Weight Loss to Reduce Post-Menopausal Breast Cancer Risk

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Obesity and adult weight gain are important risk factors for several cancers, including postmenopausal breast cancer. One of the mechanisms believed to link adiposity and breast cancer risk is elevated levels of sex hormones. After menopause, adipose tissue is the main source of enzymes that catalyze the formation of estrone, estradiol and testosterone.

A recent randomized controlled trial led by Dr. Anne McTiernan, Public Health Sciences Division, now provides some of the first data comparing the independent and combined effects of physical activity and weight loss on putative pathways linking lifestyle and breast cancer.

For 12 months, 439 overweight and obese postmenopausal women who were not taking any menopausal hormones, were randomized to either a reduced-calorie diet, aerobic exercise, combined diet plus exercise, or control. The average weight loss was 3.3% in the exercise group, 10.8% in the diet alone group, and 11.9% in the diet plus exercise group.

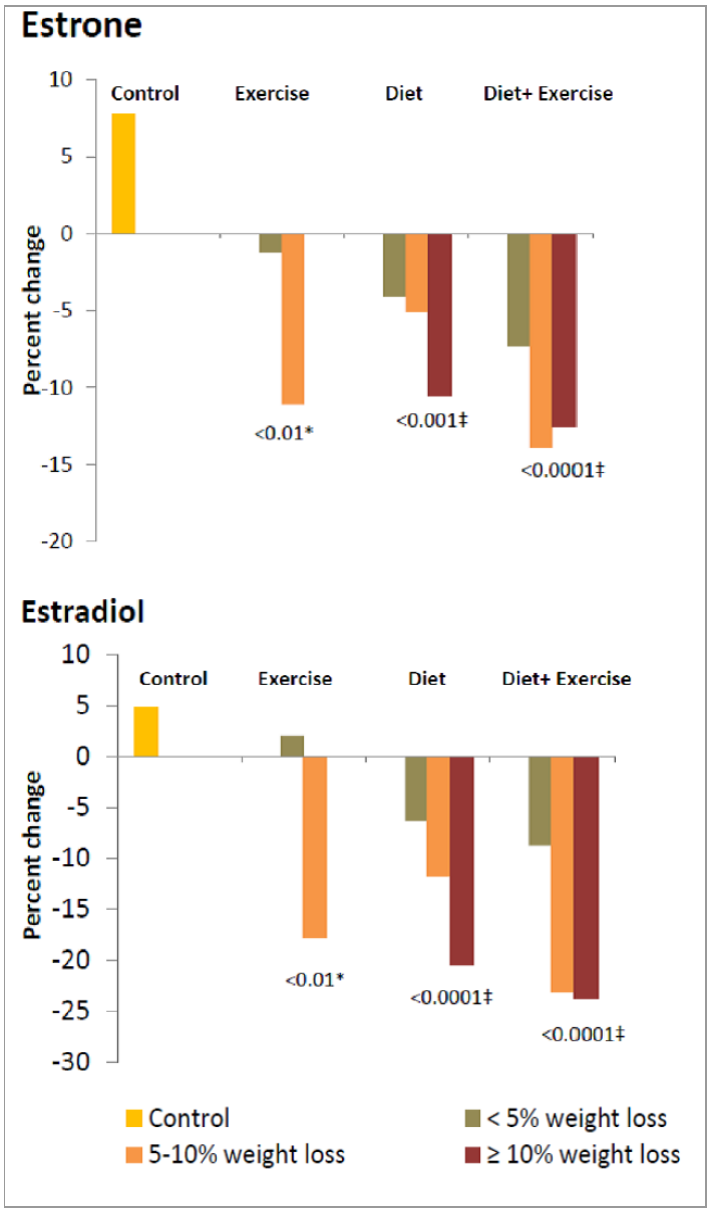
Compared to controls, estrone and estradiol concentrations were significantly decreased in women assigned to diet alone (-9.6% and -16.2%; both $p \leq 0.001$) and diet plus exercise (-11.1% and -20.3%; both $p<0.001$), and to a lesser degree among women randomized to exercise alone (-5.5%, $p=0.01$ and -4.9%, $p=0.10$). Sex hormone-binding globulin (SHBG), which reduces the bioactivity of estrogens and androgens, significantly increased in the diet (+22.4%, $p<0.001$) and diet plus exercise (+25.8%, $p<0.001$) groups, with no change in the exercise alone group (-0.7%, $p=0.41$). Total testosterone was not significantly changed in any group compared to controls but free testosterone was significantly reduced in the diet (-10.0%, $p<0.001$) and diet plus exercise groups (-15.6%, $p<0.001$). Similarly, free estradiol was also reduced in the diet (-21.4%) and diet plus exercise groups (-26.0%) compared to controls (+6.3%, both $p<0.001$). No significant changes in androstenedione, a steroid necessary for the production of sex hormones, were noted in any of the groups.

The observed benefit of weight loss on estrogens and SHBG highlights the potential role of lifestyle behaviors in reducing postmenopausal breast cancer risk. Together with risk estimates from

previous studies, the results of this trial suggest that a relatively modest weight loss of 5-10% of initial body weight could decrease the risk of estrogen-sensitive breast cancers by a quarter to a half for overweight and obese postmenopausal women. However, the true magnitude of breast cancer risk reduction associated with changes in sex hormones will need to be confirmed in future studies.

Beneficial effects of weight loss on other proposed biomarkers of breast cancer risk including insulin, C-reactive protein, leptin and adiponectin were also observed in this trial, suggesting that weight loss is an efficacious means of affecting several biologic pathways implicated in the lifestyle-cancer association.

Campbell KL, Foster-Schubert KE, Alfano CM, Wang CC, Wang CY, Duggan CR, Mason C, Imayama I, Kong A, Xiao L, Bain CE, Blackburn GL, Stanczyk FZ, McTiernan A. (2012). Reduced-Calorie Dietary Weight Loss, Exercise, and Sex Hormones in Postmenopausal Women: Randomized Controlled Trial. *Journal of Clinical Oncology*, Epub ahead of print, doi: 10.1200/JCO.2011.37.9792



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Twelve month changes in serum estrone and estradiol among overweight and obese postmenopausal women. (*) Testing for a trend in 12 month change from controls across weight loss <5% and ≥5% (exercise only). (‡) Testing for a trend in 12 month change from controls across weight loss ≥10%.