PROJECT TITLE.

Effects of an adapted multicomponent training program (Adapted Physical and Sports Activity - AFA) for promoting mental and physical well-being in cancer survivors currently in physiological or chronic-stabilized condition.

LABORATORY/DEPARTMENT

Laboratory of Exercise and Sport Sciences, CdS Sport Sciences and Techniques, Department of Translational Biomedicine and Neuroscience (DiBraiN), University of Bari - Aldo Moro

EXPERIMENTAL DESIGN

Interventional

PLANNED START AND END DATE OF THE PROJECT

January 2025 – June 2025

FUNDS USED FOR THE PROJECT: NO

DATA OF THE DOCUMENT

20/02/2025

BACKGROUND

Cancer is a major public health problem worldwide. Cancer patients are often treated multiple times with chemotherapy, radiation, and/or biological therapy, interspersed with active surveillance. As a result, cancer patients and survivors carry physiological and psychological side effects, including muscle atrophy, weight changes, reduced aerobic capacity, decreased strength and flexibility, depression, fatigue, nausea, and an overall decrease in quality of life (Courneya et al., 2009; Siegel et al., 2023; Sung et al., 2021). Of all the side effects, cancer-related fatigue is the most common. It differs from normal fatigue in daily activities and affects up to 70% of cancer patients during chemotherapy and radiation therapy. In addition, sedentary habits lead to the development of a self-perpetuating cycle of fatigue, which results in increasing levels of catabolic processes at all levels (physical, emotional, social). Exercise interrupts this downward cycle and decreases cancer-related fatigue (Lucía et al., 2003). Exercise is recognized as one of the most effective nonpharmacological interventions to improve the quality of life of cancer survivors. (Meneses-Echavez et al., 2019; Mishra, 2014; Young-McCaughan & Arzola, 2007). Exercise, both during and after treatment, is an effective tool for improving functional capacity, muscle strength, functional mobility (i.e., improving balance will reduce the risk of falls and fractures), fatigue, psychological well-being (reducing the risk of anxiety and depression), and health-related quality of life in cancer patients and survivors (Dash et al., 2016). Evidence-based studies recommend resistance training and combined aerobic-resistance training interventions (Ficarra et al., 2022; Wang et al., 2023). The multicomponent training program has reported benefits in body composition and functional efficiency in cancer survivors (Bartolomeu et al., 2016).

PURPOSE AND HYPOTHESIS OF THE PROJECT

Primary outcome:

The purpose of this study is to evaluate the effectiveness of a multicomponent training protocol (MCT) on the following parameters: psychological, physical fitness, mental well-being, and quality of life, in cancer survivors currently in a stabilized condition, compared to an aerobic training protocol (AT) and a waiting control group (WLCG). In addition, the aim is to evaluate the impact of training in participants' coping strategies, i.e., the ways in which they manage stress, emotional difficulties and daily challenges, in order to foster better psychological adaptation and greater autonomy.

Secondary outcome:

To assess adherence to protocols through analysis of dropout rates and number of sessions completed.

Hypothesis

We hypothesize that both groups will demonstrate improvements in physiological parameters, physical fitness, mental well-being, and overall quality of life compared to the WLCG. Furthermore, the MCT group is expected to achieve greater enhancements in physiological parameters than the AT group. Additionally, the MCT group is anticipated to have a more significant impact on strengthening coping strategies, promoting better stress management, and fostering more effective psychological adaptation.

PARTICIPANTS

The study aims to recruit at least 60 cancer survivors currently in physiological or chronic-stabilized condition between 18-80 years of age.

Inclusion criteria.

- Women/Men;
- Age between 18 and 80 years at the time of initial treatment;
- Subjects in remission for at least 3 months;
- No diagnosis of secondary cancer at baseline;
- No physical impediment to physical activity (Eastern Cooperative Oncology Groups (ECOG) performance status 0-1);
- Signature of a written informed consent form (or their legally recognized representatives must sign) indicating that the patient understood the purpose and procedures required for the study and is willing to participate in the study;
- Sedentary lifestyle (subjects who have not followed WHO guidelines for aerobic and resistance exercise in the past 3 months).
- Currently in treatment, as long as not hospitalized, in stabilized chronic condition,
- Positive medical specialist assessment of noncompetitive physical activity practice.

Exclusion criteria.

- Metastasis;
- Uncontrolled hypertension or untreated heart disease;

- Severe musculoskeletal or joint disorders with severe mobility limitations;
- Psychiatric disorders;
- Taking psychotropic drugs;
- Inability to engage in physical activity;
- Lack of fitness to practice sports.
- Expected absence of more than two weeks during the intervention period.

SAMPLE NUMEROSITY

G*Power software (version 3.1) was used to determine the sample size needed to ensure adequate statistical power.

The calculation was performed assuming a mean effect (with a value of 0.25 for effect size f), which is a value commonly used in studies of similar size. A significance level of 0.05 was set and a statistical power of 85% (0.85) was adopted, which is generally considered an adequate value to minimize the risk of type II errors.

For the calculation, two groups (multicomponent training and aerobic training) and two measurement times (before and after the intervention) were considered. An average correlation (0.5) was estimated between the repeated measurements on participants, as it is expected that the collected data are fairly correlated between the different surveys. Finally, it was assumed that there were no violations of sphericity by setting a correction for nonsphericity equal to 1.

Based on these parameters, the calculation indicated the need for a sample size of 32-40 total participants, with 16-20 participants per group, to ensure sufficient statistical power to detect any significant effects.

PROCEDURES

Participants will be recruited through days dedicated to raising awareness and promoting the project, also organized in the area in collaboration with relevant bodies, associations and health facilities. During these events, detailed information will be provided on the objective of the study, potential benefits, and how to participate. Informational materials, such as brochures and posters, will also be used and distributed at major gathering places. Then participants will be randomly assigned to one of three groups:

- MCT
- AT

- WLCG

Data collection

Prior to the intervention, all subjects will sign an informed consent upon authorization from their attending physician. All subjects will participate in physiological assessments, functional and psychological tests before (T0) and at the end of the intervention (T1). Data will be collected anonymously by assigning each participant a random ID number.

Measurements:

Anthropometric parameters:

- Height
- Weight
- BMI
- BIA

Physical parameters:

- Timed Up and GO (TUG);
- 30 Seconds Chair Stand Test (30" CST);
- 2 Minutes Step Test (TMST);
- Back Stretch Test;
- Chair Sit and Reach Test;
- Handgrip Strength Test (HGS).

Psychological Parameters:

- The State-Trait Anxiety Inventory (STAI-Y);
- Beck Depression Inventory (BDI);
- Fatigue Severity Scale (FSS);
- The EORTC Core Quality of Life questionnaire (EORTC QLQ-C30);
- Brief COPE.

<u>Experimental Design</u>

After initial evaluations, subjects will be randomly assigned to one of two groups. All protocols will last 24 weeks and will be conducted at the Angiulli Artistic Gymnastics Society (Bari).

Sessions will be conducted in small groups. These groups will be closely supervised by exercise professionals, adapted physical activity (AFA) specialists to ensure the safety of the participants, maintain the right level of intensity, and correct execution technique. To monitor and adjust the training intensity (internal load) during the ongoing sessions, Borg's Fatigue Perception Scale (RPE) (6-20) (Borg, 1982) will be used at the end of each exercise set to adjust the load in Borg = 10-15 points (Gary Liguori & American College of Sports Medicine (ACSM), 2021). Participants will be previously familiarized with the scale.

Participants in the WLCG will not perform any structured physical activity during the entire intervention period, maintaining their usual lifestyle and placed on a waiting list to receive adapted physical activity after the 24-week intervention period.

Multi-component Training:

Each training session will include an initial 10-minute muscle activation phase (low-intensity walking, Borg = 10-11) to increase heart rate, improve muscle blood flow, and prepare the major joints for the next phase of work, a 40-minute main period of exercise (aerobic exercise, mobility exercises, and resistance training), and a 10-minute defatigue period (breathing and stretching exercises). Cardiorespiratory training will consist of progressive aerobic exercises: controlled and rhythmic jumping jacks, step-ups on a stable platform (such as a low step or stable surface), alternating knee lifts, quick side steps or lateral leg lifts. Finally, 3 minutes of low-intensity walking to facilitate recovery for the next phase of training.

Mobility training will consist of specific exercises (chest extensions, cat to cows, overhead stretching with stick, and active internal rotation of the hips) targeting the major joints, performed at maximum (1 to 3 sets) but avoiding pain. Duration will gradually increase from 30 to 60 seconds per repetition, repeating one to three times. Providing recovery intervals of 30 to 60 seconds between sets and exercises.

The counter-resistance training will consist of exercises targeting the different muscle groups (8 exercises): quadriceps (leg extensions with ankle bar/half squat with chair), biceps brachii (unilateral curl with dumbbell), shoulders (shoulder press with dumbbell), triceps brachii (french press with dumbbell), pectorals (dumbbell chest press/dumbbell flyes), and back (dumbbell paddles). The counter-resistance training program will follow the principle of gradual progressive loading. Initially, participants will perform one set of 10-15 repetitions, which will increase to three sets of 10-15 repetitions, over the course of the intervention. Load adjustments will be made to ensure that the perception of effort (RPE) remains between 13 and 15 points on the Borg Scale (6-20). During the protocol, participants will be provided recovery intervals of 60 to 120 seconds between sets and

exercises. To prevent premature muscle fatigue, exercises were performed using an alternating training method based on the division of muscle groups (upper muscle exercises will be performed in the first session and lower muscle exercises in the second).
The cool-down period will consist of breathing and stretching exercises. Stretching will be performed seeking maximum stretch on all major muscle groups (1 to 3 sets per muscle group) while avoiding joint pain. The duration will gradually increase from 10 to 30 seconds per stretch, repeating one to three times for a total of 60 seconds per exercise.

Aerobic training:

Each training session, again, will include an initial 10-minute muscle activation phase (low-intensity walking, Borg = 10-11) to increase heart rate, improve muscle blood flow, and prepare major joints for the next work phase, a 40-minute main exercise period. During the main exercise period, aerobic training will consist of 25 minutes of progressive aerobic exercises: controlled and rhythmic jumping jacks, step-ups on a sturdy platform (such as a low step or stable surface), standing knee raises (alternating legs), fast side steps or side leg raises. This will be followed by 15 minutes of walking. Exercises will be performed at an intensity to ensure that perceived exertion (RPE) will remain between 13 and 15 points on the Borg Scale (6-20). Progression over the weeks will be by maintaining the intensity in this range. The main goal of this phase will be to maintain a constant duration of exercise, increasing the intensity gradually.
The cool-down period will consist of breathing and stretching exercises on all major muscle groups (1-3 sets per muscle group) while avoiding joint pain. The duration will be gradual, 10 to 30 seconds per stretch, repeated one to three times for a total of 60 seconds per stretch.

EXPECTED RESULTS AND RELEVANCE

Although the positive effect of physical activity in cancer survivors currently in physiological or chronic-stabilized condition has already been demonstrated, the impact of integrating multiple exercise modalities into an MCT or TA, remains poorly explored. It is still not entirely clear what may be the most efficient protocol for improving physiological and psychological parameters in cancer survivors. At the end of this exercise program, we expect to find an overall improvement in physiological, motor and psychological parameters, with a greater increase in the MCT group. Furthermore, we believe that this new research modality may provide a new approach to propose

physical activity that is particularly engaging, motivating, and designed to improve quality of life (physiologically and psychologically). To date, exercise remains an essential factor in promoting psychological and biological improvements with profound implications for public health. Indeed, physical activity promises to be an important tool to be used alone or in combination with traditional therapies (such as drugs or medicines) to increase the effectiveness of strategies for prevention and treatment of various chronic noncommunicable diseases.

Critical situations and possible adverse effects

Rare but considered major risks could include:

● Acute cardiovascular events: participants could, in rare cases, be subject to episodes of angina, arrhythmias, or increased blood pressure during exercise sessions.

● Falls or injuries: the proposed exercises, if performed incorrectly or without supervision, could present a risk of falls or musculoskeletal injuries.

Risk Management Strategies:

● Continuous monitoring during sessions: each training group will be supervised by trained professionals in adapted physical activity (AFA). Borg scale will be used to monitor perceived exertion during exercise, keeping it in a moderate range (10-15 points).

● Emergency procedures: to ensure safety, an emergency plan will be available. AFA workers are adequately trained in order to recognize any symptoms of fatigue or cardiovascular discomfort and to intervene promptly if necessary.

● Medical support: before starting, participants will provide an exercise fitness assessment signed by the relevant physician/cardiologist, ensuring that they are fit to participate. In addition, the proximity (approximately 3 minutes by car, 1.4 km) to the main local medical facility (Policlinico di Bari - azienda ospedaliero universitaria consorziale policlinico, p.zza Giulio Cesare,11, 70124, Bari) was considered to allow quick access to emergency services.

Documentation in the Research Protocol:

All preventive measures and management strategies are included in the protocol:

● Structure of training sessions, control of exercise intensity, and supervision by qualified personnel are provided in the "intervention" section.

● Cardiovascular and musculoskeletal risk management is addressed in the inclusion/exclusion criteria, which exclude participants with acute or unstable conditions to ensure the safety of the study sample.

REFERENCES

Akram, M., Iqbal, M., Daniyal, M., & Khan, A. U. (2017). Awareness and current knowledge of breast cancer. *Biological Research*, *50*(1), 33. https://doi.org/10.1186/s40659-017-0140-9

Aaronson, N. K., Ahmedzai, S., Bergman, B., Bullinger, M., Cull, A., Duez, N. J., ... & Takeda, F. (1993). The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute, 85(5), 365-376.

Bartolomeu, R. F., Barros, V., Peixoto, C., & Monteiro, A. M. (2016). The effects of a multicomponent training on body composition and functional fitness in breast cancer women patients. *Proceedings of the International Congress of the Research Center in Sports Sciences, Health Sciences & Human Development*, 168–169.

Beck, A. T., & Steer, R. A. (1984). Internal consistencies of the original and revised Beck Depression Inventory. Journal of clinical psychology, 40(6), 1365-1367.

Borg, G. A. (1982). Psychophysical bases of perceived exertion. Medicine and science in sports and exercise, 14(5), 377-381.

Catania, G., Bell, C., Ottonelli, S., Marchetti, M., Bryce, J., Grossi, A., & Costantini, M. (2013). Cancer-related fatigue in Italian cancer patients: validation of the Italian version of the Brief Fatigue Inventory (BFI). Supportive Care in Cancer, 21, 413-419.

Courneya, K. S., Sellar, C. M., Stevinson, C., McNeely, M. L., Peddle, C. J., Friedenreich, C. M., Tankel, K., Basi, S., Chua, N., Mazurek, A., & Reiman, T. (2009). Randomized Controlled

Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients. *Journal of Clinical Oncology*, *27*(27), 4605–4612. https://doi.org/10.1200/JCO.2008.20.0634

Cuzzolaro, M., Vetrone, G., Marano, G., & Garfinkel, P. (2006). The Body Uneasiness Test (BUT): development and validation of a new body image assessment scale. Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity, 11, 1-13.

Dash, C., Randolph-Jackson, P. D., Isaacs, C., Mills, M., Makambi, K., Watkins, V. V., & Adams-Campbell, L. L. (2016). An exercise trial to reduce cancer related fatigue in African American breast cancer patients undergoing radiation therapy: Design, rationale, and methods. *Contemporary Clinical Trials*, *47*, 153–157. https://doi.org/10.1016/j.cct.2016.01.004

Ficarra, S., Thomas, E., Bianco, A., Gentile, A., Thaller, P., Grassadonio, F., Papakonstantinou, S., Schulz, T., Olson, N., Martin, A., Wagner, C., Nordström, A., & Hofmann, H. (2022). Impact of exercise interventions on physical fitness in breast cancer patients and survivors: A systematic review. *Breast Cancer*, *29*(3), 402–418. https://doi.org/10.1007/s12282-022-01347-z

Gary Liguori & American College of Sports Medicine (ACSM). (2021). ACSM's Guidelines for Exercise Testing and Prescription (10th ed.). Wolters Kluwer Health.

Kang, H. (2021). Sample size determination and power analysis using the G*Power software. Journal of Educational Evaluation for Health Professions, 18, 17. https://doi.org/10.3352/jeehp.2021.18.17

Kilgour, R. D., Vigano, A., Trutschnigg, B., Lucar, E., Borod, M., & Morais, J. A. (2013). Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Supportive Care in Cancer*, *21*(12), 3261–3270. https://doi.org/10.1007/s00520-013-1894-4

Lucía, A., Earnest, C., & Pérez, M. (2003). Cancer–related fatigue: Can exercise physiology assist oncologists? *The Lancet Oncology*, *4*(10), 616–625. https://doi.org/10.1016/S1470-2045(03)01221-X

Meneses-Echavez, J. F., Rodriguez-Prieto, I., Elkins, M., Martínez-Torres, J., Nguyen, L., & Bidonde, J. (2019). Analysis of reporting completeness in exercise cancer trials: A systematic review. *BMC Medical Research Methodology*, *19*(1), 220. https://doi.org/10.1186/s12874-019-0871-0

Mishra, S. I. (2014). Are Exercise Programs Effective for Improving Health-Related Quality of Life Among Cancer Survivors? A Systematic Review and Meta-Analysis. *Number 6 / November 2014*, *41*(6), E326–E342. https://doi.org/10.1188/14.ONF.E326-E342

Nichols, H. B., Trentham-Dietz, A., Egan, K. M., Titus-Ernstoff, L., Holmes, M. D., Bersch, A. J., Holick, C. N., Hampton, J. M., Stampfer, M. J., Willett, W. C., & Newcomb, P. A. (2009). Body Mass Index Before and After Breast Cancer Diagnosis: Associations with All-Cause, Breast Cancer, and Cardiovascular Disease Mortality. *Cancer Epidemiology, Biomarkers & Prevention*, *18*(5), 1403–1409. https://doi.org/10.1158/1055-9965.EPI-08-1094

Patel, A. V., Friedenreich, C. M., Moore, S. C., Hayes, S. C., Silver, J. K., Campbell, K. L., ... & Matthews, C. E. (2019). American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. Medicine and science in sports and exercise, 51(11), 2391.

Rikli, R. E., & Jones, C. J. (1999). Development and validation of a functional fitness test for community-residing older adults. Journal of aging and physical activity, 7(2), 129-161.

Schmitz, K. H., Courneya, K. S., Matthews, C., Demark-Wahnefried, W., Galvão, D. A., Pinto, B. M., Irwin, M. L., Wolin, K. Y., Segal, R. J., Lucia, A., Schneider, C. M., von Gruenigen, V. E., Schwartz, A. L., & American College of Sports Medicine. (2010). American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Medicine and Science in Sports and Exercise*, *42*(7), 1409–1426. https://doi.org/10.1249/MSS.0b013e3181e0c112

Sibilia, L., Schwarzer, R., & Jerusalem, M. (1995). Italian adaptation of the General Self-Efficacy Scale: self-efficacy generalized. *Procedia-Social and Behavioral Sciences.*

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*, *73*(1), 17–48. https://doi.org/10.3322/caac.21763

Streckmann, F., Kneis, S., Leifert, J. A., Baumann, F. T., Kleber, M., Ihorst, G., Herich, L., Grüssinger, V., Gollhofer, A., & Bertz, H. (2014). Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy. *Annals of Oncology*, *25*(2), 493–499. https://doi.org/10.1093/annonc/mdt568

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Wang, T.-C., Chen, P.-L., Liao, W.-C., & Tsai, I.-C. (2023). Differential Impact of Exercises on Quality-of-Life Improvement in Breast Cancer Survivors: A Network Meta-Analysis of Randomized Controlled Trials. *Cancers*, *15*(13), Articolo 13. https://doi.org/10.3390/cancers15133380

Young-McCaughan, S., & Arzola, S. M. (2007). Exercise Intervention Research for Patients With Cancer on Treatment. *Seminars in Oncology Nursing*, *23*(4), 264–274. https://doi.org/10.1016/j.soncn.2007.08.004