Structural Drivers of Cancer: miRNA Expression as a Link Between Transportation Burden and TNBC Progression

Nubaira Rizvi[1], Amjila Bam[1], Xiao-Cheng Wu[2], Meng Luo[3], Luis Del Valle[4], Lang Wu[5], Lucio Mieli[6], Edward Trapido[2], and Qingzhao Yu[1]*

[1] Department of Biostatistics & Data Science, School of Public Health, LSU Health [2] Department of Epidemiology, School of Public Health, LSU Health [3] Department of Microbiology, Immunology & Parasitology, School of Medicine, LSU Health [4] Department of Pathology, School of Medicine, LSU Health [5] Department of Interdisciplinary Oncology, School of Medicine, LSU Health [6] Department of Genetics, School of Medicine, LSU Health.

LSU Health NEW ORLEANS School of Public Health

publichealth.lsuhsc.edu

Background

- **Triple-Negative Breast Cancer (TNBC):** An aggressive subtype lacking ER, PR, and HER2 receptors.
- Incidence is relatively low (13 per 100,000), but high mortality with a **77.1% five-year survival rate** in the U.S.
- Residential proximity to high-volume transportation infrastructure (airports, railways, highways) is linked to elevated risk.
- The precise molecular mechanisms driving this environmental impact remain unclear.

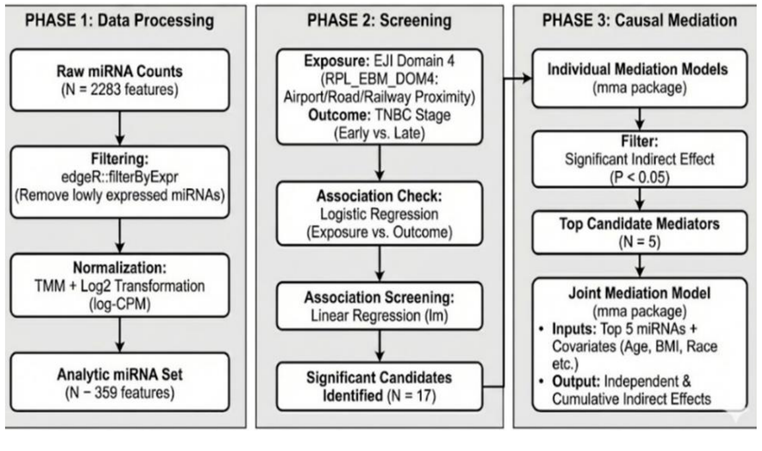
Hypothesis

- Specific microRNA (miRNA) expression profiles serve as the biological link between transportation infrastructure proximity and TNBC stage at diagnosis.

Data Sources

- **Study Sample:** N=434 Formalin-Fixed, Paraffin-Embedded (FFPE) TNBC specimens (2009–2019) obtained from the Louisiana Tumor Registry.
- **Environmental Exposure:** 2022 EJI transportation burden, measuring cumulative residential proximity to major roads, railways, and airports.
- **Molecular Profiling:** High-throughput miRNA sequencing (normalized via TMM).

Methodology



Key Results

Transportation Burden Increases Late-Stage Risk

- A one-unit increase in the transportation burden percentile rank was associated with a **2.16-fold higher odds** of a late-stage TNBC diagnosis (95% CI: 1.12–4.14, ***P* = .021**).

Five Individual miRNA Mediators Identified

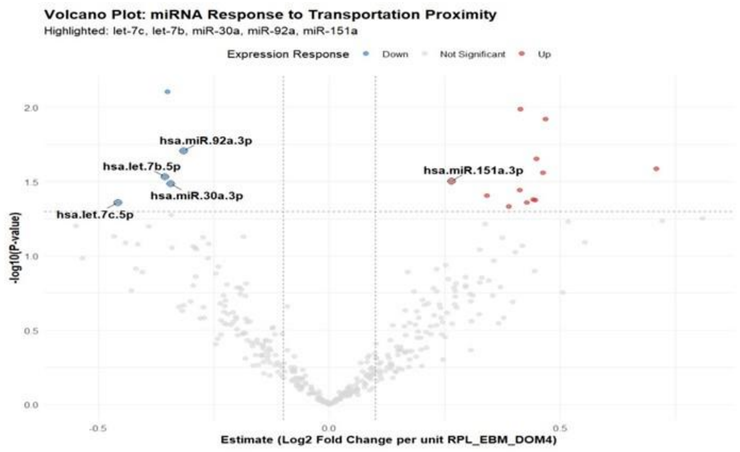


Figure: Volcano Plot of miRNA Association with RPL_EBM_DOM4

Table 1: Estimates of significant miRNA from individual mediation analysis.

miRNA	Indirect Effect Estimate	95% CI Lower	95% CI Upper	P-value
hsa-let-7b-5p	0.354	0.026	0.614	.035
hsa-let-7c-5p	0.248	0.002	0.678	.049
hsa-miR-151a-3p	0.148	0.016	0.378	.025
hsa-miR-30a-3p	0.141	0.008	0.267	.035
hsa-miR-92a-3p	0.104	0.006	0.264	.035

Multiple Mediation Analysis

Table 2: Estimates from the multiple mediation analysis.

Effect Type	Estimate	95% CI Lower	95% CI Upper	P - value
Total Effect	0.916	0.133	1.761	0.024
Direct Effect	0.591	-0.167	1.376	0.147
Joint Indirect Effect	0.324	0.048	0.745	0.027
IE via hsa-let-7c-5p	0.238	0.022	0.652	0.031

Descriptive Statistics For Covariates

	Overall N = 434[1]	Early Stage N = 184[1]	Late Stage N = 250[1]	P-value[2]
Transportation Burden	0.56 (0.29)	0.52 (0.29)	0.59 (0.30)	.02
Age (years)	62 (13)	62 (11)	62 (15)	>0.9
Race				.11
White	226 (52%)	104 (57%)	122 (49%)	
Black	208 (48%)	80 (43%)	128 (51%)	
Body Mass Index	32 (9)	31 (8)	33 (9)	.12

[1] Mean (SD); n (%) [2] Wilcoxon rank sum test, Pearson's Chi-squared test

Pathway Analysis

KEGG Pathway	Description Pathway	P-adjust*	Gene Counts
hsa04010	MAPK signaling pathway	3.233e-18	258
hsa04110	Cell cycle	1.828e-14	143
hsa04310	Wnt signaling pathway	2.811e-11	150
hsa04115	p53 signaling pathway	7.068e-11	72
hsa04151	PI3K-Akt signaling pathway	2.060e-09	281
hsa04210	Apoptosis	1.332e-07	115
hsa05224	Breast cancer	4.120e-07	122
hsa04350	TGF-beta signaling pathway	3.862e-06	92
hsa04330	Notch signaling pathway	1.218e-05	55
hsa04340	Hedgehog signaling pathway	8.645e-05	49
hsa04915	Estrogen signaling pathway	2.656e-03	104
hsa04914	Progesterone-mediated oocyte Maturation	2.148e-02	81

Discussion

- The identified miRNAs may serve as potential biomarkers or therapeutic targets to mitigate the impact of environmental stressors.
- Pathway analysis revealed that these five miRNAs regulate core networks driving tumor progression and metastasis, notably the MAPK, PI3K-Akt, Wnt, and p53 signaling cascades.
- By establishing a "biological roadmap," this work demonstrates that urban planning and environmental policy can directly improve cancer outcomes in high-risk communities.

Acknowledgement

- We acknowledge that part of this research was conducted with high-performance computational resources provided by the Louisiana Optical Network Infrastructure.
- Funding: Supported by NIH grants 2R15MD012387-02, R01CA275089, and P42ES013648