Influence of soy isoflavones on metabolism and activity of 17beta-estradiol in human mammary gland

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17β-Estradiol contributes to breast cancer development by estrogen receptor (ER)-mediated induction of proliferation and/or DNA adduct formation. Since both beneficial and adverse effects of isoflavones on human mammary gland have been discussed repeatedly, their influence on estrogen levels, ER activation and on fluxes of estrogen-DNA adducts was investigated in human mammoplasty specimen with and without previous isoflavone intervention for 7 days. Levels of 17β-estradiol, estrone, metabolites and conjugates thereof were quantified by GC- and UHPLC-MS/MS, respectively. DNA adducts were determined by computational-based metabolic network modeling, comprising of reactions of estrogen and energy metabolism, using levels of 17β-estradiol and estrone as well as transcript levels, determined by TaqMan® qPCR (estrogen metabolism) and RNA sequencing (energy metabolism) as flux constraints. Explanatory variables (ExVARs) affecting the dependent variables 17β-estradiol, estrone, transcript levels of either enzymes involved in estrogen (biotrans)formation or indicating ER activation as well as DNA adduct fluxes were identified by stepwise forward selected multiple linear regression models. Besides the ExVARs "intervention" and various ExVARs related to isoflavone-levels (derived from tissue levels of genistein, daidzein and conjugates thereof determined in glandular tissues by UHPLC-MS/MS), other variables possibly affecting the dependent variables were identified and taken into account. The session will introduce practical obstacles occurring during study design, tissue collection, data acquisition, statistical data analysis and overcoming thereof so that novel insights could be obtained in the end.
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