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Obesity and endometrial cancer: using proteomics to identify underlying mechanistic pathways

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Background
Obesity is a major risk factor for endometrial cancer (EC), but the underlying mechanisms are not well understood. Using proteomics and causal mediation analysis, we examined 155 circulating protein markers in 624 cases and 624 matched controls in a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.
Methods
Anthropometric measures and blood samples were collected at cohort recruitment. Protein levels were measured in pre-diagnostic plasma samples using Proximity Extension Assay technology (Olink Bioscience AB, Sweden) and reported in Normalised Protein eXpression (NPX), which correlates to 2-fold increase in protein concentration. The body mass index (BMI)-protein associations were estimated among controls using multivariate linear regression. The protein-EC associations were estimated using conditional multivariate logistic regression including adjustment for BMI. For each protein associated with both BMI and EC, we decomposed the total effect of obesity [BMI ≥30kg/m2 vs <25kg/m2] on risk of EC into natural indirect effect (NIE) mediated by the protein and natural direct effect, and calculated the proportion mediated.
Results
IL6 [odds ratio (OR) per NPX = 1.32 (95% confidence interval (CI) = 1.05–1.65)], HGF [1.48 (1.06–2.07)], PIK3AP1 [1.22 (1.00–1.50)] and CLEC4G [1.52 (1.00–2.32)] were positively associated with risk of EC, and HSD11B1 [0.67 (0.49–0.91)], SCF [0.68 (0.49–0.94)], and CCL25 [0.80 (0.65–0.99)] were inversely associated with risk. Of these, IL6 [NIE OR = 1.19 (1.09–1.31); proportion mediated = 15%], HSD11B1 [1.25 (1.15–1.36); 19%], HGF [1.10 (1.03–1.18); 8%], and SCF [1.06 (1.00–1.11); 5%] could represent mediators of the effect of obesity on risk of EC [total OR = 3.17 (2.68–3.75)].
Conclusion
Protein markers related to inflammation (IL6, PIK3AP1, HGF), cortisol-cortisone conversion (HSD11B1), immunoregulation (CLEC4G, CCL25), and angiogenesis (HGF) could influence risk of EC. Some of these markers may represent pathways involved in mediating the effect of obesity on risk of EC, and may be potential targets for cancer prevention in women with obesity.

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