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ORIGINAL RESEARCH

Seipin as a Putative Protective Factor for Breast Cancer: Evidence from Mendelian Randomization Analysis

Junfeng Zeng[1], Xinxu Wang[2], Luxuan Fan[1], Tao Bai[3], Hongyan Jia[4], Jing Yang[1]

[1]School of Basic Medical Sciences, Shanxi Medical University, Taiyuan, Shanxi, 030001, People's Republic of China; [2]Department of First Clinical Medicine, Shanxi Medical University, Taiyuan, Shanxi, 030001, People's Republic of China; [3]Department of Pathology, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, 030001, People's Republic of China; [4]Department of Breast Surgery, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, 030001, People's Republic of China

Correspondence: Jing Yang, School of Basic Medical Sciences, Shanxi Medical University, 85 Jiefang South Road, Taiyuan, Shanxi, 030001, People's Republic of China, Email jyang@sxmu.edu.cn; Hongyan Jia, Department of Breast Surgery, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, 030001, People's Republic of China, Email swallow_jhy@163.com

Objective: To investigate the causal association between Seipin and breast cancer risk using the Mendelian randomization (MR) approach.

Methods: Genome-wide association study (GWAS) data for Seipin and breast cancer were analyzed, and genetic variants associated with Seipin were selected as instrumental variables (IVs). Inverse variance weighting (IVW) was used as the primary analytical method, supplemented by MR-Egger, weighted median, simple mode, and weighted mode MR analyses to evaluate the causal relationship between Seipin and breast cancer risk. Furthermore, immunohistochemistry was performed to detect Seipin expression in pathological specimens from patients with breast cancer and those with mammary hyperplasia, and the correlation between Seipin expression and clinicopathological characteristics was analyzed.

Results: MR analyses indicated that Seipin was inversely associated with breast cancer risk (IVW: OR = 0.89, 95% CI: 0.83–0.96, $P < 0.05$). Consistent with this, immunohistochemical results showed lower Seipin expression in breast cancer tissues than in mammary hyperplasia tissues, and its low expression was correlated with adverse clinicopathological features. Further independent validation using the TCGA-BRCA cohort recapitulated reduced BSCL2 expression in tumor versus adjacent normal tissues ($P = 9.58 \times 10^{-3}$).

Conclusion: MR combined with immunohistochemistry and independent public database validation suggests that Seipin may serve as a potential protective factor closely related to the occurrence and progression of breast cancer. Further functional studies are needed to elucidate the underlying mechanisms.

Keywords: mendelian randomization, seipin, breast cancer

Introduction

Cancer represents one of the major global public health challenges at present. Breast cancer is among the most common malignancies in women, with its incidence and mortality rates increasing year by year.[1] Studies have reported that newly diagnosed breast cancer cases accounted for 31% of all female malignant tumors in 2023.[2] Although multiple therapeutic approaches are available for breast cancer, including surgery, radiotherapy, chemotherapy, and endocrine therapy, the prognosis remains unsatisfactory in some patients.[3] Therefore, exploring the pathogenesis, influencing factors, and potential therapeutic targets of breast cancer has become an urgent issue to be addressed. Clinical studies have revealed that breast cancer is characterized by substantial heterogeneity, and tumor metastasis, gene phenotypes, and molecular expression levels vary considerably across individual patients, leading to diverse prognostic outcomes.[4,5] Consequently, it is particularly crucial to identify potential therapeutic targets and screening indicators for breast cancer at the molecular and genetic levels.[6]

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Seipin is an endoplasmic reticulum (ER) transmembrane protein encoded by the BSCL2 gene, which was initially identified in association with congenital generalized lipodystrophy syndrome.[7,8] Recent studies have demonstrated that Seipin plays vital roles in multiple physiological processes, including lipid metabolism, adipocyte differentiation, and maintenance of energy homeostasis.[9,10] Accumulating evidence indicates that abnormal lipid metabolism serves a key function in the occurrence and progression of breast cancer.[11] As a critical regulator of lipid metabolism, Seipin may exert important effects on breast cancer development; however, studies investigating the relationship between Seipin and breast cancer remain limited. Notably, BSCL2 is located on chromosome 11q12.3, a region implicated in cancer susceptibility, and emerging evidence suggests that metabolic regulatory genes such as ADAR1 play important roles in breast cancer biology,[12,13] highlighting the biological significance of exploring metabolic mediators including Seipin in this malignancy. Additionally, immune signaling pathways, including the JAK/STAT and PI3K-AKT-mTOR axes, have been identified as important targets in cancer immunotherapy,[14] providing a broader context for understanding how metabolic regulators such as Seipin may interact with the tumor immune microenvironment. These emerging connections provide a rationale for systematically evaluating the causal role of Seipin in breast cancer using genetic epidemiological approaches.

Mendelian randomization (MR) employs single nucleotide polymorphisms (SNPs) associated with exposure risk factors as instrumental variables (IVs) to evaluate the causal relationship between exposures and outcomes.[15] Compared with traditional observational studies, MR can effectively reduce biases caused by confounding factors and reverse causality, yielding more reliable results, and has become an important tool in contemporary epidemiological research.[16] MR has demonstrated distinct advantages in cancer research, highlighting its significant value in breast cancer studies. Previous MR investigations have confirmed causal associations between obesity, sex hormone levels, metabolism-related indicators and breast cancer risk, providing novel targets for disease prevention and intervention.[17] Recently, several large-scale genome-wide association studies (GWAS) have accumulated abundant SNP data on breast cancer susceptibility, further improving the statistical power and reliability of MR analyses.

In the present study, MR analysis was performed to investigate the association between Seipin and breast cancer using the IEU Open GWAS database, combined with immunohistochemical staining of pathological specimens from clinical breast cancer patients to verify the relationship between Seipin and breast cancer risk. The potential role of Seipin in breast cancer was systematically evaluated, providing initial evidence that Seipin may act as a potential protective factor against breast cancer.

Materials and Methods

Study Design

The present investigation employed a two-sample MR strategy to explore the causal links between Seipin, encoded by the BSCL2 gene, and breast cancer. In this context, Seipin was designated as the exposure variable, while breast cancer served as the outcome (Figure 1). To further substantiate the causal relationship between Seipin and breast cancer, immunohistochemical staining was performed on clinical pathological samples obtained from patients diagnosed with breast cancer. Additionally, public datasets were analyzed to validate differences in BSCL2 expression between normal and malignant breast tissues.

Data Source

This study utilized two publicly available datasets. (1) IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/): the exposure dataset for BSCL2 expression (eqtl-a-ENSG00000168000) was derived from the eQTLGen Consortium, comprising 31,684 participants of predominantly European ancestry, with gene expression quantified in whole blood from both sexes; the outcome dataset for breast cancer (ieu-a-1135) was obtained from the Breast Cancer Association Consortium (BCAC), including 9655 cases and 45,494 controls, all of European ancestry and female. Documentation indicated that informed consent was obtained from all participants, and all studies included in the GWAS received approval from a suitable review board. (2) Bulk RNA-seq data from The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA) project were obtained from the NCI Genomic Data Commons Data Portal (https://portal.gdc.cancer.gov). The TCGA-BRCA cohort

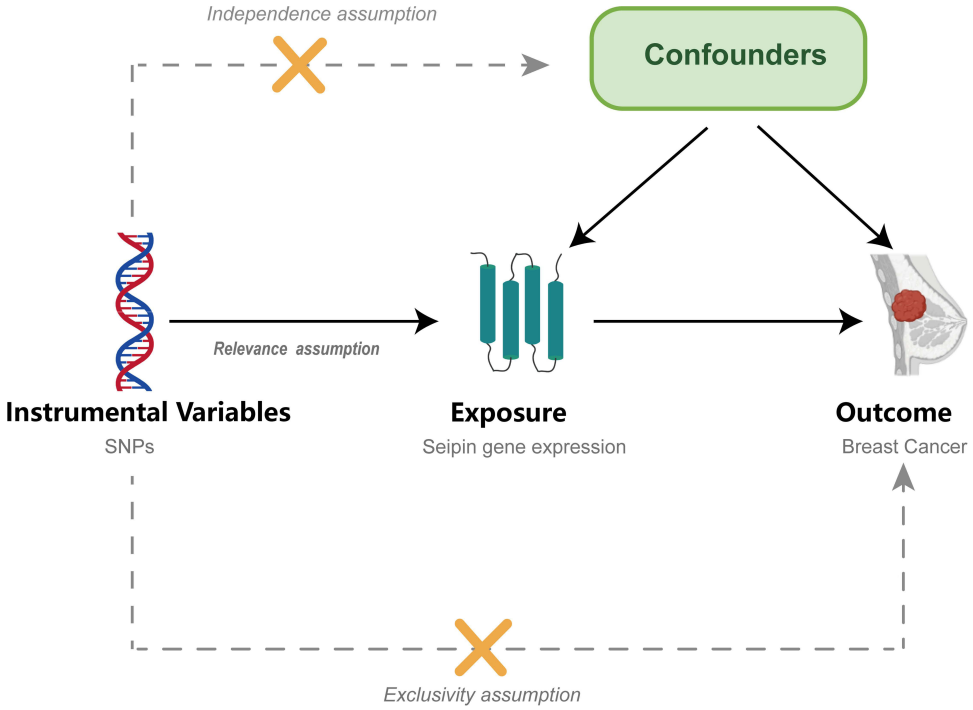

Figure 1 Schematic diagram of the two-sample MR analytical framework. Cross symbol indicates that the assumption is not valid. The solid line represents a correlation, while the dotted line indicates no correlation.

comprises 1111 primary breast tumor samples and 113 adjacent normal tissue samples from female patients of predominantly European ancestry.

MR Analysis

This study adhered to the most recent guidelines for MR analyses, as detailed in the STROBE-MR guidelines, and was based on three essential assumptions: 1. the instrumental variables exhibited a strong correlation with BSCL2; 2. the chosen instrumental variables were not influenced by any potential confounding factors; and 3. the genetic variations did not have an association with breast cancer except through their correlation with BSCL2.

Selection of Instrument Variables

In this research, the choice of instrument variables was informed by relevant cis-MR studies, employing a threshold of $P < 5 \times 10^{-6}$ to initially pinpoint SNP loci that exhibit statistical significance from the GWAS summary data for BSCL2.[18] This relaxed threshold (compared with the genome-wide significance threshold of $P < 5 \times 10^{-8}$) was adopted because only cis-acting SNPs within the BSCL2 locus were considered, reducing the risk of horizontal pleiotropy while ensuring sufficient instrument strength.[19] All selected SNPs satisfied the F-statistic criterion ($F > 10$), confirming strong instrument relevance. Additionally, parameters for linkage disequilibrium were established, with an r^2 value of 0.001 and a region width of 10,000 kb, aimed at minimizing the influence of genetic pleiotropy on the findings.[20] F-statistics were utilized to determine if the chosen instrument variables could be classified as weak instruments, adhering to the standard criterion of $F>10$ ($F=Beta^2/SE^2$), which indicates the absence of bias from weak instruments.[21] Furthermore, the MR-PRESSO test was employed to evaluate potential horizontal pleiotropy, and any influence from pleiotropic effects was addressed by excluding outliers. To enhance the assessment of whether individual SNPs have a strong association with BSCL2 and to reduce potential confounding variables, the secondary phenotype of each SNP was manually reviewed using PhenoScanner.[22]

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MR Analysis Method

In the current study, five distinct analytical approaches were employed to evaluate the causal relationship, including MR-Egger regression (MR-Egger), the IVW method, the Weighted Median method, the simple mode, and the weighted mode. These techniques aimed to confirm the causal association between BSCL2 and breast cancer. The Weighted Median method organizes the effect estimates from various instrumental variables and derives the causal effect estimate through a weighted median calculation. This approach is capable of accommodating situations where as many as half of the instrumental variables are unbiased and is resistant to outliers. The IVW method, a widely adopted strategy in MR analysis and a model averaging technique, calculates a weighted mean of the effect estimates of each genetic variant, taking into account their variances and covariances. It is premised on the notion that genetic variants act as unbiased instrumental variables that share a common causal effect. This method yields a comprehensive estimate of the causal effect. On the other hand, the MR-Egger technique is primarily used to tackle horizontal pleiotropy.[23] It facilitates the estimation of causal effects even when horizontal heterogeneity is present, based on the condition that the genetic variants adhere to the fundamental assumptions of instrumental variables. A critical assumption underlying the MR-Egger approach is the unbiasedness of the pleiotropy factor, implying that there is no correlation between the influence of the genetic variant on the outcome variable and its influence on the exposure variable.[24] Horizontal pleiotropy describes a scenario in which genetic variants affect both exposure and outcome variables through alternative pathways, rather than solely through the anticipated exposure-outcome link. In this study, the primary analytical method employed was the IVW approach, while the additional methods were utilized as supplementary analyses to support the findings of the IVW method.

Sensitivity Analysis

The sensitivity analysis included tests for pleiotropy, an evaluation of heterogeneity, and the leave-one-out method. To evaluate pleiotropy, both MR-Egger and the MR-PRESSO method were utilized.[25] The MR-PRESSO method is particularly effective in identifying outliers and providing a causal estimate after the removal of those outliers, thereby addressing horizontal pleiotropy. Heterogeneity assessment was carried out using Cochran's Q statistic. In instances of heterogeneity, the IVW method was applied for MR analysis. Furthermore, the analysis was reiterated through the leave-one-out validation method to determine whether any individual SNP had an undue effect on the association.[26]

Collection of Clinical Pathological Specimens

Fresh tumor tissue specimens surgically resected from patients with pathologically confirmed breast cancer who were admitted to the Department of Pathology at the First Hospital of Shanxi Medical University over the past five years, along with corresponding specimens of mammary hyperplasia, were collected. Additionally, detailed clinicopathological data of the patients were gathered, including age, pathological type, tumor size, and lymph node metastasis status (Supplementary Table S1).

Immunohistochemistry

Immunohistochemical Staining

Paraffin-embedded tissue sections (4 μm thick) were deparaffinized in xylene and rehydrated through a graded series of ethanol. Antigen retrieval was performed by heating in EDTA buffer (pH 8.0) using a pressure cooker for 3 min. Endogenous peroxidase activity was blocked with 3% H_2O_2, and non-specific binding was blocked with 5% BSA for 30 min at room temperature. The sections were subsequently incubated overnight at 4°C with a primary antibody against SEIPIN (1:200 dilution, Abcam, ab106793), followed by HRP-conjugated secondary antibody (ZSGB-BIO, ZB-2301) for 20 min at 37°C. Immunoreactivity was visualized using a DAB substrate kit (Thermo Scientific, 34002), and sections were counterstained with hematoxylin. After dehydration, slides were mounted with neutral balsam.

Analysis of Immunohistochemical Results

Immunohistochemical staining was quantitatively analyzed using StrataQuest software (TissueGnostics, Vienna, Austria). A standardized image analysis pipeline was implemented to segment nuclear and cytoplasmic compartments.

Median staining intensities within cells and adjacent background regions were subsequently quantified. Following data normalization, a random subset of 30% of the cells was selected for further statistical analysis to ensure both efficiency and representativeness. The cell/background intensity ratio was calculated as follows: (Median cell intensity − Median background intensity) / Median cell intensity. The upper limit of the 95% confidence interval (CI) of the median ratio was established as the threshold for immunopositivity. A cell was defined as immunopositive if its individual ratio exceeded this threshold. Immunopositive cells were further categorized into weak, moderate, and strong staining groups based on tertile distribution of the cell/background intensity ratio across all analyzed cells (0–18, 18–30, and 30–120), with the proportion of cells in each category calculated for each specimen. This data-driven tertile-based approach was chosen to ensure balanced group sizes for statistical comparison and to avoid arbitrary threshold selection. While conventional approaches such as H-score or IRS scoring are widely used, the StrataQuest software-based quantitative image analysis provides continuous intensity measurements that were then categorized by data-driven tertile cutpoints, and the results were independently validated by two pathologists in a double-blind fashion. Discrepancies with a Kappa coefficient < 0.75 were arbitrated by a third senior pathologist.

Statistical Analysis

All data in this study were statistically analyzed using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA). The chi-square test or Fisher's exact test was applied to compare the expression levels of Seipin between breast cancer tissues and mammary hyperplasia specimens. Fisher's exact test was adopted when the theoretical frequency of any cell was less than 5. All tests were two-tailed, and a P-value < 0.05 was considered statistically significant.

TCGA-BRCA Bulk RNA-Seq Validation

To independently validate BSCL2 expression differences between tumor and normal breast tissue, we analyzed bulk RNA-seq data from TCGA-BRCA project. We queried STAR-aligned count files (workflow type: STAR – Counts) under the data category "Transcriptome Profiling" and data type "Gene Expression Quantification", with gene annotation based on GENCODE v36. BSCL2 expression was extracted as unstranded transcripts per million (TPM) from each sample's augmented STAR gene counts file. Samples were classified as primary solid tumor (TCGA barcode sample type "01") or solid tissue normal (barcode sample type "11") based on the TCGA sample type code embedded in the aliquot submitter ID. After quality filtering, 1111 primary tumor samples and 113 adjacent normal tissue samples with valid BSCL2 TPM values were retained for analysis. Differential expression was assessed using the two-sided Mann–Whitney *U*-test and Student's *t*-test, with effect size quantified by Cohen's d and fold change. All statistical analyses were performed in Python (v3.11) using SciPy (v1.14).

Results

MR Analysis Indicated That Seipin Was a Protective Factor for Breast Cancer

Seipin was defined as the exposure and breast cancer as the outcome, with eight SNPs selected as instrumental variables (Supplementary Table S2). We adopted five MR approaches to assess their causal association. In the primary IVW analysis, Seipin exerted a protective effect against breast cancer (OR = 0.89, 95% CI: 0.83–0.96), indicating a significant inverse correlation between its expression and breast cancer risk. The four supplementary MR methods produced consistent estimates: MR-Egger (OR = 0.90, 95% CI: 0.82–1.00), weighted median (OR = 0.91, 95% CI: 0.84–0.99), weighted mode (OR = 0.91, 95% CI: 0.84–1.00) and simple mode (OR = 0.93, 95% CI: 0.79–1.10), corroborating the IVW results (Figure 2). Collectively, all five MR analyses supported a significant inverse association between Seipin expression and breast cancer risk (Figure 3).

Furthermore, MR-Egger intercept test, MR-PRESSO, and Cochran's Q test were used to assess heterogeneity and horizontal pleiotropy. Global tests showed P > 0.05, indicating no significant heterogeneity or horizontal pleiotropy, thus providing robust evidence for the reliability of the results (Supplementary Table S3). Leave-one-out (LOO) sensitivity analysis, in which each SNP was sequentially omitted, revealed no notable changes in the overall causal estimate, further supporting the stability of the MR results (Figure 4).

id.exposure	method	nsnp	OR (95% CI)	pval
eqtl-a-ENSG00000168000	MR Egger	8	0.90 (0.82 to 1.00)	0.085015622
eqtl-a-ENSG00000168000	Weighted median	8	0.91 (0.84 to 0.99)	0.029337949
eqtl-a-ENSG00000168000	Inverse variance weighted	8	0.89 (0.83 to 0.96)	0.002769889
eqtl-a-ENSG00000168000	Simple mode	8	0.93 (0.79 to 1.10)	0.424328685
eqtl-a-ENSG00000168000	Weighted mode	8	0.91 (0.84 to 1.00)	0.091170776

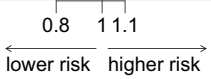

Figure 2 Association of genetically predicted Seipin with breast cancer.

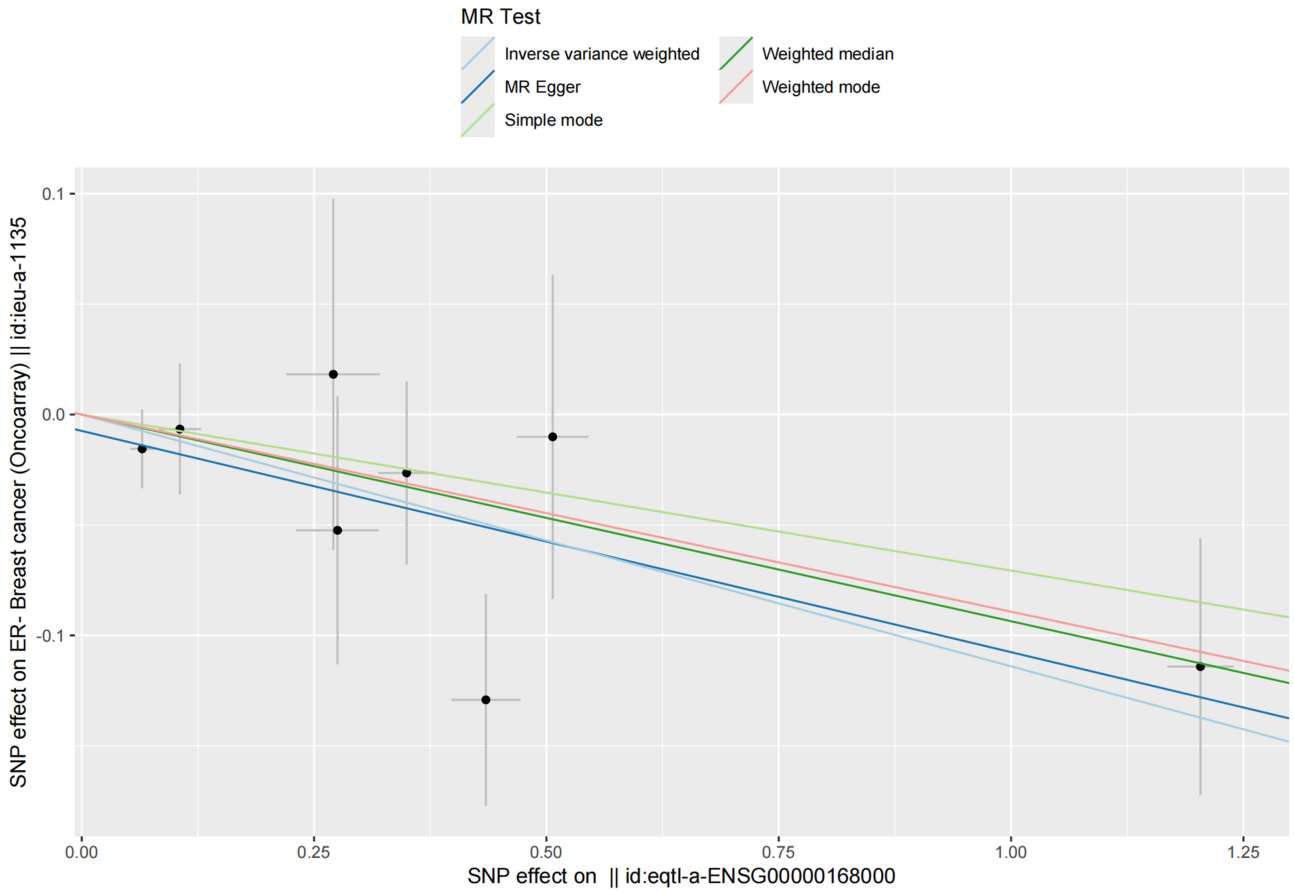

Figure 3 Scatter plots of significant causality of the Seipin and breast cancer.

Immunohistochemical Results Showed Decreased Seipin Expression in Invasive Breast Cancer

The expression level of Seipin in invasive breast cancer and mammary hyperplasia tissues was detected by immunohistochemical staining. The results demonstrated that Seipin expression was significantly lower in invasive breast cancer tissues, while more intense Seipin staining was observed in mammary hyperplasia tissues (Figure 5). Negative controls were performed by omitting the primary antibody (Supplementary Figure S1).

Staining intensity analysis revealed a statistically significant difference in the weak (0–18) expression category between the mammary hyperplasia group and the breast cancer group (Figure 6A and Supplementary Table S4), while no statistically significant difference was observed in the moderate (18–30) staining category (Figure 6B). In addition, the (30–120) strongly positive staining category was significantly more frequent in the mammary hyperplasia group than in the breast cancer group, showing a highly statistically significant difference (Figure 6C). Overall, Seipin displayed sparse

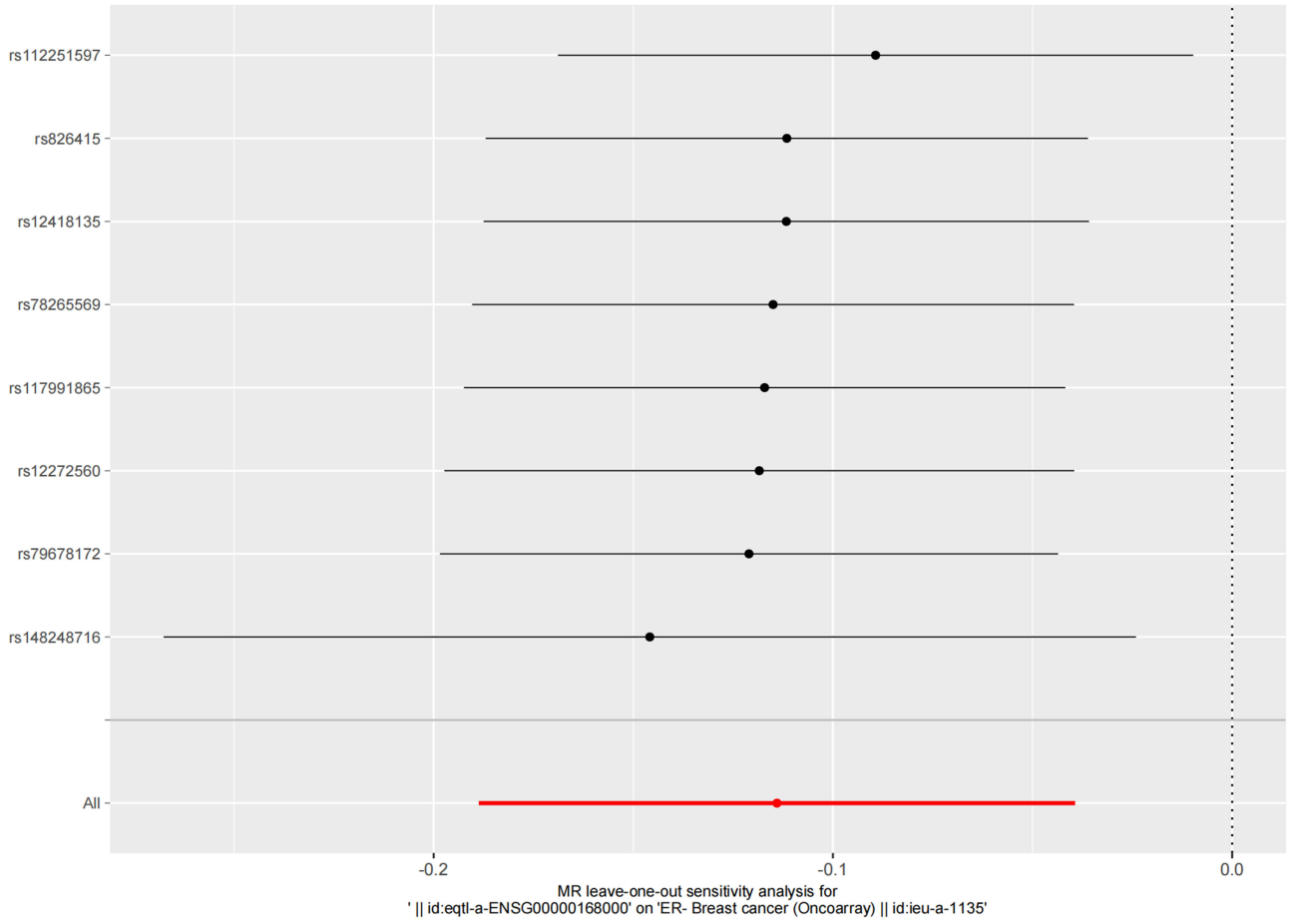

Figure 4 MR leave-one-out sensitivity analysis for Seipin on breast cancer.

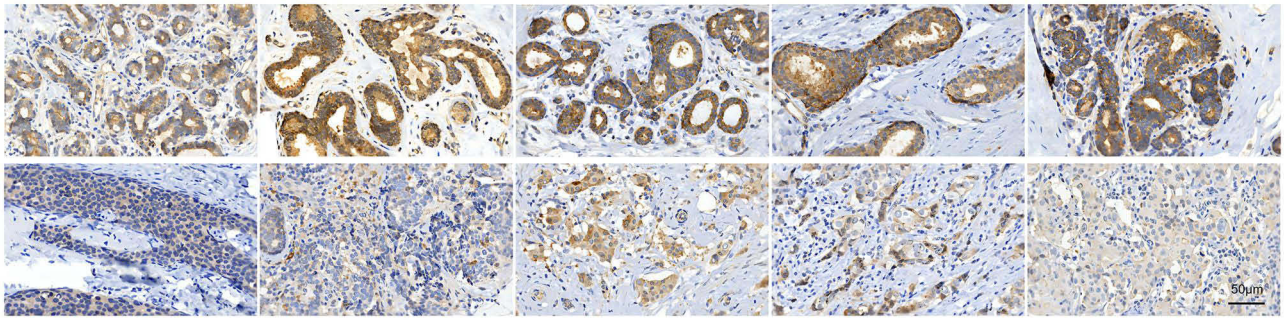

Figure 5 Immunohistochemical staining of mammary hyperplasia and breast cancer tissues. The upper row shows mammary hyperplasia, while the lower row represents breast cancer. Seipin staining is predominantly localized to the cytoplasm of epithelial cells. Original magnification: 200×; scale bars represent 50 μm.

weak-positive staining in mammary hyperplasia but substantially elevated strong-positive staining relative to breast cancer. These findings imply that reduced Seipin expression contributes to breast cancer initiation and progression.

TCGA-BRCA Validation of BSCL2 Expression in Tumor versus Normal Breast Tissue

To address the comparison between malignant and normal breast tissue, we analyzed BSCL2 expression in the TCGA-BRCA cohort, comprising 1111 primary tumor samples and 113 adjacent normal tissue samples. BSCL2 was significantly downregulated in tumor tissues (median TPM = 1.566) compared with adjacent normal tissues (median TPM = 1.847; Mann–Whitney *U*-test P = 9.58×10^{-3}; Student's *t*-test P = 2.07×10^{-2}; Cohen's d = 0.149; fold change = 1.179)

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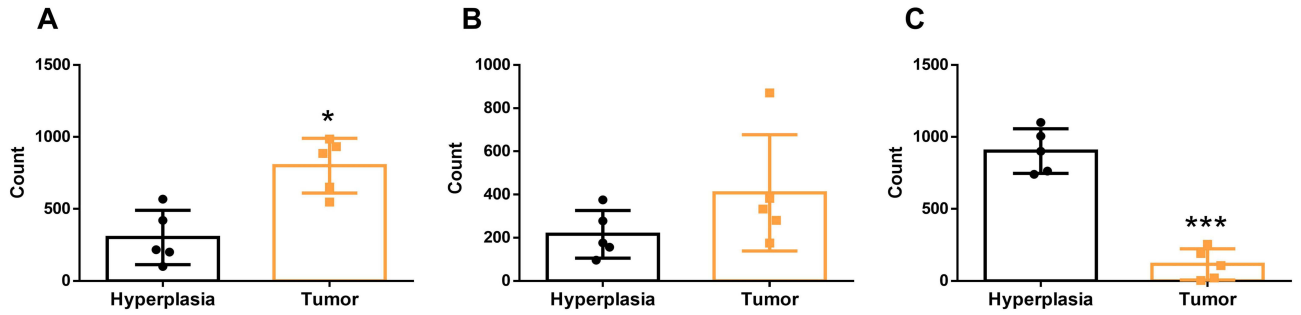

Figure 6 Comparative analysis of staining intensity among subgroups with weak (0–18), moderate (18–30), and strong (30–120) staining. (**A**) Weak staining; (**B**) Moderate staining; (**C**) Strong staining. * indicates P < 0.05, *** indicates P < 0.001.

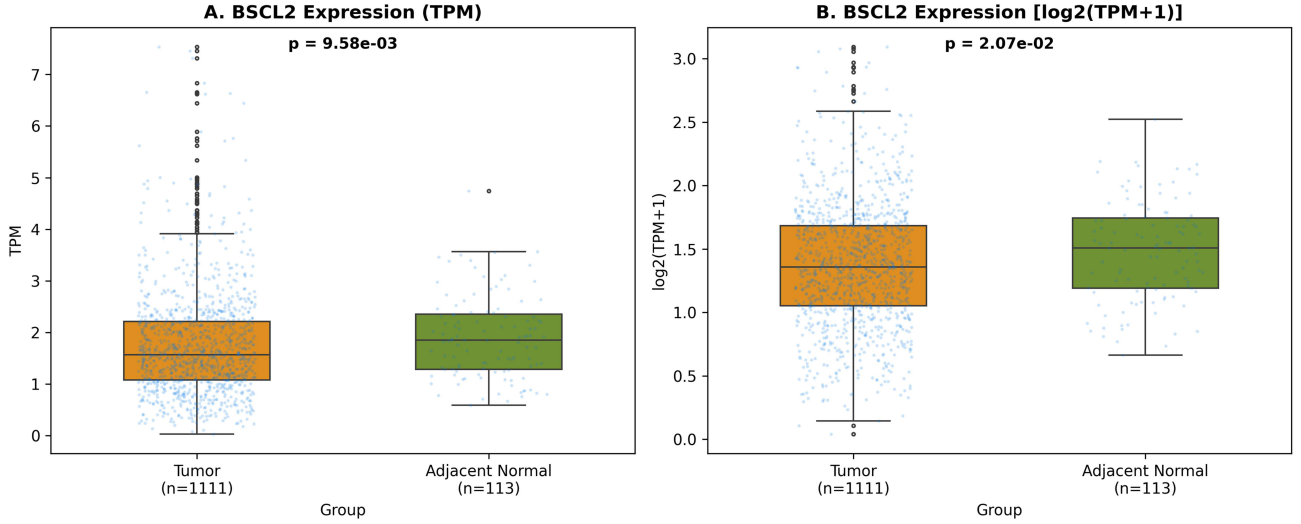

Figure 7 BSCL2 expression in TCGA-BRCA tumor versus adjacent normal tissues. (**A**) BSCL2 TPM values; (**B**) BSCL2 log2(TPM+1) values. Mann–Whitney *U*-test and Student's *t*-test were used for statistical comparison.

(Figure 7). These results independently corroborate the Immunohistochemical findings and extend the comparison to normal breast tissue.

Discussion

Breast cancer is one of the most common malignant tumors worldwide and poses a substantial threat to women's health globally. Although considerable progress has been made in its treatment in recent years, recurrence and drug resistance remain major challenges in breast cancer management.[27] Therefore, the continued exploration of novel therapeutic targets is critical to improving the prognosis of patients with breast cancer. Conventional therapies primarily target the proliferation and survival pathways of cancer cells, often neglecting the metabolic processes of malignant cells. Compared with normal cells, cancer cells exhibit marked reprogramming of lipid metabolism to meet the demands for membrane components and energy required for their rapid proliferation.[28,29] Moreover, lipid metabolic reprogramming in cancer cells can also reshape the tumor microenvironment, facilitating immune evasion and metastasis.[30] Thus, targeting the metabolic processes of cancer cells may offer novel therapeutic opportunities for breast cancer.

Seipin is an oligomeric integral membrane protein of the ER, encoded by the BSCL2 gene.[31] It critically maintains ER homeostasis and regulates lipid metabolism by stably localizing to ER–lipid droplet (ER–LD) contact sites, where it facilitates the transfer of neutral lipids synthesized in the ER into growing LDs, thereby protecting cells from ER stress and lipotoxicity. Systemic Seipin knockout not only impairs lipid storage in adipocytes and causes severe adipose tissue loss, but also paradoxically drives massive LD accumulation in non-adipose cells such as hepatocytes and sperm

cells.[10,32,33] Tumor cells likewise exhibit markedly increased LD number, size, and content relative to normal cells.[10] The LD accumulation represents a conserved metabolic adaptation across many cancer types, supplying energetic, biosynthetic, and cytoprotective advantages.[34] Beyond that, LDs assist tumor cells in adapting to hypoxic microenvironments and confer tolerance to cytotoxic anticancer treatments.[35,36] In multiple human cancer cell lines, Seipin accumulates at ER–LD junctions and is indispensable for the assembly, structural stability, and lipid cargo transfer at these membrane interfaces, directly governing LD biogenesis and expansion.[37,38] Notably, Seipin depletion in HeLa cells upregulates DFCP1, a Rab18 effector that engages the Rab18–ZW10 complex to reinforce ER–LD tethering and further enlarge LD compartments.[39] This compensatory regulatory cascade may enable cancer cells to maintain LD biogenesis and growth despite Seipin downregulation. Additionally, as a core tethering factor at membrane contact sites, Seipin expression positively correlates with favorable clinical outcomes in several malignancies, including pancreatic and ovarian carcinoma.[40] Taken together, Seipin may restrain tumor proliferation by repressing lipogenic signaling cascades, limiting aberrant LD accumulation, and preserving lipid metabolic homeostasis in cancer cells.

Excessive reactive oxygen species (ROS) in the breast cancer microenvironment promote tumor cell invasion and metastasis by inducing oxidative stress.[41,42] Seipin counters this process through two complementary mechanisms. First, Seipin is positively correlated with the expression of peroxisome-related proteins and reduces lipid peroxidation by limiting ROS production, thereby alleviating oxidative cellular damage.[43,44] Seipin overexpression further enhances the expression of antioxidant enzymes, including catalase (CAT) and superoxide dismutase (SOD), strengthening cellular tolerance to oxidative stress and inhibiting malignant transformation and metastasis.[44] Second, Seipin stabilizes ER–LD junctions to restrict lipid droplet motility and enable efficient sequestration of fatty acids as neutral lipids. Seipin ablation disrupts this lipid trafficking, causing free fatty acid accumulation and consequent lipotoxicity. This cascade further drives lipid peroxidation, exacerbates oxidative stress, and activates pro-tumor inflammatory signaling, collectively accelerating breast cancer progression.[37,45,46]

Studies have shown that cancer cells maintain high proliferative activity by activating autophagy, and elevated autophagy levels have been observed in numerous tumors. Notably, Beclin-1 is upregulated in colorectal, gastric, hepatic, breast, and cervical cancers,[47–50] suggesting that enhanced autophagy contributes to tumorigenesis. In breast cancer specifically, elevated basal autophagy serves a cytoprotective function, enabling tumor cells to survive metabolic stress and therapeutic insult.[51] Seipin opposes this cytoprotective autophagy by promoting a distinct, pro-death autophagic program. As an ER–LD junction protein, Seipin represses GPAT, thereby reducing cellular phosphatidic acid (PA), a potent endogenous inhibitor of peroxisome proliferator-activated receptor γ (PPARγ).[52,53] When Seipin is intact, PPARγ translocates to the nucleus and induces tumor-suppressive autophagy through two complementary pathways. First, synthetic PPARγ ligands upregulate HIF1α and its downstream effector BNIP3, which is required for autophagosome formation; knockdown of HIF1α abolishes this autophagy.[54,55] Second, natural PPARγ ligands, including ω-3 PUFA conjugates, dissociate the Beclin-1/Bcl-2 complex to liberate Beclin-1 for autophagosome nucleation, reduce p38 phosphorylation, and enhance LC3 lipidation.[56,57] Crucially, this PPARγ-driven autophagy is not cytoprotective but functions as an early pro-death event that transitions into intrinsic apoptosis upon sustained ligand exposure, marked by caspase-9 cleavage and upregulation of the tumor suppressor syndecan-1.[56,57] Seipin may further reinforce this autophagy-to-apoptosis cascade indirectly by enabling PPARγ-mediated upregulation of PTEN, which suppresses the PI3K/AKT/mTOR axis. When constitutively active, this axis inhibits autophagy and promotes tumor progression; for instance, in glioblastoma, TRIM29-mediated ubiquitination of NEFL activates PI3K/AKT signaling to suppress autophagic cell death and accelerate tumor growth.[58] Accordingly, in Seipin-deficient breast cancer cells, PA accumulation inhibits PPARγ nuclear translocation, silencing the pro-death autophagy program and leaving cytoprotective autophagy unopposed; simultaneously, unchecked PI3K/AKT/mTOR signaling further suppresses autophagic cell death, collectively accelerating breast cancer progression.

In summary, the present MR analysis revealed an inverse causal relationship between genetically predicted Seipin expression and breast cancer risk (IVW: OR = 0.89, 95% CI: 0.83–0.96). This finding was corroborated by immunohistochemical validation showing significantly lower Seipin expression in breast cancer tissues than in mammary hyperplasia tissues, and further supported by independent TCGA-BRCA bulk RNA-seq data demonstrating reduced BSCL2 expression in tumor versus adjacent normal tissues ($P = 9.58 \times 10^{-3}$). The proposed mechanisms by which Seipin

may exert its protective effect — limiting aberrant LD accumulation, modulating oxidative stress, and regulating autophagy — derive primarily from studies outside breast cancer and should be regarded as hypotheses requiring direct experimental validation in breast cancer models.

Limitations and Future Perspectives

However, several limitations should be acknowledged. First, although MR is a robust approach for inferring causality, it may still be affected by pleiotropy. While we used multiple analytical methods to control and verify potential bias, such confounding effects cannot be entirely excluded. Second, only eight SNPs were selected as instrumental variables using a relaxed significance threshold ($P < 5 \times 10^{-6}$), and the reported effect size is relatively modest (OR = 0.89). Although this threshold is commonly used in cis-MR studies and was supported by F-statistic filtering and comprehensive sensitivity analyses, the robustness of the causal inference should be interpreted with appropriate caution. Third, the sample size of our clinical immunohistochemical study was relatively small; thus, larger cohorts are warranted to improve the stability and reliability of the findings. Fourth, our immunohistochemical analysis compared breast cancer tissues with mammary hyperplasia tissues rather than adjacent normal breast tissues. While the TCGA-BRCA validation addressed this gap by demonstrating reduced BSCL2 expression in tumor versus adjacent normal tissue, future studies should include normal breast tissue controls in the pathological validation. Fifth, the MR analysis was based on GWAS data from individuals of European ancestry, and the immunohistochemical specimens were obtained from a single center in China. The generalizability of these findings to other ethnic populations and clinical settings requires further investigation through multi-ethnic GWAS data and multi-center clinical studies. Additionally, more research is needed to elucidate the specific molecular pathways by which Seipin influences breast cancer, as this may provide potential therapeutic targets and experimental evidence for breast cancer treatment.

Conclusion

MR establishes an inverse causal relationship between Seipin expression and breast cancer risk, which is robust across various methods and sensitivity analyses. Immunohistochemistry and TCGA-BRCA transcriptomics confirm reduced Seipin expression in breast cancer, collectively nominating Seipin as a candidate tumor suppressor. Mechanistically, Seipin may protect against breast cancer by limiting aberrant LD accumulation, modulating oxidative stress, and regulating autophagy; however, these mechanisms are derived from non-breast cancer models and require direct functional validation in breast cancer systems.

Data Sharing Statement

All raw data supporting this study can be downloaded from the corresponding public database websites, and the analytical codes are available upon request from the corresponding author.

Ethics Approval and Consent to Participate

All procedures performed in this study involving human participants were in accordance with the ethical standards laid down in the Declaration of Helsinki and its subsequent revisions. Documentation confirmed that informed consent was secured from all participating individuals, primarily of European descent and all studies included in the GWAS were approved by a relevant review board. Patients whose clinical specimens were used in this research provided informed consent, in accordance with the Declaration of Helsinki. The hospital gathered pathological specimens from breast cancer patients, with ethical approval (KYLL-2025-058) granted by the Ethics Committee of the First Affiliated Hospital of Shanxi Medical University.

Clinical trial number: not applicable.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest related to this study.

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