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LETTER

Multisite Chronic Pain and the Risk of Breast Cancer and Its Subtypes: A Mendelian Randomization Study [Letter]

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Dear editor

We read with considerable interest the Mendelian randomization (MR) study by Li et al recently published in the *Journal of Pain Research*.[1] As the first investigation to apply MR methodology to explore the causal relationship between chronic pain (CP) and breast cancer (BC), the study commendably emphasizes the need for further research and potential clinical applications to enhance breast cancer prevention and management. The findings provide valuable genetic insights into this complex relationship. We raise several methodological considerations that may influence the interpretation of the findings and their broader applicability, aiming for constructive dialogue.

Considerations on Instrumental Variable Validity

The use of heterogeneous significance thresholds for IV selection across pain phenotypes lacks a clear biological rationale. Specifically, employing a less stringent threshold ($P < 5\times10^{-6}$) for abdominal pain IVs compared to others ($P < 5\times10^{-8}$) may increase susceptibility to weak instrument bias. The absence of reported F-statistics for these IVs further limits the assessment of instrument strength. To strengthen the analysis, we recommend reanalyzing all exposures using a uniform genome-wide significant threshold ($P < 5\times10^{-8}$), reporting F-statistics for all IV sets.[2] This would address potential heterogeneity.

Potential for False Positives Due to Multiple Testing

The substantial number of statistical tests performed (7 pain types × 6 cancer outcomes) raises concerns about false positives. Interpreting results based solely on nominal significance ($P < 0.05$) may inflate type I error. For instance, the association between abdominal pain and overall breast cancer (OR=3.41, P=0.045) might not survive appropriate multiple testing correction such as Bonferroni (α=0.0012). The extreme effect estimates for abdominal pain on HER2+ breast cancer (OR=86.3, P=0.012) further suggests possible outlier-driven bias. To improve robustness, we suggest applying a False Discovery Rate (FDR) correction to all P-values, explicitly denoting associations not surviving correction as exploratory findings requiring replication, and performing leave-one-out sensitivity analyses for estimates with exceptionally high odds ratios.

Addressing Potential Reverse Causality and Confounding

Chronic pain phenotypes defined in the UK Biobank cohort may include pain secondary to undiagnosed cancer, particularly given the cohort's older demographic. This could violate the MR temporality assumption if pain arises from occult metastases or treatment effects. Furthermore, the association between neck/shoulder pain and Luminal A breast cancer might reflect age confounding rather than direct causation. To mitigate these concerns, incorporating age

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as a covariate within multivariable MR and stratifying analyses by relevant age groups would strengthen causal inference.

Conclusion and Suggestions

While this study offers valuable genetic insights, addressing these methodological limitations is essential for robust causal inference. Future research should prioritize validation in multi-ancestry cohorts, integrate longitudinal biomarker data, develop standardized chronic pain phenotyping frameworks, and implement risk-stratified analyses accounting for hormonal profiles and treatment histories. Such efforts would advance personalized breast cancer prevention and pain management strategies.

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