Original Article

Association between serum urate levels, gout and breast cancer: observational and Mendelian randomization analyses

Shuai Wang[1], Zhiyuan Zhang[1], Yuqing Su[1], Shoukai Wang[1], Wenwen Li[1], Qi Liu[1], Pilei Si[1,2], Wentao Li[1,2]

[1]Department of Breast Surgery, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Zhengzhou, China; [2]Department of Breast Surgery, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, Zhengzhou, China

Contributions: (I) Conception and design: Wentao Li, P Si, Shuai Wang; (II) Administrative support: Wentao Li, P Si; (III) Provision of study materials or patients: Wentao Li, Shuai Wang; (IV) Collection and assembly of data: Shuai Wang, Z Zhang, Y Su, Shoukai Wang, Wenwen Li, Q Liu; (V) Data analysis and interpretation: Shuai Wang, Z Zhang, Y Su; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wentao Li, MD, PhD; Pilei Si, MD, PhD. Department of Breast Surgery, Henan Provincial People's Hospital, Zhengzhou University People's Hospital, No. 7, Weiwu Road, Zhengzhou 450003, China. Email: lwt9225@163.com; siplei2013@pku.edu.cn.

Background: It is hypothesized that uric acid acts as an antioxidant and may prevent cancer. However, observational studies regarding the relationship between serum urate levels, gout, and breast cancer have provided discrepant evidence. Therefore, the objective of our study was to investigate the potential causal relationship between them.

Methods: This study included 12,451 participants from the National Health and Nutrition Examination Survey (NHANES) 2009–2018. Associations between urate levels, gout, and breast cancer were examined using multivariate logistic regression analysis. In addition, to assess the causal link among them, Mendelian randomization (MR) analysis was conducted, primarily using the inverse variance weighted (IVW) approach, supplemented by MR Egger and weighted median approaches, and a set of sensitivity analyses to test the robustness of the results, and finally, multivariate MR was used to adjust for confounders.

Results: In cross-sectional studies, urate levels [odds ratio (OR) 0.99, 95% confidence interval (CI): 0.89–1.09, P=0.80] and gout (OR 0.96, 95% CI: 0.53–1.76, P=0.90) were negatively associated with breast cancer risk after controlling for multiple confounders, although the P value was not significant. Two-sample MR analysis showed that serum urate levels were negatively associated with the estrogen receptor-negative (ER–) breast cancer (IVW, OR 0.916, 95% CI: 0.848–0.989, P=0.03) risk, but not significantly associated with overall and the estrogen receptor-positive (ER+) breast cancer (IVW, both P>0.05). In addition, gout was negatively associated with overall (IVW, OR 0.07, 95% CI: 0.008–0.594, P=0.02), ER+ (IVW, OR 0.062, 95% CI: 0.005–0.742, P=0.03), and ER– breast cancer (IVW, OR 0.041, 95% CI: 0.004–0.472, P=0.01) risk. These associations persisted after multivariate MR adjustment for smoking status, alcohol intake frequency, and body mass index (BMI).

Conclusions: Our study elucidated the relationship between uric acid, gout and breast cancer, and further studies are still needed in the future to clarify the mechanisms involved.

Keywords: Breast cancer; serum urate levels; gout; NHANES; Mendelian randomization (MR)

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Introduction

Breast cancer is the most frequent type of cancer in women globally and the primary cause of cancer-related death in women, with 2,261,419 new cases reported in 2020 (1). Women have a high lifetime risk of being diagnosed with breast cancer (2). Identifying risk factors associated with breast cancer is critical to the prevention, treatment, and management of breast cancer.

Uric acid is the metabolic final product of purines through xanthine oxidoreductase and is present in the blood in the form of urate. It is primarily eliminated via the kidneys and intestines (3). Obesity, alcoholism, and a diet high in purines are risk factors for increased serum uric acid, which can lead to hyperuricemia and gout (4). Hyperuricemia is defined as a serum uric acid concentration over 6.8 mg/dL (5), whereas gout is a progressive metabolic and arthropathic disease resulting from excessive urate deposits and characterized by symptomatic hyperuricemia (6). Clinically, many cancer treatment factors including radiotherapy, chemotherapy, targeted therapy can lead to hyperuricemia, and some patients even appear in the form of acute tumor lysis syndrome, because after the application of antitumor therapy, the tumor cells are destroyed, lysed and release a large amount of nucleic acid, which leads to an increase in uric acid by degradation. In addition, some chemotherapeutic drugs themselves or through their impact on renal function can also lead to an increase in the level of serum uric acid (7).

Uric acid is reported to be a potent antioxidant that may prevent cancer (8). However, current observational epidemiologic studies on uric acid, gout, and cancer associations provide inconsistent evidence (9-12). Decreased xanthine oxidoreductase activity in mouse and human mammary epithelial cells is associated with increased invasiveness, and uric acid increases the migration rate of human breast cancer cells and mouse mammary epithelial cells, suggesting a potential link between uric acid and breast cancer (13). But the relationship between serum urate levels, gout, and breast cancer remains controversial. There is evidence that urate levels and gout are negatively correlated with breast cancer (14,15), In particular, a multicenter cohort study showed that higher levels of uric acid were associated with a lower risk of breast cancer and cancer death (14). In addition, a large cohort study of 493,281 individuals aged 20 years and older also showed that serum uric acid levels were negatively associated with breast cancer risk (15). However, some studies have suggested otherwise (16-18). Observational studies are vulnerable to many confounders that can bias results. Mendelian randomization (MR) uses genetic variants strongly related to exposure as instrumental variables (IVs) to study the relationship between exposure and outcome. Due to the random assignment and temporal prioritization of genetic variants, MR can effectively overcome the effects of reverse causation and residual confounding that are difficult to avoid in observational studies (19,20). Therefore, we first explored the observational associations based on the National Health and Nutrition Examination Survey (NHANES) 2009–2018, and then further assessed the causality using MR. In addition, studies have shown that risk factors have different effects on estrogen receptor (ER)-positive and negative breast cancers (21), so we additionally assessed the causal associations between uric acid and gout with these two subtypes of breast cancer. We present this article in accordance with the STROBE-MR reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1141/rc).

Highlight box

Key findings

- Serum urate levels and gout are negatively associated with breast cancer risk.

What is known and what is new?

- Previous studies have indicated the relationship between serum urate levels, gout and certain cancers, but the relationship between serum urate levels, gout and breast cancer is controversial.
- This is the first study to examine the relationship between urate, gout and breast cancer using the National Health and Nutrition Examination Survey (NHANES) and Mendelian randomization (MR). In addition, we further evaluated the causal relationship between urate, gout and breast cancer based on estrogen receptor status.

What is the implication, and what should change now?

- Our study found that uric acid can inhibit the incidence of breast cancer, which provides some reference for the management of uric acid levels in hyperuricemic patients who have high risk factors for breast cancer. Further studies can explore the related mechanisms and targets to develop relevant antitumor drugs.

Methods

Overall study design

This study is divided into two sections. First, we utilized data from NHANES to explore the observational link

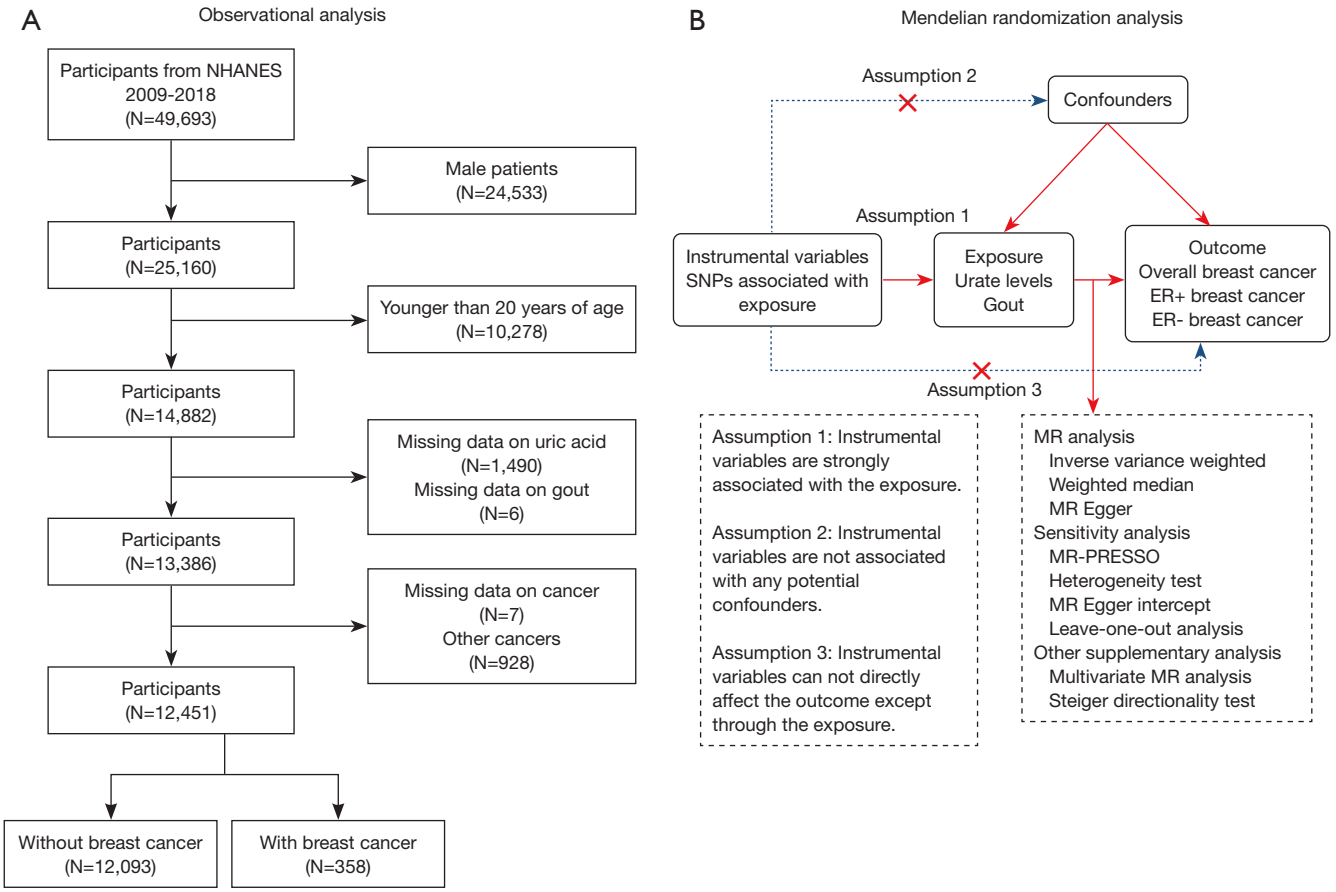

Figure 1 The study design and flow chart. (A) The flowchart of NHANES participants. (B) The study design and flow chart for MR analysis. NHANES, National Health and Nutrition Examination Survey; MR, Mendelian randomization; SNP, single nucleotide polymorphism; ER+, estrogen receptor-positive; ER–, estrogen receptor-negative.

between urate, gout and breast cancer. Then, we carried out MR analyses utilizing summary statistics of genome-wide association studies (GWAS) to evaluate the causal effects of serum urate levels and gout on breast cancer. The study design and flow chart are presented in *Figure 1*.

Observational analysis

Participants in NHANES

NHANES is a cross-sectional survey performed by the National Center for Health Statistics (NCHS), part of the Centers for Disease Control and Prevention (CDC), to evaluate the health and nutritious condition of the American population (22). This survey has received ethical approval from the NCHS Ethics Review Board (ERB), and all subjects have provided informed consent. For more details, see this website (https://www.cdc.gov/nchs/nhanes/irba98.htm). To investigate the relationship between uric acid, gout, and breast cancer, we performed a retrospective analysis using the NHANES dataset from 5 cycles (2009–2018). The participant exclusion criteria are as follows: (I) male patients (N=24,533), (II) participants under the age of 20 years (N=10,278), (III) participants with missing uric acid data (N=1,490) or missing gout data (N=6), and (IV) participants with missing cancer data (N=7) or with other cancers (N=928). *Figure 1* illustrates the entire recruiting process.

Assessment of uric acid and gout

Serum uric acid levels were measured by the Beckman Unicel DxC 800 Synchron. Information on gout was obtained from medical conditions in the questionnaire data. Based on participants' self-reported responses to the question "Has a medical professional ever told you that

you have gout?", participants were defined as having gout or not, and if the answer was "Don't know/Refused", they were regarded as patients with missing gout data.

Assessment of breast cancer

Information on breast cancer was also obtained from medical conditions in the questionnaire data. According to participants' self-reported answers to the question "Have you ever been told by a medical professional that you have cancer or any type of malignancy? Participants were defined as having cancer or not, and if the answer was "don't know/refused", they were regarded as participants with missing cancer data. Then based on the self-reported answer, "What type of cancer is it?", participants were defined as having breast cancer if the answer was "breast cancer", and participants who answered with other types of cancer were excluded from the study.

Covariate

This study included the following covariates: age, race, education level, marital status, cholesterol, triglycerides, fasting blood glucose, body mass index (BMI), age at menarche, age at menopause, ever been pregnant, smoking status, and alcohol use. Individuals who had consumed 100 cigarettes or more over their lives were regarded as smokers. Individuals who reported consuming a minimum of 12 alcoholic beverages annually were regarded as alcohol drinkers.

Statistical analysis

This study considered the sampling weights of NHANES. The continuous variables were represented as mean ± standard deviation (SD), and the differences between the non-breast cancer group and the breast cancer group were derived by weighted linear regression models. The categorical variables were represented as percentages, and the differences between the non-breast cancer group and the breast cancer group were derived by weighted chi-square test. The link between uric acid, gout and breast cancer was estimated using a multivariate logistic regression model. Model 1 was unadjusted, Model 2 was adjusted for race and age, and Model 3 was adjusted for race, age, education level, BMI, marital status, fasting blood glucose, triglycerides, cholesterol, smoking status, and alcohol use, age at first menstruation, age at menopause, ever been pregnant. All analyses were carried out using R 4.3.2 or Empowerstats 2.0. The statistical significance threshold was $P<0.05$.

MR

Data sources

GWAS data regarding urate levels and gout exposures in the study were acquired from the UK Biobank. The Urate Levels Cohort is a 2021 study that included 437,354 samples and 4,231,909 single nucleotide polymorphisms (SNPs), and the Gout Cohort is also a 2021 study that included 484,598 samples and 9,587,836 SNPs. Meanwhile, we got GWAS data regarding breast cancer outcomes from the Breast Cancer Association Consortium (BCAC). The overall breast cancer dataset included 106,776 samples and 10,680,257 SNPs, the ER+ breast cancer dataset included 83,691 samples and 10,680,257 SNPs, and the ER– breast cancer dataset included 55,149 samples and 10, 680,257 SNPs. In addition, we acquired datasets on smoking status, frequency of alcohol intake, and BMI for multivariate MR analysis. All data are from European populations and are available in the database of the IEU Open GWAS project (https://gwas.mrcieu.ac.uk/datasets/). Specific GWAS cohort characteristics are shown in Table S1.

IVs extraction

The selection of SNPs as IVs to assess the causal effects of urate levels and gout on breast cancer incidence required the fulfillment of three assumptions of MR as shown in *Figure 1*. The following were the specific SNP inclusion criteria: (I) SNPs linked to exposure with genome-wide significance ($P<5\times10^{-8}$). (II) there was no linkage disequilibrium between SNPs ($r^2<0.001$ and within 10,000 kb window). (III) We searched for each included SNP using the PhenoScannerV2 website (http://www.phenoscanner.medschl.cam.ac.uk/), and SNPs closely related to confounders should be eliminated prior to MR analysis. Meanwhile, SNPs with frequencies of palindromic intermediate alleles were excluded. Because the SNPs for breast cancer outcomes were from studies at the same institution, we ultimately obtained 24 SNPs as IVs for gout and 300 SNPs as IVs for urate levels, regardless of whether the outcome was overall, ER+, or ER– breast cancer. The main data are available at https://cdn.amegroups.cn/static/public/TCR-24-1141-1.xlsx.

Statistical analysis

Two-sample MR analysis

Three methods were used for MR analysis: inverse variance weighted (IVW) random effects model (23), weighted median (24), and MR Egger (25), with the IVW as the primary analytical approach.

Sensitivity analysis

Heterogeneity was evaluated using Cochran's Q test (26) and horizontal pleiotropy was mainly identified using the MR-Egger intercept test (25). MR-PRESSO was also performed to detect horizontal polytropy and to test for differences between the results of the MR analysis before and after outlier correction (27). In addition, the Steiger directionality test was implemented to avoid reverse causality. Finally, the leave-one-out plot and funnel plot were utilized to perform additional sensitivity analysis.

Multivariate MR analysis

We searched for SNPs obtained from two-sample MR analysis using the PhenoScannerV2 website (http://www.phenoscanner.medschl.cam.ac.uk/) and found that some of them were strongly related to smoking status, alcohol intake frequency, and BMI, regardless of whether the exposure was urate levels or gout. To avoid bias, we adjusted for these three confounders using multivariate MR analysis (28).

All analyses were conducted utilizing version 4.2.3 of the R software and the TwoSampleMR R package. The statistical significance threshold was P<0.05.

Results

Observational analysis

Participants characteristics of NHANES

This study ultimately included 12,451 participants, 358 participants with breast cancer, and 12,093 without breast cancer. *Table 1* summarizes the characteristics of NHANES participants. The mean weighted ages of the breast cancer and control groups were 65.61±11.88 and 46.55±16.68 years, respectively. Individuals with and without breast cancer differed significantly (P<0.05) in age, race, education level, marital status, ever been pregnant, alcohol consumption, presence of gout, uric acid, cholesterol, triglycerides, fasting blood sugar, and age at menopause. Breast cancer patients, compared to patients who did not have breast cancer, were more likely to be older, non-Hispanic White, have a higher education level, be widowed/divorced/separated, have been pregnant, have gout, not drink alcohol, have a later age of menopause, and have higher uric acid, cholesterol, triglycerides, and fasting glucose (P<0.05).

Association between urate, gout and breast cancer

The findings of the multivariate logistic regression analyses of the relationship between urate, gout and breast cancer are shown in *Table 2*. In the unadjusted model (Model 1), there was a positive correlation between serum urate levels and the risk of breast cancer [odds ratio (OR) 1.29, 95% confidence interval (CI): 1.20–1.38, P<0.001]. However, in model 3, which adjusted for multiple covariates, there was a negative correlation between urate levels and the risk of breast cancer, despite the lack of statistical significance in the P value (OR 0.99, 95% CI: 0.89–1.09, P=0.80). Similarly, in the unadjusted model (Model 1), gout was linked to an elevated risk of breast cancer (OR 2.40, 95% CI: 1.52–3.78, P<0.001). However, in Model 3, which controlled for confounding, gout was observed to be linked to a lower incidence of breast cancer, despite the lack of statistical significance in the P value (OR 0.96, 95% CI: 0.53–1.76, P=0.90).

MR study

Two-sample MR analysis

Two-sample MR analysis suggested that elevated serum urate levels were related to decreased risk of ER– breast cancer (IVW, OR 0.916, 95% CI: 0.848–0.989, P=0.03), but not to overall and ER+ breast cancer risk (IVW, both P>0.05). Gout was negatively associated with overall (IVW, OR 0.07, 95% CI: 0.008–0.594, P=0.02), ER+ (IVW, OR 0.062, 95% CI: 0.005–0.742, P=0.03), and ER-breast cancer risk (IVW, OR 0.041, 95% CI: 0.004–0.472, P=0.01). The results in detail are illustrated in *Figures 2,3*.

Sensitivity analysis

The sensitivity analysis findings are presented in *Table 3*. Cochran's Q test shows that there is heterogeneity in most of our results, but we used random effects IVW in our study, which effectively mitigates the effects of heterogeneity, so it does not affect the reliability of our results. The findings of the MR-Egger intercept test revealed no horizontal pleiotropy (P all >0.05). The results were not significantly changed before or after MR-PRESSO correction for outliers. The Steiger directionality test also shows that there is no reverse causality in our analyses, as detailed in Table S2. *Figure 4* and Figure S1 illustrate the scatter plots and forest plots of the MR analysis. As shown in Figure S2, the funnel plot indicates that there is no significant heterogeneity in the results. As shown in Figure S3, the leave-one-out analyses indicated that no individual SNP had a significant impact on the MR estimate results, as the OR values were all on the one side of the zero-line.

Table 1 Baseline characteristics of NHANES participants

Variable	Non-breast cancer (N=12,093)	Breast cancer (N=358)	P
Age (years)	46.55±16.68	65.61±11.88	<0.001
Uric acid (mg/dL)	4.76±1.24	5.17±1.26	<0.001
Cholesterol (mg/dL)	195.22±41.04	201.43±40.95	0.003
Triglycerides (mg/dL)	132.76±105.38	149.01±82.74	0.002
Fasting glucose (mg/dL)	97.54±32.20	107.47±37.68	<0.001
BMI (kg/m^2)	29.38±7.69	29.56±6.72	0.66
Age when first menstrual period occurred (years)	12.71±1.72	12.61±1.76	0.26
Age at last menstrual period (years)	44.60±8.85	46.00±7.74	0.004
Race			<0.001
Mexican American	8.74	3.83	
Other Hispanic	6.49	3.12	
Non-Hispanic White	63.30	82.56	
Non-Hispanic Black	12.52	6.35	
Other race	8.95	4.14	
Education level			0.02
Less than 9th grade	5.22	3.61	
9–11th grade	9.44	7.38	
High school graduate/GED or equivalent	21.54	21.06	
Some college or AA degree	33.77	30.33	
College graduate or above	30.03	37.61	
Marital status			<0.001
Married/living with partner	60.69	51.98	
Widowed/divorced/separated	21.64	43.10	
Never married	17.68	4.93	
Ever been pregnant			<0.001
Yes	80.78	90.66	
No	19.22	9.34	
Gout			<0.001
Yes	2.19	5.53	
No	97.81	94.47	
Smoking			0.86
Yes	36.11	36.53	
No	63.89	63.47	
Alcohol consumption			0.01
Yes	69.44	62.20	
No	30.56	37.80	

Continuous variables were reported as weighted mean ± standard deviation (SD), and categorical variables were reported as weighted percentages. NHANES, National Health and Nutrition Examination Survey; BMI, body mass index; GED, General Educational Development; AA, Associate of Arts.

Table 2 Multivariate logistic regression of urate levels and gout for breast cancer

Exposure	Model 1		Model 2		Model 3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Serum urate (mg/dL)	1.29 (1.20, 1.38)	<0.001	1.04 (0.97, 1.13)	0.27	0.99 (0.89, 1.09)	0.80
Gout						
No	Reference		Reference		Reference	
Yes	2.40 (1.52, 3.78)	<0.001	1.12 (0.70, 1.79)	0.64	0.96 (0.53, 1.76)	0.90

Model 1 was not adjusted for covariates. Model 2 was adjusted for age and race. Model 3 was adjusted for age, race, education level, marital status, body mass index, fasting blood glucose, triglycerides, cholesterol, age at first menstruation, age at menopause, ever been pregnant, smoking status, and alcohol use. OR, odds ratio; CI, confidence interval.

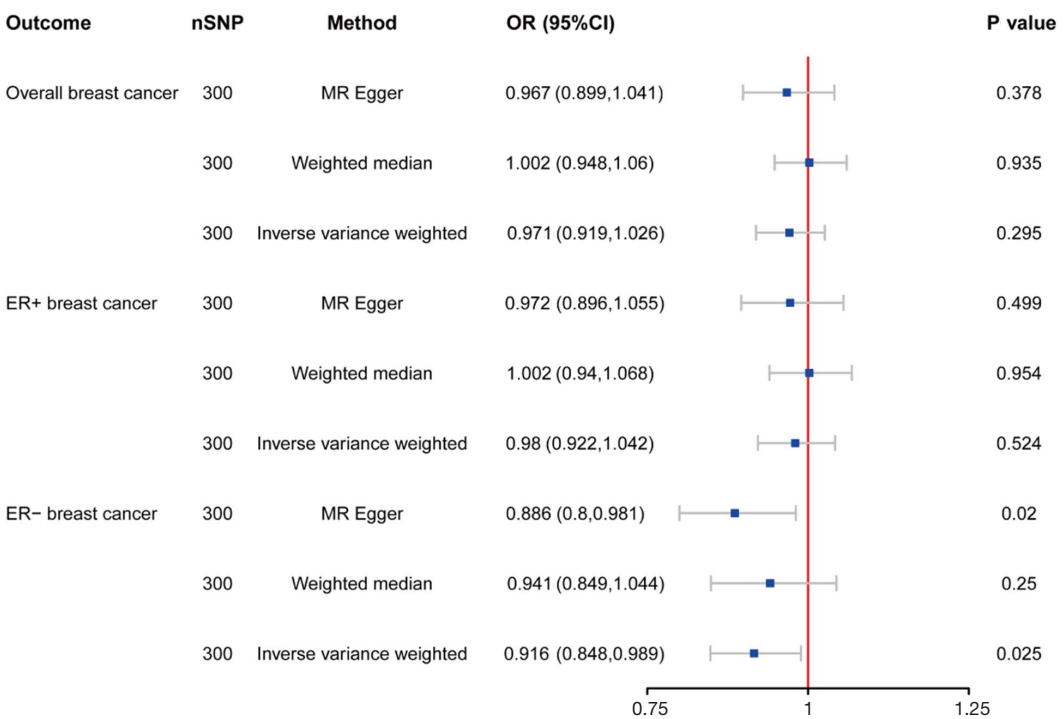

Figure 2 Forest plot of the causal effect of urate levels on breast cancer and its subtypes. nSNP, number of single nucleotide polymorphism; ER+, estrogen receptor-positive; ER–, estrogen receptor-negative; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

Multivariate MR analysis

As shown in *Table 4*, after adjusting for smoking status, alcohol intake frequency, and BMI using multivariate MR, urate levels continued to have a negative correlation with ER– breast cancer (OR 0.899, 95% CI: 0.826–0.977, P=0.02). In addition, gout was still negatively associated with overall (OR 0.069, 95% CI: 0.012–0.385, P=0.002), ER+ (OR 0.069, 95% CI: 0.010–0.476, P=0.007), and ER– breast cancer risk (OR 0.021, 95% CI: 0.002–0.306, P=0.005).

Discussion

This is the first study to examine the relationship between uric acid, gout and breast cancer using NHANES and MR, to our knowledge. We comprehensively examined the relationships between urate levels, gout and breast cancer by combining an observational analysis using data from

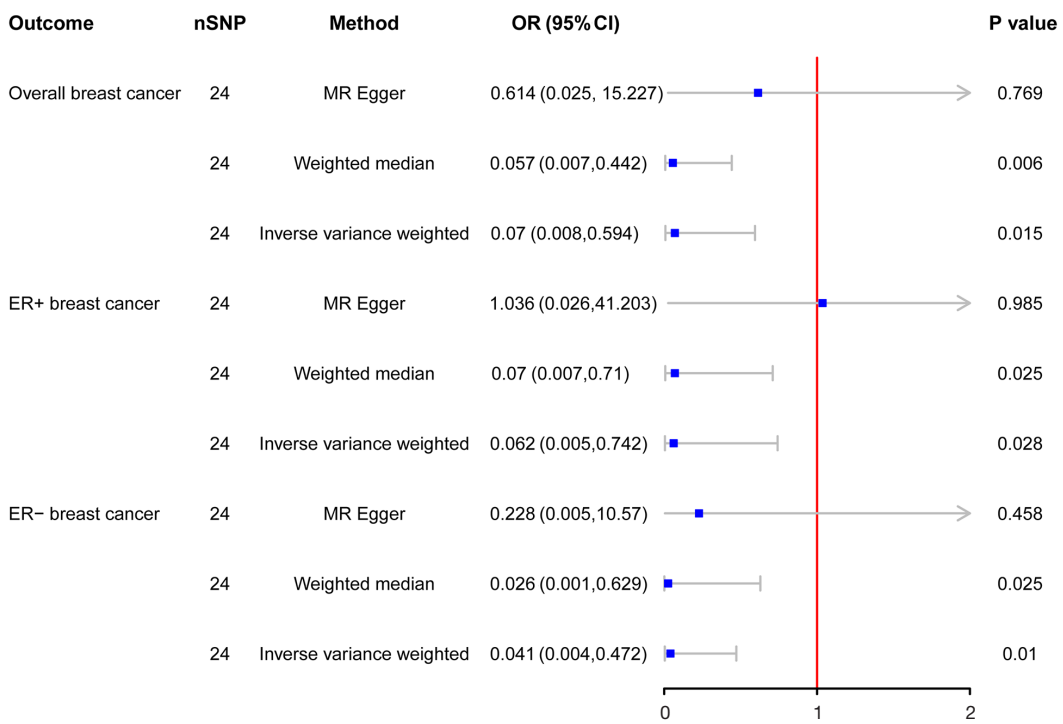

Figure 3 Forest plot of the causal effect of gout on breast cancer and its subtypes. nSNP, number of single nucleotide polymorphism; ER+, estrogen receptor-positive; ER–, estrogen receptor-negative; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

Table 3 Sensitivity analysis of the causal effects of urate levels and gout on breast cancer and its subtypes

Exposure	Outcome	Heterogeneity (IVW, P for Cochran Q)	Pleiotropy (MR-Egger, P for Intercept)	Outlier examination by MR-PRESSO					
				Before correction			After correction (if necessary)		
				MR analysis causal estimate	SD	P	MR analysis causal estimate	SD	P
Urate levels	Overall breast cancer	<0.001	0.881	−0.029	0.028	0.30	−0.021	0.023	0.35
	ER+ breast cancer	<0.001	0.763	−0.018	0.031	0.57	−0.008	0.026	0.76
	ER− breast cancer	<0.001	0.328	−0.084	0.039	0.03	−0.081	0.038	0.03
Gout	Overall breast cancer	<0.001	0.100	−2.477	1.084	0.03	−2.415	0.854	0.01
	ER+ breast cancer	<0.001	0.064	−2.595	1.259	0.05	−2.470	0.931	0.02
	ER− breast cancer	0.583	0.269	−2.977	1.189	0.02	NA	NA	NA

IVW, inverse variance weighted; MR, Mendelian randomization; SD, standard deviation, ER+, estrogen receptor-positive; ER–, estrogen receptor-negative; NA, not available.

NHANES 2009–2018 and an MR analysis using data from the large-scale GWAS. In the present study, cross-sectional observational analysis found that urate levels and gout were negatively related to breast cancer risk, even though the P value was not significant. Two-sample MR analysis showed that serum urate levels were negatively related to the risk of ER– breast cancer, but not significantly related to overall or ER+ breast cancer. In addition, gout was negatively associated with the risk of overall, ER+, and ER– breast cancer. The results of the sensitivity analysis

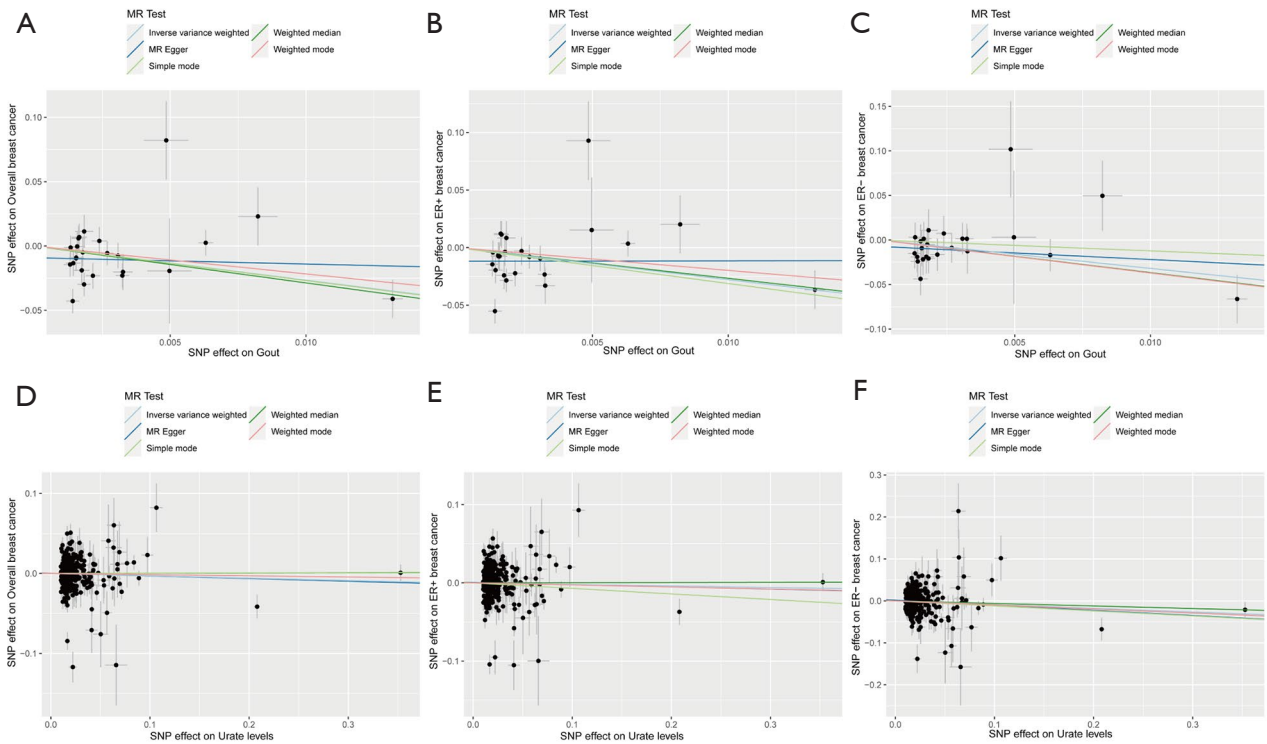

Figure 4 The MR analysis scatter plots. The estimated effect of MR for each method is denoted by the slope of each line. (A) Gout on overall breast cancer. (B) Gout on ER+ breast cancer. (C) Gout on ER– breast cancer. (D) Urate levels on overall breast cancer. (E) Urate levels on ER+ breast cancer. (F) Urate levels on ER– breast cancer. MR, Mendelian randomization; ER, estrogen receptor; SNP, single nucleotide polymorphism.

also showed the reliability of our MR results. These associations persisted after multivariate MR adjustment for smoking status, alcohol intake frequency, and BMI. Our study elucidated the link between uric acid, gout and breast cancer. In summary, our findings support the antioxidant role of uric acid in inhibiting breast carcinogenesis, and provide some reference for the management of uric acid levels in hyperuricemic patients who have high risk factors for breast cancer. However, the use of high uric acid levels or gout to combat breast cancer in the general population is not advocated until the mechanisms involved are clear, and further studies could explore the mechanisms and targets to develop relevant antitumor drugs.

It is speculated that uric acid, as a potent antioxidant, may be able to prevent cancer (8). However, there is still controversy about the connection between serum urate levels, gout and cancer. Similarly, the connection between urate levels, gout and breast cancer is inconclusive. A cohort study of 4,350 men followed for 38 years showed that higher serum uric acid levels were linked to a reduced risk of death from any malignancy [hazard ratio (HR) (95% CI): 0.85 (0.73–0.97)] (9). Horsfall *et al.* (10) discovered that smokers with low serum uric acid levels had a higher chance of getting lung cancer. This suggests that uric acid may help protect against cancer. In line with our findings, a population-based prospective study found that uric acid levels were inversely linked with breast cancer risk and death from cancer, but not significantly connected with prostate, lung, and colorectal cancer risk (14). In addition, Yiu *et al.* also revealed a negative link between serum uric acid levels and breast cancer in the AMORIS study (15). However, in a cross-sectional study including 1,050 women, Fan *et al.* discovered a J-shaped correlation between uric acid and the risk of breast cancer, but the sample size was small and there was no record of dietary habits associated with elevated uric acid (16). In a bidirectional MR analysis and prospective cohort study, Feng *et al.* found that uric acid mediated the link between BMI and increased incidence of postmenopausal breast cancer, but the study crossed MR and cohort studies rather than using both to

Table 4 Multivariate MR of breast cancer and its subtypes

Outcome	Exposure	nSNP	OR (95% CI)	P
Overall breast cancer	Smoking	13	1.049 (0.630, 1.746)	0.85
	Alcohol intake	24	1.063 (0.907, 1.246)	0.45
	BMI	125	0.868 (0.759, 0.993)	0.04
	Urate levels	197	0.963 (0.910, 1.019)	0.19
ER+ breast cancer	Smoking	13	1.020 (0.583, 1.785)	0.94
	Alcohol intake	24	1.075 (0.904, 1.279)	0.41
	BMI	125	0.859 (0.741, 0.996)	0.04
	Urate levels	197	0.971 (0.912, 1.034)	0.36
ER– breast cancer	Smoking	13	0.787 (0.371, 1.667)	0.53
	Alcohol intake	24	1.152 (0.916, 1.451)	0.23
	BMI	125	0.857 (0.703, 1.045)	0.13
	Urate levels	197	0.899 (0.826, 0.977)	0.01
Overall breast cancer	Smoking	42	1.495 (1.111, 2.012)	0.008
	Alcohol intake	43	1.104 (0.978, 1.246)	0.11
	BMI	341	0.817 (0.748, 0.892)	<0.001
	Gout	12	0.069 (0.012, 0.385)	0.002
ER+ breast cancer	Smoking	42	1.389 (0.996, 1.937)	0.053
	Alcohol intake	43	1.066 (0.931, 1.220)	0.35
	BMI	341	0.839 (0.760, 0.926)	<0.001
	Gout	12	0.069 (0.010, 0.476)	0.007
ER– breast cancer	Smoking	42	1.470 (0.932, 2.319)	0.10
	Alcohol intake	43	1.320 (1.098, 1.586)	0.003
	BMI	341	0.748 (0.654, 0.856)	<0.001
	Gout	12	0.021 (0.002, 0.306)	0.005

MR, Mendelian randomization; nSNP, number of single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; BMI, body mass index; ER+, estrogen receptor-positive; ER–, estrogen receptor-negative.

mutually validate the association (17). Gremke *et al.* found gout to be related to an increased risk of breast cancer in a retrospective cohort study including 67,598 German cases, but the authors did not consider any external confounders that might have influenced the results of the study (18). Moreover, urate levels and the risk of cancer have been positively correlated in some studies (11,12). In general, the evidence regarding the connection between uric acid and the risk of cancer seems to be fairly inconsistent. Observational studies are vulnerable to many confounders that can bias results. We combined the NHANES cross-sectional study with MR analysis for a comprehensive investigation of the relationship between urate levels, gout and risk of breast cancer, with more reliable results.

It was initially reported that uric acid acts as an antioxidant, a scavenger of unilinear oxygen and radicals, and may be able to protect against cancer (8). Uric acid was found to reduce reactive oxygen species (ROS) production by systemic administration of uric acid to healthy volunteers (29). Some evidence also supports the antioxidant effects of uric acid (30,31). The uric acid transporter SLC2A9 has been demonstrated to be a key downstream target of p53, and the p53-SLC2A9 pathway has been found to prevent the accumulation of ROS-associated damage that may lead

to cancer development (32). Conversely, cells exposed to uric acid develop oxidative stress (33), and ROS activates signaling pathways associated with proliferation, survival, angiogenesis, and metastasis, promoting tumorigenesis, progression, and metastasis (34). The dual role of uric acid as an antioxidant and pro-oxidant (35), as well as the dual role of uric acid in cancer, may explain the different associations between uric acid and different cancers. However, we have not yet found strong experimental evidence that uric acid plays a specific negative role in breast carcinogenesis, and further studies are still needed in the future to explore the mechanisms involved.

The primary advantage of the present study is the combination of a large cross-sectional observational study and MR analysis to more fully investigate the link between urate levels, gout and breast cancer, as conclusions were drawn from multiple lines of evidence. In addition, we applied various sensitivity analyses in the MR analysis to ensure the reliability and robustness of our results. Despite this, there are some limitations in this study. In the observational study, the number of cases of breast cancer and gout was too small, even though we used a large NHANES sample. Second, although we adjusted for multiple confounders, residual confounding may still exist when examining observational associations. In addition, we did not perform stratified analyses. In the MR analysis, horizontal pleiotropy could not be completely avoided due to the complexity of genetic variation, despite a series of sensitivity analyses. Finally, the participants in our cross-sectional study were from the U.S. population, whereas the population in the MR analysis were all from the European population, and there was demographic heterogeneity.

Conclusions

Our study elucidated the link between uric acid, gout and breast cancer. In summary, our findings support the antioxidant role of uric acid in inhibiting breast carcinogenesis, and provide some reference for the management of uric acid levels in hyperuricemic patients who have high risk factors for breast cancer. However, the use of high uric acid levels or gout to combat breast cancer in the general population is not advocated until the mechanisms involved are clear, and further studies could explore the mechanisms and targets to develop relevant antitumor drugs.

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Footnote

Reporting Checklist: The authors have completed the STROBE-MR reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1141/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1141/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This survey has received ethical approval from the NCHS Ethics Review Board (ERB), and all subjects have provided informed consent. For more details, see this website (https://www.cdc.gov/nchs/nhanes/irba98.htm).

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