EFFECTS OF A PHYSICAL EXERCISE PROGRAM ON CARDIOVASCULAR, METABOLIC, PHYSICAL FITNESS AND QUALITY OF LIFE IN CANCER SURVIVORS' ADULT WOMEN

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Study documents

SCIENTIFIC BACKGROUND: In Chile, in the year 2022, it was reported that the main causes of death are diseases of the circulatory system (31,606) and cancer (with 28,453 deaths) (1). Both causes of death come from diseases such as arterial hypertension, diabetes, obesity, highly linked to sedentary lifestyles (i.e., spending long hours sitting), physical inactivity (i.e., not adhering to the international recommendations of physical activity per week of 150 to 300 min of low to moderate intensity physical activity, or 75 to 150 min of vigorous physical activity per week) (2) and lifestyle (i.e., healthy eating, and inflammation processes such as cancer). Worryingly, in the Bío-Bío region alone, women's deaths from cancer reported 1,380 deaths, one of the highest in the country (3).

Exercise training (i.e., defined as a particular type of physical activity guided by a professional and regulated overtime) has demonstrated evidence of the prevention and treatment of cancer (4), as well as in diabetes and arterial hypertension (co-morbidities). This has been raised by the American College of Sports Medicine (ACSM) (4), emphasizing the evidence in favor of the practice of exercise training (i.e., particularly aerobic and strength-type exercise) from the strongest (anxiety, depression, fatigue, quality of life, lymphedema, physical function) to the least amount of evidence (cardio-vascular, pain, etc).

Despite the “solid” evidence in favor of the effects of exercise training in cancer survivors (CS) to improve variables such as anxiety, depressive symptoms, fatigue, quality of life, lymphedema, and physical function, unfortunately they are still unknown and there is minimal evidence about the effects of exercise training on cardio-vascular and metabolic variables in cancer survivors’ persons (4). The phenomenon of the exercise training in CS persons is of relevance, because as it is pointed out, cancer is the second cause of death in Chile, and in particular breast cancer is the first cause among all types of cancer, and where the exercise training has a relevant value as a treatment and post-

treatment. Thus, it is required to fill the scientific gap in terms of the need to increase the evidence of exercise training in cardio-vascular physiology, such as parameters related to blood pressure (5), and endothelial dysfunction such as carotid intima-media thickness (cIMT), dilation-mediated flow (FMD) and pulse wave velocity (PWV) (6), as well as metabolic factors related to metabolism during exercise of oxidative and glycolytic type, which determine the oxidation of fat and glucose during exercise. There is consolidated or "solid" evidence (7), about the effects of physical exercise (i.e., exercise guided by a professional and planned over time), according to the American College of Sports Medicine (ACSM) exercise recommendations guide for CS (4).

Different types of exercise training modalities have been reported in CS individuals during and following the completion of their treatment (Radiotherapy, Chemotherapy, Hormonal therapy), where the benefits of aerobic nature exercise training predominantly (i.e., exercises that promote an increase in aerobic enzymatic activity, mitochondrial biogenesis and in general oxidative metabolism [that promote the elaboration of ATP via fatty acids]) in combination with muscle strength as resistance training with the use of external overloads (i.e., controlled exercises with a certain level of muscle load based on prior assessment of maximal strength, usually measured by means of 1-repetition maximal test on different muscle groups), which are exercises that promote an increase in protein synthesis, muscle mass formation, and therefore both types of exercise training (Moderate-intensity continuous [MICT] + resistance training [RT]) are usually referred to in the literature as combined exercise or concurrent exercise (MICT+RT) (8). Among the main effects or benefits of exercise training in CS individuals, particularly in terms of reducing anxiety, depressive symptoms, fatigue, quality of life, lymphedema, and physical function (4). It has also been reported that there is only "moderate" evidence on the effects of exercise in CS at the level of bone health,

and sleep, but worryingly, there is insufficient evidence in favor of physical exercise at the level of vascular function, falls, cognitive function, and pain, among other health parameters (sexual function, nausea, peripheral neuropathies). The potential results of the project will ultimately translate into greater technical, scientific and management knowledge to be able to analyze the increase in the offer of physical exercise programs or workshops for CS persons in Chile. The latter should translate into an improvement not only in the physical condition and health of CS people, but also in a lower risk of relapsing into cancer, mental illnesses (depression) and, of course, a reduction in mortality. From here, high-intensity interval training, a particular exercise modality of brief intense exercise intervals have been poorly studied in breast CS (9). Similarly, RT using lower exercise intensities (i.e., one repetition maximum test [1RM] load of ≤60% of 1 RM) have been also little tested for cardio-vascular (i.e., PWV, FMD, and cIMT) and metabolic health in breast CS women. Preliminary evidence show that concurrent exercise training decrease blood pressure, and that HIIT also decrease arterial stiffness in adult women. Sawyer et al. reported that 8-weeks of HIIT was superior to MICT for increasing FMD in HIIT vs MICT (Δ+8.9 *vs*. 5.1%) (10). Deisenroth et al. (11) showed that 12-week of HIIT (four sets [4 min] intervals at 80-90% HR_{max} with resting periods of 60-70% HR_{max} cycling) reduced minimally PWV ($-0.1\ m \cdot s^{-1}$) in hypertensive older adults (11). One-year of HIIT (60 s interval, 60 s of resting at 90% of the reserve oxygen consumption) decreased both systolic [SBP] (Δ−6.5)/diastolic [DBP] blood pressure (Δ−4.2 mmHg), and decreased $cIMT_{av}$ (Δ−0.95 mm) (12).

Thus, concurrent training of both HIIT plus RT in lower 1RM intensities could promote potential benefits for both cardiovascular health and metabolic and physical condition parameters of breast CS women, however, there is scarcity of studies about this

exercise modalities in patients who are CS and that have been exposure to higher and lower chemotherapy doses (13-15).

RESEARCH PROBLEM: Despite the "solid" evidence in favor of the effects of exercise training in breast CS to improve variables such as anxiety, depressive symptoms, fatigue, quality of life, lymphedema and physical function, however, unfortunately, the effects of exercise training on cardio-vascular and metabolic variables, there is still unknown the effects of concurrent exercise training including HIIT plus RT in lower 1RM doses in CS women at level of their cardio-vascular and metabolic health.

This is due to the fact that year after year there is an increase in the number of early diagnoses, as well as an increase in the number of CS with a successful completion of their breast cancer treatment (Radiotherapy, Chemotherapy, Hormonal Therapy), which also leads as an effect to an inherent increase in the number of CS persons, requiring the insertion of this population back into active life. Another effect of the scientific rationale lies in the scarce offer of physical activity and/or exercise training programs for this population of women between 40 and 70 years of age, which would be significantly overcome with the application of the present intervention project that would report cardiovascular, metabolic, physical condition, quality of life and eating patterns variables. OBJECTIVES; GENERAL: To determine the effects of traditional therapy added to physical exercise on cardio-vascular, metabolic and physical fitness in female breast cancer survivors who received lower (≤ 7 sessions) and higher (≥8 sessions) of chemotherapy.

This study will follow the CONSORT guidelines for randomised trials, will be developed in accordance with the Declaration of Helsinki (2013), and has been approved by the BIOETICAL COMMITTEE OF UNIVERSIDAD ANDRES BELLO (Approval 005/2024 of April 12th). **Design:** An experimental clinical randomized study. **Methods:**

Adult women breast cancer survivors who have undergone all the stages related to breast cancer treatment (chemotherapy, radiotherapy, hormone therapy). The study will be carried out in the facilities of the Exercise Physiology Laboratory of the Exercise and Rehabilitation Sciences Institute of the Universidad Andrés Bello, Concepción city, from different community cancer survivors' social groups of the Concepcion, Chile will be invited to participate of this study. The groups will be randomly allocated to an experimental group of high chemotherapy exposure (EG-HCHT, n=15) or to and experimental group of low chemotherapy exposure (EG-LCHT, n=15), that will adhere to 6-weeks of an exercise training program of concurrent training of HIIT plus RT three weekly.

Inclusion criteria: a) breast cancer diagnosed, b) with or without chemotherapy treatment, c) normal weight body mass index [BMI] 18.6 to 24.9 or overweight/obesity condition by BMI 25.0 to 39.9 kg/m^2, d) age 30 to 75 years, e) with or without other associated co-morbidities (diagnosed of elevated fasting glucose, prediabetes or diabetes, hypertension or prehypertension, or metabolic syndrome, fatty liver or hypercholesterolemia or screened by our research team), f) with or without hormonal therapy, and g) with or without other pharmacotherapy for specific muscle-groups such as morphine patches, morphine droplets or other pharmacological therapy for SOS pain treatment. **Exclusion criteria:** a) history of abnormal ECG, or diagnosis of other cardio-vascular condition/history other than hypertension, vasculopathy, b) history of uncontrolled stage 3 of hypertension or hypertensive crisis, c) diabetes complications such as varicose ulcers, nephropathies, d) skeletal muscle abnormalities (*e.g.*, knee, or hip arthrosis, muscle pain), e) using weight loss treatment/pharmacotherapy or being active in exercise training programs (or within the past three months), and f) use other pharmacotherapy that can influence body weight loss, g) respiratory disease type (chronic

obstructive disease), h) kidney disease, i) pregnancy, and j) smoking behaviour or dependence on other substances.

REFERENCES

1. MINSAL. Tabla de resumen de mortalidad por causa, según sexo y región 2023 [Available from: https://informesdeis.minsal.cl/SASVisualAnalytics/.
2. WHO. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva; 2021.
3. García Jofré N. Tendencia temporal de la tasa de mortalidad por cáncer de mama en mujeres en Chile, periodo 2007-2020. 2024.
4. Campbell KL, Winters-Stone K, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Medicine and science in sports and exercise. 2019;51(11):2375.
5. WHO. Global report on hypertension: The race against a silent killer. Geneva; 2023. Contract No.: CC By-NC-SA 3.0 IGO.
6. Cameron AC, Touyz RM, Lang NN. Vascular complications of cancer chemotherapy. Canadian Journal of Cardiology. 2016;32(7):852-62.
7. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. The journal of supportive oncology. 2012;10(5):171.
8. Vallerand JR, Rhodes RE, Walker GJ, Courneya KS. Correlates of meeting the combined and independent aerobic and strength exercise guidelines in hematologic cancer survivors. International Journal of Behavioral Nutrition and Physical Activity. 2017;14(1):1-10.
9. Gibala MJ, Little JP, MacDonald MJ, Hawley JA. Physiological adaptations to low-volume, high-intensity interval training in health and disease. The Journal of physiology. 2012;590(5):1077-84.
10. Sawyer BJ, Tucker WJ, Bhammar DM, Ryder JR, Sweazea KL, Gaesser GA. Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults. Journal of Applied Physiology. 2016;121(1):279-88.
11. Deiseroth A, Streese L, Köchli S, Wüst RS, Infanger D, Schmidt-Trucksäss A, et al. Exercise and arterial stiffness in the elderly: a combined cross-sectional and randomized controlled trial (EXAMIN AGE). Frontiers in physiology. 2019;10:1119.
12. Magalhães JP, Melo X, Correia IR, Ribeiro RT, Raposo J, Dores H, et al. Effects of combined training with different intensities on vascular health in patients with type 2 diabetes: a 1-year randomized controlled trial. Cardiovascular diabetology. 2019;18(1):1-13.
13. Beitzen-Heineke A, Rolling CC, Seidel C, Erley J, Molwitz I, Muellerleile K, et al. Long-term cardiotoxicity in germ cell cancer survivors after platinum-based chemotherapy: cardiac MR shows impaired systolic function and tissue alterations. European Radiology. 2024;34(6):4102-12.
14. Austin D, Maier RH, Akhter N, Sayari M, Ogundimu E, Maddox JM, et al. Preventing cardiac damage in patients treated for breast cancer and lymphoma: the PROACT clinical trial. Cardio Oncology. 2024;6(5):684-96.

15. Vo JB, Ramin C, Veiga LH, Brandt C, Curtis RE, Bodelon C, et al. Long-term cardiovascular disease risk after anthracycline and trastuzumab treatments in US breast cancer survivors. JNCI: Journal of the National Cancer Institute. 2024:djae107.
16. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2013.

STATISTICAL ANALYSIS PLAN (SAP): Data will be presented as the mean ± standard deviation (SD). Normality and homoscedasticity assumptions will be tested by using Shapiro-Wilk tests and homoscedasticity by the Levene test. For those outcomes with normal distribution, paired *t*-test was applied to test differences, while to those with no normal distribution, unpaired *t*-test was applied. Cohen's *d* effect size (<0.2 = negligible, 0.2-0.49 = small, 0.5-0.79 = moderate, ≥0.8 = large) for interactions that showed statistically significant (16). Each delta (Δ), pre-post changes, of main and secondary outcomes will be calculated in all groups. To test the associations among main vascular outcomes (PWV, FMD, $cIMT_{av}$, $cIMT_{max}$) with anthropometric, body composition, metabolic, cardio-vascular outcomes, and physical fitness outcomes, simple linear regression (to parametric) with R^2 prediction percentage, or the *Rho* Spearman nonparametric correlation (r_s =) will be applied. Statistical analyses will be developed using Prism 8.0 software (Graph Pad, San Diego, CA, United States), and the SPSS™ software 29 version for Windows (IBM SPSS Inc., Chicago, IL, USA). The alpha level will be fixed at ($P \leq 0.05$) for all statistical significance.