Discover Oncology

Analysis

Causality between autoimmune diseases and breast cancer: a two-sample Mendelian randomization study in a European population

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Abstract

Background The incidence of autoimmune diseases and breast cancer is significantly higher in women compared to men. Previous observational studies have not conclusively determined the relationship between these two conditions. This study utilizes the Mendelian randomization approach to investigate the genetic association between autoimmune diseases and breast cancer.

Method Two-sample Mendelian randomization was conducted on a European population using the GWAS database. The inverse variance-weighted method served as the primary analytical approach. The MR-PRESSO test was applied to detect horizontal pleiotropy. To ensure result robustness, the FDR correction method was used.

Result The study revealed that Sjögren's syndrome lowers the overall risk of breast cancer (OR 0.96, 95% CI [0.93–0.99], $p = 0.011$). Idiopathic inflammatory myopathy shows a protective effect against overall breast cancer (OR 0.98, 95% CI [0.97–0.99], $p = 0.035$). An association was identified between rheumatoid arthritis and overall breast cancer (OR 0.98, 95% CI [0.96–1.00], $p = 0.050$). No causal link was found between systemic lupus erythematosus, systemic sclerosis, and overall breast cancer. The study also suggests that Sjögren's syndrome, rheumatoid arthritis, and idiopathic inflammatory myopathy might reduce the risk of developing HER + breast cancer. Specifically, Sjögren's syndrome (OR = 0.90, 95% CI [0.83–0.98], $p = 0.02$), rheumatoid arthritis (OR = 0.94, 95% CI [0.91–0.98], $p = 0.006$), and idiopathic inflammatory myopathy (OR = 0.96, 95% CI [0.93–0.99], $p = 0.036$). Additionally, systemic lupus erythematosus was found to lower the risk of HER- breast cancer (OR = 0.95, 95% CI [0.91–0.99], $p = 0.046$). The study did not establish a causal relationship between these five autoimmune diseases and ER + or ER- breast cancer.

Conclusion This study found that autoimmune diseases may act as protective factors against breast cancer risk.

Keywords Autoimmune diseases · Breast cancer · Mendelian randomization · Causality · European population

Hengheng Zhang, Guoshuang Shen, Ping Yang have contributed equally (Co-first authors).

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1 Introduction

Breast cancer ranks as one of the most common malignant tumors in women, exhibiting the highest incidence and mortality rates among female cancers [1]. Current data show about 2.26 million new cases of breast cancer diagnosed globally each year [1, 2]. Breast cancer can be categorized into four subtypes based on hormone receptor (estrogen receptor, progesterone receptor) and human epidermal growth factor receptor 2 (HER2) status: HR + /HER2-, HR-/HER2-, HR + /HER2 + , and HR-/HER2 + . These subtypes are clinically important as receptor expression directly impacts treatment strategies [3]. Additionally, breast cancer is a highly heterogeneous disease. The molecular characteristics of breast cancer subtypes do not appear to be fixed but rather represent a dynamic entity that can change during tumor progression and metastasis. This presents a challenge for clinicians. Further research into the etiology of breast cancer and its subtypes will provide effective management strategies for disease prevention and treatment [4–6]. This presents a challenge for clinicians. Further research into the etiology of breast cancer and its subtypes will provide effective management strategies for disease prevention and treatment [7]. Studies have identified a clear link between diet, alcohol intake, and the development of breast cancer. Furthermore, there is a proposed connection between chronic inflammation and the progression of breast cancer [8–10].

Autoimmune diseases (ADs) are the most common chronic inflammatory conditions [11]. ADs occur when the immune system mistakenly attacks healthy cells, tissues, or organs, causing inflammatory damage [12]. As research delves into the molecular aspects of diseases, increasing attention is being paid to the relationship between autoimmune diseases and malignant tumors [13]. Nonetheless, the association between autoimmune diseases and breast cancer remains controversial. Some studies suggest that autoimmune diseases may increase the risk of breast cancer, while others indicate a possible reduction in this risk. For example, research by S. Bernatsky indicates a decreased risk of breast cancer among patients with SLE [14]. Similarly, Warren David Raymond's findings align with this perspective, showing reduced odds of colorectal, breast, and skin cancers but higher rates of hematologic malignancies in SLE patients [15]. Meanwhile, Wenjie Li et al.'s research reports no causal relationship between SLE and overall breast cancer, ER + breast cancer, or ER- breast cancer in European cohorts, with a lower risk of breast cancer in East Asian SLE patients [16].

To better understand the relationship between autoimmune diseases and breast cancer, this study employed Mendelian randomization (MR) to investigate potential genetic correlations. MR is a causal inference method that uses genetic variations to study causal relationships, helping to reduce the influence of confounding factors [17]. Additionally, MR can lessen the chance of reverse causation since genetic variations are generally not affected by disease onset or progression [18]. This study considered five common autoimmune diseases as potential exposures and evaluated breast cancer and its various subtypes as outcome variables.

2 Methods

2.1 Study design

This study conducted two-sample Mendelian randomization (MR) analyses using summarized genetic data and IEU OpenGWAS database to evaluate the potential causal relationship between autoimmune diseases (ADs) and breast cancer risk. The instrumental variables (IVs) in this analysis adhered to three criteria: First, IVs had a strong association with ADs. Second, IVs were independent of potential confounders between ADs and cancer. Third, IVs influenced cancer risk solely through ADs without interference from other factors. Figure 1 illustrates this process.

2.2 GWAS data source for autoimmune diseases (ADs)

The study examined five common autoimmune diseases: Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and idiopathic inflammatory myopathy. Genetic data for these diseases were obtained from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/). Instrumental variables were selected based on a genome-wide significance threshold of $p < 5 \times 10^{-8}$, with an LD threshold of (LD $r^2 < 0.001$, kb = 10,000) to ensure effective linkage disequilibrium [19]. For idiopathic inflammatory myopathy and systemic sclerosis, a significance level of $p < 1 \times 10^{-6}$ was used, with an LD $r^2 < 0.01$ criterion. These standards are consistent with previous studies [20]. To reduce bias from weak instrumental variables, the study calculated R^2 to determine the proportion of phenotypic variance each instrumental

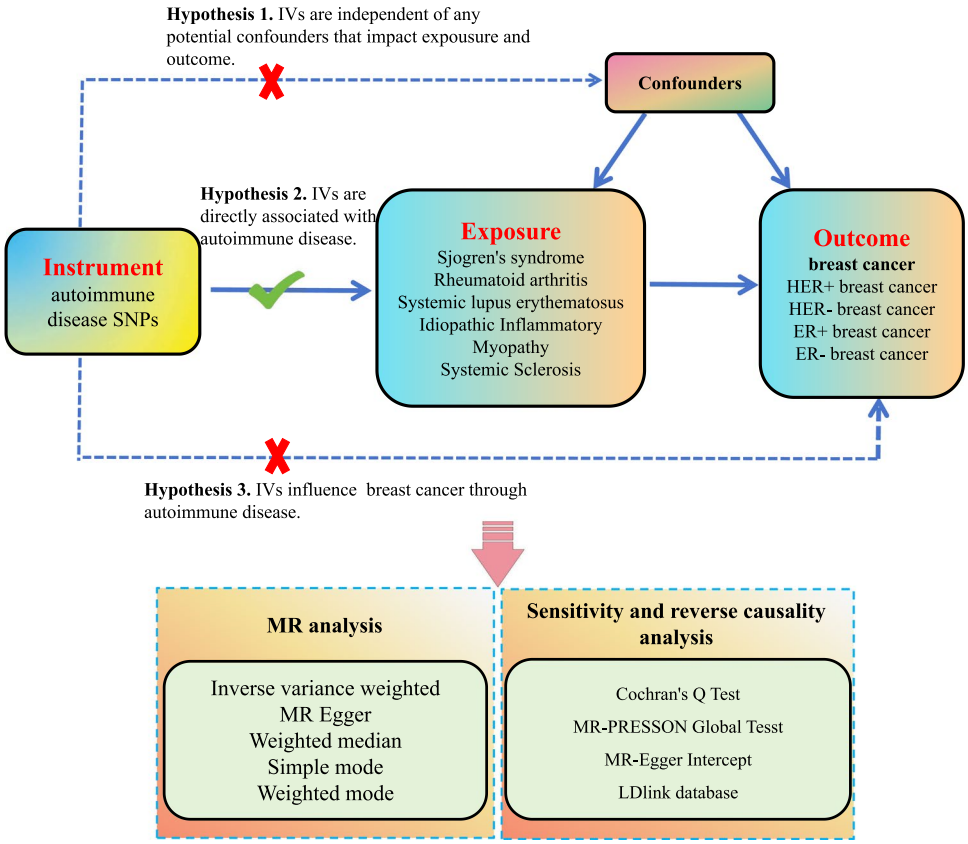

Fig. 1 Flow diagram for study

variable explained. The R^2 formula: $R^2 = [2 \times EAF \times (1\text{-}EAF) \times (\beta)\text{^}2]/[(2 \times EAF \times (1\text{-}EAF) \times (\beta)\text{^}2) + (2 \times EAF \times (1\text{-}EAF) \times N \times se\ (\beta)\text{^}2)]$, where EAF is the effect allele frequency, β the effect size, N the sample size, and se(β) the standard error of the genetic effect [18]. F-statistics were then computed to assess the strength of each instrumental variable, using the formula: $F = [r^2 \times (N\text{-}k\text{-}1)]/[(1\text{-}R^2) \times k]$, where k is the number of instrumental variables [21]. SNPs with an F-value < 10 were deemed weak and excluded from further analysis. For comprehensive details on the genetic instruments selected for each autoimmune disease, see Table 1.

2.3 GWAS data source for breast cancer

For breast cancer data, this study used statistical information on European populations from the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/) and previous studies. Data were mainly derived from the Breast Cancer Association Consortium (BCAC) GWAS, which included 228,951 European women, 122,977 of whom had breast cancer and 105,974 were controls [22]. Furthermore, GWAS data from Saori Sakaue's study, involving 17,389 breast cancer patients and 240,341 controls, were also incorporated [23]. Detailed information about the GWAS data for breast cancer is presented in Table 2.

Table 1 Information on the dataset for breast cancer

GWAS ID	Trait	Year	Consortium	N. cases	N. controls	Sample size	Number of SNPs
ebi-a-GCST90018799	Breast cancer	2021	NA	17,389	240,341	257,730	24,133,589
finn-b-C3_BREAST_HERPLUS	HER + breast cancer	2021	NA	4,263	119,039	NA	16,379,780
finn-b-C3_BREAST_HERNEG	HER- breast cancer	2021	NA	3,092	115,947	NA	16,379,675
ieu-a-1127	ER + breast cancer	2017	BCAC	69,501	105,974	175,475	10,680,257
ieu-a-1136	ER- breast cancer	2017	BCAC	7,333	42,892	50,225	10,680,257

BCAC Breast Cancer Association Consortium, *NA* not available

2.4 Statistical analysis

The statistical analysis in this research focused on determining the causal relationship between ADs and breast cancer, and we performed MR analyses using inverse variance weighting (IVW), weighted median, simple modal, weighted modal, and MR Egger methods. IVW is the primary MR analysis method, which includes the MR effects of individual snp to derive an overall weighted effect [24]. We used the other four methods as complementary methods to test for possible violations of the MR second and third hypotheses. When the Egger-intercept of linear regression approaches 0, there is no directional pleiotropy in IVs and the exclusion hypothesis can be considered valid [25]. The hypothesis can be considered valid. The analysis by the above method can make our results more robust.

We used the MR-PRESSO method to detect and remove outliers and then generated inverse variance-weighted estimates [26]. After removing the outliers, we calculated the inverse variance-weighted estimates again and used the *P*-value of the MR-PRESSO distortion test to assess whether the difference between the estimates before and after removal was significant. We then performed a sensitivity analysis on the remaining SNPs [27].

We searched the LDlink database (https://ldlink.nih.gov/?tab=home) for potentially causal SNPs to verify whether the instrumental variables (IVs) met the independence assumption [28]. The results of the search showed that seven SNPs were confounders, so we removed them when performing the MR analysis (Supplementary Table 1). In addition, we used Cochrane's Q-test and MR multivariate residual sums to assess heterogeneity, thus increasing the reliability of our findings. egger_intercept of *P*_value and MR-egger intercept derived *P*_value greater than 0.05 did not heterogeneity existed [29]. Leave-One-Out (LOO) analysis validated the MR estimates' robustness and identified any SNP-driven associations.

Statistical analyses were conducted using R software version 4.3.1, with TwoSampleMR and MR-PRESSO packages. To ensure conclusion reliability, the study applied False Discovery Rate (FDR) correction, using q-values to manage the FDR. The FDR-corrected threshold was set at 0.05, allowing for up to 5% of positive findings to be false positives.

3 Results

3.1 Association between autoimmune diseases and overall breast cancer risk

The study conducted a two-sample MR analysis using European population-based breast cancer GWAS data from Saori Sakaue's study to explore the link between autoimmune diseases and overall breast cancer risk. According to Fig. 2, results from the Inverse Variance Weighted (IVW) method indicated a significant reduction in overall breast cancer risk for patients with Sjögren's syndrome(OR 0.96, 95% CI [0.93–0.99], $p = 0.011$) and idiopathic inflammatory myopathy (OR 0.98, 95% CI [0.97–0.99], $p = 0.035$).Additionally, rheumatoid arthritis was found to have a correlated risk of breast cancer (OR 0.98, 95% CI [0.96–1.00], $p = 0.050$). The findings remained consistent after applying the FDR correction. The MR-Egger and Weighted Median method estimates aligned with the IVW results.

We analyzed exposure factors with breast cancer one by one. Two SNPs, rs3129962, rs3132487, were found to have palindromic sequences when analyzing desiccation syndrome with breast cancer, and we deleted them. No SNPs with horizontal pleiotropy were found when MR-PRESSO test was performed. rs3129767, rs9272305, two SNPs with palindromic sequences were found when analyzing idiopathic myositis myopathy with breast cancer, and we deleted them but did not find the presence of SNPs with horizontal pleiotropy. Analyzing the relationship between rheumatoid arthritis and overall breast cancer, we identified three SNPs, rs1858037, rs34536443, and rs7278257, contained palindromic

Table 2 Information on the datasets for exposures

GWAS ID	Trait	Year	Consortium	N. cases	N. controls	Sample size	Number of SNPs
ebi-a-GCST90018920	Sjogren's syndrome	2021	NA	1,296	482,717	484,013	24,197,329
ebi-a-GCST90013534	Rheumatoid arthritis	2020	NA	14,361	43,923	58,284	13,108,512
ebi-a-GCST90011866	Systemic lupus erythematosus	2021	NA	4,222	8,431	12,653	5,691,661
finn-b-M13_POLYMYO	Idiopathic Inflammatory Myopathy	2021	NA	119	213,145	NA	16,380,450
ebi-a-GCST003566	Systemic Sclerosis	2016	NA	4888	10,395	15,283	7,910,365

NA not available

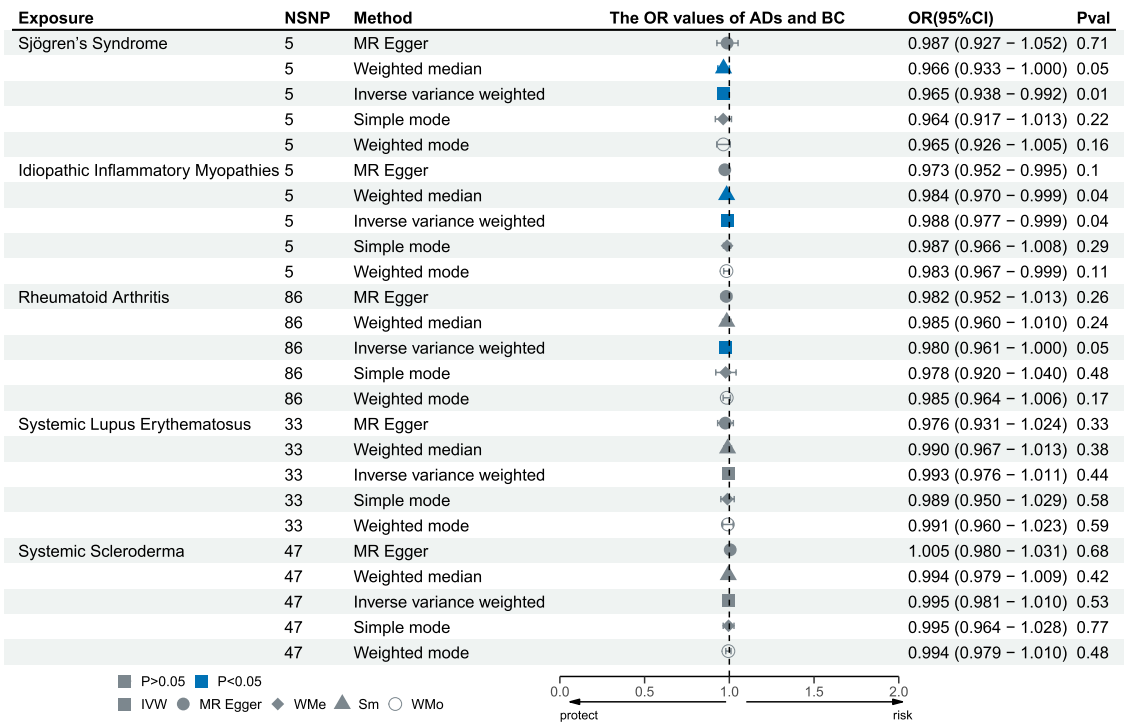

Fig. 2 Forest plot of OR values between five autoimmune diseases and overall breast cancer

sequences and therefore decided to remove them. In addition, when performing the MR-PRESSO test, we identified two SNPs, rs1950897 and rs3025669, as having horizontal pleiotropy, and therefore excluded them as well. Finally, the data after removing the SNPs were analyzed to obtain the above results.

Figures 3, 4 and 5 include a scatter plot illustrating the relationship between autoimmune diseases and overall breast cancer, as well as a leave-one-out method analysis plot. The information on heterogeneity and MR-PRESSO test for autoimmune diseases and overall breast cancer in Table 3. We provide SNP data for the analysis of exposure factors with breast cancer in Supplementary Tables 2–6.

3.2 Autoimmune diseases and HER- and HER + breast cancer risk

Research indicates a strong link between human epidermal growth factor receptor (HER) expression status in breast cancer and patient prognosis. Utilizing data from the Breast Cancer Association Consortium (BCAC) GWAS, this study explored the potential causal relationship between autoimmune diseases and HER- and HER + breast cancer. According to Fig. 6, analysis via the Inverse Variance Weighted (IVW) method suggests that Sjögren's syndrome, rheumatoid arthritis, and idiopathic inflammatory myopathy might reduce the risk of developing HER + breast cancer. Specifically, Sjögren's syndrome showed an odds ratio (OR) of 0.90(95% CI [0.83–0.98], $p = 0.02$), indicating a significant reduction in risk. Rheumatoid arthritis had an OR of 0.94 (95% CI [0.91–0.98], $p = 0.006$), suggesting a lower likelihood of HER + breast cancer in individuals with this condition. Idiopathic inflammatory myopathy was associated with a reduced risk (OR 0.96, 95% CI [0.93–0.99], $p = 0.036$). Additionally, systemic lupus erythematosus was linked to a slightly decreased risk of HER- breast cancer (OR 0.95, 95% CI [0.91–0.99], $p = 0.046$). After applying False Discovery Rate (FDR) corrections, the results indicated significant causal relationships between rheumatoid arthritis, idiopathic inflammatory myopathy, and HER + breast cancer, but not between Sjögren's syndrome and HER + breast cancer. Also, a significant causal link was found between systemic lupus erythematosus and a reduced risk of HER- breast cancer.

When analyzing exposure factors with HER + breast cancer, a palindrome sequence was found in the SNP (rs34536443) analyzed for rheumatoid arthritis with HER + breast cancer, which was removed. Also when we analyzed dry syndrome and idiopathic inflammatory myopathy with HER + breast cancer, no palindromic sequences were found. There was no horizontal pleiotropy when MR-presso test was performed (P_value > 0.05).

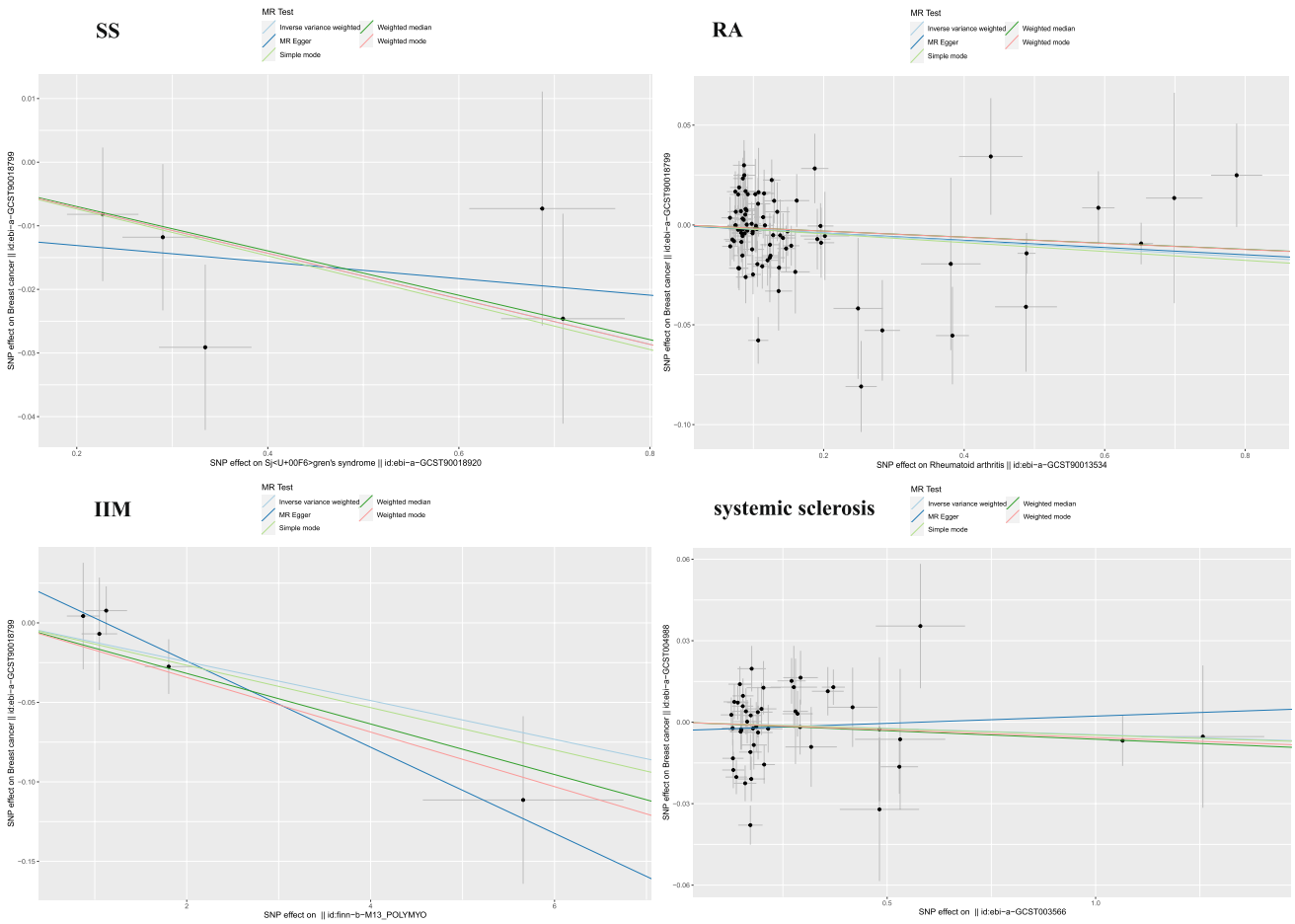

Fig. 3 Scatter plot of association between five autoimmune diseases and overall breast cancer

The association between systemic lupus erythematosus (SLE) and HER-breast cancer was investigated. We found that rs11185603 was associated with Fasting glucose, and rs5749502 with Red blood cell traits, while rs4844538 was associated with type 2 diabetes. These SNPs may have confounding effects and were therefore excluded from the analysis. In addition, we found the presence of palindromic sequences for rs11059928 and rs11185603, which were also excluded for analytical accuracy considerations. Horizontal pleiotropy was not present at MR-presso test (P_value = 0.763).

Leave-One-Out analysis revealed that no instrumental variables significantly influenced the causal relationship between autoimmune diseases and HER + and HER- breast cancer. Supplementary Tables 7–10, we also provide SNP data that provide an analysis of exposure factors with HER + /HER- breast cancer.

3.3 Autoimmune diseases and ER- and ER + breast cancer risk

Other studies have highlighted differences in prognosis among breast cancer patients based on estrogen receptor (ER) expression status. This study reanalyzed data from the Breast Cancer Association Consortium (BCAC) GWAS dataset for ER + and ER- breast cancer. However, the analysis using the Inverse Variance Weighted (IVW) method found no causal relationship between the five autoimmune diseases and ER + or ER- breast cancer in Fig. 6.

Supplementary Figs. 1 to 2 (eFig.1–2) include a scatter plot illustrating the relationship between autoimmune diseases and breast cancer subtype, as well as a leave-one-out method analysis plot. The information on heterogeneity and MR-PRESSO test for autoimmune diseases and breast cancer subtype in Supplementary Table 11 to 14 (eTable.11–14).

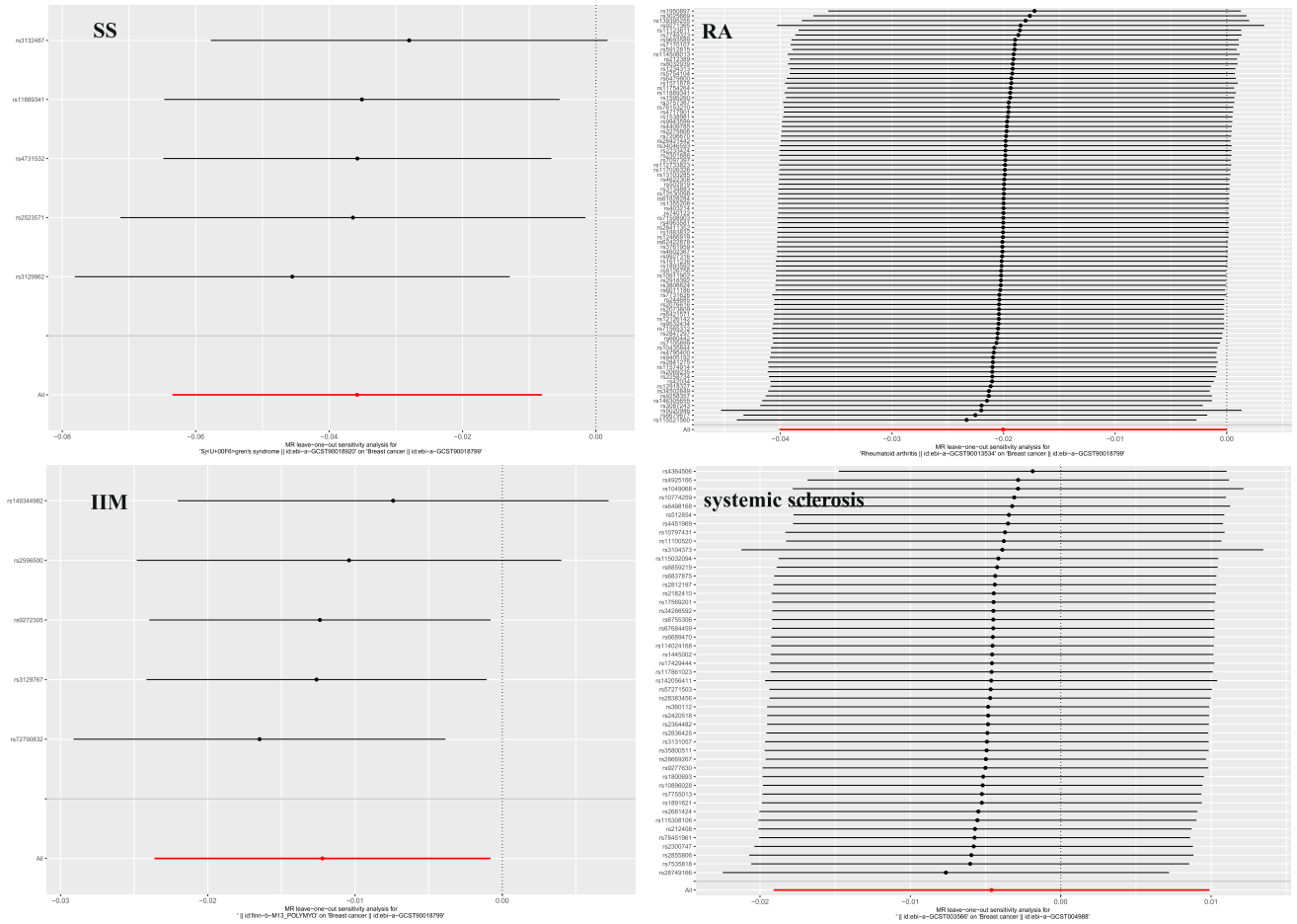

Fig. 4 A forest plot illustrating 'leave-one-out' sensitivity analysis, showcasing individual SNP influences on results

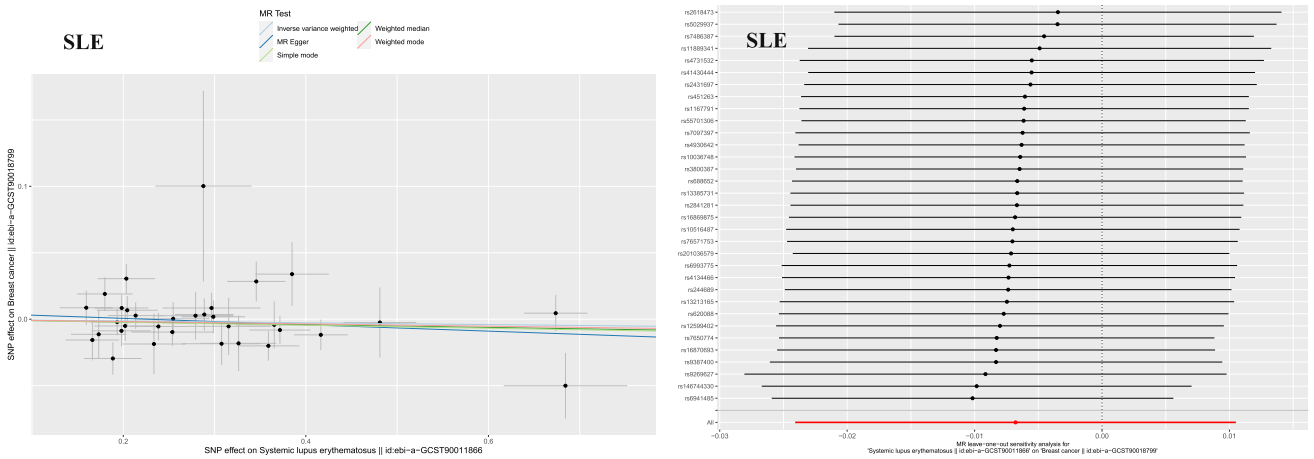

Fig. 5 Scatter plot and Leave-one-out analysis of the causal relationship between systemic lupus erythematosus and overall breast cancer

4 Discussion

Breast cancer is a major health challenge for women worldwide, and its etiology is complex and diverse [2]. Currently, clinical therapeutic strategies are mainly based on the classification of estrogen receptor (ER) and human epidermal

Table 3 The information on heterogeneity and MR-PRESSO test for autoimmune diseases and overall breast cancer

Exposure	Outcome	Cochran's Q derived p value		MRPRESSO global test derived p value	Egger_intercept	MR-egger intercept derived p value
		MR Egger	Inverse variance weighted			
Sjogren's syndrome	Overall breast cancer	0.568089161	0.620239177	0.673	0.568089161	0.620239177
Rheumatoid arthritis	Overall breast cancer	0.0001845	0.00023908	< 0.001	− 0.000412295	0.8758976
Systemic lupus erythematosus	Overall breast cancer	0.136516792	0.145738383	0.124	0.005411465	0.4489015
Polymyositis	Overall breast cancer	0.885359	0.568738925	0.576	0.03014041	0.2276465
Multiple sclerosis	Overall breast cancer	7.33307E-07	6.56256E-07	0.796	0.00127764	0.7860478

NA not available

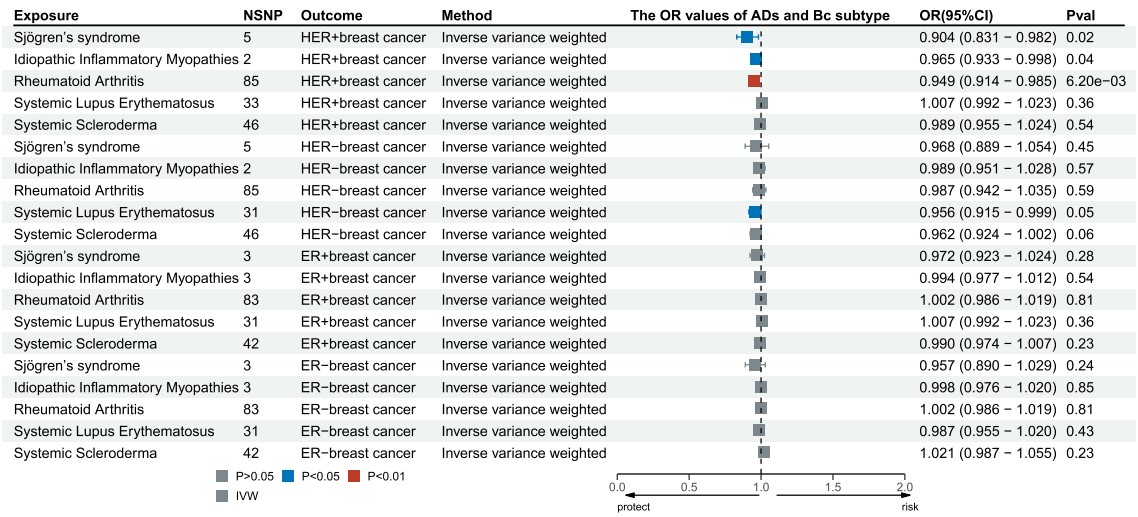

Fig. 6 Forest plot of OR values between five autoimmune diseases and breast cancer subtype

growth factor receptor 2 (HER2) status [6]. The classification of breast cancer subtypes is closely related to the expression of ER and HER2 receptors, and it is important to explore the pathogenic factors of breast cancer subtypes for clinical prevention and treatment. Autoimmune diseases such as dry syndrome, rheumatoid arthritis and systemic lupus erythematosus have a high prevalence in women, while breast cancer is the most common malignant tumor in women [30, 31]. To investigate whether there is a correlation between the two, we conducted the present study.

The findings indicate a reduced risk of breast cancer in patients with Sjögren's syndrome, idiopathic inflammatory myopathy, and rheumatoid arthritis, showing odds ratios(OR) of 0.96 (95% CI [0.93–0.99], $p = 0.011$), 0.98 (95% CI [0.97–0.99], $p = 0.035$), and 0.98 (95% CI [0.96–1.00], $p = 0.050$), respectively. The observed protective effect of Sjögren's syndrome on breast cancer risk corroborates Jian Deng's research findings [32].

Moreover, the study delved into the association between autoimmune diseases and breast cancer across different HER and ER expression states. It revealed that systemic lupus erythematosus significantly reduces the risk of HER- breast cancer (OR = 0.95, 95% CI [0.91–0.99], $p = 0.046$). Idiopathic inflammatory myopathy significantly lowered the risk of HER + breast cancer (OR = 0.96, 95% CI [0.93–0.99], $p = 0.036$). Sjögren's syndrome and rheumatoid arthritis also appeared to act as protective factors against HER + breast cancer, with statistically significant differences observed (Sjögren's syndrome, OR = 0.90, 95% CI [0.83–0.98], $p = 0.02$; Rheumatoid arthritis, OR = 0.94, 95% CI [0.91–0.98], $p = 0.006$).

Notably, the analysis on the correlation between systemic sclerosis and HER- breast cancer yielded a p-value close to 0.05 ($p = 0.06$), suggesting a non-significant statistical difference. However, this trend might still indicate a protective effect in patients with HER- breast cancer. The relationship between systemic sclerosis and breast cancer warrants further exploration in future studies as the database expands and more data become available.

According to the results of this study, autoimmune diseases may reduce the risk of developing breast cancer. We believe that the specific mechanisms are as follows. Firstly, the "immunosurveillance" hypothesis proposes that autoimmune diseases are due to an increase in immune tone, which improves immunosurveillance [33].

Immune surveillance refers to the immune system's process of recognizing and eliminating abnormal cells, such as cancer cells, which includes the phases of elimination, equilibrium, and escape [34]. Research indicates that tumors can be recognized by the immune system and controlled or prevented through immune surveillance processes [35]. The specificity of tumor immune responses lies in the recognition of tumor antigens. The immune system identifies and clears nascent tumors by recognizing tumor-specific neoantigens expressed on tumor cells, similar to allograft rejection, thus maintaining tissue homeostasis in complex multicellular organisms [34, 36]. In clinical settings, the restoration of immune surveillance is considered a measure of the effectiveness of chemotherapy, targeted therapy, and radiotherapy in breast cancer patients [37].

Supporting this, studies have shown that individuals with broad autoantibody specificity can decrease their risk of breast cancer by 60% [38]. Additionally, research has reported a decreased risk of breast cancer in patients with systemic lupus erythematosus (SLE), which may be associated with anti-DNA antibodies. These antibodies exert direct anti-cancer effects on cells with DNA repair deficiencies [38]. This aligns with findings that systemic lupus erythematosus significantly lowers breast cancer risk, which is consistent with the results of this study [39]. Further mechanistic studies have revealed

that a cell-penetrating lupus autoantibody (3E10) is synthetically lethal to BRCA2-deficient human cancer cells and can enhance the effectiveness of low doses of doxorubicin, thereby improving chemotherapy outcomes [40]. Additionally, James Gardner Thorpe's study reported that lupus-associated anti-ribosome P autoantibodies could directly induce apoptosis in cancer cells [41]. From the treatment perspective of autoimmune diseases, certain studies have noted that using non-steroidal anti-inflammatory drugs or aspirin can boost tumor immune surveillance and lower cancer risk [42, 43]. On the contrary, glucocorticoid use may disrupt immune surveillance and elevate cancer risk [44].

Previous studies on Sjögren's syndrome (SS) have consistently reported a decreased incidence of breast cancer, which aligns with our findings. Hemminki et al. compared 1516 Swedish SS patients with the general population, noting a standardized incidence ratio (SIR) for breast cancer of 0.46 (95% confidence interval: 0.26–0.75) [45]. Several factors may explain the lower risk of breast cancer in SS patients. SS primarily affects exocrine glands, especially the lacrimal and salivary glands, which share anatomical, histological, and immunological similarities with the breast. SS patients display different immune patterns in breast-associated mucosal tissues, with higher proportions of CD4 + T cells. This suggests a distinct immune response to local antigens, such as tumor cells, potentially establishing a more robust mucosal immune system dynamic that may reduce breast cancer incidence [45, 46]. Additionally, studies have identified lower estrogen levels in SS patients, which significantly contribute to reducing breast cancer incidence [47]. Estrogen is a known risk factor for breast cancer development, so lower estrogen levels may provide protective effects against the disease.

Our findings suggest that rheumatoid arthritis may reduce the risk of developing HER + breast cancer. It has been shown that rheumatoid arthritis (RA) may reduce breast cancer risk, which is consistent with our findings [48]. The mechanisms may include the following: Firstly, the peak incidence of female RA often occurs during menopause, characterized by decreased hormone secretion, including estrogen. Lower estrogen levels are known to reduce breast cancer risk. Furthermore, studies have demonstrated significant differences in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels between RA patients and healthy individuals. These hormones are crucial in regulating reproductive function and sex hormone levels, and their fluctuations may further influence breast cancer risk [49]. In cohorts of patients with idiopathic inflammatory myopathies, reports indicate that individuals with breast and ovarian cancers often carry anti-synthetase antibodies, which possess anticancer properties [50, 51]. These observations suggest a complex interplay between autoimmunity and cancer incidence, necessitating further exploration through in vivo and in vitro studies. Overall, these findings highlight the significant role of the immune system and autoimmune diseases in regulating breast cancer risk.

However, to date, no significant link between ER + and ER- breast cancer and autoimmune diseases has been established in genome-wide association studies (GWAS) using European population samples. Future updates to these databases may provide opportunities for more in-depth exploration of this relationship. This study has several strengths: Primarily, it is the first to utilize Mendelian Randomization (MR) to investigate potential causality between autoimmune diseases and breast cancers with varying HER and ER states. MR methodology significantly minimizes the effects of confounding factors and reverse causation. Compared to traditional observational studies, the analysis of single nucleotide polymorphisms (SNPs) reduces the impact of multiple potential confounders, offering more robust research evidence.

Nonetheless, there are limitations to this study. First, the sample predominantly consisted of the European population. Whether these findings are applicable to other regions and populations remains uncertain, necessitating further validation in diverse populations and regions. Secondly, the potential for pleiotropy is an issue that cannot be entirely ruled out in MR studies and requires additional investigation and discussion. Furthermore, due to variations in data collection times, disease progression stages, and treatment phases in GWAS data, our study has some limitations. These factors may affect the research outcomes to a certain extent, but we can still derive valuable SNP data analysis results from them. Further, our study is based on genome-wide association study (GWAS) data, revealing potential genetic factors in relation to disease. However, these findings are limited to statistical associations and do not provide direct mechanistic causality. Therefore, our findings need to be validated by in vivo experiments in future studies to further reveal the underlying biological mechanisms.

5 Conclusion

The Mendelian Randomization (MR) analysis in this study indicates that autoimmune diseases may act as protective factors against breast cancer risk. Based on studies in European populations, there is a potential genetic correlation between desiccation syndrome, rheumatoid arthritis, idiopathic inflammatory myopathies and HER + breast cancer. In addition, we observed a potential genetic correlation between systemic lupus erythematosus and HER-breast cancer as well.

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Author contributions H.h.Z and Y.Z orchestrated the conception and design of the study. Data collection and analysis were spearheaded by C.r.Z. R.h.w and J.m.L The initial manuscript was drafted by H.h.Z and M.j.Wu, M.t.D, H.x.L, P.Y and G.h.S significantly contributed to data analysis and interpretation. F.x.Z, Z.t.L, Y.Z and J.d.Z meticulously revised the manuscript. H.h.Z Drawing.Every author actively participated in writing the article and endorsed the final version submitted for publication. Furthermore, all authors have thoroughly reviewed and approved the published manuscript.

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Availability of data and materials The data used in this study was obtained from public databases and previous studies. Data sources and handing of these data were described in the Materials and Methods. Further information is available from the corresponding author upon request. All data involved in this study are available in the public database. For further information, please contact the corresponding authors. Data is provided in a manuscript or supplementary information file where our data is available.

Declarations

Ethics approval and consent to participate Not needed.

Informed consent The consent of the patients was not required because the informed consent had already been given in the original study.

Competing interests On behalf of all authors, the corresponding author states that there is no conflict of interest.

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