Title: The Modulating Effect of Metabolic and Socioeconomic Factors on Protein Levels for Breast Cancer Risk: An Interaction Analysis in the *All of Us* Cohort

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Background: While specific protein biomarkers have been linked to Breast Cancer (BC) susceptibility, the predictive utility of these proteins may not be uniform across diverse physiological and socioeconomic contexts. Factors such as obesity and lifestyle-related stressors may dynamically modulate how the proteins influence oncogenesis. This study aimed to identify context-specific proteins whose association with BC risk depends on an individual's Body Mass Index (BMI), employment status, or birth origin to refine risk assessment strategies.

Methods: Using MESA-derived protein genetic prediction models and large-scale GWAS summary statistics of BC risk, we identified candidate proteins with genetically regulated expression to be associated with BC risk in European population. In the *All of Us* study, we analyzed a cohort of 273,828 participants (8,029 BC cases and 265,799 controls). We calculated genetically predicted protein levels for 114 candidate proteins by applying the established genetic prediction models of such proteins to the whole-genome sequencing data. Multivariable logistic regression was employed to test for interactions between each protein of interest and three key risk factors: BMI, employment status (employed vs. not employed), and birthplace (US-born vs. non-US-born). Significance was determined using Likelihood Ratio Tests (LRT) comparing full interaction models against reduced main-effects models, adjusting for baseline covariates.

Results: Out of the interaction models tested, 10 significant protein-risk factor interactions were identified across two primary categories. First, BMI emerged as a significant modulator for six proteins (including seq.17783.9, seq.21940.12, seq.3214.3, seq.4407.10, seq.7239.9 and seq.8427.118), suggesting that metabolic state significantly alters the associations of these proteins with BC risk. Second, four proteins (seq.10608.9, seq.12682.5, seq.21696.80 and seq.9756.6) demonstrated significant interactions with employment status, indicating that socioeconomic or environmental stressors associated with occupation may unmask specific protein effects. Notably, no significant interactions were observed with birthplace, suggesting that effects of these proteins may be relatively stable across geographic origins within this cohort.

Conclusions: These findings demonstrate that the protein risk landscape for Breast Cancer is not static, rather, it is "filtered" by a patient's metabolic and socioeconomic profile. BMI and employment status act as key modulators that can amplify or attenuate the predictive value of specific protein biomarkers. If validated in additional studies, our findings suggest that incorporating these interaction effects into polyproteomic risk scores could be essential for developing more accurate, context-aware risk assessment tools for breast cancer.