Gene-hormone therapy interaction and fracture risk in postmenopausal women

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ABSTRACT

Background: Previous evidence supports a protective effect of menopausal hormone therapy (HT) on fracture risk. Given the completed meta-genome-wide association studies (GWAS) on bone, we test the hypothesis that a genetic risk score (GRS) for fracture modifies the association of HT and fracture risk.
Methods: We constructed two GRSs in 9,922 European American postmenopausal women from the Women's Health Initiative HT randomized clinical trials based on 16 fracture-associated variants (Fx-GRS) and 50 bone mineral density (BMD) variants (BMD-GRS) weighted by effect sizes from the published meta-GWAS. We used Cox proportional hazards regression to estimate the main effects of GRSs and their interactions with HT on total fracture risk. We estimated the relative excess risk due to interaction (RERI) as a measure of additive interaction and evaluated interaction on the multiplicative scale using an interaction term in the model. We also utilized the case-only approach to test for a multiplicative interaction.
Results: Both GRSs were associated with total fracture risk; the hazard ratio (HR) (95% CI) per one unit increment in weighted GRS was 1.04 (1.02, 1.06) for Fx-GRS and 1.03 (1.02, 1.04) for BMD-GRS. We found no evidence for multiplicative interaction in Cox models for either of the GRS (Fx-GRS p-interaction=0.491, BMD-GRS p-interaction=0.633), nor indications of significance in case-only analyses. However, we observed a significant additive interaction, where the highest quartile of both GRSs and randomization to placebo have excess fracture risk: (Fx-GRS RERI (95% CI)=0.35 (0.01, 0.69; p=0.047), BMD-GRS RERI (95% CI)=0.38 (0.01, 0.75; p=0.046)).
Interpretation: Our study demonstrates the utility of clinical trial data for gene-environment interaction studies. These results suggest that HT reduces fracture risk in postmenopausal women especially in those at highest genetic risk of fracture and bone loss. GRS may be an additive factor to consider in evaluating the risk-benefit profile of HT in those populations.

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