Investigation of Gut Microbiota and Metabolic Signatures as Predictive Biomarkers of Breast Cancer Development and Neoadjuvant Chemotherapy Response

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Abstract: Breast cancer is the most common cancer among women worldwide. Despite significant advances in treatment, the underlying causes of breast cancer remain incompletely understood. Recently, increasing attention has been directed toward the gut microbiota—its potential role in breast cancer development and its influence on patients' responses to therapy. Dysbiosis, or an imbalance in gut microbial communities, along with alterations in microbiota-derived metabolites, may contribute to cancer progression. Metabolomics and metagenomics have emerged as powerful tools for identifying novel biomarkers that could predict responses to neoadjuvant chemotherapy (NAC). This study aimed to investigate the complex interplay between gut microbiota and breast cancer, with a focus on identifying potential biomarkers for treatment response. To this end, we performed metataxonomic and metabolomic analyses of fecal samples from eight patients with ER+/PR+ invasive ductal carcinoma undergoing NAC (FEC100 regimen). Using Illumina sequencing and NMR spectroscopy, we observed significant shifts in gut microbiota composition and fecal metabolic profiles during treatment. Post-chemotherapy samples revealed a decrease in Actinobacteria and Firmicutes, and an increase in Bacteroidetes and short-chain fatty acid (SCFA)-producing genera such as *Faecalibacterium, Akkermansia*, and members of the *Lachnospiraceae* family. Network analysis indicated substantial restructuring of the microbial community, particularly in poor responders, who exhibited an increase in potentially pathogenic taxa such as *Euryarchaeota* and a lower Firmicutes/Bacteroidetes ratio. Metabolomic profiling identified 27 significantly altered metabolites; notably, amino acids were upregulated, while lactate and fumaric acid levels decreased across treatment cycles, suggesting metabolic reprogramming related to therapeutic response. Many of these metabolites, particularly SCFAs, are of microbial origin and may serve as non-invasive biomarkers for monitoring treatment efficacy. Overall, our findings underscore the significant impact of chemotherapy on gut microbiota composition and fecal metabolomic signatures in breast cancer patients. These insights may contribute to the development of improved clinical tools for monitoring disease progression and predicting treatment outcomes.

Keywords: Breast cancer; gut microbiota; dysbiosis; metabolomics; metataxonomic; chemotherapy