Alcohol-related breast cancer in postmenopausal women - effect of CYP19A1, PPARG and PPARGC1A polymorphisms on female sex-hormone levels and interaction with alcohol consumption and NSAID usage in a nested case-control study and a randomised controlled trial - DTU Orbit (13/12/2018)

Alcohol consumption is associated with increased risk of breast cancer (BC), and the underlying mechanism is thought to be sex-hormone driven. In vitro and observational studies suggest a mechanism involving peroxisome proliferator-activated receptor gamma (PPARγ) in a complex with peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) and interaction with aromatase (encoded by CYP19A1). Use of non-steroidal anti-inflammatory drugs (NSAID) may also affect circulating sex-hormone levels by modifying PPARγ activity. In the present study we assessed whether genetic variation in CYP19A1 is associated with risk of BC in a case-control study group nested within the Danish "Diet, Cancer and Health" cohort (ncases = 687 and ncontrols = 687) and searched for gene-gene interaction between CYP19A1 and PPARGC1A, and CYP19A1 and PPARG, and gene-alcohol and gene-NSAID interactions. Association between the CYP19A1 polymorphisms and hormone levels was also examined among 339 non-HRT users. Incidence rate ratios were calculated based on Cox proportional hazards model. Furthermore, we performed a pilot randomised controlled trial to determine the effect of the PPARG Pro(12)Ala polymorphism and the PPARγ stimulator Ibuprofen on sex-hormone levels following alcohol intake in postmenopausal women (n = 25) using linear regression. Genetic variations in CYP19A1 were associated with hormone levels (estrone: P rs11070844 = 0.009, estrone sulphate: P rs11070844 = 0.01, P rs749292 = 0.004, P rs1062033 = 0.007 and P rs10519297 = 0.03, and sex hormone-binding globulin (SHBG): P rs3751591 = 0.03) and interacted with alcohol intake in relation to hormone levels (estrone sulphate: P interaction/rs2008691 = 0.02 and P interaction/rs1062033 = 0.03, and SHBG: P interaction/rs11070844 = 0.03). CYP19A1/rs3751591 was both associated with SHBG levels (P = 0.03) and with risk of BC (Incidence Rate Ratio = 2.12; 95 % Confidence Interval: 1.02-4.43) such that homozygous variant allele carriers had increased levels of serum SHBG and were at increased risk of BC. Acute intake of alcohol decreased blood estrone (P =

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