The Association Between Systemic Inflammation and Prostate Cancer: Based on the National Health and Nutrition Examination Survey and Mendelian Randomization Analysis

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Purpose: This combined study aimed to examine the relationship between systemic inflammation and the risk of prostate cancer (PCa) using a cross-sectional study from the National Health and Nutrition Examination Survey (NHANES) and a two-sample Mendelian randomization (MR) analysis.

Materials and Methods: We included NHANES data from 2001 to 2010. The exposure was systemic inflammation, evaluated using the systemic immune-inflammation index (SII), and the outcome was PCa. We performed multivariate logistic regression and restricted cubic spline (RCS) analyses to test the correlation between SII and PCa. Furthermore, a two-sample MR analysis was used to identify causal associations between specific immune cells and PCa.

Results: A total of 7,706 participants (age $\geq$ 40 years) were included in the cross-sectional study, comprising 350 PCa cases and 7,356 controls. Higher SII levels were associated with increased odds of PCa ($p < 0.05$). The odds ratio (OR) for PCa was 1.51 (95% CI, 1.09-2.08) for the highest versus the lowest quartile of SII in the fully adjusted model. The RCS analysis showed a threshold effect, with SII levels above 8.90 associated with increased odds of PCa. Additionally, MR results suggested a causal relationship between CD62L- monocytes, CD62L- HLA DR+ monocytes, CD14+ CD16+ monocytes, CD62L- Dendritic Cells, Monocytic Myeloid-Derived Suppressor Cells, CD28- CD8dim T cells, CD39+ resting CD4 regulatory T cells, and PCa ($p < 0.05$).

Conclusion: This combined analysis provides evidence for a significant causal relationship between systemic inflammation and PCa risk. These findings highlight systemic inflammation and inflammatory immune responses as potential modifiable risk factors for PCa.

Keywords: Systemic inflammation; Prostate cancer; NHANES; Mendelian randomization; Causality

INTRODUCTION

Prostate cancer (PCa) ranks fifth in cancer-related fatalities and is the third most commonly diagnosed malignancy among men globally.[1] PCa is a leading cause of cancer-related morbidity and mortality among men worldwide. A study by Basiri et al. provides valuable insights into the landscape of prostate cancer in Iran, reporting an average 3-year age-standardized incidence rate of 11.52 per 100,000 males during the 2008-2010 period.[2] The incidence and mortality rates of PCa vary significantly across racial and ethnic groups.[3,4] Proven risk factors for PCa include advanced age, a familial predisposition, and genetic variants; however, the etiology of PCa remains poorly understood.[5]

Recent research has identified promising new systemic treatments for metastatic PCa. Rizzo et al. suggest that modulating the gut microbiome could be a novel therapeutic strategy.[6] Mollica et al. reviewed the use of bone-targeting agents like radium-223 and denosumab.[7] Sahin et al. and Guven et al. explored prognostic factors, such as the Royal Marsden Hospital score and serum albumin, which may guide treatment selection and predict response, including to immune checkpoint inhibitors.[8,9] Rosellini et al. discussed the potential of antibody-drug conjugates, a new class of targeted therapies, in prostate cancer.[10]

Chronic inflammation has emerged as a potential pathogenic factor influencing prostate carcinogenesis and progression.[11] Several lines of evidence from epidemiological, clinical, and experimental studies imply that chronic activation of inflammatory pathways contributes to genomic instability, angiogenesis, and uncontrolled proliferative signaling, facilitating prostatic neoplastic transformation and metastasis.[12,13] Systemic inflammation, characterized by circulating pro-inflammatory cytokines and activated immune cells, may exert direct effects within the prostate tumor microenvironment as well as indirect effects mediated through obesity, insulin resistance, and metabolic dysfunction.[14,15] The systemic immune-inflammation index (SII) has been identified as a prognostic biomarker for numerous cancers, including PCa. It is calculated using peripheral neutrophil, lymphocyte, and platelet counts.[16] Higher SII levels, reflecting increased neutrophilia

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Table 1. The sequences of the primers pairs for Real-Time PCR analysis.

Characteristic	Non-prostate cancer (n=7356)	Prostate cancer (n=350)
Age (y)		
40-49	2004 (27.2%)	1 (0.3%)
50-59	1710 (23.2%)	13 (3.7%)
≥60	3642 (49.5%)	336 (96.0%)
Race		
Hispanic	1738 (23.6%)	30 (8.6%)
Non-Hispanic white	4048 (55.0%)	224 (64.0%)
Non-Hispanic black	1331 (18.1%)	88 (25.1%)
Other	239 (3.2%)	8 (2.3%)
Education beyond high school	5048 (68.6%)	240 (68.6%)
Marital status		
Never married	510 (6.9%)	8 (2.3%)
Married or living with partner	5355 (72.8%)	261 (74.6%)
Divorced, separated, or widowed	1491 (20.3%)	81 (23.1%)
BMI (kg/m²)		
< 25	1784 (24.3%)	91 (26.0%)
25-29	3089 (42.0%)	149 (42.6%)
≥30	2483 (33.8%)	110 (31.4%)
ALT (U/L)	25.0 (18.0-35.1)	22.0 (17.0-32.0)
AST (U/L)	25.0 (20.8-32.0)	25.0 (21.0-32.0)
HbA1c (%)	5.7 (5.3-6.3)	5.8 (5.4-6.3)
Alcohol user	6568 (89.3%)	302 (86.3%)
Smoker	4603 (62.6%)	213 (60.9%)
Diabetes	1719 (23.4%)	89 (25.4%)
Hypertension	3900 (53.0%)	247 (70.6%)
Hyperlipidemia	5774 (78.5%)	285 (81.4%)
LogSII		
Q1 (2.838-8.437)	1855 (25.2%)	72 (20.6%)
Q2 (8.438-8.934)	1845 (25.1%)	81 (23.1%)
Q3 (8.934-9.427)	1842 (25.0%)	84 (24.0%)
Q4 (9.428-14.739)	1814 (24.7%)	113 (32.3%)

Note: Categorical data are displayed as n (%). Non-normally distributed data are displayed as median (Q1-Q3).
Abbreviations: BMI, body mass index; SII, systemic immune-inflammation index; HbA1c, glycosylated hemoglobin type A1C; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

and thrombocytosis along with relative lymphopenia, are associated with poor clinicopathologic characteristics and survival outcomes in PCa patients.[17-19] The components of SII have also been independently associated with PCa risk and mortality, suggesting the potential utility of this integrated marker.[20,21]

Despite accumulating evidence linking systemic inflammation with PCa, the causal nature and magnitude of this relationship remain uncertain. Observational studies demonstrating associations between inflammatory biomarkers and cancer outcomes are susceptible to residual confounding and reverse causation. Mendelian randomization (MR) analyses use genetic variants as instrumental variables to infer causal relationships, minimizing biases inherent in conventional epidemiology.[22] Although MR studies have identified putative causal roles of circulating cytokines and immune cells in multiple cancers, comprehensive MR analyses focused specifically on PCa are lacking.[23,24]

The assessment of the genetic etiology of prostate cancer has become increasingly important in understanding the disease's molecular landscape. By examining the expression patterns and functional roles of lncRNAs, researchers have uncovered potential biomarkers and therapeutic targets.[25] As our understanding of the genetic underpinnings of prostate cancer continues to evolve, it becomes evident that comprehensive genetic etiology assessments are crucial for advancing diagnostic accuracy, developing targeted therapies, and ultimately improving patient outcomes.

In this work, using a nationally representative population sample from the National Health and Nutrition Examination Survey (NHANES), we examine the relationship between systemic inflammation, as assessed by SII, and PCa risk. We further explore potential causal immune factors related to PCa through a large-scale MR analysis. Clarifying causal inflammatory pathways underlying PCa development could identify novel targets for risk stratification, prevention, and treatment.

MATERIALS AND METHODS

Data from the continuous NHANES between 2001 and 2010 were examined. The National Center for Health Statistics (NCHS) continuously conducts the cross-sectional NHANES survey, which is intended to assess the nutritional status and general health of non-institutionalized civilians in the United States. The survey includes laboratory testing, physical examinations, and interviews using a multistage, stratified, complex probability sampling design. All participants provided written informed consent, and the NCHS research ethics review board approved the NHANES protocol. For this analysis, we included NHANES participants aged 40 years and older who had available data for the primary exposure and outcome variables from 2001 to 2010. Individuals who had been previously diagnosed with other cancers, failed to provide fasting morning blood samples, or lacked covariates were excluded.

Exposure Assessment

The primary exposure was systemic inflammation, quantified using the SII.[16] SII is calculated as (platelet count × neutrophil count) / lymphocyte count, utilizing differential blood cell counts from the complete blood count assay in NHANES.[26] Higher SII levels indicate increased systemic inflammation. Due to its skewed distribution, SII was analyzed after a log2 transformation (LogSII) and as a continuous variable.

Table2. Odds Ratios for associations between LogSII and prostate cancer

Model	Q1	Q2	Q3	Q4
Unadjusted	Ref.	1.13 (0.82-1.56)	1.18 (0.85-1.62)	1.61 (1.19-2.17), $p < 0.001$
Model 1	Ref.	1.16 (0.83-1.61)	1.18 (0.84-1.64)	1.46 (1.06-2.00), $p = 0.03$
Model 2	Ref.	1.16 (0.83-1.62)	1.20 (0.86-1.67)	1.49 (1.08-2.05), $p = 0.02$
Model 3	Ref.	1.17 (0.83-1.63)	1.19 (0.85-1.66)	1.51 (1.09-2.08), $p = 0.03$

Note: Model 1 was adjusted for age and race. Model 2 was adjusted for age, race, education level, marital status, smoking status, and alcohol use. Model 3 was adjusted for age, race, education level, marital status, smoking status, alcohol use, BMI, hypertension, hyperlipidemia, and diabetes.

Outcome Assessment

The primary outcome was PCa status, defined using self-reported data from the NHANES questionnaire, where participants were asked, "Have you ever been told by a doctor or other health professional that you had prostate cancer?" Those who answered "yes" were classified as PCa cases.[27]

Covariate Assessment

Demographic information, socioeconomic status, lifestyle factors, and medical history were gathered through in-home questionnaires and physical exams. Covariates

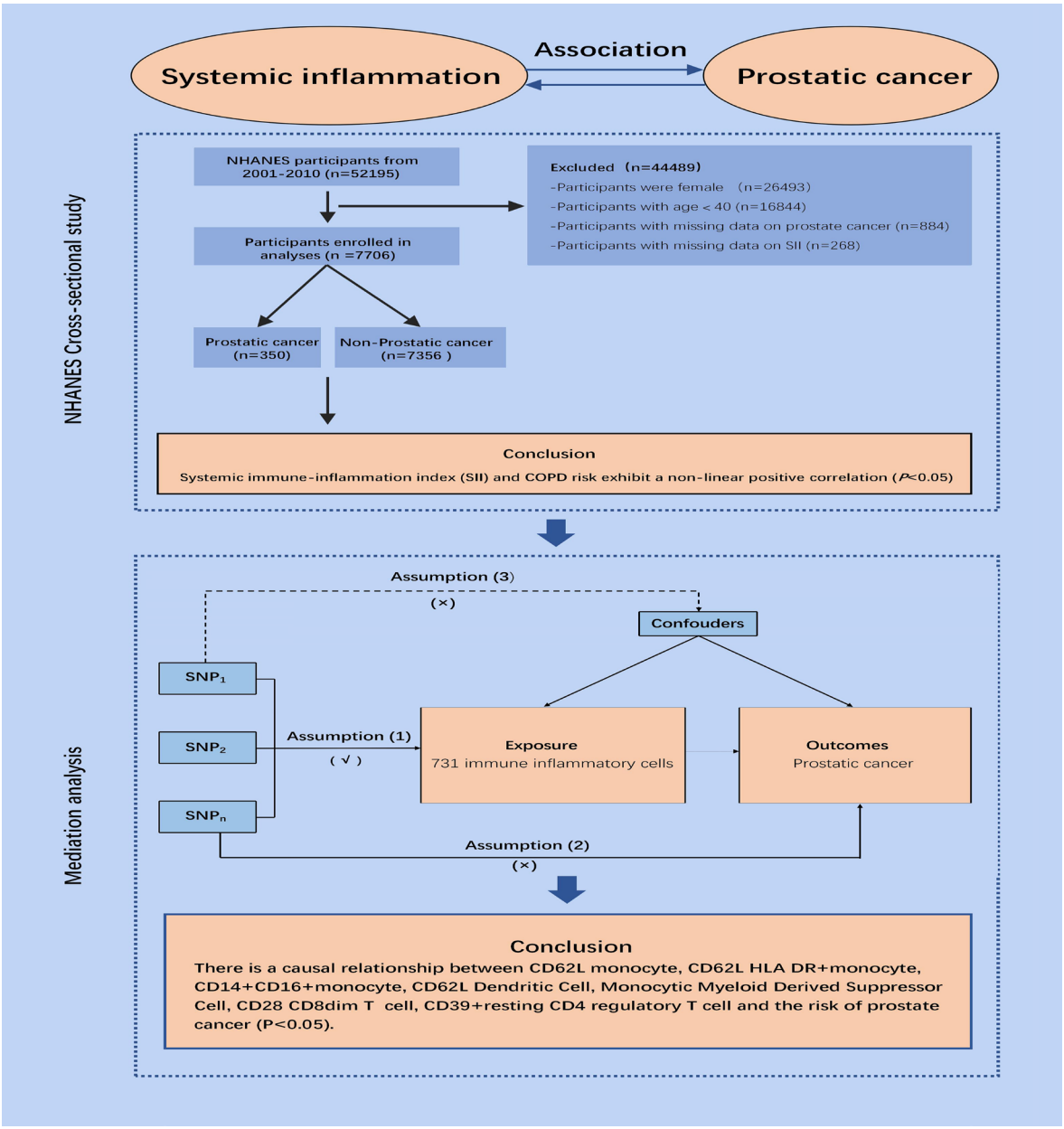

Figure 1. Flow diagram of the combined NHANES cross-sectional and MR study.

Table 3. Threshold effect analysis of LogSII on Odds Ratios for prostate cancer using the RCS model.

Inflection point		Adjusted OR (95% CI)	*P*-value
LogSII (Overall)		1.18 (1.04-1.35)	0.012
< Inflection point	8.90	0.86 (0.66-1.11)	0.240
≥ Inflection point		1.40 (1.10-1.78)	0.006

Note: OR represents the increased odds ratio for prostate cancer when LogSII increased by 1 unit.

included age, race/ethnicity, education level, income, body mass index (BMI), smoking status, alcohol intake, and comorbidities. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other. Educational attainment was dichotomized as beyond high school or not. BMI was classified using standard categories. Blood sample indicators included Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), and Hemoglobin A1C (HbA1c). The presence of comorbidities, including diabetes, hypertension, and hypercholesterolemia, was determined by self-report or relevant medication use.

MR analysis

To supplement the cross-sectional analysis, we performed a two-sample MR to evaluate potential causal relationships between specific immune cell types and PCa risk. This methodology employs summary-level data from publicly accessible genome-wide association studies (GWAS) and is less prone to confounding and reverse causation. We selected the largest available GWAS for peripheral blood immunophenotypes, which included 117 absolute cell (AC) counts from 3,757 Sardinian samples.[28,29] GWAS data on PCa were obtained from the UK Biobank (id: ieu-b-4809), including 9,132 PCa cases and 173,493 controls of European ancestry. We selected single nucleotide polymorphisms (SNPs) significantly associated with the exposure ($p < 5\times10^{-5}$) and harmonized the datasets. The primary MR method was inverse variance weighted (IVW) regression. Secondary methods, including MR-Egger, weighted median, and mode-based approaches, were used to assess consistency and evaluate potential biases.[30,31]

Statistical analysis

Participant characteristics were summarized using descriptive statistics. Multivariable logistic regression models were developed to assess the association between SII levels and PCa prevalence. LogSII was analyzed as both a continuous variable and in quartiles. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed.[32,33] A restricted cubic spline (RCS) model was used to test for a nonlinear relationship.[34] All data analysis was conducted using R version 3.5.2. All statistical tests were two-sided with a significance threshold of $p < 0.05$.

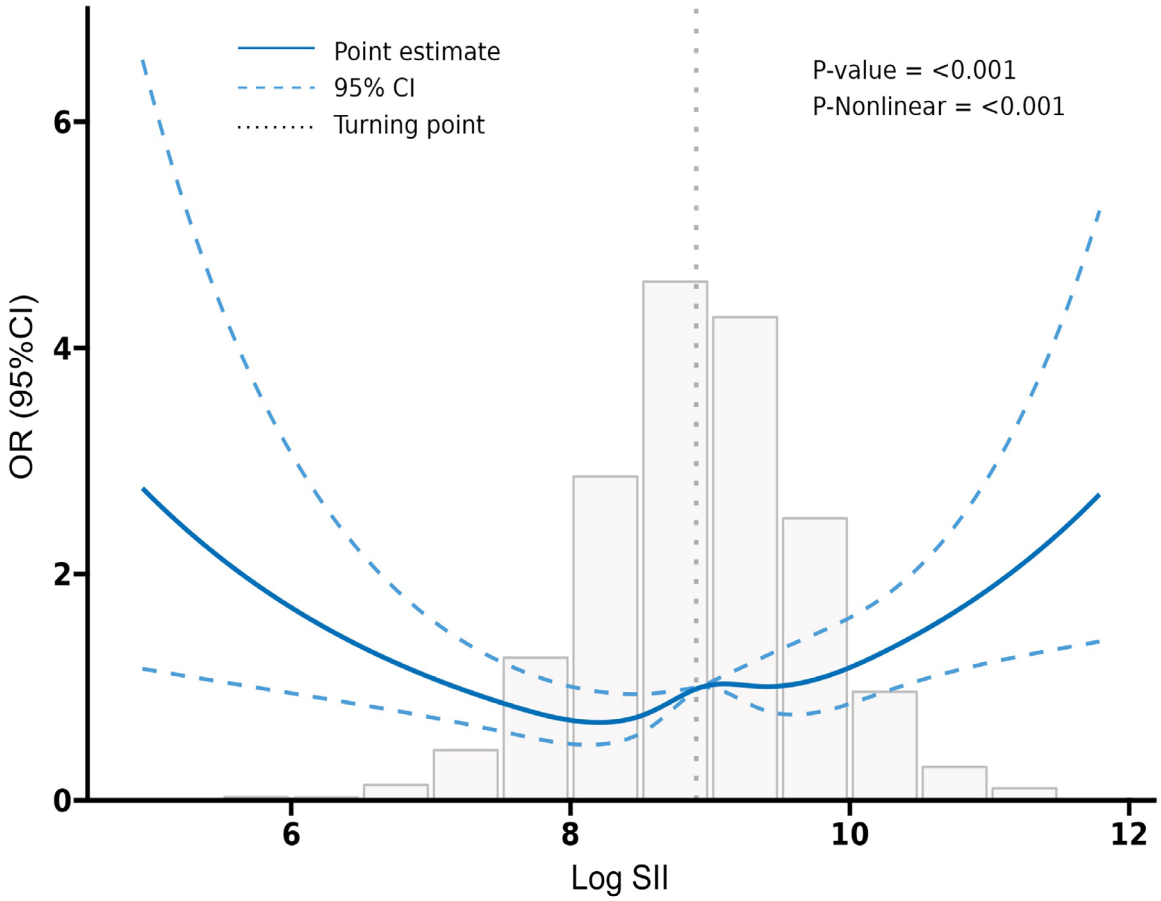

Figure 2. Dose-response association between SII and odds ratio (OR) of prostate cancer in the total population by RCS analysis.

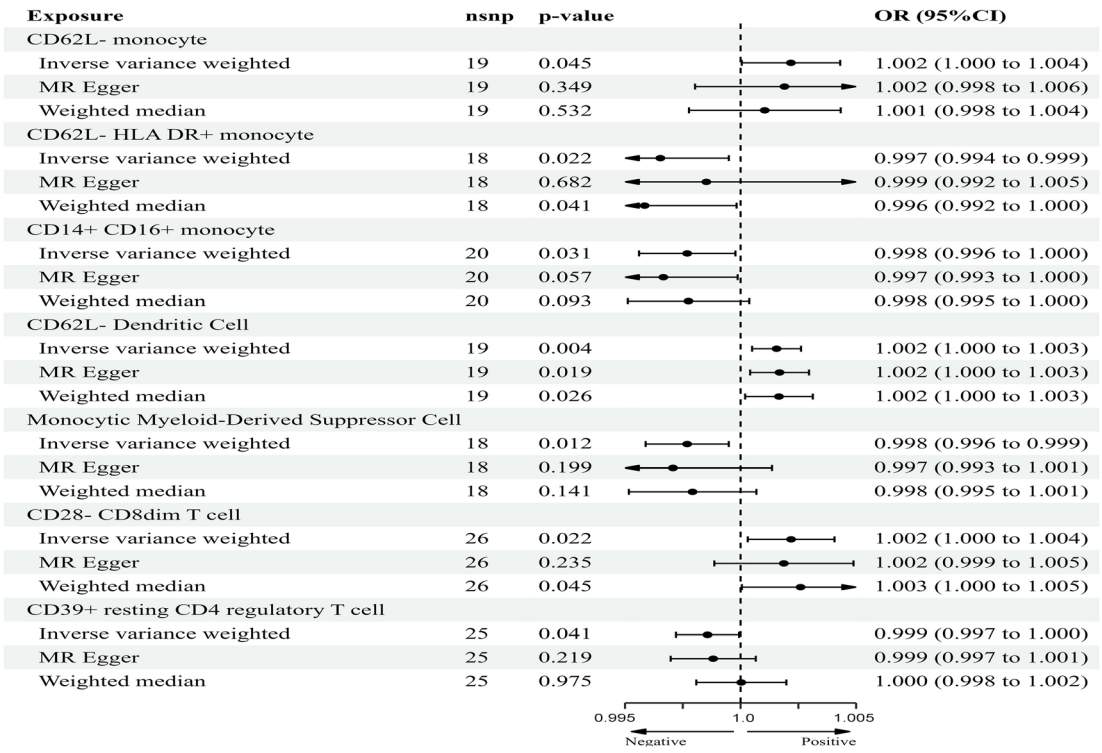

Figure 3. MR analyses of 7 types of immune cells on Prostate cancer ($p < 0.05$).

RESULTS

NHANES Cross-Sectional Study Baseline Information
A total of 7,706 NHANES participants aged ≥ 40 years were included, of whom 350 (4.5%) were prostate cancer cases. (**Table 1**) presents the baseline characteristics. PCa cases were significantly older than controls (mean age: 66.8 vs 55.2 years, $p < 0.001$). The racial/ethnic distribution differed between cases and controls ($p < 0.001$), with a higher proportion of non-Hispanic black individuals among cases (25.1% vs 18.1%). Cases were more likely to be divorced, separated, or widowed (23.1% vs 20.3%, $p = 0.002$). Hypertension was more common in cases than controls (70.6% vs 53.0%, $p < 0.001$). PCa cases had lower ALT levels (median 22 vs 25 U/L, $p = 0.006$) and higher SII levels (median 9.06 vs 8.81, $p = 0.010$) compared to controls. Other characteristics such as education, BMI, smoking, alcohol intake, and diabetes prevalence were similar between groups.

The Association Between SII and PCa

(Table 2) displays the results from logistic regression models. In the unadjusted analysis, higher LogSII levels were associated with progressively increased odds of PCa (p for trend < 0.001). This association remained statistically significant after adjusting for potential confounders. In the fully adjusted model, controlling for age, race, education, marital status, smoking, alcohol use, BMI, hypertension, hyperlipidemia, and diabetes, participants in the highest LogSII quartile had 1.51 times higher odds of PCa compared to the lowest quartile (OR = 1.51; 95% CI, 1.09-2.08; $p = 0.03$). When analyzed as a continuous variable, a one-unit increase in LogSII was associated with a 10% increase in the odds of PCa (OR = 1.10 per unit increment; 95% CI, 1.04-1.17; $p = 0.001$) in the fully adjusted model.
The Dose-Response Between SII and PCa Disease Risk
The RCS analysis indicated a significant nonlinear association between SII levels and PCa odds (p for nonlinearity = 0.012), as shown in (**Figure 2**) and (**Table 3**). An inflection point was identified at an SII level of 8.90. Below this threshold, there was no significant association between SII and PCa odds (OR = 0.86 per unit increase; 95% CI, 0.66-1.11; $p = 0.24$). However, above the SII threshold of 8.90, higher SII values were associated with significantly increased PCa odds in a dose-response manner (OR = 1.40 per unit increase; 95% CI, 1.10-1.78; $p = 0.006$).

The Causal Relationship Between Peripheral Immune Cells and PCa

The MR analysis identified several peripheral immune cell types with significant causal associations with PCa risk using the IVW method (**Figure 3**). A genetically predicted one-unit increase in CD62L- monocytes was associated with a 1.002-fold greater odds of PCa (95% CI, 1.000-1.004; $p = 0.045$). In contrast, CD62L- HLA DR+ monocytes, CD14+ CD16+ monocytes, monocytic myeloid-derived suppressor cells (MDSCs), and CD39+ resting CD4 regulatory T cells were associated with reduced odds of PCa. Genetically predicted increases in CD62L- dendritic cells and CD28- CD8dim T cells were associated with increased odds of PCa. Sensitivity analyses showed no significant horizontal pleiotropy or heterogeneity for these findings.

DISCUSSION

SII incorporates circulating neutrophil, lymphocyte,

and platelet counts into a composite score reflecting systemic immune activation and inflammation.[16] Higher SII values result from neutrophilia and thrombocytosis along with relative lymphopenia. These individual components each exert pro-tumorigenic effects that likely underlie the observed association between elevated SII and PCa odds. Neutrophils promote cancer progression through several mechanisms, including the secretion of matrix metalloproteinases and proangiogenic factors.[4,35] Relative lymphopenia impairs anti-tumor immune surveillance.[5] Thrombocytosis contributes to cancer pathogenesis by supplying growth factors that propagate tumor growth.[11]

Prior studies support links between the cellular constituents of SII and adverse PCa features.[12] Inflammation of the prostate involves inflammatory cytokines such as IL-6 and TGF-β. The coordinated expression of these cytokines promotes tumor survival and disease progression through various mechanisms, including immune regulation, epithelial-mesenchymal transition (EMT), and angiogenesis.[13] Inflammatory factors like TNF-α, IL-1β, IL-6, COX-2, and IGF-1 are all associated with a poor prognosis in PCa.[36,37]

Our MR analysis found that genetically predicted proportions of several monocyte subsets (CD62L- classical, CD62L- HLA-DR+ nonclassical, CD14+CD16+ intermediate) and CD62L- myeloid dendritic cells were positively associated with PCa odds. In contrast, higher levels of anti-inflammatory monocytic MDSCs and immunosuppressive CD39+ resting regulatory T cells (Tregs) were protective. These causal findings emphasize that shifts in the activation and composition of particular myeloid and lymphoid populations may influence prostate tumorigenesis.

Monocyte heterogeneity allows for diverse functional responses.[38] The loss of surface CD62L prevents lymph node homing, retaining monocytes in circulation where they can accumulate in tissues and drive inflammatory changes.[39,40] The paradoxical finding that CD62L- HLA-DR+ monocytes were associated with increased PCa risk implies that the loss of CD62L may create a pro-tumorigenic phenotype that offsets their antigen-presenting capabilities.[41,42] Similarly, while myeloid dendritic cells initiate adaptive immune responses, the accumulation of CD62L- dendritic cells in tumors is linked to impaired T cell activation and tolerance, which may explain their positive causal relationship with PCa in our analysis.[43,44]

MDSCs and Tregs are known to suppress anti-cancer immunity.[45,48] Increased circulating MDSCs are predictive of poorer outcomes in PCa patients.[46,47] The protective association found in our MR analysis for both MDSCs and Tregs suggests that a genetic predisposition to greater immunosuppression could hinder the early elimination of malignant cells, thereby influencing PCa risk.[49] Overall, the MR findings provide stronger evidence for direct roles of specific immune cell subsets in PCa development.[50]

Chronic inflammation is a well-recognized enabler of oncogenic transformation.[51] It can facilitate prostate carcinogenesis through both local effects in the tumor microenvironment and indirect systemic actions.[52] Circulating leukocytes and inflammatory mediators can infiltrate the prostate, leading to oxidative damage, cytokine secretion, and activation of signaling pathways that create an environment conducive to neoplastic growth.[53] Systemic inflammation also exacerbates metabolic dysfunction, insulin resistance, and obesity, which are associated with aggressive PCa.[54-56]

This study has important implications for understanding the role of systemic inflammation in prostate cancer. The robust observational findings linking elevated SII with increased PCa risk provide compelling evidence for inflammation as a modifiable risk factor. The MR analysis identified specific immune cell populations with causal influences on PCa odds, opening new avenues for targeted interventions. However, key knowledge gaps remain. The precise molecular mechanisms linking systemic inflammation to prostate carcinogenesis need to be fully elucidated. Future longitudinal and mechanistic studies are necessary. We anticipate that advances in single-cell technologies and multi-omics data integration will rapidly evolve this field, potentially leading to inflammation-based risk prediction models and novel therapeutic strategies.

While this study provides compelling evidence, some limitations should be considered. The cross-sectional design of the NHANES analysis cannot prove causation. Self-reported PCa diagnosis could be subject to misclassification bias. Nonetheless, the large, nationally representative sample and complementary MR findings provide robust evidence for the role of systemic inflammation in prostate carcinogenesis.

CONCLUSIONS

In summary, this study found a significant positive association between an elevated systemic immune-inflammation index and a higher prevalence of prostate cancer in a nationally representative sample. The cross-sectional analysis revealed a dose-response relationship, particularly above an SII threshold of 8.90. The Mendelian randomization analysis provided evidence for causal effects of several circulating leukocyte populations, including monocyte and dendritic cell subsets, on PCa risk. These findings underscore the critical role of chronic inflammation in prostate carcinogenesis.

SUMMARY

This study shows a strong link between body-wide inflammation and prostate cancer risk. Using a large US health survey and genetic data, we found that higher inflammation levels increase the odds of prostate cancer, with specific immune cells playing a causal role.

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Author Contributions

GRJ and ZCS carried out the acquisition and interpretation of data and were major contributors to drafting the manuscript. GRJ carried out the clinical partial data collection and analysis. GRJ and WZJ participated in drawing tables and diagrams. WLJ and ZCS were responsible for correcting the language and grammar. ZCS contributed to the ideas of the article and reviewed the manuscript. All authors provided final approval for publishing the manuscript.

Ethics Approval and Consent to Participate

Given that the data for this study were obtained from the open-access NHANES database and IEU project, no additional ethical approval was required.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

APPENDIX

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