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Effect of Exercise and Weight Loss Intervention on Epigenetic Age Amongst Overweight Breast Cancer Survivors

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Excess weight and insufficient physical activity are associated with higher risk of breast cancer recurrence and death in breast cancer survivors. Epigenetic age clocks, assessed by DNA methylation, may capture intervention effects. **PURPOSE:** Examine the effect of a randomized control trial of exercise and weight loss on epigenetic age clocks among breast cancer survivors with overweight or obesity (n=20). **METHODS:** Participants in the intervention group (n=10) underwent a 1-year weight loss and exercise training program. DNA was collected from whole blood samples at baseline and 1-year post-intervention. Whole-genome methylation (EPIC V2 array) was used to calculate five separate measures of epigenetic age: the Horvath clock, Hannum clock, GrimAge, PhenoAge, and the DunedinPACE. Intrinsic Epigenetic Age Acceleration (IEAA), a measurement of the Horvath epigenetic age acceleration, controlling for immune cell proportions, was also computed. Associations between epigenetic age and fitness capacity and body composition at baseline and post-intervention were assessed using linear regressions. Effect of intervention on epigenetic age was measured by mixed regression models with the adjustment of age at baseline and immune cell proportions. Correlations of changes in epigenetic age with changes in body composition and fitness capacity were assessed. **RESULTS:** At baseline, there was a positive association between IEAA and lean mass (β=0.23 year/kg, p=0.05), as well as muscle mass (β=0.25 year/kg, p=0.04). At 1 year, there was a positive association between IEAA and lean mass (β=0.34 year/kg, p<0.02), muscle mass (β=0.34 year/kg, p<0.02), as well as fat mass (β=0.22 year/kg, p<0.03). Changes in epigenetic age in the intervention group was significantly lower than the control groups of several clocks (p<0.05): Hannum clock: mean change (standard error) for intervention was 0.28 (0.55), control 2.02 (0.37). GrimAge clock: intervention 0.10 (0.67), control 1.30 (0.36). Horvath clock: intervention -1.01 (0.86), control 1.91 (0.67). PhenoAge: intervention 0.28 (0.55), control 2.01 (1.07). Lastly, the change in age calculated by the Horvath clock is highly positively correlated with change in fat mass (r=0.47, p<0.05) and % body fat (r=0.49, p<0.05). **CONCLUSION:** In this pilot study, combined weight loss and exercise intervention slowed epigenetic aging in breast cancer survivors with overweight or obesity. **SIGNIFICANCE/ NOVELTY:** A younger epigenetic age following the combination of exercise and weight loss intervention represents a favorable modulation because of its association with lower risk of breast cancer recurrence and mortality. Encouraging breast cancer survivors with excess weight to lose weight and exercise more may decrease the risk of breast cancer recurrence and mortality.