Integrating Environmental Risk Factors and mRNA Expression Profiles as Prognostic Biomarkers in Triple-Negative Breast Cancer

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Background

TNBC is an aggressive breast cancer subtype that comprises approximately 10-15% of all breast cancer cases and is associated with poor prognosis and substantial heterogeneity in clinical outcomes. While the internal genomic drivers of TNBC are well-documented, the influence of external environmental risk factors (ERFs) on tumor molecular shifts remains a significant knowledge gap in current oncology.

Purpose

This study aims to identify biomarkers that bridge the gap between multi-exposure environmental data and tumor molecular features that are essential for understanding disease trajectory and personalizing prevention strategies.

Methods

We analyzed tumor molecular profiles derived from mRNA expressions in 253 TNBC tumor samples collected by the Louisiana Tumor Registry among cases diagnosed between 2009 and 2019. Molecular data were linked to registry-derived clinical outcomes and to environmental variables obtained from the 2022 Environmental Justice Index (EJI), respectively. To fill the gap in multi-exposure biomarker discovery, we developed an analysis framework based on Mutual Information (MI). mRNAs were prioritized using a composite MI product score, defined as the product of a gene's maximum information shared with 13 significant ERFs and its shared information with clinical outcomes (stage or grade). To characterize biological significance, these ranked lists were analyzed using an adaptive Gene Set Enrichment Analysis (GSEA) to determine if the environment-stage interaction was concentrated within specific Hallmark pathways.

Results

Of the environmental factors screened, 13 showed significant associations with TNBC outcomes, including tumor stage and histological grade ($p<0.05$). Moreover, 880 unique mRNAs were found to be differentially expressed across stage and at least one of the ERFs associated with it and 253 unique mRNAs were found to be differentially expressed across grade and at least one of the ERFs associated with it, after adjusting for covariates age, race and bmi. Further, integrative GSEA revealed that mRNAs highly responsive to these ERFs were significantly enriched for hallmark pathways that play central roles in TNBC tumor progression and aggressiveness. Notably, five pathways emerged as consistently significant for both tumor stage and grade: HALLMARK_MYC_TARGETS_V1,HALLMARK_MTORC1_SIGNALING, HALLMARK_E2F_TARGETS, HALLMARK_MITOTIC_SPINDLE, and HALLMARK_G2M_CHECKPOINT. Together, these pathways reflect a coordinated activation of proliferative signaling, cell-cycle dysregulation, and metabolic reprogramming, which are core biological features of high-risk TNBC. These prioritized gene–environment signatures highlight distinct molecular patterns through which external exposures may

amplify oncogenic transcriptional programs, disrupt cell-cycle control, and accelerate disease progression in TNBC patients.

Conclusion

Our study identifies a distinct set of environmental risk factors that are associated with TNBC progression. By mapping these external exposures to internal molecular shifts through an adaptive MI-based framework, we demonstrate that ERFs may serve as external indicators of tumor behavior. This integration of multi-exposure environmental data with tumor molecular profiles offers a more comprehensive characterization of TNBC heterogeneity and informs future precision prevention and therapeutic strategies.