Am J Transl Res 2025;17(12):9881-9893
www.ajtr.org /ISSN:1943-8141/AJTR0169638

Original Article

Association between red blood cell distribution width to albumin ratio and prostate specific antigen based on NHANES data

Zhe Yang[1*], Meihui Zhang[2*], Lulu Liu[2], Xiaomei Qiu[2], Yitong Shi[2], Nuo Li[3], Haoyong Ning[2]

[1]The Second School of Clinical Medicine, Southern Medical University, Guangzhou 510515, Guangdong, China; [2]Department of Pathology, Hainan Hospital of Chinese People's Liberation Army (PLA) General Hospital, Sanya 572013, Hainan, China; [3]Department of General Medicine, Fenghuang Health Center, Tianya District, Sanya 572023, Hainan, China. [*]Equal contributors and co-first authors.

Received October 29, 2025; Accepted December 5, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: As the most common cancer in men in the United States, risk factors for prostate cancer (PCa) need to be identified. Serum prostate specific antigen (PSA) levels are used for the screening of prostate cancer due to its association with the disease. Investigations have indicated that the risk of prostate cancer determined based on PSA can be further stratified on the basis of total PSA (tPSA) and f/t PSA. Further, the red blood cell distribution width-to-albumin ratio (RAR) has recently been identified as a novel biomarker for multiple inflammatory diseases. The relationship between RAR and PSA remains unclear. Here, we intended to study the association between RAR and PSA. National Health and Nutrition Examination Surveys (NHANES) represents a cross-sectional observational study within the United States. We obtained clinical data throughout the 2003 - 2010 NHANES study period. In 41,156 NHANES men, we selected 5,992 men aged 40 years or older. Missing data were imputed using multiple imputation. The association between RAR and PSA was assessed using multivariable adjusted linear regression analysis. Variance inflation factor (VIF) values were also calculated to exclude collinearity of independent variables. The association of the threshold effects was assessed using inflection points. The effect of RAR levels on PSA was significant in 5,992 subjects after adjusting the confounders (β = 1.13, 95% CI: 0.59-1.67). The notion of a threshold level was supported by the presence of inflection point at RAR = 3.762. The effect of a 1 unit increase in the RAR was a consistently increasing function of quartile of RAR. For instance, in the highest quartile of RAR, if RAR rises by 1 unit, PSA rises by 1.36 (β = 1.36, 95% CI: 0.90-1.83), suggesting a non-linearity of the two. For example, when RAR is below 3.762, higher RAR levels seem associated with higher PSA levels. This is important for understanding the factors that may play an important role in the occurrence and development of prostate cancer. Future studies must do assessments of prostate cancer incidence within the cohorts described.

Keywords: RAR, PSA, NHANES, cross-sectional study

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer in American males and an estimated 1.4 million new cancer cases were diagnosed during 2020, with that number rising to 2.9 million in 2040 [1]. Genetic, environmental, and lifestyle factors contribute to the disease in that its etiology and pathogenesis are poorly understood and are areas of active prevention and treatment research [2]. Prostate-specific antigen (PSA), a glycoprotein produced by prostatic ductal and acinar epithelial cells, is crucial for maintaining prostate health. Prostate-specific antigen testing is key in the diagnosis of PCa, but serum PSA is affected by several variables, so finding determinants of PSA variation is essential for the test's clinical use. When patients have a total PSA (tPSA) > 10 ng/mL or a tPSA of 4-10 ng/mL with a free/total PSA (f/t PSA) ratio of less than or equal to 25%, they are PSA - based high - risk group. The rest are classified as PSA - based low - risk group [3-5].

Multiple studies have determined inflammation's role in the development of prostate cancer [6]. Persistent tissue damage from chronic

https://doi.org/10.62347/CYCT4046

inflammation or dysregulated inflammatory mechanisms promotes the release of inflammatory mediators, the recruitment of cytokines, the expansion of leukocytes, and genomic instability. PCa is associated with DNA damage, including mutagenesis in epithelial cells [7, 8], and inflammation-related markers have been evaluated for their utility in PCa screening.

The red blood cell distribution width (RDW), which expresses the heterogeneity of red blood cell volume, is associated with systemic inflammation [9]. While most studies have looked at the role of the RDW as predictor of cancer prognosis (survival in pancreatic ductal adenocarcinoma [10], breast cancer activity [11], and hepatocellular carcinoma outcomes [12]), its role in cancer risk is still to be determined. However, prior meta-analyzes have found that RDW is associated with an increased risk of rectal cancer [13] and lung cancer [14]. One potential mechanism is the inflammation-induced erythropoietic dysfunction caused by chronic inflammation. This combination is characterized by (i) an elevated RDW as a result of altered red blood cell maturation and (ii) the induction of DNA injury and cancer by pro-inflammatory cytokines such as IL-6 and TNF-α [9, 15]. However, direct evidence of an association between RDW and the risk of prostate cancer is limited and requires further investigation.

Albumin (ALB) is an important nutritional and inflammatory marker with anti-inflammatory and anti-oxidative properties [16, 17]. According to past research, albumin plays an important prognostic role in metastatic castration-resistant prostate cancer (mCRPC) patients [18]. Low albumin levels are related to continuous systemic inflammation and the body's nutritional state [19]. Because of their important physiological roles and ease of testing, RDW and albumin can help predict inflammatory disorders by acting as a composite biomarker of chronic low-grade inflammation.

The red blood cell distribution width to albumin ratio (RAR), defined as the RDW divided by albumin, is associated with several inflammatory disorders, including diabetes mellitus and its complications [20], rheumatism, sepsis, stroke [21], and heart failure [22]. RAR is a novel inflammatory marker [23]. However, no studies have explored the relationship between RAR and PSA. Thus, the present study was conducted to assess the association between these two variables, using data collected from the 2003-2010 NHANES, a nationally representative survey of the US population.

Materials and methods

Data availability

NHANES is a multistage, probability-based, cross-sectional series of surveys, conducted through the National Center for Health Statistics (NCHS) [24], with the goal of obtaining nationally representative data on the health and nutritional status of the civilian in non-institutionalized United States population. Every two years, interviews, physical examination, home visits, and laboratory tests provide information on a wide range of topics. The survey collects data on a wide range of sociodemographic, dietary, and behavioral and risk factors to inform research and policy development. NHANES is also conducted according to the Declaration of Helsinki, and is governed by the review of the NCHS Institutional Review Board (IRB). All subjects give written informed consent prior to enrollment. Information about the surveys' methodology and the data they collect is available on the CDC's website. https://www.cdc.gov/nchs/nhanes.

Study population

The RAR and PSA analysis used four NHANES cycles in a row: 2003-2004, 2005-2006, 2007-2008, and 2009-2010. The NHANES study began with 41,156 subjects. For the purpose of the present study, for ascertainment of the association of RAR and PSA levels in the selected cycles, and for the validity and accuracy of the study results, we systematically excluded: (1) persons under 40 years of age (n = 9,650), (2) females (n = 20,785), (3) participants with incomplete RAR measurements (n = 26), (4) participants with missing PSA data (n = 4,703). The final analytical sample consisted of 5,992 eligible participants (see **Figure 1**).

Calculation and stratification of RAR

RAR is defined as the red blood cell distribution width (RDW) divided by the serum albumin (ALB). Baseline NHANES blood test data were

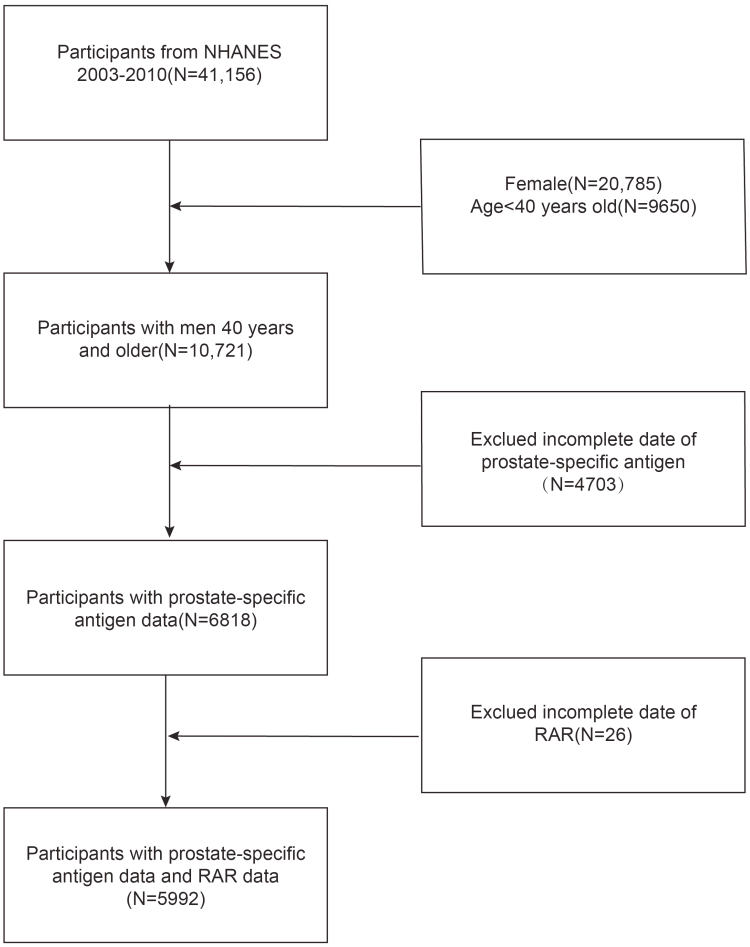

Figure 1. Flowchart of the participant's selection from NHANES 2003-2010. RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen.

collected before prostate-specific diagnosis at the first encounter. Peripheral blood RDW in percentage was collected by a Coulter analyzer at the MEC as a part of the NHANES survey. Serum albumin (g/dL) levels were measured using the bromocresol purple (BCP) method. The RAR was calculated using the formula RAR = RDW (%)/albumin (g/dL) [25]. Participants were separated into quartiles according to the RAR value inside of the study: Q1 (less than 2.81), Q2 (2.81 to 3.00), Q3 (3.00 to 3.23) and Q4 (3.23 or more). The first quartile against (Q1, RAR < 2.81) served as the reference group against which others were compared.

Definition of PSA and PSA-based risk stratification

Venous blood samples were collected from all NHANES participants. Serum PSA concentration (ng/ml) was determined using a standardized immunoenzymatic sandwich assay, and total PSA data were used as outcome variables in our analysis.

Total PSA or tPSA and free-to-total PSA ratio or f/tPSA are PSA biomarkers that predict prostate cancer risk. The PSA-based high-risk and low-risk groups have these definitions: in the high-risk group the tPSA exceeds 10 ng/mL, or tPSA is between 4 and 10 ng/mL and f/tPSA ratio is below 25%. All others were considered low-risk [3-5].

Covariates

Race, age, education, marital status, poverty-income ratio (PIR), body mass index (BMI), history of drinking alcohol, diabetes, and hypertension are potential confounders of PSA as found by prior studies [26, 27]. Smoking is also a known risk factor of many cancers [28]. Prostate cancer is one of these cancers. Total cholesterol was a covariate because prostate cancer studies indicate cholesterol levels correlate to serum PSA [29]. Self-reported race/ethnicity included those identified as Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, and Other Races. Participants were asked to report data according to their educational attainment (less than high school, high school graduate, and college or above) and marital status (unmarried, married/living with partner, and divorced/widowed/separated). The poverty income ratio defined socioeconomic status in these categories: low, less than 1.3; medium, 1.3 to 3.5; high, greater than 3.5. Body mass index or BMI included these categories for normal (< 25 kg/m^2), overweight (25-30 kg/m^2), and obese (≥ 30 kg/m^2). Smoking status was defined as current smoker which means 100 or more lifetime cigarettes and currently smoking, former smoker which means

100 or more lifetime cigarettes but quit, or non-smoker which means less than 100 lifetime cigarettes [30]. Alcohol consumption was defined as yes or no. Laboratory parameters were serum albumin (g/dL), RDW (%), and TC (mg/dL). Diabetes was defined as: a history of diabetes, use of insulin or antidiabetic medications, hemoglobin A1c ≥ 6.5%, fasting plasma glucose ≥ 126 mg/dL, or 2-hour postprandial glucose ≥ 200 mg/dL [31]. Hypertension was defined as a history of hypertension, systolic blood pressure (SBP) > 140 mmHg, or diastolic blood pressure (DBP) > 90 mmHg.

Statistical analysis

NHANES samples with multistage probability methodology to provide a national representative sample. Therefore, in analyzes, we accounted for primary sampling units, sampling weights, and stratification using the "survey" package in the R statistical software. The statistical packages accounted for sampling design and weights for national estimates and made the results generalizable to the U.S. non-institutionalized population and prevented overestimation of statistical significance. To ensure that small subpopulations were sufficiently represented in the analyses, the sampling weights from National Health and Nutrition Examination Survey (NHANES) were applied, and data were stratified according to RAR quartile at baseline. Continuous variables were expressed as weighted mean ± standard deviation (SD), while categorical variables were expressed as percentages (%). Analysis of variance (ANOVA) and chi-square test were used for comparing between-group baseline characteristics. Three multivariable-adjusted linear regression models were employed to examine the associations of RAR and PSA, and another three multivariable-adjusted logistic regression models compared the relationship between RAR and the high-risk group based on PSA. Additionally, trend tests were conducted to determine linear trends after the continuous RAR was converted into a categorical variable. The regression models adjusted for these items: 1) unadjusted model, 2) model adjusted for age and race, 3) model adjusted for age, race, marital status, educational level, PIR, BMI, hypertension, diabetes, smoking status, alcohol intake, and total cholesterol. Researchers assessed multicollinearity that co-linearity between independent variables caused using the variance inflation factor (VIF). A value > 10 implies severe collinearity. We used smooth curve fitting, generalized additive models (GAM), threshold effect analysis via two-stage linear regression, and interaction tests based on the RAR-PSA relationship to assess the presence of nonlinear associations; and used Restricted cubic spline (RCS) plots to visualize data. We sought to corroborate the robustness of our findings of RAR and PSA associations using a priori defined subgroups to evaluate effect modification. Covariate groupings were selected a priori based on prior findings and frequently evaluated prostate cancer risk factors: age [26], race [27], BMI, smoking status, alcohol intake, chronic inflammatory diseases (hypertension and diabetes) [32, 33], and potential modifiers of social behavior (marital status) [30]. Missing data were imputed using the R "mice" package. Sensitivity analyses evaluated result robustness via log transformation of RAR, unweighted data analysis, and by excluding individuals with missing data. Statistical significance was set at $P < 0.05$. Data were analyzed and plotted using the Storm statistical system (Zstats software, version 1.0 www.zstats.net) and R version 4.4.0 (24 Apr 2024).

Results

Weighted baseline characteristics of the research population

In the case of the study population composed of 5,992 men aged 40 years and over, age (in years) was 59.67 ± 0.18, RAR was 3.08 ± 0.01, and mean tPSA was 1.87 ng/mL (standard deviation, 0.06). Of those patients, 54.76% were non - Hispanic white (**Table 1**). RAR is divided into four groups (quartiles): Q1 = RAR below 2.81, Q2 = 2.81 ≤ RAR to below 3.00, Q3 = 3.00 ≤ RAR to below 3.23, Q4 = RAR ≥ 3.23. 3.00 is at most RAR which is at most 3.23 and RAR is at least 3.23. As shown in **Table 1**, age, race, education, marital status, smoking, alcohol consumption, diabetes, and hypertension did not differ in a statistically meaningful way between the RAR quartiles (Q1, Q2, Q3, and Q4) ($P > 0.05$). When comparing quartiles, only differences in BMI, PIR, and total cholesterol had a statistically meaningful *P*-value under 0.05. For example,

Table 1. Baseline characteristics of the participants

Variable	Q1 (n = 1512)	Q2 (n = 1455)	Q3 (n = 1507)	Q4 (n = 1518)	*P*_value
RAR, Mean (SE)	2.68 (0.00)	2.90 (0.00)	3.10 (0.00)	3.61 (0.01)	< 0.001
Age,years (SE)	55.95 (0.32)	55.92 (0.35)	56.00 (0.37)	55.29 (0.30)	0.244
Race/ethnicity, n (%)					0.331
Mexican American	276 (6.88)	246 (5.83)	243 (5.79)	269 (6.12)	
Other Hispanic	95 (3.09)	101 (3.36)	95 (3.28)	96 (3.08)	
Non-Hispanic White	810 (75.98)	814 (79.08)	818 (75.85)	798 (75.39)	
Non-Hispanic Black	280 (9.54)	251 (7.93)	278 (8.81)	293 (9.88)	
Other Races	51 (4.50)	43 (3.80)	73 (6.28)	62 (5.53)	
Education level, n (%)					0.528
< High school	464 (18.97)	462 (18.07)	451 (18.27)	501 (19.61)	
High school	360 (25.08)	325 (24.14)	378 (27.86)	346 (24.74)	
> High school	688 (55.95)	668 (57.79)	678 (53.87)	671 (55.64)	
Marital.status, n (%)					0.328
Married/Living with partner	1074 (74.92)	1057 (76.38)	1085 (74.87)	1110 (78.49)	
Widowed/divorced/separated	333 (18.33)	304 (18.06)	314 (18.69)	304 (15.24)	
Never married	105 (6.75)	94 (5.56)	108 (6.44)	104 (6.28)	
PIR, n (%)					0.004
< 1.3	394 (16.00)	370 (15.23)	381 (14.93)	406 (14.92)	
1.3-3.5	573 (34.18)	594 (34.26)	569 (33.72)	558 (32.26)	
≥ 3.5	545 (49.82)	491 (50.51)	557 (51.35)	554 (52.82)	
BMI, n (%)					< 0.001
< 25	394 (27.84)	330 (23.54)	318 (23.02)	375 (26.55)	
25-30	730 (49.36)	652 (46.98)	620 (42.73)	512 (34.35)	
≥ 30	388 (22.80)	473 (29.48)	569 (34.25)	631 (39.10)	
Smoking status, n (%)					0.950
Current smoker	594 (41.33)	519 (41.11)	576 (40.46)	588 (42.55)	
Former smoker	582 (37.15)	592 (36.35)	597 (37.42)	575 (35.09)	
Nonsmoker	336 (21.53)	344 (22.54)	334 (22.12)	355 (22.36)	
Drink, n (%)					0.758
No	285 (17.32)	252 (15.61)	273 (16.48)	283 (17.27)	
Yes	1227 (82.68)	1203 (84.39)	1234 (83.52)	1235 (82.73)	
Diabetes, n (%)					0.833
No	1165 (81.88)	1114 (82.22)	1116 (80.67)	1153 (81.67)	
Yes	347 (18.12)	341 (17.78)	391 (19.33)	365 (18.33)	
High blood pressure, n (%)					0.594
No	736 (53.20)	708 (53.66)	727 (53.64)	766 (56.20)	
Yes	776 (46.80)	747 (46.34)	780 (46.36)	752 (43.80)	
PSA-Based Risk Category, n (%)					< 0.001
PSA-based low risk	1453 (95.45)	1363 (93.62)	1409 (92.03)	1341 (87.71)	
PSA-based high risk	59 (4.55)	92 (6.38)	98 (7.97)	177 (12.29)	
RDW, Mean (SE)	12.17 (0.01)	12.56 (0.02)	12.95 (0.02)	14.15 (0.06)	< 0.001
ALB, Mean (SE)	4.55 (0.01)	4.33 (0.01)	4.18 (0.01)	3.92 (0.01)	< 0.001
TC (SE), mg/dL	208.99 (1.12)	201.19 (1.39)	197.46 (1.42)	184.32 (1.33)	< 0.001
tPSA (SE), ng/ml	1.46 (0.05)	1.63 (0.07)	1.92 (0.09)	2.68 (0.19)	< 0.001
fPSA (SE), ng/ml	0.37 (0.01)	0.42 (0.02)	0.46 (0.02)	0.60 (0.03)	< 0.001
f/tPSA (SE), %	30.60 (0.39)	30.14 (0.39)	29.62 (0.41)	30.16 (0.46)	0.420

SE: standard error; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; tPSA: total prostate specific antigen; fPSA: free prostate specific antigen; f/t PSA: free/total prostate specific antigen; ALB: Albumin; TC: total cholesterol; PIR: poverty-income ratio; BMI: body mass index. Data for categorical variables are expressed as numbers (%).

Table 2. Associations between RAR and PSA

Exposure	Non-adjusted model (model 1)		Incomplete adjusted model (model 2)		Fully adjusted model (model 3)	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
RAR	1.08 (0.56-1.60)	< 0.001	1.08 (0.56-1.61)	< 0.001	1.13 (0.59-1.67)	< 0.001
RAR						
Q1	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Q2	0.16 (-0.04-0.35)	0.119	0.15 (-0.04-0.35)	0.125	0.19 (-0.01-0.38)	0.070
Q3	0.44 (0.24-0.64)	< 0.001	0.44 (0.24-0.64)	< 0.001	0.51 (0.31-0.71)	< 0.001
Q4	1.27 (0.82-1.72)	< 0.001	1.28 (0.83-1.73)	< 0.001	1.36 (0.90-1.83)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

CI: confidence interval; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen. Model 1: Crude. Model 2: Adjust: Age, Race. Model 3: Adjust: Age, Race, Education level, Marital. status, PIR, BMI, Smoking status, Alcohol consumption, TC, High blood pressure, Diabetes.

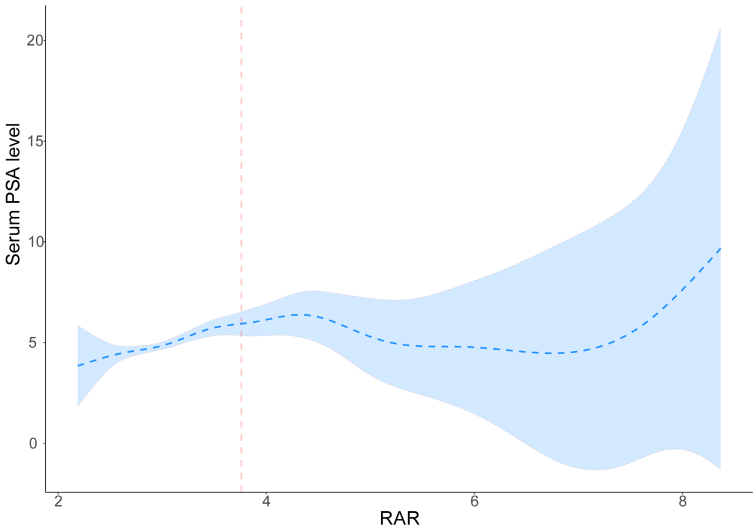

Figure 2. The non-linear relationship between red blood cell distribution width-to-albumin ratio (RAR) and prostate specific antigen (PSA). The blue dashed line shows the smooth curve fitting for these variables. The 95% confidence intervals of this fit are indicated by the blue bands.

more participants in Q4 had BMI ≥ 30 than in Q1 (39.10% vs. 22.80%). MEAN of total cholesterol was 184.32 mg/dL for Q4 and 208.99 mg/dL for Q1. Percent of people with PIR ≥ 3.5 was also higher in Q4 than Q1.

The relationship between RAR and PSA, as well as PSA-based risk stratification

The relationship between RAR and PSA is shown in **Table 2**. In the fully adjusted linear regression model, with every 1-unit increase in the RAR, PSA increased by 1.13 ng/mL (95% CI: 0.59-1.67). Multicollinearity was evaluated through variance inflation factor or VIF. VIF > 10 indicates a high likelihood of covariate multicollinearity. No multicollinearity was found as all covariates had VIF < 10 (Table S1). To further corroborate this observation, RAR was divided into quartiles. The association was also seen across these quartiles (P for trend < 0.001). In the fully adjusted model, PSA was 1.36 ng/mL higher (95% CI: 0.90-1.83) in the highest quartile (Q4) compared with the lowest RAR quartile (Q1). β coefficients of 0.19 (95% CI: -0.01 to 0.38), 0.51 (95% CI: 0.37-0.71) and 1.36 (95% CI: 0.90-1.83) existed in Q2, Q3 and Q4 respectively showing a dose-response effect. This effect on PSA however may not be linear. The fully adjusted (see Table S2) logistic regression model analysis showed that a 1-unit increase in RAR was associated with a 1.87-fold (95% CI: 1.50-2.34) higher odds of being in the PSA-based high-risk group. The odds of being in the PSA-based high-risk group was 222% higher in Q4 compared to Q1 (OR = 3.22; 95% CI: 2.17-4.78).

Nonlinear association of RAR with PSA

To evaluate the potential non-linear relationship between RAR and PSA, we also employed a smooth curve fitting (**Figure 2**). The piecewise linear regression model has better fitness

Table 3. Analysis of the threshold effects of RAR on PSA using the two - segment linear regression model

Outcome	β (95% CI)	*P*_value
Fitting model by standard linear regression	0.98 (0.78-1.18)	< 0.001
Fitting model by two-piecewise linear regression		
Inflection point	3.762	
< 3.762	1.48 (1.20-1.76)	< 0.001
≥ 3.762	-0.55 (-1.82-0.72)	0.399
P for likelihood test		< 0.001

RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; CI: confidence interval. Covariates involved in this model was the same as Adjust III model presented.

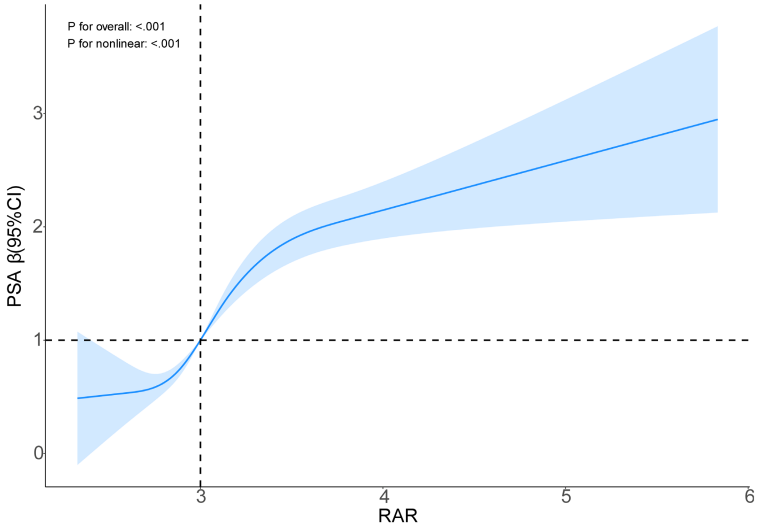

Figure 3. Dose-response relationship between red blood cell distribution width-to-albumin ratio (RAR) and prostate specific antigen (PSA) (RCS Analysis).

than the customary linear regression model based on model comparison tests (P < 0.001). Using an iterative technique, we identified RAR = 3.762 as the best inflection point threshold (**Table 3**). Below this threshold, each 1 unit increase of RAR was associated with a 1.48 ng/ml increase of PSA (β = 1.48 (95% CI: 1.20-1.76)). Once RAR was shown to be above 3.762, however, there was no statistically significant association between RAR and PSA (β = -0.55, 95% CI: -1.82-0.72, P = 0.399). This non-linearity of association can also be validated by the use of restricted cubic splines (**Figure 3**). Both overall association and non-linearity mattered with statistical significance (P < 0.001). To summarize, these observations support the idea that RAR and PSA relate non-linearly and threshold-dependently to each other.

Subgroup analysis

Subgroup analyzes from Table S3 were conducted to determine if the RAR-PSA associations were modified by age, race, marital status, BMI, smoking status, alcohol use, hypertension, and diabetes. RAR-PSA associations did not interact in a statistically meaningful way for age, race, BMI, smoking status, hypertension, and diabetes (P for interaction > 0.05) (**Figure 4**). The association of RAR and serum PSA level was not modified by age, ethnic group, marital status, BMI, smoking, alcohol use, hypertension, and diabetes. The magnitude of the association of RAR and serum PSA level was consistent across the subgroups (coefficient β = 1.08; 95% confidence interval: 0.56-1.60).

Sensitivity analyses

Sensitivity analyses on log-transformed RAR and weighted linear regression (Table S4) showed similar findings. In Model 3, a log-transformed RAR as a continuous variable was positively associated in value with PSA (β = 4.18, 95% CI: 2.37-5.99). Log-RAR's second quartile (β = 0.17, 95% CI: -0.03-0.37), third quartile (β = 0.53, 95% CI: 0.33-0.73), and highest quartile (β = 1.36, 95% CI: 0.90-1.83) were associated linearly with PSA, while a weighted linear regression excluded all missing values when it did not impute for similar results (Table S5). Model 3 also replicated the positive RAR asso-

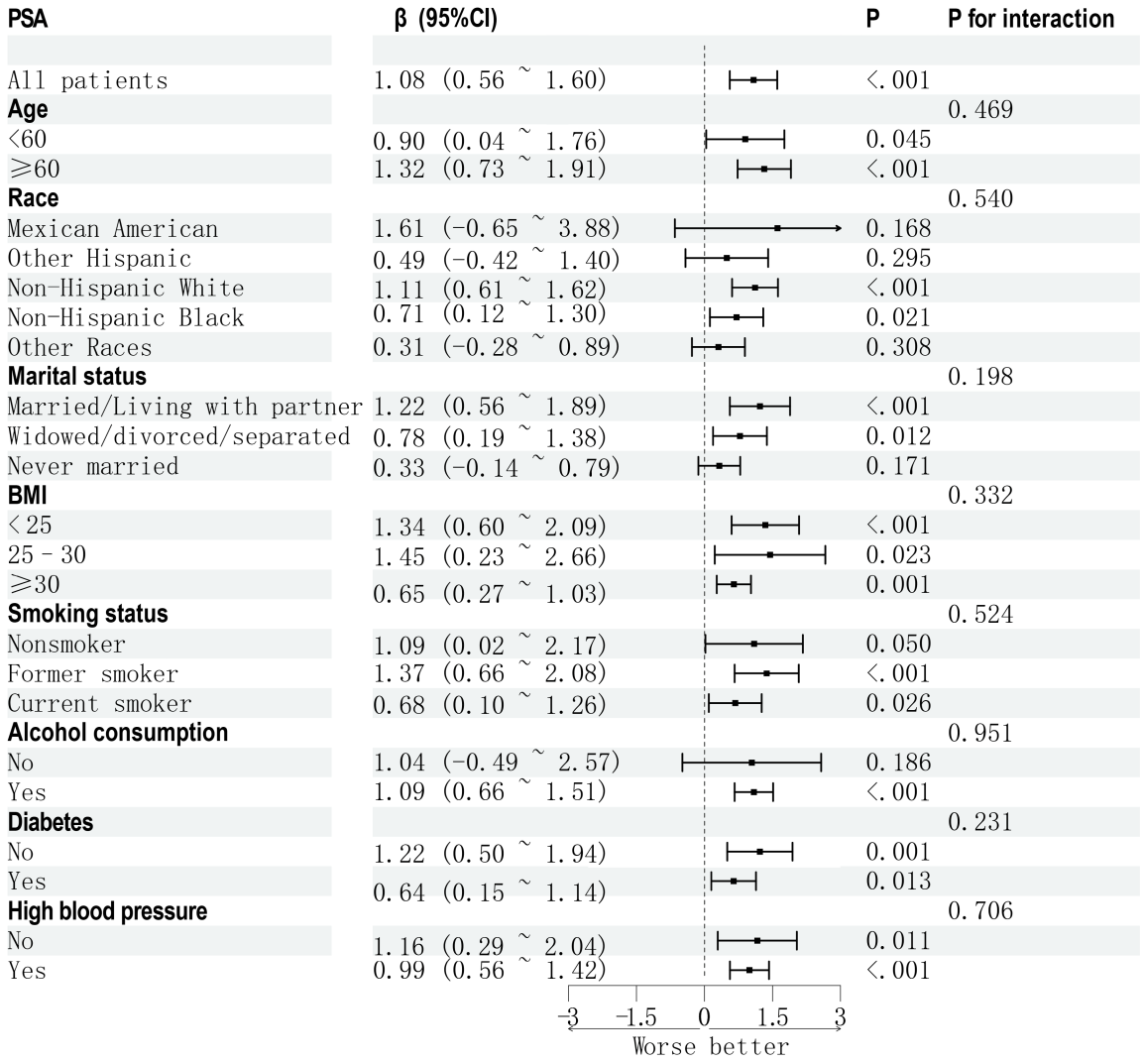

Figure 4. Subgroup analysis of the relationship between red blood cell distribution width-to-albumin ratio (RAR) and prostate specific antigen (PSA). β: regression coefficient; CI: confidence interval; BMI: body mass index.

ciations (β = 1.17, 95% CI: 0.68-1.65), within the continuous model and within the increasing PSA across RAR quartiles model (for Q2, β = 0.25, 95% CI: 0.05-0.45; for Q3, β = 0.49, 95% CI: 0.28-0.69; for Q4, β = 1.40, 95% CI: 0.85-1.96). Tables S6 and S7 show that linear regression analyses performed using unweighted imputed data or after excluding extreme PSA values (> 10 ng/mL) have repeatedly verified the positive correlation between RAR and PSA in Models 1, 2, and 3. In other words, positive associations between RAR and PSA were still meaningful in Model 3, which was a continuous model (β = 1.17, 95% CI: 0.68-1.65), and in the increasing PSA across RAR quartiles model. In summary, we performed sensitivity analyses that showed a strong positive association between RAR and the level of serum PSA.

Discussion

As a cross - sectional survey of 5,992 males aged 40 years and above, it was shown in the study that in men with RAR < 3.762, increase of RAR will result in important increase of PSA. To our knowledge, this is the first study to evaluate the association between RAR and PSA in American men. A higher RAR has also been linked to diabetes, a greater prevalence of chronic kidney disease [23], an increased in-hospital mortality after an acute exacerbation of chronic obstructive pulmonary disease

(COPD) [34], and a higher incidence of depression. Red blood cell distribution width (RDW) measures variation in RBC volume. A high RDW is indicative of systemic inflammation and a poor prognosis for many diseases, including cardiovascular and renal disease, diabetes, hepatic transplantation, and other pulmonary and chronic diseases in the general population [9]. Albumin may bind to other pro inflammatory mediators, reducing the body's inflammatory response capacity. It is also a marker of systemic inflammatory disease [35]. Thus, a high RAR may be related to a higher RDW, along with a low level of albumin, and the RAR is believed to be an indicator of inflammation [36]. The RDW, along with the concentration of albumin, may be a better guide for determining inflammation.

The inflammatory response is one of the more salient factors to stimulate cancer. The first person to document the connection between inflammation and tumors was Rudolf Virchow [15]. Previous studies have shown that inflammation is associated with the following tumors: gastric, colon, skin, liver, breast and lung cancer [32]. Simultaneously, chronic inflammation is a fundamental factor in tumorigenesis [37]. Inflammatory molecules and signaling pathways can drive the onset and development of various tumors through progression. Numerous factors play a role including pro-inflammatory cytokines like Interleukin (IL)-1, IL-6, IL-1β, and Tumor Necrosis Factor (TNF)-α, and transcription factors such as Nuclear Factor kappa-light-chain-enhancer of activated B-cells (NF-κB) and Signal Transducer and Activator of Transcription 3 (STAT3) [38-41]. IL-1, IL-6, necrosis factor and acute - phase reactants stimulate the leakage of albumin from capillaries and govern albumin production in the liver [42, 43]. This reduction in albumin further intensifies inflammation. Malnutrition also weakens the immune system and increases the risk of cancer [44]. Also, the inflammatory process induces the injury of endothelial cells and erythrocytes, which triggers the RDW increase [45]. On the opposite side, the dysfunction of erythroid cells generates inflammation and oxidative stress [46, 47].

Inflammation is a major risk factor for prostate cancer, and also has a deep influence on the tumor microenvironment [33]. Chronic prostatic inflammation can cause tumor-promoting events for affecting the microenvironment. Events include cells that proliferate, survival, immune evasion, remodel prostatic tissue, plus angiogenic factor production, metastasize, and resist therapy [48]. NF-κB, a pro-inflammatory transcription factor, is activated via TNF-α in response to injury/infection. In PCa, it is a powerful promoter in tumorigenesis, chemoresistance, and metastasis through regulation of IL-6 and other factors that drive cancer progression and metastasis, such as VEGF and IL-8 [49, 50]. Cytokines and reactive species are secreted by inflammatory lymphocytes and macrophages that cause DNA damage and inflammatory cell reprogramming resulting in prostatic carcinogenesis [51]. Additionally, migration and clonal amplification of inflammatory cells give rise to DNA DSBs and activation of the AR in prostatic epithelial cells. If the senescence-associated secretory phenotype (SASP) is activated, non-repairable oxidative stress damage to DNA caused by free radicals induces upregulation of DNA repair pathways and activation of tumor suppressors in a cellular DNA damage response, which causes the upregulation of mutagenic damage to DNA. Inherited mutations in DNA repair genes speed up the process of carcinogenesis due to repair deficiency [52]. Microorganisms, such as bacteria and viruses, can promote prostatic inflammation and PCa [53]. More recently, Doat et al. reported that men treated with non-steroidal anti-inflammatory drugs (NSAIDs) with strong COX-2 inhibitory activity have lower risk of PCa [54]. This further reinforces the relationship between inflammation and PCa, and suggests the regulation of inflammation as a possible means of risk reduction against PCa development.

Because of the importance of PSA screening in the diagnosis of prostate cancer but the unclear relationship between RAR and PSA, a secondary analysis of NHANES was done to further describe this relationship. In the current study a non - linear correlation between RAR and PSA was noted for RAR values less than 3.762. It was found that with each 1 unit increase in RAR, there was an increase of 1.48 ng/ml in the PSA (β = 1.48, 95% CI: 1.20-1.76). Similar results were observed after stratifying the risk of prostate cancer according to the PSA, with RARs positively correlated with those at a high risk of prostate cancer (OR = 1.87 (1.50, 2.34), when the RDW increased or the

albumin decreased). Increasing RDW indicates damaged vascular endothelial and red blood cells by decreasing albumin levels which in turn acts as a promoter for an inflammatory reaction and oxidative imbalance. As shown by Richter et al., a decrease in albumin levels leads to a decrease in albumin - bound testosterone levels with an increase in free testosterone levels. Free testosterone is another important risk factor in the pathogenesis of PCa [55], and is also an important factor affecting the serum level of PSA. Inflammation plays a great role in the pathogenesis of cancer [56]. Thus, as inflammatory marker, RAR may be involved in the inflammatory processes that cause the increase of PSA, and may also be a risk factor in the pathogenesis and development of PCa. As a composite indicator, it integrates information related to inflammation, nutrition, and hormone regulation. This multi-dimensional characteristic may provide 'additional information beyond inflammation' for PSA-based risk assessment. It may involve more complex pathophysiological mechanisms that require further dissection in subsequent studies. In our study, the threshold effect of RAR and PSA was found with an inflection point of 3.762. However, the threshold effect can be explained from the following two aspects. The first one is the saturation effect within the biological mechanism: the inflammation-driven effect on tumors may have a "ceiling effect". When RAR reaches greater than 3.762, this may actually be where the body does not have the capacity to mount a large enough inflammatory response. Beyond this point, inflammatory systems (i.e. NF-κB, IL-6/STAT3) can be activated all the time and a greater RAR (inflammatory marker) can no longer drive PSA elevation. In addition, a high RAR may not always suggest the involvement of RAR, but it may also reflect the severity of the underlying disease. Other studies have reported changes in androgens and testosterone levels in patients with liver cirrhosis, which may alter the generation and metabolism of serum PSA and the chances of developing prostate cancer [57]. On the other hand, individuals with high RAR (> 3.762) make up an extremely small proportion of the population studied (15% of Q4 in this study). Thus, differences in sample sizes for clinical data could cause reduced statistical power and wider confidence intervals for the association of interest above the threshold.

The strengths of the study include that the data were drawn from NHANES, a nationally representative dataset collected with standardized protocols. Additionally, confounding variables were controlled for, and stratified analyzes were conducted, in which the association between RAR and PSA levels was assessed within specific strata of the NHANES population. However, there are some limitations to our study that should be noted. First, since our study is cross-sectional, we cannot draw any causal inferences between RAR and PSA or risk of PCa from our findings. Second, our study is only generalizable to US population, as we only performed analysis on the US population. Third, covariates were adjusted during analyses but residual confounding cannot be excluded due to possible unmeasured confounders. Future studies should consider how other potential confounders, including dihydrotestosterone levels, impact the relationship between RAR and the risk of developing PCa. PSA is not specific to prostate cancer. It may be raised in benign prostatic hyperplasia and infection. Clinical data can reflect biases. Random errors can increase because sample sizes differ. Assessment of the association beyond the threshold becomes difficult. In the future, studies could integrate multiple databases, collect data from clinics, and perform cross-validation in potential studies for more precise prediction.

Conclusion

Ultimately, a non-linear relationship between RAR and serum PSA was observed for US males aged 40 years or older. A positive relationship was noted between RAR and PSA levels when RAR was less than 3.762. RAR may serve as a background marker under inflammatory or metabolic conditions, complementing PSA testing. There is some evidence that high levels of RAR increase susceptibility to prostate cancer or the progression of existing prostate cancer but these results require confirmation in prospective studies of prostate cancer incidence.

Acknowledgements

This research was funded by the grants from the Natural Science Foundation of Hainan Province (821MS114).

Written informed consent was obtained from all participants.

Disclosure of conflict of interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Address correspondence to: Haoyong Ning, Department of Pathology, Hainan Hospital of Chinese People's Liberation Army (PLA) General Hospital, No. 80 Jianglin Road, Sanya 572013, Hainan, China. E-mail: ninghaoyong73@163.com

References

[1] James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, Trujillo B, Al-Lazikani B, Attard G, Bray F, Compérat E, Eeles R, Fatiregun O, Grist E, Halabi S, Haran Á, Herchenhorn D, Hofman MS, Jalloh M, Loeb S, MacNair A, Mahal B, Mendes L, Moghul M, Moore C, Morgans A, Morris M, Murphy D, Murthy V, Nguyen PL, Padhani A, Parker C, Rush H, Sculpher M, Soule H, Sydes MR, Tilki D, Tunariu N, Villanti P and Xie LP. The lancet commission on prostate cancer: planning for the surge in cases. Lancet 2024; 403: 1683-1722.

[2] Sekhoacha M, Riet K, Motloung P, Gumenku L, Adegoke A and Mashele S. Prostate cancer review: genetics, diagnosis, treatment options, and alternative approaches. Molecules 2022; 27: 5730.

[3] Moses KA, Sprenkle PC, Bahler C, Box G, Carlsson SV, Catalona WJ, Dahl DM, Dall'Era M, Davis JW, Drake BF, Epstein JI, Etzioni RB, Farrington TA, Garraway IP, Jarrard D, Kauffman E, Kaye D, Kibel AS, LaGrange CA, Maroni P, Ponsky L, Reys B, Salami SS, Sanchez A, Seibert TM, Shaneyfelt TM, Smaldone MC, Sonn G, Tyson MD, Vapiwala N, Wake R, Washington S, Yu A, Yuh B, Berardi RA and Freedman-Cass DA. NCCN guidelines® insights: prostate cancer early detection, version 1.2023. J Natl Compr Canc Netw 2023; 21: 236-246.

[4] Miao S, Bao C, Zhang Y, Wang L, Jin X, Huang B, Zhang Z and Wang W. Associations of the geriatric nutritional risk index with high risk for prostate cancer: a cross-sectional study. Nutrition 2023; 115: 112164.

[5] Yao W, Wu J, Wang H, Jia Z, Zhou Y, Yang C, Xu F, Kong Y and Huang Y. Association between visceral adiposity index and prostate cancer in men aged 40 years and older: a nationwide cross-sectional study. Aging Male 2025; 28: 2449341.

[6] Fernandes R, Costa C, Fernandes R and Barros AN. Inflammation in prostate cancer: exploring the promising role of phenolic compounds as an innovative therapeutic approach. Biomedicines 2023; 11: 3140.

[7] Lu H, Ouyang W and Huang C. Inflammation, a key event in cancer development. Mol Cancer Res 2006; 4: 221-233.

[8] Ames BN, Gold LS and Willett WC. The causes and prevention of cancer. Proc Natl Acad Sci U S A 1995; 92: 5258-5265.

[9] Salvagno GL, Sanchis-Gomar F, Picanza A and Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci 2015; 52: 86-105.

[10] Niu T, Wang Y, Lu L, Li J, Cheng T and Dai Y. The value of preoperative RDW for post-pancreatectomy haemorrhage and surgical prognosis in patients with pancreatic cancer: a retrospective study. BMC Cancer 2025; 25: 437.

[11] Thakur AS, Indoria C, Sahu R, Kujur P and Gahine R. Preoperative evaluation of red blood cell distribution width as a promising biomarker for discriminating between benign and malignant breast tumors and assessing breast cancer activity. Indian J Pathol Microbiol 2024; 67: 324-327.

[12] Vidili G, Zinellu A, Mangoni AA, Arru M, De Murtas V, Cuccuru E, Fancellu A and Paliogiannis P. Red cell distribution width as a predictor of survival in patients with hepatocellular carcinoma. Medicina (Kaunas) 2024; 60: 391.

[13] Virdee PS, Marian IR, Mansouri A, Elhussein L, Kirtley S, Holt T and Birks J. The full blood count blood test for colorectal cancer detection: a systematic review, meta-analysis, and critical appraisal. Cancers (Basel) 2020; 12: 2348.

[14] Liu Y, Qu J, Hu C, Zhao W, Zhang Y, Luo Y and Qu Y. Relationship between red cell distribution width and lung cancer: evidence from Mendelian randomization and national health and nutrition examination survey. Discov Oncol 2025; 16: 867.

[15] Balkwill F and Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357: 539-545.

[16] Che R, Huang X, Zhao W, Jiang F, Wu L, Zhang Z, Bian T, Ma Q, Yu Z, Zhang Q, Dong K, Song H and Ji X. Low serum albumin level as a predictor of hemorrhage transformation after intravenous thrombolysis in ischemic stroke patients. Sci Rep 2017; 7: 7776.

[17] Wiedermann CJ. Hypoalbuminemia as surrogate and culprit of infections. Int J Mol Sci 2021; 22: 4496.

[18] Uzun M, Gokcek S, Kaya E and Semiz HS. The prognostic role of systemic immune-inflamma-

tion index, SII, in metastatic castration-resistant prostate cancer patients. Discov Oncol 2025; 16: 317.
[19] Mukai H, Villafuerte H, Qureshi AR, Lindholm B and Stenvinkel P. Serum albumin, inflammation, and nutrition in end-stage renal disease: C-reactive protein is needed for optimal assessment. Semin Dial 2018; 31: 435-439.
[20] Hong J, Hu X, Liu W, Qian X, Jiang F, Xu Z, Shen F and Zhu H. Impact of red cell distribution width and red cell distribution width/albumin ratio on all-cause mortality in patients with type 2 diabetes and foot ulcers: a retrospective cohort study. Cardiovasc Diabetol 2022; 21: 91.
[21] Zhao N, Hu W, Wu Z, Wu X, Li W, Wang Y and Zhao H. The red blood cell distribution width-albumin ratio: a promising predictor of mortality in stroke patients. Int J Gen Med 2021; 14: 3737-3747.
[22] Ni Q, Wang X, Wang J and Chen P. The red blood cell distribution width-albumin ratio: a promising predictor of mortality in heart failure patients - a cohort study. Clin Chim Acta 2022; 527: 38-46.
[23] Liu J, Wang X, Gao TY, Zhang Q, Zhang SN, Xu YY, Yao WQ, Yang ZH and Yan HJ. Red blood cell distribution width to albumin ratio associates with prevalence and long-term diabetes mellitus prognosis: an overview of NHANES 1999-2020 data. Front Endocrinol (Lausanne) 2024; 15: 1362077.
[24] Terry AL, Chiappa MM, McAllister J, Woodwell DA and Graber JE. Plan and operations of the national health and nutrition examination survey, august 2021-august 2023. Vital Health Stat 1 2024; 1-21.
[25] Hao M, Jiang S, Tang J, Li X, Wang S, Li Y, Wu J, Hu Z and Zhang H. Ratio of red blood cell distribution width to albumin level and risk of mortality. JAMA Netw Open 2024; 7: e2413213.
[26] Bergengren O, Pekala KR, Matsoukas K, Fainberg J, Mungovan SF, Bratt O, Bray F, Brawley O, Luckenbaugh AN, Mucci L, Morgan TM and Carlsson SV. 2022 update on prostate cancer epidemiology and risk factors-a systematic review. Eur Urol 2023; 84: 191-206.
[27] Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, Kibel A, Stattin P, Van Poppel H and La Vecchia C. Epidemiology and prevention of prostate cancer. Eur Urol Oncol 2021; 4: 877-892.
[28] Jochems SHJ, Fritz J, Häggström C, Järvholm B, Stattin P and Stocks T. Smoking and risk of prostate cancer and prostate cancer death: a pooled study. Eur Urol 2023; 83: 422-431.
[29] Zapata D, Howard LE, Allott EH, Hamilton RJ, Goldberg K and Freedland SJ. Is PSA related to serum cholesterol and does the relationship differ between black and white men? Prostate 2015; 75: 1877-1885.
[30] Yao W, Wu J, Kong Y, Xu F, Zhou Y, Sun Q, Gao Q, Cai Z, Yang C and Huang Y. Associations of systemic immune-inflammation index with high risk for prostate cancer in middle-aged and older US males: a population-based study. Immun Inflamm Dis 2024; 12: e1327.
[31] Jiang K, Luan H, Pu X, Wang M, Yin J and Gong R. Association between visceral adiposity index and insulin resistance: a cross-sectional study based on US adults. Front Endocrinol (Lausanne) 2022; 13: 921067.
[32] Munn LL. Cancer and inflammation. Wiley Interdiscip Rev Syst Biol Med 2017; 9.
[33] Li W and Wang J. The current state of inflammation-related research in prostate cancer: a bibliometric analysis and systematic review. Front Oncol 2024; 14: 1432857.
[34] Qiu Y, Wang Y, Shen N, Wang Q, Chai L, Liu J, Chen Y and Li M. Association between red blood cell distribution width-albumin ratio and hospital mortality in chronic obstructive pulmonary disease patients admitted to the intensive care unit: a retrospective study. Int J Chron Obstruct Pulmon Dis 2022; 17: 1797-1809.
[35] Artigas A, Wernerman J, Arroyo V, Vincent JL and Levy M. Role of albumin in diseases associated with severe systemic inflammation: pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. J Crit Care 2016; 33: 62-70.
[36] Zhou D, Wang J and Li X. The red blood cell distribution width-albumin ratio was a potential prognostic biomarker for diabetic ketoacidosis. Int J Gen Med 2021; 14: 5375-5380.
[37] Xie Y, Liu F, Wu Y, Zhu Y, Jiang Y, Wu Q, Dong Z and Liu K. Inflammation in cancer: therapeutic opportunities from new insights. Mol Cancer 2025; 24: 51.
[38] Yi M, Li T, Niu M, Zhang H, Wu Y, Wu K and Dai Z. Targeting cytokine and chemokine signaling pathways for cancer therapy. Signal Transduct Target Ther 2024; 9: 176.
[39] Isaacson KJ, Martin Jensen M, Subrahmanyam NB and Ghandehari H. Matrix-metalloproteinases as targets for controlled delivery in cancer: an analysis of upregulation and expression. J Control Release 2017; 259: 62-75.
[40] Yip C, Foidart P, Somja J, Truong A, Lienard M, Feyereisen E, Schroeder H, Gofflot S, Donneau AF, Collignon J, Delvenne P, Sounni NE, Jerusalem G and Noël A. MT4-MMP and EGFR expression levels are key biomarkers for breast cancer patient response to chemotherapy and erlotinib. Br J Cancer 2017; 116: 742-751.
[41] Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer 2009; 9: 361-371.

[42] Deehan DJ, Heys SD, Simpson W, Herriot R, Broom J and Eremin O. Correlation of serum cytokine and acute phase reactant levels with alterations in weight and serum albumin in patients receiving immunotherapy with recombinant IL-2. Clin Exp Immunol 1994; 95: 366-372.
[43] Nakashima J, Tachibana M, Ueno M, Miyajima A, Baba S and Murai M. Association between tumor necrosis factor in serum and cachexia in patients with prostate cancer. Clin Cancer Res 1998; 4: 1743-1748.
[44] Van Cutsem E and Arends J. The causes and consequences of cancer-associated malnutrition. Eur J Oncol Nurs 2005; 9 Suppl 2: S51-63.
[45] Li D, Long J, Zhang J, He M, Zeng Q, He Q, Zhan W, Chi Y and Zou M. Association between red cell distribution width-and-albumin ratio and the risk of peripheral artery disease in patients with diabetes. Front Endocrinol (Lausanne) 2024; 15: 1272573.
[46] Robbie L and Libby P. Inflammation and atherothrombosis. Ann N Y Acad Sci 2001; 947: 167-179; discussion 179-180.
[47] Toledo SLO, Guedes JVM, Alpoim PN, Rios DRA and Pinheiro MB. Sickle cell disease: hemostatic and inflammatory changes, and their interrelation. Clin Chim Acta 2019; 493: 129-137.
[48] Archer M, Dogra N and Kyprianou N. Inflammation as a driver of prostate cancer metastasis and therapeutic resistance. Cancers (Basel) 2020; 12: 2984.
[49] Jin R, Yi Y, Yull FE, Blackwell TS, Clark PE, Koyama T, Smith JA Jr and Matusik RJ. NF-κB gene signature predicts prostate cancer progression. Cancer Res 2014; 74: 2763-2772.
[50] Staal J and Beyaert R. Inflammation and NF-κB signaling in prostate cancer: mechanisms and clinical implications. Cells 2018; 7: 122.
[51] Sfanos KS and De Marzo AM. Prostate cancer and inflammation: the evidence. Histopathology 2012; 60: 199-215.
[52] de Bono JS, Guo C, Gurel B, De Marzo AM, Sfanos KS, Mani RS, Gil J, Drake CG and Alimonti A. Prostate carcinogenesis: inflammatory storms. Nat Rev Cancer 2020; 20: 455-469.
[53] De Marzo AM, Platz EA, Sutcliffe S, Xu J, Grönberg H, Drake CG, Nakai Y, Isaacs WB and Nelson WG. Inflammation in prostate carcinogenesis. Nat Rev Cancer 2007; 7: 256-269.
[54] Doat S, Cénée S, Trétarre B, Rebillard X, Lamy PJ, Bringer JP, Iborra F, Murez T, Sanchez M and Menegaux F. Nonsteroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk: results from the EPICAP study. Cancer Med 2017; 6: 2461-2470.
[55] Sejima T, Iwamoto H, Masago T, Morizane S, Yao A, Isoyama T, Kadowaki H and Takenaka A. Low pre-operative levels of serum albumin predict lymph node metastases and ultimately correlate with a biochemical recurrence of prostate cancer in radical prostatectomy patients. Cent European J Urol 2013; 66: 126-132.
[56] Lin WW and Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. J Clin Invest 2007; 117: 1175-1183.
[57] Wang A, Lazo M, Carter HB, Groopman JD, Nelson WG and Platz EA. Association between liver fibrosis and serum PSA among U.S. Men: National Health and Nutrition Examination Survey (NHANES), 2001-2010. Cancer Epidemiol Biomarkers Prev 2019; 28: 1331-1338.

Table S1. Variance inflation factor (VIF) results

Variable	VIF Value
Age (years)	1.150
Race/ethnicity	1.039
Education Level	1.089
Marital.status	1.025
PIR	1.075
BMI	1.010
Smoking Status	1.057
TC	1.022
Alcohol Consumption	1.038
High blood pressure	1.059
Diabetes	1.045

VIF (Variance Inflation Factor) values are used to check multicollinearity between covariates.

Table S2. Associations between RAR and PSA-based high risk

Exposure	Non-adjusted model (model 1)		Incomplete adjusted model (model 2)		Fully adjusted model (model 3)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
RAR	1.84 (1.50-2.26)	< 0.001	1.85 (1.50-2.27)	< 0.001	1.87 (1.50-2.34)	< 0.001
RAR						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	1.43 (0.91-2.24)	0.128	1.42 (0.90-2.24)	0.138	1.49 (0.95-2.33)	0.091
Q3	1.81 (1.31-2.52)	< 0.001	1.80 (1.29-2.51)	< 0.001	1.92 (1.38-2.67)	< 0.001
Q4	2.94 (2.00-4.32)	< 0.001	2.93 (1.99-4.32)	< 0.001	3.22 (2.17-4.78)	< 0.001
p for trend		< 0.001		< 0.001		0.031

OR: Odds Ratio, CI: Confidence Interval; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; CI: confidence interval. Model 1: Crude. Model 2: Adjust: Age, Race. Model 3: Adjust: Age, Race, Education level, Marital. status, PIR, BMI, Smoking status, Alcohol consumption, TC, High blood pressure, Diabetes.

Table S3. Subgroup analysis of the association between RAR and PSA

Variables	β (95% CI)	P	P for interaction
All patients	1.08 (0.56-1.60)	< .001	
Age			0.469
< 60	0.90 (0.04-1.76)	0.045	
≥ 60	1.32 (0.73-1.91)	< .001	
Race			0.540
Mexican American	1.61 (-0.65-3.88)	0.168	
Other Hispanic	0.49 (-0.42-1.40)	0.295	
Non-Hispanic White	1.11 (0.61-1.62)	< .001	
Non-Hispanic Black	0.71 (0.12-1.30)	0.021	
Other Races	0.31 (-0.28-0.89)	0.308	
Marital status			0.198
Married/Living with partner	1.22 (0.56-1.89)	< .001	
Widowed/divorced/separated	0.78 (0.19-1.38)	0.012	
Never married	0.33 (-0.14-0.79)	0.171	
BMI			0.332
< 25	1.34 (0.60-2.09)	< .001	
25-30	1.45 (0.23-2.66)	0.023	
≥ 30	0.65 (0.27-1.03)	0.001	

Smoking status			0.524
Nonsmoker	1.09 (0.02-2.17)	0.050	
Former smoker	1.37 (0.66-2.08)	< .001	
Current smoker	0.68 (0.10-1.26)	0.026	
Alcohol consumption			0.951
No	1.04 (-0.49-2.57)	0.186	
Yes	1.09 (0.66-1.51)	< .001	
Diabetes			0.231
No	1.22 (0.50-1.94)	0.001	
Yes	0.64 (0.15-1.14)	0.013	
High blood pressure			0.706
No	1.16 (0.29-2.04)	0.011	
Yes	0.99 (0.56-1.42)	< .001	

Table S4. Associations between logRAR and PSA

Exposure	Non-adjusted model		Incomplete adjusted model		Fully adjusted model	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
logRAR	3.97 (2.22-5.72)	< 0.001	3.98 (2.22-5.73)	< 0.001	4.18 (2.37-5.99)	< 0.001
logRAR						
Q1	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Q2	0.14 (-0.05-0.33)	0.164	0.14 (-0.06-0.33)	0.171	0.17 (-0.03-0.37)	0.101
Q3	0.45 (0.25-0.65)	< 0.001	0.45 (0.25-0.65)	< 0.001	0.53 (0.33-0.73)	< 0.001
Q4	1.27 (0.82-1.72)	< 0.001	1.28 (0.83-1.73)	< 0.001	1.36 (0.90-1.83)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

CI: Confidence Interval; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; CI: confidence interval. Model 1: Crude. Model 2: Adjust: Age, Race. Model 3: Adjust: Age, Race, Education level, Marital.status, PIR, BMI, Smoking status, Alcohol consumption, TC, High blood pressure, Diabetes.

Table S5. Associations between RAR and PSA

Exposure	Non-adjusted model		Incomplete adjusted model		Fully adjusted model	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
RAR	1.12 (0.74-1.49)	< 0.001	1.12 (0.74-1.49)	< 0.001	1.17 (0.68-1.65)	< 0.001
RAR						
Q1	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Q2	0.25 (0.06-0.44)	0.012	0.26 (0.07-0.45)	0.011	0.25 (0.05-0.45)	0.020
Q3	0.48 (0.32-0.64)	< 0.001	0.48 (0.32-0.64)	< 0.001	0.49 (0.28-0.69)	< 0.001
Q4	1.33 (0.95-1.72)	< 0.001	1.33 (0.94-1.72)	< 0.001	1.40 (0.85-1.96)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

CI: Confidence Interval; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; CI: confidence interval. Model 1: Crude. Model 2: Adjust: Age, Race. Model 3: Adjust: Age, Race, Education level, Marital.status, PIR, BMI, Smoking status, Alcohol consumption, TC, High blood pressure, Diabetes.

Table S6. Associations between RAR and PSA

Exposure	Non-adjusted model		Incomplete adjusted model		Fully adjusted model	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
RAR	0.94 (0.75-1.14)	< 0.001	0.94 (0.75-1.14)	< 0.001	0.98 (0.78-1.18)	< 0.001
RAR						
Q1	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Q2	0.22 (-0.02-0.46)	0.077	0.21 (-0.03-0.45)	0.081	0.24 (0.01-0.48)	0.048
Q3	0.43 (0.19-0.67)	< 0.001	0.43 (0.19-0.67)	< 0.001	0.49 (0.25-0.73)	< 0.001
Q4	1.21 (0.97-1.44)	< 0.001	1.21 (0.97-1.45)	< 0.001	1.28 (1.03-1.52)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

CI: Confidence Interval; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; CI: confidence interval. Model 1: Crude. Model 2: Adjust: Age, Race. Model 3: Adjust: Age, Race, Education level, Marital.status, PIR, BMI, Smoking status, Alcohol consumption, TC, High blood pressure, Diabetes.

Table S7. Associations between RAR and PSA

Exposure	Non-adjusted model		Incomplete adjusted model		Fully adjusted model	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
RAR	0.34 (0.16-0.51)	< 0.001	0.34 (0.16-0.51)	< 0.001	0.33 (0.15-0.50)	< 0.001
RAR						
Q1	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)	
Q2	0.12 (-0.01-0.25)	0.080	0.12 (-0.01-0.25)	0.079	0.14 (0.01-0.27)	0.045
Q3	0.33 (0.18-0.48)	< 0.001	0.33 (0.18-0.48)	< 0.001	0.35 (0.21-0.50)	< 0.001
Q4	0.46 (0.31-0.62)	< 0.001	0.47 (0.31-0.62)	< 0.001	0.48 (0.32-0.63)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001

CI: Confidence Interval; RAR: red blood cell distribution width-to-albumin ratio; PSA: prostate specific antigen; CI: confidence interval. Model 1: Crude. Model 2: Adjust: Age, Race. Model 3: Adjust: Age, Race, Education level, Marital.status, PIR, BMI, Smoking status, Alcohol consumption, TC, High blood pressure, Diabetes.