Endocrine-targeted Therapies Shift The Breast Tissue Microbiome For Potential Anti-cancer Activities

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Studies have shown that breast tissue has a distinct microbiome, which is shifted in the presence of tumors or diet. However, whether orally administered endocrine-targeting therapies used in the adjuvant setting to reduce ER+ breast cancer recurrence modifies the breast microbiome is unknown. We now demonstrate that tamoxifen modulates the breast microbiome, suggesting a potential role for specific bacterial species to enhance therapeutic responsiveness and reduce breast cancer risk. DNA isolated from mammary gland (MG) tissue from female C57BL/6 mice, MG from female C57BL/6 mice administered 37 ppm tamoxifen citrate (human equivalent dose) for 12-weeks, breast tissue from ovariectomized (OVX) non-human primates (NHP), or OVX NHP administered 20 mg/day tamoxifen citrate for 2.5 years were used to perform 16S bacterial sequencing. In both models, tamoxifen significantly shifted β-diversity and was associated with increased Firmicutes phyla proportional abundance. At the species level, tamoxifen was associated with increased Lactobacillus spp., Streptococcus luticea, and Staphylococcus sciuri. Immunohistochemistry staining of breast tissue against CD163 and Lipoteichoic acid (LTA) show differences in tissue macrophage and Gram-positive bacteria abundance with oral endocrine-targeted therapy administration. Western diet-fed MMTV-PyMT mice were intra-nipple injected with Lactobacillus bacteria into the mammary gland at 5, 7, 9, and 11 weeks of age and palpated weekly for tumor formation. Elevated MG Lactobacillus presence was associated with reduced mammary tumorigenesis and multiplicity with an associated decrease in Ki67 tumor proliferation. Breast tumor sections from estrogen receptor-positive and progesterone receptor-positive (ER+/PR+) patients treated in the neoadjuvant setting with aromatase inhibitors (AI), Faslodex, or AI + Faslodex were stained against antibodies for Gram-positive bacteria (LTA), Gram-negative bacteria (Lipopolysaccharide; LPS), or Ki67. Elevated intratumoral LTA-positivity was associated with decreased Ki67 tumor proliferation. Overall, these results suggest oral endocrine-targeting therapies may enrich breast Gram-positive bacteria, increase anti-inflammatory macrophage localization, and elevate bacterial-processed metabolites that decrease proliferation, which may reduce mammary cancer risk.

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