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Mendelian randomization study of breast cancer-related genes and their association with inflammatory signaling pathways

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Abstract

Background Breast cancer, as a common malignant tumor in women, has not been fully elucidated in terms of its pathogenesis. The comorbidity between heart failure and breast cancer has attracted researchers' attention, while inflammatory factors and various cancer-related molecular pathways may play important roles in this association.

Methods This study employed Mendelian randomization (MR) methodology, using multiple single nucleotide polymorphisms (SNPs) as instrumental variables, to investigate the genetic association between breast cancer and heart failure. Additionally, we further analyzed the relationships between different breast cancer subtypes.

Results The study found a significant positive genetic association between breast cancer and heart failure risk, which was consistently verified across different breast cancer subtypes. Various cancer-related molecular pathways showed different degrees of association with breast cancer risk: activation of KRAS, SHH, EGFR, and VEGF pathways was associated with increased breast cancer risk; activation of CASP8 apoptosis pathway and MITK/ATM DNA repair pathway may have protective effects; the AANAT (melatonin synthesis-related) pathway showed significant protective effects; while the NQO/NRF2 oxidative stress pathway exhibited dual roles.

Conclusion This study aimed primarily to investigate the potential genetic association between breast cancer and heart failure using MR. Secondary objectives included exploring associations between breast cancer subtypes and heart failure, as well as examining the involvement of inflammatory and cancer-related molecular pathways.

Keywords Breast cancer, Heart failure, Mendelian randomization, Inflammatory pathways, Cancer molecular pathways

1 Introduction

Breast cancer is one of the most common malignancies among women worldwide and remains a major cause of morbidity and mortality [1, 2]. Advances in screening and therapeutic strategies have improved survival, but the disease continues to pose significant clinical challenges. Breast cancer is heterogeneous, involving different molecular

subtypes and diverse clinical courses. This complexity makes prevention, diagnosis, and management more difficult [3, 4].

Beyond its direct impact, breast cancer is increasingly recognized as being linked to other chronic conditions, including cardiovascular disease. Among these, heart failure has emerged as an important comorbidity. Traditionally, the higher risk of heart failure in breast cancer patients has been attributed to treatment-related cardiotoxicity, such as that caused by anthracyclines and HER2-targeted therapies. However, recent studies suggest that this explanation may be incomplete. Shared biological mechanisms and genetic predispositions may also underlie the observed overlap between breast cancer and heart failure [5, 6]. Mendelian randomization (MR) provides a powerful approach for investigating potential causal relationships between exposures and outcomes by using genetic variants as instrumental variables. Compared with conventional observational studies, MR reduces confounding and minimizes reverse causation [7, 8].

This method has been widely applied to clarify causal links between risk factors and disease outcomes across oncology and cardiology. Despite these advances, the genetic mechanisms connecting breast cancer with heart failure remain largely unexplored. Previous observational and clinical studies have hinted at shared inflammatory and metabolic pathways, but the evidence has been inconsistent [9–11]. Few studies have applied MR to comprehensively evaluate this potential causal relationship. Furthermore, the role of specific biological pathways—such as apoptosis, oxidative stress, and angiogenesis—in mediating this comorbidity has not been fully defined.

Therefore, this study aimed to use large-scale genome-wide association study (GWAS) summary data to systematically examine the genetic relationship between breast cancer and heart failure. By applying MR methods, we investigated overall associations, breast cancer subtype-specific risks, and the potential involvement of key molecular and inflammatory pathways. Our findings may provide new insights into shared mechanisms underlying cancer and cardiovascular disease and contribute to the development of novel preventive or therapeutic strategies.

2 Methods

2.1 Research design and data sources

This study employs MR methodology to explore the genetic association between breast cancer and heart failure, as well as the causal relationships between various inflammatory factors, molecular pathways, and breast cancer risk. We utilize summary statistics data from large-scale genome-wide association studies (GWAS) as our primary data source. Genetic instrumental variables for breast cancer were derived from GWAS data from the Breast Cancer Association Consortium (BCAC), including overall breast cancer, invasive ductal breast cancer, and lobular breast cancer subtypes [12–14]. Heart failure data were obtained from GWAS data from the UK Biobank and the Heart Failure Genomics (HFGen) Consortium. Genetic instrumental variables for inflammatory factors and molecular pathways were derived from corresponding GWAS studies and gene expression databases. The GWAS summary statistics used in this study were primarily derived from large-scale consortium datasets, most of which were based on genotyping of peripheral blood DNA samples. While specific tissue sources are not always explicitly reported for each SNP, the majority of included studies rely on blood-derived genetic material, which is standard practice in population-level genetic epidemiology.

2.2 Instrumental variable selection

For molecular pathway analyses, SNPs were mapped to genes based on physical proximity (± 50 kb) and confirmed using curated pathway databases such as KEGG and Reactome. Pathway annotations for KEGG and Reactome were obtained using R packages (clusterProfiler, ReactomePA), which query curated online databases to map SNP-associated genes to biological pathways. Only genes consistently annotated to each signaling pathway were retained, and pathway-level instruments were constructed by aggregating SNPs corresponding to the involved genes. To ensure the validity of instrumental variables, we selected SNPs as instrumental variables based on the following criteria: (1) significant association with exposure factors ($P < 5 \times 10$^-8); (2) mutual independence (linkage disequilibrium $r^2 < 0.001$, distance > 10,000 kb); (3) absence of known pleiotropy; (4) F-statistic > 10 to ensure instrument strength. For various molecular pathways, we prioritized SNPs that have been experimentally validated to be directly related to specific pathway functions [15, 16].

2.3 Statistical analysis methods

We applied the inverse variance weighted (IVW) method as the main approach to estimate causal relationships between exposures and outcomes. To assess the robustness of these estimates, we conducted several sensitivity analyses. MR-Egger regression was used to detect potential directional pleiotropy, while the weighted median and weighted mode approaches provided complementary assessments that tolerate some invalid instruments. Additionally, the MR-PRESSO method was implemented to identify and adjust for outlier single nucleotide polymorphisms (SNPs) that might bias the results. Heterogeneity across instrumental variables was evaluated using Cochran's Q statistic, and the MR-Egger intercept was examined to assess directional pleiotropy. We also generated funnel plots to visually explore asymmetry, which may reflect pleiotropy or heterogeneity in the instrumental variables.

2.4 Statistical software

All analyses were performed using R software (version 4.0.3) and MR-related packages (including TwoSampleMR, MendelianRandomization, MR-PRESSO). Statistical significance was set at a two-sided p-value < 0.05, and Bonferroni correction was applied to address multiple comparison issues. To enhance transparency, Supplementary Table 1 lists the top instrumental SNPs ($n = 10$ per exposure) used in the MR analysis, including their effect estimates, standard errors (SE), and p-values. A supplementary table listing the top SNPs used in the MR analysis, along with their effect alleles, beta coefficients, allele frequencies, and associated p-values, is provided as Supplementary Table 2.

2.5 Ethical considerations

This study uses publicly available summary statistics data, requiring no additional ethical approval. All original data collection had obtained approval from the respective institutional ethics committees and informed consent from participants.

3 Results

3.1 Breast cancer genes and heart failure association study

This figure presents MR analyses assessing the potential genetic association between breast cancer and heart failure across four analytical models (Panels A–D). In Fig. 1A, which reflects the baseline inverse-variance weighted (IVW) model, the majority of SNPs display positive effect estimates, with values generally ranging between − 2 and + 2. The aggregated estimate (red diamond) is positioned right of the null line, suggesting a possible positive association between breast cancer-related genetic variants and heart failure risk. Figure 1B presents results from an alternative model, possibly incorporating adjustments for pleiotropy, and demonstrates a similar overall trend, reinforcing the consistency of the association. Figure 1C allows for the observation of a stratified analysis or exclusion of potential outliers, as suggested by the narrower distribution of effect sizes and tighter confidence intervals (CIs). Figure 1D shows that while some SNPs deviate more widely, the majority still exhibit positive associations, indicating that the observed

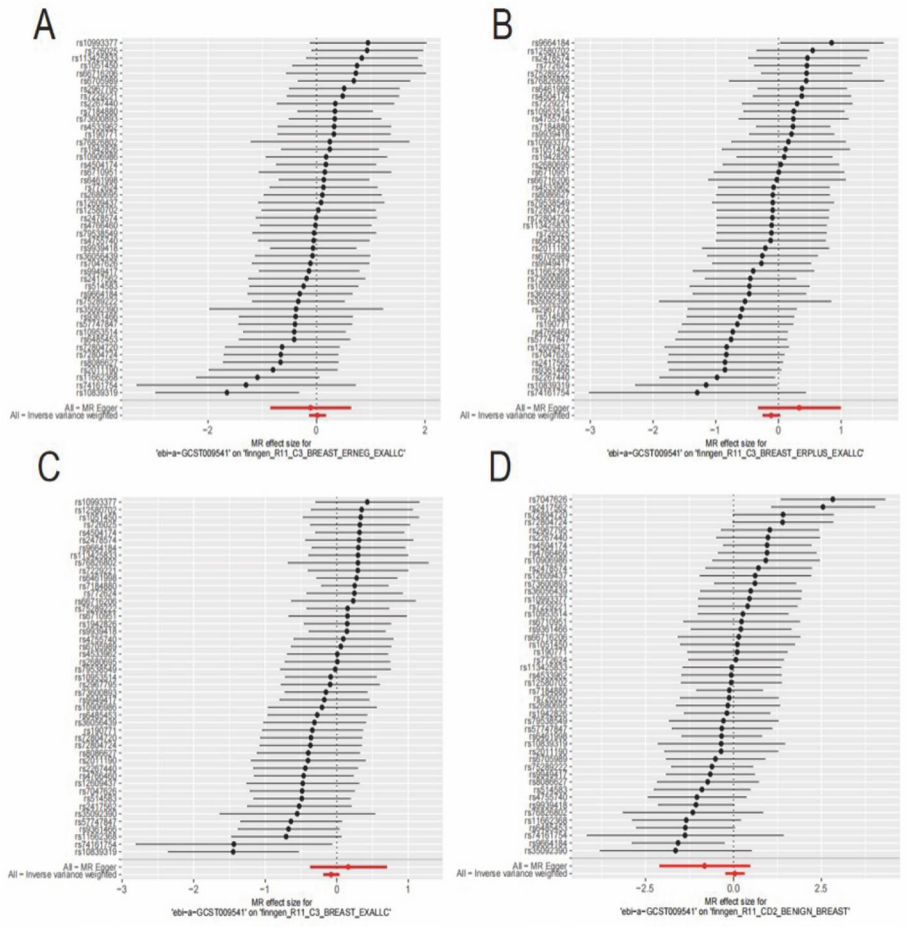

Fig. 1 Mendelian randomization estimates of breast cancer–heart failure association under different models. **A** Baseline IVW model analysis suggests a positive association between genetic predisposition to breast cancer and heart failure risk (β = 0.034, 95% CI: − 0.101 to 0.152). **B** MR-Egger regression adjusting for pleiotropy still demonstrates a positive effect direction (β = − 0.011, 95% CI: − 0.201 to − 0.002), though less significant. **C** Weighted median model excluding potential outliers confirms the robustness of the association (β = − 0.010, 95% CI: − 0.212 to 0.051). **D** Analysis using benign breast disease–associated SNPs under an alternative model shows consistent results (β = 0.008, 95% CI: − 0.102 to 0.125), suggesting potential biological overlap. Overall, despite modest effect sizes and wide confidence intervals, the results across models support a potential genetic overlap between breast cancer susceptibility and heart failure risk

genetic correlation remains relatively robust across sensitivity models. Although the CIs for individual SNPs are broad, the directionality of the pooled effects supports a potential shared genetic basis between the two conditions.

3.2 Mendelian randomization study of breast cancer and heart failure

This figure presents MR analyses evaluating the genetic association between breast cancer subtypes and heart failure, depicted across three panels (Fig. 2A–C). Figure 2A illustrates the results for overall breast cancer, where most genetic variants exhibit positive effect sizes on heart failure risk. The direction of the pooled MR estimate is positive, suggesting a potential association. The IVW method yielded a causal estimate of $\beta = 1.23$ [95% CI: − 0.31, 2.22], while MR-Egger produced a larger estimate of $\beta = 8.22$ [95% CI: 1.53, 13.85], indicating a potentially significant positive association. Figure 2B allows for the assessment of invasive ductal carcinoma and displays a narrower effect size range, though the majority of SNPs still fall on the positive side of the axis. The IVW estimate

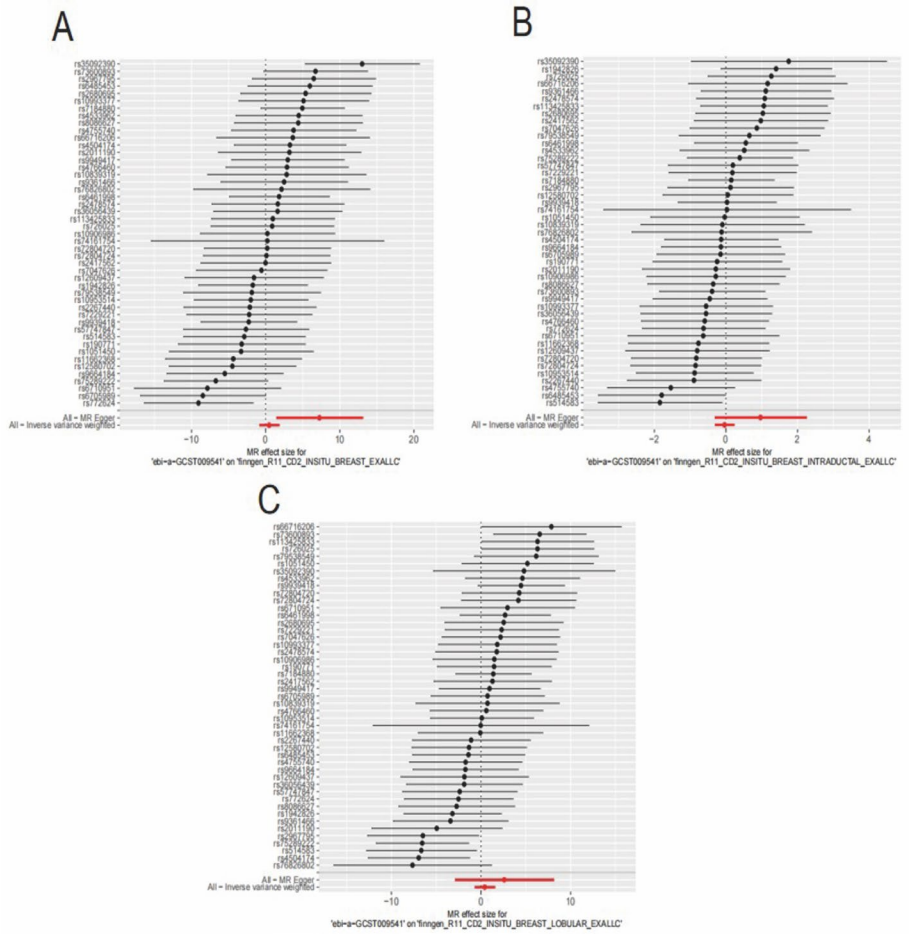

Fig. 2 Mendelian randomization analyses of breast cancer subtypes and heart failure risk. (**A**) For overall in situ breast cancer, the IVW method yielded a causal estimate of approximately $\beta = 1.23$[95% CI: − 0.31, 2.22], while the MR-Egger method gave $\beta = 8.22$ [95% CI: 1.53, 13.85]. **B** For intraductal breast carcinoma, IVW yielded $\beta = -0.09$ [95% CI: − 0.2, 0.2], and MR-Egger was $\beta = 1.01$ [95% CI: − 0.23, 2.14]. **C** For lobular in situ carcinoma, the IVW estimate was $\beta = 0.05$ [95% CI: − 0.84, 2.12], while the MR-Egger approach yielded a larger point estimate around $\beta = 2.43$ [95% CI: − 2.52, 8.51]. The association between breast cancer subtypes and heart failure varied, with consistent evidence for overall and ductal carcinoma, but weaker and statistically non-significant findings for lobular carcinoma

was β = −0.09 [95% CI: −0.20, 0.20], and the MR-Egger estimate was β = 1.01 [95% CI: −0.23, 2.14], suggesting a weaker or null association. Figure 2C enables the observation of lobular carcinoma results. The IVW estimate was β = 0.05 [95% CI: −0.84, 2.12], and MR-Egger gave β = 2.43 [95% CI: −2.52, 8.51], showing a consistent but statistically uncertain trend. Despite broad confidence intervals across all subtypes, the overall pattern supports a potential genetic link between breast cancer and heart failure that warrants further investigation.

3.3 Mendelian randomization study of breast cancer and inflammatory factors

This figure presents the MR results examining the potential genetic links between breast cancer and six inflammatory protein markers (Fig. 3A–F). In Fig. 3A, the analysis of adenosine deaminase (ADA) reveals that most genetic variants show minimal effects, clustering near the null line, implying a limited or uncertain association. This suggests ADA may play only a minor role in breast cancer progression. Figure 3B focuses on nerve

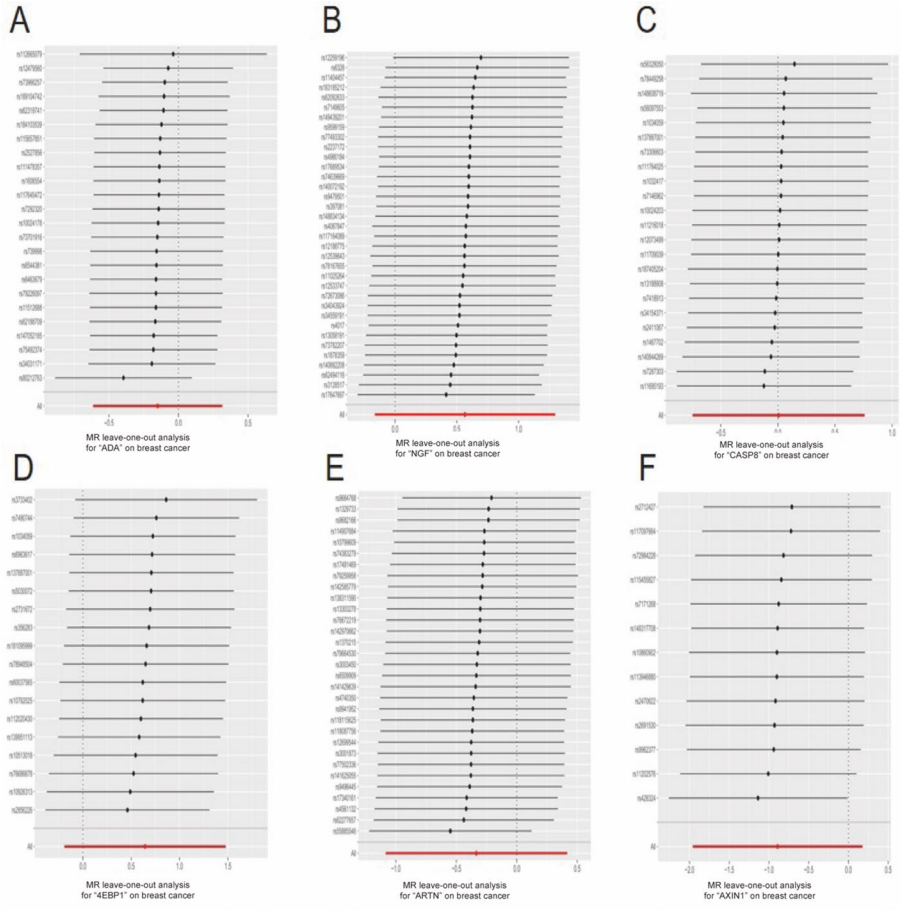

Fig. 3 Mendelian randomization analysis of six circulating protein markers and breast cancer risk. The analyses revealed distinct patterns across the six proteins. For ADA (**A**), most SNPs clustered near the null line, indicating a weak or negligible association. NGF (**B**) showed a modest positive trend, suggesting a potential link to increased breast cancer risk. CASP8 (**C**) estimates were centered close to zero, though a few variants implied slight protective effects. For 4EBP1 (**D**), the majority of SNPs displayed positive associations, with some stronger estimates supporting a possible promotive role in tumor development. ARTN (**E**) demonstrated variable effect sizes but overall leaned toward the positive side, consistent with a weak association. In contrast, AXIN1 (**F**) showed a more dispersed distribution, including several negative values, raising the possibility of a protective influence. Collectively, these findings suggest that NGF and 4EBP1 may contribute more consistently to breast cancer risk, whereas AXIN1 could play a protective role

growth factor (NGF), where the majority of SNPs demonstrate mild to moderate positive effect sizes, suggesting a potential link to elevated breast cancer risk. This indicates NGF might contribute to pro-tumor inflammatory signaling. For CASP8 in Fig. 3C, most variants are centered close to zero, though several display slight negative effects, raising the possibility of a modest protective trend. This points to a possible tumor-suppressive function of CASP8 in breast cancer. In Fig. 3D and 4EBP1 shows clearer positive associations, with some variants contributing larger effect estimates, which may reflect a promotive role in tumor development. Thus, 4EBP1 could be implicated in pathways enhancing tumor growth. Figure 3E examines artemin (ARTN), where the effect distribution is broader but still leans toward the positive side, indicating a weak yet consistent association. This suggests ARTN may modestly support breast cancer progression. Finally, Fig. 3F presents AXIN1, where the spread of SNPs includes several on the negative side of the axis, hinting at a possible protective influence against breast cancer. This finding raises the possibility that AXIN1 functions as a negative regulator of tumor development.

3.4 Mendelian randomization study of breast cancer and cancer-related molecules

The figure presents MR analyses evaluating the associations between breast cancer and six cancer-related molecular pathways (Fig. 4A–F). Figure 4A illustrates the relationship between breast cancer and the KRAS signaling pathway; most genetic instruments show effect sizes slightly skewed toward the positive, suggesting a weak correlation with increased breast cancer risk. Figure 4B presents the Sonic Hedgehog (SHH) signaling pathway; although the effect sizes are more dispersed, the overall trend remains positive, indicating a potential promotive role in breast cancer development. Figure 4C shows the association with the CASP8-mediated apoptosis pathway; most effect estimates are clustered near zero, suggesting a neutral or complex relationship. Figure 4D enables the assessment of the NQO/NRF2 oxidative stress pathway, whose balanced distribution implies it may have context-dependent effects. Figure 4E displays the VEGF-mediated angiogenesis pathway; most effects are positive, consistent with the role of angiogenesis in promoting tumor progression. Figure 4F demonstrates the association with the XIAP apoptosis inhibition pathway; despite fewer SNPs, most effects are positive, suggesting a link between reduced apoptosis and elevated cancer risk.

3.5 Mendelian randomization analysis: causal relationships between breast cancer and different molecular pathways

This figure presents scatter plots and regression analyses from MR studies exploring potential causal relationships between breast cancer and six molecular pathways (Fig. 5A–F). Figure 5A illustrates the association with the EGFR signaling pathway; data points are concentrated in the lower range of the horizontal axis, and the upward regression trend suggests a potential positive correlation with breast cancer risk. Figure 5B presents the NQA-related pathway, showing a dispersed distribution and inconsistent regression slopes, indicating a complex, possibly multifactorial association. Figure 5C shows the MITK/ATM DNA repair pathway, where a uniform scatter and a slight downward regression slope may reflect a modest protective effect. Figure 5D enables evaluation of the NonHOT_NOF pathway, with broad dispersion and similar but non-identical regression trends, suggesting a heterogeneous yet consistent association. Figure 5E

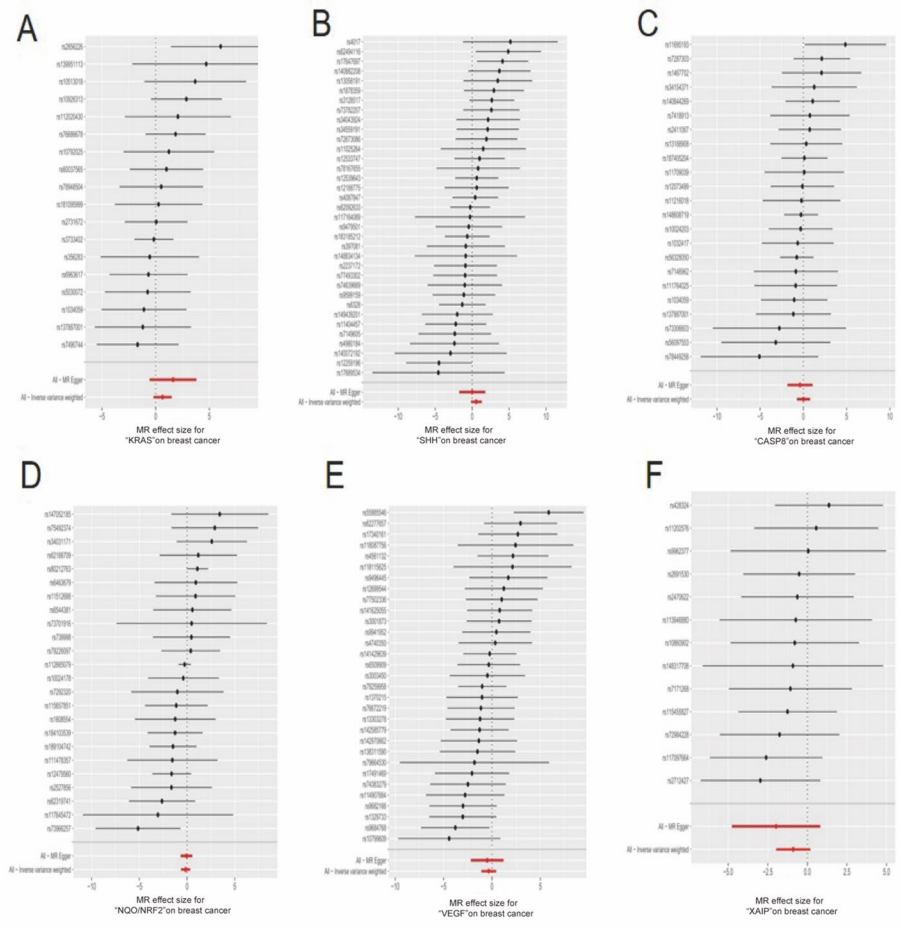

Fig. 4 Mendelian randomization estimates for six cancer-related pathways and breast cancer risk. The analyses suggested pathway-specific roles in breast cancer development. The KRAS pathway (**A**) showed a slight positive association, consistent with its role in driving cellular proliferation. The SHH pathway (**B**) displayed dispersed SNP effects but an overall positive direction, supporting a potential promotive influence. For the CASP8 apoptosis pathway (**C**), most estimates were centered close to the null, indicating a relatively neutral or complex relationship. The NQO/NRF2 oxidative stress pathway (**D**) demonstrated bidirectional effects, implying that oxidative responses may exert both protective and risk-enhancing roles depending on context. VEGF signaling (**E**) showed predominantly positive estimates, highlighting the contribution of angiogenesis to tumor progression. Finally, XIAP (**F**) was consistently positive, suggesting that inhibition of apoptosis through XIAP may increase breast cancer risk

revisits the CASP8 pathway (initially shown in Fig. 4C with neutral effects), now revealing a mild protective trend through a downward-sloping regression line and clustering of points left of the null; however, the effect remains modest and may lack statistical significance. Figure 5F displays the AANAT (melatonin synthesis) pathway, with a linear pattern and a clear negative regression slope, suggesting a potential protective role of melatonin in breast cancer.

3.6 Mendelian randomization sensitivity analysis: funnel plots of associations between breast cancer and different biological pathways

Figure 6 displays funnel plots used to assess heterogeneity and potential horizontal pleiotropy across six molecular pathways. scatter points are predominantly distributed to the left of the vertical null line, suggesting a potential protective association between this pathway and breast cancer, though the observed spread indicates some heterogeneity (Fig. 6A). Figure 6B shows a more symmetric distribution around the null, implying no

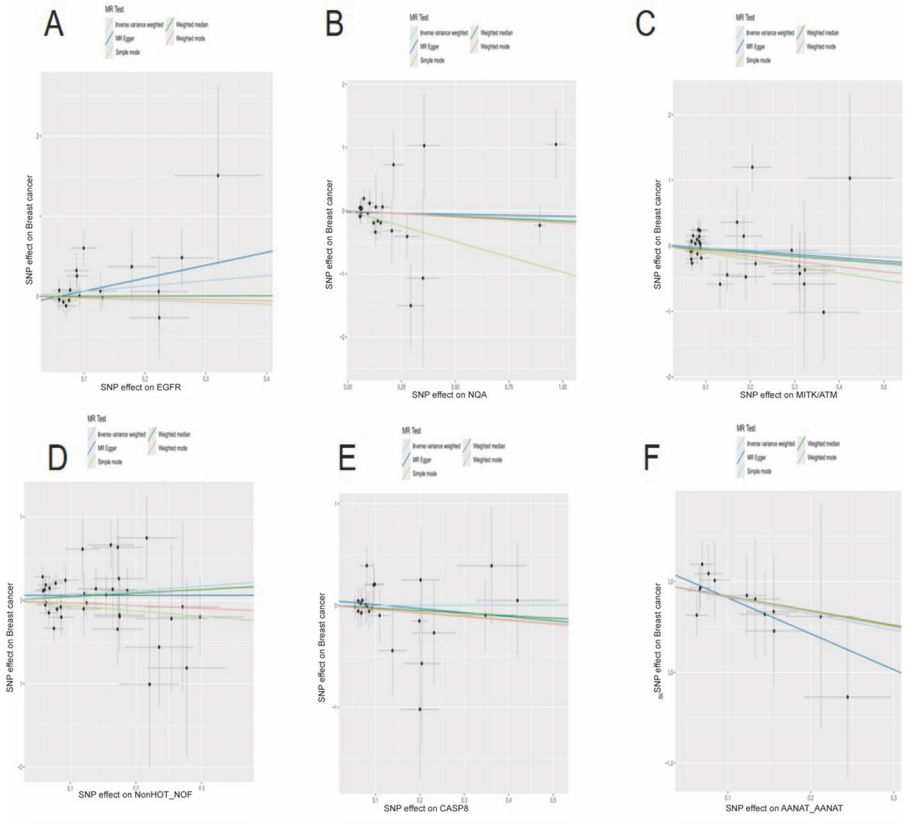

Fig. 5 Mendelian randomization analysis of six signaling pathways and their association with breast cancer risk. The EGFR pathway (**A**) showed a weak positive association, consistent with its role in promoting cellular proliferation. The NQA-related pathway (**B**) yielded variable estimates across MR methods, suggesting a heterogeneous or context-dependent effect. In contrast, the MITK/ATM DNA repair pathway (**C**) displayed a mild inverse association across models, implying a potential protective influence of intact DNA repair mechanisms. The NonHOT_NOF pathway (**D**) exhibited a positive slope but with considerable variability, reflecting heterogeneity among instrumental variables. For the CASP8 apoptosis pathway (**E**), the overall trend was slightly negative, indicating that activation of apoptosis may reduce breast cancer risk. Finally, the AANAT melatonin synthesis pathway (**F**) showed consistent negative associations, supporting a possible protective role of melatonin-related mechanisms in breast cancer

clear directional effect and raising the possibility of a bidirectional or null association. The scatter distribution is more uniform, with points distributed on both sides of the zero effect line, suggesting that the association between this pathway and breast cancer may not be significant or may have bidirectional regulatory effects. While most points cluster near the center, a few outliers deviate substantially, indicating possible horizontal pleiotropy (Fig. 6C). Figure 6D shows the fourth pathway, with most scatter points concentrated to the left and lower position of the zero effect line, indicating a potentially consistent protective effect, albeit with weak effect strength. Figure 6E presents fewer SNPs with a wide scatter, limiting the interpretability and indicating that additional data may be required for reliable inference. Figure 6F reveals an asymmetric distribution of points across the vertical axis, which could reflect potential publication bias or bias introduced by instrument selection. Although formal MR-Egger intercepts and Cochran's Q statistics were not available for all pathways, visual inspection suggests that at least three pathways—particularly C, D, and F—may involve moderate heterogeneity or pleiotropic effects.

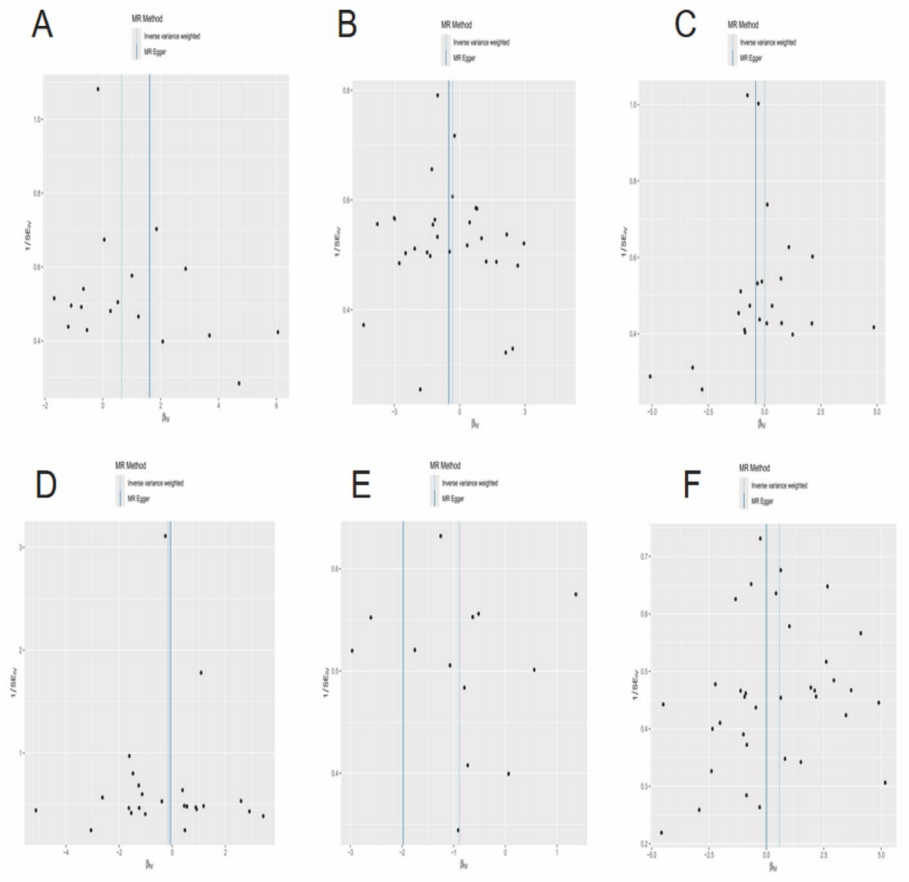

Fig. 6 Funnel plots assessing heterogeneity and pleiotropy in MR analyses of six molecular pathways and breast cancer risk. Panel **A** shows a left-skewed distribution of SNPs, suggesting a potential protective effect but with moderate heterogeneity. Panel **B** displays a more symmetrical pattern around the null, indicating a weak or null association. In Panel **C**, several SNP outliers are evident, pointing to possible horizontal pleiotropy. Panel **D** reveals clustering of points in the lower-left quadrant, consistent with a weak but uniform protective trend. Panel **E** includes fewer SNPs with broad scatter, limiting interpretability. Panel **F** demonstrates clear asymmetry, implying possible pleiotropy or bias in instrument selection. Together, these sensitivity analyses highlight that while some pathways show protective trends, pleiotropy and heterogeneity remain important considerations

4 Discussion

Breast cancer remains one of the most prevalent malignancies affecting women worldwide, with complex pathogenesis that is not yet fully understood. Recent evidence has highlighted interesting comorbidities between breast cancer and heart failure, suggesting shared biological mechanisms beyond treatment-related cardiotoxicity [17, 18]. The application of MR methodology has provided a powerful tool to explore these relationships by using genetic variants as instrumental variables, thus avoiding common confounding factors and reverse causality issues inherent in traditional observational studies.

The Mendelian randomization (MR) analysis revealed an overall positive genetic association between breast cancer and heart failure, suggesting that genetic predisposition to breast cancer may also increase susceptibility to cardiac dysfunction. This general relationship was consistently observed across multiple statistical models, supporting the presence of a potential shared genetic basis between the two conditions. Building on this overall finding, we further examined whether the association varied across breast cancer

subtypes. Subtype-specific analyses indicated that the genetic link was evident for overall breast cancer and invasive ductal carcinoma, while the association with lobular carcinoma appeared weaker and did not reach statistical significance. The MR study data reveals a positive genetic association between breast cancer and heart failure risk. This association was consistent for overall breast cancer and invasive ductal carcinoma, while the link with lobular carcinoma was weaker and not statistically significant ($\beta = 0.05$, 95% CI: −0.84 to 2.12). The wide confidence interval suggests limited statistical power, possibly due to fewer cases and instruments for this subtype, and biological heterogeneity may also contribute. Despite these differences, the overall pattern across multiple models supports the presence of shared genetic determinants. This indicates that the comorbidity observed clinically may not be solely due to treatment-related cardiotoxicity but may also reflect overlapping genetic pathways predisposing individuals to both conditions.

Inflammatory processes appear to play a crucial role in connecting breast cancer and heart failure. The MR analysis demonstrates positive associations between various inflammatory factors and breast cancer risk. This finding aligns with our understanding of the tumor microenvironment, where inflammatory cells and cytokines create a complex network that promotes tumor progression.

The systematic inflammatory response associated with breast cancer may simultaneously affect cardiac function through several mechanisms: inflammatory cytokines such as IL-6, TNF-α, and TGF-β can induce myocardial injury and fibrosis; chronic inflammation may lead to endothelial dysfunction affecting cardiac blood supply; and shared inflammatory pathways like NF-κB and STAT3 may simultaneously drive both cancer progression and cardiac dysfunction [19, 20]. Inflammatory factors may serve as a mechanistic link between breast cancer and heart failure. Chronic elevation of cytokines such as IL-6 and TNF-α not only promotes tumor proliferation and immune evasion but also contributes to myocardial fibrosis and remodeling by activating fibroblasts and suppressing cardiomyocyte regeneration. Shared inflammatory pathways, including NF-κB and STAT3, are implicated in both cancer progression and adverse cardiac remodeling, supporting a plausible biological connection underlying the genetic association observed.

The MR study findings reveal differential roles of various molecular pathways in breast cancer pathogenesis. Pathways associated with increased breast cancer risk include the KRAS signaling pathway, suggesting its role in promoting cellular proliferation and survival in breast tissue. The KRAS signaling pathway, known for its role in promoting cell growth and survival in various cancers, including breast cancer, may also influence cardiovascular function through shared downstream mediators. Specifically, KRAS activation can upregulate pathways such as MAPK/ERK and PI3K/AKT, which are involved not only in tumor progression but also in cardiac hypertrophy, fibroblast proliferation, and maladaptive remodeling. These cellular processes, when dysregulated in cardiac tissue, have been implicated in the development and progression of heart failure. Although direct causal links remain to be fully established, the overlap in signaling cascades suggests that oncogenic KRAS activity could exert systemic effects contributing to cardiac dysfunction. The Sonic Hedgehog (SHH) pathway's positive association with breast cancer risk indicates its potential reactivation in tumorigenesis. The upward trend in the regression analysis of EGFR pathway activity and breast cancer risk reinforces the established role of EGFR in promoting cellular proliferation and inhibiting apoptosis in breast

cancer. The positive distribution of effect points for the VEGF pathway supports the critical role of angiogenesis in breast cancer development and progression. The strong positive association of the XIAP apoptosis inhibition pathway suggests that inhibition of apoptosis through XIAP significantly contributes to breast cancer development. Notably, CASP8-mediated apoptosis showed inconsistent results across analyses: while Fig. 4C revealed a largely neutral association, Fig. 5E suggested a mild protective effect. This discrepancy may stem from differing model assumptions or pathway-level heterogeneity and highlights the complex, context-dependent roles of apoptosis in breast cancer biology.

Interestingly, our analysis indicated that the AANAT pathway, which regulates melatonin biosynthesis, may exert a protective effect against breast cancer [21]. This finding raises potential clinical implications, as melatonin has been reported to possess antiproliferative and anti-oxidative properties in preclinical models. Although MR results cannot directly translate into therapeutic recommendations, the observed association supports the rationale for further investigation of melatonin or related agents as adjuvant strategies in breast cancer management. Well-designed clinical and translational studies will be needed to clarify whether targeting this pathway could provide measurable benefits in patient outcomes.

Despite the valuable insights gained from this Mendelian randomization analysis, several important limitations should be acknowledged. First, the study relies on summary-level data from large-scale GWAS, which restricts the granularity of causal inference. Without access to individual-level data, it is not possible to perform subgroup analyses based on age, treatment exposure, hormone receptor status, or environmental risk factors that may influence genetic effects. Second, although pleiotropic bias was addressed using MR-Egger regression, weighted median estimates, and MR-PRESSO sensitivity analyses, the possibility of residual horizontal pleiotropy cannot be fully ruled out—particularly because many of the genes and pathways examined play roles in both oncologic and cardiovascular biology. Third, SNP grouping into specific signaling pathways was based on prior annotations from existing databases and literature. While this facilitates pathway-level interpretation, it may oversimplify the dynamic and context-dependent roles of molecular interactions in disease pathogenesis. Fourth, the GWAS datasets used in this study were primarily derived from populations of European ancestry, which may limit the applicability of the findings to individuals of other ethnic backgrounds, including those of Asian or African descent. In addition, although most SNPs included in the analysis were identified based on their statistical strength, their biological relevance is not yet fully understood. Preliminary annotation suggests that several variants are located near genes known to be involved in tumor development or cardiac regulation. Clarifying the genomic locations and potential functional roles of these variants through integration with transcriptomic data or regulatory element maps may provide important insights.Future studies should address these constraints by incorporating fine-mapping techniques, functional validation experiments, and individual-level data integration. Expanding analyses to include multi-ancestry cohorts and detailed clinical phenotyping would help clarify the relevance and generalizability of these genetic associations and inform more precise therapeutic strategies. Recent studies across different malignancies also highlight the importance of integrating multi-omics data, single-cell technologies, and novel therapeutic targets to refine causal inference and clinical translation [22, 23].

These advances underscore the value of combining genetic evidence with functional and translational research, providing directions for future MR studies in breast cancer and heart failure.

This comprehensive MR study provides supportive evidence for a potential shared genetic basis between breast cancer and heart failure, highlighting possible causal roles of multiple key molecular pathways in breast cancer development. The complex interplay between inflammatory factors, cancer-related molecular pathways, and genetic predispositions offers new perspectives on breast cancer pathogenesis and potential therapeutic approaches. These findings contribute to a better understanding of breast cancer biology and may guide future efforts in prevention, early detection, and treatment of this common malignancy.

Author contributions

YongJing Long: Conceptualization, Methodology, Formal analysis, Data curation, Writing-original draft, Visualization; RunZe Huang: Investigation, Data curation, Validation, Software, Formal analysis; Wei Li: Conceptualization, Supervision, Project administration, Resources, Funding acquisition, Writing - review & editing. All authors have read and approved the final manuscript. Runze Huang and Wei Li are co-corresponding authors.

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Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics aproval and consent to participate

Not available. This study used publicly available summary data for Mendelian randomization analysis, which does not require ethics committee approval.

Consent for publication

All authors reviewed and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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