Gene-hormone therapy interaction and fracture risk in postmenopausal women

Youjin Wang¹, Jean Wactawski-Wende¹, Lara Sucheston-Campbell², Leah Preus¹,², Jing Nie¹, Rebecca D. Jackson³, Samuel K. Handelman⁴, Rami Nassir⁵, Carolyn J. Crandall⁶, and Heather M. Ochs-Balcom¹

¹Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, The State University of New York, Buffalo, NY
²Department of Cancer Prevention and Control, Division of Cancer Prevention and Population Sciences, Roswell Park Cancer Institute, Buffalo, NY
³Department of Internal Medicine, Division of Endocrinology, Diabetes and Metabolism, The Ohio State University, Columbus, OH
⁴Center for Pharmacogenomics, Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University, Columbus, OH
⁵Department of Biochemistry and Molecular Medicine, University of California Davis, Davis, CA
⁶Division of General Internal Medicine and Health Sciences Research, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA

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 GRSs (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.
Youjin Wang
PhD Candidate, Epidemiology
Department of Epidemiology and Environmental Health
School of Public Health and Health Professions
University at Buffalo
265 Farber Hall
Buffalo, NY 14214-8001
E-mail: youjinwa@buffalo.edu
Telephone: 716-208-0390