

## An open-label randomized trial of exercise $\pm$ creatine supplementation to augment the adaptations of exercise training in cancer survivors.

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**Background:** Breast cancer survivors face a heightened risk of skeletal muscle wasting, which can be worsened by cancer treatments, adversely affecting their ability to perform daily activities. Additionally, lower extremity muscle weakness has been linked to persistent fatigue in survivors. Research on resistance exercise interventions has demonstrated significant improvements in strength, endurance, and body composition among breast cancer survivors. Nonetheless, developing effective strategies to optimize exercise adaptations for this population remains a critical area of focus. Creatine phosphate (CP) supplementation has gained attention in the medical field because of the numerous health and quality of life benefits. CP is crucial to maintaining muscle energetics because of its role in rephosphorylating adenosine diphosphate to adenosine triphosphate (ATP). To date, few studies have examined the use of CP supplementation to augment exercise adaptations in breast cancer survivors. As such, we propose the THRIVE clinical trial to assess the effects of 12-weeks of CP supplementation in combination with home-based resistance exercise on outcomes of strength, body composition, physical function and mechanistic biomarkers. **Methods:** The THRIVE clinical trial is a prospective, open-label, randomized trial aiming to recruit thirty breast cancer survivors that have completed infusion chemotherapy less than 6 months prior to study enrollment. Patients will be randomized (1:1) to either the CP plus exercise group or exercise only group. Participants who are randomized to receive CP will be initially dosed at 20 g per day for 7 days to boost the availability of CP systemically. Thereafter, the dose will be reduced to 5 g per day for maintenance throughout the duration of the 12-week protocol. All participants will engage in 3 virtually supervised, home-based exercise session each week. Each session will last roughly 1 hour and include a 10-minute warm-up and a 50-minute stimulus phase consisting of upper body and lower body resistance exercises. Primary outcomes will be strength, body composition (DXA scan), physical function (6 min walk test) and mechanistic biomarkers (growth factor and inflammatory biomarkers). Secondary objective will be muscle cross-sectional area and intramuscular creatine, phosphocreatine and ATP as measured by magnetic resonance imaging and spectroscopy, respectively. Tertiary outcomes will be patient reported outcomes on quality of life. To date, 11 of the planned 30 patients have been enrolled. This study is registered with clinicaltrials.gov (NCT06395506). Clinical trial information: NCT06395506. Research Sponsor: Thrivewell Cancer Foundation.