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Exercise Improves Drug-associated Joint Pain in Breast Cancer Survivors

SAN ANTONIO — Breast cancer survivors taking aromatase inhibitors (AIs) such as anastrozole, letrozole, and exemestane experienced a reduction in joint pain if they exercised while on treatment, according to results presented here at the 2013 San Antonio Breast Cancer Symposium, held Dec. 10–14.

Five years of AI use after surgery or other primary treatment is recommended for postmenopausal women diagnosed with stages 1-3 hormone receptor-positive breast cancers, which account for nearly 70 percent of all newly diagnosed breast cancer cases. Up to 50 percent of patients on AIs report experiencing arthralgia, or joint pain and stiffness. This side effect is the most common reason patients stop taking the drug.

"AIs play an important role in the effective treatment of hormone receptor-positive breast cancer," said Melinda L. Irwin, Ph.D., M.P.H., associate professor of chronic disease epidemiology at the Yale School of Public Health and co-leader of the Cancer Prevention and Control Research Program at the Yale Cancer Center. "Unfortunately, many patients discontinue the drug because of its unpleasant side effects. In this study, we discovered that exercise improves joint pain, the most common side effect of AI use. These results are a promising first step in developing clinical interventions that can improve AI-associated joint pain and, in turn, AI adherence, breast cancer survival, and quality of life."

In this randomized trial, Irwin and colleagues investigated the impact of a yearlong exercise program compared with usual care on women who were taking AIs and experiencing joint pain. Measures of worst pain, pain severity, and pain interference dropped 20 percent among participants who were assigned to the exercise program, compared with modest increases or no change in joint pain among participants who were assigned to usual care. Exercisers experienced these improvements regardless of age; disease stage; whether they received chemotherapy, radiation, or both; and how long they had been taking AIs.

The researchers also observed a dose-response effect: Women who attended at least 80 percent of the supervised exercise sessions experienced a 25 percent decrease in worst pain scores, while women who attended fewer than 80 percent of the supervised exercise sessions experienced a 14 percent decrease. Similarly, women who experienced a 5 percent increase in cardiorespiratory

fitness had a 29 percent decrease in worst pain scores, compared with a 7 percent decrease in worst pain scores among women who experienced a smaller increase in cardiorespiratory fitness.

The 121 study participants were postmenopausal women diagnosed with stages 1-3 hormone receptor-positive breast cancers who were taking an AI. All reported at least mild joint pain and were not exercising at enrollment, but were physically able to exercise. Sixty-one participants were randomly assigned to an exercise program that entailed twice-weekly supervised resistance and strength training sessions and 150 minutes per week of at least moderate-intensity aerobic exercise, such as brisk walking. This exercise prescription is the current recommendation for healthy adults and cancer survivors.

Irwin and colleagues will next examine in more detail the mechanisms that may be influencing the effect of exercise on AI-associated joint pain, including body weight, inflammation, and muscular strength, as well as whether improvements in joint pain occurred at the beginning, middle, or end of the yearlong intervention.

This study was funded by the National Cancer Institute. Irwin declares no conflicts of interest.

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The mission of the 2013 San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR), and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR's scientific prestige in basic, translational, and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. For more information about the symposium, please visit www.sabcs.org.

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Title: Randomized trial of exercise vs. usual care on aromatase inhibitor-associated arthralgias in women with breast cancer: The hormones and physical exercise (HOPE) study

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PURPOSE: Arthralgias occur in up to 50% of women with breast cancer treated with adjuvant aromatase inhibitors (AIs), and are one of the most common reasons for poor adherence to therapy. We examined whether a year-long exercise program improves arthralgias in breast cancer survivors taking AIs.

METHODS: Postmenopausal women diagnosed with hormone receptor-positive breast cancer were identified via the Connecticut Tumor Registry. Women who were taking an AI for at least 6-months and reported > 3 out of 10 on the worst joint pain item of the Brief Pain Inventory-Short Form (BPI) were eligible and randomized to either exercise (150 min/wk of moderate-intensity aerobic exercise and twice-weekly supervised resistance exercise sessions) or usual care. The BPI questionnaire was completed at baseline, 6- and 12-months. VO2 max testing and Dual Energy X-ray Absorptiometry (DEXA) scans were also collected at baseline, 6- and 12-months. The primary outcome was change in BPI worst joint pain score between 0 and 12 months. We performed intent-to-treat statistical analyses including analysis of covariance, where each participant's change in outcome was modeled as a function of randomization group

RESULTS: Out of 728 women screened that were taking an AI, we randomized 121 women, with 61 women randomized to exercise and 60 women randomized to usual care. Baseline characteristics were comparable between the two groups. Over 12 months, women randomized to exercise attended, on average, 80% + 14% of the twice-weekly supervised resistance training exercise sessions and participated in an average 146 + 75 min/wk of at least moderate-intensity aerobic exercise. Worst joint pain scores decreased by 20% at 12 months among women randomized to exercise vs. a 3% decrease among women randomized to usual care ($p = .017$). Joint pain severity also decreased significantly in exercise vs. usual care groups ($p=0.025$), as well as joint pain-related interference ($p=0.005$). The exercise intervention also favorably impacted body weight ($p=0.0057$) and cardiorespiratory fitness ($p=0.024$).Baseline to 12 month changes in BPI joint pain scores (mean (SD))

Baseline Values Change from baseline to 12 months BPI Item Exercisers Usual Care p-value Exercisers Usual Care p-value Worst Pain 5.5 (1.9) 5.9 (1.9) 0.29 -1.1 (2.5) -0.2 (1.6) 0.017 Pain Severity 3.9 (1.6) 4.3 (1.8) 0.27 -0.8 (2.1) 0.0 (1.5) 0.025 Pain Interference 2.8 (2.1) 2.9 (2.3) 0.81 -0.8 (2.0) 0.2 (1.9) 0.005

Body weight (kg) 80.9 (16.8) 74.6 (14.5) 0.11 -3.5 (6.0) 0.1 (3.7) 0.0057 VO2max (ml/kg/min) 23.5 (4.8) 23.1 (4.3) 0.75 1.9 (1.9) 0.4 (2.7) 0.024

CONCLUSION: We found that participating in an exercise intervention led to clinically meaningful improvements in AI-induced arthralgias in breast cancer survivors experiencing moderate joint pain. The intervention also induced favorable changes in body weight and cardiorespiratory fitness, factors that may be linked to incidence and severity of AI-induced arthralgias. Further work is needed to determine whether exercise leads to increased AI adherence and possibly better outcomes in women with breast cancer.