1496 Association of Genistein with 17β-Estradiol and Estrogen Receptor Activation but Not with Metabolic Fluxes to Estrogen-DNA Adducts in the Human Breast

R. Hauptstein[5], D. Pemp[5], B. Spielmann[5], C. Kleider[5], S. Weck[5], K. Schmalbach[5], S. T. Soukup[1], L. N. Geppert[3], C. Köllmann[3], S. E. Kulling[1], T. Dandekar[5], P. Eckert[2], I. Neshkova[4], R. Jakubietz[4], H. L. Esch[5] , and L. Lehmann[5]. *[1]MRI, Karlsruhe, Germany; [2]Practice for Plastic and Aesthetic Surgery, Wuerzburg, Germany; [3]TU Dortmund, Dortmund, Germany; [4]University Hospital of Wuerzburg, Wuerzburg, Germany; and [5]University of Wuerzburg, Wuerzburg, Germany.*

17β-estradiol (E2) contributes to breast cancer development by induction of proliferation and formation of DNA adducts and isoflavones may have impact thereon. Thus, influence of genistein (GEN) on E2 levels, estrogen receptor (ER) activation and estrogen-DNA adducts was investigated in mammoplasty specimen derived from 47 women exposed to GEN via their usual diet or by intake of isoflavone-rich extract for 7 days prior to surgery. Glandular tissues were isolated, characterized histologically and oil contents were determined gravimetrically. Metabolic fluxes to estrogen-DNA adducts were determined by computational-based metabolic network modeling, comprising of 159 reactions of estrogen metabolism, using levels of E2 and estrone (E1), determined by GC-MS/MS, and transcript levels, determined by TaqMan® qPCR, as flux constraints. Levels of GEN were quantified using UHPLC-MS/MS. Associations of the dependent variables metabolic fluxes to estrogen-DNA adducts ("estrogen-DNA adducts"), tissue levels of E2 ("E2 levels") as well as transcript levels of progesterone receptor ("ER activation") with multiple explanatory variables (ExVARs) were investigated by stepwise forward selected multiple linear regression models. The ExVAR semiquantitative tissue levels of GEN ("GEN") was tested in addition to "isoflavone-rich extract", "estrogen-active drugs", "smoking", "BMI", "lobule type" and "age". Models describing "E2 levels" further tested "menopause", "oil", "adipocyte-rich tissue", "E1 levels", as well as 13 transcripts and 2 polymorphisms of estrogen-metabolizing (iso)enzymes. Models describing "ER activation" further tested transcript levels of ERs and E2 levels. Despite "GEN" was significantly positively associated with "E2 levels", no effect on "estrogen-DNA-adducts" and even negative association with "ER-activation" was observed. Supported by DFG, Le-1329/10-1