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Movement and Health Beyond Care, MOVIS:

Exercise and Nutrition Plan for Patients after

Breast Cancer Treatment

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Supervisor:

Prof. Elena Barbieri

Ph.D. student:

Dr. Andrea R. Panìco

Co-Supervisor:

Dr. Rita Emili

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ABSTRACT

The health benefits of physical activity (PA) have been extensively described, highlighting its positive influence on physical, psychological, cognitive, and social condition, as well as its role in disease prevention, treatment, and improvement of quality of life (QoL). Concerning breast cancer (BC), physical activity may be an important element in the reduction of risk factors, mortality, and relapse. It diminishes the sequelae produced by the treatments against BC, such as the loss of joint mobility and muscle strength, pain, fatigue, anxiety, and depression. Exercise prescription is recently considered a component of the global treatment of BC disease; practicing PA does not cause adverse events and improves the overall condition of BC survivors (BCSs). MOVIS, Movement and Health Beyond Care, is a randomized controlled trial that aims to evaluate the potential health benefits of exercise and proper nutritional habits. In particular, this thesis focuses on the efficacy of aerobic exercise training in improving QoL, fatigue and health-related factors in high-risk BCSs.

The work presented in this thesis is outlined in three chapters organized as three different scientific articles in which results are highlighted to guide research within a bio-psycho-social conceptual framework and with evident transformative effects on BC care systems.

The first chapter of the thesis provides the description of the clinical trial design (approval of the local Ethics Committee, permission number: 21/19 10 July 2019, ClinicalTrials.gov reference number: NCT04818359). Patients randomized to the intervention arm will receive lifestyle recommendations (nutrition and exercise) and will undergo the MOVIS Training program, whereas control arm patients will receive lifestyle recommendations. The 'MOVIS Training' program consists of 3 months, 3 times per week, aerobic exercise, which will be supervised both directly (2 days each week) and remotely (1 day each week). Exercise intensity (40% to 70% of heart rate reserve) and duration (20 to 60 mins) will be gradually increased throughout the training period. Both arms will receive counseling on psychological well-being. The primary outcome is the improvement of QoL. The secondary outcome is the improvement of the health-related QoL parameters (HRQoL).

The second chapter of the thesis evaluates the cardiometabolic effects of a home-based lifestyle intervention in the first group of MOVIS BCSs, enrolled in January 2020, four weeks before the Italian COVID-19 lockdown. This group of BCSs have been encouraged to start a 3-month lifestyle intervention based on nutrition and exercise which comprised a short term

(6 months) and long term (12 and 24 months) follow-up. However, due to the imposed COVID-19 pandemic restrictions, after the approval of the institutional ethics committee, the study protocol was amended (Protocol N. 29/20 22.04.2020) and the forced changes in the study protocol made the difference between intervention arm and control arm interventions negligible, providing similar adaptations between groups. Therefore, due to the lack of significant differences between the two interventions, the results and discussion of the two groups were combined. In this section of the study it is described how a 3-month home-based lifestyle intervention, focused on Mediterranean diet and aerobic exercise - adapted to the imposed COVID-19 pandemic restrictions - significantly improved cardiorespiratory fitness, metabolic parameters, leading to significant cardiometabolic amelioration, even during two years of COVID-19 pandemic.

The third chapter of the thesis describes the psychological aspects and global health-related QoL data obtained for the first group of MOVIS BCSs, who received a 3-month lifestyle intervention based on nutrition and exercise during the first year of COVID-19 pandemic, as partially described in the second chapter of this thesis. Psychological questionnaires (brief fatigue inventory, distress thermometer, psychological distress inventory, verbal rating scale, European organization for research and treatment of cancer: quality-of-life, EORTC-QLQ-C30; profile of mood states questionnaire) were evaluated at baseline, immediately after the lifestyle intervention and at 3rd, 6th and 12th months of follow-up. Analysis showed statistical significance between the different assessments of: depression, anger, confusion, strength/vigor, distress evaluation, social functioning, general health scale, and fatigue. There were no significant changes in role and emotional functioning. Considering the timeline difference between assessments, almost all the scores were significantly improved after the lifestyle intervention compared to baseline, also showing the effect in the long-term follow-up, despite the home-confinement, lifestyle intervention surprisingly improved HRQoL in BCSs. The current study provides preliminary support to foster confidence through successful PA experiences achieved through effective goal setting and action planning. The development of a plan of lifestyle intervention including what (exercise dose, intensity, frequency, time and duration), possible where (GYM or location of exercise) may contribute in translating the intention into exercise behavior change and favor the development of an evidence base action for promoting exercise in cancer survivors improving their HRQoL.

CONTENT

Summary

ORIGINAL RESEARCH ARTICLES 7
INTRODUCTION 8
AIM OF THE THESIS 13

CHAPTER 1 15

Movement and health beyond care, MOVIS: study protocol for a randomized clinical trial on nutrition and exercise educational programs for breast cancer survivors 16
Abstract 17
Introduction 18
Trial Design 20
Methods: Participants, interventions and outcomes 20
Assignment of Interventions: allocation 25
Data Collection and management 25
Discussion 31
Trial Status 33
References 35

CHAPTER 2 39

Effect of a Home-Based Lifestyle Intervention Program on Cardiometabolic Health in Breast Cancer Survivors During Two Years of COVID-19 Pandemic 40
Abstract 41
Introduction 42
Materials and Methods 44
Results 48
Discussion 51
Conclusions 55
References 56

CHAPTER 3 64

Home-based lifestyle intervention for breast cancer survivors: a surprising improvement in the quality of life during the first year of COVID-19 pandemic 65

Abstract 66

Introduction 67

Materials and Methods 68

Outcome measures 72

Results 75

Discussion 78

References 82

CONCLUSIONS 90

Study limitations 92

Final considerations and acknowledgments 93

REFERENCES 94

ORIGINAL RESEARCH ARTICLES

This Thesis is based on the following original research articles, which will be referred to by their Roman numerals.

I. Valentina Natalucci, Carlo Ferri Marini, Mauro De Santi, Giosuè Annibalini, Francesco Lucertini, Luciana Vallorani, Andrea Rocco Panico, Davide Sisti, Roberta Saltarelli, Sabrina Donati Zeppa, Deborah Agostini, Marco Gervasi, Giulia Baldelli, Eugenio Grassi, Alessandra Nart, Massimo Rossato, Vincenzo Biancalana, Giovanni Piccoli, Piero Benelli, Anna Villarini, Matteo Somaini, Vincenzo Catalano, Stefania Guarino, Alice Pietrelli, Silvia Monaldi, Donatella Sarti, Simone Barocci, Marco Flori, Marco Bruno Luigi Rocchi, Giorgio Brandi, Vilberto Stocchi, Rita Emili and Elena Barbieri. **Movement and health beyond care, MOVIS: study protocol for a randomized clinical trial on nutrition and exercise educational programs for breast cancer survivors.** *BMC TRIALS,Accepted with minor revisions.*

II. Andrea Rocco Panico et al. **Effect of a Home-Based Lifestyle Intervention Program on Cardiometabolic Health in Breast Cancer Survivors During Two Years of COVID-19 Pandemic.** *In preparation.*

III. Vagnini Denise, Natalucci Valentina, Moi Sara, Vallorani Luciana, Pietrelli Alice, Panico Rocco Andrea, Ferri Marini Carlo, Lucertini Francesco, Annibalini Giosuè, Sisti Davide, Rocchi Marco Bruno Luigi, Catalano Vincenzo, Saita Emanuela, Emili Rita and Barbieri Elena. **Home-based lifestyle intervention for breast cancer survivors: a surprising improvement in the quality of life during the first year of COVID-19 pandemic.** *Submitted to PlosOne, Under revision.*

INTRODUCTION

In the last two years we have been fighting the most important challenge of recent decades, the spread of "COVID-19", a worldwide event. The World Health Organization (WHO) in an official statement expressed a strong concern about this emergency, declaring a state of pandemic (Beccia F. et al., 2022; World Health Organization. Coronavirus Disease Pandemic. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 - accessed on 10 February 2021).

This virus threatens the health of every individual and forces collective habits to change. Studies claim that among the subjects considered most at risk, we find those who have had a diagnosis of cancer. Indeed, the COVID-19 pandemic was a particularly worrying time for vulnerable groups with pre-existing health conditions, such as breast cancer (BC) survivors (BCSs), because the mandatory directives for the first lockdown (in Italy between 9th March to 3rd May 2020) certainly altered the daily routine in clinical settings (Oldani C. et al., 2020).

The BC is the most common invasive tumor in women worldwide and from the AIRC source "Cancer numbers in Italy 2021 and 2022" it is clear that it is the most common type of tumor in all age groups, albeit at different rates (41% in young women *vs.* 22% in older women). In Italy, there were an estimated 50.500 new cases in 2017 and the average 5-year survival rate (87%) in our country is higher than the European average (82%) (AIRC I numeri del cancro: fotografia dal mondo, 16 Marzo 2021). Also important is the update to 2021 of the survey carried out by the secretaries of the Italian Group of Mammary Pathology (GIPAM) and of the Digestive System Pathology Study Group (GIPAD) of the Italian Society of Pathological Anatomy and Cytology (SIAPeC), to describe the impact of SARS-CoV-2 infection on surgical treatment of breast cancer. The results of this updated survey show, in general, an increase in cases operated on 2021 compared to 2020 and an increase in the percentage of pTis tumors (i.e. in the initial stage) in 2021 compared to previous years, confirming a recovery in the cancer screening activities. An increase in both N0 and N1a category tumors should also be reported, a likely indicator of earlier management of diagnosed tumors (AIRC I Numeri Del Cancro In Italia 2022). This malignant tumor is a heterogeneous disease and differs greatly among patients (inter- intra-tumor heterogeneity) as the result of interaction among genetic, epigenetic and environmental factors. Among the most significant factors influencing the risk of BC onset and relapse are aging, gender, family history, inherited factors (mutations in the BRCA1 and BRCA2 genes), menstrual and reproductive history, dense breasts, race and ethnicity, radiation exposure, birth control pills, combined post-

menopausal hormone therapy, and diethylstilbestrol exposure (Katsura C. et al., 2022). Although in western countries the incidence of BC is increasing, mortality is steadily decreasing mainly due to prevention strategies able to protect women from developing BC with regular mammography screenings for early detection of BC (primary prevention) and to act on behavioral risk factors related to lifestyle with the aim to prevent the onset, recurrence and improve BCSs Quality of Life (QoL) (primary, secondary and tertiary prevention) (Sung H. et al., 2021).

The impact of COVID-19 on QoL of BCSs is substantial. In a general view, the pandemic impact should be considered as a continuum of bio-psycho-social interconnections, within the unique concept of global health-related QoL (HRQoL).

In particular, the WHO defines QoL as "The condition of life resulting from the combination of the effects of a complete range of factors such as those determining health, happiness including comfort in the physical environment and a satisfying occupation, education, social and intellectual attainments, freedom of action, justice, and expression" (https://www.who.int/tools/whoqol; Social Science & Medicine The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization Volume 41, Issue 10, November 1995) and represents an important outcome measure in BC clinical investigations and survivorship studies (Gordon N.H. et al., 2010; Srivastava S. et al., 2019).

In a more recent approach, QoL can be described by a series of areas or dimensions of human experience that relate not only to physical conditions and symptoms, but also to a person's ability to function, from the physical, social and psychological point of view and to derive satisfaction from what the person does, in relation to both his own expectations, ability to achieve (FAO, UNEP, WHO, and WOAH. 2022. One Health Joint Plan of Action 2022-2026. Working together for the health of humans, animals, plants and the environment. Rome. https://doi.org/10.4060/cc2289en).

In the contest of BCSs, a lifestyle intervention program with psychological support can profoundly influence both short- and long-term health and QoL and could represent an important non-pharmacological intervention that might positively influence survival, especially during the pandemic emergency.

Recent evidence confirms the effectiveness of healthy lifestyle choices (modifiable factors) such as not smoking, adopting a healthy diet and doing regular physical activity (PA) in ameliorating cancer treatments' side-effects, such as musculoskeletal pain and fatigue, and

improving physical, cardiometabolic and inflammatory markers (e.g., levels of insulin, estrogen and IGF-1, hs-Reactive-C-Protein), emotional wellbeing, and global HRQoL and not less important lower recurrence risk (Villarini A et al. 2015; Kang D.W. et al., 2017; De Santi M. et al., 2019; World Cancer Research Fund/American Institute for Cancer Research 2018; Riebe D. et al., 2018; Gianfredi V. et al., 2020; Morishita S. et al. 2020; Natalucci V. et al., 2021; Hardcastle S.J., Maxwell-Smith C., Hagger M.S. 2022).

In this regard, attention to modifiable behaviors such as exercise and nutrition has grown in recent years, with particular attention to the strategies to be adopted in the clinical outcomes of BCSs even more during the COVID-19 era. Therefore, facilitating and helping the maintenance of a healthy lifestyle at the end of primary treatments for BC represents a real challenge in the daily practice of medicine.

In Italy, although increasing literature suggests that a multidisciplinary approach is essential for achieving and maintaining HRQoL in the long term, few clinical studies provide evidence of the effect of prescribing healthy lifestyle habits in BCSs.

Health-related QoL is a recognized endpoint in cancer clinical trials. It has been shown that assessing QoL in patients with cancer could contribute to improved treatment and could even serve as a prognostic factor along with medical parameters (Mokhtari-Hessari P. et al., 2020). Not by chance, QoL or specifically health-related QoL might be influenced by diagnosis, treatment, post-treatment, and survivorship as assessed by using well validated instruments. In recent years, studies and meta-analysis on PA effects on BC QoL have received much attention. Moreover, positive effects and significant benefits of supervised combined aerobic resistance exercise on fatigue and QoL were reported in patients during their adjuvant therapy. As a result of recent research, it was found that BC had a deterioration in the psycho-emotional status and a decrease in most criteria of QoL, which were directly related to the severity of post-mastectomy edema, pain, and neurological disorders (Cáceres MC et al., 2022; Cvetković J et al., 2016; Villar RR. et al., 2017).

Women with BC have an increased risk of developing depression, anxiety, sexual dysfunction, sleep disturbances, cognitive problems, fatigue, and sexual problems. Assessment of life quality parameters has become a significant criterion of women's cancer rehabilitation. The credibility of a possible role of physical exercise in improving the QoL must be confirmed and maybe better investigated in a long-term evaluation.

Understanding QoL is important for improving symptom relief, care, and rehabilitation of patients. Problems revealed by patients' self-reported QoL may lead to modifications and improvement in treatment and care or may show that some therapies offer little benefit.

For instance, QoL has been shown to be a strong predictor of survival. This prognostic ability suggests that there is a need for routine assessment of QoL in clinical trials. Despite the importance of QoL in health and medicine, there is a continuing conceptual and methodological debate about the meaning of QoL and about what should be measured.

Today, QoL surveys are an important issue in healthcare, especially in oncological research. The time of diagnosis, the initial stages of treatment and the months following completion of treatment are difficult times for patients both physically and emotionally. During these periods, poor adjustment and decreased QoL in patients with BC can easily occur. Therefore, it is critical for health care professionals to become familiar with the impact of a BC diagnosis and its treatment on patients' QoL.

The current pandemic emergency situation has led the Italian government to take containment measures to counter the spread of the virus in Italy, which include reducing the movement of people from their homes, social distancing and working from home. This involves a change in lifestyles, first of all for what concerns the possibility of carrying out motor activities, but also for the control of eating habits. Therefore, paying attention, even in this situation, to maintaining a balanced lifestyle is very important to avoid that, once we emerge from the emergency, we find ourselves facing, individually and as a population, an increase in all those diseases that they are favored or aggravated by bad behavioral habits, such as diabetes, cardiovascular disease and cancer. The decision to join the MOVIS project "Movement and Health beyond care", in collaboration with the Italian DianaWeb project, Department of Predictive Medicine and Prevention of the National Cancer Institute of Milan, essentially arises from the desire to provides the opportunity to assess the feasibility of a randomized controlled trial design in the field of exercise-oncology as a model from a single institution and examine the effectiveness of a lifestyle intervention based on early patient support and mixed-approach that includes nutritional and exercise counseling, and specific exercise program (3-month of supervised aerobic exercise) to improve the QoL, ameliorate the prognosis and hopefully, increase survival rates in women with diagnosis of BC. In the next chapters, lifestyle changes before and during COVID-19 in a BCSs subgroup of the MOVIS Cohorte were examined.

AIMS OF THE THESIS

Among the malignant pathologies, BC is the most common invasive cancer in women and evidence has shown that exercise can significantly improve the outcomes of BCSs.

The principal aim of this thesis was to design a randomized controlled trial to evaluate the potential health benefits of exercise and proper nutritional habits favoring the correction of risk factors, potentially translating into a prognostic advantage in BCSs.

The primary outcome was to assess the efficacy of aerobic exercise training on the improvement of the QoL.

The secondary outcomes were the improvement of health-related parameters, including fatigue, anthropometric measurements, functional, metabolic and psychological parameters.

Due to the imposed COVID-19 pandemic restrictions, the aims of the work were adapted from the study protocol to the contest of BCSs enrolled in the COVID Era.

CHAPTER 1

Original Article

Movement and health beyond care, MOVIS: study protocol for a randomized clinical trial on nutrition and exercise educational programs for breast cancer survivors

Valentina Natalucci[1], Carlo Ferri Marini[1], Mauro De Santi[1], Giosuè Annibalini[1], Francesco Lucertini[1], Luciana Vallorani[1], **Andrea Rocco Panico[1]**, Davide Sisti[1], Roberta Saltarelli[1], Sabrina Donati Zeppa[1], Deborah Agostini[1], Marco Gervasi[1], Giulia Baldelli[1], Eugenio Grassi1, Alessandra Nart[1], Massimo Rossato[1], Vincenzo Biancalana1, Giovanni Piccoli[1], Piero Benelli[1], Anna Villarini[2], Matteo Somaini[3], Vincenzo Catalano[4], Stefania Guarino[4], Alice Pietrelli[4], Silvia Monaldi[4], Donatella Sarti[4], Simone Barocci[5], Marco Flori[6], Marco Bruno Luigi Rocchi[1], Giorgio Brandi[1], Vilberto Stocchi[7], Rita Emili[4] and Elena Barbieri[1].

[1]*Department of Biomolecular Sciences, University of Urbino Carlo Bo, 61029 Urbino, Italy*
[2]*Department of Research, Epidemiology Unit, Fondazione IRCCS Istituto Nazionale deiTumori, 20133 Milan, Italy*
[3]*School of Specialization in Nutrition Science, University of Milano, Milano, Italy.*
[4]*Medical Oncology, Hospital Santa Maria della Misericordia di Urbino, 61029 Urbino, Italy.*
[5]*Clinical Pathology, Hospital Santa Maria della Misericordia di Urbino, 61029 Urbino, Italy.*
[6]*Cardiology, Hospital Santa Maria della Misericordia di Urbino,61029 Urbino, Italy.*
[7]*Department of Human Sciences for the Promotion of Quality of Life, University San Raffaele, 20132 Rome, Italy.*

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Abstract

Background: Breast Cancer (BC) is the most common invasive cancer in women, and exercise can significantly improve the outcomes of BC survivors. MOVIS (Movement and Health Beyond Care) is a randomized controlled trial aimed to evaluate the potential health benefits of exercise and proper nutritional habits. This study aims to assess the efficacy of aerobic exercise training in improving quality of life (QoL) and health-related factors in high-risk BC.**Methods**: 172 BC survivor women, aged 30-70 years, non-metastatic, stage 0-III, non-physically active, 6-12 months post-surgery, and post chemo-or radio-therapy, will be recruited in this study. Women will be randomly allocated to the intervention arm (lifestyle recommendations and MOVIS Training) or control arm (lifestyle recommendations). The MOVIS Training consists of 12 weeks of aerobic exercise training (2 d/week of supervised and one d/week of unsupervised exercise) with a progressive increase in exercise intensity (40-70% of heart rate reserve) and duration (20-60 min). Both arms will receive counseling on healthy lifestyle habits (nutrition and exercise) based on the World Cancer Research Fund International (WCRF) 2018 guidelines. The primary outcome is the improvement of the QoL. The secondary outcomes are improvement of health-related parameters such as Mediterranean diet adherence, physical activity level, flexibility, muscular fitness, fatigue, cardiorespiratory fitness (estimated maximal oxygen uptake), echocardiographic parameters, heart rate variability (average of the standard deviations of all 5 min normal to normal intervals (ASDNN/5 min) and 24 h very low- and low-frequency), and metabolic, endocrine, and inflammatory serum biomarkers (glycemia, insulin resistance, progesterone, testosterone, and high-sensitivity C-reactive protein.**Discussion**: This trial aims to evaluate if supervised exercise may improve QoL and health-related factors of BC survivors with a high risk of recurrence. Findings from this project could provide knowledge improvement in the field of exercise oncology through the participation of a multidisciplinary team that will provide a coordinated program of cancer care to improve healthcare quality, improve prognosis, increase survival times and QoL, and reduce the risk of BC recurrence.

Trial registration: Clinical trial Identifier NCT04818359. MOVIS was retrospectively registered on March 26, 2021.

Keywords

Breast cancer, Physical activity, Exercise, Mediterranean Diet, Quality of life, Health-related parameters, Prevention.

Introduction

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title{1}	Movement and health beyond care, MOVIS: study protocol of a randomized clinical trial on nutrition and exercise educational programs for breast cancer survivors
Trial registration {2a and 2b}.	Clinical trial Identifier NCT04818359
Protocol version {3}	This study was undertaken in accordance with the Declaration of Helsinki, following the guidelines and approval of the local Ethics Committee (permission number: 21/19 10. July 2019).
Funding {4}	Ateneum project: Promozione della salute e della sicurezza alimentare (D.R. 446/2020)
Author details {5a}	[1] Department of Biomolecular Sciences, University of Urbino Carlo Bo, 61029 Urbino, Italy [2] Department of Research, Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, 20133 Milan, Italy [3] School of Specialization in Nutrition Science, University of Milano, Milano, Italy. [4] Medical Oncology, Hospital Santa Maria della Misericordia di Urbino, 61029 Urbino, Italy [5] Clinical Pathology, Hospital Santa Maria della Misericordia di Urbino, 61029 Urbino, Italy [6]Cardiology, Hospital Santa Maria della Misericordia di Urbino, 61029 Urbino, Italy [7] Department of Human Sciences for the Promotion of Quality of Life, University San Raffaele, 20132 Rome, Italy [¥] Should be considered joint first author [§] Should be considered joint senior author * correspondence: mauro.desanti@uniurb.it; giosue.annibalini@uniurb.it

Name and contact information for the trial sponsor {5b}	Not applicable
Role of sponsor {5c}	Not applicable

Introduction

Background and rationale {6a}

Breast cancer (BC) is the most common invasive cancer in women in all age groups. The number of new cases diagnosed worldwide in 2018 reached 2.1 million, and this value is expected to reach 3.2 million in 2050, with the highest incidence in industrialized countries [1]. While the incidence tends to rise, early diagnosis and more targeted therapies have resulted in a significant increase in the 5-year survival rate [2]. Although this finding is undoubtedly positive, it should nevertheless be emphasized that treatments such as surgery, radiotherapy, axillary emptying, chemotherapy, and hormonal therapy can cause long-term effects such as depression, anxiety, and fatigue that contribute to worsening patients' quality of life (QoL) [3].

Cohort studies conducted on patients in post-treatment follow-up have shown that physical exercise may be particularly suitable in this phase, as it improves psychophysical and cardiometabolic health in the patients who have completed adjuvant therapy [4, 5].

Regular physical activity is able to facilitate the improvement and recovery of autonomy through functional re-education and postural re-equilibrium, promotes socialization, and reduces anxiety and depression [6]. Furthermore, it has recently been reported that aerobic exercise can help to alleviate the typical cancer related fatigue in patients with breast cancer after diagnosis or treatment [7].

Nutritional aspects are also important in cancer post-treatment follow-up, by the modulation of hormonal levels related to cancer progression such as hyperglycemia, abdominal fat, and IGF-1 [8, 9]. It has been shown that the risk of recurrences could be prevented through a proper diet, weight control, and physical activity [10].

Physical exercise and healthy nutrition should be then considered during cancer follow-up, which aims to improve QoL, physiological parameters, and prognosis [11].

Objectives {7}

The main objective of the MOVIS project is to evaluate if supervised exercise may improve QoL and health-related factors of BC survivors with a high risk of recurrence. The intervention aims at changing the lifestyle of BC women, evaluated through monitoring physical, functional, psychological, and metabolic parameters.

Trial design {8}

MOVIS is a randomized controlled trial (RCT) on the effect of aerobic exercise training on QoL in BC survivors. Participants will be randomized to undergo either a supervised exercise program and lifestyle recommendations or lifestyle recommendations only. Groups will be divided following a parallel arm design with a 1:1 ratio.

Methods: Participants, interventions and outcomes

Study setting {9}

Patients taken in charge by the oncology clinic of the Medical Oncology Department of the Urbino Hospital (PU, Italy) will be pre-recruited and carefully informed on the modalities through which the project will take place. Patients that meet all the inclusion criteria described below will be recruited and randomized for the intervention phase.

Eligibility criteria {10}

Patients (women only) will be enrolled following the inclusion criteria:

- Diagnosis of BC (stage 0 to III, without metastases or recurrences diagnosis at recruitment);
- After surgery (maximum 12 months) and chemotherapy and/or radiotherapy treatments (minimum 6 months);
- Risk of recurrence, which was identified if the participants present at least 1 of the following conditions: BMI at diagnosis $\geq$ 25 kg/m^2; testosterone $\geq$ 0.4 ng/mL; serum insulin $\geq$ 25 μU/mL (170 pmol/L); metabolic syndrome. Metabolic syndrome was defined as the presence of at least 3 of the following 5 factors: i) glycemia $\geq$ 100 mg/dL (6.05 mmol/L); ii) triglycerides $\geq$150 mg/dL (1.69 mmol/L); iii) HDL-C < 50 mg/dL (1.29 mmol/L); iv) waist circumference $\geq$ 80 cm; v) blood pressure $\geq$ 130/85 mmHg.
- Non-physically active, namely participants must be not regularly active (according to the International Physical Activity Questionnaire [IPAQ]) for at least 6 months.

Exclusion criteria:

- Not suitable for non-competitive physical activity after the cardiological medical

examination;
- Disabling pneumological, cardiological, neurological, orthopedic comorbidities and mental illnesses that prevent the exercise performance;
- Treatment with drugs that alter the heart rate response to exercise;
- Treatment with antidepressant drugs.

Who will take informed consent? {26a}

In compliance with Good Clinical Practice (GCP) guidelines, all subjects will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to their future medical care at the center. Each subject will agree to cooperate in all aspects of the study and will give informed written acknowledgment (signed informed consent form [ICF]) to the Investigator prior to participation in the study. If necessary, ICF is revised during the study, and active subjects will sign the new version in order to continue participating in the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Not applicable.

Interventions

Explanation for the choice of comparators {6b}

Leisure-time physical activity is a well-known strategy for the prevention of cancer recurrences [12]. Therefore, for ethical reasons, the nutritional and physical activity counseling will be administered to the control arm, and its effects will be compared to the effects of the supervised MOVIS training performed by the intervention arm.

Intervention description {11a}

Patients will be randomly allocated to the intervention arm (lifestyle recommendations and MOVIS Training) or the control arm (lifestyle recommendations). The MOVIS Training consists of 3 months of aerobic exercise training (2 d/week of directly supervised by an exercise specialist and 1 d/week of remotely supervised exercise) with a progressive increase in exercise intensity (40-70% of heart rate reserve [HRR]) and duration (20-60 min). Even though several methods can be used to tailor exercise intensity [13], in the present trial exercise intensity will be prescribed using percentages of HRR corresponding to moderate

and vigorous intensity categories as suggested by the current breast cancer specific guidelines [14, 15]. Additionally, to account for several physiological adjustments that happens during prolonged aerobic exercises (e.g., cardiovascular drift), heart rate responses will be monitored throughout the training sessions and external exercise intensities (e.g., bike wattage or treadmill speed and grade) will be adjusted to maintain the target HR throughout each training session [16].

Both arms will receive counseling by dieticians on healthy lifestyle habits (nutrition and exercise) based on the World Cancer Research Fund (WCRF) 2018 guidelines through the DIANA-Web platform. The DianaWeb Project is a community-based participatory research that uses a specific interactive website that contributes to the growth of knowledge about lifestyle to be adopted by sharing recipes, movement strategies, and how to manage the change in daily practice involving Italian women with a BC diagnosis [17]. All patients will also undergo psychological well-being counseling by a psychologist, which comprises evaluation for anxiety and depression.

Criteria for discontinuing or modifying allocated interventions {11b}

Participants will be withdrawn from the trial if they are considered not suitable for non-competitive physical activity. The following criteria will be considered: disabling pneumological, cardiological, neurological, orthopedic comorbidities, or mental illnesses that affect the exercise performance; treatment with beta blockers, non-dihydropyridine calcium channel blockers, or amiodarone due to their potential effect on heart rate response to exercise; treatment with antidepressant drugs; recurrence diagnosis.

Strategies to improve adherence to interventions {11c}

Before the intervention phase, motivational interviews will be organized. These meeting will be structured in 15 minutes of personalized interviews in which the nutritionists and exercise specialists to explain the oncological lifestyle recommendations based on the WCRF 2018 and the recent guidelines on nutritional and exercise for breast cancer patients, approved by the Ministry of Health 2017 and 2019 [10, 14, 15, 18].

At each follow-up, the patient will be able to fill in specific questionnaires about nutrition and exercise to assess adherence to lifestyle changes.

Relevant concomitant care permitted or prohibited during the trial {11d}

Information on concomitant medication (prescription, over-the-counter, herbal and

naturopathic remedies, etc.) will be collected at beginning and during the study.

The research team will not interfere with the medication prescription, which will be chosen by the health care providers (i.e., oncologist and general practitioner). If the concomitant medications are incompatible with the inclusion criteria of the study, the participants will be excluded from the study.

Provisions for post-trial care {30}

At the end of the trial subjects will continue to follow the standard of care within the Clinical oncology Unit involved in the project.

Outcomes {12}

The primary outcome is the improvement of the QoL assessed by the European Organization for Research and Treatment of Cancer QoL (EORTC QLQ-C30) questionnaire [19].

The secondary outcomes are the improvement of health-related parameters, including fatigue (BFI questionnaire), anthropometric measurements, cardiac function indexes (echocardiography and heart rate variability), and functional (cardiorespiratory fitness and muscles characteristics), psychological (mood profile), metabolic parameters (HOMA-IR, IGF-1, and C-reactive protein), gut microbiota (next generation sequencing, NGS), and osteoporosis. Information about recurrences, diet habits, and physical activity levels will also be collected.

Participant timeline {13}

Figure. 1. Project timeline. Schedule of enrolment, intervention, and list of assessments across the study timepoints.

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation (months)					Close-out
TIMEPOINT**	$-t_1$	0	t_1(0)	t_2(3)	t_3(6)	t_4(12)	t_5(24)	t_x
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Educational counseling			X					
INTERVENTIONS:								
Intervention Arm (aerobic training)			◆					
Control Arm			◆					
ASSESSMENTS:								

Evaluation of eligibility criteria	X							
QoL (Primary outcome)			X	X	X	X	X	
Fatigue			X	X	X	X	X	
Anthropometry and body composition			X	X	X	X	X	
Cardiac function indexes			X	X				
Heart rate variability			X	X				
Cardiorespiratory fitness			X	X	X	X	X	
Flexibility, muscular fitness			X	X	X	X	X	
Proprioceptive recalibration, posture balance			X		X			
Upper limb muscles viscoelastic characteristics			X	X				
Psychological well-being			X	X	X	X	X	
HOMA-IR Index, IGF-I, C-reactive protein			X	X	X	X	X	
Gut microbiota			X	X	X	X	X	
Osteoporosis level			X			X	X	
Recurrences			X	X	X	X	X	
Dietary habits and physical activity level			X	X	X	X	X	
Post-trial care								X

Sample size {14}

The sample size was calculated with the aim of verifying the differences between the QoL changes in the two groups (i.e., intervention and control arm), after three months of intervention.

The QoL expected improvement in the experimental group at 12 weeks is 15.1 ± 17.7, while in the control arm it is 6.1 ± 17.1 [20]. Using a t-test for independent samples, with alpha of 0.05 and statistical power of 0.80, to find differences in QoL improvements between the two groups at the end of the intervention 60 subjects per group will be needed. Considering an expected drop-out of 30%, a total of 172 patients will be recruited. The sample size was calculated using Stata statistical software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Recruitment {15}

During routine hospital visits, patients will be informed by the oncologist about the benefits of physical activity and nutrition for recurrences prevention and the MOVIS trial will be presented in detail. In addition, the project will be promoted by social media and public events. Patients who wish to participate will be screened for the evaluations for the eligibility

criteria.

Assignment of interventions: allocation

Sequence generation {16a}

In order to ensure balanced groups, subjects will be randomized to the two arms (with a 1:1 ratio) using permuted block (n = 4) randomization, stratified according to the anthracycline treatment.

Concealment mechanism {16b}

Not applicable

Implementation {16c}

Participants will be enrolled by the oncologists of the Medical Oncology Department of the Urbino Hospital (PU, Italy). The allocation to the intervention program will be randomly assigned by statisticians, who will be blinded to participants' information. Randomization will take place using a manual list accessed electronically via Interactive Web Response System (IWRS) after randomization eligibility is determined (Figure 1).

Assignment of interventions: Blinding

Who will be blinded {17a}

Patient allocation and intervention will not be blinded. However, blinded data analysis of primary and secondary outcomes will be performed by researchers and statisticians.

Procedure for unblinding if needed {17b}

Not applicable

Data collection and management

Plans for assessment and collection of outcomes {18a}

The primary outcome is the improvement of the QoL assessed by EORTC QLQ-C30 questionnaire [19]. Scores obtained by the questionnaire range from 0 to 100, with higher

scores that indicate better quality of life.

The secondary outcome is the improvement of health-related parameters, including fatigue, anthropometric measurements, cardiac function indexes, and functional, psychological, and metabolic parameters. Fatigue will be assessed by the brief fatigue inventory (BFI) questionnaire; questionnaire scores range from 0 to 90, with higher scores associated with more severe fatigue. Anthropometric measurements in terms of weight (kg), height (cm), BMI (kg/m^2), and fat mass (%) will be assessed by bioelectrical impedance analysis. Cardiac function will be assessed by echocardiography and speckle tracking imaging analysis. Measurements will include volumetric measure by the modified Simpson's rule, doppler measurement of mitral inflow (E and A wave), tissue doppler lateral mitral annulus peak velocity (e' wave) and speckle tracking peak global longitudinal strain. Heart rate variability (HRV) will be assessed by 24 h monitoring of mean heart rate (HR in bpm), total number of premature ventricular and supraventricular beats (as percentage of total beats), time domain HRV parameters (standard deviation of the averaged normal to normal intervals), root mean square of successive differences of normal to normal intervals, percentage of adjacent normal to normal intervals that varied by more than 50 ms (pNN50 in %), frequency domain and total power HRV parameters.

Functional parameters will include muscle flexibility (assessed by sit & reach test) and strength (assessed by isometric hand grip strength test), proprioceptive recalibration (stabilometry analysis by mean square deviation of velocity from mean), posture balance (stabilometry analysis by Romberg quotient test – European variant) [21], upper limb muscle viscoelastic characteristics evaluation by a hand-held myotonometer, and cardiorespiratory fitness. Participants' cardiorespiratory fitness will be assessed by estimating the maximal oxygen uptake ($\dot{V}O_{2max}$) using an individualized submaximal incremental walking test performed on a treadmill [15, 22]. The test will comprehend multiple 3-min stages with incremental exercise intensities individualized according to the predicted $\dot{V}O_{2max}$ of each individual. The walking speed, which will be individually chosen for each participant, will be kept constant throughout the test. Hence, treadmill grade will be modified at each stage to induce an exercise intensity of the first stage at about 30% of the predicted oxygen uptake ($\dot{V}O_2$) reserve ($\dot{V}O_2R$), with about 10% $\dot{V}O_2R$ increase in exercise intensity for each stage. Exercise intensity will be increased until participants will reach 70% of heart rate (HR) reserve (HRR) [22]. The HR or $\dot{V}O_2$ values corresponding to the desired percentages of the reserve values (%$\dot{V}O_2R$ or %HRR) will be calculated as follows: (maximal value - resting value) x desired percentage + resting value. Resting $\dot{V}O_2$ will be assumed to be 3.5 $mL \cdot min^{-}$

^{1}·kg^{-1}[15], $\dot{V}O_{2max}$ will be predicted by means of a non-exercise model [23], and $\dot{V}O_2$ will be converted to treadmill speed and grade using the ACSM's walking equation [15]. Resting HR will be measured after sitting for 10 min, while maximal HR (HR_{max}) will be predicted as proposed by Gellish et al. [24]. Participants' HR will be recorded at each stage and used to create individual submaximal HR-$\dot{V}O_2$ relationship which will be extrapolated to the predicted HR_{max} in order to estimate $\dot{V}O_{2max}$ [15, 22]. The individualized testing protocols will be created once at T_1 and repeated at the following timepoints.

Psychological well-being will be assessed through the evaluation of mood profile change (Profile of Mood States (POMS) questionnaire). The analysis of metabolic, hormonal, and inflammatory risk factors will include Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) Index, Insulin-like growth factor (IGF-1), and C-reactive protein.

Gut microbiota will be assessed by the analysis of microbial diversity (NGS of the V3-V4region of the 16S rDNA gene). Osteoporosis level will be assessed by computerized bone mineralometry (T-Score). Recurrences free interval defined as time from registration to time of documented recurrent disease will be assessed.

Diet habits, physical activity level, pharmacological treatments and comorbidity will be recorded as confounding factors and covariates. Change in dietary intake will be assessed by questionnaire (14-item Mediterranean diet adherence screener, MEDIET) through the DIANAWeb platform [17, 25]. Change in physical activity level will be assessed by the SenseWear armband activity monitor (BodyMedia Inc., Pittsburgh, PA) and by the International Physical Activity Questionnaire Short Form (IPAQ-SF) [26, 27]. The output of both assessments will be expressed in metabolic equivalents (MET·min·week^{-1}).

Plans to promote participant retention and complete follow-up {18b}

Informative and social events will be organized to promote participant retention to complete the follow-up. Social events such as healthy dinners, cooking sessions, or walks are very important to create a group on a healthy lifestyle. Throughout the follow-up period, patients will take part in group chats and webinars on healthy nutrition and exercise behavior. From the moment of enrollment, all patients will be registered on the DianaWeb platform [17, 25], in which they will be invited to cook and eat some dishes prepared according to the WCRF/AICR recommendations and inspired by a Mediterranean diet.

Data management {19}

Electronic Case Report Forms (eCRF) will be used to capture and organize data as defined in the study protocol. The system will include the eCRF to collect primary data and serve as a conduit to transfer sensitive data. A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical, or potentially erroneous. Concurrent manual data review will be performed based on parameters dictated by the plan.

Confidentiality {27}

Individual subject's medical information obtained as a result of this study is considered confidential and disclosure to unauthorized parties is prohibited. Subject's confidentiality will be assured by utilizing unique subject numbers instead of names. If the results of this study will be reported in medical journals or at meetings or may be submitted to competent regulatory authorities in connection with regulatory procedures, the subject's identity will not be disclosed. With the subject's authorization, medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

In compliance with GCP guidelines, all subjects will be informed of the purpose of the research, the possible risks, and their right to withdraw at any time from the study without prejudice and without jeopardy to their future medical care at the center. Each subject must agree to cooperate in all aspects of the study and must give informed written acknowledgment (signed ICF) to the Investigator prior to participation in the study. If the ICF is revised during the study, active subjects must sign the new version in order to continue participating in the study.

The Investigator will maintain adequate records for the study including completed eCRFs, medical records, laboratory reports, signed ICFs, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with theInstitutional Review Board (IRB) and Independent Ethics Committee (IEC), and other pertinent data.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Serum samples will be anonymously stored for further molecular or biological activity analyses. Samples will be aliquoted to avoid freeze/thaw cycles and frozen at -80°C until their use.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

A mixed-design ANOVA will be used to compare the changes over time (from T1 to T2, within factor) in the primary outcome between intervention and control arms (between factor). The sample size was calculated to test the hypothesis of no differences between the changes in the primary outcome of the two groups (i.e., interaction effect of the between and within factors of the mixed-design ANOVA). If a significant effect is found, post-hoc pairwise comparisons will be used.

Secondary outcomes will be analyzed using repeated measures MANOVA models, with differences-based contrasts.

For all tests, a 2-sided α level of significance of 0.05 will be used and, if necessary, the α level inflation due to multiple tests will be accounted for by using the appropriate correction (e.g., Bonferroni, false discovery rate, etc.). The statistical test assumptions will be assessed and, if not met, either data transformation or alternative statistical methods (e.g., GEE, non-parametric analyses, etc.) will be performed.

Interim analyses {21b}

Due to the low risks associated with the interventions and well-known beneficial effects of physical activity and nutritional counseling, interim analyses are not planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

An exploratory analysis will be conducted through the principal component analysis (PCA), in order to highlight any subgroups showing a homogeneous response pattern. Additional exploratory analyses will also be performed using participants' characteristics (e.g., age, fitness status, physical activity level, and metabolic and clinical profile) as covariates to assess possible underlying confounding variables on the primary and secondary outcomes results.

Methods in analysis to handle protocol non-adherence and any statistical methods to

handle missing data {20c}

The MOVIS trial is a per protocol study.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Not applicable

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

Not applicable.

Composition of the data monitoring committee, its role and reporting structure {21a}

Not applicable

Adverse event reporting and harms {22}

Adverse events, including serious adverse events, will be collected throughout the study period, beginning from the time the subject signs the ICF until the 2 weeks after the end of study. All adverse events persisting at the time of study completion will be followed by the Investigators through contact with the subject until resolution or stabilization, or the subject is lost to follow-up and cannot be contacted. The outcomes of the adverse event will be documented in the subject's source documents. The Investigators will report any serious adverse events that occur after the protocol specified reporting period if, according to the Investigators' assessment, there was a reasonable possibility that the serious adverse event was related to any study procedures.

Frequency and plans for auditing trial conduct {23}

Not applicable.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Before applying any amendments to the study protocol, the proposed amendment will be submitted to the ethical committee. Then, after approval from the ethical committee, the amendments will be communicated to the participants, who will sign an amended informed consent if they are willing to continue the study.

Dissemination plans {31a}

Results obtained from this trial will be disseminated through participation in national and international conferences with abstracts, posters, and oral communications. Definitive results will be published in peer-reviewed international journals. Moreover, dissemination events will be organized in order to make available the knowledge improvement about the benefits of supervised exercise to healthcare workers, BC survivors, and all interested people.

Discussion

In the MOVIS Trial, we will estimate the effectiveness of a lifestyle intervention based on proper nutrition (Mediterranean diet) and exercise (supervised aerobic exercise) on the QoL of inactive BC survivor women. In addition, we will investigate the cardiometabolic effect and the feasibility of a structured exercise program in BC survivor women recruited at the Oncology Unit of Urbino.

Previous RCTs in the field of exercise-oncology have shown beneficial effects of lifestyle changes, in particular on the risk of distance recurrence [12] and improvement of the quality of life [28–33]. Many beneficial effects are also attributable to the potential effect of exercise and a correct diet in mitigating the side effects due to surgery and adjuvant therapy (e.g., chemotherapy, radiotherapy, immunotherapy, and hormone therapy), such as physical and psychological deconditioning [34, 35]. However, the questions to improve the approach of women with BC still need clear answers. The existing RCTs in the field of exercise-oncology described how different types of exercise interventions can be beneficial for physical function, cancer-related fatigue, pain, and muscle strength [36, 37]. Such effects are due, in part, to physical exercise leading to improvements in physical fitness, cardiorespiratory function, muscular endurance, and body composition [14]. Emerging evidence suggests the beneficial effects of the exercise are greater if the exercise is supervised and follows the key components of exercise (i.e., frequency (F), intensity (I), time (T), type (T), volume (V), and progression (P) over time, namely the FITT-VP principle) [15, 38]. In this context, it is well known that the adherence of BC survivors to exercise is low [39] and that engagement to motivation to exercise plays an important role in promoting and adhering to physical activity guidelines in BC survivors [40–42].

This multidisciplinary project is based on the dynamic and structured interaction between different expertise such as those of medical oncologists, nutritionists, exercise experts, and

biochemists/molecular biologists, and is part of innovative research projects related to wellness, health, and biomedicine. For these reasons, results will have an impact both on clinical practice and on the area of personal wellbeing. This approach can be particularly useful for patients reluctant to start physical activity programs because they fear that an intense activity may worsen BC-related symptoms, such as fatigue, and pain, as well as to undertake a dedicated nutritional strategy [43].

The success of this project will give a double support to the oncologist's in-patient management, and to the patients in overcoming the barriers related to the management of a correct lifestyle. The existence of a multidisciplinary team working in synergy from a holistic point of view allows us to manage, to face and to overcome different and specific needs of patients. Therefore, creating a safe environment represents an important action plan in the care of cancer patients, promoting a healthy lifestyle in clinical practice reduces risk factors involved in BC recurrence and ensures psycho-physical well-being.

Despite its potential strengths mentioned above, the proposed MOVIS Trials presents certain limitations. The first one and more actual is the exceptional pandemic context where the experimentation has been developed. During COVID-19 restrictions, cancer patients and survivors easily regress to sedentary lifestyles [44], which results in declining health and quality of life, particularly for patients undergoing treatment or suffering adverse effects of treatment. Home-confinement made it more difficult to reach the guidelines of oncological prevention for both nutrition and regular PA [44]. The final analysis, thus, could potentially and partially be affected by the COVID-19 pandemic.

Moreover, it is worth noting that RCTs in the field of exercise-oncology have several limitations, such as drop-out and loss of follow-up of patients during the entire course of the study. For this reason, we estimate an expected drop-out of 30% for a total of 172 patients after the 12-week interventions, which will probably increase over the two years follow-up. To ensure that the drop-out rate is not affected by the present study design and consequently affects the results of the present study, trial retention will be scored as the rate of drop-out after signing informed consent for the study and registered for both groups. Then, exploratory analyses will be performed to assess if several factors (e.g., trial arm, clinical, and characteristics) affected the drop-out rate.

Moreover, since the control arm is aware of participating to the trial and received counseling regarding the benefits of physical activity, a possible increase in physical activity levels in the control arm, which could be caused by several factors (e.g., motivation to change their lifestyle after diagnosis), could happen and dampen the differences between the two arms

regarding their physical activity levels. However, due to the well-known beneficial effect of physical activity in breast cancer survivors, for ethical reasons we have decided to decrease the barriers to perform physical activity and promote it also in the control arm. Notwithstanding, physical activity levels will be evaluated using the IPAQ and the Sensewear armband and their effect will be evaluated as a possible confounding variable of this study. The ethical decision of promoting physical activity also in the control arm was made necessary because using other types of study design (e.g., using a wait-list control group) would have made impossible to obtain longer term follow-up without compromising the optimal patient's care.

Patients are enrolled within 12 months after diagnosis because at this time most of these patients have finished their primary treatment (e.g., chemotherapy and/or radiotherapy) but most of these continuing the hormone therapy for at least 5 years. In this period, the impact of diagnosis and neoadjuvant/adjuvant treatment on normal daily living (e.g., complaints of fatigue, impaired quality of life) become more impactful. Although several studies have shown that exercise has a beneficial effect on the QoL and treatment-related symptoms of patients with breast cancer in this period, adherence to nutrition and exercise guidelines is low. This study provides the opportunity to assess the feasibility of a RCT design in the field of exercise-oncology as a model from a single institution and examine the effectiveness of a lifestyle intervention based on early patient support and mixed-approach that including nutritional and exercise counseling, and specific therapeutic exercise (12 weeks of supervised aerobic exercise). The proposed intervention will examine its effect on the QoL and other several health-related parameters of patients with breast cancer in the short term (6 months) and medium-long term (12 and 24 months).

Trial status

The recruitment began in January 2020 and will end approximately May 31, 2023. Data collection is continuing.

Abbreviations

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; HRR: Heart rate reserve, HRrest: Resting heart rate; RCT: Randomized controlled trial; RM: VO2peak: Peak oxygen uptake.

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Authors' contributions {31b}

EB and RE are the Principal Investigators, they conceived the study and led the proposal. FL led the protocol development and design of the study. LV, DA, VB, PB, and GP contributed to the development of the proposal. VN is responsible for delivering and supervising the exercise intervention and for the exercise educational program. FL, CFM and VN are responsible for functional parameters and fitness evaluations. GA, MDS, RS, AN, MR, GBa, MG, and EG: outcome conception, planning of data collection, and laboratory analysis. DSi and ARP: planning of data collection and statistical analysis. AV, MS, and SDZ are responsible for draft and planning the nutritional educational program. RE, VC, SG, AP, SM, SB, MF and DSa are part of the clinical staff involved in patient recruitment definition and clinical management plan. MBLR, VS, and GBr: conceptualization and revision. MDS, CFM, VN, ARP, EB, and LV, drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials {29}

The datasets generated and/or analyzed during the current study are not publicly available but are available from the Principal investigator (PI) on reasonable request. Source documentation

(e.g., case histories, progress notes of the physician, hospital records, etc..) will be available at monitoring visits to verify entries made on eCRFs, as needed.

Ethics approval and consent to participate {24}

This study will be conducted according to the principles of the Declaration of Helsinki (Forteleza, October 2013: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). The study has been approved by the Ethics Committee of the University of Urbino Carlo Bo (Approval Number: 21/10.07.2019). Written informed consent to participate will be obtained from all participants.

Consent for publication {32}

Not applicable

Competing interests {28}

The authors declare that they have no competing interests.

Authors' information (optional)

Not applicable

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CHAPTER 2

Original Article

Effect of a Home-Based Lifestyle Intervention Program on Cardiometabolic Health in Breast Cancer Survivors During Two Years of COVID-19 Pandemic

Panico Rocco Andrea [1] et al.

[1]*Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy.*

In preparation.

Abstract

Background: The focus of this study is to evaluate the cardiometabolic effects of a home-based lifestyle intervention (LI) in breast cancer survivors (BCSs) during the 2 years of COVID-19 pandemic period.

Material and methods: A total of 30 BCSs (women; stages 0–II; non-metastatic; aged 53.5 ± 7.6 years; non-physically active) with a risk factor for recurrence, due to metabolic or endocrine disorders, underwent a 3-month LI based on nutrition and exercise.

Anthropometrics, Mediterranean diet adherence, physical activity level (PAL), cardiorespiratory fitness ($\dot{V}O_{2max}$), biomarkers (metabolic, hormonal and cardiotoxicity parameters) such as: glycemia, insulin, triglycerides, high-density lipoprotein (HDL), low density lipoproteins (LDL), total cholesterol, progesterone, testosterone, and hs-troponin, were evaluated before (T0), immediately after the 3-month LI (T1), in the short- (6 months, T2) and long-term (12 and 24 months, T3 and T4, respectively).

Results: Significant beneficial effects of the LI were observed on several variables (i.e., body mass index, waist circumference, $\dot{V}O_{2max}$, Mediterranean diet adherence, glycemia, insulin, LDL, total cholesterol, and testosterone) immediately after the 3-month of LI. The significant effect on $\dot{V}O_{2max}$ and Mediterranean diet adherence persisted up to 24-month follow-up. Significant decreases in glycemia, insulin, and triglycerides were observed up to 12 months, but did not persist afterward. The other parameters did not change after LI.

At T1 *vs*. T0 there were improvements in: body mass index (kg/m^2): T0 = 26.1±4.97, T1 = 25.7±4.6, $p<0.05$); $\dot{V}O_{2max}$ (mL·min^{-1}·kg^{-1}): T0 = 30.5±5.6, T1 = 33.9±6.4, $p<0.01$; Mediterranean diet adherence (Mediet score): T0 = 6.9±2.3, T1 = 8.8±2.2, $p<0.001$; LDL (mg/dL): T0 = 136±28.9, T1 = 125.1±28.2, $p<0.001$); total cholesterol (mg/dL): T0 = 216.4±39.2, T1 = 207.3±37.4, $p<0.05$; testosterone (ng/mL): T0 = 0.3±0.2, T1 = 0.2±0.1; $p<0.001$.

Conclusions: This study provides evidence supporting the relationship between LI and the improved cardiometabolic health in BCSs during the 2-year pandemic period.

Keywords

COVID-19; breast cancer survivors; home-based lifestyle intervention; Mediterranean diet; exercise; cardiorespiratory fitness.

Introduction

The COVID-19 pandemic was a particularly worrying time for vulnerable groups with pre-existing health conditions, such as breast cancer (BC) survivors (BCSs), because the mandatory directives for the first lockdown (in Italy between 9th March to 3rd May 2020) certainly altered the daily routine in clinical settings, routine cancer care, including health and supportive care interventions (Natalucci V. et al., 2021; Mentrasti G. et al., 2022). In Italy the pandemic hits in "waves", however the studies assessing the longitudinal impact of the pandemic in the BCS are not fully described. BC is the most common global malignancy and the leading cause of cancer deaths (Katsura C. et al., 2022)and independently from the COVID-19 infection, in Italy, more than 85% of women survive for 5 years or longer and their long-term health-related quality of life (HRQoL) has become an important issue for the public health (AIOM AIRTUM PASSI PASSI d'Argento and SIAPEC-IAP Working Group 2019; Nardin S. et al., 2020). With an increasing population of BCSs, it is important to study the long-term perceived health and wellbeing of these population, to identify those with impairments in health-related quality of life (HRQoL) able to emeliorate their habits during and after BC treatment (Roine E. et al., 2020), especially during the COVID-19 Era.

Furthermore, as regards behavioral risk factors, the data collected during the two-year period 2020-2021 mark a moment of acceleration mostly in a pejorative sense. This is a figure that cannot fail to cause concern if we consider that 40% of cases and 50% of cancer deaths can be avoided by intervening on preventable risk factors, especially on lifestyles (AIOM AIRC I Numeri Del Cancro in Italia 2022). In this light, during the pandemic emergency, many of the factors that impact risk of recurrence, such as lifestyle choices, have been modified and it is possible that some women with BC have altered their behaviors by facing additional barriers to healthy choices, beyond those already documented (Brunet J. et al., 2013). In this context, particular attention should be focused on patients at high risk of BC recurrence such as sedentary patients and those affected by the metabolic syndrome. Physical inactivity and metabolic syndrome are associated with a significant increase in BC risk (Dixon-Suen S.C. et al., 2022), with three-fold increase in BC recurrence and about two-fold increase in BC specific mortality (Pasanisi P. et al., 2006). The BC management is based on a primary approach including surgery, radiation therapy and circulating and oral endocrine-, chemo-, anti-HER2. In addition, interventions based on lifestyle habits and complementary therapies should also be taken into consideration for the BC outcomes, and represent important

strategies for the BCS care. A large body of evidence shows that lifestyle interventions (LI) that includes exercise and nutrition are able to improve the psycho- physical well-being of BCSs (Oldani C. et al., 2020; Mills R.C. et al., 2017). The beneficial effects induced by exercise are commonly attributed to long-term adaptations (i.e., months/years) and related to improvements in cardiorespiratory fitness, strength, body composition and fatigue reduction (Harbeck N. et al., 2019; Irwin M.L. et al., 2005). Exercise can have numerous beneficial effects, in various follow-up periods, on the quality of life, physical function, social life, fatigue and self-esteem. According to WHO data, a percentage ranging from 9 to 19% of all cancers is attributable to a lack of movement. It has been also proven that exercise programs can improve quality of life and reduce the adverse effects of endocrine therapy in patients with premenopausal and postmenopausal BC (Hojan K. et al., 2013; Winters-Stone K.M. et al., 2012). Cancer patients who performed aerobic exercise during and after radiotherapy and chemotherapy treatment demonstrated measurable improvement in quality of life, oxygen uptake, and body composition (Hojan K. et al., 2013). Training programs can help improve medical treatment outcomes for cancer and are also advisable for the prevention and treatment of many ailments (Meneses-Echavez J.F. et al., 2015; Ferrer R.A. et al., 2011). It has been shown that aerobic and resistance exercise, separately or in combination, can improve physical functioning and manage some symptoms in BCSs. Observational studies have shown that physically active people, once diagnosed with breast, colorectal or prostate cancer, have a lower risk of relapse than sedentary subjects (Patel A.V. et al., 2019). In addition, physical activity is also recommended during therapies, as it can help reduce side effects and improve the quality of life of patients. It is important to remember that exercise can have primary prevention effects against cancer, but it does not represent a strategy to eradicate a tumor that has already formed, it can only slow down its growth, bringing benefits to the whole organism. The studies measured physical activity using the metabolic equivalent of task (MET), the rate at which the body uses energy (oxygen) during physical activity compared with the energy used at rest. One MET is equivalent to 3.5 ml oxygen per kg of body weight per minute. 10 MET hours per week equates approximately to 75 minutes of vigorous activity or 150 minutes of moderate activity (Craig C.L. et al., 2003; Mendes M.A. et al., 2018).

As exercise, also the diet is an important pillar for lifestyle, and in a global perspective can be used to help prevent cancer, and more specifically BC (Glade M.J. 1999). In addition, it may also reduce the risk of cancer progression and improve treatment outcomes. About diet, it is known that the Mediterranean diet is one of the best recommendations in BC prevention

(Turati F. et al., 2018; Li Y. et al., 2018). A diet rich in whole grains, vegetables and legumes reduces, for example, the risk of metabolic syndrome, one of the risk factors for BC. Moreover, preferring unrefined foods and limiting animal fats is another healthy advice because these tend to slow down the action of insulin and glycemia, both factors associated with greater risk (Turati F. et al., 2018; Bruno E. et al., 2021).

The pandemic period probably exacerbated health risks, since it might have also changed food consumption patterns and physical activity levels (PALs), potentially impacting on the longer-term health of BC populations. Indeed, lifestyle interventions are necessary to potentially favor BC outcomes and reduce the risk of comorbidities and recurrences (Di Renzo L. et al., 2020; Montemurro, N. 2020).

The aim of this study was to describe the effects of a home-based lifestyle intervention in women with BC at high risk of recurrence due to metabolic or endocrine disorders on cardiometabolic health during the 2 years of COVID-19 period.

Materials and Methods

Setting and participants

The study was conducted at the Santa Maria della Misericordia Hospital in Urbino and the Department of Biomolecular Sciences of University of Urbino Carlo Bo in the Marche region (central Italy). Ethical approval was granted from the local Ethics Committee (permission number: 21/19 10 July 2019) and the MOVIS trial was registered (protocol: NCT 04818359). Written informed consent was obtained from all participants. Participants were recruited by the oncology clinic of the Medical Oncology Department of the Urbino Hospital (PU, Italy) on the basis of inclusion and exclusion criteria. Eligibility criteria included women with histologically confirmed BC (stage 0-I-II-III) with no evidence of recurrent or progressive disease; within 1 year of diagnosis; completed surgery, radiotherapy, and/or chemotherapy (within 12-month) with or without current hormone therapy use; age between 30 and 70 years; at risk of recurrence identified with the present of at least 1 of the following conditions: body mass index (BMI) at diagnosis ≥ 25 kg/m2, testosterone ≥ 0.4 ng/mL; serum insulin ≥ 25 μU/mL (170 pmol/L); metabolic syndrome (at least 3 of the following 5 factors): a, glycemia ≥ 100 mg/dL (6.05 mmol/L); b, triglycerides ≥ 150 mg/dL (1.69 mmol/L); c, HDL-C < 50 mg/dL (1.29 mmol/L); d, waist circumference ≥ 80; e, blood pressure ≥ 130/85 mmHg. Women were excluded if they had evidence of recurrent disease, had previously

engaged in any formal exercise programs during the 6 months prior to participation in this study, or if they had pneumological, cardiological, neurological, orthopedic comorbidities, or mental illnesses that prevent the exercise performance.

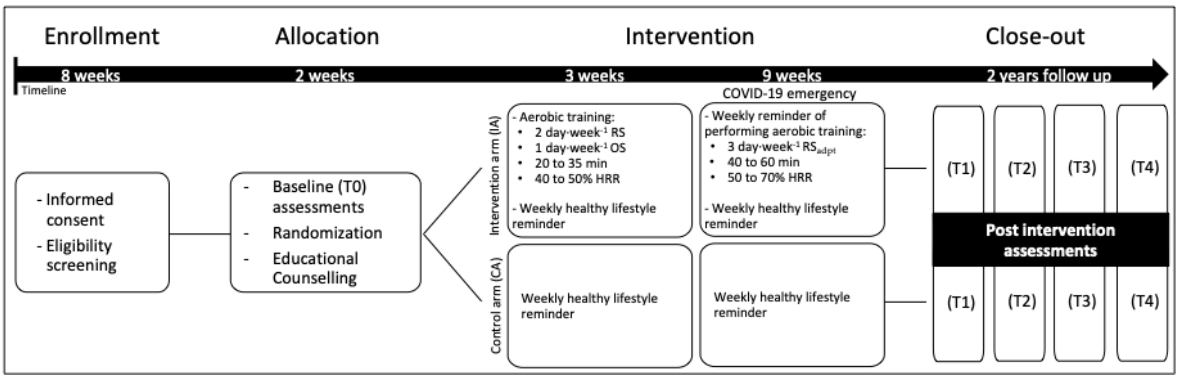
Study design and procedures

MOVIS trial (protocol: NCT 04818359) was an open randomized controlled trial with two parallel groups (1:1 randomization ratio with the control arm). Briefly, patients were randomly assigned to the intervention arm (IA) (lifestyle recommendations and MOVIS training) or the control arm (CA) (lifestyle recommendations).

Amended protocol

As reported in Natalucci V. et al. (2021) the two arms (intervention and control arm) were combined. Briefly, the restriction imposed by the COVID-19 pandemic resulted in a modification of the study protocol which was approved by the institutional ethics committee (Protocol No. 29/20 22.04.2020) (Figure 1).

Figure 1. Flowchart of the study design.



Abbreviation: HRR, heart rate reserve; RS, remotely supervised; OS, on-site supervised; RSadpt, remote supervision adapted due to COVID-19 pandemic restrictions; T1, after 3 months; T2, after 6 months; T3 after 12 months; T4 after 24 months.

Intervention description

Lifestyle intervention included exercise and nutritional recommendations for both arms (intervention and control arm). While, a targeted exercise intervention, the MOVIS Training, was carried out only in the intervention participants. The original MOVIS Training consisted of 3 months of aerobic exercise training (2 d/week of directly supervised by an exercise specialist and 1 d/week of remotely supervised exercise) with a progressive increase in exercise intensity (40-70% of heart rate reserve (HRR)) and duration (20-60 min). Due to COVID-19 pandemic restrictions, from the 4th week the type of supervision was adapted to solely remotely supervised exercise (3 sessions per week). The supervision was performed weekly, using phone calls from the exercise specialist, who provided the weekly exercise prescription and personalized feedback according to the training logs. Additional information is reported in Natalucci V. et al. (2021).

Assessments

Demographic and clinical information was collected by the oncologist at baseline. Participants baseline characteristics are shown in Table 1.

Table 1. Participants baseline characteristics (N = 30).

	N	**%**
Menopausal status	18	64.3
Surgery Type		
Mastectomy	3	10.0
Quadrantectomy	26	87.7
Lumpectomy	1	3.3
Treatment in addition to surgery		
Only radiation	2	6.7
Only chemotherapy	13	43.3
Radiation and chemotherapy	4	13.3
None	11	36.7

Current endocrine therapy		
None	6	20.0
Tamoxifen	8	26.7
AromataseInhibitor	16	53.3

Submaximal cardiorespiratory fitness test was performed at all of the assessment times. The submaximal testing protocol consisted of multiple 3 min stages with incremental exercise intensities tailored for each individual according to their predicted $\dot{V}O_{2max}$. The exercise intensity (treadmill speed and grade) of the first stage was set at about 30% of the predicted oxygen uptake (VO_2) reserve (VO_2R) using the ACSM's walking equation (Riebe D. et al., 2018) and was increased by about 10% VO_2R each stage. The tests were interrupted when participants reached 70% of heart rate (HR) reserve (HRR) or if safety contraindication or concerns appeared during the test (Jones, L.W. et al., 2008). The HR or VO_2 values corresponding to the desired percentages of the reserve values (%VO_2R or %HRR) were calculated with the following formula: (maximal value − resting value) x desired percentage + resting value. In the calculation of %VO_2R, the resting VO_2 was assumed to be 3.5 $mL \cdot min^{-1} \cdot kg^{-1}$ (Riebe, D. et al., 2018), while $\dot{V}O_{2max}$ was predicted by means of a non-exercise model using the Excel spreadsheet provided by Ferri Marini et al. (2021). In the calculation of %HRR, the resting HR was measured after a 10 min resting period with the participants sitting quietly in a chair, while maximal HR (HR_{max}) was predicted using the formula proposed by Gellish et al. (2007). If the test assumptions and recommendations were met, the $\dot{V}O_{2max}$ of each participant was estimated according to her HR responses during the test by extrapolating her submaximal HR-VO_2 relationship to the predicted HR_{max} (Riebe D. et al., 2018; Jones L.W. et al., 2008); otherwise, the test was repeated. The personalized submaximal testing protocols were created at baseline and repeated after each follow-up.

Metabolic and hormonal parameters were collected by fasting (≥12 h) blood at baseline and after 3, 6, 12 and 24 months. Blood glucose, insulin, triglycerides, HDL-C, LDL and total cholesterol concentrations were determined by colorimetric assays on Beckman Coulter AU Analyzers (Bondar R.J. et al., 1974; Roeschlau P. et al., 1974). Progesterone, estradiol and testosterone were determined by chemiluminescence on Beckman Coulter DXi Analyzers (Gerhard I. et al., 1984; Newman J.D. et al., 2014).

Adherence to a Mediterranean diet was assessed by the Mediet questionnaire, which was analyzed using the DianaWeb Platform and Mediet Score, while PAL was assessed by using the interviewer-administered IPAQ-SF questionnaire as reported in Natalucci V. et al., 2021.

Statistical analyses

Statistical analyses on the variables of this study were performed to assess if during time the sample showed differences, over two years. The clinical and functional parameters analyzed were the following: BMI, cardiorespiratory fitness, waist circumference, fat mass, $\dot{V}O_{2max}$, PAL, adherence to Mediterranean diet and biomarkers, such as: glycemia, insulin, triglycerides, HDL, LDL, total cholesterol, progesterone, estradiol, testosterone and hs-troponin. The outcomes were analyzed using repeated measures ANOVA models, with differences-based contrasts (reference was measured at T0). Analysis was performed using SPSS Data and was analyzed using IBM SPSS Statistical Software version 27.0.

4. Results

Subject characteristics

Characteristics of the study cohort of BCSs that participated in the MOVIS trial are listed in Table 1. During the 2 years of follow-up From January 2020 to February 2022, there were no adverse effects recorded, one dropout at T1 was recorded due to knee cartilage damage and 1 relapse at T4 occurred.

Changes in Anthropometric, Body Composition, Physical Activity Level, Dietary Habits, and Cardiorespiratory Fitness

Anthropometric measurements of all the patients are listed in Table 2. BMI was significantly reduced by − 0.41 kg/m^2 immediately after 3-months of LI (T1 *vs.* T0, $p<0.05$), however, it was not maintained at follow-up points T2, T3 and T4. Waist circumference was maintained similar between T0 and T1 and was significantly reduced by − 2.6 cm in BCS at T2 (T2 vs. T0, $p<0.01$), but did not persist at the other follow-up points, and weight slightly decreased by − 0.8 kg after 3-months of LI (T1 vs. T0 without significance). Based on submaximal incremental walking test, the cardiorespiratory fitness improved significantly at T1 and values were maintained over the short- (T2) to long-term (T3 and T4) period. The mean±SD $\dot{V}O_{2max}$ values from the baseline (T0) 30.5±5.6 mL·min−1·kg−1 significantly increased in BCS at T1

(+3.4), T2 (+3.3), T3 (+2.2), and T4 (+2.1) *vs.* T0 ($p<0.01$). The adherence to Mediterranean diet improved significantly at T1 ($p<0.01$), as shown in Table 2, and remained mainly constant over the short- and long-term follow-up T2 *vs*. T0 ($p<0.01$), T3 *vs.* T0 ($p<0.01$), and T4 *vs.* T0 ($p<0.01$).

Table 2. Comparison between T0 *vs.* T1, T2, T3 and T4 anthropometric, body composition, physical activity level, dietary habits, and cardiorespiratory fitness parameters.

	Mean ± SD T0	**Mean ± SD (T1)**	**Mean ± SD (T2)**	**Mean ± SD (T3)**	**Mean ± SD (T4)**
Weight (kg)	67.6±11.5	66.8±10.7	66.8±10.7	67.4±11.8	68.2±11.8
BMI (kg/m2)	26.1±4.97	**25.7±4.6***	26±4.7	26±5.05	26.2±4.7
Waist Circumference (cm)	85.3±11.3	85±10.6	**82.4±10.1***	86±12.3	85.6±11.3
Fat mass (%)	21.7±8.1	21.1±7.5	21.7±8.40	21.9±8.8	**23.1±8***
$\dot{V}O_{2max}$ ($mL \cdot min^{-1} \cdot kg^{-1}$)	30.5±5.6	**33.9±6.4****	**33.8±6.3****	**32.7±5.8****	**32.6±5.4****
PAL (MET-min/week)	1.4±0.2	1.4±0.2	1.3±0.3	1.4±0.2	**1.3±0.21***
Adherence to Mediterranean Diet (Mediet Score DianaWeB)	6.9±2.3	**8.8±2.2**	**8.1±1.9**	**8.1±1.8**	**8.2±1.7**

*Abbreviations: BMI, body mass index; $\dot{V}O_{2max}$, maximal oxygen uptake; PAL, physical activity level. T0, baseline; T1, after 3 months; T2, after 6 months; T3, after 12 months; T4, after 24 months; *p <0.05; **p <0.01: ***p<0.001*

Changes in biomarkers

BCSs experienced significant reductions in most of the metabolic and hormonal biomarkers immediately after the 3 months of LI (i.e., glycemia, insulin, triglycerides, LDL, total cholesterol, and testosterone), significant decreases in glycemia and insulin were also observed up to 12 months follow-up time points (T1, T2, and T3), by contrast at 24 months (T4) values were only slightly reduced *vs.* T0. In detail, the LI improves glycemic control: -8.51% comparing T1 *vs.* T0 ($p<0.05$), -10.02% comparing T2 *vs.* T0 ($p<0.001$), -5.08%

comparing T3 *vs.* T0 ($p<0.001$) and -2.82% comparing T4 *vs.* T0 respectively (no significant difference was found). A similar effect was observed for insulin: -13.95% T1 *vs.* T0 ($p<0.05$), -21.30% T2 *vs.* T0 ($p<0.001$), -15.85% T3 *vs.* T0 ($p<0.05$), and -12.59% T4 *vs.* T0 respectively (no significant difference was found). The circulating concentrations of LDL and total cholesterol decreased at T1, but their level was not maintained at follow-up points T3 and T4. Triglycerides levels slightly decreased at the T2 and T3 follow-up points. The other parameters did not change along the follow-up time points. The detailed comparison between T0 and the other time for all biomarkers is reported in Table 3.

Table 3. Comparison of prognostic biomarkers between T0 *vs.* T1, T2, T3 and T4.

	Mean ± SD (T0)	**Mean ± SD (T1)**	**Mean ± SD (T2)**	**Mean ± SD (T3)**	**Mean ± SD (T4)**
Glycemia (mg/dL)	100.5±11.9	**91.9±11.19***	**90.4±10.8*****	**95.4±11.2*****	97.7±12.1
Insulin (microU/mL)	7.8±4.8	**6.7±4.4***	**6.1±3.6*****	**6.5±3.6***	6.8±3.7
Triglycerides (mg/dL)	103.1±44.3	94.2±41.3	**89.8±36.2***	**86.7±42.6***	94.8±41.9
HDL (mg/dL)	62.6±16.1	61±13.7	60.6±13.5	65.4±12.8	64.3±15.6
LDL (mg/dL)	136±28.9	**125.1±28.2*****	129.1±27.3	129.5±24.2	**127.7±23.6***
Total cholesterol (mg/dL)	216.4±39.2	**207.3±37.4***	208.4±37.2	206.5±32.0	**214.8±33.5***
Progesterone (ng/mL)	0.4±0.4	0.4±0.2	1.1±3.5	1.0±3.3	0.7±1.3
Testosterone (ng/mL)	0.3±0.2	**0.2±0.1*****	**0.2±0.1****	1.8±6.9	0.2±0.1
hs-Troponin (ng/L)	2.9±1.2	2.8±2.8	2.9±1.1	3.1±1.9	2.6±1.5

*Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs, high sensitive; T0, baseline; T1, after 3 months; T2, after 6 months; T3, after 12 months; T4, after 24 months; * $p<0.05$; ** $p<0.01$: *** $p<0.001$*

4. Discussion

MOVIS project originates from the hypothesis that the end of the primary treatment for BC is a "critical moment" for changes in lifestyle behaviors. This project aims to educate patients with cancer on the benefits of physical activity and proper nutritional plan, specifically targeting patients diagnosed with BC at the end of their primary treatments (surgery and chemotherapy and/or radiotherapy). As part of MOVIS, the first group of patients enrolled in January 2020, 4 weeks before the Italian COVID-19 lockdown, has been encouraged to start a 3-month LI based on nutrition and exercise which comprised a short term (6 months) and long term (12 and 24 months) follow up. The study started with the enrollment and the physio-clinical assessments, which comprises also a series of sessions with motivational interviews encouraging BCSs to adopt a proper nutritional plan, a subscription to an on-line platform such as the DianaWeb.org (Gianfredi V. et al., 2021) and promoting physical activity, in agreement with the actual recommendation (Campbell K.L. et al., 2019). Enrolled participants, randomly allocated to an intervention and a control arm, received a 3-month lifestyle intervention and the assessments were repeated at the follow-up point as mentioned in the experimental design (Figure 1). As described in Natalucci V. et al., 2021, due to the imposed COVID-19 pandemic restrictions, after the approval of the institutional ethics committee, the study protocol was amended (Protocol N. 29/20 22.04.2020) and the forced changes in the study protocol made the difference between IA and CA interventions negligible providing similar adaptations between groups. Therefore, in the present article, due to the lack of meaningful differences between the two interventions, the results and discussion of the two groups were combined. The 4 weeks of LI before the COVID-19 lockdown has probably made it possible to motivate the BCS enrolled to let them maintain the LI program during the entire lockdown and pandemic period. Home-confinement made it more difficult to reach the guidelines of oncological prevention for both nutrition and regular PA. Therefore, in this context, home-based LI may represent a valid strategy to better control nutritional habits and mitigate physical inactivity in this fragile population (Natalucci V. et al., 2021b; Grazioli E. et al., 2020).

This LI examined the changes related to anthropometrics, Mediterranean diet adherence, levels of physical activity, cardiorespiratory fitness levels and prognostic biomarkers. The main finding of this study is that the LI led to a cardiometabolic improvement. Consistent with our hypotheses, salutary effects were found not only immediately after the LI as

described in Natalucci V. et al. (2021), but also after a short- (6 months) and long-term (12 and 24 months) follow-up, thus during the two year of COVID-19 pandemic period. In this study, a 3-month aerobic exercise training associated with the Mediterranean Diet improved metabolic prognostic factors for both short- and long-term throughout the entire pandemic period. About the change in $\dot{V}O_{2max}$ with training, data obtained in this study show how cardiorespiratory fitness increase and maintain over time with a significant improvement for $\dot{V}O_{2max}$values (increase of 11.21% T1 *vs.* T0, 11.08% T2 *vs.* T0, 7.19% T3 *vs.* T0 and 7.04% T4 *vs.* T0, respectively). The changes in Mediterranean diet adherence were also significant and persisted through follow-up points (0.28% T1 *vs.* T0, 0.17% T2 *vs.* T0, 0.17% T3 *vs.* T0 and 0.2% T4 *vs.* T0, respectively).

These effects agree with previous investigations for lifestyle modification strategies in BCS population (Holick C.N. et al., 2008; Lashinger L.M. et al., 2014; Irwin M.L. et al., 2014; Meneses-Echávez J.F. et al., 2016; Reis R.S. et al., 2016; Kang D.W. et al., 2017; Hamer J, and Warner E, 2017; Arnett D.K et al., 2019; Lloyd-Jones D.M et al., 2020; Dimauro I. et al. 2021). With the increasing trend of adopting remotely on-line technologies during this period of pandemic, the need for assessing a home-based LI, with a specific counseling on exercise recommendations and remotely supervised aerobic exercise, has become crucial and it turned out is an effective intervention to improve the prognosis of the BCS involved in the study (Grazioli E. et al., 2020; Di Blasio A. et al., 2021). Although the mechanisms underpinning the exercise-training mediated improvement in $\dot{V}O_{2max}$ have not been studied, they may be due to favorable changes in terms of changes in cardiac or skeletal muscle function (Haykowsky M.J. et al., 2016). Furthermore, similar improvements were observed in metabolic parameters such as glycemia (the decrease was -8.51% T1 *vs.* T0, -10.02% T2 *vs.* T0, -5.08% T3 *vs.* T0 and -2.82% T4 *vs*. T0 respectively) and insulin (-13.95% T1 *vs.* T0, -21.30% T2 *vs.* T0, -15.85% T3 *vs.* T0 and -12.59% T4 *vs.* T0). Glycemia is a very important parameter to control in BCS population, since hyperglycemia is a risk factor for cancer progression and it is also associated with metabolic alterations, comorbidities and relapses (Viskochil R. et al., 2020). In this line, it is also known that BCSs' risk of recurrence is associated with chronic inflammation, metabolic syndrome and physical inactivity (Jiralerspong S. and P. J. Goodwin, 2016; Sternfeld B. et al., 2009). Moreover, the recent evidence associating insulin to BC recurrence is emerging and exercise and nutrition actions in the last decade have been recommended to modulate insulin levels (Kang D.W. et al., 2017), even though the evidence is still under debate (Fairey A.S. et al., 2003; Fairey A.S. et al., 2005). Our data agree with the

epidemiological study Diet and Androgen-5 study (DIANA-5) (Berrino F. et al., 2014; Villarini, A. et al., 2012), where a structured 3-month aerobic exercise training associated with Mediterranean Diet improves fasting insulin levels, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index and body composition parameters in BCSs (Bruno E. et al., 2016). These results have been confirmed also by others (Dittus K.L. et al., 2018; Van Kruijsdijk, R.C. et al., 2009), in line with the health benefits of PA, healthy eating, and weight management for BCSs.

It is well known that the adherence to the Mediterranean diet is associated with a reduced BC risk (Turati F. et al., 2018; Li Y. et al., 2018). The nutritional choices inspired by the principles of the Mediterranean diet made by the BCS involved in the study go towards an improvement in eating habits, more adherent to the Mediterranean Diet. In this group of study, it is notable an increase in the consumption of dried fruit and cereal-based meals; a reduction of red meat, desserts and glasses of wine *per* week (data not shown). The improvement of the MeDiet score obtained from the LI and maintained along the follow-up points (Table 2) is particularly interesting for the purposes of glycemic control, as highlighted by the amelioration of metabolic prognostic factors.

Overweight, metabolic syndrome accompanied by sedentary behaviors have been established as notable risk factors for BCSs (Kabat G.C. et al., 2017; Kerr J. et al., 2017). We also noted to a certain extent of time point of follow-up a reduction in metabolic and hormonal circulating factors such as LDL (−8.4% T1 *vs.* T0), total cholesterol (−4.3% T1 *vs.* T0) and testosterone (−28.9% T1 *vs.* T0), whereas progesterone, estradiol, HDL and triglycerides did not change compared with baseline. High-sensitivity troponin was stable during each time point analyzed.

During COVID-19 pandemic, BCS faced multidimensional issues. The quarantine period, with home-confinement worsened the BC cancer care and outcomes; prolonged staying home has been associated with a sedentary lifestyle, modified diet patterns and higher levels of stress suffering adverse effects of cancer treatment (Montemurro N. et al., 2020; Bourdillon N. et al., 2020; Raymond E. et al., 2020; Curigliano C. et al., 2020) along the two years of COVID-19 pandemic the cancer patients had to adapt to a longer term of suboptimal or delayed care. In this regard, a recent study showed that 90% of physically active BCSs decreased PAL and increased sedentary time (Gurgel A.R.B et al., 2021). Moreover, a survey analysis with special attention to understanding the barriers that may influence an active lifestyle in the Italian BC women from the DianaWeb court (781 BC women) underlines the

negative impact of the pandemic on MET-min/week of walking, vigorous intensity, and total PA (Natalucci V. et al., 2021). By contrast, our data suggest an improvement in the cardiorespiratory fitness, despite the impact of the COVID-19 pandemic on cancer outcomes (Richards M. et al., 2020). Indeed, COVID-19 pandemic made it difficult to reach the oncological guidelines for both exercise and nutrition, however, our data showed that home-based LI may represent a valid health strategy to better control nutritional behavior and reduce inactivity in this fragile population even in pandemic restriction. This supports the feasibility of a 3-month home-based lifestyle intervention taking the advantage of using remote control technologies to optimize the service (Oba K. et al., 2022). The importance of promoting lifestyles has been confirmed by a series of studies that attribute it a fundamental role in the context of many diseases, especially chronic ones (Lavie C.J. et al., 2019; Izquierdo M. et al., 2021). These concepts were taken up with modern medicine, but only in recent years has research work led to the identification of the biochemical mechanisms through which physical activity exerts its favorable effects on human health (Chow L.S. et al., 2022; Gleeson M. et al., 2011; Nieman D.C. and Wentz L.M. 2018; McTiernan A. et al., 2019).

However, if the results of a lifestyle change are positive, why is it so difficult to implement them in a large-scale comprehensive prevention program?

In this regard, introducing permanent changes in patients' lifestyles is notoriously a difficult undertaking; it is a difficult task that must be faced and managed with determination and without improvisations by clinicians with training and organizational support (Pistelli M. et al., 2021). It is well known that the simple advice to lose weight, quit smoking or do physical activity has no practical effect in the vast majority of patients with chronic disease and even less in asymptomatic patients. In this context, the proposal of a *learning by doing study* such as the MOVIS Project, which include the prescription of lifestyles and a period of training for both exercise and Mediterranean diet with a specific interactive website program of lifestyles could contributes to improving the patient's adherence to the indications to change their habits of life with a preventive purpose. The main strengths of this work were the importance of timeliness with assessments, the long-term follow-up of 2 years during the COVID-19 pandemic period, and the wide range of clinical and functional outcomes. The intervention was grounded using multiple components and specifically addressing the barriers present in this highly vulnerable population and the COVID-19 pandemic. It was thought to limit patients' travel-related exposure by mixing remote controlled and home-based sessions. These

sessions have been though and tailored to fit with the comings and goings at the hospital of the patients receiving their BC clinical follow up. The 'compliance' of LI has progressively assumed a fundamental role in achieving the best possible therapeutic result, so adherence to the modification of an incorrect behavior or lifestyle, as a complementary aspect of therapy, leads to greater effectiveness of the drug itself as well as expressing all its potential and effectiveness in improving health. This project therefore not only aims to lay the groundwork for the development of a consultancy service on the importance of an active lifestyle for BC patients, but also to create an educational program that could be adopted by oncology units as part of a broader regional strategy promoting healthy lifestyles and cancer prevention and moving beyond clinical treatment.

5. Conclusions

With the outbreak of the COVID-19 in late 2019, governments increasingly imposed containment strategies, including social distancing as well as restricted population movement, potentially having negative impacts on mental and physical health. In this study we observed that a 3-month home-based LI focused on Mediterranean diet and aerobic exercise, which was adapted to the imposed COVID-19 pandemic restrictions, significantly improved cardiorespiratory fitness, metabolic parameters leading to significant cardiometabolic amelioration even during two year of COVID-19 Pandemic. The challenge for further therapeutic assistance line guide for these patients is to provide safe and effective exercise for BC patients with a better compliance that patients can adhere to in the longer term. New remote technologies and adaptations in patient management may well achieve this much of what has been rapidly advanced because of COVID-19.

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CHAPTER 3

Original Article

Home-based lifestyle intervention for breast cancer survivors: a surprising improvement in the quality of life during the first year of COVID-19 pandemic

Vagnini Denise[1], Natalucci Valentina[2*], Moi Sara[1], Vallorani Luciana[2], Pietrelli Alice[3], Panico Andrea Rocco[2,] Ferri Marini Carlo[2], Lucertini Francesco2, Annibalini Giosuè[2], Sisti Davide[2], Rocchi Marco Bruno Luigi[2], Catalano Vincenzo[3], Saita Emanuela[1], Emili Rita[3] and Barbieri Elena[2]

[1] *Department of Psychology, Università Cattolica del Sacro Cuore, Milan, Italy.*
[2] *Department of Biomolecular Sciences, University of Urbino Carlo Bo, Urbino, Italy.*
[3] *U.O.C. Oncologia, ASUR Area Vasta 1, Ospedale Santa Maria della Misericordia, Urbino, Italy.*

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Abstract

The COVID-19 pandemic induced an extraordinary impact on public mental health to a degree not completely understood, especially in vulnerable populations such as breast cancer (BC) patients. This study aimed to assess the quality of life (QoL) and global health-related QoL during the first year of COVID-19 pandemic (short, 3-month, and long term, 12-month follow-up, period) in BC survivors (BCSs) who received a multidisciplinary home-based lifestyle intervention (LI). In total, 30 BCSs who took part in the MOVIS clinical trial (protocol: NCT 04818359) with a risk factor for recurrence underwent a 3-month LI based on psychological counseling, nutrition and exercise. Psychological questionnaires (Brief Fatigue Inventory, BFI; Distress Thermometer, DT; Psychological Distress Inventory, PDI; Verbal Rating Scale, VRS; European Organization for Research and Treatment of Cancer: Quality-of-Life, EORTC-QLC-C30; Profile of Mood States Questionnaire, POMS) were evaluated at three time points: baseline (T0), and after 3- (T1), 6- (T2) and 12- (T3) months. Friedman non-parametric test and Wilcoxon signed rank test were conducted to investigate statistically significant differences in psychometric scores and differences between assessment times. Analysis showed statistical significance between the different assessments of: Depression (POMS), Anger (POMS), Confusion (POMS), Strength/Vigor (POMS), Distress Evaluation (DT), Social Functioning, General Health Scale (EORTC-QLQ-C30) with $p<0.001$, and in Fatigue (POMS, BFI, and EORTC-QLQ-C30), Anxiety (POMS), Distress (PDI), Verbal rating Scale (VRS), and Cognitive Functioning (EORTC-QLQ-C30) with $p<0.05$. There were no significant changes in Role and Emotional Functioning (EORTC-QLQ-C30). Considering the timeline difference between assessment, almost all the scores were significantly ($p < 0.05$) improved after the LI (T1) compared to baseline (T0), also showing the effect in the follow-up (T2 and T3) phases, with the exception of Cognitive and Social Functioning (EORTC-QLQ-C30) in which respondents reported worsening ($p < 0.05$). Despite the home-confinement, LI surprisingly improved HRQoL in BCSs.

Introduction

More than two years after the lockdown due to the "Coronavirus Disease 2019" pandemic (COVID-19), the population and global health system have learned a lot about managing the virus SARS-CoV-2. Although the viral transmission and pathogenesis have been well documented in the scientific literature, little is known about the long-term physical and psychological consequences (e.g., experiences of distress, psychiatric disorders, and engagement in pandemic-related health behaviors), especially in vulnerable populations such as breast cancer (BC) patients. In these patients, the BC diagnosis and treatment have a strong impact on women's emotional health and quality of life (QoL) (1). Indeed, cancer treatments (i.e., surgery and neo/adjuvant therapies) could lead to short- and long-term physical (e.g., chronic pain, phantom breast pain, axillary web syndrome, lymphedema, decreased strength, aerobic capacity and mobility) and psychological (e.g., cancer-related-fatigue, perception of a lack of psycho-physical self-integrity, or psycho-physical impairment such as anxiety and depressive symptoms, distress, and social/relational isolation) side effects that can persist over time and worsen cancer survivors' QoL (2-8). Moreover, BC patients are not only characterized by increased vulnerability because of modified living, but they also had to adapt to delays and changes in clinical procedures due to the COVID-19 emergency (9-11). Indeed, BC patients appeared to be more vulnerable to worse outcomes of infection not only in terms of clinical care (12), but also on the physiological and psychological responses, which have been negatively modulated with escalating symptoms and diagnoses of depression and anxiety (13-18). During the first year of the COVID-19 pandemic, there were changes not only in the clinical context of BC, but also in lifestyle habits (12, 17, 19), leading these women to face further barriers.

In a holistic view of the BC patient, these side effects should be considered as a continuum of bio-psycho-social interconnections (20), within the unique concept of global health-related QoL (HRQoL).

In particular, the World Health Organization defines QoL as *"The condition of life resulting from the combination of the effects of a complete range of factors such as those determining health, happiness including comfort in the physical environment and a satisfying occupation, education, social and intellectual attainments, freedom of action, justice, and expression"*(21) and represents an important outcome measure in BC clinical investigations and survivorship studies (22-26).

In this contest, an intervention program for a healthy and active lifestyle with psychological support can profoundly affect both short- and long-term health and QoL and could represent an important non-pharmacological intervention that might positively influence cancer survival (27). Emerging evidence confirms the safety, feasibility, and effectiveness of specific exercise training in mitigating cancer treatments' side-effects, such as musculoskeletal pain and fatigue, and improving physical, cardiometabolic, emotional wellbeing, and global HRQoL. In this regard, attention to modifiable behaviors such as exercise and nutrition has grown in recent years, with particular attention to the strategies to be adopted in the clinical outcomes of BCSs (28-39) even more during the COVID-19 era.

Therefore, facilitating and helping the maintenance of a healthy lifestyle at the end of primary treatments for BC represents a real challenge in the daily practice of medicine.

In Italy, although increasing literature suggests that a multidisciplinary approach is essential for achieving and maintaining HRQoL in the long term, few clinical studies provide evidence of the effect of prescribing healthy lifestyle habits in BCSs (30).

The present study aims to investigate the short- (after 3 months) and long- (after 12 months) term effects on QoL and global HRQoL of a multidisciplinary home-based lifestyle intervention, based on psychological counseling, adherence to Mediterranean Diet and exercise, in BC survivor women at high risk of recurrence during the first year of COVID-19 pandemic.

Materials and Methods

Study design and Population

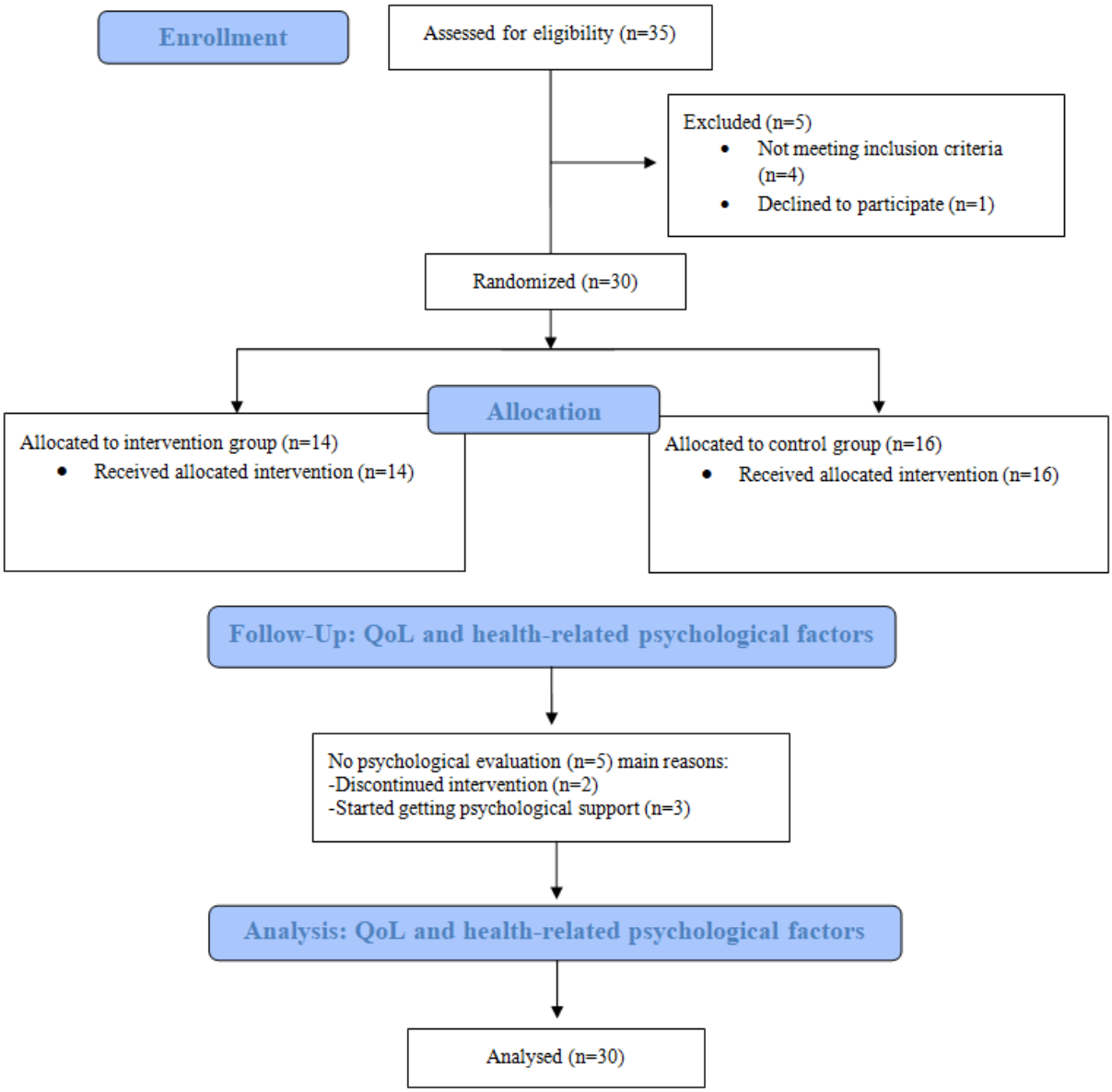
Initially, study design (protocol: NCT 04818359) was projected as an open randomized controlled trial with two parallel groups (1:1 randomization ratio with the control arm). However, due to the imposed COVID-19 pandemic restrictions, after the approval of the institutional ethics committee, the study protocol was amended (Protocol N. 29/20 22.04.2020) (Figure 1). As reported in Natalucci et al., 2021 (19), the forced changes in the study protocol made the difference on cardiometabolic and psychological parameters between intervention arm and control arm interventions negligible, providing similar adaptations between groups. Therefore, due to the lack of meaningful differences between the two interventions, the results of the two groups were combined.

Informed consent was obtained from all individual participants included in the study. Inclusion criteria included the following: ≤ 12-month post-surgery and post chemo- or radio-

therapy adjuvant; stage 0 to III BC without metastases or recurrence diagnosis at recruitment in follow-up; aged 30–70 years; non-physically active (i.e., not engaged in at least 60 min/week of structured exercise during the previous 6 months); with a risk factor for recurrence. As reported in previous studies (30, 40-42), the risk factors for recurrence were the present of at least 1 of the following conditions: body mass index (BMI) at diagnosis ≥ 25 kg/m^2, testosterone ≥ 0.4 ng/mL; serum insulin ≥ 25 μU/mL (170 pmol/L); metabolic syndrome (at least 3 of the following 5 factors): a, glycemia ≥ 100 mg/dL (6.05 mmol/L); b, triglycerides ≥ 150 mg/dL (1.69 mmol/L); c, HDL-C < 50 mg/dL (1.29 mmol/L); d, waist circumference ≥ 80; e, blood pressure ≥ 130/85 mmHg.

Exclusion criteria were disabling pneumological, cardiological, neurological, orthopedic comorbidities, or mental illnesses that prevent the exercise performance; treatment with beta blockers, non-dihydropyridine calcium channel blockers, or amiodarone due to their potential effect on heart rate response to exercise; treatment with antidepressant drugs.

Figure 1. Flow diagram



Sample collection

Recruitment occurred in January 2020 from the Santa Maria della Misericordia Hospital of Urbino (PU) in the Marche region (central Italy). Between January 2020 and January 2021, a trained research assistant collected data through printed copies of face-to-face self-report questionnaires with patients at the following three time points: baseline (T0), and after 3- (T1), 6- (T2) and 12- (T3) months.

Intervention

The intervention took place after surgery and upon completion the primary treatments (post chemo- or radio-therapy adjuvant). As previously described, participants (intervention and control arm) were supposed to receive a 3-month lifestyle (Mediterranean Diet and exercise) educational counseling (19). Briefly, the intervention comprised two phases: (i) the study enrollment in which participants received structured meeting lasting about one hour (45 min group and 15 personalized minutes) with focus on exercise and nutrition and with the psychological support by the psycho-oncologist of the U.O.C. of Oncology; (ii) the intervention phase in which all participants received the nutritional advice was based on Mediterranean diet, while only intervention arm received a 3-month on-site (2 sessions per week) and remotely (1 session per week) supervised aerobic exercise training program having progressive increases in exercise intensity (from 40% to 70% of heart rate reserve) and duration (from 20 to 60 min). Exercise intensity and duration were gradually increased to reach and exceed the recommended quality (exercise intensity) and quantity (volume) of aerobic exercise (34, 43). However, due to the imposed COVID-19 pandemic restrictions, from the 4th week the type of supervision was adapted to solely remotely supervised exercise (3 sessions per week). The supervision was performed weekly, using phone calls from the exercise specialist, who provided the weekly exercise prescription and personalized feedback according to the training logs. Both remotely and on-site supervised training sessions consisted of aerobic exercise (i.e., walking, running, or cycling). On-site supervised sessions were performed in a gym using a treadmill or stationary bikes, whereas the remotely supervised sessions were performed both indoors and outdoors according to participants' possibilities and preferences. Regardless of the exercise modality, the sessions were performed at individualized exercise intensities (e.g., walking speed and grade or cycling wattage), allowing each participant to reach and maintain the prescribed target heart rate (HR) during the training sessions.

Outcome measures

Socio-demographic (i.e., sex, age, educational level, working status, and marital status) and clinical data (i.e., side affected by carcinoma, months since diagnosis, type of surgery, and information about therapies) were collected by an oncologist (Table 1).

Psychometric measures were collected by a psycho-oncologist through validated questionnaires and were filled in by the participants in 15–20 min.

Psychological questionnaires

Brief Fatigue Inventory (BFI)

BFI consists of 9-items rated on 11-point Likert scale (from 0 = lowest level; to 10 = highest level). The subject is asked to evaluate the severity of his fatigue and the interference of this with the general daily activity, the mood, the ability to walk, the ability to work at home and outside, the interpersonal relationships, and the ability to have fun. Example items: "Please rate your general activity"; "Please rate your relations with other people". The validity and reliability of the original BFI have been established with a strong internal consistency coefficient of 0.96 (44).

Distress Thermometer (DT)

DT consists of a single-item rated on a 11-point Likert scale (from 0 = no distress; to 10 = extreme distress; with a midpoint of 5 = moderate distress) which measures the subjective stress experienced in the last week and evaluates it through a visual analog scale with the shape of a thermometer. The item is: "Please circle the number 0-10 that best describes how much distress you have been experiencing in the past week including today" (45).

Psychological Distress Inventory (PDI)

PDI consists of a self-administered 13-item questionnaire rated on a 5-point Likert scale (from 1 = not at all; to 5 = extremely), ranging from 13 to 65 (present mood of the patient, with 1 week reference period). It measures the general emotional lability of cancer patients and more specifically disorders tied to adjustment: (a) reactive anxiety to cancer, such as inner tension and worry; (b) reactive depression; and (c) emotional reactions to changes in the body image, and disturbances in the interpersonal context. Example items: "In the last week have you felt worthless?"; "In the last week has your interest in the world that surrounds you diminished?". Internal consistency was reported at 0.84 to 0.88 Cronbach alpha rating (46, 47).

Verbal Rating Scale (VRS)

It is composed of a single-item rated on a 6-point Likert Scale (from 1 = none, to 6 = very severe) to evaluate cancer related fatigue (CRF). The item is: "Choose below the level of fatigue you are experiencing" (48).

European Organization for Research and Treatment of Cancer: Quality-of-Life (EORTC-QLC-C30)

EORTC-QLC-C30 consists of a global health and quality of life scale (GHS) rated on a 7-point Likert (from 1 = very poor; to 7 = excellent) that is based on two questions about physical condition and overall quality of life, and nine multi-item scales on a 4-point Likert (from 1 = not at all, to 4 = very much) that reflect the multidimensionality of the quality-of-life construct and incorporate five Functional Scales (FS: physical, role, cognitive, emotional, and social), and three Symptom Scales (SS: fatigue, pain, and nausea and vomiting) (49). The remaining single items assess additional symptoms commonly reported by cancer patients (e.g., dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), as well as the perceived financial impact of the disease and treatment. Example items: "Have you had difficulty concentrating on things, like reading a newspaper or watching television?"; "Has your physical condition or medical treatment interfered with your social activities?". The scale and subscale structures meet the minimal standard for reliability (Cronbach's alpha coefficient ≥ 0.70). In this study the Italian version, validated by Marzorati et al., 2019 (50) was used.

Profile of Mood States Questionnaire (POMS)

The Italian version consists of 65-items rated on a 5-point Likert scale (from 0 = not at all; to 4 = extremely) for the assessment of mood states. It is divided into six subscales (i.e., depression, anger, fatigue, confusion, strength/vigor, and tension/anxiety). Example items: "Describe how you feel right now: confused"; "Describe how you feel right now: nervous". Internal consistency was reported at 0.63 to 0.96 Cronbach alpha rating (51, 52).

Statistical analysis

The participants who completed the assessments at every time point (T0: baseline; T1: 3-month post-intervention; T2 and T3: 6- and 12-month from baseline, respectively) were

included in the analysis. In this way we were able to answer hypothesis 1 (i.e., the lifestyle intervention was effective in the immediate post-intervention: T1) and hypothesis 2 (i.e., the intervention's efficacy on psychological well-being was maintained over time: T2 and T3).

Cronbach's Alpha coefficient was used to measure internal consistency of each psychometric measure with acceptable values ≥ 0.65 for self-report questionnaires (53).

Normality of distributions and extreme values were studied using visual analysis on Q-Q plots and the Shapiro-Wilk test, considering a normal distribution for $p > 0.05$.

Descriptive statistics (i.e., frequency, mean, and SD) were performed to describe participants' demographics, clinical and psychological characteristics.

A graphical display of a non-parametric correlation matrix, based on Spearman's R, ordered according to hierarchical clustering, was obtained using the corrplot R package. Considering the small sample size and the non-normal distribution of the data, non-parametric tests have been used. We primarily assessed the absence of psychometric differences at baseline (T0) between the intervention arm and the control arm using the non-parametric Mann Whitney U Test and considering no statistically significant differences with a $p > 0.05$. We compared the two groups longitudinally without finding significant differences on anthropometric and cardiometabolic (data reported in Natalucci et al., 2021 (19)) nor on psychometric variables.

So, as previously described (19), the analyzes were conducted considering the 30 participants as a single group and we assessed the efficacy of the intervention with the non-parametric Friedman Test (for $k > 2$ related-measures).

Mean, SD, significance, and Kendall's W effect sizes (ranging from 0 = no relationship, to 1 = perfect relationship) were provided (54, 55).

Post hoc comparisons with non-parametric Wilcoxon signed rank tests (for two related-measures: T0-T1; T0-T2; T0-T3) were then conducted to determine where there were significant changes, and effect sizes for $r = Z\sqrt{N}$, in which N represents the number of observations (56), were provided using Cohen (1988) criteria for interpretation (54).

Data were analyzed using IBM SPSS Statistical Software version 27.0 and R Project for Statistical Computing (version 4.2.1.). The significance threshold was fixed at the standard level of 0.05.

Results

Sample characteristics

Thirty women were enrolled (demographic, clinical characteristics of the sample and descriptive statistics of the study variables appear in Table 1).

The mean age of the sample was 53.6 ± 7.6 (range 39-69). Mean time since diagnosis at recruitment (T0) was 10.37 ± 2.87 months, ranging from 4 to 12 months.

Most of the participants were married (n=21; 70%), about 10% (n=3) of the sample was divorced, and 20% (n=6) was not in a stable romantic relationship.

More than half (66.7%; n=20) had a university degree, about 20% (n=6) of patients completed secondary school, and the 13.3% (n=4) had an elementary school educational level. Almost all the participants (90%; n=27) were employees, one patient (3.3%) had a sick leave, and two (6.7%) were retired.

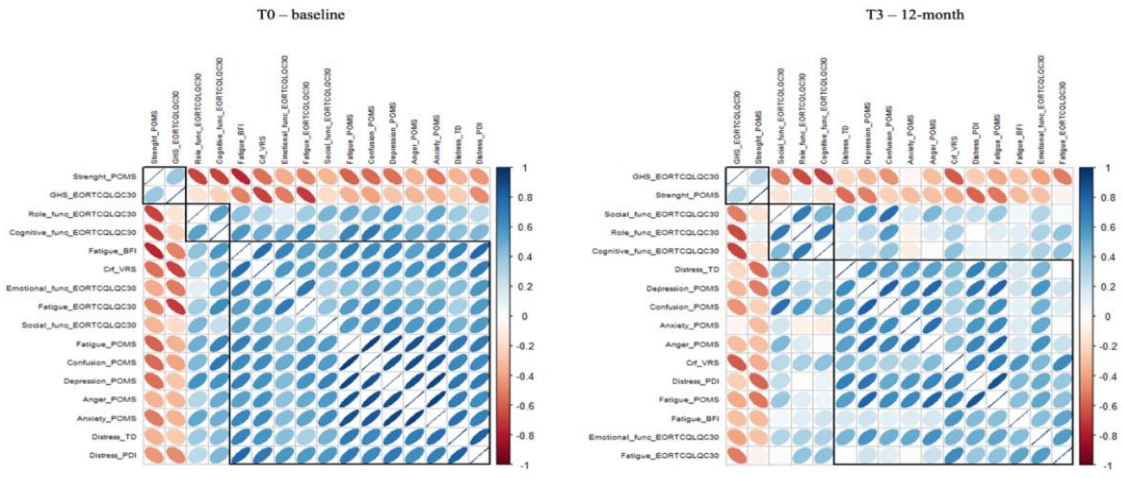
Concerning the medical characteristics, half of participants (50%; n=15) were diagnosed with right and half with left (50%; n=15) breast cancer. About 86.9% (n=26) had a quadrantectomy, three patients (10%) had a mastectomy, and only one (3.3%) had a lumpectomy. Most have received radiotherapy (80%, n=24), 43.33% (n=13) chemotherapy, 26.77% (n=8) hormonal therapy with Tamoxifen, and 53.33% (n=16) Aromatase inhibitors. In the total sample (N=30), 76.77% (n=23) received at least two of the treatments described.

Table 1. Socio-demographic and clinical characteristics (N = 30).

Variables	***n* (%)**
Marital status	
Single	6 (20)
Married	21 (70)
Divorced	3 (10)
Educational level	
Elementary school	4 (13.33)
Secondary school	6 (20)
College degree	0 (0)
University degree	20 (66.67)
Working status	
Employee	27 (90)
Sick leave	1 (3.33)
Retired	2 (6.67)
Side affected by carcinoma	
Right	15 (50)
Left	15 (50)

Months Since Diagnosis	
≤6	5 (16.66)
>6	25 (83.34)
Surgery	
Quadrantectomy	26 (86.67)
Mastectomy	3 (10)
Lumpectomy (partial mastectomy)	1 (3.33)
Radiotherapy	
Yes	24 (80)
No	6 (20)
Chemotherapy	
Yes	13 (43.33)
No	17 (56.67)
Hormonal therapy	
Tamoxifen	8 (26.67)
Aromatase inhibitors	16 (53.33)
No	6 (20)

Figure 2. Corr-plot at T0 (baseline) and T3 (12-month) of psychometric variables.



Longitudinal intra-group (n=30) comparisons over a year

Friedman non-parametric test was significant with $p < 0.001$ for Depression (POMS), Anger (POMS), Confusion (POMS), Strength/Vigor (POMS), Distress Evaluation (DT), Social Functioning (EORTC-QLCQ-C30), and General Health Scale (EORTC-QLQ-C30). Also, Fatigue (POMS, BFI, and EORTC-QLQ-C30), Anxiety (POMS), Distress (PDI), Verbal rating Scale (VRS), and Cognitive Functioning (EORTC-QLQ-C30) with $p < 0.05$. Only Role and Emotional Functioning (EORTC-QLQ-C30) showed no significant intra-group

differences. Table 2 summarizes the results and provides descriptive statistics for all psychometric measures.

Post hoc pairwise comparisons with Wilcoxon signed rank test showed between which assessment times there was a statistically significant difference in psychometric scores. Almost all the scores but Distress (PDI) and Confusion (poms) were significantly ($p < 0.05$) improved after the intervention (T1) compared to before (T0), with the exception of Cognitive and Social Functioning (EORTC-QLQ-C30) in which respondents reported worsening ($p < 0.05$). Likewise, in the follow-up measures (T2 and T3) most of the scores, also including Distress (PDI) and Confusion (POMS), were improved ($p < 0.05$) compared to baseline (T0). Pairwise Comparisons (T0-T1; T0-T2; T0-T3) are described in Table 3.

Table 2. Friedman test for all psychometric measures.

Measures (range)	T0 $\bar{x}$± SD	T1 $\bar{x}$ ± SD	T2 $\bar{x}$ ± SD	T3 $\bar{x}$ ± SD	χ^2 (*p*)	Effect Size (Kendall's W)[a]
BFI (0-10)	3.14 ± 1.92	1.92 ± 1.06	1.97 ± 1.53	2.03 ± 1.24	11.23_3 ($p = 0.011$)*	0.13
DT (0-10)	5.08 ± 3.05	3.08 ± 2.33	3.96 ± 2.51	3.32 ± 2.58	16.65_3 ($p <0.001$)**	0.21
PDI (1-5)	2.21 ± 0.62	2.04 ± 0.52	1.89 ± 0.62	1.87 ± 0.70	10.43_3 ($p = 0.015$)*	0.14
VRS (1-6)	3.38 ± 0.97	2.38 ± 1.32	2.62 ± 1.28	2.81 ± 1.03	9.90_3 ($p = 0.019$)*	0.12
EORTC-QLQ-C30						
FS-Role (1-4)	1.23 ± 0.46	1.07 ± 0.22	1.13 ± 0.23	1.25 ± 0.52	6.73_3 ($p = 0.081$)	0.08
FS-Cognitive (1-4)	1.55 ± 0.83	1.20 ± 0.37	1.36 ± 0.41	1.34 ± 0.51	8.63_3 ($p = 0.035$)*	0.10
FS-Emotional (1-4)	1.73 ± 0.56	1.54 ± 0.55	1.54 ± 0.47	1.54 ± 0.48	2.38_3 ($p = 0.498$)	0.03
FS-Social (1-4)	1.57 ± 0.70	1.00 ± 0.01	1.02 ± 0.10	1.05 ± 0.28	37.24_3 ($p <0.001$)**	0.45[xx]
SS-Fatigue (1-4)	1.75 ± 0.69	1.33 ± 0.42	1.45 ± 0.40	1.29 ± 0.35	15.38_3 ($p = 0.002$)*	0.18
GHS (1-7)	4.91 ± 1.03	5.52 ± 0.86	5.76 ± 0.85	5.56 ± 1.03	18.00_3 ($p <0.001$)**	0.22
POMS (0-4)						
Depression	0.99 ± 0.98	0.42 ± 0.55	0.31 ± 0.52	0.33 ± 0.48	22.74_3 ($p <0.001$)**	0.32[x]
Anger	1.41 ± 1.12	0.80 ± 0.74	0.65 ± 0.63	0.53 ± 0.57	18.59_3 ($p <0.001$)**	0.26
Fatigue	1.47 ± 1.06	0.90 ± 0.80	0.76 ± 0.67	0.62 ± 0.54	12.82_3 ($p = 0.005$)*	0.18
Confusion	1.39 ± 0.79	1.05 ± 0.54	0.88 ± 0.61	0.76 ± 0.61	19.08_3 ($p <0.001$)**	0.27
Strength/Vigor	2.02 ± 0.65	2.49 ± 0.71	2.77 ± 0.79	2.23 ± 0.67	18.34_3 ($p <0.001$)**	0.26
Anxiety	1.41 ± 0.81	0.92 ± 0.67	0.89 ± 0.66	0.80 ± 0.51	12.49_3 ($p = 0.006$)*	0.17

Abbreviations: BFI, Brief Fatigue Inventory; DT, Distress Thermometer; PDI, Psychological Distress Inventory; VRS, Verbal Rating Scale; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer-Quality of life questionnaire; FS, functional scales; SS, Symptom scales; GSH, Global Health Status; POMS, Profile of Mood States Questionnaire.

*a Effect Size (Kendall's W): $|0.1| \leq W < |0.3|$ small effect; $|0.3| \leq W < |0.5|$ medium effectx; $W \geq |0.5|$ = large effect xx; *p < 0.05; **p < 0.001*

Table 3. Post hoc Wilcoxon signed rank test: Pairwise comparisons.

	T0-T1 (baseline – 3-month)		T0-T2 (baseline – 6-month)		T0-T3 (baseline – 12-month)	
	Z (*p*)	**Effect Size (r)[a]**	**Z (*p*)**	**Effect Size(r)[a]**	**Z (*p*)**	**Effect Size (r)[a]**
BFI	–2.99 ($p = 0.003$)*	–0.39[x]	–2.87 ($p = 0.004$)*	–0.38[x]	–3.04 ($p = 0.002$)*	–0.40[x]
DT	–4.23 ($p<0.001$)**	–0.55[xx]	–1.88 ($p = 0.06$)	–0.25	–3.02 ($p = 0.002$)*	–0.40[x]
PDI	–1.29 ($p = 0.20$)	–0.17	–2.57 ($p = 0.01$)*	–0.34[x]	–2.95 ($p = 0.003$)*	–0.39[x]
VRS	–2.78 ($p = 0.005$)*	–0.39[x]	–2.39 ($p = 0.02$)*	–0.33[x]	–2.80 ($p = 0.01$)*	–0.39[x]
EORTC-QLQ-C30						
FS-Role	NA	NA	NA	NA	NA	NA
FS-Cognitive	–2.42 ($p = 0.02$)*	–0.31[x]	–1.34 ($p = 0.18$)	–0.18	–1.79 ($p = 0.07$)	–0.23
FS-Emotional	NA	NA	NA	NA	NA	NA
FS-Social	–3.50 ($p<0.001$)**	–0.45[x]	–3.27 ($p = 0.001$)*	–0.43[x]	–3.37 ($p<0.001$)**	–0.44[x]
SS-Fatigue	–3.14 ($p = 0.002$)*	–0.41[x]	–1.94 ($p = 0.05$)	–0.25	–2.89 ($p = 0.004$)*	–0.38[x]
GHS	–3.14 ($p = 0.002$)*	–0.41[x]	–3.54 ($p<0.001$)**	–0.46[x]	–3.00 ($p = 0.003$)*	–0.39[x]
POMS						
Depression	–3.24 ($p<0.001$)**	–0.42[x]	–2.89 ($p = 0.004$)*	–0.38[x]	–3.43 ($p<0.001$)**	–0.46[x]
Anger	–2.90 ($p = 0.004$)*	–0.38[x]	–2.83 ($p = 0.005$)*	–0.38[x]	–2.96 ($p = 0.003$)*	–0.40[x]
Fatigue	–2.42 ($p = 0.015$)*	–0.32[x]	–3.17 ($p = 0.002$)*	–0.42[x]	–3.64 ($p<0.001$)**	–0.49[x]
Confusion	–1.50 ($p = 0.13$)	–0.20	–3.06 ($p = 0.002$)*	–0.41[x]	–3.45 ($p<0.001$)**	–0.46[x]
Strength/Vigor	–2.01 ($p = 0.04$)*	–0.26	–3.29 ($p<0.001$)**	–0.44[x]	–1.58 ($p = 0.12$)	–0.21
Anxiety	–2.72 ($p = 0.01$)*	–0.35[x]	–2.71 ($p = 0.01$)*	–0.36[x]	–3.05 ($p = 0.002$)*	–0.41[x]

Abbreviations: BFI, Brief Fatigue Inventory; DT, Distress Thermometer; PDI, Psychological Distress Inventory; VRS, Verbal Rating Scale; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer-Quality of life questionnaire; FS, functional scales; SS, Symptom Scales; GSH, Global Health Status; POMS, Profile of Mood States Questionnaire.
AEffect Size (r): $|0.1| \leq r < |0.3|$ small effect; $|0.3| \leq r < |0.5|$ medium effectx; $r \geq |0.5|$ = large effectxx
*NA = not applicable (Friedman Npar test with $p > 0.05$); * $p < 0.05$; ** $p < 0.001$*

Discussion

The present contribution explored psychological well-being of thirty Italian women treated for BC and aimed to study over 12-month the efficacy on HRQoL of a home-based multidisciplinary lifestyle intervention proposed at the beginning of COVID-19 pandemic.

In a BC diagnosis, long-term survival rates are constantly increasing. Although this is encouraging, clinicians must equally recognize that it represents new challenges for the medical practices. Health care professionals must manage the long-term sequelae of the different therapeutic modalities as BC transitions from a life-threatening illness to a chronic condition as a result of advancements in early diagnosis and more efficient treatments. For the features just described, BCSs are a special and complex group of patients. Indeed, for many women, coping with cancer- and treatment-related issues means being at the site of a tricky and stressful process which could bring to negative and long-lasting psycho-social impairment (57, 58). Moreover, they have the challenge of dealing with several long-term side effects from therapy and many of them also have to treat the previous comorbidities. In addition, BC

patients during COVID-19 pandemic have been involved in a number of additional difficulties from the disruptions in routine health care to the dramatic reduction in social support. The COVID-19 related anxiety has been an expected and common reaction to the pandemic situation (59, 60). Although psychological distress affected several people during the pandemic emergency, it was observed that it confused cancer patients to the point that many of them refuse to continue treatment for the fear of infection and worsening of their condition (61).

Thus, for all these reasons long-term QoL issues in BCSs during the pandemic period are of particular interest in this field (62). Previous research (63-67) has highlighted the benefits resulting from the proposal of complementary or integrative mind-body therapies (such as mindfulness, yoga, physical training, and appropriate nutrition) to increase the psychological health and improve emotional experiences of patients. In agreement, some studies (63, 68-70) also highlighted a reduction of inflammatory markers and steeper cortisol slopes, elements that would indicate a healthier physiology. These results showed the importance of inserting exercise into patients' weekly habits and committing to maintaining the training in the medium-long term with simple sequences at home (71-73).

In addition, in some cases, exercise oncology protocols are proposed in group setting including, basically at the end of the training, moments of discussion and comparison on the lived experiences within a network of peers; precious opportunity for learning functional skills for positive adaptation and to restore independence and full participation in life (74-76).

The current scientific field of exercise interventions in BC is very large (28, 77-81). Although there is good evidence for short-term effects (e.g., post-intervention), few data are reported for long-term (follow-up) effects of peer-groups, also due to high drop-out rate (82).

COVID-19 pandemic and restrictions have forced practitioners and cancer survivors to embrace modern technological solutions to maintain health care provision and support interventions (32, 73). At the same time some TRIALs assessing physical activity have shifted to digital platforms showing encouraging results for professionals in the field (13, 83-85).

Despite the small sample size, our research highlighted the usefulness of the proposed home-based lifestyle intervention in improving psycho-social well-being in the short- and long term, exploiting the potential of new approaches to support cancer patients during COVID-19 pandemic.

Furthermore, contrary to what was expected given the particular pandemic context in which the research took place, women showed on average a non-alarming psycho-social status, with

all the psychometric scores obtained for depression, anger, confusion, strength/vigor, distress, social functioning, fatigue, emotional functioning and general health scale by using validated test such as EORTC-QLQ-C30, PDI, POMS (46, 50-52) in a normal range during all pandemic period. The lack of differences between groups previously verified between the intervention-arm and the control-arm allowed us to exclude a bias related to allocation and, therefore, to the awareness of being part of one group rather than the other.

In addition, most patients are in a couple relationship, are highly educated and work independent, and have received a quadrantectomy. These are socio-demographic and medical characteristics that previous studies (86-88)identified as protective factors towards the perception of greater distress and powerlessness in coping with adverse life events such as illness. Furthermore, a previous study (89) conducted 3 months after the beginning of the COVID-19 outbreak in Italy with oncological patients and a control group from the general population, stood out with interesting results to support our clinical data. In this study (89), cancer patients seemed to be less afraid, and psychologically healthier during the pandemic, and authors explained this by considering the overall life context of the patient. The experience of a cancer disease, when the patient perceives proper hospital care and high engagement, can act as a protective factor on the psychological distress. Since cancer is a frightening condition, other serious and potentially fatal risks (i.e., COVID-19 infection) may be perceived as less threatening and therefore may not contribute to the worsening of the patient's general psycho-physical health when BCSs feel that they have learned coping and adaptive skills in their long-lasting care path (89, 90).

In this regard, the intervention showed a significantly positive effect on the improvement of psychological well-being, even if women did not show clinically significant levels of psychological discomfort at the beginning of the program. The most interesting result seems to be the achievement, and subsequent maintenance over 12-months, of well-being and quality of life levels higher than the basal state substantially in all psychological dimensions.

As desired, one of the most effective interventions to prevent cancer-related mental illness in the follow-up is physical activity, and sedentary patients who engaged in our lifestyle program experienced relief from their symptoms of distress and fatigue and demonstrated an increase in psychological health (91-93).

Only the sub-dimensions concerning cognitive functioning and the perception of an adequate possibility of exchange and social interaction showed an opposite trend and worsened during the program. Previous studies in the scientific literature have shown that physical activity is a

promising intervention for cancer-related cognitive decline (94), but we verified a decrease in this dimension after the first three months of intervention. However, to read and interpret this outcome, we cannot ignore the environmental context and the evolution of the first year of the pandemic, characterized by frequent restrictions and lockdowns. It is possible that the negative effect of isolation, the perception of alienation given by living in the same restricted ambience for a prolonged time, and loss of daily activities have somehow conditioned cognitive and relational stimulation. A previous study with an Italian sample conducted during the first wave in Italy, in addition, identified the female-gender, and the home confinement (e.g., due to teleworking conditions) as relevant risk factors for worsening cognition (95) during COVID-19 pandemic. However, further research is needed to investigate the relationship between these variables.

Moreover, the global health status scale showed its significant improvement at every stage, and this is an almost paradoxical outcome considering the general worsening of the QoL of the world population in 2020 as highlighted by the scientific literature (93, 96).

Our preliminary study also provides a further opportunity for reflection and initial evidence to support the hypothesis that home-based interventions could be effective and alternative methods for improving QoL among cancer survivors (97-99). Another key point in favor of this research also concerns the absence of drop-outs between recruitment and follow-up phases, contrary to what tendentially was highlighted by clinical TRIALs, especially those delivered remotely for long periods (100-102).

In a moment of progressive isolation from daily human contacts for the entire population, the sense of being part of a group care path -symbolized as an emotional belonging rather than a physical presence- probably played a decisive role in the adherence of the participants to the program. This also leads us to reflect on the importance of involving clinical professionals in the TRIALs who are able to maintain solid relationships within the group and use the potential of this network to better support and involve patients. Therefore, the multidisciplinary home-based lifestyle intervention can be proposed as an ad hoc treatment context, in which the patients were the protagonists despite the distance, the isolation, and the pandemic condition: this may have contributed to high levels of participant satisfaction, and mood improvement (e.g., patients feel better understood and more confident about the experience) (103-106).

Some limitations should be taken into consideration. Despite these results, we are aware of the need to validate the presented intervention on a wider sample and through a more articulated

research design, for example by including the presence of a control group (as foreseen by the original protocol of the present trial research, protocol: NCT 04818359) and evaluating the possibility of stratifying the sample based on medical characteristics (e.g., type of diagnosis and surgical operation). Then, further research will be able to integrate an evaluation from a relational perspective to understand which figures support the patients, their role, and the motivation they have to be eventually included in a similar intervention, which could also promote the caregiver's and dyadic health (74).

However, recognizing the limitations set out above and the need for further studies, we believe that our findings could have important repercussions on clinical practice, and they highlight the potential of this specific multidisciplinary intervention, which is configured as an opportunity for the women involved to acquire healthy lifestyle habits in the long-term period, even in the absence of their specific request for intervention or expression of a specific and conscious need.

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CONCLUSIONS

Movement and Health Beyond Care, MOVIS: Nutrition and Exercise Educational Programs for Breast Cancer Survivors: **an example of an innovative project for women who have undergone breast cancer surgery, that confirms the relationship between physical activity, nutrition and quality of life, in terms of overall psycho-physical well-being**

Today we can no longer think that women who have undergone surgery following a diagnosis of breast cancer will not return to a full and active life. There is growing scientific interest in the types of exercise that can best play a role in terms of both primary and secondary prevention for BC. Furthermore, women who have undergone surgery following diagnosis of BC are becoming more and more aware of the benefits of an active lifestyle. The therapies used to treat breast cancer have various physical and psychological consequences on the life of patients. The post-treatment is a period in which fear and anxiety of experiencing a tumor recurrence emerge significantly and some cancer survivors experience negative emotional outcomes.

Adequate PA and proper nutrition programs are associated with a reduction in fatigue and a general improvement in the QoL in BCSs.

In this regard, exercise oncology (i.e., exercise medicine in the management of cancer) represents an important option for patients during rehabilitation, aftercare, and survival, with the aim of making the patient more active in everyday life. A growing body of literature shows the positive influence of PA and exercise on the reduction of recurrence and mortality. Additionally, exercise can have a favorable impact on cancer- and treatment-related side effects (including fatigue, depression, and physical functioning) and QoL of cancer survivors. However, there are differences in outcomes depending on the clinical setting of the BC patients and functional factors related to exercise, such as type, intensity, and physical activity level. Indeed, there is a positive correlation between high level of cardiorespiratory fitness and probability of survival, anyhows, a high level of activity is not necessarily associated with the best QoL.

The **clinical trial MOVIS**: 'Movement and health beyond care' as an ongoing randomized controlled trial wants to compare the benefits of exercise and proper nutritional plan *versus* usual care on QoL in BC within the 24-month post-surgery period.

Recruiting started in January 2020 with the recruitment of the first 30 BC patients who were followed until February 2022 for the short and long-term follow-up, as described in this thesis

and data collection is continuing. The incremental aerobic training of the fifth group is currently underway (N = 19). At the moment, one hundred and thirteen patients (N = 113) are recruited into the project, of which: 30 from group I, 25 from group II; 26 from group III; 13 from group IV and 19 from group V. All the participants followed an educational program to healthy lifestyles, with psychological support, nutritional advice and the intervention arm included a supervised aerobic exercise training for about 3 months. For both arms, interim analyses for clinical and functional parameters at short- (6 months) and long-term (12 and 24 months) follow-ups are performed. The project as described will last until 2025, and within the end we plan to recruit up to 172 patients to reach the statistical power of the primary objective of improving the quality of life measured through validated tests (European Organization for Research and Treatment of Cancer Quality of Life, EORTC QLQ-C30).

Study limitations

Despite the expected results to establish the significance of our study, the "MOVIS" project has some limitations. The first one is relative to the exceptional pandemic context in which the experimentation developed. About the project, the recruitment of patients during the pandemic was very difficult, it is an objective fact that in the context of national and international research there has been a slowdown in numerous clinical studies. The emergency has resulted in a diversion of almost all resources on COVID-19 and a reduction in the number of patients enrolled in studies conducted for other diseases. The COVID-19 emergency has generally resulted in a reduction in the number of patients enrolled to reach the number predicted by statistical power; we expect at least two next recruitments in September 2022 and January 2023. Moreover, during the COVID-19 restrictions, in fact, a regression to a sedentary lifestyle, a worsening of health and quality of life was observed, in particular for patients with previous breast cancer undergoing treatment or suffering adverse effects of the treatment. Home confinement has made it more difficult to reach the guidelines of cancer prevention for both nutrition and physical activity. The final analysis, therefore, could potentially and partially be influenced by the COVID-19 pandemic. Furthermore, since the control group is aware of participating in the trial and has received advice on the benefits of PA and adequate nutrition, a possible increase in physical activity levels in the control group, which could be due to several factors (such as e.g. motivation to change one's lifestyle after

diagnosis), could lead to a reduction of differences between the two groups (control and experimental) in this area.

Final considerations and acknowledgments

Conventional oncological post-treatment interventions have long been developed, including for example psychological interventions, the use of biological drugs, physical manipulation and the adoption of an active and healthy lifestyle, to counteract the negative effects of the disease. However, this awareness has not yet been sufficiently translated either in the direct involvement of PA specialists in the clinical team, or in highly integrated interventions with psychological support and physical exercise.

When the diagnosis is "breast cancer", the negative connotations associated with this pathology generate the impression of being invaded and overwhelmed by something malignant. It was in this particular scenario, that the role of exercise in primary and secondary cancer prevention was examined. The project 'MOVIS: Movement and health beyond care, physical and nutritional activity education path in the follow-up of patients with previous breast cancer' (ClinicalTrials.gov reference number: NCT04818359; CESU verbal approval n. 21 / 10.07. 2019) is part of the research line of Health promotion of the health and food safety (D.R. 446/2020) of the University and the Department of Biomolecular Sciences in collaboration with the ASUR Marche AV1 (U.O.C. Oncology, Cardiology, Clinical Pathology, Physiatry, Radiology and Breast Surgery of the 'Santa Maria della Misericordia' Hospital of Urbino), the National Cancer Institute of Milan, the Golden Brain ETS cultural association, also sees the support of associations and foundations present in the area particularly sensitive to the needs of cancer patients 'Le Contrade di Urbino', 'Valeria' Onlus; Cassa di Risparmio di Pesaro Foundation and Banca di Credito Cooperativo (BCC) Metauro.

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Chapter 1

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Chapter 2

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Chapter 3

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