Multi-omics analysis of breast cancer with subtype classification

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Background

In breast cancer, changes in the fecal metabolites and gut microbiota have been shown to influence drug sensitivity and resistance; however, differences in microbial composition between subtypes and their impact on cancer risk remain poorly understood. Here, we compared the fecal metabolites and gut microbiota between healthy controls (HCs) and breast cancer (BC) patients with subtype-specific analyses.

Methods

43 HCs and 29 BC patients feces were collected. Samples from BC patients were collected before treatment initiation, when pre-treatment samples were unavailable, samples were collected during treatment. Metabolomic analysis was performed with LC-TOFMS/MS. 16S metagenomic analysis was performed and the composition was evaluated using ALDEx2. Statistical analysis was conducted using the Wilcoxon-Mann-Whitney test, and *p* values were adjusted for multiple comparisons using the Benjamini-Hochberg method.

Table 1. Characteristics of BC patients.

	BC patients (n=29)	(%)		BC patients (n=29)	(%)
Median age	57 (range: 32 - 87)		**Clinical Stage**		
Subtype			Stage 0	2	6.9
HR+HER2-	18	62.1	Stage Ⅰ	9	31.0
HER2	6	20.7	Stage ⅡA	8	27.6
TNBC	5	17.2	Stage ⅡB	1	3.4
Histopathological type			Stage ⅢA	3	10.3
Invasive ductal carcinoma	24	82.8	Stage ⅢB	2	6.9
Invasive lobular carcinoma	2	6.9	Stage Ⅳ (de novo)	1	3.4
Mucinous carcinoma	1	3.4	Stage Ⅳ (recurrence)	3	10.3
Ductal carcinoma in situ	1	3.4			
Malignant tumors/Sarcomas	1	3.4			

Results 1

The median age was 71 years (range: 36–95) for HCs and 57 years (range: 32–87) for BC patients. The subtypes included 18 cases of hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative, 6 cases of HER2-positive, and 5 cases of triple-negative breast cancer (TNBC).

Results 2

Concerning metabolomic analysis, the PCA plot indicated that the metabolomic profile was different between the HCs and BC patients. AMP, asparagine, diethanolamine, N-Acetylglucosamine 1-phosphate, NAD$^+$, nicotinamide, riboflavin, terephthalate and UMP were increased in the BC patients. ROC analysis for these metabolites yielded an AUC over 0.79 in discriminating BC patients from HCs.

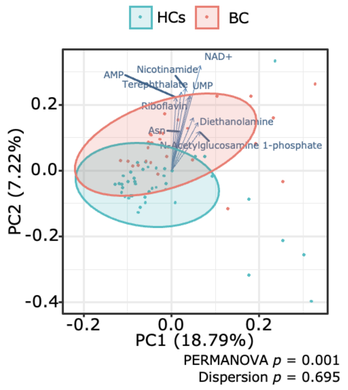


Figure 1. Difference of metabolome between HCs and BC.
Principal component analysis (PCA) plot. Euclidian distance between samples were used in the PCA. Distance between the groups was tested using permutational multivariate analysis of variance (PERMANOVA) and dispersion test.

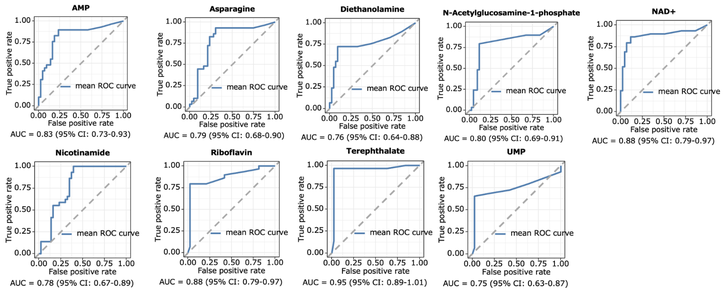


Figure 2. Receiver operating characteristic (ROC) curves of the HCs-BC discriminant models.
For each compound or component, a HCs-BC discriminant model was constructed as a logistic regression model with an explanatory variable. Concentration of the compounds or score of the components were used as the explanatory variable. In the model construction, we used 5-fold cross validation (cv) and synthetic minority over-sampling technique (SMOTE).

Results 3

In gut microbial analysis, β diversity assessed showed no significant difference between HCs and BC patients, while α diversity measured by the Chao1 was reduced in BC patients (q< 0.001). Similarly, the HR+/HER2- group showed no significant difference in β diversity, but α diversity assessed by Chao1 was reduced in the HR+/HER2- group (p< 0.05). Because the number of HER2-positive and TNBC was small, we couldn't come to the conclusion about the difference in these two groups. ALDEx2 revealed that *Clostridiales* and *Bacteroidales* at the order level were changed when comparing HCs and BC patients (effect size > 0.4, p < 0.01, adjusted p = 0.27, 0.19). Furthermore, comparison between the HR+/HER2- and TNBC subtypes showed several changes in *Clostridiales* (effect size > 0.8, p < 0.05, adjusted p = 0.86). Even within the same species, the direction of change varied among subtypes.

Conclusions

This study provides novel insights into the metabolome in breast cancer, highlighting as potential biomarkers. Microbial diversity was reduced in BC patients and the gut microbiota was different between breast cancer subtype.

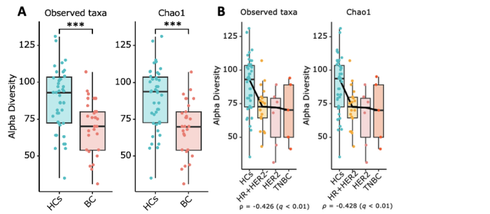


Figure 3. Result of diversity analyses.
(A) Alpha diversity indices (observed taxa and Chao1) were compared between HCs and BC groups. The statistical test was performed with Wilcoxon-Mann-Whitney test. Benjamini-Hochberg method was used for p value adjustment in multiple tests. ***: adjusted p (q) < 0.001. (B) Trends of the two indices across subconditions (HCs, HR+HER2-, HER2, and TNBC).

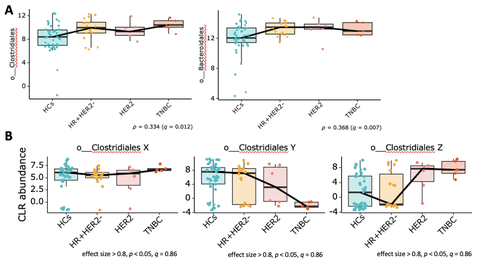


Figure 4. Trends of centered log-ratio (CLR) abundance of the taxa across subconditions.
(A) Plots for the taxa selected in the HCs vs BC test.
(B) Plots for the taxa selected in the HR+HER2- vs TNBC test.

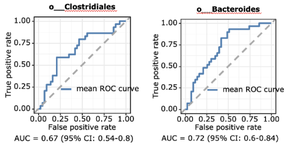


Figure 5. Receiver operating characteristic (ROC) curves of the HCs-BC discriminant models.
For each taxon which had a correlation with the subcondition, a HCs-BC discriminant model was constructed as a logistic regression model with a CLR abundance explanatory variable. In the model construction, we used 5-fold cross validation (cv) and synthetic minority over-sampling technique (SMOTE).

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The authors have no conflict of interest to declare, in this study.

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