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The Microbiome of Aseptically Collected Human Breast Tissue in Benign and Malignant Disease

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More recently, 16S rDNA analysis has shown that milk samples from lactating women have diverse bacterial communities, but it is unknown whether these also are present in breast tissues16. Interestingly, the milk microbiome seems to recapitulate some risk features that are associated with breast cancer. For instance, the breast milk microbiome appears to differ from other human niches and a different, less diverse bacterial community has been observed in obese versus lean mothers.

We hypothesized a resident microbiome in human breast tissue that is distinct from that of the overlying skin.

We further explored di erences in the microbiome of human breast tissue from women with benign and malignant disease in order to evaluate a potential role for a breast microbiome in carcinogenesis.

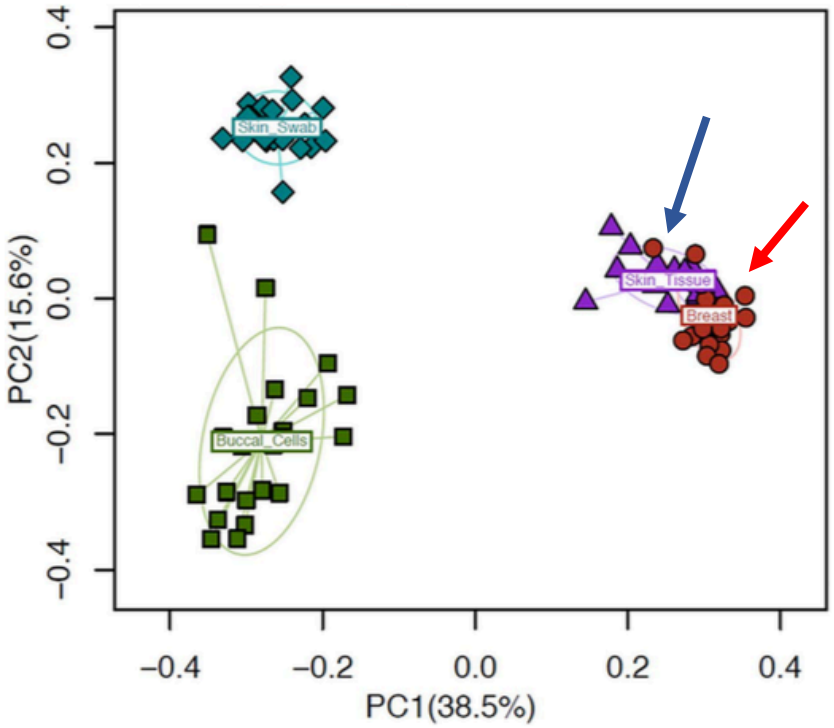
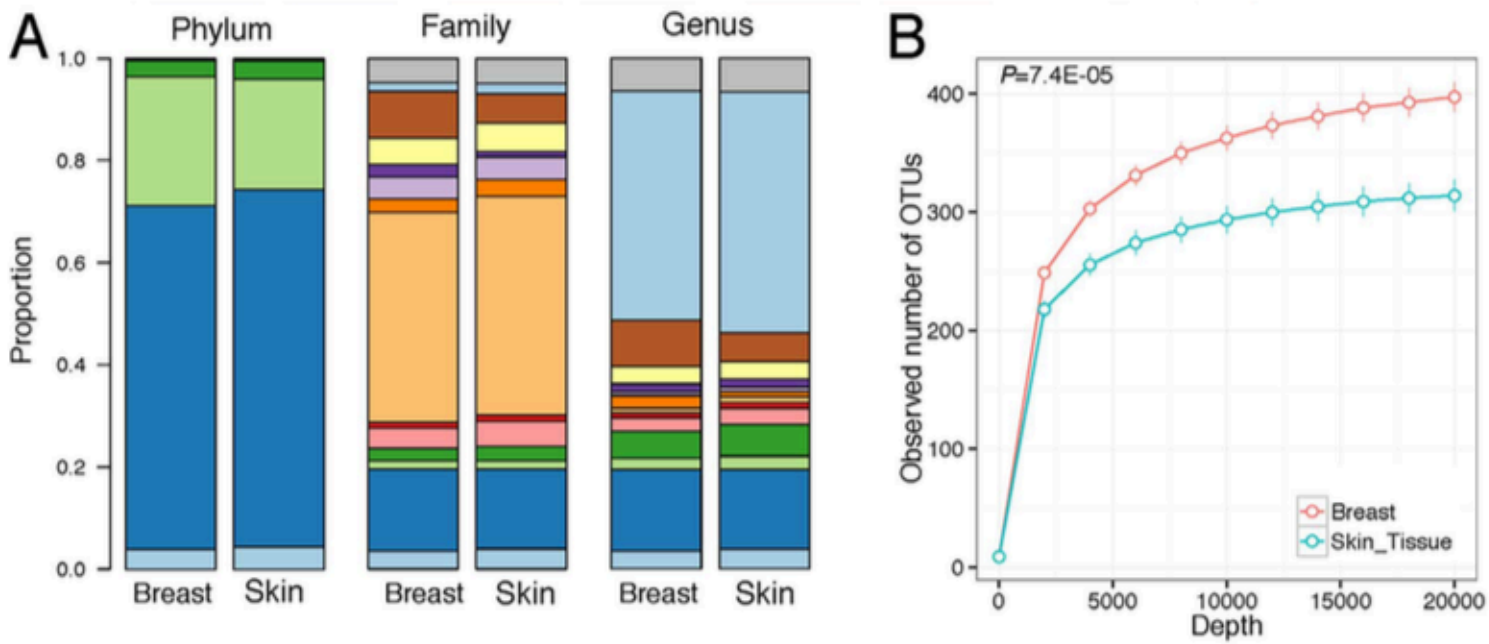
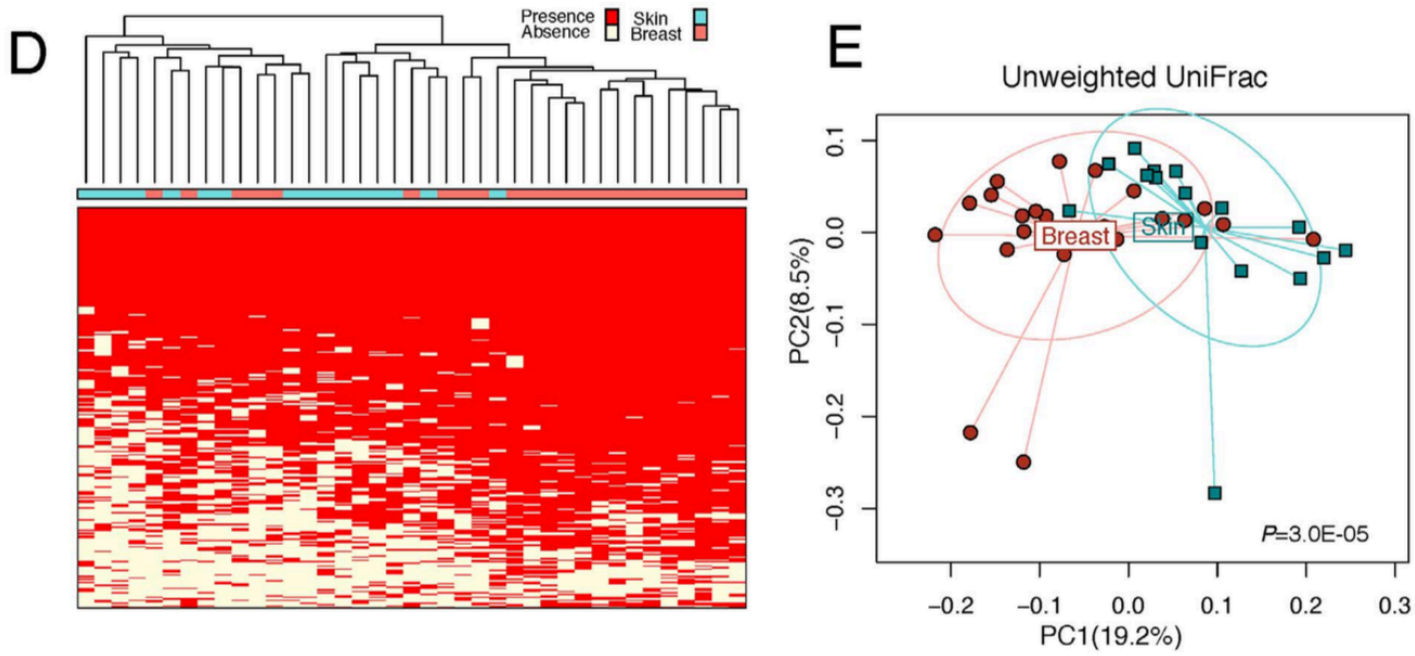


Figure 1. Ordination plot of samples from 33 women shows a distinct clustering pattern of different sample types (breast tissue, breast skin tissue, skin swab and buccal swab). The microbiota samples are embedded in the two-dimensional space based on the first two principal coordinates (PCs) from PCoA on the unweighted UniFrac distance. The percentage of explained variability of each PC is indicated on the axis. Each point represents a sample and is colored by sample types (blue diamonds - skin swab, green squares - buccal swab, purple triangles - breast skin tissue, red circles - breast tissue). The ellipse reflects the probability distribution of each sample type.


A
Phylum
Family
Genus
Proportion
1.0
0.8
0.6
0.4
0.2
0.0
Breast
Skin
Breast
Skin
Breast
Skin
B
P=7.4E-05
Observed number of OTUs
400
300
200
100
0
0
5000
10000
15000
20000
Depth
Breast
Skin_Tissue


D
Presence
Absence
Skin
Breast
E
Unweighted UniFrac
Breast
Skin
P=3.0E-05
PC2(8.5%)
PC1(19.2%)
0.1
0.0
−0.1
−0.2
−0.3
−0.2
−0.1
0.0
0.1
0.2
0.3

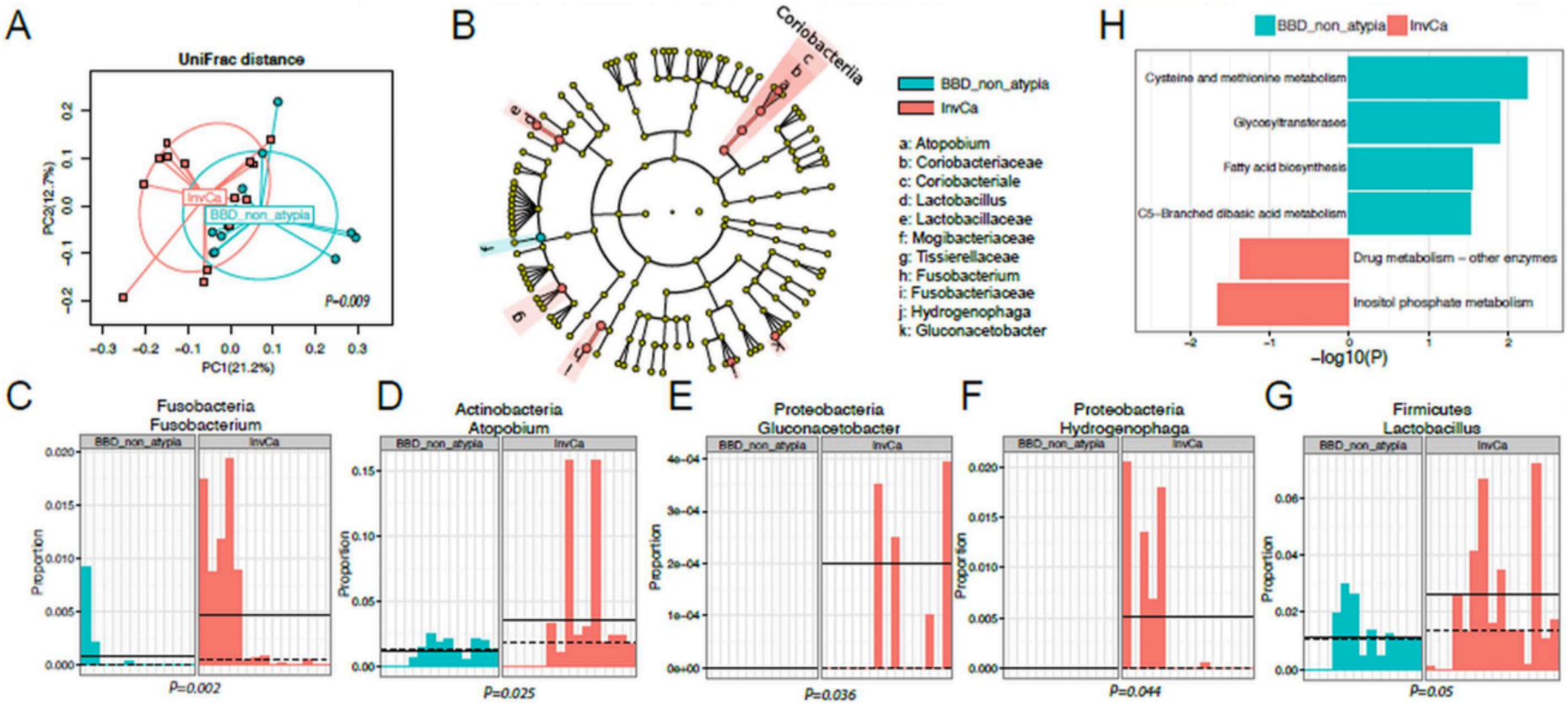


Figure 3. The microbiota of breast tissue adjacent to invasive cancer is distinguishable from that adjacent to benign disease (BBD-non-atypia). (**A**) Ordination plot based on unweighted UniFrac distance shows the clustering pattern of the breast tissue microbiota between the two disease states. (**B**) Differential taxa between the breast tissue microbiota of malignant and benign states based on a permutation test. Taxa with a nominal p value < 0.05 are highlighted on the cladogram with red and blue indicating increase and decrease in invasive cancer respectively. (**C–G**) Barplots show the abundances of the five differential genera between the two disease states. Each bar represents a sample. (**H**) The differential KEGG pathways with a nominal p value < 0.05 between the microbiota of the two states as revealed by PIRCRUSt analysis.

Specific genus-level taxa that were **significantly enriched in breast tissue from women with malignant disease** include ***Fusobacterium*, *Atopobium, Gluconacterobacter, Hydrogenophaga* and *Lactobacillus*.** *Fusobacterium* has been reported in association with other epithelial malignancies including colon cancer and may act by secreting virulence factors as well as creating a pro-inflammatory environment that pro- motes carcinogenesis

We further investigated the functional role of these bacteria within these microenvironments. Using KEGG pathways as the basis for our analysis, **we identified 6 differentially abundant pathways** between benign and malignant disease states. *In patients with malignant disease, pathways involving cysteine and methionine metabolism, glycosyltransferases, fatty acid biosynthesis and C5-branched dibasic acid metabolism were depleted*. Interestingly, methionine dependence is a general metabolic derangement across multiple cancers and it is postulated that depleting methionine might reverse cancer progression, either using methioninase or a methionine-restricted diet.