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Association between the red blood cell distribution width-to-albumin ratio and risk of colorectal and gastric cancers: a cross-sectional study using NHANES 2005–2018

Jie Luo[1], Peng Zhu[1] and Shiji Zhou[1*]

Abstract

Background The red blood cell distribution width-to-albumin ratio (RAR) is a novel biomarker that concurrently reflects nutritional status and inflammation. Unlike traditional cancer risk markers that focus on either inflammation or nutrition independently, RAR provides a more integrated assessment of these interrelated processes, making it a promising tool for cancer risk prediction. This study aims to investigate the relationship between RAR and the risk of digestive tract tumors (DTT), with particular emphasis on colorectal cancer (CC) and gastric cancer (GC).

Methods This study explored the relationship between RAR and the risk of DTT using data from 32,953 participants in the 2005–2018 National Health and Nutrition Examination Survey (NHANES). Although weighted multivariate logistic regression models were used to adjust for potential confounders, residual confounding and selection bias may still affect the accuracy and generalizability of the findings, potentially influencing causal inferences. Additionally, subgroup analyses, interaction tests, and restricted cubic splines were performed to further examine potential associations. A two-sample Mendelian randomization analysis was also conducted to investigate the causal relationship between RAR and DTT.

Results Among the participants, 234 were diagnosed with DTT, including 215 cases of CC and 19 cases of GC. Higher RAR levels were significantly associated with an increased risk of CC (OR = 1.48, 95% CI = 1.04–2.11, $P < 0.027$), but not with GC (OR = 1.33, 95% CI = 0.45–3.94, $P = 0.60$). A non-linear association between RAR and CC was also observed. Mendelian randomization analysis indicated that albumin was negatively associated with CC risk (OR = 0.84, 95% CI = 0.73–0.97), while erythrocyte distribution width (RDW) showed no significant association.

Conclusion This study reveals a significant association between RAR and colorectal cancer (CC) risk, indicating that RAR may serve as a valuable biomarker for risk stratification. For individuals with abnormal RAR values, the integration of supplementary screening tools—such as fecal occult blood testing, colonoscopy, or additional biomarkers—could enhance early detection rates for CC. This strategy would allow healthcare providers to more effectively identify high-risk individuals and tailor personalized prevention strategies.

*Correspondence:
Shiji Zhou
zhoushiji@hospital.cqmu.edu.cn

Keywords Nutrition, Inflammation, Colorectal cancer, Gastric cancer, NHANES, Mendelian randomization, Biomarker, Cancer screening, Predictive biomarker

Introduction

Colorectal and gastric cancers (CC and GC) are prevalent malignant tumors of the digestive tract, ranking among the top five in both incidence and mortality rates globally, contributing significantly to the global cancer burden [1, 2].

Previous studies have shown that the development and progression of colorectal cancer (CC) and gastric cancer (GC) are driven by a complex interplay of genetic, environmental, and dietary factors. [3]. Notably, malnutrition and inflammation are pivotal in the pathogenesis of digestive tract tumors (DTT). Chronic inflammation, characterized by persistent epithelial proliferation in an inflammatory environment, has been shown to significantly increase the risk of CC, as evidenced in patients with chronic colitis compared to those with sporadic colorectal cancer [4, 5]. Anti-inflammatory drugs, such as aspirin, have shown significant risk-reduction benefits for colorectal cancer (CC), leading to their inclusion in primary prevention guidelines for select populations. [6–8]. Similarly, in GC, Helicobacter pylori infection serves as a key risk factor, driving chronic inflammation and oxidative stress that promote tumorigenesis [9, 10]. Moreover, cell pyroptosis mediated by inflammatory cytokines such as IL- 1β and IL- 18 has been closely linked to DTT development [11].

While endoscopy remains the gold standard for detecting pre-cancerous and cancerous lesions in the digestive tract, there is a pressing need for simple, reliable, and widely accessible biomarkers to complement existing screening methods, particularly in primary care settings. Common inflammatory indices, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have demonstrated predictive value for the prognosis of DTT, particularly in assessing disease progression, treatment response, and survival outcomes [12, 13]. However, their limited sensitivity and specificity, coupled with a primary focus on prognostic rather than predictive capabilities, restrict their broader clinical application. Most existing studies primarily address the utility of biomarkers in disease prognosis, while their ability to predict the early stages of DTT remains underexplored.

Erythrocyte distribution width (RDW) and albumin are routinely measured and widely available clinical parameters that have been independently associated with inflammation, malnutrition, and various disease states. RDW reflects variability in erythrocyte size, with an increase potentially resulting from impaired erythropoiesis, altered cell survival, or systemic inflammation. Studies have shown that elevated RDW is closely associated with an increased risk of various cancers, including CC and GC [14–16]. Albumin, as a key plasma protein, reflects nutritional status and modulates inflammatory responses, and low albumin levels are often associated with cancer cachexia (such as weight loss and muscle wasting) [17–19]. Furthermore, both RDW and albumin are closely linked to phenotypic age and biological age [20, 21]. Given that inflammation, malnutrition, and aging are significant factors contributing to the risk of digestive tract tumors (DTT), combining RDW and albumin into a single parameter—RAR—may provide a more integrated and reliable biomarker for DTT risk prediction.

RAR offers a novel approach that integrates inflammatory status, nutritional status, and aging assessment into a single measure, potentially addressing the limitations of traditional biomarkers such as NLR and PLR, which primarily reflect inflammation and are mainly used for prognostic prediction [12, 13]. Therefore, we hypothesize that RAR may have greater predictive value in identifying individuals at high risk for early-stage DTT.

Mendelian randomization is a widely adopted genetic epidemiological method that utilizes genetic variations as instrumental variables to infer causal relationships between exposures and outcomes [18, 19]. As genetic variants are randomly allocated during gamete formation, they remain largely unaffected by confounding factors [22].

This study aimed to explore the association between RAR levels and the risk of DTT using a combination of observational data and Mendelian randomization analysis. These findings enhance our understanding of the potential role of RAR as a marker for cancer risk stratification and support the need for further validation in future studies.

Methods and materials

Study population

Data for this cross-sectional study were obtained from the National Health and Nutrition Examination Survey (NHANES), a nationally representative research program designed to assess the health and nutritional status of adults and children in the United States. This study utilized data from seven NHANES cycles spanning 2005 to 2018, incorporating demographic information,

laboratory assessments, dietary data, and questionnaire responses, resulting in a final sample of 32,953 eligible participants (Fig. 1). Participants were included if they had complete data on serum albumin levels, RDW, and responses to cancer-related questionnaires. Individuals were excluded if they had missing data or had been diagnosed with cancers other than gastric or colorectal cancer to minimize potential bias and reduce concerns regarding reverse causation. The NHANES protocol was approved by the Institutional Review Board (IRB) of the National Center for Health Statistics (NCHS), and all participants provided written informed consent prior to participation. As NHANES data are publicly available and de-identified, this study was deemed exempt from further IRB review.

Exposure variable and outcomes

The independent variables in this study included the RAR. Serum albumin concentration was measured using the Bromocresol Purple method (normal reference range: 3.5–5.0 g/dL). RDW (percentage) was determined using a Coulter analyzer in the mobile examination centers (normal reference range: 11.5%– 14.5%), based on peripheral blood samples. RAR was calculated by dividing RDW by the serum albumin concentration (RAR = RDW/albumin) [23].

The diagnosis of gastric cancer (GC) and colorectal cancer (CC) was determined based on responses to two questions from the Medical Condition Questionnaire (MCQ): (1) "Have you ever been told by a doctor or other health professional that you had cancer or malignancy?" and (2) "What kind of cancer was it?" Participants who responded with "stomach cancer" or "colorectal cancer" were categorized as having the outcome variables.

Covariates

To control for potential confounders, this study adjusted for demographic characteristics, including gender, age, ethnicity, and education level. Lifestyle factors such as smoking status (current smoker or non-smoker), alcohol consumption (drinker or non-drinker), and body mass index (BMI) were also considered. Additionally, dietary factors strongly linked to gastrointestinal neoplasia, such as the intake of carbohydrates, proteins, and fats from the first day of dietary recall, were included in the analysis. Participants were classified according to BMI into four

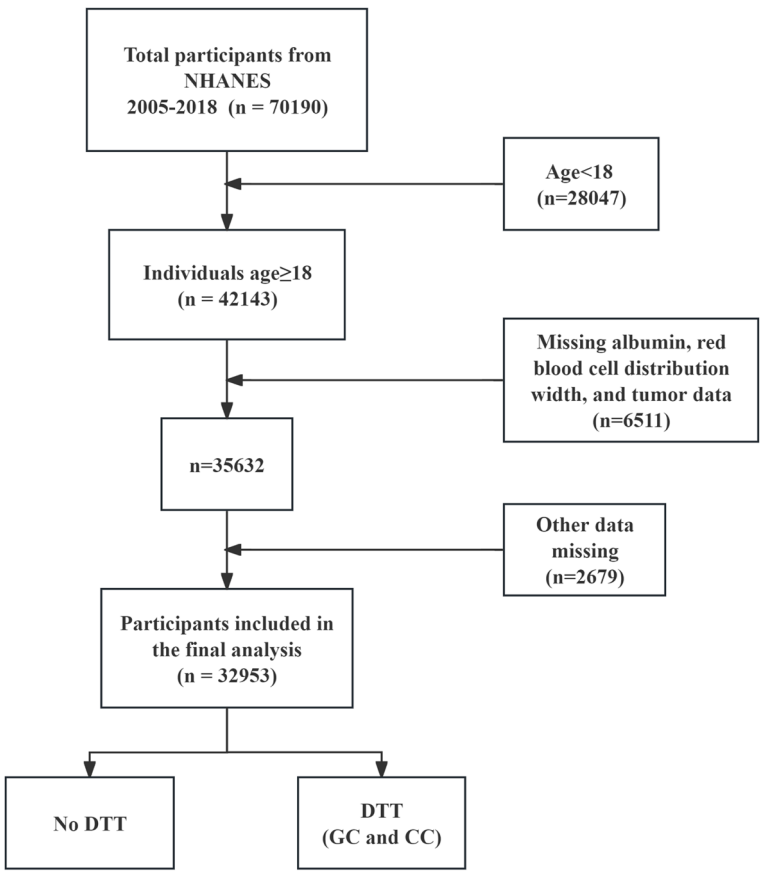

Fig. 1 Flowchart of the NHANES study participants. DTT: digestive tract tumors; GC: gastric cancer; CC: colorectal cancer

categories: underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥ 30.0).

Genome-wide association study (GWAS) sources

The genome-wide association study (GWAS) data used in this study were sourced from the MRC-IEU database (https://gwas.mrcieu.ac.uk/), which compiles and analyzes GWAS data from the UK Biobank, FinnGen Biobank, and published studies. Mendelian randomization analysis was conducted under three key assumptions: (1) the genetic variants are strongly associated with the exposure; (2) the variants are not associated with potential confounders; and (3) the variants affect the outcome solely through the exposure, without direct associations [19, 22, 24]. We investigated the causal relationship with colorectal cancer (CC) by considering albumin and erythrocyte distribution width as exposure factors. To ensure study accuracy, instrumental variables were selected based on a stringent significance threshold ($P < 5 \times 10^{-8}$) and filtered to remove variants with linkage disequilibrium (LD $r^2 < 0.1$, kb = 10,000). For erythrocyte distribution width, the significance threshold for instrumental variables was adjusted to $P < 5 \times 10^{-6}$. Detailed data on exposures and outcomes are provided in Table S1.

Statistical analysis

Data collation and analysis were conducted using R (version 4.3.2). All analyses were weighted to account for the complex sampling design and national representativeness of NHANES. The study population was categorized into a DTT group (including those with gastric cancer (GC) or colorectal cancer (CC)) and a No DTT group. The DTT group was further subdivided into GC and CC groups. Continuous variables were expressed as medians with interquartile ranges (IQR), and categorical variables were expressed as frequencies and percentages. The Wilcoxon rank-sum test and Pearson chi-squared test were used to compare distributions between groups. To explore the relationship between RAR levels and DTT, three weighted logistic regression models were employed: Model 1 was unadjusted; Model 2 adjusted for gender, age, and race; and Model 3 further adjusted for education, smoking status, alcohol consumption, BMI, and dietary intake of carbohydrates, proteins, and fats. Stratification and interaction analyses were performed based on Model 3. We used the Wald test to assess potential interactions between RAR and key variables, including sex, age group (18–45, 45–65, ≥ 65 years), race, education, smoking status, alcohol consumption, and BMI category. Additionally, we stratified the analyses by these variables to evaluate the stability of the results across different subgroups. The nonlinear relationship between RAR levels and DTT was evaluated across different model conditions using restricted cubic spline regression. Additionally, participants were divided into quartiles based on RAR levels (Q1: 2.15–2.86; Q2: 2.86–3.09; Q3: 3.09–3.39; Q4: 3.39–10.21), with Q2 used as the reference group for quartile analysis in the DTT and CC groups. For trend analysis, the quartiles were treated as an ordinal variable, and regression analysis was performed to examine the trend across these quartiles.

In Mendelian randomization analyses, the inverse variance weighted (IVW) method was considered the most robust for detecting causality [25], and was therefore used as the primary assessment method. A significant causal relationship between exposure and outcome was defined as $P < 0.05$. Heterogeneity was evaluated using Cochran's Q statistic, with $P < 0.05$ indicating the presence of heterogeneity. To address potential biases from horizontal pleiotropy, the MR-Egger regression method was employed, with an intercept P-value > 0.05 suggesting the absence of horizontal pleiotropy. Additionally, the MR-PRESSO outlier test was performed to assess the accuracy of effect estimates. Finally, a leave-one-out analysis was performed to assess sensitivity and check if any single SNP influenced the exposure-outcome relationship.

Results

Characteristics of Study Population from NHANES

A total of 32,953 individuals aged 18 years or older with complete data were included from the 2005–2018 NHANES database; the specific inclusion and exclusion process is detailed in Fig. 1. Table 1 presents the baseline characteristics of the study population, stratified by the type of digestive tract tumors (DTT). Among the participants, 234 were diagnosed with DTT, including 215 with colorectal cancer (CC) and 19 with gastric cancer (GC). Analysis revealed that patients with CC or GC were generally older (mean ages: 70 vs. 51 vs. 47, $p < 0.001$), had a higher proportion of non-Hispanic individuals, and reported lower intake of carbohydrates, proteins, and fats on the first day of dietary recall compared to those without DTT ($p < 0.001$, $p < 0.004$, $p < 0.001$). Significant differences were observed in RDW, albumin, and RAR levels among the three groups ($p = 0.003$, $p = 0.001$, $p < 0.001$). Additionally, albumin levels outside the clinically normal range were observed in 1,028 participants, with 837 participants below the lower limit and 191 above the upper limit. RDW levels outside the clinically normal range were found in 4,321 participants, with 429 participants below the lower limit and 3,892 above the upper limit.

Table 1 Characteristics of participants

Characteristic	NO DTT(*N* = 32,719)	DTT(N = 234)		*p*-value
		Colorectal Cancer(*N* = 215)	Gastric Cancer(*N* = 19)	
Sex(%)				0.089
female	16,820 (52)	109 (56)	10 (79)	
male	15,899 (48)	106 (44)	9 (21)	
Age(median (IQR))	47 (33, 60)	70 (61, 80)	51 (48, 70)	**< 0.001**
Age.group(%)				**< 0.001**
18–45 years	14,034 (46)	5 (2.0)	2 (7.0)	
45–65 years	11,156 (36)	48 (34)	7 (61)	
65 + years	7,529 (18)	162 (64)	10 (32)	
Race(%)				**< 0.001**
Mexican American	5,254 (8.7)	12 (3.5)	2 (3.3)	
Non-Hispanic Black	6,774 (11)	40 (7.6)	7 (15)	
Non-Hispanic White	14,131 (67)	140 (84)	7 (73)	
Other Hispanic	3,148 (5.5)	12 (1.9)	2 (6.4)	
Other Race	3,412 (7.8)	11 (3.0)	1 (2.3)	
Education.attainment(%)				0.4
< High schoo	7,973 (16)	63 (17)	7 (23)	
High school or equivalent	7,530 (23)	56 (24)	2 (3.0)	
≥ College or above	17,216 (61)	96 (59)	10 (74)	
Smoke.group(%)				**0.047**
NO	26,025 (80)	188 (88)	13 (76)	
YES	6,694 (20)	27 (12)	6 (24)	
Alq.group(%)				0.1
NO	13,550 (38)	98 (46)	10 (62)	
YES	19,169 (62)	117 (54)	9 (38)	
BMI(median (IQR))	28 (24, 33)	28 (25, 32)	26 (25, 28)	0.2
BMI.group(%)				0.080
Normal(< 18.5)	8,728 (28)	44 (25)	4 (14)	
Obese(18.5–24.9	12,712 (38)	89 (36)	7 (19)	
Overweight(25.0–29.9)	10,777 (33)	81 (38.8)	6 (60)	
Underweight(≥ 30)	502 (1.0)	1 (0.2)	2 (7.0)	
Carbohydrates(median (IQR))	234 (170, 317)	207 (150, 273)	193 (92, 211)	**< 0.001**
Proteins(median (IQR))	76 (54, 104)	70 (50, 89)	51 (46, 84)	**0.004**
Fats(median (IQR))	75 (51, 106)	63 (45, 91)	54 (29, 71)	**< 0.001**
RDW(median (IQR))	13.00 (12.40,13.60)	13.30 (12.60,14.20)	12.57 (12.00,14.07)	**0.003**
Albumin(median (IQR))	4.30 (4.10, 4.50)	4.10 (3.90, 4.40)	4.40 (4.21, 4.40)	**0.001**
RAR(median (IQR))	3.02 (2.81, 3.31)	3.20 (3.00, 3.56)	2.85 (2.73, 3.49)	**< 0.001**

Data are expressed as median (IQR) for biased variables and percentage (%) for categorical variables. The *p*-value for biased variables was assessed by Wilcoxon rank sum test and the p-value for categorical variables was determined using Pearson chi-square test

Bold values indicate $p < 0.05$

Association of RAR with DTT (CC and GC)

The results of the multivariate regression analysis of RAR with digestive tract tumors (DTT, CC, GC) are summarized in Table 2. In the crude model, the odds ratios (ORs) of RAR for DTT, CC, and GC were 1.86 (95% CI = 1.54–2.25, $p < 0.001$), 1.88 (95% CI = 1.57–2.26, $p < 0.001$), and 1.78 (95% CI = 0.64–4.74, $p = 0.2$), respectively. These associations remained consistent across the adjusted models. In Model 3, a significant association was observed between RAR and the occurrence of DTT and CC (DTT: OR = 1.48, 95% CI = 1.05–2.08, $p < 0.024$; CC: OR = 1.48, 95% CI = 1.04–2.11, $p < 0.027$), whereas no statistically significant association was found between RAR and GC (OR = 1.33, 95% CI = 0.45–3.94, $p = 0.60$).

To further evaluate the stability of the association between RAR and DTT across different populations,

Table 2 Association of Ratio of Red Blood Distribution Width to Albumin and digestive tract tumors

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
DTT	1.86(1.54–2.25)	**< 0.001**	1.47(1.04–2.07)	**< 0.027**	1.48(1.05–2.08)	**< 0.024**
Colorectal Cancer	1.88(1.57–2.26)	**< 0.001**	1.47(1.05–2.08)	**< 0.025**	1.48(1.04–2.11)	**< 0.027**
Gastric Cancer	1.78(0.64–4.74)	< 0.2	1.34(0.30–6.09)	< 0.7	1.33(0.45–3.94)	< 0.6

OR odds ratio, *CI* confidence interval

Model 1: crude model

Model 2: adjusted for sex, age, and race

Model 3: adjusted for sex, age, race, education.attainment, smoking status, alcohol consumption, BMI, carbohydrates, proteins, and fats

The bold values mean $p < 0.05$

subgroup analyses were conducted, stratified by gender, age, race, education, smoking status, alcohol consumption status, and BMI, as presented in Fig. 2. The results indicated that elevated RAR levels were positively associated with DTT across most subgroups, except for Mexican Americans and overweight individuals. No significant interactions were observed between RAR levels and any subgroup factors. These findings suggest that RAR's predictive value may differ across population characteristics, warranting further investigation.

To further investigate the nonlinear relationship between RAR and both DTT and CC, restricted cubic spline regression analyses were separately conducted for each group (Fig. 3). In Model 3, the results indicated a U-shaped nonlinear relationship between RAR and the risk of both DTT and CC ($p = 0.038$ and $p = 0.0458$, respectively). Specifically, both low and high RAR levels were associated with an increased risk of CC, highlighting the potential dual roles of malnutrition and inflammation in cancer development.

Finally, RAR levels were divided into quartiles (Q1: 2.15–2.86; Q2: 2.86–3.09; Q3: 3.09–3.39; Q4: 3.39–10.21) to assess the association between each quartile and DTT and CC, respectively, based on the restricted cubic spline regression results, with Q2 serving as the reference. Although the p-values for Q1, Q3, and Q4 did not reach statistical significance compared to Q2 in both groups (Fig. 4), a notable trend in OR values was observed. Specifically, Q1 showed a higher OR relative to Q2, and the OR values for Q3 and Q4 exhibited a gradual increase, suggesting a potential nonlinear relationship between RAR and the outcomes, consistent with the restricted cubic spline regression findings. Although these results did not achieve statistical significance, the observed trends warrant further investigation in larger sample sizes or future studies.

Causal relationship of albumin and RDW with CC

In observational studies, RAR was positively associated with the occurrence of colorectal cancer (CC). To further explore the causal relationship, Mendelian randomization analysis was conducted. However, since GWAS data for RAR were not directly available, we separately investigated the causal effects of albumin and RDW on CC (Fig. S1). The IVW method demonstrated that higher albumin levels significantly reduced the risk of CC (OR = 0.841, 95% CI = 0.730–0.969, $p = 0.016$), aligning with the trends observed in the observational studies. In contrast, no statistically significant association was found between RDW and CC (OR = 0.998, 95% CI = 0.918–1.084, $p = 0.963$). Additionally, no evidence of pleiotropy or heterogeneity was detected in either group (Fig. S2), and leave-one-out analyses indicated that none of the instrumental variables substantially influenced the results (Figs. S3 and S4).

Discussion

This study is the first to explore the association between RAR and the risk of developing digestive tract tumors (DTT), with subgroup analyses focusing on two common DTTs: colorectal cancer (CC) and gastric cancer (GC). The findings showed that elevated RAR levels were positively associated with the risk of DTT, particularly CC, and this association remained significant after adjusting for confounders. Restricted cubic spline analysis further revealed a U-shaped relationship between RAR and both DTT and CC, a pattern also observed in the quartile analysis. This U-shaped curve suggests that both extremely low and high RAR levels are linked to an increased risk of CC.

The U-shaped relationship between RAR and digestive tract tumors can be explained as follows: Low RAR levels may result from reduced RDW, indicating lower systemic inflammation, or reflect subtle immune dysfunction and

Characteristic	OR(95%CI)	p-value	p for interaction
Sex			0.066
female	1.12(0.62,2.04)	0.7040	
male	2.17(1.51,3.12)	<0.0001	
Age.group			0.220
18-45 years	3.00(2.09,4.30)	<0.0001	
45-65 years	1.20(0.52,2.74)	0.6675	
65+ years	1.63(1.17,2.26)	0.0045	
Race			0.088
Mexican American	0.52(0.25,1.10)	0.0895	
Non-Hispanic Black	2.27(1.74,2.95)	<0.0001	
Non-Hispanic White	1.34(0.87,2.08)	0.1887	
Other Hispanic	2.15(0.90,5.16)	0.0899	
Other Race	1.93(0.72,5.22)	0.1975	
Education.attainment			0.987
<High school	1.58(1.16,2.13)	0.0043	
High school or equivalent	1.53(0.91,2.57)	0.1089	
⩾College or above	1.51(0.89,2.56)	0.1304	
Smoke.group			0.893
NO	1.52(1.03,2.26)	0.0400	
YES	1.57(1.08,2.28)	0.0199	
Alcohol Consumption.group			0.557
NO	1.38(0.80,2.37)	0.2495	
YES	1.70(1.12,2.60)	0.0156	
BMI.group			0.100
Normal	1.21(0.49,2.97)	0.6831	
Obese	2.20(1.51,3.21)	<0.0001	
Overweight	0.97(0.51,1.85)	0.9267	
Underweight	2.07(1.43,3.01)	0.0002	

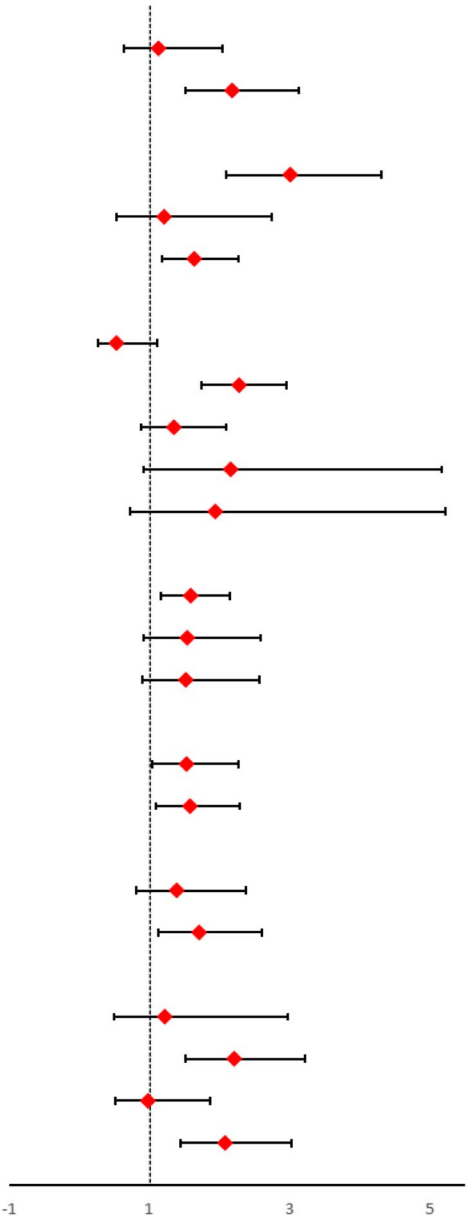

Fig. 2 Association of RAR in various subpopulations with DTT Adjusting for the information in Model 3, the p-value for the interaction was calculated using the likelihood ratio test

oxidative stress, which can promote early tumorigenesis. Moderate RAR levels likely represent a balanced state of inflammation and nutritional status, supporting optimal immune surveillance and minimizing tumor risk. High RAR levels, driven by elevated RDW and/or hypoalbuminemia, reflect chronic inflammation and malnutrition, which exacerbate oxidative stress, immune dysregulation, and epithelial proliferation—key mechanisms in colorectal carcinogenesis [26–28]. These findings underscore the dual role of inflammation and nutrition in tumor biology, where both ends of the RAR spectrum contribute to distinct tumor-promoting pathways.

Clinically, the U-shaped relationship highlights the potential of RAR as a biomarker for stratifying individuals across the risk spectrum. Individuals with low RAR

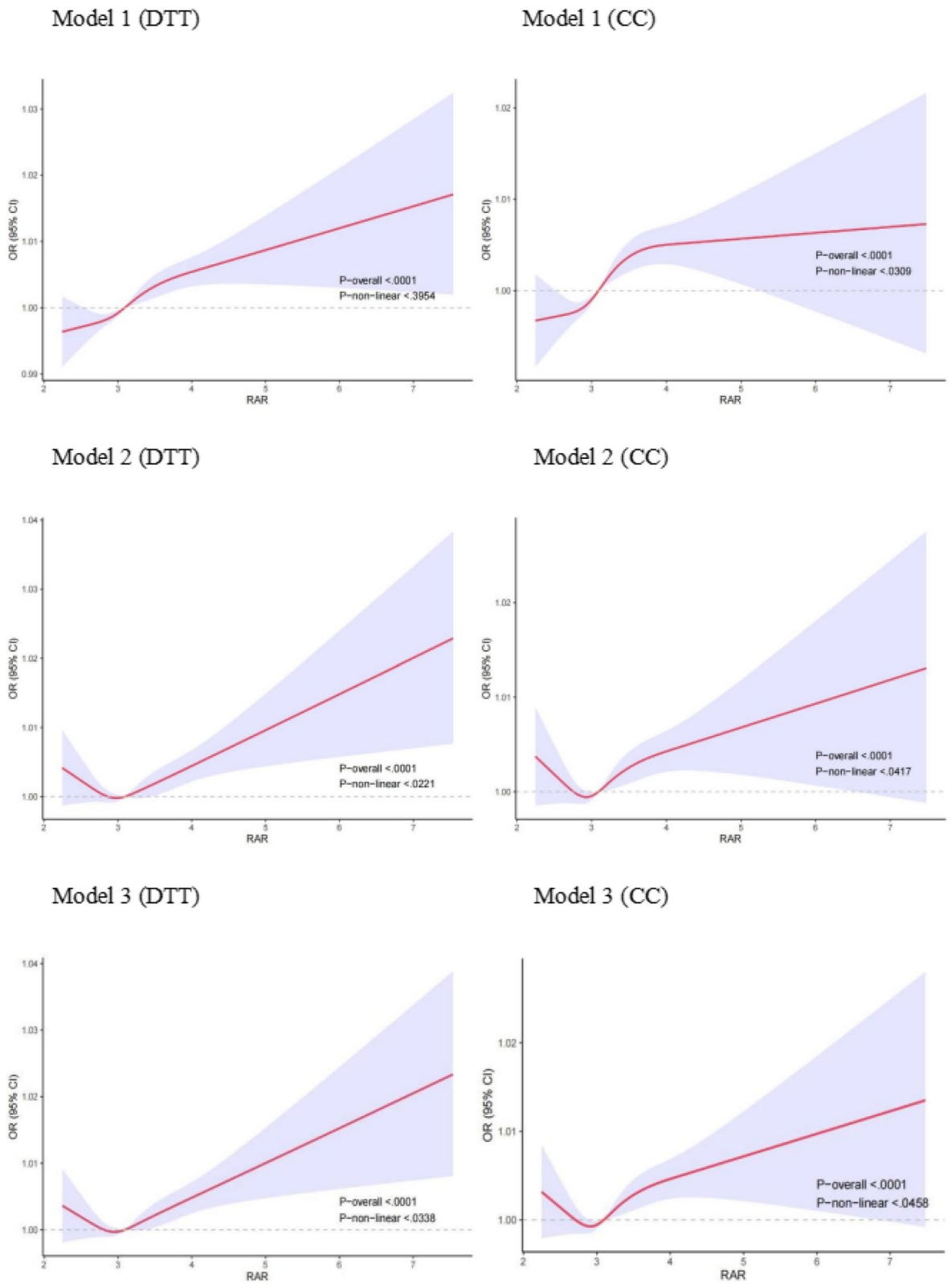

Fig. 3 Model 1: crude model. Model 2: adjusted for sex, age, and race. Model 3: adjusted for sex, age, race,education.attainment, smoking status, alcohol consumption, BMI, carbohydrates, proteins, and fats. DTT: digestive tract tumors; CC: colorectal cancer

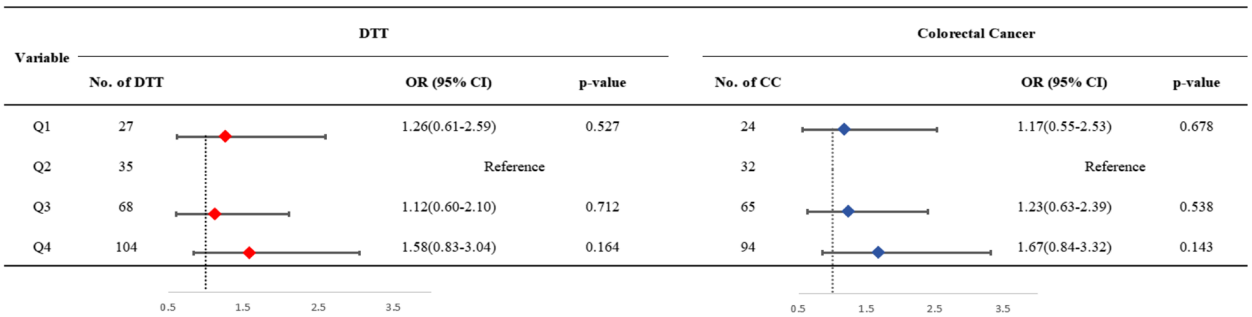

Fig. 4 Association between quartiles of RAR and digestive tract tumors. Quartile tests for DTT and CC in model 3 conditions, using Q2 as a reference

levels may benefit from interventions targeting subtle immune dysfunction or oxidative stress, while those with high RAR levels may require targeted anti-inflammatory therapies or enhanced surveillance for early cancer detection. The ability of RAR to capture the interplay between systemic inflammation and nutritional status highlights its potential in personalized risk assessment and guiding tailored intervention strategies.

In the context of subgroup analyses, we observed no significant associations between RAR and CC risk in certain populations, such as Mexican Americans and overweight individuals. For Mexican Americans, variations in dietary patterns, genetic predispositions, and healthcare access may mitigate the association between RAR and CC risk. For instance, dietary habits unique to this subgroup, such as higher fiber or antioxidant intake, could reduce systemic inflammation and counteract malnutrition, potentially weakening the RAR-cancer risk relationship [29]. In overweight individuals, higher BMI levels may mask malnutrition-related changes in albumin or inflammation-related variations in RDW, potentially attenuating the observed association. Additionally, the chronic low-grade inflammatory state commonly associated with obesity could obscure RAR's ability to differentiate between high- and low-risk individuals [30, 31].

The absence of detailed tumor staging and colorectal cancer (CC) subtypes, such as proximal vs. distal or microsatellite instability (MSI) vs. microsatellite stability (MSS), is a notable limitation. Tumor stage and subtype are essential for understanding cancer progression and heterogeneity. Advanced-stage cancers often exhibit increased inflammation and nutritional deficiencies, potentially strengthening the RAR-DTT association. In contrast, early-stage cancers may exhibit weaker effects, and different colorectal cancer (CC) subtypes may have distinct inflammatory profiles that influence the RAR association. [32, 33]. The lack of such data in the NHANES dataset prevented stage- or subtype-specific analyses. Future studies should incorporate tumor staging and subtypes to assess whether RAR has differential predictive value across stages or subtypes of CC.

The Mendelian randomization (MR) analysis provided additional insights into the potential causal relationships between components of RAR and CC. Albumin was inversely associated with CC risk, supporting the protective role of adequate nutritional status, while RDW showed no significant association. However, due to the lack of GWAS data for RAR, the MR analysis could not directly assess the composite effects of RAR, potentially limiting the causal inferences drawn from this study. Future genetic research should prioritize developing GWAS data for composite markers like RAR to enhance causal inference and provide stronger evidence for its role in cancer risk prediction.

In contrast to colorectal cancer, no significant association was observed between RAR and gastric cancer (GC) in our study. Several factors may explain this lack of association. First, the pathophysiology of GC differs from that of CC. While systemic inflammation and malnutrition are key drivers in CC, GC is more strongly influenced by localized inflammatory processes within the gastric microenvironment, such as those caused by Helicobacter pylori (H. pylori) infection. H. pylori induces chronic gastric inflammation, oxidative stress, and DNA damage, all of which promote gastric carcinogenesis [34]. However, RAR, as a systemic marker, may not fully capture the localized effects of gastric-specific inflammation, potentially attenuating its association with GC risk [35]. Second, the relatively small number of gastric cancer (GC) cases in the NHANES dataset likely limited the statistical power to detect significant associations. With only 19 GC cases included, this sample size may not have been sufficient to identify subtle relationships between RAR and GC. Additionally, variations in dietary patterns, alcohol consumption, and genetic predisposition across populations may differentially influence GC risk compared to colorectal cancer (CC) [36].These population-specific factors could further obscure potential associations

between RAR and GC. Third, the role of nutritional status in GC development may differ from its role in CC. Hypoalbuminemia is well-documented as a prognostic factor in GC, but its contribution to early GC development is less established [37].Unlike CC, where systemic nutritional and inflammatory imbalances play a prominent role in carcinogenesis, the etiology of GC may be more dependent on localized factors, such as gastric acid production, mucosal integrity, and H. pylori-induced changes [38, 39].This could partly explain why RAR, an integrative systemic marker, showed no significant association with GC in this study.

These findings suggest that RAR could serve as a blood-based biomarker for colorectal cancer risk stratification. While current screening methods like FOBT and colonoscopy are effective, they have limitations [40]. RAR, routinely measured in hematology tests, could complement these methods by helping to identify high-risk individuals. However, due to the lack of colonoscopy data in the NHANES database, we were unable to perform an incremental analysis. Future studies are needed to validate RAR's clinical utility and assess its added value in combination with existing screening tools.

While this study provides valuable insights into the association between RAR and digestive tract tumors (DTT), further research is needed to validate and expand upon these findings. First, longitudinal studies are crucial for establishing the temporal relationship and causality between RAR levels and cancer risk. These studies could track changes in RAR over time and assess its predictive utility for cancer development in high-risk populations. Second, since our findings are primarily based on NHANES data, which predominantly represents European and American populations, future studies should aim to include more diverse populations. Validation studies in non-European populations, including Asian, African, and Hispanic cohorts, are critical to determine whether the associations observed in this study are generalizable across different ethnic and geographic groups. These studies would also help to identify potential population-specific factors, such as genetic predispositions, dietary habits, and environmental exposures, that may influence the relationship between RAR and cancer risk. Third, further exploration is needed to integrate RAR with other emerging biomarkers or imaging-based tools to assess its potential contribution to early cancer risk prediction. For instance, combining RAR with genetic, proteomic, or metabolomic data may offer opportunities to develop more comprehensive risk assessment models. Investigating how RAR interacts with other systemic inflammatory and nutritional markers could improve our understanding of its broader role in cancer biology and its relevance to multi-factorial risk prediction frameworks. Finally, interventional studies are warranted to explore whether targeting factors reflected by RAR, such as nutritional or inflammatory states, could influence cancer risk. Such trials could provide valuable insights into the utility of RAR as a risk predictor and its broader role in guiding preventive strategies.

Conclusion

This study identified a significant association between RAR levels and the risk of digestive tract tumors (DTT), particularly colorectal cancer (CC), with a U-shaped relationship suggesting increased risk at both low and high RAR levels. RAR may have potential as an adjunctive biomarker for CC risk stratification, complementing existing screening tools, pending further validation. However, the lack of significant findings for gastric cancer (GC) requires further investigation in diverse populations. Future studies should validate these findings through longitudinal research and investigate the potential clinical applications of RAR, particularly its role in reflecting nutritional and inflammatory states relevant to cancer risk.

Abbreviations

RAR	The erythrocyte distribution width-to-albumin ratio
DTT	Digestive tract tumors
CC	Colorectal cancer
GC	Gastric cancer
NHANES	National Health and Nutrition Examination Survey
MR	Mendelian randomization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Shiji Zhou and Jie Luo participated in the design of the study. Peng Zhu performed the data analysis and prepared the tables. Jie Luo participated in the analysis of the tables and data. Jie Luo prepared and revised the manuscript. Shiji Zhou reviewed the results and revised the manuscript. Jie Luo confirmed the uthenticity of all the raw data.

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Data availability

All data used in this study can be accessed at https://www.cdc.gov/nchs/nhanes/and https://gwas.mrcieu.ac.uk/.

Declarations

Ethics approval and consent to participate
All data in this study are sourced from public databases, and participants have provided informed consent, eliminating any ethical concerns.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Gastrointestinal Surgery, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

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