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Endocrine-targeted therapy and diet interactions on gut permeability and the microbiome

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Studies implicate the gut microbiome as a risk factor for estrogen receptor-positive (ER+) breast cancer and a factor modifying therapeutic response. Alterations in gut microbial composition associated with obesity result in increased intestinal permeability and elevated LPS bioavailability. We propose oral endocrine-targeting therapies may differentially affect gut microbiome populations in mice consuming a healthy or western diet to affect intestinal permeability mediating chronic low-grade inflammation, leading to tumor recurrence. 6-week-old female C57BL/6 mice were placed on a healthy control (HC; 21% kcal from fat derived from olive oil and fish oil) or a Western diet (45% kcal from fat derived from corn oil, lard, milk-fat) for 6 weeks. They were randomized based on body fat composition into 6 groups: HC, HC+tamoxifen (TAM; 37 ppm tamoxifen citrate), HC+aromatase inhibitor (AI; 5 ppm letrozole), Western diet, Western+TAM and Western+AI. Body weight measurements, glucose tolerance test (GTT), intestinal permeability assays, plasma LPS ELISA, immunohistochemistry (IHC) and fecal metagenomics sequencing were performed. Increases in body weight and body fat composition were significantly different across groups. In the GTT, Western+AI had higher fasting blood glucose and area-under-the-curve. Intestinal permeability measurements indicate endocrine therapies alter intestinal permeability, with plasma LPS and FITC dextran displaying decreasing trends with endocrine therapy. Ultrasound colon thickness measurements were increased in Western plus endocrine therapy. Differences in microbiota and phage populations with endocrine therapy demonstrate oral endocrine therapies differentially shift *Lactobacillus* and *Lactococcus* populations. Our study indicates oral endocrine therapies affect the gut microbiome and intestinal permeability that are sensitive to dietary-influenced baseline microbiota populations, which result in differential drug metabolic outcomes. Future studies modifying gut *Lactobacillus* abundance in ER+ tumor bearing mice will be performed to determine relevance of this population modifying anti-cancer tamoxifen efficacy.

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