%)			0.966
BMI < 25	1893 (25.0%)	80 (25.6%)	
25 ≤ BMI < 30	3172 (41.8%)	129 (41.2%)	
BMI ≥ 30	2516 (33.2%)	104 (33.2%)	
Smoking, n (%)			< 0.001
Nonsmoker	2903 (37.7%)	121 (37.7%)	
Former smoker	3018 (39.2%)	170 (53.0%)	
Current smoker	1778 (23.1%)	30 (9.3%)	
History of diabetes, n (%)			0.912
Yes	1182 (15.4%)	53 (16.5%)	
No	6517 (84.6%)	268 (83.5%)	
History of hypertension, n (%)			< 0.001
Yes	2178 (28.3%)	118 (36.8%)	
No	5519 (71.7%)	203 (63.2%)	
Total energy (kcal)	2137.0 (1576.8–2801.3)	1905.5 (1452.3–2403.5)	< 0.001
Protein (gm)	81.7 (58.8–109.9)	74.5 (53.4–98.1)	< 0.001
Carbohydrate (gm)	251.8 (183.3–338.4)	227.2 (169.2–292.0)	< 0.001
Total fat (gm)	78.2 (52.1–109.4)	69.1 (50.0–98.9)	< 0.001
Total polyunsaturated fatty acids (gm)	15.7 (9.9–23.6)	14.5 (9.3–21.5)	0.048
Cholesterol (mg)	258.0 (151.0–457.4)	236.6 (140.0–426.3)	0.038
Calcium (mg)	786.0 (498.0–1164.1)	772.9 (510.8–1079.3)	0.293
Magnesium (mg)	290.0 (209.0–388.9)	265.5 (200.8–354.0)	0.006
C-reactive protein (mg/dl)	0.2 (0.1–0.4)	0.2 (0.1–0.5)	0.182
Lymphocyte counts, 10^3/μl	1.9 (1.5–2.4)	1.6 (1.2–2.1)	< 0.001
Neutrophil counts, 10^3/μl	4.0 (3.1–5.1)	4.0 (3.1–5.0)	0.387
Platelet counts, 10^3/μl	234.0 (200.0–275.0)	228.0 (187.0–266.0)	0.012
Systemic immune-inflammation index	484.2 (343.3–684.0)	526.8 (373.5–772.9)	< 0.001

BMI, body mass index.
The values are presented as weighted median (Quartile 1 – Quartile 3) or unweighted counts (weighted %).

prostate cancer. We included a total of 8,020 participants for analysis, and found that SII was associated with a 7% increased risk of prostate cancer although this correlation was not statistically significant (OR 1.07, 95% CI 0.99–1.15, $p = 0.094$). Furthermore, individuals in the highest SII group had a 33% increased risk of prostate cancer than those in the tertile 1 group (OR 1.33; 95% CI 1.01–1.81; $p = 0.044$; *P* for trend = 0.046). These positive associations were independent of potential covariates including demographics, socioeconomic factors, smoking, history of diabetes and hypertension, total energy intake, protein intake, carbohydrate intake, total fat intake, total polyunsaturated fatty acids intake, cholesterol intake, calcium intake, magnesium intake and C-reactive protein. In addition, subgroup analysis revealed that higher SII level was associated with a 137% increased risk of prostate cancer in the diabetes subgroup (OR 2.37; 95% CI 1.08–5.21; $p = 0.031$).

As an emerging noninvasive indicator, SII has been confirmed to possess high diagnostic and prognostic value in many diseases (13, 14, 16, 17, 25). Moreover, several studies have determined the relationship between preoperative SII levels and oncological outcomes in patients with prostate cancer (26, 27). Rajwa et al. included 214 patients with radio-recurrent prostate cancer, and treated them with salvage radical prostatectomy (26). The authors found that higher preoperative SII was predictive for lymph node metastasis (OR 3.32, 95% CI 1.45–7.90, $p = 0.005$), and non-organ confined disease (OR 2.55, 95% CI 1.33–4.97, $p = 0.005$) (26). After full adjustment, higher SII was associated with worse cancer-specific survival (HR 22.11, 95% CI 1.23–398.12, $p = 0.036$) and overall

Table 2. Baseline characteristics of participants by tertile of Systemic Immune-Inflammation index in NHANES 1999–2010.

	Tertile 1	Tertile 2	Tertile 3	*P* value
Number	2673	2673	2674	
Age, years	58.0 (47.0–68.0)	58.0 (47.0–70.0)	62.0 (50.0–73.0)	< 0.001
Race, n (%)				< 0.001
Mexican American	506 (18.9%)	536 (20.1%)	459 (17.2%)	
Other Hispanic	175 (6.5%)	169 (6.3%)	145 (5.4%)	
Non-Hispanic White	1139 (42.6%)	1474 (55.1%)	1659 (62.0%)	
Non-Hispanic Black	765 (28.6%)	410 (15.3%)	321 (12.0%)	
Other race	88 (3.3%)	84 (3.1%)	90 (3.4%)	
Ratio of family income to poverty, n (%)				0.019
Less than 1.3	639 (26.1%)	603 (24.6%)	660 (26.7%)	
1.3 – 3.5	951 (38.9%)	919 (37.5%)	987 (40.0%)	
Over 3.5	856 (35.0%)	929 (37.9%)	822 (33.3%)	
Education level, n (%)				0.038
Less than high school	903 (34.0%)	823 (31.0%)	819 (30.9%)	
High school	575 (21.6%)	618 (23.3%)	672 (25.3%)	
Above high school	1171 (44.1%)	1209 (45.5%)	1153 (43.4%)	
Missing	7 (0.3%)	8 (0.3%)	10 (0.9%)	
BMI, kg/m^2, n (%)				< 0.001
BMI < 25	636 (24.1%)	602 (22.8%)	735 (28.1%)	
25 ≤ BMI < 30	1170 (44.3%)	1095 (41.5%)	1036 (39.6%)	
BMI ≥ 30	833 (31.6%)	939 (35.6%)	848 (32.4%)	
Smoking, n (%)				< 0.001
Nonsmoker	1085 (40.6%)	1031 (38.6%)	908 (34.0%)	
Former smoker	1005 (37.6%)	1082 (40.5%)	1101 (41.2%)	
Current smoker	583 (21.8%)	560 (20.9%)	665 (24.9%)	
History of diabetes, n (%)				0.015
Yes	410 (15.3%)	373 (14.0%)	452 (16.9%)	
No	2263 (84.7%)	2300 (86.0%)	2222 (83.1%)	
History of hypertension, n (%)				0.518
Yes	759 (28.4%)	764 (28.6%)	773 (28.9%)	
No	1913 (71.6%)	1909 (71.4%)	1900 (71.1%)	
Total energy (kcal)	2137.0 (1573.0–2767.4)	2152.0 (1630.0–2860.0)	2080.0 (1519.0–2723.1)	< 0.001
Protein (gm)	81.2 (58.2–109.0)	83.1 (60.0–111.5)	79.7 (57.4–107.6)	0.007
Carbohydrate (gm)	253.5 (183.3–334.1)	255.8 (187.7–345.2)	243.2 (176.0–330.7)	< 0.001
Total fat (gm)	76.1 (51.0–107.2)	80.3 (53.9–111.7)	76.2 (50.6–108.0)	0.001
Total polyunsaturated fatty acids (gm)	15.6 (9.8–23.4)	16.2 (10.3–24.4)	15.0 (9.5–22.8)	< 0.001
Cholesterol (mg)	257.0 (150.7–458.5)	263.0 (159.0–456.0)	250.3 (143.3–455.0)	0.066
Calcium (mg)	757.0 (484.0–1110.0)	801.0 (524.2–1186.0)	796.1 (489.2–1169.3)	< 0.001
Magnesium (mg)	288.0 (207.0–378.8)	295.1 (216.0–393.0)	283.0 (203.0–387.0)	0.004
C-Reactive protein (mg/dl)	0.2 (0.1–0.3)	0.2 (0.1–0.4)	0.3 (0.1–0.6)	< 0.001
Lymphocyte counts, 10^3/μl	2.2 (1.8–2.7)	1.9 (1.6–2.4)	1.6 (1.3–2.0)	< 0.001
Neutrophil counts, 10^3/μl	3.0 (2.4–3.7)	4.1 (3.4–4.8)	5.2 (4.3–6.3)	< 0.001
Platelet counts, 10^3/μl	205.0 (174.0–238.0)	236.0 (203.0–270.0)	267.0 (229.0–306.0)	< 0.001
Prostate cancer, n (%)				0.003
Yes	85 (3.2%)	103 (3.9%)	133 (5.0%)	
No	2588 (96.8%)	2570 (96.1%)	2541 (95%)	

BMI, body mass index.
The values are presented as weighted median (Quartile 1 – Quartile 3) or unweighted counts (weighted %).

Table 3. Association between systemic immune-inflammation index and prostate cancer in NHANES 1999–2010.

	OR (95% CI), *P* value		
Systemic immune-inflammation index Group	Crude Model	Model I	Model II
Continuous	1.15 (1.08, 1.22), < 0.001	1.09 (1.02,1.14), 0.045	1.07 (0.99, 1.15), 0.094
Tertile			
1	1	1	1
2	1.22 (0.91, 1.63), 0.182	1.26 (0.93, 1.71), 0.140	1.24 (0.91, 1.70), 0.164
3	1.59 (1.21, 2.10), < 0.001	1.40 (1.04, 1.88), 0.027	1.33 (1.01, 1.81), 0.044
P for trend	< 0.001	0.032	0.046

Model I: adjust for age, race and BMI.
Model II: adjust for age, race, ratio of family income to poverty, education level, BMI, smoking, diabetes, hypertension total energy, protein, carbohydrate, total fat, total polyunsaturated fatty acids, cholesterol, calcium, magnesium and C-reactive protein.

survival (HR 5.98, 95% CI 1.67–21.44, $p = 0.006$) (26). Additionally, Wang et al. included 291 patients with pathologically confirmed localized prostate cancer who underwent radical prostatectomy for analysis (27). Their results demonstrated that higher preoperative SII levels were associated with unfavorable pathological T stage (HR 1.243; 95% CI, 0.806–1.917, $p = 0.039$) and Gleason score (HR 1.577; 95% CI, 0.965–1.578, $p = 0.038$) (27). Kaplan-Meier analysis also revealed an independent association between SII and shorter

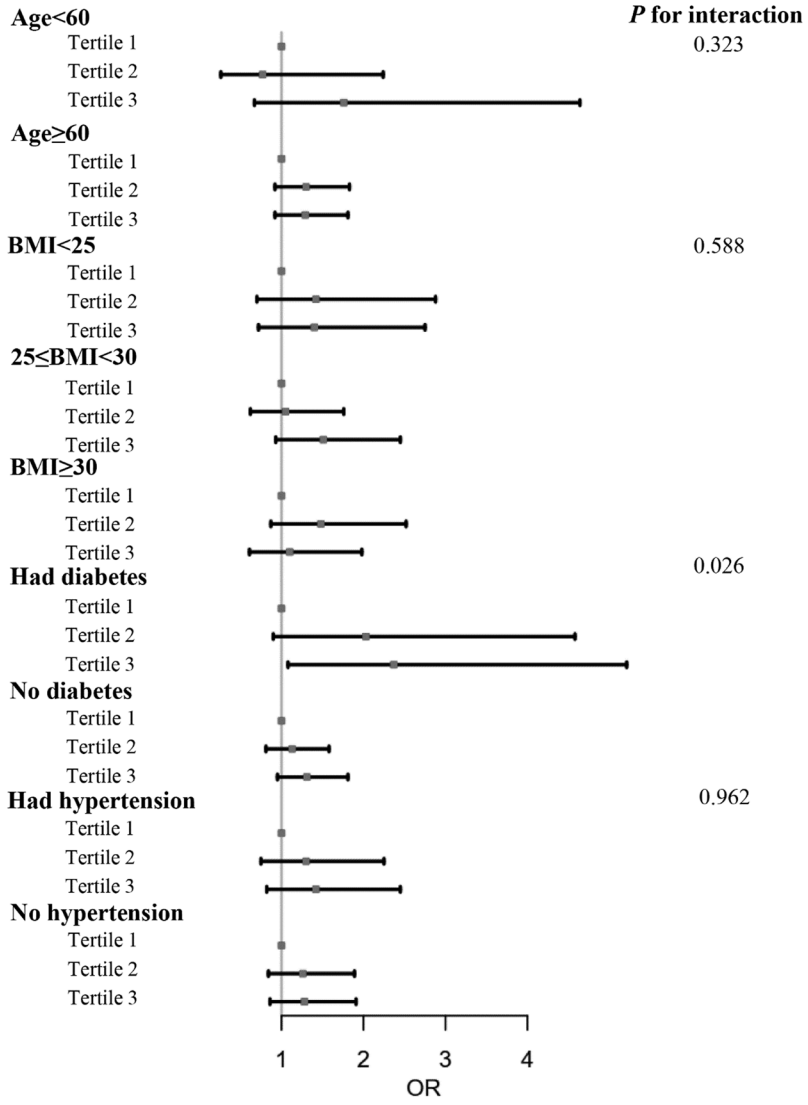

Figure 2. Subgroup analysis for the association between SII and prostate cancer.

biochemical recurrence-free survival (27). However, whether SII is significantly related to prostate cancer development remains unclear. In our study, we found that participants in the highest SII group had a 33% increased risk of prostate cancer than those in the tertile 1 group. This might be explained by the SII value being calculated from neutrophil, platelet counts and lymphocytes, which simultaneously reflect host inflammatory response, thrombus formation and adaptive immunity. Neutrophils exert pro-tumor functions by producing reactive oxygen species and reactive nitrogen species, which are genotoxic and can promote tumor initiation (28). Besides, neutrophils can contribute to immune tolerance by the release of arginase, interleukin 10 and inducible nitric oxide synthase (28). A large number of studies demonstrate that platelets are involved in all phases of cancer development (29). For instance, platelets could be activated and recruited by cancer cells, then secreting vascular endothelial growth factor to promote cell proliferation and angiogenesis (29). CD4 and CD8 T cells eliminate cancer cells by the production of interferon-gamma and tumor necrosis factor-alpha (30).

Our subgroup analysis revealed that a higher SII level was associated with a 137% increased risk of prostate cancer in the diabetes subgroup. This might be attributed by that the individuals with diabetes demonstrated higher levels of insulin/insulin-like growth factor and inflammatory cytokines, which provides good circumstances for cancer cell proliferation and differentiation (31, 32). In addition, we observed that compared with those whose age < 60, men with age ≥60 years were associated with an increased risk of prostate cancer although this correlation was not statistically significant. Further studies are needed to verify our results.

Our research still has several limitations. First, the cross-sectional design of the NHANES means that causal relationships cannot be established. Second, the data of neutrophil, platelet counts and lymphocyte counts were obtained from a single blood test, which might not accurately reflect the long-term inflammatory and immune status. Third, the current study only included the U.S. population for analysis, Forth, additional potential confounding factors might be missed and affects our results.

Conclusion

Overall, our study revealed that higher SII levels were closely related to increased risks of prostate cancer. SII is a convenient and noninvasive indicator derived from routine blood measurements, and it should be fully included in the diagnosis and management of prostate cancer.

Acknowledgments

Zhumei Luo, Wei Wang and Liyuan Xiang contributed equally to this work and should be considered as co-first author.

Ethical Approval

Written informed consent was provided for each participant and the National Center for Health Statistics Research Ethics Review Board approved the project

Authors' Contributions

LZ and WW proposed the conception and design. LZ and WW provided administrative support. LZ, WW, and XL supplied the study materials. LZ and JT collected and assessed the data. XL analyzed the data. All authors contributed to the article and approved the submitted version.

Informed consent

The data of participants were obtained from the public dataset NHANES in an anonymous form. Thus, additional consents were waived in the present study.

Disclosure Statement

The authors declare that they have no conflict of interest.

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Data Availability Statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: NHANES.

References

1. Prostate cancer. Nat Rev Dis Primers. 2021;7(1):8.
2. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: a systematic review of autopsy studies. Int J Cancer. 2015;137(7):1749–57. doi:10.1002/ijc.29538
3. Jansson KF, Akre O, Garmo H, Bill-Axelson A, Adolfsson J, Stattin P, Bratt O. Concordance of tumor differentiation among brothers with prostate cancer. Eur Urol. 2012;62(4):656–61. doi:10.1016/j.eururo.2012.02.032
4. Amin Al Olama A, Dadaev T, Hazelett DJ, Li Q, Leongamornlert D, Saunders EJ, Stephens S, Cieza-Borrella C, Whitmore I, Benlloch Garcia S, et al. Multiple novel prostate cancer susceptibility signals identified by fine-mapping of known risk loci among Europeans. Hum Mol Genet. 2015;24(19):5589–602. doi:10.1093/hmg/ddv203
5. Cook LS, Goldoft M, Schwartz SM, Weiss NS. Incidence of adenocarcinoma of the prostate in Asian immigrants to the United States and their descendants. The Journal of Urology. 1999;161(1):152–5. doi:10.1016/S0022-5347(01)62086-X
6. Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL, Jr., Freedland SJ. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. Cancer Epidemiol Biomarkers Prev. 2014;23(12):2936–42. doi:10.1158/1055-9965.EPI-14-0795
7. Brookman-May SD, Campi R, Henríquez JDS, Klatte T, Langenhuijsen JF, Brausi M, Linares-Espinós E, Volpe A, Marszalek M, Akdogan B, et al. Latest Evidence on the Impact of Smoking, Sports, and Sexual Activity as Modifiable Lifestyle Risk Factors for Prostate Cancer Incidence, Recurrence, and Progression: a Systematic Review of the Literature by the European Association of Urology Section of Oncological Urology (ESOU). Eur Urol Focus. 2019;5(5):756–87. doi:10.1016/j.euf.2018.02.007
8. Sfanos KS, Yegnasubramanian S, Nelson WG, De Marzo AM. The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol. 2018;15(1):11–24. doi:10.1038/nrurol.2017.167
9. Arthur R, Williams R, Garmo H, Holmberg L, Stattin P, Malmström H, Lambe M, Hammar N, Walldius G, Robinsson D, et al. Serum inflammatory markers in relation to prostate cancer severity and death in the Swedish AMORIS study. Int J Cancer. 2018;142(11):2254–62. doi:10.1002/ijc.31256
10. Toriola AT, Laukkanen JA, Kurl S, Nyyssönen K, Ronkainen K, Kauhanen J. Prediagnostic circulating markers of inflammation and risk of prostate cancer. Int J Cancer. 2013;133(12):2961–7. doi:10.1002/ijc.28313
11. Ugge H, Downer MK, Carlsson J, Bowden M, Davidsson S, Mucci LA, Fall K, Andersson SO, Andrén O. Circulating inflammation markers and prostate cancer. Prostate. 2019;79(11):1338–46. doi:10.1002/pros.23842

12. Salciccia S, Frisenda M, Bevilacqua G, Viscuso P, Casale P, De Berardinis E, Di Pierro GB, Cattarino S, Giorgino G, Rosati D, et al. Comparative Prospective and Longitudinal Analysis on the Platelet-to-Lymphocyte, Neutrophil-to-Lymphocyte, and Albumin-to-Globulin Ratio in Patients with Non-Metastatic and Metastatic Prostate Cancer. Curr Oncol. 2022;29(12):9474–500. doi:10.3390/curroncol29120745
13. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, Zhou J, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212–22. doi:10.1158/1078-0432.CCR-14-0442
14. Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, Chen CQ, He YL, Cai SR. Systemic immune-inflammation index for predicting prognosis of colorectal cancer. World J Gastroenterol. 2017;23(34):6261–72. doi:10.3748/wjg.v23.i34.6261
15. Li J, Cao D, Huang Y, Xiong Q, Tan D, Liu L, Lin T, Wei Q. The Prognostic and Clinicopathological Significance of Systemic Immune-Inflammation Index in Bladder Cancer. Front Immunol. 2022;13:865643. doi:10.3389/fimmu.2022.865643
16. Huang Y, Chen Y, Zhu Y, Wu Q, Yao C, Xia H, Li C. Postoperative Systemic Immune-Inflammation Index (SII): A Superior Prognostic Factor of Endometrial Cancer. Front Surg. 2021;8:704235. doi:10.3389/fsurg.2021.704235
17. Liu J, Li S, Zhang S, Liu Y, Ma L, Zhu J, Xin Y, Wang Y, Yang C, Cheng Y. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab. J Clin Lab Anal. 2019;33(8):e22964. doi:10.1002/jcla.22964
18. Sen A, Papadimitriou N, Lagiou P, Perez-Cornago A, Travis RC, Key TJ, Murphy N, Gunter M, Freisling H, Tzoulaki I, et al. Coffee and tea consumption and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer. 2019;144(2):240–50. doi:10.1002/ijc.31634
19. Wang M, Jian Z, Yuan C, Jin X, Li H, Wang K. Coffee Consumption and Prostate Cancer Risk: results from National Health and Nutrition Examination Survey 1999-2010 and Mendelian Randomization Analyses. Nutrients. 2021;13(7):2317. doi:10.3390/nu13072317
20. Wang W, Lu X, Shi Y, Wei X. Association between food insecurity and kidney stones in the United States: Analysis of the National Health and Nutrition Examination Survey 2007-2014. Front Public Health. 2022;10:1015425. doi:10.3389/fpubh.2022.1015425
21. Yang Z, Wang W, Lin L, Xiao K, Peng L, Gao X, Zhou L. The association between urinary organophosphate insecticide metabolites and erectile dysfunction in the United States. Int J Impot Res. 2022; https://pubmed.ncbi.nlm.nih.gov/36513813/. doi:10.1038/s41443-022-00655-4
22. Wang W, Ma Y, Chen J, Peng L, Gao X, Lin L, Zhang F, Xiong Y, Qin F, Yuan J. The Association Between 2, 4-Dichlorophenoxyacetic Acid and Erectile Dysfunction. Front Public Health. 2022;10:910251. doi:10.3389/fpubh.2022.910251
23. Wang W, Xiang LY, Ma YC, Chen JW, Peng L, Gao XS, Zhang FX, Xiong Y, Qin F, Yuan JH. The association between heavy metal exposure and erectile dysfunction in the United States. Asian J Androl. 2023;25(2):271–6. doi:10.4103/aja202237
24. Cheng Y, Wang Z, Yang T, Lv W, Huang H, Zhang Y. Factors influencing depression in primary caregivers of patients with dementia in China: A cross-sectional study. Geriatr Nurs. 2021;42(3):734–9. doi:10.1016/j.gerinurse.2021.03.017
25. Geraghty JR, Lung TJ, Hirsch Y, Katz EA, Cheng T, Saini NS, Pandey DK, Testai FD. Systemic Immune-Inflammation Index Predicts Delayed Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage. Neurosurgery. 2021;89(6):1071–9. doi:10.1093/neuros/nyab354
26. Rajwa P, Schuettfort VM, Quhal F, Mori K, Katayama S, Laukhtina E, Pradere B, Motlagh RS, Mostafaei H, Grossmann NC, et al. Role of systemic immune-inflammation index in patients treated with salvage radical prostatectomy. World J Urol. 2021;39(10):3771–9. doi:10.1007/s00345-021-03715-4
27. Wang S, Yang X, Yu Z, Du P, Sheng X, Cao Y, Yan X, Ma J, Yang Y. The Values of Systemic Immune-Inflammation Index and Neutrophil-Lymphocyte Ratio in Predicting Biochemical Recurrence in Patients With Localized Prostate Cancer After Radical Prostatectomy. Front Oncol. 2022;12:907625. doi:10.3389/fonc.2022.907625
28. Sounbuli K, Mironova N, Alekseeva L. Diverse Neutrophil Functions in Cancer and Promising Neutrophil-Based Cancer Therapies. Int J Mol Sci. 2022;23(24):15827. doi:10.3390/ijms232415827
29. D'Ambrosi S, Nilsson RJ, Wurdinger T. Platelets and tumor-associated RNA transfer. Blood. 2021;137(23):3181–91. doi:10.1182/blood.2019003978
30. Ostroumov D, Fekete-Drimusz N, Saborowski M, Kühnel F, Woller N. CD4 and CD8 T lymphocyte interplay in controlling tumor growth. Cell Mol Life Sci. 2018;75(4):689–713. doi:10.1007/s00018-017-2686-7
31. Wang M, Yang Y, Liao Z. Diabetes and cancer: epidemiological and biological links. World J Diabetes. 2020;11(6):227–38. doi:10.4239/wjd.v11.i6.227
32. Zhu D, Toker M, Shyr W, Fram E, Watts KL, Agalliu I. Association of Obesity and Diabetes With Prostate Cancer Risk Groups in a Multiethnic Population. Clin Genitourin Cancer. 2022;20(3):299–.e210. doi:10.1016/j.clgc.2022.01.016