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Exercise Oncology: the value of exercise among cancer patients and survivors

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Abstract

The World Health Organization reported increases in cancer incidence and considers this disease a health concern, as it represents a threat to life expectancy increase. Therapies and cancer side effects are positively impacted by exercise interventions. Research investigating exercise effects on cancer symptoms and therapies' side effects or cancer survival has been classified as "Exercise Oncology". The benefits of exercise have been largely demonstrated for common cancer types, and guidelines have been produced by several healthcare and exercise science institutions. The American College of Sports Medicine suggests a minimum of three times/week (30 min/session) of moderate aerobic training together with 2 sessions/week of resistance training (8–15 repetitions at 60% of 1-Repetition Maximum) for all cancer survivors. The same institution also emphasizes the need to individualize exercise interventions to cancer types and treatment highlighting the need to investigate more. For this reason, this thesis focuses on exercise oncology studies.

Chapter II will summarize studies not directly including cancer patients but exploring potential relevant outcomes or interventions for this population. Two original investigations are here reported proposing the assessment of an easy-to-administer cardiovascular health test and the implementation of a manual therapy that can replace classic stretching interventions. In the same chapter a narrative review assessing the influence of different exercise types on tissue stiffness, a parameter which can be related to cancer onset and symptoms.

Chapter III summarizes exercise oncology studies carried out during the PhD course. A total of 5 studies are presented involving breast (2) lung (1) or mixed cancer patients and survivors (2). A review and an original investigation have been proposed for breast cancer. A systematic review only is reported for lung cancer patients and survivors. Two more investigations have been summarized within this chapter, targeting samples with mixed cancer diagnoses, of which one is also a systematic review and one is an original investigation. The review target resistance training benefits on sleep variables.

In conclusion, the studies shown in this thesis provided promising results highlighting the benefits of exercise intervention in the cancer population on a wide variety of outcomes. Interestingly, resistance training seems to be valuable in improving physical fitness variables and sleep quality. The field of exercise oncology should still advance on less studied cancer types and outcomes to provide exhaustive guidelines for clinical operators and exercise specialists.

Acknowledgements

This file's original name was "Prof. Bianco meeting – Notes" and contained the first indications that Professor Antonino Bianco provided to start drafting my thesis. That makes it easier to thank this mentor first: his dreams and energy, in everything he does, were extremely contagious and I would not have had the strength to complete this path without keeping him in mind as a role model.

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List of abbreviations

1RM = 1-Repetition Maximum
ACE = Angiotensin-Converting Enzyme
ACSM = American College Of Sports Medicine
ANS = Autonomous Nervous System
AT = Aerobic Training
BC = Breast Cancer
BCP = Breast Cancer Patients
BCS = Breast Cancer Survivors
CG = Control Group
COMB = Combined AT And RT
CRF = Cardiorespiratory Fitness
DBP = Diastolic Blood Pressure
ECW = Extracellular Water
EX = Exercise Group
F = Fatigue
FFM = Free Fat Mass
FM = Fat Mass
FRS = Framingham Risk Score
HDL = High-Density Lipoprotein Cholesterol
HIIT = High-Intensity Interval Training
HRpeak = Peak Heart Rate
HRQOL = Health-Related Quality Of Life
HRV = Heart Rate Variability
ICW = Intracellular Water
IPAQ = International Physical Activity Questionnaire
IQR = Interquartile Ranges
LC = Lung Cancer
LDL = Cardiovascular Disease
LDL = Low-Density Lipoprotein Cholesterol
MFR = Myofascial Release
MST = Maximal Strength Training
MTJ = Myotendinous Junction
MTU = Muscle Tendon Unit
NCI = National Cancer Institute
OACCUs = Outdoor Against Cancer Connect Us
PA = Physical Activity
PNF = Proprioceptive Neuromuscular Facilitation
PSLR = Passive Straight Leg Raise
PTR = Positional Transversal Release
RCTs = Randomized Controlled Trials
RMSSD = Root Mean Square Of Successive Differences
Rob =Risk Of Bias
ROM = Range Of Movement
RT = Resistance Training
SBP = Systolic Blood Pressure
SF-36 = SHORT FORM-36 Questionnaire
SS = Static Stretching
ST = Strength
TNM = Tumour, Lymph Nodes, Metastasis
UC = Usual Care Group
WHO = World Health Organization

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Chapter I - Introduction

1.0 Cancer overview

The term "cancer" comes from the Greek word "Karkinos" (=crab, translated with the Latin version "cancer" later on), and it was first used by Hippocrates, who compared the tumour to a crab shape. The term "oncology" was first used by Galen instead, who preferred the Greek term "Oncos" (=swelling), to identify this disease[1].

Today, the word "cancer" represents a type of tumour. This term identifies a group of diseases predominantly forming a "mass" when the cell pathways get altered, initiating an uncontrolled cellular duplication[2,3]. Cells usually have the ability to interrupt this phenomenon, inducing "apoptosis" (cellular death). However, some factors may limit this capacity and increase the chances for masses to form[4].

Once the mass (tumour) is formed, it can be differentiated into two categories: benign and malignant[5]. The latter are those identified with the term "cancer", while benign tumours are masses formed by cells similar to the tissue they originate from, grow slowly, and have scarce to absent diffusion capacity. Benign tumours also usually have a better prognosis than cancer and are less likely to be lethal.

Cancers, on the contrary, have a higher diffusion capacity, forming "metastasis". This ability comes from the characteristics of the cells forming the mass, which are profoundly different from those of the original tissue and poorly differentiated, conferring faster growth speed. These and other characteristics (vascularization, irregular edges, cells not differentiated) confer cancer lower prognosis, making it life-threatening.

Each type of cancer, usually classified according to its histological derivation into 6 classes[6] (carcinomas, leukaemia, lymphomas, myelomas, sarcomas, and mixed types), is then differentiated for their progression using the TNM (Tumour, Lymph Nodes, Metastasis)[7] classification to provide prognosis and proper treatments. A five-stage classification is also considered in clinical and research practice: 0 (representing only carcinomas in situ) – I – II (for local masses) – III (for local masses spread to lymph nodes) and IV when distant metastases are present.

The World Health Organization (WHO) showed an increase in cancer incidence and deaths[8-10]. Breast Cancer (BC) is the most commonly diagnosed cancer, followed by lung, colorectal and prostate cancer when considering both sexes[10]. When considering mortality, the first cause of cancer death is lung cancer (LC) followed by colorectal and liver cancer[10]. Cancer is hence becoming a threat to life expectancy increases, being one of the leading causes of death (ranking first, second, or third) in people younger than 70 years old (in 135 countries out of 183)[10]. It appears clear that the cancer burden is increasing, and when a diagnosis arises, it represents not only an individual challenge but also a psychosocial menace, requiring efforts on a larger social and economic scale. It is extremely relevant to understand cancer's risk and prognostic factors to prevent and fight this disease.

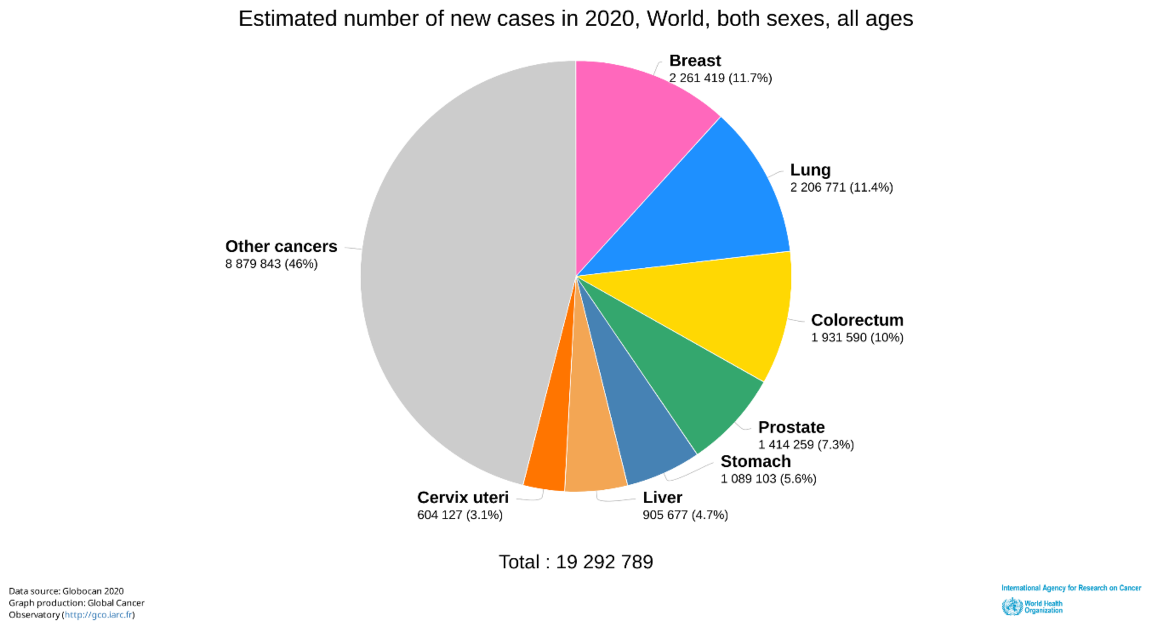

***Fig. 1.1** Cancer incidence worldwide (retrieved from https://gco.iarc.fr/today/home)*

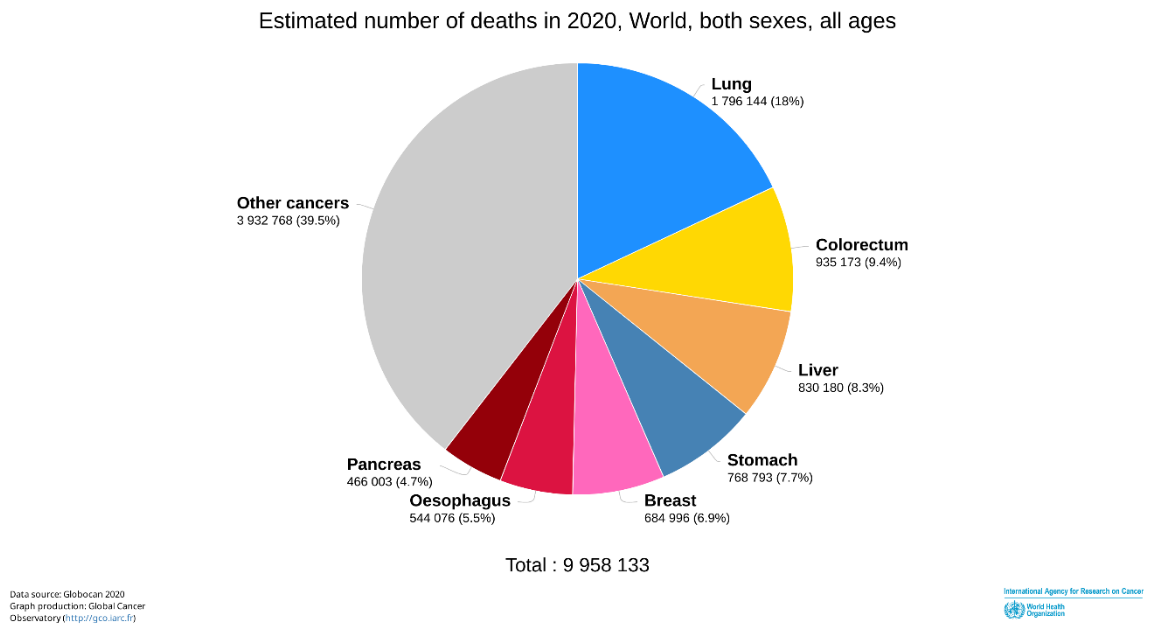

***Fig 1.2** Cancer mortality worldwide (retrieved from https://gco.iarc.fr/today/home)*

1.1 Cancer risk factors: the role of physical activity and tissue stiffness

When considering cancer's risk factors, two types may be identified: "intrinsic risk factors" (unmodifiable) and "non-intrinsic risk factors" (modifiable)[11]. Lifestyles, as modifiable risk factors, may have a predominant role in increasing cancer risk. Cancer prevention should start with the modification of unhealthy behaviours. These strategies should be promoted, considering that future incidence estimations of cancer are increasing.

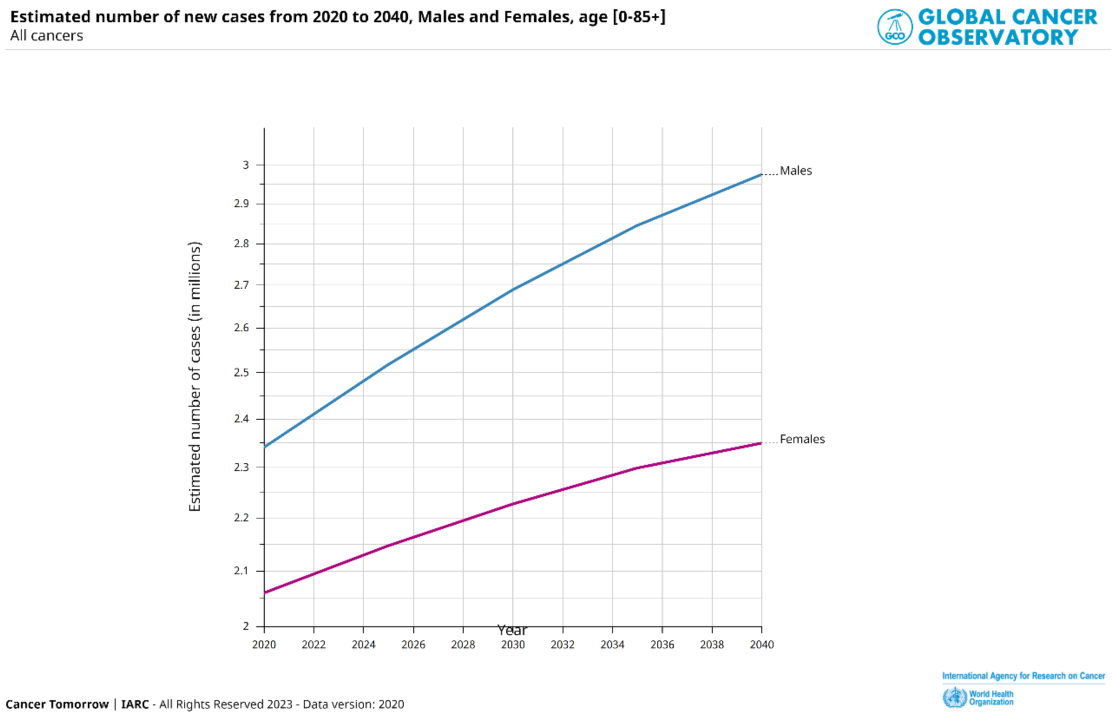

Fig 1.3 *Future cancer incidence estimations (retrieved from https://gco.iarc.fr/overtime/en)*

In particular, physical activity (PA) levels may be a key determinant of cancer risk. A recent prospective cohort study (on 1.44 million participants) demonstrated that PA is associated with the risk reduction of 13 types of cancer (of the 26 investigated), with a total cancer risk reduction of 7%[12]. The risk reduction was moderate for common cancer forms such as colon, rectal, breast, myeloma, head and neck and bladder cancer. However, cancer remains a multifactorial complex disease, and a comprehensive healthy behaviour should be adopted to significantly reduce the risk. Nevertheless, PA and exercise play a direct and indirect role in reducing the risk itself, as well as reducing other risk factors such as obesity, inflammation, and hormonal imbalance[13], and should be promoted along with other primary prevention strategies.

It is also worth noting that, as a multifactorial disease, microscopical interactions play a relevant role in macroscopic events, and vice versa. Recent studies support the potential role played by tissue stiffness: the capacity of the tissue to resist to external mechanical deformation. This property seems to drive cellular division, migration and differentiation[14,15]. Considering these factors, appears reasonable to consequently connect tissue stiffness and cancer, especially when the stiffness increases above the physiological levels of the specific tissue[16]. Strategies to counteract abnormal stiffness levels among healthy individuals should be implemented as a potential prevention strategy. Different exercise interventions might have various outcomes on tissue stiffness, which can also be different according to the targeted tissue. The role of PA and exercise should not be underestimated in the treatment of tissue stiffness and its potential relationship with cancer onset.

1.2 Cancer treatments' side effects

Cancer patients face different symptoms and once a diagnosis is made (usually confirmed with a biopsy), different treatments can be administered according to cancer site and stage.

Surgery is often performed to resect the mass and when this happens all the additional treatments administered before surgery are called "neoadjuvant"[17] while those administered after surgery are called "adjuvant"[18]. In synthesis, cancer patients may follow one or more of the following treatments[19,20]: chemotherapy[17,18], radiotherapy[21], hormone therapy[22], immunotherapy[23], targeted therapy[24], stem cell transplant[25,26], hyperthermia[27] and photodynamic therapy[28].

Both neo- and adjuvant treatments can cause detrimental side effects. Cancer therapies are not only toxic for the affected tissue (the cancerous mass itself) but for the whole organism compromising healthy cell function. One of the most frequent side effects is fatigue (also known as cancer-related fatigue), which is also a cancer symptom[29]. Fatigue (F) is defined as a condition in which the patient feels tired, independently of the daily activities performed, and it is present even after a full rest[30]. This condition is multifactorial[29] and could be exacerbated by other side effects. Both psychological and physical factors can play a role in the determination of F levels and duration (acute or chronic). Anxiety, depression, insomnia and compromised cognitive function may contribute to cognitive components of F. Compromised cardiac, respiratory, muscular and neural function may exacerbate physical components of F[31]. Thus, strategies to decrease F levels should be comprehensive to target multiple F factors. In addition, F may be also increased by a deconditioned status generated by both cancer and therapies. It is likely that a vicious circle in which side effects and deconditioning takes place, worsening F and patients' health-related quality of life

(HRQoL)[30]. Deconditioning results as a side effect, lowering cardiorespiratory fitness (CRF) and strength levels (ST)[32] which are counterintuitively treated with rest. Symptoms may hence last for longer periods, even after the treatment is over, or when long-term therapies are still in place, and cancer itself is defeated[33]. It is a relevant concern to find approaches able to reduce short and long-term side effects to improve patients and survivors' HRQoL.
Exercise strategies may play a role in all treatment and post-treatment phases potentially reversing the vicious circle and improving life quality. However, exercise seems to be efficient in reducing deconditioning and physical components of F only and psychological needs may remain unsolved[34].
Other side effects may be caused by chemotherapy alone. For example, specific types of chemotherapeutic drugs (anthracyclines) have cardiotoxic consequences[35,36], while others may be neurotoxic causing chemotherapy-induced peripheral neuropathy[37]. The latter is a condition which influences peripheral neurons' capacity to deliver information to the central nervous system thus affecting sensorial afference. It is reported by the patients as pain ranging from tingling to burning and numbness (both to mechanical and temperature stimuli)[38]. Exercise interventions, as well as nerve gliding strategies and proprioceptive approaches, seem to be able to improve chemotherapy-induced neuropathy[39]. Also, chemotherapy cardiotoxicity seems to be reduced or reversed with exercise strategies[36] which should be considered to improve long-term survival.
It is unquestioned that exercise is a non-pharmacological strategy to consider within the cancer care continuum, although its value for specific symptoms and cancer types is still under investigation as well as how to prescribe it to obtain better outcomes. Below we will further discuss the implementation of exercise in counteracting deconditioning of the muscular tissue.

1.3 Implications of exercise on muscle wasting: cancer cachexia

Our tissues physiologically perform more than one function. Our muscles, for example, generate contractions allowing joint movements, performing deposit and endocrine functions releasing cytokines, named myokines[40,41]. The presence of healthy skeletal muscle tissue is then intuitively linked to the health of the whole organism and should be preserved. However, cancer may lead to skeletal muscle loss which may be exacerbated by cancer therapies, although sex differences may be present[42,43]. It is clear that cancer itself together with treatments, can hence increase the chance of developing "sarcopenia" and then "cachexia": a metabolic syndrome characterized by the presence of muscle mass wasting due to the imbalance between anabolic and catabolic process[44]. Researchers are highlighting the multifactorial nature of cancer cachexia, identifying more components than only skeletal muscle waste[45].

Exercise interventions are known to promote muscular growth, especially when performed in the form of resistance training (RT)[46,47]. However, the knowledge on this matter is still insufficient. A recent review to assess the feasibility and the effectiveness of exercise on cancer cachexia showed inconclusive results due to the inclusion of only 4 studies[48]. Another study proposed a mechanism which may justify potential exercise benefits[49]. Nevertheless preserving the muscular tissue and facing cancer cachexia is crucial and exercise seems intuitively linked to this phenomenon, further studies are needed to address this issue.

1.4 Mechanism linking cancer and exercise

Exercise generates effects, from a molecular to the whole organism level. Healthy individuals benefit from exercise primarily by obtaining cardiorespiratory and ST improvements coming from short and long-term cell adaptations: increased enzymatic function, metabolic capacity, vascularization, cardiovascular performance, muscular strength and hypertrophy[50]. Opposite physical fitness changes have been observed among individuals diagnosed with cancer[32]. As we also showed above, exercise can be implemented as a strategy to counteract symptoms and side effects worsening trends among cancer populations. In recent years, the role of exercise in cancer prevention and treatment has become popular. At a molecular level, it seems that exercise can, not only modify the biochemical pathways to improve the entire organism's physical fitness but also affect tumour growth. The latter effect, identified as "intrinsic" to the tumour, seems to reduce the rate of growth in a variety of histological solid cancers (in vitro and on animal models), highlighting an inhibition trend which may be translated into a metastatic capacity reduction[49].

Moreover, at a cellular level, exercise seems also to be a competitor to cancer metabolism, which is predominantly oriented to glucose aerobic recruitment, to sustain the altered fast cellular proliferation[49]. In this direction, skeletal muscles during activity augment glucose recruitment, ensuring a higher quantity of glucose channels as well as boosting glycolytic energetic pathways[50]. Cancer is also able to grow due to its resistance to immune response. Exercise, on the contrary, has been shown to influence tumour growth through exercise-produced cytotoxic immune cells, together with the potential role of myokines (specific muscular cytokines)[49].

The “extrinsic” exercise effects are instead those related to cancer and side effects symptoms. As we previously mentioned, the benefits of exercise on muscle mass could contribute to the prevention and control of cancer cachexia[49]. Conversely, for those in which weight gain is associated with systemic inflammation (breast and prostate cancer), exercise may contribute to lowering adipose tissue and markers of inflammation, primarily acting on circulating hormones[49]. Other side effects, including cancer-related fatigue, sleep disorders, depression and anxiety can be dampened by implementing exercise strategies[51]. For example, skeletal muscles are able to metabolize tryptophan metabolites, which can usually cross nervous system barriers and induce depression and F[49]. These effects are confirmed in healthy individuals and are not confirmed yet among cancer populations, although this molecular interaction appears to be promising.

Furthermore, even if exercise seems only to inhibit tumour growth instead of stopping or reversing it, it may help in drug administration and delivery. Chemotherapy and immunotherapy need to be delivered to the target tissue: the cancer. Exercise has the capability to increase vascularization and angiogenesis at the cancer level. This phenomenon intuitively increases the chances of appropriate drug delivery[49]. Also for radiotherapy, vascularization plays a relevant role, delivering oxygen to the targeted tissue facilitating the development of reactive oxidative compounds with therapeutic capabilities[49].

In conclusion, exercise, known to be a valuable prevention strategy, should also be considered as a complementary therapy due to its valuable contribution to improving patients' HRQoL and its potential role in driving cancer therapy success[52].

In the following paragraphs, the implications for breast and LC patients and survivors of exercise interventions will be explored considering their burden among the general populations (first for incidence and cancer mortality, respectively). This focus is also presented for the attention that has been given to these two cancer types during the research carried out during the PhD course and which will represent part of the research summarized within **Chapter III**.

1.5 Breast Cancer

Female BC incidence is the highest compared to other cancers. More than 2 million new cases were diagnosed in 2020, ranking first in almost all around the globe[10]. It is also the leading cause of cancer mortality in 110 countries[10]. Its incidence is greater in developed countries, due to higher risk factors presence (e.g. contraceptives, unhealthy diet and alcohol, obesity, late or non-pregnancy) and efficient early screening and detection[10,53].

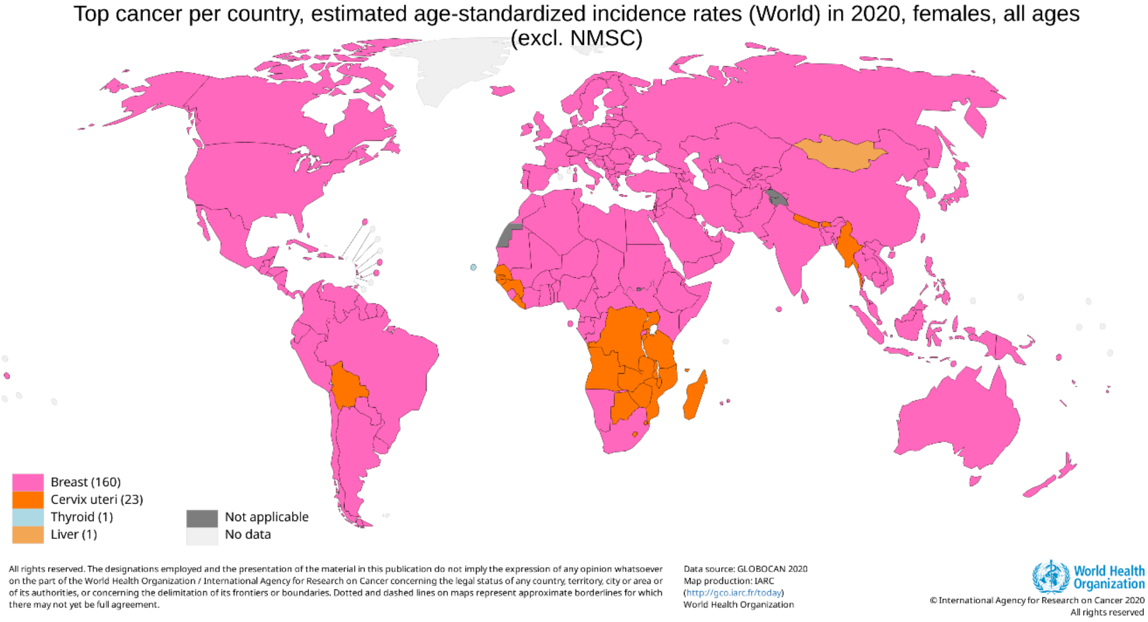

Fig 1.4 *Most diagnosed cancer per country among women (retrieved from https://gco.iarc.fr/today/home)*

The high incidence may also be related to the existence of different types of BC, which are identified according to the original cells that start the cancerous process[54].

BC therapy combines different approaches specific to cancer type and stage. Its management includes radiotherapy, chemotherapy, targeted therapies, hormonal treatment, and surgery[53]. These approaches are not without side effects. Independent of the surgical technique, surgery requires a significant amount of time before complete recovery and allows HRQoL to return at pre-surgery levels causing physio- and psychological side effects[53,55]. Radiotherapy and chemotherapy may also alter physical fitness and tissues[56], contributing to the manifestation of common symptoms, such as: cancer-related fatigue, nausea, insomnia, vomiting, neuropathy, strength and cardiovascular impairment[32,56,57]. Despite the side effects, neo- and adjuvant therapies have contributed to survival rate increases. Mortality has decreased by 40% (in the USA, since 1989[58]) and will decrease by 35% in the next years (in Europe)[59]. Side effects can also occur long-term, impacting HRQoL for longer periods after therapies[29,30]. Physical fitness, including CRF and ST, are usually impaired in this population[32] and their reductions can compromise independence and HRQoL[60].

Therefore, BCP and breast cancer survivors (BCS), could enter the vicious cycle, usually experienced by cancer populations, wherein side effects and deconditioning increase sedentary levels and consequently amplify the initial side effects and symptoms[30,61,62].

Exercise may help to counteract the adverse effects of therapies and deconditioning that will reduce HRQoL in BCP and BCS. Exercise has been shown to mitigate deconditioning[63]. The usefulness of exercise has been also demonstrated to be a valuable strategy to improve survival[12,64-66] (also for higher stages BCP)[67-69].

Moreover, BC mortality is usually led by cardiovascular consequences[70,71]. Due to increased survivorship, BCS are threatened by cardiovascular side effects sequelae rather than cancer itself. It is essential to target cardiovascular outcomes of BCS to limit this risk. In order to approach this issue it would be necessary to find a simple, not invasive assessment, to evaluate cardiovascular health. Hearth Rate Variability (HRV) may be one of the options for this need. HRV is a comprehensive assessment of inter-beat intervals which allows, with a single recording, to estimate characteristics of the cardiovascular system and the influence of the autonomous nervous system (ANS) branches on the hearth beat[72]. HRV assessment consists of the recording of heartbeats and the distance of the interbeat intervals (in milliseconds) and can be completed in 24 hours or only in 5 or even 2 minutes. The 24-hour recording has been used in clinical settings for diagnostic and prognostic purposes and exceeds the aim of this thesis. The 5 minutes recording has been used in exercise contexts and has a simple/fast assessment to evaluate cardiovascular health and ANS branches balance. It may be applied by exercise specialists to understand the effects of exercise on cardiovascular health and to design exercise interventions accordingly.

HRV assessments will be explored in one of the preparatory studies presented in **Chapter II** while overall exercise effects on BCP or survivors will be explored in a systematic review summarized in **Chapter III.**

1.6 Lung Cancer

LC has been recognized to be the most diagnosed cancer in the 2018 global cancer report[9] and, even if it was surpassed by female BC cases in 2020, it is still a concern as the second most diagnosed cancer and first cause of cancer death[10]. Also for LC patients therapies can have detrimental effects. Surgery is usually implemented when the cancer stage allows it, and it may present complex challenges[73], which may appear to be harder than those expected after BC surgery. LC surgery directly impairs respiratory function limiting patients' respiratory capacity, independence and consequently HRQoL according to the surgery procedure[74-76].

Due to these patients' needs and especially the necessity to restore pulmonary function, pulmonary rehabilitation strategies are usually implemented. PR is a comprehensive rehabilitation strategy that consists of behavioural management strategies (treatment side effect awareness and management, smoking cessation, diet and psychosocial interventions), together with exercise and breathing techniques[77,78].

However, the need to individualize exercise is crucial for cancer patients[51,79] and should be further considered when patients' physical fitness is impaired. The administration of multidisciplinary approaches including exercise (PR) might reduce the clear understanding of exercise effects among LC populations and hence reduce the possibility to properly individualize interventions. Thus, understanding the effects of exercise alone should be a priority in the research context, while in the last decade trials and systematic reviews tested multicomponent interventions. Considering the benefits of exercise on cancer populations and the need to individualize, a systematic review assessing the effectiveness of exercise intervention alone among LC patients and survivors will be summarized in **Chapter III**.

1.7 Exercise Oncology

Considering the interest of research and clinical practice on the effectiveness of exercise on cancer populations a new field has been identified: Exercise Oncology[80]. Research within this field aims at determining the benefits of exercise for cancer patients and survivors, ranging from feasibility studies to randomized controlled trials (RCTs) assessing specific exercise parameters/type influence on relevant outcomes. These needs arise due to the fact that, although the benefits of exercise are intuitive and demonstrated for some aspects of the cancer continuum, dose-effect relationships for specific cancer types, therapies side effects and survival are still unknown. Cancer treatments and cancer itself should be always taken into account when exercise implementation is considered and trainers still need directions to better design the interventions. In order to accomplish this task, exercise oncology guidelines have been published in the past[81] and in recent years as the research on this field expands[51,79,82].

The updated American College of Sports Medicine (ACSM) guidelines[51] and the Exercise and Sports Science Australia position statement for cancer patients[79] suggest individualized exercise prescriptions to specific patients' needs while declaring exercise to be safe and efficient in improving health-related outcomes when performed as follows:

-Minimum three times/week (30 min/session) of moderate aerobic training (AT) + 2 sessions/week of RT (8–15 repetitions at 60% of 1-Repetition Maximum—1RM) for all cancer survivors[51].

In spite of these general recommendations, once oncologist approval is obtained when comorbidities are present, tailoring the intervention must be trainers' first concern to booster adherence and, consequently, benefits and safety[51,83]. These strategies apply to healthy individuals as well as to other diseases and should be, once more, carefully considered for cancer populations.

It seems clear that, although the benefits of exercise for cancer patients and survivors have reached consensus around the world, there's still a need to assess specific exercise effects for each type of cancer adding the challenge of understanding the interaction between exercise and each specific therapy as well. Less commonly investigated outcomes could also provide valuable information within this field.

In the following chapters, studies carried out to preliminary investigate new outcomes for future exercise oncology research implementation, as well as studies carried out to train the researcher are shown (Chapter 2). Specific research projects on exercise oncology are also shown (Chapter 3) to highlight new findings and future directions.

1.8 Terminological notes

Before diving into the studies presented in the following chapters, some terminological clarifications should be made. As it could have been noted, this thesis focuses on "cancer" populations, including all individuals who received a cancer diagnosis which is different (as previously mentioned) from benign tumour formations. The latter, although representing a different significant disease, is not taken into account within the following paragraphs. Moreover, when analysing cancer populations it is crucial to highlight the definition of "cancer survivors" provided by the National Cancer Institute (NCI)[84]. This definition may lead to misinterpretation considering its broad meaning which includes all individuals diagnosed with cancer independently of cancer presence (on or off treatment, healed) from the time of diagnosis to the moment of death. However, this definition makes it more difficult to differentiate cancer populations according to treatment phase and actual health state. Authors have proposed different meanings compared to the one proposed by the NCI, to facilitate research practice[85]. In particular a different meaning for the word "survivor" has been utilised. This term tends to identify only those who completed primary treatment and live cancer-free, and instead of including all individuals diagnosed with cancer, the term can be used in contrast to the word "patients". The latter is used to include all the individuals from the moment of a cancer diagnosis to the moment in which the disease is defeated.

To clarify and to underline the use of these terms in the next paragraphs, the words "cancer patients" identify those with a cancer diagnosis currently "on (primary) treatment" while the words "cancer survivors" identify those who are "off (primary) treatment" and are living cancer free. These terminological uses have been selected to better differentiate two types of individuals who may be profoundly different due to the high impact represented by cancer treatments.

Chapter II - Preliminary and research training studies

2.0 Overview

Within this chapter, some of the preliminary research projects are summarized. These have to be intended as preliminary investigations for specific variables or as research methodology training, keeping in mind the potential for future applications on individuals diagnosed with cancer. For this reason, each of the following paragraphs will discuss one published research project. Each study will be summarized highlighting the relationships between each research question and the main topic "Exercise Oncology".

List of publications/projects discussed within Chapter II:

-2.1 Ficarra, S., Thomas, E., Pillitteri, G., Migliore, D., Gómez-López, M., Palma, A., & Bianco, A. (2022). CHANGES IN QUALITY OF LIFE, STRENGTH AND HEART RATE VARIABILITY AFTER 4-WEEKS OF SUPERVISED ONLINE BURPEES TRAINING DURING THE COVID-19 QUARANTINE IN HEALTHY YOUNG ADULTS: A PILOT STUDY. Kinesiology, 54(1), 116-125.

-2.2 Thomas, E., Ficarra, S., Nakamura, M., Paoli, A., Bellafiore, M., Palma, A., & Bianco, A. (2022). Effects of Different Long-Term Exercise Modalities on Tissue Stiffness. Sports Medicine - Open, 8(1), 71. doi:10.1186/s40798-022-00462-7.

-2.3 Thomas, E., Ficarra, S., Scardina, A., Bellafiore, M., Palma, A., Maksimovic, N., Drid, P., & Bianco, A. (2022). Positional transversal release is effective as stretching on range of movement, performance and balance: a cross-over study. BMC Sports Science, Medicine and Rehabilitation, 14(1), 202. doi:10.1186/s13102-022-00599-8.

2.1 "Changes in quality of life, strength and heart rate variability after 4-weeks of supervised online burpees training during the covid-19 quarantine in healthy young adults: a pilot study" *(Ficarra, S., Thomas, E., Pillitteri, G., Migliore, D., Gómez-López, M., Palma, A., & Bianco, A. (2022). CHANGES IN QUALITY OF LIFE, STRENGTH AND HEART RATE VARIABILITY AFTER 4-WEEKS OF SUPERVISED ONLINE BURPEES TRAINING DURING THE COVID-19 QUARANTINE IN HEALTHY YOUNG ADULTS: A PILOT STUDY. Kinesiology, 54(1), 116-125.)*

Introduction

This study was carried out right after the first waves of COVID-19, while online telecommunication strategies were still mainly implemented for different reasons[86-88]. The pandemic restrictions on social events caused a decline in HRQoL[89,90] both in the general population as well as in children and adolescents[91]. Thus, strategies to counteract sedentary levels were warranted to restore fitness levels limiting cardiovascular diseases along with other health-related and psychosocial concerns[92-96]. This project was the first implemented within our laboratory to overcome the barrier represented by the pandemic and its future application on the oncological populations is unquestionably valuable. The need to implement online exercise strategies may be useful for those who are impaired and can not leave their home or are at risk when performing exercise outdoors. Also, we presented an easy-to-administer burpees bodyweight training, with basically no monetary cost[97-99]. Bodyweight training has also ranked third as fitness trend worldwide in 2023[100] and burpees have been demonstrated to require higher energetic demands than other commonly implemented resistance exercises[101]. Exercise interventions with only burpees are rare in research practice and to our knowledge, no study assessed burpees' influence on HRQoL and HRV. HRV is a valuable non-invasive assessment which can provide a representation of the ANS branches balance[102] through the observation of the heartbeat behaviours. Different exercise interventions have benefits on cardiovascular parameters and HRV in young and middle-aged individuals[103] but the effects of bodyweight workouts have not been tested yet. For the abovementioned reasons, we constructed a progressive burpees intervention, administered online, to test its feasibility and its potential effect on physiological (HRV) and psychological (HRQoL) variables. Therefore, the aim of this study is to assess adherence to our progressive online burpees protocol and its potential benefits on HRQoL, HRV, cardiovascular health, and ST in young adults during the quarantine.

Methods

This study was a single-arm pilot of a 4-week, online burpees intervention for young adults. The research project was approved by the University of Palermo Ethical Committee (n. 45/2021). Healthy 18 to 30 years old, young adults with no exercise contraindications were recruited. Fourteen young adults (10 males) took part in the study but one (male) participant, did not return for post-test due to COVID-19 infection. At the end of the study, 13 participants (22.5±1.39 years, BMI 24.5±2.89 kg*m^{-2}) completed post-test assessments and were analysed.

An expert trainer was prepared to deliver the online exercise intervention which is presented in Table 2.1. An online videoconferencing software was used to fully supervise the intervention. Classes were delivered once a day, 5 days/week as follows: a warm-up with joint mobility exercises and 10 push-ups, 5 squats and 5 squat jumps; main burpees phase; and a 10 minutes cool-down with static stretching exercises. The main phase comprised burpees, a bodyweight exercise done performing a push-up and a squat jump together[97-99]. A progressive volume of burpees (sets x repetitions) was administered each week, following the progression principle[50].

Table 2.1 Burpees Intervention progression

	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Sets	Reps	Rest	Sets	Reps	Rest	Sets	Reps	Rest	Sets	Reps	Rest
	Warm-up			Warm-up			Warm-up			Warm-up		
Burpees	10	10	1’	10	12	1’	11	12	1’	12	12	1’
	Cool-down			Cool-down			Cool-down			Cool-down		
Daily Volume	**100**			**120**			**132**			**144**		
Weekly Volume	**500**			**600**			**660**			**720**		

Variables and Materials

A single evaluation session was used for each participant to assess all the variables. Included outcomes are listed below. The maximal fitness tests were administered after all the other tests. Assessments were carried out by two expert investigators before and after the 4-week intervention. COVID-19 spreading prevention strategies were implemented to ensure participants' safety[104].

Assessed variables were: HRQoL using the Italian version of the SHORT FORM-36 questionnaire (SF-36)[105,106]; height and weight; body composition (free fat mass (FFM), fat mass (FM), intracellular water (ICW) and extracellular water (ECW)) through an AKERN 101 (AKERN SRL, RJL Systems, Detroit, USA) impedance analyser[107]; Systolic and Diastolic blood pressure (SBP and DBP) using an OMRON EVOLV HEM-7600T-E digital sphygmomanometer and HRV with a POLAR H10 heart rate sensor during a 5-minute recording[72,108]; handgrip strength A digital dynamometer (KERN MAP 80K1, KERN&Sohn GmbH, Barlinger, Germany), the counter-movement squat jump height (CMJ) using the OPTOJUMP (MICROGATE) and the maximum number of push-up to exhaustion were assessed. The rate of perceived exertion (RPE, Borg scale) was administered at the end of the push up test to estimate subjective effort and to confirm participants' exhaustion[109].

The R-based software JAMOVI (The jamovi project (2021). jamovi (Version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org) was used to analyse the data. Normality was assessed (Shapiro-Wilk test) and Paired sample t-test or the Wil**c**oxon ranks were implemented for normal and non-normal distributed data, respectively, to test the difference between pre and post-intervention values. The test-retest reliability coefficient was calculated using the Pearson r correlation. GRAPHPAD PRISM 8 was used to design graphs.

Results

All the participants completed the full training program (including the participant who did not complete the post-test assessment due to COVID-19 infection).

A significant improvement in the participants' HRQoL was found after the online intervention (p=0.025) (Fig. 2.1).

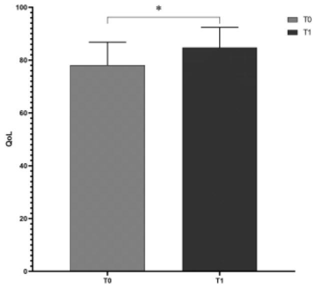

Fig 2.1. *HRQoL Pre (T0) and Post (T1) assessment*

No difference was found in participants' weight and BMI after the intervention. Consistently, no differences were found regarding body composition variables (FFM, FM, ICW and ECW). No significant differences regarding both hands' grip strength and the CMJ elevation were found. However, a significant difference (p=0.017) in the number of repetitions on the push-up test to exhaustion was found (Fig. 2.2). No difference was found in the RPE, confirming the same level of effort to perform the test to exhaustion, at the end of the intervention period, despite the increased number of repetitions performed**.**

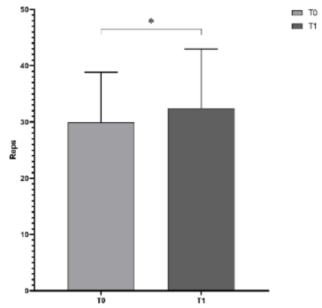

Fig 2.2 *Push-up repetitions Pre (T0) and Post (T1) assessment*

Blood pressure analysis showed no difference after the intervention on SBP (p=0.784), while a significant difference was found in DBP (p=0.004). The HRV assessment showed significantly increased mean RR (p=0.005); decreased mean HR (p=0.004); increased RMSSD (root mean square of successive differences) (p=0.014) (Fig. 3); and increased TINN (p=0.020). Non-significant increase was noted regarding SDNN (p=0.053). No difference**s** were found on NN50 and Triangular Index instead.

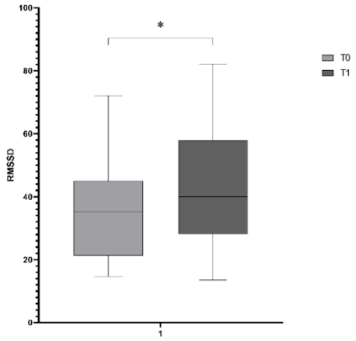

Fig 2.3. *RMSSD Pre (T0) and Post (T1) measurements*

Discussion

The aim of this pilot study was to understand the feasibility and potential benefits of a progressive online burpees program for young adults during the COVID-19 quarantine. The feasibility and safety of our protocol seem to be confirmed. Furthermore, some potential benefits on participants' HRQoL, muscular endurance performance, and HRV (with a tendency to parasympathetic predominance) were found.

No studies assessing HRQoL used an only-burpees intervention. However, two studies[110,111] assessed HRQoL with the SF-36 questionnaire before and after high-intensity interval training (HIIT) bodyweight interventions. In the first study, improvements in some HRQoL dimensions, physical fitness and body composition after 9 weeks of bodyweight exercises in overweight women[110]. The second, showed that a 4-week mobile-based bodyweight HIIT was effective on HRQoL among young adults but no differences in CRF or body composition[111], consistent with what we reported. Another study from Evangelista et al. did not find body composition changes after a 6-week bodyweight HIIT protocol (although improvements in the push-up test results were found)[112]. The short intervention period together with no diet counselling and the healthy condition of our sample potentially brought us to similar outcomes on body composition.

A significant increase in the number of push-ups performed during a test to failure was also found. These outcomes are consistent with those previously mentioned[110,111]. However, it was the only ST measurement showing a significant increase. Handgrip strength did not show significant changes probably because grip is not trained during burpees[113]. These results are consistent with those presented by McRae et al demonstrating significant improvements in the aerobic and muscular endurance of females, but no grip strength after a 4-week Tabata intervention[102]. Only one study[99] implemented a burpees intervention similar to ours. Army cadets performed burpees protocol or standard military training. The authors demonstrated that the 4-week HIIT burpees protocol can maintain army cadets' aerobic and anaerobic capacity[99].

Despite our pilot trial, promising results among HRV variables were also found showing an increased parasympathetic activity[72,108]. The significant reduction of mean HR in bpm was found with other time-domain variables underlined this variation. The RMSSD is strictly related to vagal activity[72], and its value showed a significant increase. No significant variations were found in frequency-domain outcomes. However, ANS activity results from the sympathetic and parasympathetic branches' balance activities that are not mutually exclusive[108]. Consistently no significant difference regarding the LF/HF ratio, which represents ANS branches' balance, was also found. Nonetheless, our HRV results are consistent with those reported by Zaffalon Júnior et al in which active women present better HRV when compared to sedentary women[114]. Moreover, our results suggest that a single exercise performed daily for 4-weeks could be enough to target HRV changes.

We also found a significant DBP reduction but no significant differences in SBP. Our result may be related to the session duration rather than exercise volume. Cornelissen et al. systematic review and meta-analysis demonstrated that shorter sessions (30-45') significantly decrease DBP but not SBP[115]. This explanation considered with the short-intervention pilot design should be considered when examining our BP results.

Overall this study was limited by the absence of an untrained control group, lacking in the design of our pilot investigation, a small sample size and the short intervention period.

However, our fully supervised burpees intervention delivered online had a 100% adherence rate for all the participants (including the participant who was not able to complete post-test assessments). This confirms that our exercise protocol is feasible and safe. Furthermore, the online supervision allowed a daily workout (5 days a week) during the quarantine. This factor could have been crucial in the observed results. More studies, with a larger sample and appropriate control, are still needed to confirm the effects of our study.

Our 4-week daily burpees intervention, administered online, is feasible and could improve quality of life, upper body endurance strength and Heart Rate Variability in young adults. This non-time-consuming approach could be easily administered to young adults, in order to promote healthy living and counteract physical inactivity thanks to its feasibility, short duration and low cost.

Online bodyweight training strategies may be implemented in future trials among cancer survivors to improve exercise adherence when participants cannot reach training structures or leaving the house represents a threat. Additionally, it may be worth it to investigate if HRQoL and HRV improvements will be possible in these fragile populations.

2.2 "Effects of Different Long-Term Exercise Modalities on Tissue Stiffness" *(Thomas, E., Ficarra, S., Nakamura, M., Paoli, A., Bellafiore, M., Palma, A., & Bianco, A. (2022). Effects of Different Long-Term Exercise Modalities on Tissue Stiffness. Sports Medicine - Open, 8(1), 71. doi:10.1186/s40798-022-00462-7)*

Introduction

The following study is a narrative review focusing on the need to understand how tissue stiffness, and capacity to resist mechanical deformations[116,117], respond to different long-term exercises. Even though this information has practical implications mainly in sport-specific contexts their application for pathological populations should not be underestimated. As we previously mentioned stiffness could drive differentiation and other cellular pathways[15,118] and its modification could have implications in cancer prevention[16] as well as in the treatment of stiffer tissue in rehabilitation or pathological conditions.

Different tissues have different stiffness levels due to the function they perform. Stiffer tissues, like bones, deform less than softer tissues, like fat[119]. In pathological conditions usually an altered tissue stiffness level is present due to increased fibrosis[117] which leads to HRQoL reductions. Such a phenomenon takes place for example when scars[120] impair mobility or calcifications[121] cause pain (reducing independence). Moreover, ageing or lifestyles can lead to atherosclerosis[122], which increases cardiovascular risk.

It appears clear that as a physiological parameter, adequate stiffness levels are essential and when achieved are maintained by external mechanical stimuli[118]. However, assessing this parameter is challenging and differs according to the analysed tissue: musculoskeletal tissues are measured through myometers[123] while other tissues' stiffness is measured using ultrasound elastography[124,125].

Both pharmacological and non-pharmacological interventions are implemented to act on tissue stiffness (beta-blockers or ACE inhibitors[126] and nutritional management[127] for arterial stiffness, manual therapy for myofascial stiffness[128] or exercise[129-132]).

Despite exercise implementation to treat pathological conditions or to improve health, there is still a lack of knowledge regarding stiffness adaptations to different exercise modalities. Therefore, the aim of this narrative review is to elucidate changes in tissue stiffness according to types of longitudinal exercise intervention.

Methods and results

Eligible articles were manually searched on Pubmed, Scopus and Web of Science (September-October 2021). Keyword search was extended screening relevant full texts bibliography. No language or search period restrictions were applied. Only longitudinal-administered exercise interventions were considered while combined or acute administrations were not selected.

The effects of different exercise types have been presented according to the different targeted tissues (muscular, tendinous, MTU, blood vessels and peripheral nerves) and adaptations to each exercise type were investigated. The main outcomes are reported in Table 2.2 which also presents the strength of evidence (Grades of Recommendation Assessment, Development and Evaluation-GRADE[133]).

Table 2.2 Synthesis of the effects of exercise mode on tissue stiffness or associated pathological condition.

Tissue	**Resistance Training**	**Plyometric Training**	**Aerobic**	**Stretching**
Muscle	↕[c]	↑[c]	↕[c]	↓[cPF] ↕[cO]
MTU	↕[c]	/	/	↓[cP]
Tendons	↑[a]	↕[c]	/	↕[c]
Vessels	↓[bLL] ↑[bHL]	/	↓[a]	↓[b]
Nerves	/	/	/	↓[c]
Pathology				
Tendinopathy	↕[c]	/	/	/
Hypertension	↓[c]	/	↓[c]	↕[c]

↑ Increase; ↓ decrease; ↕ unclear; / No Evidence; MTU Muscle Tendon Unit; HL high load;
LL low load; P Passive stretching; PF plantar flexors; O Other muscles.
Strength of evidence: A: High; B: Moderate; C: Low or insufficient.

Discussion

Muscular Tissue

Muscular tissue stiffness adaptations were different according to exercise typology. In general, a lack of studies to clearly identify different stiffness changes according to exercise typology was found. In detail studies administering RT or AT only showed contradictory results, making it impossible to define a common adaptation of muscular stiffness. On the contrary, plyometric training or stretching interventions' effects on stiffness values showed consistency across studies. Plyometric training seems to increase muscle stiffness independently of the exercise regimen administered, while stretching seems to reduce plantar flexor muscle stiffness (but unclear results for those stretches applied to a different muscle).

Tendinous Tissue

RT interventions seem to be able to increase tendon stiffness in different healthy populations (young or older adults), with an early plateau in a non-linear adaptation. Tendon stiffness increases are observed independently of the type of sport performed in athletes when compared to controls[134,135] as well as in older adults[136,137], despite differences between eccentric or concentric contractions are still unclear[138]. Interestingly, when runners are considered, tendon stiffness increases may be involved in ameliorating running economy[139].
When considering pathological populations (tendinopathy) RT seems to induce a return of stiffness values to physiological levels.

Unfortunately, no information was retrieved regarding tendon stiffness adaptations after AT, while unclear adaptations were observed when plyometric or stretching strategies were implemented.

MTU

For this peculiar aspect, stiffness adaptations were only investigated by studies administering RT or stretching interventions, showing unclear results or a decrease in the MTU stiffness, respectively. These results, together with the unclear results of stretching on muscle stiffness, suggest that adaptations after this type of training may be mainly driven by MTU adaptations rather than by muscle stiffness alterations.

Blood Vessel

Only arterial stiffness has been investigated when considering the stiffness of cardiovascular components. RT seems to influence arterial stiffness according to exercise intensity. Higher intensity RT seems to increase arterial stiffness while lower intensity corresponds to arterial stiffness reductions. Both AT and stretching have shown a reduction of arterial stiffness. Although this information may be useful for pathological populations (hypertension), results must be interpreted with caution due to the lack of studies among these populations.

Peripheral nerves

Only stretching effects on peripheral nerve stiffness have been investigated which seems to decrease tissue stiffness. However, due to a lack of studies, conclusions could be premature and further investigations should be implemented to assess potential benefits on those pathological populations presenting altered (increased) nerve stiffness[140-144].

Final consideration and conclusions

When discussing tissue stiffness adaptations across studies, the difference in the assessment methods should be considered. Additionally, various exercise modalities may be administered, even when considering only a specific type of exercise (e.g. RT: eccentric, concentric or isometric contractions), which could limit the possibility of observing clear adaptations.

However, among healthy individuals, tissue stiffness adaptations seem to be present and may change according to exercise type and mode. RT effects on muscle stiffness are unclear, while plyometric interventions seem to increase this parameter. AT, on the contrary, seems to be able to reduce arterial stiffness, which seems to decrease also after low-intensity RT and stretching. The latter is also involved in stiffness reduction of MTU and peripheral nerves.

Pathological populations could benefit from exercise interventions after which a change in stiffness towards physiological levels could be present. AT and RT were able to reduce arterial stiffness among patients with hypertension.

2.3 "Positional transversal release is effective as stretching on range of movement, performance and balance: a cross-over study" *(Thomas, E., Ficarra, S., Scardina, A., Bellafiore, M., Palma, A., Maksimovic, N., Drid, P., & Bianco, A. (2022). Positional transversal release is effective as stretching on range of movement, performance and balance: a cross-over study. BMC Sports Science, Medicine and Rehabilitation, 14(1), 202. doi:10.1186/s13102-022-00599-8)*

Introduction

The following investigation is considered a training project, but its insights could be valuable for the pathological populations. This study investigated the effects of a new technique aimed at improving the ROM of a specific joint without effort for the participant and in a short amount of time. Its implementation has been tested in healthy individuals but its promising effects easily translate to application for pathological populations. This approach takes its foundation both from stretching and manual techniques.

Recently, stretching techniques received increased interest in a variety of context[145-149]. However, the main stretching application is during sport-specific training to increase the range of movement (ROM)[148,150]. This effect has been largely demonstrated and attributed to different adaptations which range from neural to structural[151]. Changes in stretch and pain tolerance are most frequently found regardless of intervention characteristics (type and length)[152,153]. Static (SS) and dynamic stretching, and proprioceptive neuromuscular facilitation (PNF) are those largely investigated[154]. When acutely applied, these typologies improve ROM in a time-dependent manner[149,155], regardless of stretch typology[149,156].

Stretching implementation has also been tested on balance outcomes. However, clear conclusions can not be drawn yet, due to contradictory results across studies[157-162].

Other strategies different from stretching have been implemented to improve ROM. Myofascial release[163] (MFR, which includes manual techniques[164]) has been implemented by physical therapists. MFR provide effective results on ROM improvement, comparable to those found after stretching[165-168]. MFRs do not involve movements of the potentially painful joints[166] and require a short time to be completed (2 minutes)[169]. Similar to stretching, neural adaptations have been considered to explain ROM improvements after MFR[164]. However, clear conclusions on these mechanisms are yet to be defined.

Contrary to stretching, MFRs seem not to alter ST, agility and balance[164,170-172]. These, along with the benefits on ROM, led MFRs to be implemented in sport and rehabilitation[171].
Here we proposed a hybrid technique with both SS and MFR peculiarities. This technique, called Positional Transversal Release (PTR), consists of a passive stretch of the muscle, accompanied by manual stimulation of the area in which muscle and tendon form the musculotendinous junction. We aim to examine and compare PRT to SS and PNF and determine its acute effects on ROM and balance in healthy participants.

Methods

A crossover research model, with four testing days, was adopted to compare the PTR to SS and PNF. One week was provided between sessions (wash-out period). Each testing session was 1 hour long. The protocol (n°65/2021) was approved by the Bioethical Committee of the Palermo University. Thirty-two participants (19 males and 13 females, 25.34±5.56 years; 68.77±12.54 Kg; 172±8.83 cm) took part in this study. The full study protocol was delivered to participants, without information about the research aim and hypothesis. Eligible individuals had to be healthy. Exclusion criteria were any injury, neurological or musculoskeletal condition which could have prevented the interventions from being delivered. Athletes were excluded.
Each participant completed the international physical activity questionnaire (IPAQ)[173], after reading and signing the informed consent. Habitual PA levels were asked to be maintained during the duration of the study. Only stretching activities were asked to be completely avoided. Four assessment sessions, one week apart, were attended by each participant. The first session was a control, while during the following visits a different intervention (PTR, PNF or SS), in a randomized order, was administered. Both lower limbs ROM through a passive straight leg raise test (PSLR) and dynamic balance performing a Y-balance test (YBT) were assessed. Each test was delivered three times: at baseline (T0), at the end of the stretching intervention (T1) and after a fifteen-minute rest (T2). The first assessment session served as a control in which no intervention was administered and a fifteen-minute rest between T0 and T1 was provided instead.
The Gyko Bluetooth inertial sensor (Microgate, Bolzano, Italy)[174] was used to measure hip flexion ROM when performing the PSLR test with participants lying supine on a medical bed. The device was strapped on the tested leg above the rotula (distal end of the femur). A passive lift of the tested fully extended leg to maximum reachable ROM, or at the participant's pain or discomfort was performed by the assessor[175].

The YBT was adopted to assess dynamic balance (Functional Movement Systems®, Chatham, USA)[176] calculating a "balance index" for each leg using leg length measure.

All interventions were delivered by the same expert kinesiologist and manual therapist and were all aimed to stretch the hamstring muscles. The SS intervention was administered for 8 sets of 30 seconds (30-s rest between sets) in a passive manner. Participants were sitting on a mat, maintaining the legs fully extended with the feet against a wall in a 90° dorsiflexion. Each participant was assisted in flexing the trunk over the hips by the investigator to the maximum ROM[177]. The PNF procedure was administered with the same assistance applied for SS, for 8 sets with 30 seconds of rest between sets. The 10 seconds stretches were followed by 6 seconds of contraction (isometric) against the operator's hands, followed by a rest of 4 seconds[178]. The 10+6+4 seconds were repeated 3 times during each set to obtain the same volume of stretch (compared to SS).

The PTR procedure was administered in 1 to 2 stimulations at the level of the proximal insertion of the hamstring muscles targeting the myotendinous junction (MTJ), below the ischial tuberosity. The participant was asked to lie prone on one edge of the medical bed, maintaining one leg hanging from it. The operator passively stretched the participant's hanging leg towards the floor (stretch phase) to a maximum comfortable ROM. The investigator positioned his knuckle on the hamstring's MTJ (medial margin)[179,180] and performed a rapid transversal movement. The investigator evaluated the hamstring's MTJ tension before and after the technique. One additional stimulation was provided if the tension was unchanged after the first administration. If tension was perceived to be reduced the PTR was then performed on the other leg with no additional stimulation. No more than two PRT techniques per side were delivered.

For the planned analysis 32 participants were required (calculated with G*Power version 3.1.9.4, ES=0.3, 1-β=0.80, α=0.05). Jamovi (The jamovi project (2021). jamovi (Version 1.8.0.1) [Computer Software]. Retrieved from https://www.jamovi.org) was used to analyse data. Normality was assessed using a Shapiro-Wilks test. ANOVA was performed for all variables to identify time x group interactions. To assess differences between the assessments in each group post-hoc Bonferroni corrections were performed. Graphs were built using GraphPad Prism8 (GraphPad Software, San Diego, CA).

Results

Thirty-two, moderately active, participants completed the study assessment sessions and were analysed.

Table 2.3 The effects of stretching on ROM, Jumping and Balance variables

	Control			SS			PNF			PTR			ANOVA
	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	
ROM (°)													
PSLR R	87.1 ± 22.6	87.8 ± 22.5	90.3 ± 23.8	90.1 ± 22.9	96.7 ± 22.1a	96.4 ± 20.8a	89.7 ± 21.7	99.3 ± 23.8a	98.2 ± 24.2a	91.1 ± 21.7	95.8 ± 23.1a	96.5 ± 24.3a	< 0.001*
PSLR L	86.7 ± 22.4	88.7 ± 22.3	89.4 ± 25.3	89.7 ± 21.1	94.6 ± 21.6a	95.6 ± 21.8a	90.8 ± 21.1	98.4 ± 24.8a	97.8 ± 25.1a	90.1 ± 22.9	95.1 ± 22.7a	95.6 ± 24.0a	0.017*
Performance (cm)													
SLJ	167.0 ± 34.5	168.7 ± 35.4	167.3 ± 36.4	171.9 ± 36.5	173.1 ± 37.7	175.0 ± 35.0	172.7 ± 35.1	167.5 ± 38.7	170.0 ± 36.0	172.0 ± 38.1	173.3 ± 37.4	174.0 ± 39.7	0.158
Balance (%)													
YBT R	93.2 ± 7.5	94.9 ± 7.7	96.0 ± 7.6	97.1 ± 6.6	97.4 ± 6.0	97.4 ± 6.5	96.9 ± 6.5	97.9 ± 7.0	98.0 ± 7.5	97.0 ± 6.7	97.6 ± 6.8	98.0 ± 6.8	0.678
YBT L	92.5 ± 9.2	94.4 ± 7.0	95.4 ± 7.8	96.5 ± 6.7	97.3 ± 6.7	97.4 ± 6.5	96.1 ± 6.9	97.0 ± 7.1	97.4 ± 6.8	97.0 ± 6.6	97.2 ± 6.9	97.4 ± 7.1	0.605

Data are presented as means ± SD; T0: baseline evaluation; T1: post-test assessment; T2: assessment 15 m post-test; PNF: proprioceptive neuromuscular facilitation; PTR: positional transversal release; ANOVA: group × time interaction

a Post-hoc difference with T0

*Significant $p < 0.05$

The comparison of T0 across the four assessment sessions (weeks) did not show significant differences for all tests (no differences between control and intervention sessions). Similarly, no significant differences were detected for the control sessions across T0-T1 and T2.

A significant time x group interaction was found for ROM: F=4.62, p=0.0002; F=2.64, p=0.017 for right and left leg, respectively. Post-hoc corrections revealed ROM increases between T0 and T1 for all interventions (SS, PNF and PTR). ROM measures were still increased at T2 after the interventions. No differences were detected between T1 and T2 for any intervention. No differences were found throughout interventions during the same time point (Table 2.3 and Figure 2.4).

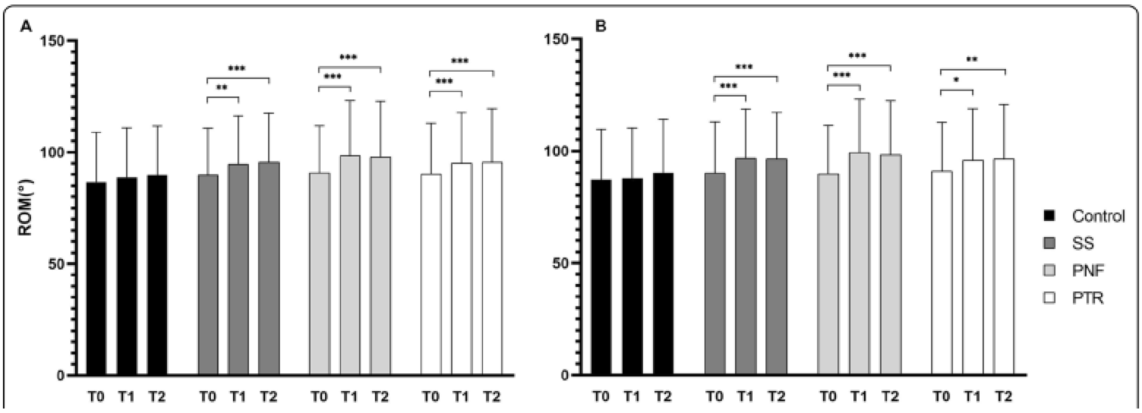

Figure 2.4 *ROM of the left (A) and right leg (B)*

No time x group interactions were observed for jump and balance performance: SLJ - F=1.53, p=0.158; YBT - Right: F=0.57, p=0.678; Left: F=0.68, p=0.605.

Discussion and conclusions

This study compared the acute effects of a PTR innovative technique to SS and PNF on lower limbs' ROM and dynamic balance. All interventions equally increased ROM, while no effects were noted for dynamic balance. Acute ROM increases consequently to stretching are commonly attributed to sensation reduction[151], which may either indicate a psychological alteration or the actual willingness to reach greater ROM, due to increased ROM expectations after stretches. Despite muscular receptor adaptations that have been suggested to justify ROM increases after MFR techniques and stretching[181], recent studies do not support these mechanisms, suggesting adaptations to pain sensation instead[182,183]. The PTR technique presents a stretching phase, which may target sensation, together with the mechanical transversal stimulus on the MTJ which is intended to stimulate muscular receptors. The latter stimulation aims to target both Pacini (with the vibration stimulus) and Ruffini receptors (using a transversal direction). In a review[184], the authors suggest the potential proprioceptive function of these receptors which may function as joint limit detectors. Although this may suggest that receptor alterations may increase ROM, there are no studies investigating this aspect. In our investigation, although the PNF intervention produced the greatest absolute increases when comparing T0 to T1, all the administered interventions (PNF, SS and PTR) were statistically comparable. These results are consistent with the Behm et al review in which different stretching techniques have been demonstrated to acutely increase ROM[149]. Longer bouts SS (>45s duration) have been observed to acutely reduce ST[160,185], which could consequently balance ability[186,187]. Different results also arise when studying PNF. Increases in both dynamic and static balance have been observed[188-192]. Results in contrast to ours since none of our interventions affected balance. However, these studies applied PNF to multiple muscles which may have improved their ST during contraction phases, therefore increasing balance[193]. Indeed, when PNF is applied to a single muscle group (hamstrings), no increase in balance is observed[194]. No effects on balance were found after the PTR technique, consistent with those studies applying MFT techniques[172,195]. Our protocol confirms the effects on ROM of PTR and is in line with previous research on balance. ROM improvements after PTR in healthy active participants are promising considering the similar effects with SS and PNF and the short time required to be administered. Future implementations will be to evaluate the feasibility and effectiveness of the PTR for cancer patients and survivors. The advantage would be to have a quick form of therapy which does not cause pain that might occur during longer treatments. Furthermore it might help cancer patients or survivors whose ROM is impaired but who are unable to perform stretching exercises.

Chapter III - Exercise Oncology research

3.0 Chapter overview

The content of this chapter is represented by the projects carried out in the field of exercise oncology. Two published articles focusing on female BC, which is the most commonly diagnosed cancer, are first summarised. The first systematic review aimed to update the current evidence regarding exercise interventions for BCP and BCS. The second is focused on a specific BC population (Hispanic or Latina) which usually faces worse cardiovascular consequences compared to white non-Hispanic women. Two more projects which were presented during conferences are then presented focusing on a general population of cancer survivors (original investigation) and LC patients and survivors (systematic review and meta-analysis). Finally, considering the potential benefits of RT intervention observed across the studies in this chapter, one more projects is discussed regarding this specific type of training. In detail, the systematic review was carried out to identify the effects of RT on sleep outcomes. The chapter concludes with final considerations extracted from the reported studies with a brief overview of future potential research implementations.

List of publications/projects discussed within Chapter III:

-3.1 Ficarra, S., Thomas, E., Bianco, A., Gentile, A., Thaller, P., Grassadonio, F., Papakonstantinou, S., Schulz, T., Olson, N., Martin, A., Wagner, C., Nordström, A., & Hofmann, H. (2022). Impact of exercise interventions on physical fitness in breast cancer patients and survivors: a systematic review. Breast Cancer. doi:10.1007/s12282-022-01347-z.

-3.2 Gonzalo-Encabo, P., Sami, N., Wilson, R. L., Kang, D.-W., Ficarra, S., & Dieli-Conwright, C. M. (2023). Exercise as Medicine in Cardio-Oncology: Reducing Health Disparities in Hispanic and Latina Breast Cancer Survivors. Current Oncology Reports. doi:10.1007/s11912-023-01446-w.

-3.3 Ficarra, S., Wilson, R. L., Encabo, P. G., Kang, D.-W., Normann, A. J., Christopher, C. N., & Dieli-Conwright, C. M. (2023). Circuit, Interval-based Aerobic And Resistance Exercise Improves Quality Of Life Among Cancer Survivors: 2852. Paper presented at the ACSM 2023 Annual Meeting and World Congress, Denver, Colorado.

-3.4 Ficarra, S., Wilson, R. L., Encabo, P. G., Kang, D.-W., Normann, A. J., Christopher, C. N., Lopez, P., Thomas, E., Bianco, A., & Dieli-Conwright, C. M. (2023). Effects of exercise intervention on physical fitness outcomes in individuals diagnosed with lung cancer: Preliminary results of a systematic review. Paper presented at the XIV National Congress SISMES, Naples, Italy.

-3.5 Di Bartolo, L., Ficarra, S., Galioto, M., Jiménez-Pavón, D., Tavares, P., Pusa, S., Vantarakis, A., Asimakopoulou, Z., Thaller, J., Seminara, D., Maric, D., Lo Mauro, M., Lavanco, G., & Bianco, A. (2023). Knowledge-based implementation of resistance training for sleep health among cancer patients and survivors living within the Mediterranean area: Preliminary results of the OACCUs project's systematic review. Paper presented at the 2nd Annual Experiential Conference with American, International and Greek Scholars, Rethymno, Crete, Greece.

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

Introduction

As we previously introduced, female BC is a world health concern due to its high incidence[10]. Although therapies and early detection increased the chances to survive[58,59], short and long-term side effects can impair HRQoL[32,53,55-57]. Between symptoms, F is often experienced among all cancer patients[29,30,196]. Impairments of CRF and ST levels, are frequent and may exacerbate other symptoms[32], as well as compromising cardiovascular health leading to cardiac events[197,198]. All these factors may contribute to BCP and BC survivors (S), vicious cycle in which symptoms, side effects and deconditioning can aggravate each other compromising HRQoL and overall health[30,61,62].

A single approach to reverse this trend is usually inadequate, and multicomponent strategies are usually implemented including for example: psychological support, behavioural changes, physical therapy, massages, and acupuncture with or without exercise therapy[199]. Exercise has been found to be particularly successful in either BC prevention or mitigating deconditioning in BCP and BCS[12,63-69]. A meta-analysis, conducted in 2006, showed the benefit of exercise on physical functioning and HRQoL[63]. However, due to the scientific progress in the field of exercise oncology for BC and BCS, we designed a systematic review to determine if isolated exercise protocols can affect variables of physical fitness and symptoms in BCP and BCS, including studies published in the last two decades.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[200] was followed during the production of this review. PROSPERO Protocol Reg.ID: CRD42021237917.

Search strategy

Peer-reviewed articles published between January 2000 and November 2020 were searched on PubMed and Scopus. Studies investigating the effects of exercise interventions among BCP and BCS were screened. The identified keywords selected for the final search were: “breast cancer”, “breast neoplasm”; “exercise” and “physical activity”. Additional eligible full-texts were searched within relevant studies’ reference lists. Excel (Microsoft Corp., Redmond, WA) was used to assess all titles retrieved after the search. After assessing title eligibility, duplicates were deleted. Consequently, the abstract and full-text screenings were conducted by two independent review authors. To resolve any conflicting judgment on the inclusion of the records a third author was involved.

The inclusion and exclusion criteria listed below were used during the screening.

-Patients – Studies recruiting female BCP undergoing treatments or BCS < 5 years from treatment completion (excluding hormonal therapy[22]) were selected. Other cancer diagnoses and male patients were excluded. Comorbidities different from other cancers were considered eligible.

-Intervention – Interventions consisting of only exercise equal to or longer than 4 weeks were included. Only studies with clear exercise interventions without any other approach were considered eligible, while studies with physical therapy, and psychological or nutritional support were excluded. Studies with stretching were also excluded, due to its potential effect on cardiovascular outcomes[145]. Studies in which the exercise protocol was not standardized (e.g. personal training and/or tailored interventions) were excluded.

-Comparators – Usual care and non-exercising control groups were considered as comparators.

-Outcomes – The following variables were included for the aim of this review: 1)CRF[201]; 2)ST[202]; 3)F symptoms (F)[29,30,196]; and 4)HRQoL[203]. Only studies with objectively assessed available data (pre and post-exercise) on CRF, ST, F and HRQoL were included.

-Studies Design – Only RCTs were included.

Study record

Studies were grouped into two categories according to the participants: 1) BCP and 2) BCS. Four subgroups according to exercise typology were created: 1)AT, 2) RT, 3) combined AT and RT (COMB) and 4) Pilates and Yoga interventions. Studies' tables, text, and graphs were carefully screened to extract pre- and post-exercise data. For graphs, data extraction was carried out using WebPlotDigitizer (version 4.2, San Francisco, CA). All data were summarized in Word tables and descriptive statistics were computed using Excel.

Risk of Bias assessment

Risk of bias (RoB) was assessed using the Cochrane RoB 2 tool for RCTs[204]. Overall study judgments were provided as follows: studies with 1 "Some Concerns" judgement were judged at "Low RoB"; studies with 2 or more "Some Concerns" judgements were considered as "Some Concerns" overall; studies with 1 domain judged at "High RoB" were judged at "High RoB". Two authors carried out the RoB assessment and negotiated disagreements.

Data Processing

Mean and std dv were used to represent data. Differences between baseline and post-intervention were extracted and reported in tables. Post-intervention percentage differences from baseline were calculated. Post-test data were calculated when studies only reported pre-tests and variations. Comparators results were extracted, but only percentage differences were reported. Mean percentage difference was obtained for each included outcome for both IGs (Intervention Groups) and CGs.

Results

The search retrieved 16891 studies. The title screening left 2017 studies of which 1568 were removed as duplicates. A total of 449 studies were screened for eligibility. The abstract screening left 337 full texts to be assessed for eligibility. Twenty-two studies were finally included (Fig. 3.0). Studies characteristics are presented in Table 3.1.

Risk of Bias

The RoB judgements were predominantly "some concerns" mostly due to the lack of additional documents available. F and HRQoL exhibited a worse RoB judgement due to the self-reported nature of the results and a lack of additional documentation (when compared to CRF and ST). Only three studies were deemed to have "high RoB"[205-207].

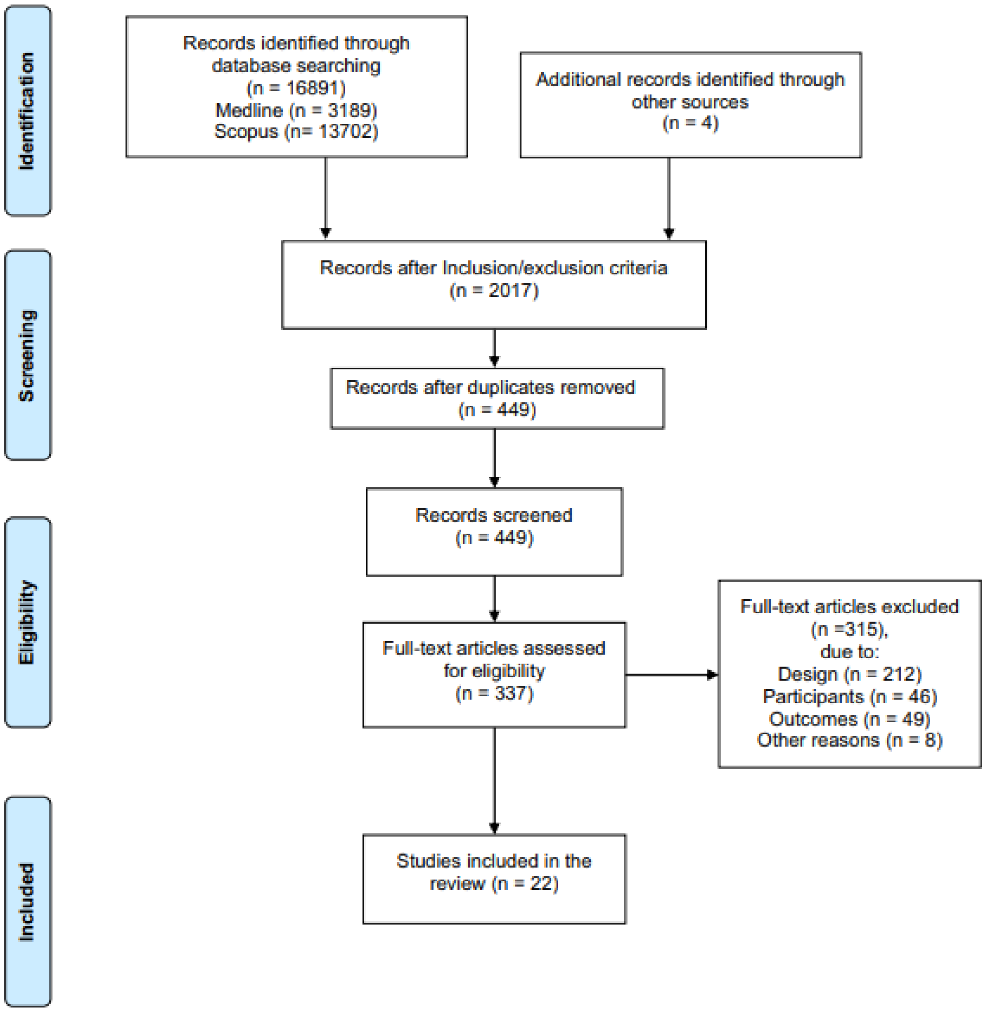

Fig 3.0 *Flow diagram of the included studies*

Table 3.1 Studies Characteristics.

Author -Year	Sample Size (n)	Mean Age (y)	Intervention typology	Weeks (n)	Frequency (n/w)	Intensity (%)	Outcomes	Assessment tools
In Therapy (ADJ)								
Cešeiko R. et al 2019[208]	27	RT 48.2±6.7 CG 49.0±8.0	RT[a]	12	2	85–90% 1RM	ST, F, QoL	Leg press 1RM test; EORTC QLQ-C30/BR23.
Cešeiko R. et al 2020[209]	27	49.0±7.0	RT[a]	12	2	85–90% 1RM	CRF	6MWT.
Courneya K. S. et al 2013[210]	298	50.0±8.9	A – STAN[a] A – HIGH[a] COMB[c]	16	3	A: 55-75% of VO_2peak RT: 60%-75% 1RM	CRF, ST, F, QoL	Maximal incremental exercise protocol; 10RM test; FACIT-F; SF-36.
Schmidt M. E. et al 2015[211]	49	52.2±9.9	RT[a]	12	2	60–80% 1RM	F, QoL.	FAQ; EORTC QLQ-C30 / BR-23.
Schmidt T. et al 2015[207]	67	RT 53.0±2.6 A 56.0±0.2 CG 54.0±1.2	A[a] - RT[a]	12	2	RT: 50% h1RM	F, QoL.	MFI-20; EORTC QLQ C-30 / BR-23.
Schwartz A. L. et al 2007[212]	66	A 48.3±12.6 RT 50.1±8.7 CG 46.3±9.8	A[b] – RT[b]	24	4	n/a	CRF, ST	12MWT; Leg extension 1RM test.
Segal R. et al 2001[213]	123	A 51.4±8.7 A 51.0±8.7 CG 50.3±8.7	A[c] - A[b]	26	5	50-60% VO_2max	CRF, QoL	mCAFT; SF-36.
Steindorf K. et al 2014[214]	77	55.2±9.5	RT[a]	12	2	60%–80% 1RM	F, QoL	FAQ; EORTC QLQ C-30/ BR-23.
Tot/mean	**734**	50.9±7.4	-	16	3	A 60%VO2max - RT 72%1RM	-	-
Survivors:								
Campbell K.L. et al 2018[215]	19	52.4±6.2	A[c]	24	4	60%-80% HRR	CRF, F	Graded maximal treadmill exercise test; FACT-F.
Courneya K. S. et al 2003[216]	52	59.0±6.0	A[a]	15	3	70-75% VO_2max	CRF, F, QoL	Incremental exercise protocol on a cycle ergometer; FACIT-F; FACT-G/B.
Dieli-Conwright C. M. et al 2018[217]	91	53.5±10.4	COMB[a]	16	3	RT: 60% and 80% 1-RM for upper and lower extremity, respectively A: 65–80% HRmax	CRF, ST, F, QoL	Single-stage submaximal treadmill test; 10RM test; BFI; FACT-G/B; SF-36.
Hagstrom A. D. et al 2016[206]	39	51.9±8.8	RT[a]	16	3	n/a	ST, F, QoL	Leg press 1RM test; FACIT-F; FACT-G.
Kiecolt-Glaser J. K. et al 2014[218]	186	51.6±9.2	Yoga[c]	12	2	n/a	F	MFSI-SF.
Murtezani A. et al 2014[219]	62	52.0±11.0	A[a]	10	3	50-75% HRR	CRF, QoL	12MWT; FACT-G/B.
Nikander R. et al 2007[220]	28	A 52.5±6.4 CG 51.3±7.3	A[c]	12	3-4	n/a	CRF, ST	2-km walk test; Isometric Leg Extension.
Nikander R. et al 2012[221]	67	COMB 53.7±6.8 CG 52.6±7.1	COMB[c]	48	3-4	n/a	CRF, ST	2-km walk test; Isometric Leg Extension.

Northey J. M. et al 2019[222]	17	62.9±7.8	A – HIIT[a] A – MOD[a]	12	3	A(Moderate): 55–65% Peak Power A(HIIT): 105% Peak Power (90%HRmax) and self-selected active recovery	CRF	Maximal cycle ergometer incremental test.
Odynets T. et al 2019[223]	70	Pilates 59.4±1.2 Yoga 59.1±1.4	Pilates[a] - Yoga[a]	48	3	Pilates: 45%-60% HRR	QoL	FACT-B.
Saarto T. et al 2012[205]	500	A 52.3 (36-68) CG 52.4 (35-68)	A[c]	48	3-4	n/a	F, QoL	FACIT-F; EORTC QLQ C-30 / BR-23.
Schmidt T. et al 2012[224]	15	58.0±8.4	RT[a]	24	1	>50% h1RM	F, QoL	EORTC QLQ-C30 / BR-23.
Scott J. M. et al 2020[225]	117	LET 59.0±9.0 NLET 58.0±9.0	A – LET[a] A – NLET[a]	16	3-4	70% VO_2peak A(linear) 55% - >95% VO_2peak A(nonlinear)	CRF, F, QoL	symptom-limited CPET; FACIT-F; FACT-G/B.
Stan D. L. et al 2016[226]	16	63.0±9.3	RT[b]	12	3-5	n/a	F, QoL	MFSI-SF; FACT-G/B.
Tot/mean	**1279**	55.7±7.0	-	22	3	A 69%VO2max/HRR - RT 60%1RM	-	-

ADJ= Adjuvant therapy; CG= Control Group; A= Aerobic Training; RT= Resistance Training; COMB= Combined aerobic and resistance training; STAN= experimental group that follow the Physical Activity Guidelines for Americans endorsed for cancer survivors by the American College of Sports Medicine and the American Cancer Society (75min/week of vigorous aerobic exercise on 3day/week); HIGH= experimental group that follow double the STAN protocol (150min/week of vigorous aerobic exercise on 3day/week); HIIT= High Intensity Interval Training; MOD= Moderate intensity continuous aerobic exercise; LET= Linear intensity Exercise Training; NLET= Nonlinear intensity Exercise Training; 1/10RM/h1RM= One/ten repetition/s maximum/hypothetical one repetition maximum; VO_2peak/max= Peak of Oxygen Consumption/Maximal Oxygen Consumption; RPE= Rate of Perceived Exertion (based on Borg Scale); HRR= Heart Rate Reserve; HRmax= Maximal Heart Rate; CRF= Cardiorespiratory Fitness; ST= Strength; F= Fatigue; QoL= Quality of Life; 6/12MWT= 6/12 Minutes Walking Test; mCAFT= modified Canadian Aerobic Fitness Test; CPET=Cardiopulmonary Exercise Test; FACIT-F= Functional Assessment of Chronic Illness Therapy – Fatigue; FAQ= Fatigue Assessment Questionnaire; MFI-20= Multidimensional Fatigue Inventory with 20 questions; MFSI-SF= Multidimensional Fatigue Syndrome Inventory-Short Form; BFI= Brief Fatigue Inventory; EORTC QLQ-C30/BR23= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30/BR23 Modules; SF-36= Short Form Health Survey with 36 items; FACT-G/B= Functional Assessment of Cancer Treatment – General/Breast; [a] =Supervised Intervention; [b] =Unsupervised Intervention; [c] =Supervised and Unsupervised Intervention.

A total of 734 BCP and 1279 BCS (2013 participants) were included in this review. Participants' mean ages were 50.9±7.41 and 55.7±7.04 years for BCP and BCS, respectively. Eight included studies recruited BCP[207-214] and 14 studies BCS[205,206,215-226].

Studies including BCP (6/8) reported high-to very high adherence (79.9%). Only two studies had attendance lower than 75% (71% and 71.5%)[211,213]. The influence of exercise type on adherence and/or attendance rates could not be determined due to the limited number of studies.

Studies recruiting BCS had high rates of adherence (83.6%) with only two studies presenting values lower than 80% (76% and 75.4%[218,221]) and only one study showing 62% attendance rate[205]. Intervention typology did not influence adherence in BCS studies. Also, weekly exercise frequency and intensity in both populations did not influence adherence.

However, fully supervised interventions seem to have higher adherence[206-211,214,216,217,219,222-225] when compared to partially supervised/unsupervised exercise interventions[205,210,212,213,215,218,220,221,226] (supervised vs. unsupervised: 83.3% vs. 71.8% mean BCP adherence; 85.5% vs. 79.2% mean BCS adherence).

Attrition rate above 20% was reported only in two studies both including BCS[224,226]. The majority of the studies reported attrition rate below 10%.

BCP

The 8 included studies with BCP, were conducted during the administration of adjuvant therapy[207-214]. Duration and frequency of exercise interventions were 16 (12-26) weeks and 3 (2-5) sessions/week. Mean exercise intensity for AT was 60% of the maximal oxygen consumption (VO_2max) and 72% of 1RM for RT. Four studies administered A interventions[207,210,212,213], 6 studies RT interventions[207-209,211,212,214], and 2 studies delivered both A and RT experimental intervention groups[207,212]. COMB intervention was administered by only one study[210]. To be noted that, in the following paragraph, values regarding CRF, ST and HRQoL represent improvements by a percentage increase(+), while F symptoms represent improvements when a percentage decrease(-).

Aerobic exercise interventions were implemented through home-based walking/jogging activities[212,213] or using different AT equipment[207,210].

CRF[209,210,213], ST[210,212], F[207,210] and HRQoL[207,210,213], showed a mean difference of +2.1% , +9.7%, +17.1% and +4%, respectively.

Of the six studies administering RT interventions[207-209,211,212,214] three studies implemented multiple exercises (averaging 2-3sets, 8-12repetitions at 50-80%1RM)[207,211,214], while the remaining administered just one exercise (4 sets, 4 repetitions at 85-90% 1RM)[208,209] or used resistance bands (2 sets, 8-10 reps for each exercise) in unsupervised setting[212].

CRF[209,212], ST[208,212], F[207,208,211,214] and HRQoL[207,208,211,214] showed a mean difference of +6.4%, +21.9%, +5.9% and +12.1%, respectively.

Only Courneya et al delivered a COMB intervetion[210] reporting changes of -13.1%, +9.9%, +14.3% and -7.3% for CRF, ST, F and HRQoL, respectively.

BCS

A total of 14 studies in BCS were included. Duration and frequency were 22 (10-48) weeks and 3 (1-4) sessions/week. Mean intensity was 69% VO_2max/Heart rate reserve and 60% 1RM, for A and RT interventions, respectively. Seven studies administered A interventions[205,215,216,219,220,222,225], 3 applied RT[206,224,226], and 2 studies with COMB interventions[217,221]. Two more studies implementing Yoga and Pilates were included[218,223].

Four studies used several aerobic training equipment[216,219,222,225]. The remaining two investigations administered aerobic step, rope-jumping and skate-jumping exercises with walking/cycling[205,220]. CRF[215,216,219,220,222,225], ST[220], F[205,215,216,225] and HRQoL[205,216,219,225] showed a mean difference of +9%, +4.7%, -15.5% and +6.8% after AT, respectively.

Two studies presented both machine-based and free-weight exercises[206] or only machines[224]. The remaining study used home-based resistance bands approach[226]. CRF was not assessed after RT interventions. Hagstrom et al measured ST showing improvements of +33.9%[206]. All RT studies assessed F and HRQoL showing a mean decrease of -39.4% for F and a mean increase of +10.5% for HRQoL[206,224,226].

Two studies applied COMB interventions[217,221]. The first delivered two A sessions and one RT session/week (in a circuit training method)[217]. In the second study, participants performed aerobic steps, rope-jumping, and skate-jumping with additional walking/cycling (AT) and free-weight exercises for upper limbs (RT)[221]. Both studies measured CRF and ST[217,221] showing a +27.6% mean CRF and a +42.6% mean ST increase. F was assessed by Dieli-Conwright et al only, showing a -59.2% mean reduction[217]. HRQoL mean improvement was +13.1%.

Only two studies with Yoga or Pilates were inclueded[218,223]. The study of Kiecolt-Glaser et al. showed a reduced F (-56.6% and -40.5% in both IG and CG, respectively) after 12 weeks of Yoga[218]. Odynets et al showed improvements in HRQoL after one year (3 sessions/week) of Pilates or Yoga (+44.5% and +38.1% in the Pilates and Yoga group, respectively)[223].

Discussion

Exercise among BCP undergoing adjuvant therapy seems to attenuate decreases in fitness and the symptoms exacerbation (usually showed by CGs). Interestingly, RT protocols, showed only minor increases of F (+5.95%) which were higher after all other protocols, and improvements of the other variables (by +6.4%, +21.9% and +12.1%, for CRF, ST and HRQoL, respectively). The role of COMB protocols among BCP was not clear since only one study with COMB intervention was included.

BCS revealed improvements in physical fitness in IGs, while no changes were observed in the CGs. COMB and RT for BCS showed encouraging data, with F decreases and CRF, ST and HRQoL improvements. RT interventions yielded higher percentage increases in HRQoL and ST as well as a substantial F reduction than A intervention changes. Promising results were also observed after Pilates and Yoga, but more studies are needed.

Cardiorespiratory Fitness

CRF is a useful indicator to understand side effects and sedentary behaviours' impact on health[227]. We detected positive results for both BCP and BCS on CRF after exercise. However, when prescribing exercise it is crucial to consider that CRF outcomes can differ according to different chemotherapy regimens[210,228]. Exercise specialists should be aware of and consider chemotherapy regimens during the design of the intervention[210]. Our overall results are consistent with Maginador et al's review, in which moderate A interventions led to no effects on CRF, while significant improvements were observed after high-intensity A for BCP during chemotherapy[227]. HIIT seems also to be more efficient than moderate intensity AT[222] among BCS.

Strength

When ST is lost functionality is reduced and patients require more help resulting in a reduction of their independence, leading to a decrease in HRQoL[229]. Assessing and improving ST seems crucial for the design of exercise interventions which can ameliorate patients' conditions in clinical trials and in practice[230,231].

ST improved consistently in BCP, independently of exercise type. Interestingly, the ST improvements observed by Cešeiko et al. in the 1RM strength test (+19.1%) were obtained after 12 weeks of maximal strength training (MST - 85-90%1RM) on a horizontal dynamic leg press[208]. This study demonstrated that MSTs are feasible, safe, and effective among BCP when performed in controlled settings[208]. However, higher percentage improvements were found by Schwartz et al. (+22.8-24.7%), which was likely due to the longer intervention and higher frequency[212].

There is a lack of studies measuring ST after A and RT among BCS. RT and COMB interventions demonstrated higher improvements (+33.9% and +42.6% in RT and COMB, respectively) than AT (+4.7%), but more evidence are needed to corroborate these results. Our results are consistent with those reported in Montaño-Rojas et al's review and in Strasser et al's review in which ST increases were found in both BCS and BCP populations[232,233].

Fatigue

F is one of the factors that could initiate the vicious cycle between symptoms, side effects, and a sedentary lifestyle that contributes to patients' deconditioning status[30]. According to a review by Kessels et al among cancer survivors, exercise can have both direct effects on F, counteracting deconditioning and indirect effects mitigating F-associated conditions (sleep disorders, pain, anxiety and depression)[234]. AT exercise (focusing on patient adherence) showed greater effects on F when compared with other and low-adherence studies[234]. These results are in contrast with ours showing that RT and COMB led to higher percentage reductions in F among BCP and BCS. However, the review by Kessels et al did not independently evaluate RT[234].

Two included studies implemented similar RT interventions[211,214]. Outcomes within these studies are mainly reported in the physical dimension of F (no significant effects on affective and cognitive F were found)[211,214]. These results are confirmed by van Vulpen J.K. et al's review among BCP during adjuvant treatment[34]. Thus, exercise alone might not be sufficient to improve other F dimensions among BCP.

All studies among BCS observed F reductions probably due to absent treatment's side effects. Again, RT interventions appeared to be more efficient on F levels, consistent with the review of systematic reviews by Jiang et al who reported that RT and AT are useful on F[235].

Health-Related Quality of life

Improving physical fitness and symptoms could improve HRQoL[229]. HRQoL questionnaires in exercise oncology studies usually include questions on tiredness, sleep/resting necessities, and ability to perform simple to complex PA tasks[106,236,237]. HRQoL assessment is essential to understand whether physiological improvements reflect on daily life. All of the studies on BCP included in this review showed HRQoL improvements, except for Courneya et al[210].

All the included studies among BCS showed HRQoL improvements in IGs while decreases were found in CGs. The only exception was Saarto T. et al's study ("high RoB" judgement)[205]. In the meta-analysis by Zhu et al similar results to ours were found. However, a broad range of interventions were presented making it challenging to identify the impact of isolated exercise stretegies[238].

Our results indicate that exercise has positive effects on HRQoL for both BCP and BCS. Two Cochrane reviews among BCP during and after adjuvant therapy, respectively[239,240] analysed the effect of exercise on HRQoL. The first found that exercise led to small, if any improvements, in HRQoL during adjuvant therapy and improved cancer site-specific HRQoL[239]. The second showed small-to-moderate improvements on HRQoL[240]. Also the review from Gebruers et al assessed exercise effects on HRQoL among BCP and, similarly to our results, highlighted that RT and COMB were able to better manage F and improve fitness levels, while HRQoL was the least affected variable[67].

This review presents some limitations. Although we aimed to understand the isolated effect of exercise is not possible to control patients daily avoiding biases due to deviation from the intervention. However, interventions were mostly supervised, reducing this possibility. Moreover, the studies usually involve patients without exercise limitations which may lead to the inclusion of patients with a higher physical fitness level.

Another limitation of this study was the impossibility to include studies among BCP undergoing neoadjuvant treatment, or among patients with lymphedema and aromatase inhibitor arthralgia. Likely, in these cases, BCP require multidimensional approaches[241,242]. No studies with metastatic BCP were included. However, the review by Singh et al showed that exercise is safe and effective for stage II+ local, regional and distant BCP patients[69].

Despite the limitations, we found similar results compared to the review of McNeely M.L. et al[63]. In our review, we expanded upon previous works by including results pertaining to both BCS and BCP for each intervention type, obtaining a higher number of included trials. However, studies with strong designs and larger samples are required to better identify exercise guidelines.

In conclusion, structured exercise interventions seem useful for preventing cancer symptoms exacerbation and physical fitness and health-related quality of life deterioration among breast cancer patients during adjuvant therapy. Exercise can also lower fatigue improving cardiorespiratory fitness, strength, and health-related quality of life in breast cancer survivors. Our results propose resistance training and combined interventions for positive modifications of the evaluated outcomes. However, exercise should be delivered and supervised by trained exercise experts. Breast cancer knowledge is essential for trainers in the design of individualized exercise procedures.

3.2 "Exercise as medicine in cardio-oncology: reducing health disparities in Hispanic and Latina breast cancer survivors" *(Gonzalo-Encabo, P., Sami, N., Wilson, R. L., Kang, D.-W., Ficarra, S., & Dieli-Conwright, C. M. (2023). Exercise as Medicine in Cardio-Oncology: Reducing Health Disparities in Hispanic and Latina Breast Cancer Survivors. Current Oncology Reports. doi:10.1007/s11912-023-01446-w)*

Introduction

This study was carried out to address cardiovascular concerns for Hispanic and Latina BCS. BCS have, in general, higher cardiovascular risk compared to non-cancer populations due to treatment side effects[70]. Cardiovascular diseases have been demonstrated to be the second cause of mortality among this population[70,71]. Between BCS, Hispanic and Latina women are those with a higher risk of incurring cardiovascular diseases with life-threatening consequences[243-246]. Exercise has been demonstrated to be efficient in cardiovascular risk reduction and, although its benefits have been tested among BCS, Hispanic and Latina populations have not been fully studied yet. Moreover, this population presents lower PA levels, compared to non-Hispanic women[247]. Thus, a brief literature review to highlight the effects of exercise among Hispanic and Latina populations on cardiovascular outcomes was carried out. Preliminary original data on this matter are also presented.

Literature review

Relevant publications were searched on PubMed and Web of Science with the following keywords: ((breast neoplasms[MeSH Terms]) OR (breast cancer)) AND ((hispanic) OR (latino) OR (latina) OR (Hispanic or Latino[MeSH Terms])) AND ((exercise[MeSH Terms]) OR (exercise) OR (physical activity)); ALL=("breast cancer" OR "breast neoplasm"); ALL=("hispanic" OR "latino" OR "latina") AND ALL=("exercise" OR "physical activity"). A total of 444 records were identified (179 – PubMed, 265 – Web of Science). Eligible studies were those assessing exercise effects on cardiovascular outcomes among Hispanic and Latina BCS.

Only 5 studies met our inclusion criteria and were summarized in **Table 3.2**. Studies included Hispanic and Latina patients (average 90.4% of the sample), 50.9±24.3 years and a mean BMI of 31.7±6.6 kg/m^2. Exercise interventions were mostly COMB interventions, administered three times a week for 16 weeks. Overall, studies have implemented surrogate outcomes to assess cardiovascular risk, showing a lack of evidence regarding exercise intervention among the investigated population. In detail, metabolic biomarkers showed no differences between the EX and the CG[248,249]. CRF changes were contradictory across studies with either no changes[249-251] or improvements after exercise[252,253]. Body composition changes also appeared to be conflicting with reductions in body weight[249] or no weight and body composition variations[248].

This review emphasizes the need for exercise oncology to focus on Hispanic and Latina BCS with regard to cardiovascular risk.

Table 3.2 Studies Characteristics and Results Summary

Author - Year	Design	Sample (N)	% of H/L	Treatment phase	Stage	Mean Age (y)	Mean BMI (kg*m^{-2})	PA Levels	Intervention Type	Study length (weeks)	Freq. (n/w)	Intensity (%)	Results CVD-related outcomes
Greenlee et al. 2012	RCT	38	79	>6 months post-treatment	0–IIIa	50.7±68.9	33.2±5.9	Sedentary	COMB (circuit)	24	3	<60% - 70–75% of HRmax (AT)	No changes in CRF (VO_2max). Significant weight loss in IG vs CG (no significant diff. by ethnicity). No changes in metabolic biomarkers (cholesterol, TGs, glucose, hsCRP, insulin, total ghrelin, adiponectin, IGF, HOMA-IR)
Hughes et al. 2008	Single arm	25	100	>6 months post-treatment	I-IV	50±8.4	n/a	n/a	COMB	10	n/a	n/a	Significant increase in CRF (VO_2max)
Lee et al. 2019 Lee et al. 2021	RCT	30	73	On chemotherapy	I-III	46.9±9.8	31.0±7.5	<30 min of PA/week	HIIT	8	3	10%/90% PPO (60rpm)	IG increased in PPO and VO_2max while CG significantly decreased both PPO and VO_2max. No timexgroup interaction. CRF (6MWT) significantly increased in IG vs CG.
Ortiz et al. 2021	RCT	89	100	>3 months post-treatment	I-IV	55.4±10	31±6.5	Not active (ACSM definition)	COMB	16	2	n/a	CRF (6MWT) increased in IG, without significant differences between IG and CG.
Owens et al. 2009	Quasi-experimental	13	100	During and after chemotherapy	I-II	51.5#	n/a	Not exercising	COMB	24	3	n/a	No significant changes in weight, BMI, % body fat and fasting glucose.

ACSM = American College of Sports Medicine; BMI = Body Mass Index; CG = Control Group; COMB = Combined Aerobic and Resistance exercise; CRF= Cardiorespiratory Fitness; Freq. = Frequency; F-U: follow-up; H/L = Hispanic/Latina; HIIT = High Intensity Interval Training; HOMA-IR = homeostasis model assessment-estimated insulin resistance; HRmax = Maximum Heart Rate; IG = Intervention Group; IGF = Insulin-like Growth Factor; n/a = not available; PA = Physical Activity; PF = Physical Fitness; PPO = Peak Power Output; RCT = Randomized Controlled Trial; VO_2max = Maximal Oxygen Consumption. #calculated based on age range.

Original investigation

A recent study implemented using the Framingham Risk Score (FRS) reported that BCS have a predicted 10-year risk 44-77% higher compared to healthy women[254]. To address the abovementioned literature gap we assessed the FRS and the 10-year risk of cardiovascular disease (CVD) in a subsample from our previous trial[255]. The FRS is a cardiovascular risk score calculated by combining six parameters: age, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), SBP, diabetes, and smoking status[256].

This RCT assessed the effects of a supervised COMB exercise intervention. The FRS was assessed at baseline and at post-test (4 months). BCS <6 months out of treatment, non-smokers, inactive, overweight or obese were recruited. Participants were randomized to exercise or usual care. The exercise intervention included two COMB and one AT-only session: RT performed at 60-80% of 1-RM and AT at 65%-80% of HRmax. The 6 parameters of the FRS were evaluated: age, SBP, LDL, HDL, presence of diabetes, and smoking status. Within-group differences were estimated using general linear models repeated-measures analyses of variance. Between-group differences were calculated with a mixed-model repeated-measures analysis. Covariates were selected a priori and included age, treatment, surgery, medication use, BMI, and caloric intake.

Fifty-six Hispanic and/or Latina BCS (EX= 29; UC=27) were selected for the secondary analyses. On average BCS were 46±10 years old, and obese (34.9±6.2 kg/m^2). The menopausal status percentage of participants was balanced. A significant reduction of the FRS was observed in the EX compared to UC ($P < 0.001$), which corresponds to a 10-year risk of CVD significant reduction (15%; $P < 0.001$).

Our 16-week COMB intervention seems efficient in reducing the FRS and the 10-year risk of CVD among Hispanic and Latina BCS who were overweight or obese, ameliorating FRS components (reducing SBP, LDL, presence of diabetes and increasing HDL). The significant FRS and predicted 10-year risk of CVD, among Hispanic and Latina BCS, appears to be higher compared to those reductions found in racially/ethnically diverse BCS[255]. However, the prevalence of diabetes and the lower PA levels in our subsample (compared to the full sample) should be considered since may magnify exercise effects[257].

Considering the promising results of this secondary analysis future larger trials targeting Hispanic and Latina BCS should be promoted to confirm our findings.

3.3 *Conference abstract:* "Circuit, interval-based aerobic and resistance exercise improves the quality of life among cancer survivors" *(Ficarra, S., Wilson, R. L., Encabo, P. G., Kang, D.-W., Normann, A. J., Christopher, C. N., & Dieli-Conwright, C. M. (2023). Circuit, Interval-based Aerobic And Resistance Exercise Improves Quality Of Life Among Cancer Survivors: 2852. Paper presented at the ACSM 2023 Annual Meeting and World Congress, Denver, Colorado.)*

Introduction, rationale and methods

As we reported for BCP and BCS, all cancer survivors may experience declines in HRQoL for similar reasons (symptoms and treatment side effects). Exercise interventions may be a strategic promising approach to improve HRQoL among all cancer survivors, through the CRF improvements. Adherence to exercise intervention should always be promoted during trials and strategies to improve this parameter need to be implemented to obtain valuable HRQoL improvements. Adherence is intuitively essential as researchers and clinicians can not expect any improvements when the administration is not followed by the patient. Time-saving approaches may be valuable in the field of exercise oncology. Reducing the burden (duration) of an exercise session could erase a relevant barrier which may prevent optimal exercise adherence rates. Therefore, the study summarized within this paragraph, which has been presented during the ACSM 2023 Annual Meeting and World Congress (Denver, Colorado), aimed to assess the benefits of circuit training intervention on HRQoL improvements and its relationship with CRF.

A supervised circuit interval-based COMB intervention was delivered for 16 weeks to cancer survivors diagnosed with breast, colorectal or prostate cancer. A total of 90 cancer survivors, 38 breast, 28 colorectal, and 24 prostate cancer survivors were recruited. Eligible participants were sedentary and overweight/obese with a BMI higher than 25.0 kg/m^2. The recruited participants were randomly assigned either to exercise (EG) or attention control (AC). Participants were assigned to group with a 2:1 ratio leading to a total of 60 participants on the EG and 30 in the AC.

The exercise intervention was a supervised, circuit interval-based COMB exercise. Participants exercised 3 times a week for 16 weeks. The exercise intervention intensity was progressive from moderate to vigorous. Participants in the AC group were asked to complete 3-4 stretching exercises with the same frequency of the EX (3 days a week). HRQoL was measured using the Short Form Survey-36 (SF-36) questionnaire, while CRF was assessed by performing a 6-minute walking test (6MWT). Repeated measures ANCOVA was applied to analyse the data, adjusting for age and sex. Correlation between HRQoL and CRF at post-test were explored using the Pearson correlation coefficient.

Results and conclusions

Of the total recruited sample, 55% were female cancer survivors. Participants were on average 63.2±10.8 years old, with obesity (87%), and were treated with radiotherapy and/or chemotherapy (75%). High intervention adherence was observed (92%). At baseline, no differences were observed between groups. At the end of the 16 weeks, all SF-36 parameters were significantly improved in the EG compared to AC ($p<0.01$). Both the physical component summary and the mental component summary significantly improved in the EG compared to AC (mean difference: 6.8; 95% CI, 3.1 to 13.0 and 6.1; 2.5 to 12.6, respectively). When exploring correlations between HRQoL and CRF in the EG at post-test PCS ($r=0.96$; $p<0.01$) and MCS subscales ($r=0.93$; $p<0.01$) were found to be significantly correlated with 6MWT results.

The circuit, interval-based COMB exercise intervention, delivered in a supervised for 16-week was able to improve HRQoL in cancer survivors with breast, colorectal or prostate cancer. Considering the correlations between CRF and HRQoL components this parameter should be carefully considered when designing exercise interventions in the field of exercise oncology.

3.4 *Conference abstract:* "Effects of exercise intervention on physical fitness outcomes in individuals diagnosed with lung cancer: Preliminary results of a systematic review"

(Ficarra, S., Wilson, R. L., Encabo, P. G., Kang, D.-W., Normann, A. J., Christopher, C. N., Lopez, P., Thomas, E., Bianco, A., & Dieli-Conwright, C. M. (2023). Effects of exercise intervention on physical fitness outcomes in individuals diagnosed with lung cancer: Preliminary results of a systematic review. Paper presented at the XIV National Congress SISMES, Naples, Italy.)

Introduction

As we previously mentioned, similarly to BC, LC is a health concern, not only due to its high incidence but also its mortality rates which are the highest in males (among cancer deaths) and the second among females[258]. Similarly to other cancers, surgery and treatments can cause detriment in patients' physical fitness, especially pulmonary function although to a different extent according to the type of surgery procedure[75]. Detriment in lung function generally continues to worsen independently of the type of surgery[74]. Rehabilitation strategies are consequently multidisciplinary and focus on lung function through the use of breathing exercises or manual therapy. Therefore, LC patients usually undergo Pulmonary Rehabilitation (PR) interventions a comprehensive rehabilitation strategy that consists of behavioural management strategies (treatment side effect awareness and management, smoking cessation, diet and psychosocial interventions), together with exercise and breathing techniques to improve HRQoL[77,78,259]. However, exercise has been proven to be effective in cancer populations to ameliorate short and long-term side effects, fitness, and HRQoL[260]. Moreover, due to LC's clinical complexity, healthcare professionals agree relevance of exercise for this cancer population[261]. Notwithstanding, studies to find the ideal exercise prescription are still required[261-263]. Pursuing this aim among LC populations seems challenging due to the multidisciplinary nature of the proposed interventions (PR). In the last decade, systematic reviews and meta-analyses attempted to define exercise benefits on this population although including multidisciplinary approaches. In research, to clearly evaluate the effects of exercise, it should be administered alone, without additional strategies.

Therefore, we carried out a systematic review with meta-analysis to assess the effects of exercise-only interventions on LC patients and survivors.

Methods

This systematic review was conducted following the updated PRISMA guidelines[264]. Protocol registration (registration ID: CRD42022376291) was carried out on the PROSPERO database. The methods used to complete the search are summarised below.

Search Strategy

MEDLINE (Pubmed), EMBASE, SportDiscus, Cochrane Central Register of Controlled Trials, and Web of Science databases were selected for this systematic search[265]. The selected keywords were determined with a snowball sampling approach and through discussion, taking into consideration the relevant MeSH terms. The search queries were computed including AND/OR operators. The COVIDENCE web software was used to complete all screening phases. The software automatically excluded duplicates after importing all references. The review team completed the search phases: title, abstract and full-text screening, during which eligibility was assessed twice for each record.

English, Italian, Korean and Spanish peer-reviewed papers were reviewed. Reference lists were also checked to ensure the inclusion of all relevant publications. The authors discussed full-text inclusions in case of disagreement. Corresponding authors were contacted when the full-text record was not available, which was excluded, for any reason, if the full-text was still not accessible. The inclusion and exclusion criteria designed for this search are listed below.

Patients

Only individuals diagnosed with LC (every stage, subtype), regardless of therapy phase, were included. For other cancer types, patients with multiple cancers were excluded. Studies in which more than one cancer type, including LC, were recruited, but data aggregation could not allow the extraction of LC participants' data.

Intervention

Exercise interventions, not integrated with other complementary approaches (e.g., PR, physical therapy, acupuncture, nutritional advice, behavioural management) were included, to understand the effects of the exercise alone. Also, when the exercise protocol type was unclear and/or a combination of multiple non-pharmacological approaches was present the study was excluded.

Comparators

Non-exercising/stretching CGs, waiting list groups and usual care groups were considered comparators. When multiple exercise types were compared exercising CGs were considered as IGs. Comparators performing other non-pharmacological interventions were excluded.

Outcomes

Only objective standardized variables were included and extracted from studies.

Study design

Only interventional studies[266] such as RCTs, non-randomized controlled trials, crossover studies, cluster randomized trials and quasi-experimental studies[267,268] were included. Reviews were collected during the screening for the reference list check.

Studies record

Studies information and data were extracted using an Excel spreadsheet. Studies characteristics and exercise protocol features were then summarized in Word tables

Statistical analysis

Totals or median [IQR] were computed using Excel to summarize information within the tables.

Mean and SD were extracted from included studies to perform a preliminary meta-analysis, which was performed using Jamovi (The jamovi project (2021). jamovi (Version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org). SD were calculated when SE or CI were available, following the guidelines Cochrane handbook for systematic review of interventions (Chapter 6, paragraph 6.5.2)[204].

Results

The systematic search, summarized in Figure 3.1 (generated using the R based PRISMA2020 tool[269]), retrieved 36,304 records which were imported into COVIDENCE. The web software automatically removed 6,932 records. After manually checking the duplicates, no relevant record was found to be accidentally removed. Therefore, 29,372 records were screened during the title and abstract screening. Three-hundred-eighty-three records were deemed eligible but only 369 full-texts were successfully retrieved and screened. A total of 356 were considered ineligible after full-text screening and only 13 publications (11 studies) were finally included in the review. Reasons for full-text exclusion are listed in Figure 3.0.

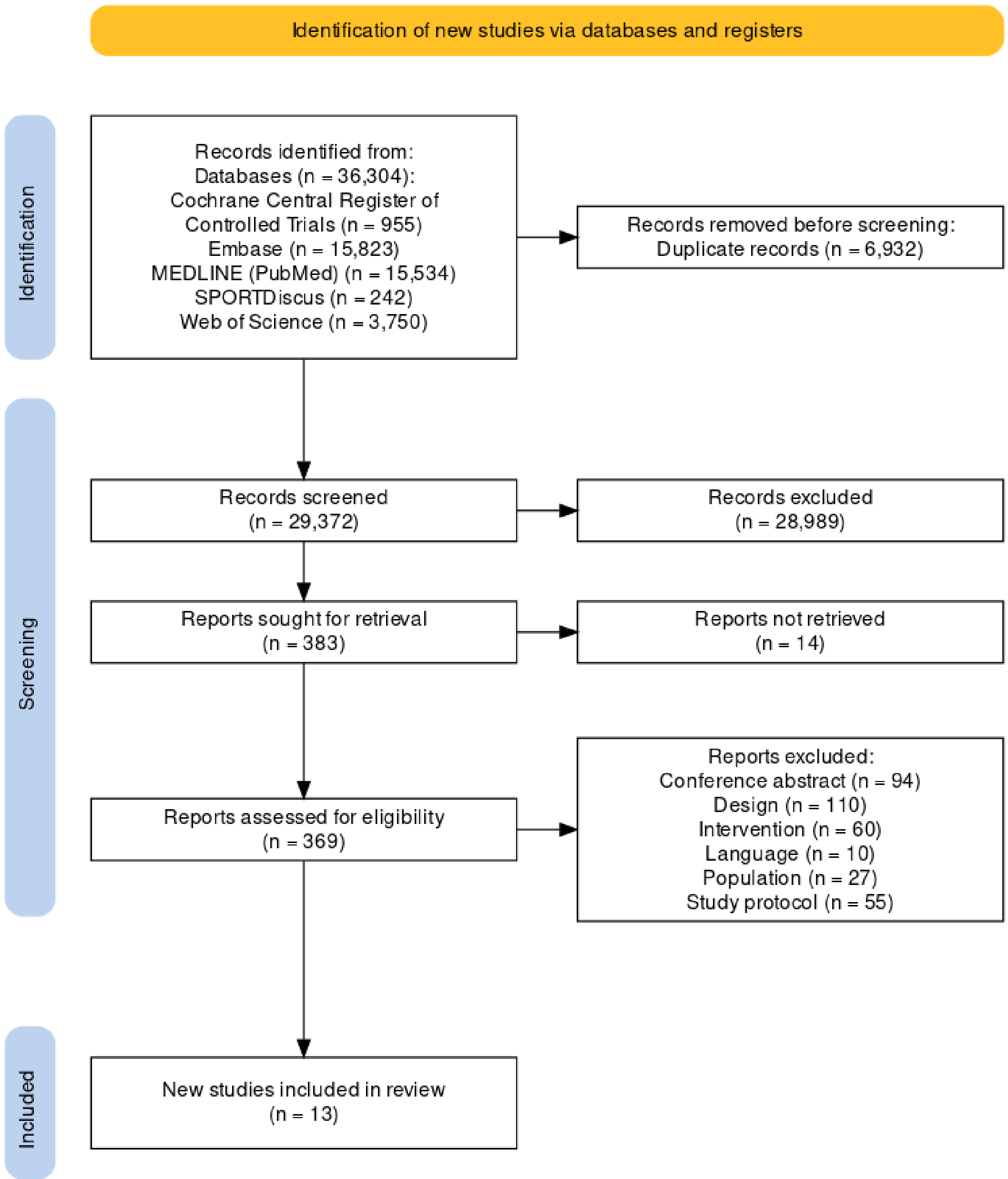

Fig 3.1 *Flow diagram of the search*

Studies and participants' characteristics

The majority of the studies were RCTs[270-278], except for 3 research projects (published across four papers) in which a quasi-experimental[279], retrospective[280] and non-randomized[281,282] designs were respectively implemented. A total sample of 547 individuals, with a diagnosis of LC were analysed, 304 assigned to IGs and 243 assigned to CGs. Patients were 63 (61-65) years old and 26 (24.1-26) $kg*m^{-2}$ BMI. Four studies assessed the effects of exercise rehabilitation interventions on LC patients early after surgery or completion of treatments[270,277,279,280], four studies evaluated exercise interventions during treatments[274-276,281,282], and only one study recruited LC participants off treatment[278]. The remaining 3 studies recruited both on and off-treatment participants[271-273]. Studies had a median (IQR) retention rate of 83 (77-88). Further details are reported in Table 3.3.

Interventions details

Administered exercise interventions are summarized in Table 3.4. Briefly, 6 studies provided COMB interventions (AT an RT)[270,273,277,278,280-282], 6 studies administered AT [271,272,274,275,278,279], and 2 RT interventions[276,278]. Interventions were 12 (9-12) weeks long. Participants attended 3 sessions per week, for 43 (34-60) minutes/session. Median intensity was 53 (35-62)% of 1RM for RT interventions, although 3 studies did not report this information[270,276,280]. AT intensity was not calculated due to high heterogeneity in measures. The majority of the studies implemented AT at a moderate-high intensity. Attendance to exercise sessions was in median 78 (71-86)%.

Table 3.3 Studies and analysed LC participants' characteristics.

Author -Year	Design	Sample Size (total (M/F))	Retention Rate (%)[a]	Mean Age (Mean years ± SD)	Mean BMI (Mean kg*m^{-2} ± SD)	IG (N)	CG (N)	Treatment Phase[b]	Cancer Type	Cancer stage
Cavalheri et al 2017[270]	pilot RCT	17 (5/12)	100	67 ± 9	26±6	9	8	Rehab	NSCLC	I-IIA
Chang et al 2014[279]	quasi-experimental	65 (36/29)	98	IG: 62.00 ± 12.15 CG: 58.39 ± 13.39	IG: 23.90 ± 3.66 CG: 24.48 ± 3.78	32	33	Rehab	NSCLC	n/a
Chen et al 2014[271]	RCT	116 (54/62)	78	64.16 ± 10.89	n/a	58	58	Mixed	n/a	I-IV
Chen et al 2016[272]		111 (49/62)	80	IG: 64.64 ± 11.54 CG: 62.51 ± 9.64	n/a	56	55			
Cheung et al 2021[273]	pilot RCT	21 (10/11)	83	IG: 61.00 ± 12.12 CG: 58.36 ± 9.32	n/a	10	11	Mixed	NSCLC	IIIB-IV
Egegaard et al 2019[274]	pilot RCT	13 (5/10)[c]	87	IG: 64.00 ± 5.80 CG: 65.00 ± 4.70	IG: 24.1 ± 4.4 CG: 24.2 ± 1.9	8	5	On	NSCLC	IIIA-IV
Harman et al 2021[280]	retrospective	9 (n/a)	n/a	61.9 ± 13.6	n/a	9	-	Rehab	NSCLC and SCLC	n/a
Hwang et al 2012[275]	RCT	24 (12/12)	75	IG: 61.0 ± 6.3 CG: 58.5 ± 8.2	IG: 22.6 ± 2.4 CG: 23.1 ± 2.6	11	13	On	NSCLC	IIIA-IV
Karvinen et al 2014[276]	pilot RCT	14 (10/4)	61	58.8 ± 12.9	31.5 ± 7.4	5	9	On	NSCLC, SCLC	I-IV
Martínez-Velilla et al 2021[281] Rosero et al 2020[282]	non-randomized	26 (20/6)	76	IG: 74.5 ± 3.6 CG: 79.0 ± 3.0	IG: 26.8 ± 4.5 CG: 25.5 ± 2.5	19	7	On	NSCLC	I-IV
Salhi et al 2015[277]	RCT	41 (36/12)[c]	85	IG: 63 [29-76][e] CG: 64 [51-79][e]	IG: 26 [17-45][e] CG: 26 [18-35][e]	20	21	Rehab	NSCLC, SCLC, mesothelioma	I-III
Scott et al 2021[278]	RCT	90 (31/59)	90	65 ± 9	28 ± 6	67[d]	23	Off	n/a	I-IIIB
Total/ *Median[IQR]*	-	**547 (268/279)**[c]	*83[77-88]*	*63 [61-65]*	*26 [24.1-26]*	**304**	**243**	-	-	-

M/F= Males/Females; CG= Control Group; IG= Intervention Group; SD= Standard Deviation; RCT= Randomized Controlled Trial; NSCLC= Non-small Cell Lung Cancer; SCLC= Small Cell Lung Cancer; IQR= Interquartile Range; n/a= not available

[a] Retention rate is the percentage of participants retained at post-test.

[b] Rehab= patients are undergoing rehabilitation through exercise early post-operative or early after treatment.; Mixed= both on and off-treatment patients are included; On= patients are on treatment undergoing therapies with curative intent; Off= patients are off-treatment and have completed all therapies with curative intent.

[c] The sex of patients who dropped out was not specified; the sex of the overall sample has been reported.

[d] Represents the sum of the 3 interventions group (Aerobic Training: 24; Resistance Training: 23; Combined training: 20)

[e] Data are presented as Median [range]

Table 3.4 Features of the exercise interventions

Author -Year	Type	Setting	Modality	Length (weeks)	Frequency (n/week)	Session Duration (minutes)	RT Intensity	AT Intensity	Attendance (% (N))
Cavalheri et al 2017[270]	COMB	mixed	AT: walking/cycling RT: free-weight, bodyweight	8	3	60	n/a	70-90%speed 60-80%Wmax	70.8%[a] (17±3)
Chang et al 2014[279]	AT	mixed	walking	12	7	6	-	Low-Moderate	n/a
Chen et al 2014[271] Chen et al 2016[272]	AT	home-based	walking	12	3	40	-	60-80%HRmax; 13-15RPE	61,1%[a] (22±16) 58.3%[a] (21±44)
Cheung et al 2021[273]	COMB	mixed	AT: walking, cycling RT: arm, leg, core exercises	12	2	60	60%1RM	50-60%HRR	75.0%[a] (18±3)
Egegaard et al 2019[274]	AT	supervised	cycling	7	5	20	-	50-95%PPO	90%[54–100%]
Harman et al 2021[280]	COMB	supervised	AT: walking, cycling, elliptical, underwater treadmill RT: machine-based, bodyweight + balance, flexibility	12	3	60	n/a	30–60% HRR	92%[b]
Hwang et al 2012[275]	AT	supervised	running/cycling	8	3	30-40	-	60-80%VO2peak 11-17RPE	83% [4–100%]
Karvinen et al 2014[276]	RT	mixed	elastic bands	12	3	30	n/a	-	79%[b]
Martínez-Velilla et al 2021[281] Rosero et al 2020[282]	COMB	supervised	AT: cycling RT: machine-based, bodyweight, bands + balance, flexibility	10	2	45-50	30-60%1RM	50–80%HRmax	86%
Salhi et al 2015[277]	COMB	supervised	AT: running, cycling RT: machine-based	12	3	n/a	50%1RM	70%Wmax	77.8%[a] (28 [10-36])
Scott et al 2021[278]	AT RT COMB	supervised	AT: cycling RT: machine-based, free weight, bodyweight	16	3	AT:20-60 RT:30-60 COMB: 30-90	50-85%1RM	55%->95%Workload	90%[4–100%]
median[IQRs]	-	-	-	*12[9-12]*	*3[3-3]*	*43[34-60]*	*53[35-62]*	-	*78[71-86]*

AT= Aerobic Training; RT= Resistance Training; COMB= Combined aerobic and resistance training; 1RM= One repetition maximum; VO_2peak= Peak of Oxygen Consumption; Wmax= Maximum Power; PPO= Peak Power Output; RPE= Rate of Perceived Exertion (based on Borg Scale); HRR= Heart Rate Reserve; HRmax= Maximal Heart Rate; IQR= Interquartile Range; n/a= not available.

[a] Percentage attendance has been calculated

[b] Values have been reported as adherence.

Outcomes included in the meta-analysis

Four of the included studies showed no significant effect of exercise on CRF (k=12; SMD = 0.0939; 95% CI: -0.1557 to 0.3434; z = 0.7372, p = 0.4610; heterogeneity; p = 0.1241; I^2 = 0.0005%)[270,274,275,277]. Results are presented in Fig 3.2a.
Two additional studies not included in the meta-analysis (lack of data reported[278] or no LC control[280]) assessed exercise effects on CRF variables. Both studies showed VO2peak improvements after AT or COMB[278,280] intervention but not after RT[278].

The meta-analysis of 3 studies[275,277,282] showed a significant effect of interventions on ST (k=11; SMD= 0.9310 (95% CI: 0.4139 to 1.4481; z = 3.5289, p = 0.0004) Fig 3.2b. A high heterogeneity was also found for this variable ($p < 0.0001$; I^2 = 74.2%).
Three studies assessing ST[270,278,280] were excluded from the meta-analysis. COMB rehabilitation intervention can GC did not differ on ST measures in one study[270]. In another study, significant improvements in estimated-1RM were found after COMB rehabilitation but not on handgrip[280]. The last study reported significant improvements in estimated 1RM in the RT group only (but not after AT and COMB)[278].

Six studies assess the effects of exercise on PF and were included in the meta-analysis[270,273,274,277,279,282]. A significant effect of interventions on PF (k=14; SMD= 0.5178; 95% CI: 0.1870 to 0.8487; z = 3.0678, p = 0.0022) was found Fig 3.2c. High heterogeneity was also observed for PF (p = 0.0116, I^2 = 53.1%).

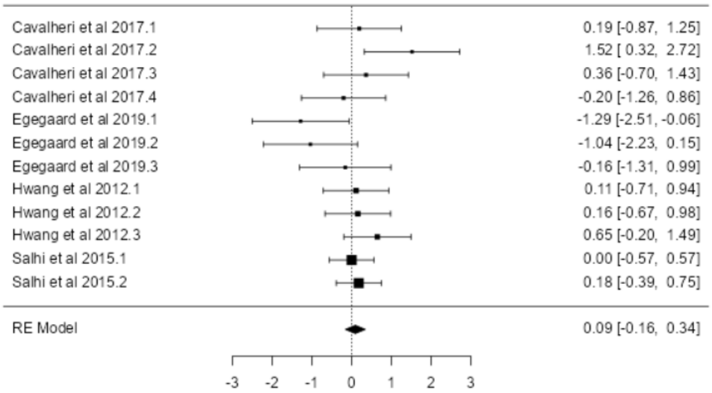

Fig 3.2a *CRF meta-analysis*

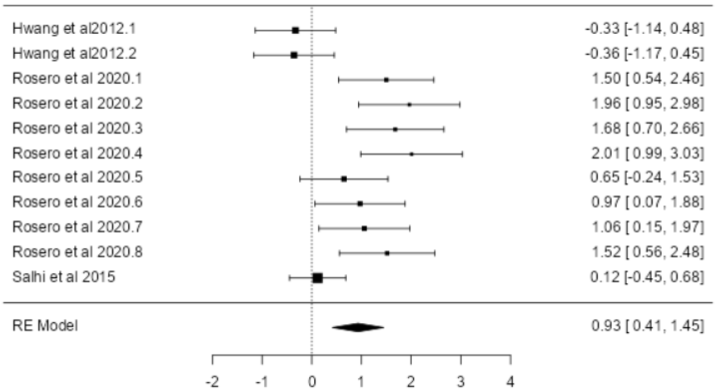

Fig 3.2b *ST meta-analysis*

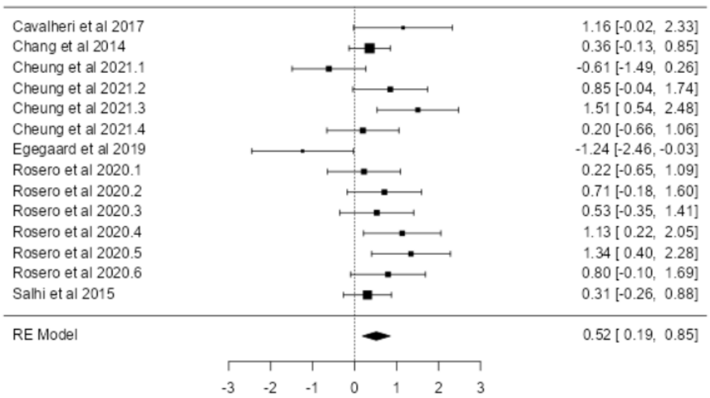

Fig 3.2c *PF meta-analysis*

Four studies[270,271,273,274] assessing exercise effects on anxiety and depression were included in the meta-analysis. No significant effects were found for Anxiety (k=4; SMD= -0.0396 (95% CI: -0.3706 to 0.2913; z = -0.2348, p = 0.8144), while a significant effect was found for depression (k=4; SMD = -0.4315; 95% CI: -0.8176 to -0.0453; z = -2.1900, p = 0.0285) Figure 3.3a-b. No relevant heterogeneity was found (Anxiety p = 0.5370, I² = 5.4%; Depression p = 0.3879; I² = 16.9 %).

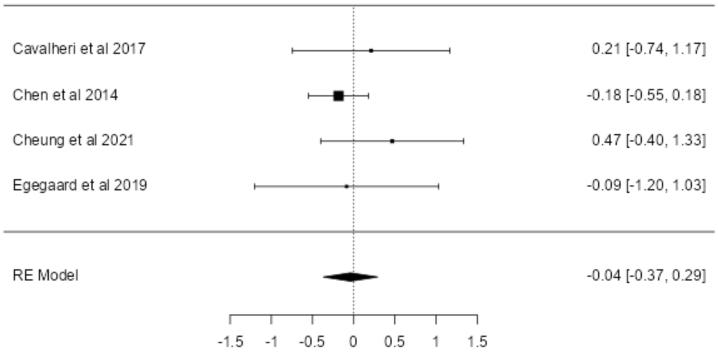

Fig 3.3a *Anxiety meta-analysis*

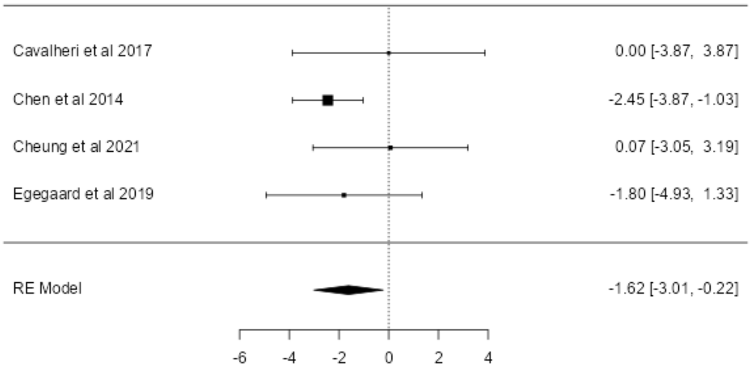

Fig 3.3b *Depression meta-analysis*

One more study[280] not included in the meta-analysis showed a non-significant depression improvement although using a different scale (Beck Depression Inventory) than those included in the meta-analysis.

Outcomes not included in the meta-analysis

Sleep

Three studies explored sleep after exercise rehabilitation[278] or in both on and off-treatment patients[272,273]. When undergoing exercise rehabilitation participants did not show significant improvement in sleep quality[278]. The other two studies, among both on and off-treatment participants, presented contradictory results: no between-group difference in objective and subjective sleep[273] or significant increases in subjective and objective sleep were found[272].

Discussion

From this study's preliminary results, promising evidence has been observed for a variety of outcomes. In particular, exercise-only interventions do not change participants' CRF (potentially limiting decline) and significantly improve ST. A previous systematic review assessed the benefits of HIIT interventions among LC patients showing a significant improvement when comparing exercise groups to controls[283]. This result is in contrast with ours, highlighting that CRF improvements may be intensity-dependent. However, only 3 out of 8 included studies in the Heredia-Ciuró et al review have been also included in our review, suggesting that reported effects may be also due to a mixed intervention modality rather than exercise alone[283]. However, our promising results on ST measures are consistent with those observed regarding respiratory muscle ST (after high-intensity breathing exercises)[284] with the advantage that our review included measures pertained to upper and lower body muscle ST. Consistently to ST, we also observed a significant effect of exercise on LC participants' PF. However, the high heterogeneity found for ST and PF should be considered when interpreting these results. Improved overall physical fitness might induce HRQoL improvements. A systematic review showed that exercise administered after lung surgery is effective in ameliorating HRQoL when performed in a COMB modality[260].

In conclusion, despite the low number of included studies and their heterogeneity in cancer settings and exercise modalities, promising effects of exercise-only intervention have been demonstrated. It is important to note that interventions administered exercise only before or after surgery when this treatment was necessary, leading to no study investigating the benefits of longer interventions with both pre- and rehabilitation components, as previously reported by other studies[285].

3.5 *Conference abstract:* "Knowledge-based implementation of resistance training for sleep health among cancer patients and survivors: preliminary results of the OACCUs project's systematic review" *(Di Bartolo, L., Ficarra, S., Galioto, M., Jiménez-Pavón, D., Tavares, P., Pusa, S., Vantarakis, A., Asimakopoulou, Z., Thaller, J., Seminara, D., Maric, D., Lo Mauro, M., Lavanco, G., & Bianco, A. (2023). Knowledge-based implementation of resistance training for sleep health among cancer patients and survivors living within the Mediterranean area: Preliminary results of the OACCUs project's systematic review. Paper presented at the 2nd Annual Experiential Conference with American, International and Greek Scholars, Rethymno, Crete, Greece.)*

Introduction and methodology

The study shown here has been designed within the outdoor against cancer connect us (OACCUs) European project which aims to promote healthy lifestyles for young cancer survivors through the implementation of exercise interventions outdoors. Considering the value of interventions implementing RT which has been shown in the abovementioned studies, it was decided to study the effects of this type of training. Additionally, we detected that current guidelines for adult cancer survivors are lacking recommendations regarding RT protocols to improve sleep quality and reduce sleep disturbance[51]. In this regard, we designed a systematic review to address this literature gap and identify the potential benefits of RT regarding sleep variables and describe dose-response relationships to allow the design of adequate RT interventions targeting sleep disturbances.

The PRISMA guidelines were also followed for this systematic review. Relevant records were searched on MEDLINE (Pubmed), Scopus, Web of Science, Cochrane Central Register of Controlled Trials and in relevant publication's reference lists. Relevant keywords were identified both through discussion and snowball sampling approach and combined with AND/OR. Covidence was used for all screening phases by two independent reviewers.

Eligible papers were English or Italian peer-reviewed manuscripts. Studies including cancer patients or survivors were considered eligible (other diseases or healthy individuals were excluded). Studies testing RT[286], or a combination between AT and RT without other approaches (e.g., behavioural management, diet or physical therapy) will be included. Only RCTs with a non-exercising, stretching, exercising control group or usual care groups were selected. AT+RT or RT control groups will be considered as IGs. Eligible variables were those objective and standardized tests used to evaluate sleep quality and disorders[287].

Studies information and results were extracted and collected in an Excel spreadsheet. Pre and post intervention data were extracted to calculate percentage differences to allow comparison between different assessed measures. Studies were classified according to exercise intervention: RT only or COMB.

Preliminary results

A total of 8,715 records were screened after duplicate removal. A total of 231 potentially relevant full texts were found and 22 eligible articles were left (Figure 3.4). An overall sample of 2,349 participants, age 54 [50-57] years (median [IQR]). Studies recruited a range variety of cancer types with the majority of them having breast (=9), colorectal (n=4) and prostate (n=5) cancer participants. Thirteen studies administered COMB AT+RT interventions while the remaining 9 implemented RT-only interventions. Exercise interventions lasted 12 [8-17] weeks.

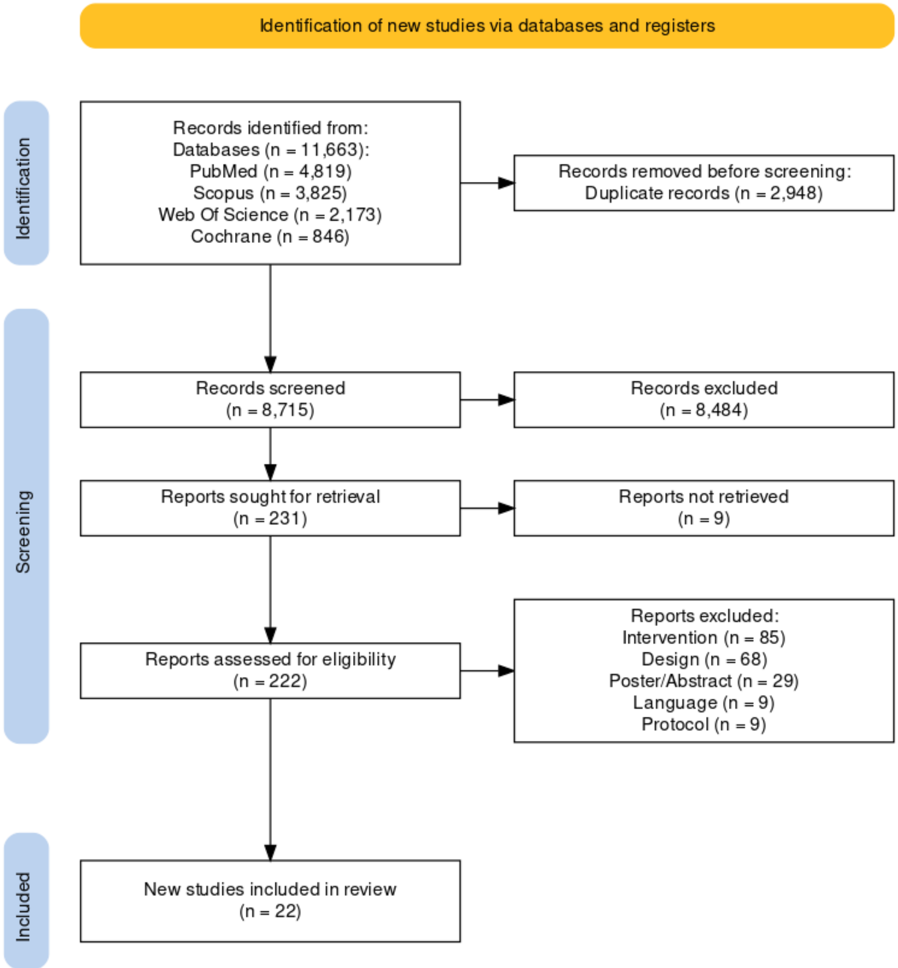

***Fig 3.4** Flow diagram of the search*

Combined aerobic and RT

Studies assessing COMB intervention influence on sleep quality display a -13.7% (reduction represents a positive influence on sleep quality). Only one study showed a negative change in sleep quality (10.3%)[288]. Positive effects were also found regarding sleep disturbance/insomnia (-18.9%), with only one study presenting symptoms increase (25.5%)[289].

RT only interventions

Only one study reported RT alone effects on sleep quality (PSQI), showing a beneficial effect. RT alone also positively influenced insomnia/sleep disturbance when considering the average percentage difference (-11.4%). However one study reported conflicting results[290], and one study reported no significant changes[291].

Conclusion

Overall both types of intervention COMB and RT alone have a positive influence on sleep outcomes. Those findings would support current guidelines for cancer populations in the administration of RT interventions to improve sleep outcomes. Exercise specialists can implement these strategies when sleep quality is impaired or sleep disturbances are present among individuals diagnosed with cancer. Within the OACCUs project, this information represents crucial evidence that can be translated into efficient exercise implementations for the young cancer survivors population considering that this specific population is still understudied.

3.6 Final considerations

The research projects presented in this chapter attempted to answer a series of research questions to allow trainers and healthcare providers to apply knowledge-based evidence when tailoring exercise interventions for cancer patients and survivors. In order to achieve that, both different or single cancer types have been selected for each project. In the first case, the aim was to address broader research questions and literature gaps to define generic guidelines. While, when a single cancer type was investigated, the aim was to identify detailed suggestions for specific variables (e.g. symptom or side effects) to allow trainers to better individualize exercise interventions.

Considering the overall cancer population, we were able to understand that circuit interval-based interventions are valuable strategies to improve HRQoL, and that RT interventions may be essential to maintain skeletal muscle tissue and sleep health. When specific cancer types are considered, briefly, we found that female BC can benefit from exercise interventions in improving CRF, ST, F and HRQoL and that Hispanic/Latina individuals are more likely to face cardiovascular diseases and thus should exercise to dampen cardiovascular risk. For LC patients, promising results were also highlighted although more research, on exercise interventions alone, is needed to corroborate the reported findings. Nevertheless, for this fragile cancer population, exercise rehabilitation and interventions after treatments have shown promising results. We can thus conclude that exercise oncology should not be only considered as a research field since its benefits have been widely demonstrated and its adjuvant action to improve patients' lives should not be underestimated. While patients are undergoing treatment or after its completion, the need to defeat the disease is crucial as the need to allow patients to live their lives with a better quality which can be accomplished with exercise and other complementary strategies.

Notwithstanding, the necessity of exercise oncology research is still present due to the lack of knowledge regarding less common cancer species or specific symptoms and side effects as well as regarding the role of exercise in tumour progression. The benefits of exercise for younger cancer populations as well as for those with a diagnosis at a higher stage should be investigated. In general, exercise oncology research should always keep in mind the final target of the results: cancer patients can receive the correct exercise prescription through the knowledge of an expert exercise oncology trainer and do not have to know how the prescription has been designed. Trainers on the other hand have the need to understand how to properly dose the exercise and should have in mind which exercise parameter can influence cancer outcomes and how to properly adjust it. However, not all the exercise specialists have additional knowledge regarding cancer diseases and should be additionally trained before approaching this category of patients. Furthermore, exercise should be only prescribed after oncologist approval and should be designed in team with health care professionals to target quality of life improvements. On the other end, exercise oncology studies need to always clearly report exercise training parameters (volume, intensity, frequency, density and progression) to allow exercise specialists to understand and carefully implement studies' recommendations.

Chapter IV - Personal skills and experiences

4.0 Learning experiences and skills at the Sport and Exercise Sciences Research Unit

In the local unit where the PhD course was mainly followed research projects were used as a training experience and a range variety of tests were performed. Different performance tests were applied to measure strength (Handgrip and T-force), muscular endurance (Push and pull-up test to exhaustion), balance (Y-balance test), jump performance (standing long jump and Optojump measurements), anaerobic capacity (Wingate test), ROM (Gyko inertial sensor). Also, body composition analysis was carried out using body impedance analysis (BIA - AKERN 101 - AKERN SRL, RJL Systems, Detroit, USA) was used. HRV variables were also assessed and needed HR data to be collected first with a Polar H10 sensor and then calculated with Kubios software. Some questionnaires were also implemented such as the SF-36 for HRQoL measurements and IPAQ for PA levels. All the abovementioned tests were first learnt and then practised and only after a satisfactory amount of practice, which could have ensured the reliability of the measures, have been applied in the research projects.

During the 3 years, I was also involved in the development of systematic reviews and meta-analyses which require a conspicuous amount of knowledge on research methodologies as well as specific review methodology and risk of bias assessment. This expertise was learned to complete the study and offer specific insights into general research methodology. It should be also considered that statistical analysis must be performed, as well as, the creation of graphs. A variety of software was explored to implement statistical analysis (SPSS, Jamovi, GraphPad PRISM, STATISTICA and R). However, Jamovi and GraphPad were mainly implemented in the presented research projects. Different software may have different statical capabilities and have been properly explored to ensure correct calculations.

4.1 International period and international collaborations

During the three-year-long PhD course in Health Promotion and Cognitive Sciences, I was able to spend one year (between April 2022 and April 2023) abroad at the Dana-Farber Cancer Institute in the Dieli-Conwright laboratory. Within this laboratory, I was able to participate in ongoing clinical trials testing a variety of exercise interventions among a broad spectrum of cancer patients or survivors. In detail, as a kinesiologist and exercise trainer, it was essential to learn how to train this category of patients who require particular attention, prior to approaching clinical trials testing and/or analysis. The skills implemented to train healthy individuals should be slightly-to-profoundly adapted to cancer populations and it is always important to keep in mind the human connection which stands behind exercise prescription and practice. These elements are essential when the aim is to obtain improved health improvements because are closely connected to exercise compliance and adherence. Once the ability to train cancer patients and survivors in either an in-person or online supervised setting, a range variety of testing skills were learned. A short list of the tests and instruments used are listed below:

-VO2 max testing on treadmill or bike: ParvoMedics metabolic gas exchange analyser.

-10RM strength testing on machines or free weights.

-Manual blood pressure recording

-Sensation and vibration loss (due to neuropathy) using monofilament and tuning fork, respectively.

-Measure of circumferences with measuring tape.

-BIA TANITA (different from the Akern shown above due to the modality of testing performed in a standing position rather than lying down) of which a similar instrument used has been explored in the local laboratory.

-6MWT and Short physical performance battery (SPPB).

-RPE Scale use (both during testing and training).

-Shoulder function tests

All the abovementioned tests represent an inestimable knowledge of testing procedures among cancer populations which could also translate to healthy individuals in some cases.

As an international collaboration, 3-months cooperation with the Faculty of Sport and Physical Education of the Novi Sad University has been completed. The research under the supervision of Professor Patrik Drid brought to the finalization of 2 manuscripts.

4.2 Other published papers

Some published papers were not reported in previous chapters and respective abstracts are shown below:

1. "Does Stretching Training Influence Muscular Strength? A Systematic Review With Meta-Analysis and Meta-Regression"

The aim of this study was to review articles that performed stretching training and evaluated the effects on muscular strength. Literature search was performed using 3 databases. Studies were included if they compared the effects on strength following stretching training vs. a non training control group or stretching training combined with resistance training (RT) vs. an RT-only group, after at least 4 weeks of intervention. The meta-analyses were performed using a random-effect model with Hedges' g effect size (ES). A total of 35 studies (n = 1,179 subjects) were included in this review. The interventions lasted for a mean period of 8 weeks (range, 4-24 weeks), 3-4 days per week, applying approximately 4 sets of stretching of approximately 1-minute duration. The meta-analysis for the stretching vs. nontraining control group showed a significant small effect on improving dynamic (k = 14; ES = 0.33; p = 0.007) but not isometric strength (k = 8; ES = 0.10; p = 0.377), following static stretching programs (k = 17; ES = 0.28; p = 0.006). When stretching was added to RT interventions, the main analysis indicated no significant effect (k = 17; ES = -0.15; p = 0.136); however, moderator analysis indicated that performing stretching before RT sessions has a small but negative effect (k = 7; ES = -0.43; p = 0.014); the meta-regression revealed a significant negative association with study length (β = -0.100; p = 0.004). Chronic static stretching programs increase dynamic muscular strength to a small magnitude. Performing stretching before RT and for a prolonged time (>8 weeks) can blunt the strength gains to a small-to-moderate magnitude. Performing stretching in sessions distant from RT sessions might be a strategy to not hinder strength development.

2. “Nature Through Virtual Reality as a Stress-Reduction Tool: A Systematic Review”

The current systematic review aims to assess the acute stress-reduction effects of virtual reality (VR) natural environments. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, while the inclusion criteria were established through population, intervention, comparison, outcome, and study design (PICOS). The studies were included if (a) based on a nonclinical population; (b) compared the exposure to virtual nature through 360° images, biophilic elements, VR prerecorded videos, or immersive environments, excluding augmented reality; (c) objective (physiological parameters) or subjective (e.g., self-report questionnaires) measures were reported; (d) the reported measures contained quantitative outcomes; and (e) the records were published between 2010 and 2023. Four hundred nine studies were initially retrieved, 19 of which were finally included for synthesis. The eligible studies comprised a total of 1,168 participants. The quality assessment of the studies revealed a score of 10.1/15, indicating that studies were of overall “moderate quality.” Heterogeneity among the type of natural environment, type of stress induction, and type of comparator (nonnatural environment) was retrieved. Differences were also present regarding either the physiological or psychological variables analyzed. The exposure to natural environments through VR seemingly reduces objective and subjective stress levels. The presence of (a) natural sounds, (b) natural lighting, and (c) water elements seem to be key elements that help VR users reducing stress.

3. “Effects of Mediterranean Diet Combined with CrossFit Training on Trained Adults’ Performance and Body Composition”

CrossFit is a high-intensity training discipline increasingly practiced in recent years. Specific nutritional approaches are usually recommended to maximize performance and improve body composition in high-intensity training regimens; notwithstanding, to date there are no targeted nutritional recommendations for CrossFit athletes. The Mediterranean Diet (MD) is a diet approach with a well-designed proportion of macronutrients, using only available/seasonal food of the Mediterranean area, whose health benefits are well demonstrated. No studies have evaluated this dietary strategy among CrossFit athletes and practitioners; for this reason, we tested the effects of 8 weeks of MD on CrossFit athletes’ performance and body composition. Participants were assigned to two groups: a diet group (DG) in which participants performed CrossFit training plus MD, and a control group (CG) in which participants partook in the CrossFit training, continuing their habitual diet. Participants were tested before and after the 8 weeks of intervention. At the end of the study, no significant difference was noted in participants’ body composition, whereas improvements in anaerobic power, explosive strength of the lower limbs, and CrossFit-specific performance were observed only in the DG. Our results suggest that adopting a MD in CrossFit athletes/practitioners could be a useful strategy to improve specific strength, endurance, and anaerobic capacity while maintaining overall body composition.

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Appendix

1. Abstracts of published studies

"Changes in quality of life, strength and heart rate variability after 4-weeks of supervised online burpees training during the covid-19 quarantine in healthy young adults: a pilot study"
In order to maintain physical fitness during the COVID-19 quarantine, we designed a short-term intervention with one body-weight exercise – burpees. Thus, the aim of this study was to understand level of feasibility and potential benefits of our protocol to different variables in young adults during the COVID-19 quarantine. An online 4-week intervention was administered to 13 young adults (age 22.5±1.39 years, weight 71.8±10.1 kg). The main phase of each session consisted of burpees, a calisthenics body-weight exercises. The training was administered daily. Data regarding quality of life (QoL), body composition, posture, heart rate variability (HRV), cardiovascular health, and strength were collected before and after the intervention period. Participants' QoL significantly increased after four weeks (p=.025). Also, participants' strength improved, assessed by the push-up test (p=.017). Systolic blood pressure showed no difference between the pre- and post-measures, while a significant reduction was found in diastolic blood pressure. The HRV assessment showed increased mean RR (p=.005) and RMSSD (p=.014) and decreased mean HR (p=.004) (in the timedomain). For the frequency-domain variables, no significant difference was found. No significant changes were noted in body composition, posture, handgrip strength and countermovement squat jump height. Our preliminary results suggest that the 4-week daily online burpees intervention is a feasible method that could improve QoL, upper body strength and HRV in young adults. This non-time-consuming approach could be easily administered to promote healthy living and counteract physical inactivity during COVID-19 restrictions thanks to its feasibility, short duration, and low cost.

"Effects of Different Long-Term Exercise Modalities on Tissue Stiffness"
Stifness is a fundamental property of living tissues, which may be modifed by pathologies or traumatic events but also by nutritional, pharmacological and exercise interventions. This review aimed to understand if specifc forms of exercise are able to determine specifc forms of tissue stifness adaptations. A literature search was performed on PubMed, Scopus and Web of Science databases to identify manuscripts addressing adaptations of tissue stifness as a consequence of long-term exercise. Muscular, connective, peripheral nerve and arterial stifness were considered for the purpose of this review. Resistance training, aerobic training, plyometric training and stretching were retrieved as exercise modalities responsible for tissue stifness adaptations. Diferences were observed related to each specifc modality. When exercise was applied to pathological cohorts (i.e. tendinopathy or hypertension), stifness changed towards a physiological condition. Exercise interventions are able to determine tissue stifness adaptations. These should be considered for specifc exercise prescriptions. Future studies should concentrate on identifying the efects of exercise on the stifness of specifc tissues in a broader spectrum of pathological populations, in which a tendency for increased stifness is observed.

"Positional transversal release is effective as stretching on range of movement, performance and balance: a cross-over study"
Background: The aim of this study was to compare the positional transversal release (PTR) technique to stretching and evaluate the acute efects on range of movement (ROM), performance and balance. Methods: Thirty-two healthy individuals (25.3±5.6 years; 68.8±12.5 kg; 172.0±8.8 cm) were tested on four occasions 1 week apart. ROM through a passive straight leg raise, jumping performance through a standing long jump

(SLJ) and balance through the Y-balance test were measured. Each measure was assessed before (T0), immediately after (T1) and after 15 min (T2) of the provided intervention. On the frst occasion, no intervention was administered (CG). The intervention order was randomized across participants and comprised static stretching (SS), proprioceptive neuromuscular facilitation (PNF) and the PTR technique. A repeated measure analysis of variance was used for comparisons. Results: No diferences across the T0 of the four testing sessions were observed. No diferences between T0, T1 and T2 were present for the CG session. A signifcant time × group interaction for ROM in both legs from T0 to T1 (mean increase of 5.4° and 4.9° for right and left leg, respectively) was observed for SS, PNF and the PTR. No diferences for all groups were present between T1 and T2. No diferences in the SLJ and in measures of balance were observed across interventions. Conclusions: The PTR is equally efective as SS and PNF in acutely increasing ROM of the lower limbs. However, the PTR results less time-consuming than SS and PNF. Performance and balance were unafected by all the proposed interventions.

"Impact of exercise interventions on physical fitness in breast cancer patients and survivors: a systematic review"

Background This systematic review aims to identify the effects of exercise interventions in patients with breast cancer (BCP) and survivors (BCS) on selected variables of physical fitness. Methods A comprehensive literature search was conducted using Medline and Scopus. Randomized controlled trials with isolated exercise interventions in BCP and BCS women (<5 years from therapy completion) were included. The risk of bias (RoB) assessment was conducted using the Cochrane RoB-2-tool. Variables regarding cardiorespiratory fitness (CRF), strength (ST), fatigue (F) and health-related quality of life (HRQoL) were discussed. Results Of the 336 studies initially identified, 22 met all the inclusion criteria and were deemed eligible. RoB assessment indicated that the studies had predominantly "some concerns" or had "low RoB", with only 3 studies presenting a "high RoB". The mean duration and frequency of exercise interventions were 19 weeks and 3 sessions/week, performed at moderate intensity (65% VO2max and 66% 1RM, for aerobic and resistance-training interventions, respectively). Conclusions Exercise interventions seem to be a valuable strategy in BCP to avoid the decline of CRF, ST, F and HRQoL. Conversely, improved physical function among BCS is observed for the same variables. Resistance training and combined interventions seem to provide the most encouraging variations of the selected outcomes.

"Exercise as medicine in cardio-oncology: reducing health disparities in Hispanic and Latina breast cancer survivors"

Purpose of Review This review aims to access the current state of the evidence in exercise as medicine for cardio-oncology in Hispanic and Latina breast cancer survivors and to provide our preliminary data on the efects of supervised aerobic and resistance training on cardiovascular disease (CVD) risk in this population. Recent Findings Breast cancer survivors have a higher risk of CVD; particularly Hispanic and Latina breast cancer survivors have a higher burden than their White counterparts. Exercise has been shown to reduce CVD risk in breast cancer survivors; however, evidence in Hispanic and Latina breast cancer survivors is scarce. Summary Our review highlights a clear need for exercise oncology clinical trials in Hispanic and Latina breast cancer survivors targeting CVD risk factors. Moreover, our exploratory results highlight that 16 weeks of aerobic and resistance training may reduce the 10-year risk of developing CVD by 15% in Hispanic and Latina breast cancer survivors.

2. Attended Conferences

"XII National Congress SISMES Padua, 8–10 October, 2021"

"ACSM 2023 Annual Meeting and World Congress, May 30 – June 2, 2023, Denver, Colorado"

"XIV National Congress SISMES Naples, 2-4 Novemeber, 2023"

4. Co-supervised master thesis

"Burpees workout for one month: effects on a group of young adults" Student: Migliore Davide; Supervisor: Professor Antonino Bianco; Co-supervisors: Professor Ewan Thomas and Salvatore Ficarra.

"Can the grip during pull ups determine performance variations? An observational study" Students: Di Bartolo Luca and Polizzi Davide; Supervisor: Professor Ewan Thomas; Co-supervisor: Salvatore Ficarra.

"The effects of two different bodyweight trainings on strength among calisthenics practitioners" Student: Geraci Marco; Supervisor: Ewan Thomas; Co-supervisor: Salvatore Ficarra.

"Performance differences between bodyweight and powerlifting athletes: an observational study" Student: Di Bernardo Luca; Supervisor: Ewan Thomas; Co-supervisor: Salvatore Ficarra.

"Lifestyles and quality of life of cancer survivors: an observational study within the OACCUs project" Students: Pappalardo Roberta and Milazzo Marika Rita; Supervisor: Professor Antonino Bianco; Co-supervisors: Salvatore Ficarra and Luca Di Bartolo.