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Association between systemic inflammation response index and female breast cancer based on NHANES data (2001–2018): A cross-sectional study

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Abstract: Breast cancer remains the most common malignancy and the leading cause of cancer-related death among women worldwide. Growing evidence implicates systemic inflammation in tumor initiation and progression. The systemic inflammation response index (SIRI), calculated as (neutrophil count * monocyte count) / lymphocyte count ($10^3/\mu L$), has been proposed as a prognostic biomarker or risk factor in various cancers. Researchers employed statistical association methods among variables, including correlation coefficients, χ^2 tests, logistic regression, and restricted cubic splines. Using data from 23,045 US women aged ≥20 years in NHANES 2001–2018, the study examined the association between SIRI and female breast cancer prevalence through descriptive statistics, multivariable logistic regression, and subgroup analyses. Women with breast cancer exhibited significantly higher SIRI values than controls, with a dose–response pattern across SIRI quartiles. A one-unit increase in SIRI was associated with a 24% higher odds of breast cancer, and participants in the highest quartile of SIRI had 133% higher breast cancer prevalence compared to those in the lowest quartile [OR = 2.33]. These findings suggest that elevated SIRI is independently associated with prevalent breast cancer in US women and may serve as a practical biomarker for early detection and risk stratification. Additionally, these results may provide important insights into individualized treatment strategies.

Keywords: *Breast cancer, Cross-sectional study, Data association analysis, NHANES, SIRI (systemic inflammation response index).*

1. Introduction

Breast cancer is a common chronic disease affecting millions worldwide [1]. If untreated, its manifestations often evolve insidiously over a prolonged period. The aetiology is multifactorial, reflecting a complex interplay between genetic predisposition and environmental exposures [2]. Modifiable behaviors, notably unhealthy diet and low levels of physical activity, have been recognized as important risk factors that increase the likelihood of breast cancer [3]. With a prevalence exceeding 20% globally, breast cancer imposes a substantial burden on patients and health systems [4]. Despite its public health significance, research identifying protective factors and effective prevention strategies remains limited, representing an ongoing challenge [5]. An increasing body of research indicates that persistent inflammation may play a role in the initiation of breast cancer [6]. Higher concentrations of inflammatory mediators, including Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), and circulating neutrophils, have been reported in hormone receptor–positive breast cancer cases, implying that these markers may hold value for early detection or clinical assessment [7].

In patients with urological malignancies, higher SIRI levels are significantly linked to poorer overall survival and shorter disease-free or recurrence-free survival. These results indicate that SIRI, as a simple and inexpensive index, may function as a practical prognostic biomarker for risk stratification and ongoing clinical follow-up [8]. Elevated SIRI levels in patients with breast cancer are significantly associated with worse overall survival. Moreover, a higher SIRI is linked to more adverse

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clinicopathological characteristics, including larger tumor size, more advanced disease stage, and an increased likelihood of lymph node metastasis [9].

SIRI has emerging clinical utility for diagnosis, risk stratification, and guiding personalized management across a range of conditions [10]. Routine measurement of SIRI may aid in longitudinal monitoring, inform the evaluation of interventions (for example, those targeting weight or muscle mass), and help identify individuals at elevated risk for specific disorders. Ongoing research is refining our understanding of the physiological determinants of SIRI and assessing its value as a prognostic biomarker for diverse outcomes, thereby supporting the design of interventions to improve body composition and general health. As a readily obtainable inflammatory index, SIRI can offer useful insights into a patient's physiological state when interpreted in the appropriate clinical context. Although SIRI shows promise for informing diagnosis and prognosis in female breast cancer, its specific relationship with breast cancer has not been comprehensively examined. Xiong et al. [11] reported an association between the Systemic Immune-Inflammation Index and breast cancer among U.S. women: analysis of NHANES 2001–2018 [11], which pertains to inflammatory response. Accordingly, this study was undertaken to investigate the association between SIRI and breast cancer.

Currently, the existing evidence regarding the relationship between SIRI and breast cancer remains insufficient. According to the aforementioned research, we hypothesize that SIRI could serve as an effective indicator of an individual's risk for breast cancer. This study aims to elucidate the correlation between SIRI and the occurrence of breast cancer. The researchers conducted a cross-sectional analysis with 23,045 people from the National Health and Nutrition Examination Survey (NHANES), carried out between 2001 and 2018.

2. Materials and Methods

2.1. Study Population

Data for this study were obtained from NHANES cycles spanning 2001–2018. NHANES is a biennial, cross-sectional survey that collects demographic, dietary, examination, laboratory, and questionnaire data, along with other population-level variables. The NHANES study protocol received ethical approval from the Research Ethics Review Board of the National Center for Health Statistics under the Centers for Disease Control and Prevention (CDC) [12]. The initial cohort comprised 26,987 female participants aged ≥20 years across nine cycles; after excluding 3,942 individuals with incomplete key data, the final analytical sample included 23,045 participants. Figure 1 depicts the procedure for sample selection.

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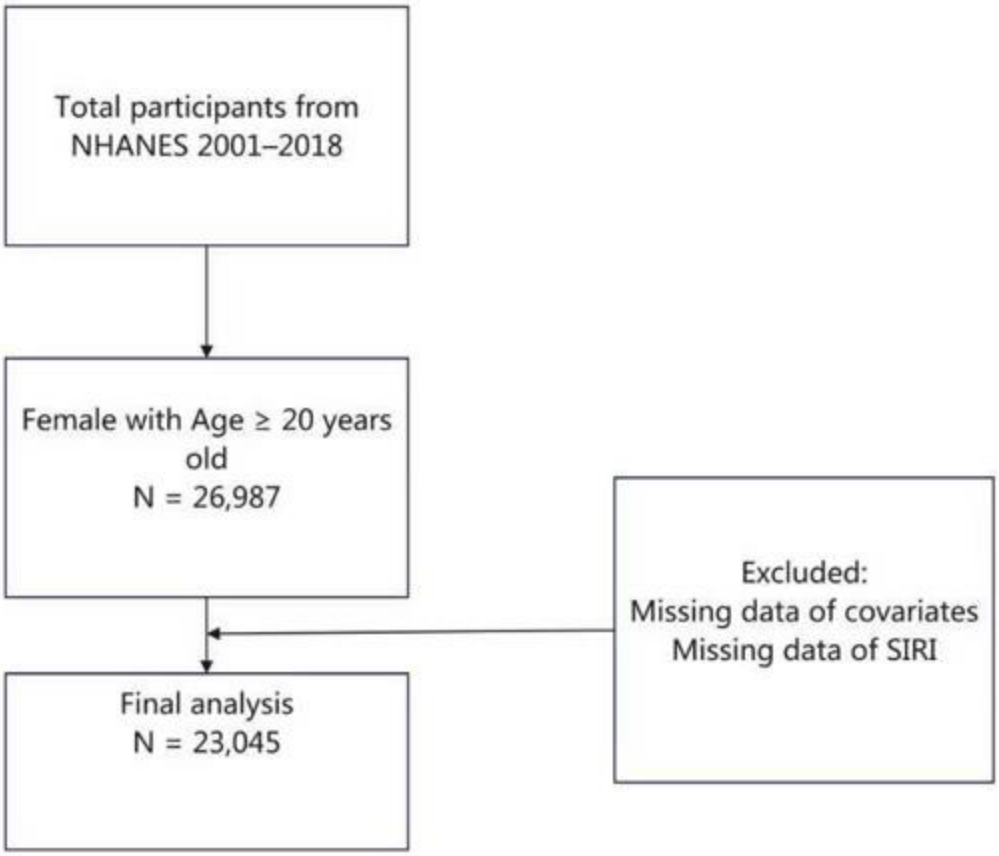

Figure 1.
Flowchart of the study population selection.

2.2. Regression Analysis and Between-Group Comparisons

To investigate the association between SIRI and breast cancer, a multivariate analysis (binary logistic regression) was performed. X was entered as a categorical variable (N quantile). Histogram distribution [13] or Q-Q plot, or Kolmogorov-Smirnov test was used to determine whether variables were normally distributed. Mean ± SD was used to describe all continuous variables that were normally distributed. The researchers presented categorical variables as percentages (%). To identify differences between different X groups, the researchers used the chi-square test (for categorical variables). The one-way ANOVA test was applied for variables with a normal distribution, while the Kruskal–Wallis H test was used for non-normally distributed data.

2.3. Nonlinear Dose–Response and Robustness Analysis

The researchers employed a constrained restricted cubic spline (RCS) approach to generate smooth curves for examining potential nonlinear dose-response relationships between X and Y. The researchers assessed non-linearity by incorporating a quadratic term into the regression models. A two-piecewise regression model was utilized to determine the threshold effect of X on Y, as indicated by the smoothing figure, following the detection of a nonlinear connection. Subgroup variables were used to conduct the predetermined subgroup analysis.

All analyses were conducted utilizing R Statistical Software [14] (Version 4.2.2, http://www.R-project.org, The R Foundation) and the Free Statistics analytic platform [15] (Version 1.9, Beijing, China, http://www.clinicalscientists.cn/freestatistics). Free Statistics is a software suite that enables the

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execution of common analyses and displays findings in an understandable format. The software utilizes R as its core statistical engine, while the graphical interface is developed in Python. Most analyses can be executed with minimal user interaction. It is designed to support reproducible and interactive data analysis. A two-tailed p-value of less than 0.05 is interpreted as evidence of a statistically significant difference.

2.4. Variable Selection

Recent evidence, Rigi et al. [16] and McEligot et al. [17], indicates that age, race, educational attainment, marital status, diabetes status, reproductive health characteristics such as age of menarche, and smoking history are significant potential confounders. For analytic purposes, participants were categorized according to racial background, including Non-Hispanic White, Non-Hispanic Black, Mexican American, and other racial identities. Educational achievement was categorized as below high school, high school graduate, and college or higher. The marital status variable was categorized into possessing both a sexual partner and an asexual partner. Diabetes status was classified into two categories: absence of diabetes and presence of diabetes. Smoking history status was categorized as those who never smoked, those who had smoked in the past, and those who currently smoke. In the NHANES MCQ module, if 'ever had cancer' is yes and cancer type variables (MCQ230A–MCQ230F), and anyone's 'cancer type' = breast cancer, set the breast cancer variable as 1; otherwise, set the breast cancer variable as 0.

3. Results

3.1. Description of the Study Population Characteristics

Table 1 shows baseline data about the researchers' study, which concerns the general characteristics of the participants. This study included 23,045 eligible women with a mean age of 49.2 years. Among all the participants, 2.6% were identified as having breast cancer. There were statistically significant between-group differences in race, educational attainment, diabetes status, marital status, and smoking. PIR is short for Poverty Income Ratio.

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Table 1.
Baseline Data Table.

Variables	Total (n = 23045)	1 (n = 5743)	2 (n = 5777)	3 (n = 5760)	4 (n = 5765)	p
Age, Mean ± SD	49.2 ± 18.1	48.4 ± 16.6	49.0 ± 17.3	49.5 ± 18.2	50.0 ± 20.2	< 0.001
Race, n (%)						< 0.001
Non-Hispanic White	10110 (43.9)	1663 (29)	2404 (41.6)	2834 (49.2)	3209 (55.7)	
Non-Hispanic Black	4700 (20.4)	2026 (35.3)	1090 (18.9)	843 (14.6)	741 (12.9)	
Mexican American	3934 (17.1)	837 (14.6)	1101 (19.1)	1077 (18.7)	919 (15.9)	
Other	4301 (18.7)	1217 (21.2)	1182 (20.5)	1006 (17.5)	896 (15.5)	
Edu, n (%)						< 0.001
Below high school	2530 (11.0)	625 (10.9)	703 (12.2)	640 (11.1)	562 (9.8)	
High school	8368 (36.4)	1979 (34.5)	2026 (35.1)	2130 (37)	2233 (38.8)	
College or above	12117 (52.6)	3134 (54.6)	3041 (52.7)	2980 (51.8)	2962 (51.5)	
Marital, n (%)						< 0.001
Sexual partner	12769 (55.4)	3179 (55.4)	3297 (57.1)	3227 (56)	3066 (53.2)	
Asexual	10264 (44.6)	2562 (44.6)	2475 (42.9)	2531 (44)	2696 (46.8)	
PIR, n (%)						0.018
Low	6963 (33.0)	1708 (32.5)	1690 (32)	1745 (33.1)	1820 (34.4)	
Middle	7963 (37.7)	1960 (37.3)	1992 (37.7)	1989 (37.7)	2022 (38.2)	
High	6180 (29.3)	1592 (30.3)	1595 (30.2)	1542 (29.2)	1451 (27.4)	
Diabetes, n (%)						< 0.001
No	20395 (88.5)	5172 (90.1)	5127 (88.7)	5077 (88.1)	5019 (87.1)	
Yes	2650 (11.5)	571 (9.9)	650 (11.3)	683 (11.9)	746 (12.9)	
Smoking status, n (%)						< 0.001
Never	14694 (63.8)	3949 (68.8)	3766 (65.2)	3601 (62.5)	3378 (58.6)	
Former	4367 (19.0)	969 (16.9)	1070 (18.5)	1096 (19)	1232 (21.4)	
Current	3981 (17.3)	824 (14.4)	940 (16.3)	1062 (18.4)	1155 (20)	
Breast cancer, n (%)						< 0.001
No	22429 (97.3)	5646 (98.3)	5629 (97.4)	5611 (97.4)	5543 (96.1)	
Yes	616 (2.7)	97 (1.7)	148 (2.6)	149 (2.6)	222 .9)	

3.2. Core Regression Results

Univariable linear regression demonstrates that a one-unit increase in SIRI was associated with a 24% increase in breast cancer risk. Table 2 shows the univariable logistic regression analysis of the association between SIRI and breast cancer risk. The interpretation of the relevant variables is presented here in Section 3.1, "Description of the study population characteristics."

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Table 2.
Univariable logistic regression analysis of the association between SIRI and breast cancer risk.

Variable	OR_95CI	P_value
SIRI(continuous variable)	1.24 (1.16~1.32)	<0.001
SIRI		
SIRI.Q1	Ref.	
SIRI.Q2	1.53 (1.18~1.98)	0.001
SIRI.Q3	1.55 (1.19~2)	0.001
SIRI.Q4	2.33 (1.83~2.97)	<0.001
Age	1.07 (1.06~1.07)	<0.001
Race		
Non-Hispanic White	Ref.	
Non-Hispanic Black	0.47 (0.37~0.59)	<0.001
Mexican American	0.34 (0.26~0.46)	<0.001
Other	0.46 (0.36~0.59)	<0.001
Education status		
Below high school	Ref.	
High school	1.18 (0.88~1.58)	0.279
College or above	1.24 (0.94~1.65)	0.13
Diabetes		
No	Ref.	
Yes	1.92 (1.57~2.36)	<0.001
Smoking status		
Never	Ref	
Former	1.73 (1.45~2.07)	<0.001
Current	0.64 (0.49~0.84)	0.001
Marital		
Sexual partner	Ref.	
Asexual	1.29 (1.1~1.52)	0.002

Table 3 shows associations between the systemic inflammation response index and breast cancer. Model I: age, marital status, and education were adjusted. Model II: age, marital status, education, race, and smoking history were adjusted. Model III: age, marital status, education, race, smoking history, BMI measurement, diabetes condition, and pregnancy history were adjusted. Multivariable logistic regression showed that higher SIRI was significantly and positively associated with breast cancer risk in women, and this association remained stable after adjustment for numerous potential confounders. Abbreviation: Q means quartile; OR, odds ratio; 95% CI, 95% confidence interval.

Table 3.
Associations between systemic inflammation response index and breast cancer.

Model	Model I		Model II		Model III	
Categories	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Q1(0-0.67)	1(Ref.)		1(Ref.)		1(Ref.)	
Q2(0.67001-0.98)	1.43 (1.1~1.85)	0.008	1.37 (1.05~1.78)	0.021	1.44 (1.09~1.9)	0.01
Q3(0.98001- 1.45)	1.32 (1.01~1.71)	0.039	1.24 (0.95~1.63)	0.111	1.32 (0.99~1.75)	0.055
Q4(1.45001-17.68)	1.74 (1.36~2.23)	<0.001	1.61 (1.25~2.08)	<0.001	1.6 (1.22~2.1)	0.001
Trend.test		<0.001		0.001		0.004

3.3. Curve Fitting and Inflection Point Analysis

Figure 2 shows a nonlinear relationship between SIRI and breast cancer risk. A nonlinear L-shaped association was observed between SIRI levels and the risk of breast cancer, indicating a potential dose–response pattern (P for nonlinearity < 0.05).

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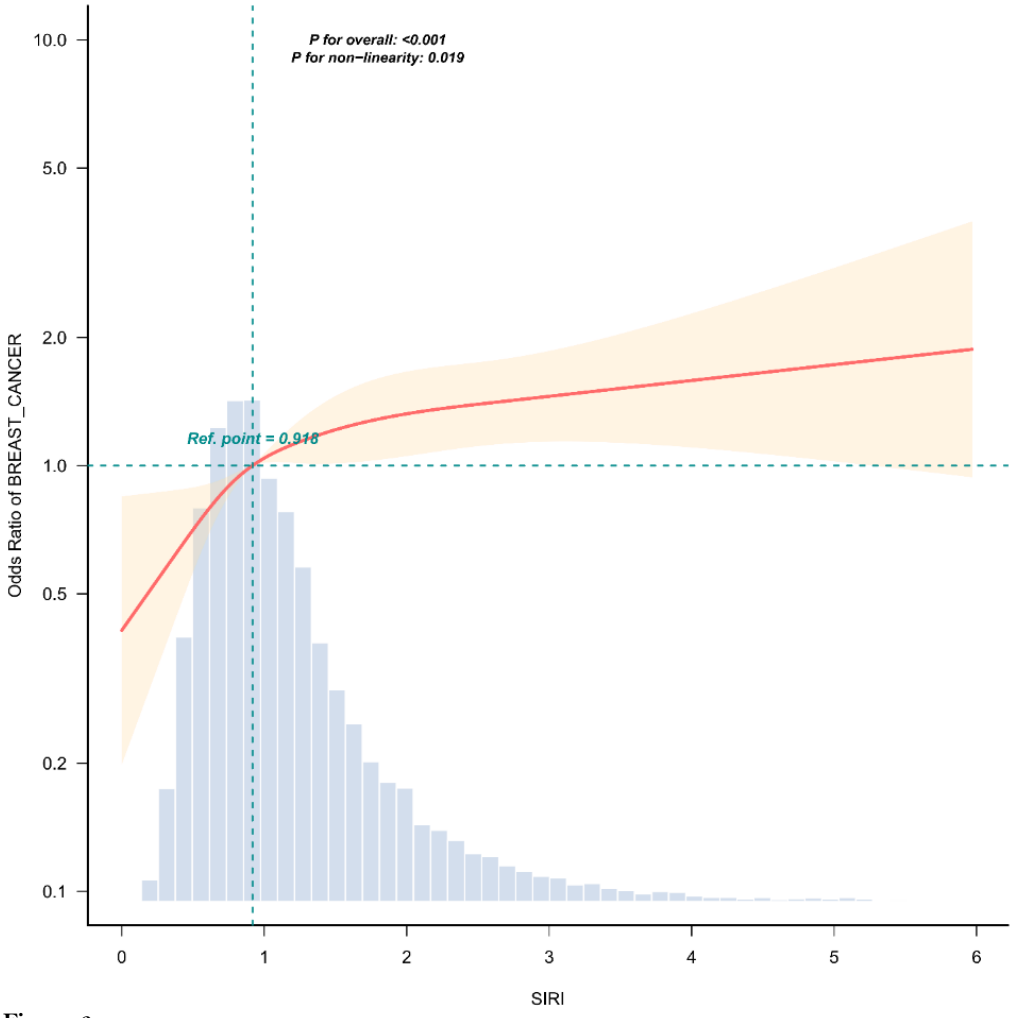

Figure 2.
A dose-dependent association exhibiting a non-proportional trend between SIRI and breast cancer risk.

Table 4 presents the inflection point analysis. A threshold was identified at 0.918 (95% CI 0.901–0.936). Below this threshold, for every one-unit increase in exposure, the odds of the outcome increased by approximately 2.81 times (OR 2.811, 95% CI 1.301–6.072; P=0.0085). Above the inflection point, the odds increased more modestly (OR 1.172, 95% CI 1.032–1.331; P=0.0145). The likelihood-ratio test favored the piecewise model over a simple linear trend (P=0.025), indicating a non-linear, threshold-type association.

Table 4.
Analysis of the inflection point in the association between exposure and outcome using a two-piecewise regression model.

Item	n	Breakpoint/OR (95%CI)	P value
Estimate_Breakpoint	22899	0.918 (0.901,0.936)	NA
Effect_Size_1	10499	2.811 (1.301~6.072)	0.0085
Effect_Size_2	12400	1.172 (1.032~1.331)	0.0145
Likelihood Ratio test	-	-	0.025

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3.4. Subgroup and Sensitivity Analyses

Figure 3 presents a Forest plot of single model analysis. The education categories variable is defined as follows: 1 represents less than 9th grade; 2 represents 9–11th grade (including 12th grade with no diploma) or high school graduate; 3 represents some college, an Associate degree, college graduate, or higher (bachelor's degree or above). The marital variable is categorized as: 1 for married or living with a partner; 2 for other. The diabetes categories variable indicates: 1 for diabetes; 0 for others. The smoking variable is classified as: 1 for never smokers; 2 for former smokers; 3 for current smokers. In most subgroups, higher SIRI was positively associated with increased event risk (OR > 1). In a few subgroups, the 95% confidence interval (CI) does not cross 1, indicating statistical significance. The association appears stronger in strata such as age ≥65, certain race groups, specific smoking exposures, certain education levels, and a particular marital category. A few strata (e.g., age <65, education less than 9th grade, and some race groups) are non-significant or only marginally significant. After stratification by race, education level, marital status, and diabetes status, no significant interactions were observed (all interaction P > 0.05), supporting the robustness of the findings across populations with different clinical characteristics.

4. Discussion

4.1. Summary of Findings

In the current large population-based cross-sectional study, the researchers consistently found a positive correlation between SIRI and the risk of breast cancer. There was some evidence of a dose-response relationship, with SIRI being linked to breast cancer in an L-shaped nonlinear way (P for nonlinearity < 0.05). The curves were flatter when SIRI was 0.918 10^3/μL. It is significant that a statistical interaction was identified between SIRI and marital status in the determination of breast cancer (P < 0.05). Results were uniform and robust across clinical subgroups and in sensitivity analyses. It may be used as a supplementary marker for the initial stratification of high-risk populations in women.

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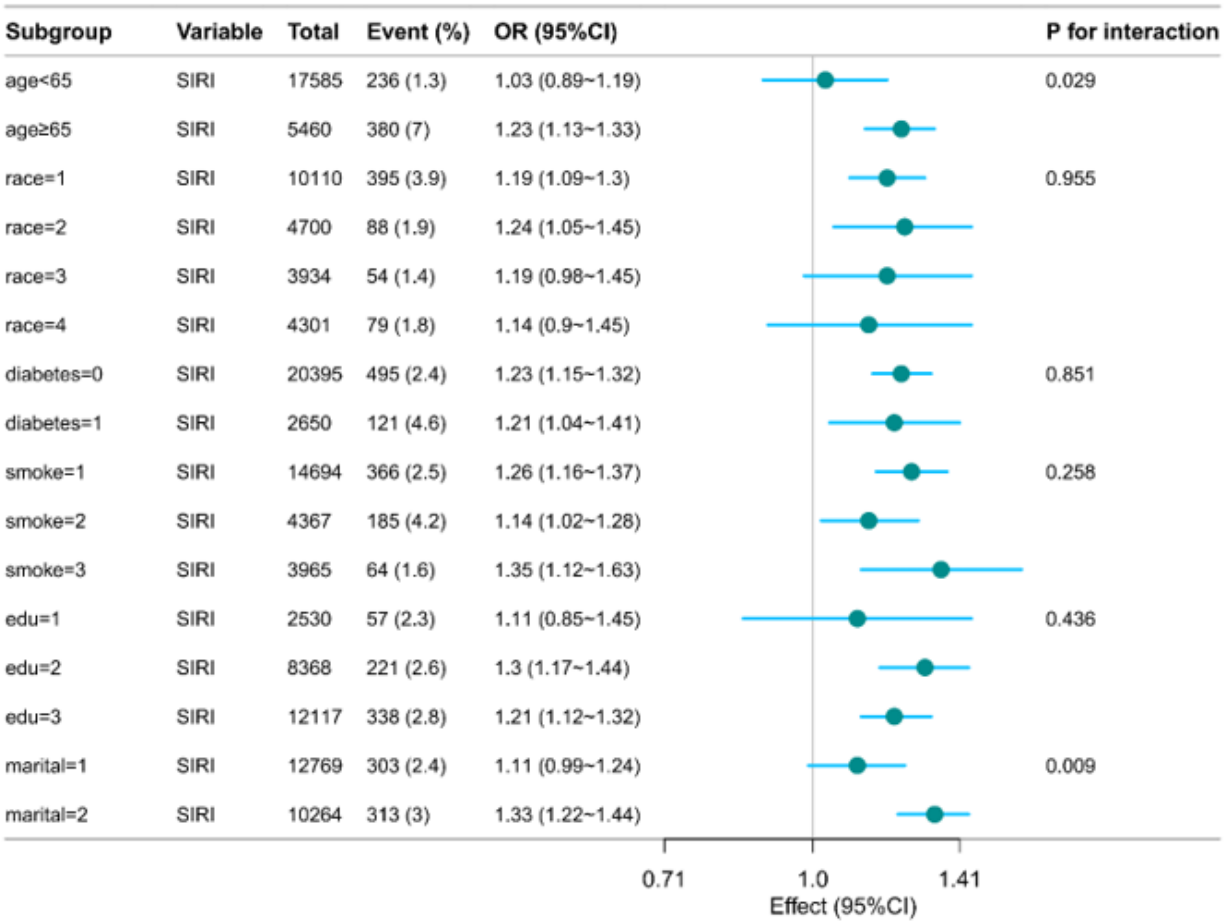

Figure 3.
Forest plot of single model analysis.

4.2. Comparative Analysis and Clinical Implications

The researchers' population-based investigation identified favorable correlations between the Systemic Inflammation Response Index (SIRI) and breast cancer. Although prior studies have investigated the correlation between SIRI and breast cancer, including a recent prospective longitudinal cross-sectional study indicating a substantial link, the researchers' results augment this body of evidence within a population-based framework. The correlations between SIRI and the occurrence of breast cancer were low yet consistent across clinically significant subgroups categorized by age, race, smoking status, and cardiovascular disease risk factors, including diabetes. Sensitivity analyses supported the robustness of the results. Further studies are needed to replicate these observations and to elucidate the biological mechanisms underpinning the association.

The researchers' findings suggest that SIRI, an inexpensive and readily available inflammation-based index derived from routine blood counts, may serve as a useful auxiliary marker for identifying women at elevated risk of breast cancer and for stratifying patients according to their systemic inflammatory status. However, given the cross-sectional design, SIRI should currently be considered a risk indicator rather than a definitive predictive or prognostic tool, and prospective studies are needed to validate its clinical utility.

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4.3. Strengths and Limitations

As far as the researchers are aware, this investigation is the first to explore the association between SIRI and breast cancer using the most up-to-date national summary data. The extensive dataset provides both a wide demographic representation and sufficient power to detect meaningful relationships. The study employed a prospective cross-sectional design with rigorous inclusion and exclusion criteria and offers an original perspective with potential therapeutic relevance. Detailed baseline information on lifestyle factors, including dietary covariates, allowed adjustment for multiple confounders and the conduct of extensive sensitivity analyses, thereby strengthening result interpretation and the robustness of the primary findings. Nonetheless, the cohort was relatively homogeneous; although key confounders were controlled for and residual confounding is unlikely to materially alter the conclusions, it cannot be completely excluded. Moreover, participants were exclusively of the resident population of the United States, which may limit the generalizability of the findings to other ethnic groups. Despite these limitations, the study provides additional, well-supported evidence of an association between SIRI and breast cancer.

5. Conclusion

The researchers' investigation established a positive connection with elevated SIRI, supported by an independent clinical sample, thereby validating the researchers' findings [18]. To improve the clinical relevance of SIRI as a prognostic risk factor in breast cancer, future research efforts with large, prospective cohorts should be directed toward examining the relationships between SIRI and breast cancer molecular subtypes [19] as well as determining the presence of a causal link between these variables [20].

Higher SIRI values were associated in a dose–response manner with an increased risk of breast cancer. We identified an L-shaped, non-linear relationship between SIRI and breast cancer risk, characterized by relatively low risk at lower SIRI values and a steeper increase at higher values. This pattern may have implications for clinicians when stratifying risk and managing patients with breast cancer. Stratified analyses by age, race, education, marital status, and diabetes revealed no significant interactions (all interaction $P > 0.05$), indicating that the association was consistent across these subgroups.

The systemic inflammation response index (SIRI) has been suggested as a potential marker in various malignancies. In this cross-sectional study of U.S. participants comparing cases and controls, higher SIRI levels were significantly associated with the presence of breast cancer, supporting its possible role as a prognostic indicator.

Institutional Review Board Statement:

The research involving human subjects received approval from the National Centre for Health Statistics Research Ethics Review Board. The research was performed in compliance with local laws and institutional regulations. The subjects submitted their written informed consent to participate in this study.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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