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Maximal Strength Training for Breast Cancer Patients Undergoing Adjuvant Treatment

Doctoral Thesis for obtaining
a doctoral degree (*Ph.D.*)

Sector – Health and Sports Sciences
Sub-Sector – Sports Medicine and Rehabilitation

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Annotation

Physical activity interventions are gradually increasing their role in cancer care. Breast cancer (BC) therapy and increased level of physical inactivity that follows treatment reduce muscle mass, maximal muscle strength, and functional performance, leading to decreased participation in daily activities thus ultimately having an impact on the health-related quality of life (HRQoL). Although maximal strength training (MST) has the potential to react against these debilitating outcomes and has shown to be superior to low and moderate-intensity strength training, it is unknown if it can cause effective adaptations in patients suffering treatment-induced adverse side effects. The objective of this thesis is to expand knowledge of strength training as part of the BC treatment. Furthermore, investigate the impact of MST for newly diagnosed BC patients undergoing adjuvant chemotherapy, on functional performance and HRQoL.

Initially, fifty-seven newly diagnosed stage I–III BC patients (50 ± 3 years) scheduled for adjuvant chemotherapy were included in the study. After pre-testing patients were randomized to an MST group or a control group. The MST group performed 4x4 repetitions of dynamic leg press at $\sim 90\%$ of one-repetition maximum (1RM) twice a week for 12 weeks, whereas the control group followed prescribed treatment without strength training.

The study aimed to examine the effect of MST on muscle strength, functional performance, walking economy and estimated quadriceps femoris muscle mass (Mqf). In the MST group, improvements in 1RM ($20\pm 8\%$; $P<0.001$) were accompanied by the improved walking economy ($9\pm 8\%$) and increased time to exhaustion during an incremental walking test ($9\pm 8\%$; both $P<0.01$). Moreover, the MST group increased 6 minutes walking distance (6MWD; $10\pm 7\%$), chair rising performance ($30\pm 20\%$), and stair climbing performance ($12\pm 7\%$; all $P<0.001$). All MST induced improvements were different from the control group ($P<0.01$) which, in contrast, reduced their 1RM ($9\pm 5\%$), walking economy ($4\pm 4\%$), time to exhaustion ($10\pm 8\%$), 6MWD ($5\pm 5\%$), chair rising performance ($12\pm 12\%$), and stair climbing performance ($6\pm 8\%$; all $P<0.01$). Finally, while MST group participants maintained Mqf, a decrease was observed in the control group ($7\pm 10\%$; $P<0.001$). The change in 1RM was associated with the change in walking economy ($r=0.754$), time to exhaustion ($r=0.793$), 6MWD ($r=0.807$), chair rising performance ($r=0.808$), and stair climbing performance ($r=0.754$; all $P<0.001$).

Additionally, the study aimed to investigate the impact of MST on the HRQoL measured by the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of life Questionnaire-C30 and additional BC module BR23 before and after the intervention. Observed improvements in 1RM significantly improved the Global health status/QoL (QoL)

by 13% for the MST group with a large effect ($P=0.002$, $d=0.6$), on the contrary, no relevant changes were observed in the control group ($P=0.44$, $d=0.2$). Importantly, results revealed changes in QoL after 12 weeks post-test period between the two groups with a large effect ($P=0.002$, $d=0.9$). The improved muscle strength diminished cancer-related fatigue (CRF) for the MST group by 24% ($P=0.03$, $d=0.6$), contrasting it got worse by 25% ($P=0.02$, $d=0.4$) for the control group. Again, the data on large effect was noticed to differ between the groups ($P=0.01$, $d=0.6$).

In conclusion, theses thesis shows that high-intensity strength training for BC patients can safely be performed during adjuvant treatment with large improvements in muscle strength, functional performance, and maintain muscle mass, thus significantly having an impact on the HRQoL. Contrary, conventional BC treatment without any strength training results in attenuated muscle mass, muscle strength, functional performance, and HRQoL. These results advocate that MST may be used to design appropriate strength training programs for clinical application during BC treatment.

Keywords: exercise oncology, chemotherapy, strength training, neuromuscular function, quality of life.

Anotācija

Fiziskās aktivitātes ieņem būtisku lomu vēža ārstēšanā. Krūts vēža (KV) terapija un pazemināts fizisko aktivitāšu apjoms, kas seko ārstēšanas procesam, samazina muskuļu masu, maksimālo muskuļu spēku un funkcionālās spējas, kā rezultātā mazinās personas līdzdalība ikdienas aktivitātēs, tādējādi atstājot iespaidu uz dzīves kvalitāti, kas saistīta ar veselību (DzK). Lai arī maksimālā spēka treniņam (MST) ir potenciāls neitralizēt šo novājinošo iznākumu un tas ir izrādījies efektīvāks par zemas un vidējas intensitātes spēka treniņu, tomēr nav zināms, vai tas var nodrošināt līdzīgus ieguvumus KV pacientēm, kuras saskaras ar ārstēšanas izraisītām nelabvēlīgām blaknēm. Promocijas darba ietvaros veiktā pētījuma mērķis ir paplašināt zināšanas par spēka treniņiem kā daļu no KV ārstēšanas, kā arī izpētīt MST ietekmi uz funkcionālajām spējām un ar veselību saistīto dzīves kvalitāti tikko diagnosticētām krūts vēža pacientēm adjuvantas terapijas laikā.

Pētījuma sākumposmā tika iekļautas piecdesmit septiņas patientes (50 ± 3 gadi), kurām tikko diagnosticēts I–III stadijas KV un kurām tika nozīmēta adjuvanta terapija. Pēc pirmreizējas novērtēšanas patientes tika randomizētas MST grupā vai kontroles grupā. MST grupa veica 4x4 dinamisku kāju spiešanas vingrinājumu, izmantojot trenažieri spiešanai ar kājām (intensitāte $\sim 90\%$) viena atkārtojuma maksimuma (1AM) 12 nedēļas, divas reizes nedēļā, turpretī kontroles grupa ievēroja noteikto ārstēšanu bez spēka treniņa.

Pētījuma mērķis bija izpētīt MST ietekmi uz muskuļu spēku, funkcionālajām spējām, iešanas ekonomiju un aprēķināto *quadriceps femoris* muskuļa masu (Mqf). MST grupā 1AM uzlabojās par ($20 \pm 8\%$; $P < 0,001$), šo uzlabojumu papildināja uzlabota iešanas ekonomija ($9 \pm 8\%$) un palielināts laiks līdz nogurumam slodzes testa laikā ($9 \pm 8\%$; abi $P < 0,01$). Turklāt MST grupa palielināja 6 minūšu iešanas testa noieto distanci (6MWD; $10 \pm 7\%$), piecelšanās un apsēšanās reizes no krēsla ($30 \pm 20\%$) un pakāpienu testa laiks samazinājās par ($12 \pm 7\%$; visi $P < 0,001$). Visi MST radītie uzlabojumi atšķīrās no kontroles grupas rādītājiem ($P < 0,01$), kurā savukārt samazinājās 1AM par ($9 \pm 5\%$), iešanas ekonomija ($4 \pm 4\%$), laiks līdz nogurumam ($10 \pm 8\%$), 6MWD ($5 \pm 5\%$), piecelšanās un apsēšanās reizes no krēsla ($12 \pm 12\%$) un pakāpienu testa laiks palielinājās ($6 \pm 8\%$; visi $P < 0,01$). Visbeidzot, kamēr MST saglabāja Mqf, kontroles grupā tika novērots Mqf samazinājums ($7 \pm 10\%$; $P < 0,001$). 1AM izmaiņas bija saistītas ar izmaiņām iešanas ekonomikā ($r = 0,754$), laikā līdz noguruma iestāšanās brīdim ($r = 0,793$), 6MWD ($r = 0,807$), piecelšanās un apsēšanās no krēsla ($r = 0,808$) un pakāpienu testa rezultātā ($r = 0,754$; visi $P < 0,001$).

Turklāt papildu mērķis bija izpētīt MST ietekmi uz ar veselību saistīto dzīves kvalitāti, izmantojot Eiropas Vēža izpētes un ārstēšanas organizācijas (*European Organisation for Research and Treatment of Cancer, EORTC*) dzīves kvalitātes anketu C30 un papildu moduli

BR23 pirms un pēc intervences. Muskuļu spēka pieaugums pēc intervences ievērojami uzlaboja MST grupas dalībnieku vispārējo veselības stāvokli (*QoL*) par 13 % ar lielu ietekmi ($P = 0,002$, $d = 0,6$), turpretim kontroles grupā šajā mērījumā netika novērotas būtiskas izmaiņas ($P = 0,44$, $d = 0,2$). Svarīgi, ka rezultāti demonstrēja izmaiņas *QoL* pēc 12 nedēļu perioda atkārtotas novērtēšanas starp abām grupām ar lielu efektu ($P = 0,002$, $d = 0,9$). Palielināts muskuļu spēks samazināja ar vēzi saistītu nogurumu (*CRF*) MST grupā par 24 % ($P = 0,03$, $d = 0,6$), turpretim kontroles grupā tas pasliktinājās par 25 % ($P = 0,02$, $d = 0,4$). Atkal tika novērots, ka dati starp abām grupās atšķiras ar lielu efekta starpību ($P = 0,01$, $d = 0,6$).

Šis pētījums parāda, ka augstākas intensitātes spēka treniņus KV pacientēm var droši veikt adjuvantas terapijas laikā, ievērojami uzlabojot muskuļu spēku, funkcionālās spējas un saglabājot muskuļu masu, tādējādi būtiski ietekmējot *DzK*. Turpretim KV ārstēšanas process bez spēka treniņu iekļaušanas veicina muskuļu masas samazināšanos, muskuļu spēka kritumu, apgrūtina funkcionālo veiktspēju un negatīvi ietekmē *DzK*. Šie rezultāti pamato to, ka MST var izmantot, lai izstrādātu atbilstošas spēka treniņu programmas klīnisko apstākļos KV ārstēšanas laikā.

Atslēgas vārdi: fiziskās aktivitātes onkoloģijā, ķīmijterapija, spēka treniņš, neiromuskulārā sistēma, dzīves kvalitāte.

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Abbreviations

BC	Breast cancer
HRQoL	Health-related quality of life
EORTC	The European Organisation for Research and Treatment of Cancer
QoL	Global health status/QoL (Presented in EORTC)
MST	Maximal strength training
1RM	One repetition maximum
Mqf	Quadriceps femoris muscle mass
6MWD	Six minutes walking distance
LBM	Lean body mass
RFD	Rate of force development
DNA	Deoxyribonucleic acid
WHO	World Health Organization
ICF	The International Classification of Functioning, Disability, and Health
CRF	Cancer-related fatigue
BMD	Bone mineral density
DEXA	Bone densitometry
VO_{2max}	Maximal oxygen uptake
ACSM	American College of Sports Medicine
COPD	Chronic obstructive pulmonary disease
PAD	Peripheral arterial disease

Introduction

Breast cancer (BC) is the most frequently diagnosed type of cancer among women, with more than 2 million new cases and over 600 000 deaths annually (Bray et al., 2018), and its global incidence is steadily rising. BC patients through the cancer continuum experience complex health and psychosocial challenges. BC and anti-cancer treatment accompanied by an inactive lifestyle may further impair muscle strength and muscle force development characteristics. Historically, patients diagnosed with cancer were advised to rest and avoid vigorous activity following their diagnosis, but this dogma has changed markedly over the last 20 years as exercise oncology intervention studies have gained broad acceptance and acknowledgment. Strength training can optimally affect muscles and increased muscle strength may contribute to participation in daily activities, thus potentially improving the health-related quality of life (HRQoL). However, the optimal type, intensity, and frequency of strength training, as a part of cancer care, that will most enhance muscle strength during anti-cancer treatment is yet unknown.

Christensen et al. (Christensen et al., 2014) investigated newly confirmed (breast, gastric, colorectal, lung, and pancreas) cancer patients and concluded that these patients had 0.9 kg lower muscle mass compared with healthy controls even before the initiation of anti-cancer treatment. Furthermore, during adjuvant chemotherapy, BC patients lost 1.3 kg lean body mass (LBM) and continued to lose LBM after therapy was completed. Ultimately, BC survivors evaluated after completion of primary therapy displayed 20–30% lower muscle strength compared with healthy counterparts. Most physical activity interventions for BC patients combine aerobic endurance training with strength training and diverse relaxation therapies, hence making it more complicated to evaluate the impact of training type. There has been a limited number of well-defined clinical trials on BC patients that include higher intensity strength training, moreover when intervention is administered during adjuvant treatment.

Training intensities vary substantially across cancer studies ranging from 25–80% of one-repetition maximum (1RM), although, it has been documented that higher training intensities yield greater strength gains in young healthy individuals (Campos et al., 2002). Similarly, greater gains in muscle strength are documented with increasing intensity for cancer patients, however, these patients are likely to have some improvements even at low training intensities (Fairman et al., 2017). The common consent from clinical trials when strength training interventions were applied for cancer patients states that training programs were well tolerated, they are safe, feasible and showed strength improvements that led to improved physical functioning and improved HRQoL (Segal et al., 2003), (De Backer et al., 2007), (Battaglini et al., 2014a). Recognizing that training intensity during strength training is a key

factor to improve maximal muscular strength and strength-related characteristics. Therefore, well-defined training methods with high intensity could also be preferable to induce greater physiological adaptations, thus contribute to faster recovery from specific cancer treatment and enhancing the completion of prescribed anti-cancer treatment.

Thesis perspective

Anti-cancer treatment and inactivity following BC diagnosis induce loss of muscle strength and thus have created a large number of BC patients with very low physical capacities. Despite the well-documented neuromuscular and functional adaptations resulting from strength training, very few studies, quite surprisingly, have investigated the effects of strength training in the early critical phase of BC treatment. Furthermore, the few previous studies (Courneya et al., 2007b), (Battaglini et al., 2007), (Campbell et al., 2012), (Cheema et al., 2008) that have applied clinical strength training also appear to have applied low to moderate loading intensities ($< 75\%$ of 1RM). Results from strength intervention studies document reduced lower extremity muscle strength following chemotherapy for BC (Schwartz and Winters-Stone, 2009) and others present no relevant effects (Buffart et al., 2020; Cornette et al., 2016; Courneya et al., 2007a; Mijwel et al., 2018b; Schmidt et al., 2015; Travier et al., 2015; van Waart et al., 2015a).

Of note, aerobic endurance-related exercise interventions are the primary choice for cancer patients during clinical trials. Thus, few trials that involve strength training are gaining its recognition but still adds to a conflicting body of evidence that inconsistency between observations may be attributable to the type, duration, and cumulative dose of chemotherapy. Typically, strength training interventions in an oncology setting include conventional strength training methodology which is characterized using low to moderate intensity 25–75% of one-repetition maximum (1RM), using 1–3 sets with 8–12 repetitions in each set, with a slow movement in the concentric phase, interventions last from 4 weeks to 12 months, typically including cancer survivors and initiating strength training once treatment is completed (Buffart et al., 2020; Cornette et al., 2016; Mijwel et al., 2018b; Schmidt et al., 2015).

To our knowledge, there are no studies that have applied high-intensity strength training methodology in BC setting and especially during adjuvant chemotherapy. Therefore, in this study, MST to induce neural adaptations using few repetitions (≤ 5) with a higher intensity ($\sim 85\text{--}95\%$ 1RM), and resting periods longer than ≥ 3 minutes between sets, 2 times a week for 12 weeks was applied, moreover, training was carried out during adjuvant chemotherapy. Importantly, the dynamic leg press apparatus was chosen as a testing and training modality not

only because it closely reflects functional performance during daily tasks (Unhjem et al., 2017), but also involving multi-joint execution in the lower extremities.

Recognizing the adverse early phase side effects of adjuvant therapy, in particular, due to the impact of anthracyclines, and low functional status immediately after treatment it remains unknown whether high-intensity strength training could yield similar neuromuscular and functional effects as observed in other patient populations, and whether it is feasible in BC patients shortly after surgery.

Importantly, in the Republic of Latvia medical rehabilitation for cancer patients is limited, and not all effective strength exercise methods have been recognized. As concluded by Health authorities – rehabilitation for patients with cancer are lacking and for a long time has not been a priority (L.R.V.K, 2018). A decrease in physical capacities and functionality are expected, especially during the early phase of treatment (Klassen et al., 2017), thus as a result of impaired physical capacities majority of patients are more likely to experience reduced HRQoL (Møller et al., 2020).

Therefore, ascertain the growing number of BC patients and survivors, this thesis covers an important knowledge of strength exercise benefits for BC patients and could encourage health care professionals and health policymakers to use this information and results for an innovative, cost-effective, and time-efficient strategy to develop effective rehabilitation programs, and further contribute to exercise oncology research field.

Aim and hypothesis

The objective of this doctoral thesis was to investigate the effects of maximal strength training (MST) on one-repetition maximum (1RM), functional performance, walking economy, muscle mass, and health-related quality of life (HRQoL) in women with I–III stage breast cancer undergoing adjuvant chemotherapy.

General hypothesis

It was hypothesized that 12 weeks of MST with emphasis on maximal mobilization of force in the concentric action will increase maximal muscle strength of lower extremities and result in improved functional performance, walking economy, HRQoL, and maintain muscle mass during adjuvant chemotherapy. In contrast, maximal strength, functional performance, walking economy, muscle mass, HRQoL would decrease following adjuvant chemotherapy without strength training.

Objectives of the study

- Explore the effect of leg press MST on muscle strength of lower extremities, applying high training intensity ~ 90% of one-repetition maximum (1RM) and emphasizing maximal intended velocity in the concentric phase of the movement.
- Elucidate whether MST has an impact on quadriceps femoris muscle mass (Mqf) for BC patients during treatment.
- Explore whether MST affects aerobic endurance capacities.
- To investigate MST-induced effects on functional performance applying standardized functional tests before and after the intervention.
- To determine whether MST has an impact on HRQoL using the European Organisation for Research and Treatment of Cancer (EORTC) core questionnaire (C30) and supplementary questionnaire (BR23).

Ethical aspects

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Rīga Stradiņš University and the Scientific Department of Riga East University Hospital.

Personal contribution

The author of the study has carried out all pre and post-testing (110 procedures) and (1248 training sessions). Collected scientific data, interpretation of data, performed statistical analysis, and has written these theses. The thesis consists of 5 chapters: Literature review, Methods, Results, Discussion, Conclusion. The thesis is written on 93 pages, including 6 tables, 8 figures, list of 221 references.

1. Literature review

1.1. Cancer: Major health challenge

Cancer is one of the many noncommunicable diseases and together with diabetes, cardiovascular diseases, chronic respiratory diseases, and mental disorders are responsible for more than 68% of deaths worldwide (Pedersen, 2019). Cancer is a major public health problem worldwide and is expected to rank as the leading cause of death and the single most significant challenge to increasing life expectancy in every country of the world in the 21st century (Siegel et al., 2019). Cancer incidence and mortality are increasingly growing worldwide, in 2018 reaching 18.1 million new cases and 9.6 million cancer deaths worldwide (Bray et al., 2018). Cancer is a general name for a group of more than 100 diagnoses and constitutes with most primary diagnosis further subcategorized based on gene – mutational profile and/or anatomical position. It is a systemic process that involves acquired genetic mutations. All cancers start because abnormal cells growth spins out of control. Cancer cell growth is different from normal cell growth due to deoxyribonucleic acid (DNA) damage. Instead of undergoing apoptosis, cancer cells continue unrestricted proliferation and form new, abnormal cells, therefore cancer cells can also grow invasively into other tissues, contrary to normal cells. Growing out of control and breaking into other tissues are the defining properties of the cancer cell, it can start almost anywhere in the human body and untreated cancer can cause serious illness and burden overall life quality (Nowell, 1986).

1.2. Breast cancer

Breast cancer (BC) is a malignant tumor that originates in the cells of the breast. It is the most frequently diagnosed type of cancer among women, with more than 2 million new cases diagnosed in 2018 worldwide (Bray et al., 2018). Similarly, in the Republic of Latvia, BC also is the most frequently diagnosed cancer among women with more than 1000 new cases diagnosed each year (constituting about 21% of newly diagnosed cancers in Latvia). Incidence tends to increase and in the next decade, new BC cases are expected to increase 1100–1200 cases each year (SPKC, 18.06.2019).

Due to diverse mutational profiles and gene expression patterns among the patients and within tumors, BC is a thoroughly heterogeneous disease in terms of biology, clinical process, and response to treatment (Nature, 2012). BC develops due to DNA damage and genetic mutations that can be influenced by exposure to estrogen. Periodically there will be an inheritance of DNA defects or pre-cancerous genes including *BRCA1* and *BRCA2*. Thus the

family history of ovarian or BC increases the risk of being diagnosed with BC (Harbeck et al., 2019). Estrogen receptor-positive (ER+) BC is the largest and most diverse group of BC patients, accounting for 65–70% of all BC cases, human epidermal growth factor receptor 2 (HER2) positive BC is characterized by amplification and/or overexpression of ERBB2 gene and accounts for 15–22% of cases, whereas triple-negative BC accounts for 10–20% of all BCs and is the most aggressive type, having a different pattern of metastasis and poor survival rates (Minami et al., 2011), (Criscitiello et al., 2012). In a normal individual, the immune system attacks cells with abnormal DNA or abnormal growth. This fails in those with BC disease, leading to tumor growth and spread (Ferguson, 2019).

The incidence of BC increases with age, reaching a median age for diagnosis at ~ 61 years (Bidoli et al., 2019). The reasons for these growing numbers are complex and not always easy to explain, but include both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are related to socio-economic development. Cancer risk factors are overall similar worldwide and include external factors: such as alcohol, tobacco, infectious agents, insufficient physical activity (physical inactivity), increased consumption of unhealthy food, and internal factors: inherent genetic mutations, hormonal disorders, and abnormal immune conditions (Stein and Colditz, 2004), (Kamińska et al., 2015).

Importantly, the five leading behavioral and dietary risks such as high body mass index, low fruit and vegetable consumption, lack of physical exercise, tobacco use, and alcohol intake are responsible for around one-third of cancer deaths. Indicating that lifestyle behavioral factors play an important role in the overall incidence of disease (Kotsopoulos et al., 2005), (Arem and Loftfield, 2017).

1.3. Treatment and side effects

During the past two decades, improvements in screening programs and treatment options in women with BC have led to longer life spans (Hershman et al., 2018). BC can be detected in the early – stages, thus reducing surgery side effects and increase the efficacy of chemotherapy. Currently, the five-year relative BC survival rate is continuously improving and approaching 90% in many countries (Bray et al., 2018). Multidisciplinary treatment options vary substantially from patient to patient, thus surgery and radiation therapy or systemic treatments (chemotherapy, endocrine therapy, targeted therapy, immunotherapy) constitute the mainstay in the management of BC and are considered key contributors to the steadily increasing survival rates.

Yet, its widespread application comes at the expense of numerous side-effects: including loss of muscle strength and muscle mass (Christensen et al., 2014), osteoporosis (Cheung et al., 2013), cardiovascular disease (Hershman et al., 2018), a decline in aerobic endurance capacity (Courneya et al., 2007b), (Peel et al., 2014), metabolic syndrome (Rosato et al., 2011), lymphedema (DiSipio et al., 2013), fatigue (Schneider et al., 2007) and inactivity/disuse syndrome (Huneidi et al., 2018), nausea (Warr, 2008) and pain (Courneya et al., 2003), (Cheema et al., 2008). All these side effects adversely affect patients' health, functional performance and considerably reduce health-related quality of life (HRQoL) (Perry et al., 2007). Older age at diagnosis and promising long-term survival rates have resulted in a large population of BC patients and survivors that will experience unfavorable alterations in physical and mental health as a result of aging and side-effects of improved anti-cancer treatment (De Backer et al., 2008), and counteracting strategies are requested to advance current BC treatment.

1.4. Rehabilitation

Rehabilitation is a set of actions that assist individuals, who experience or have a risk to experience disability, to achieve and maintain optimal functioning in interaction with the environment they reside (WHO, 2011). Rehabilitation is a highly person-centered health strategy and is a fundamental health service, throughout all stages of the life-course, and during all phases of acute, sub-acute, and long-term care (Krug and Cieza, 2017). World Health Organization (WHO) has highlighted during an influential meeting “Rehabilitation 2030: A Call for Action” the global necessity for rehabilitation, emphasizing coordinated actions to maximize the attention of rehabilitation as a health strategy essential to all people across the lifespan and the continuum of care (WHO, 2019), and further to accentuate the immense role of rehabilitation in health service.

Goal setting is a fundamental part of rehabilitation to help a person achieve the maximum degree of independent functioning within limits imposed by their remaining physical, functional, and cognitive impairments. It aims to focus on broad outcomes which include prevention of the loss of function, slowing the rate of loss of function, improvement or restoration of function, adaptation for lost function, maintenance of current function.

To more optimal for health care professionals to organize clinical work and set goals, The International Classification of Functioning, Disability and Health (ICF) is designed to ensure common language for describing the impact of disease at different levels (WHO, 2001). ICF describes “functioning” or “activity” as the mutual interaction between an individual and

their health condition. Additionally, ICF includes “environmental” factors (physical, social and cultural environment) that interact with individual life and management of their life's and the personal factors that influence positive adaptation. Within this framework, rehabilitation specialists together with medical doctors give structured and framed guidelines on further and optimal treatment strategies (Amatya et al., 2017).

1.4.1. Cancer rehabilitation

Cancer rehabilitation accessibility is increasing rapidly in modern cancer management, the majority of cancer patients who received a battery of curative or palliative treatments, substantially increased both the number of cancer survivors living without detectable cancer disease, also the years, cancer patients may live with their diagnosis (Smith et al., 2020). However, in the Republic of Latvia, clinical rehabilitation is critically urgently needed to cope with the disease and treatment-induced reduction of physical capacities. Despite recognition from health policymakers, urgent strategies are required during anti-cancer treatment, which together with the administered anti-cancer treatment, may improve treatment response and lower toxicity burden, and improve independent functioning. To this end, exercise training tailored to cancer patients as a fundamental component of clinical rehabilitation needs to be highlighted in cancer care. Again, person-centered rehabilitation goals and activities are primarily focused to maximize persons' HRQoL.

Recognizing that rehabilitation is an increasingly important health service worldwide, and in light of the aging population and the rising prevalence of cancer, few Latvia non-governmental organisations in recent years have shown acknowledgeable activity, rising patients' needs by offering psychosocial rehabilitation. Additionally, the Oncology Patient Support Society with government contribution has created a Psychoemotional Support Center at The Oncology Center of Latvia, mainly offering psychoemotional support. Although these activities are very beneficial, access to physical rehabilitation still is very limited. The need for physical rehabilitation currently in The Republic of Latvia and the World mostly exceeds its availability, therefore actions are needed to maximize effectiveness, impact, and availability for a person dealing with cancer at any stage of the disease.

1.5. Physical activity and exercise training

Physical activity has consistently been identified as a central element of rehabilitation for many chronic diseases (O'Keeffe et al., 1998), (Remme and Swedberg, 2002), and has been effective for improving HRQoL and reducing all-cause mortality (Nelson et al., 2004). Physical

activity has been defined as any movement of the body provided by skeletal muscles which substantially increases energy expenditure above basal levels (at least, 50% of maximum capacity for work or exercise) (Caspersen et al., 1985b). Exercise, which is planned, structured, purposeful and repetitive, is a mode of physical activity with defined intensity, duration and frequency, and therefore final or an intermediate objective of the exercise is the maintenance, or improvement, of physical capacities. Therefore, an exercise to improve physical capacity components differs from recreational activities: leisure time, household chores, self-care activities with type, intensity, frequency and duration (Irwin et al., 2004). The WHO defines capacity as an individual's ability to execute a task or action, indicating the highest level of function that may be reached for individuals under standardized conditions (WHO, 2007). Thus, capacity is considered widely comparable across different populations. Generally, exercise training (concentrates on specific goals) considered being health-promoting for all humans (Pedersen and Saltin, 2015). Of importance, improved physical capacities as a result of exercise training are generally associated with positive changes in, body composition, and physical functioning as well as in patient-reported outcomes such as fatigue, pain, sleep quality, or HRQoL in more than 26 chronic diseases including cancer (Pedersen and Saltin, 2015).

The most cited measurable components that contribute to physical capacities are aerobic endurance, muscular endurance, muscular strength, body composition, and flexibility (Caspersen et al., 1985a). Muscular strength and aerobic endurance have been recognized as the core components of the physical capacities (Dallmeijer et al., 1996), (Adamsen et al., 2003), thus the main focus when applying exercise training in patient groups in general would be in priority to improve muscle strength and/or aerobic endurance.

1.6. Role of physical activity in cancer prevention

Exercise training is increasingly implemented in the oncology setting in the last 3 decades. With almost 700 studies reporting on exercise interventions in cancer patients, it has been firmly established that exercise training is safe and feasible modality across a broad range of cancer diagnoses and results demonstrate that exercise improves physical functioning, HRQoL, and reduces cancer-related fatigue (CRF) (Schmitz et al., 2010), (Segal et al., 2003), (De Backer et al., 2007), (Battaglini et al., 2014b). All these studies have certainly advanced the field of exercise oncology, providing valuable scientific insight into the role of exercise in the regulation of physiological and psychosocial outcomes (Christensen et al., 2018).

Aerobic endurance and strength training has been advocated as an integral part of cancer prevention, treatment and rehabilitation (Egan et al., 2013), (Christensen et al., 2018).

Besides, regular aerobic endurance and strength training not only reduces the risk of cancer but it also has been shown to reduce treatment side effects, decrease recurrence rate, and improve overall survival in BC patients (Lemanne et al., 2013), (Kraschnewski and Schmitz, 2017), (Hojman et al., 2018) and it has been documented that the relative risk reduction of developing BC for women who engaged in moderate to vigorous physical activity for 3–5 days per week, ranged between 20–40% compared to sedentary counterparts (Lynch et al., 2011), (Cleveland et al., 2012), (Baumann et al., 2013), (Schmidt et al., 2013), (Lahart et al., 2014). Moreover, experiments in murine model tumors have demonstrated that exercise leads to a significant reduction in tumor size and incidence, and these effects are associated with remodeling of the immune tumor microenvironment (Idorn and Thor Straten, 2017). This suggests that apart from the well-documented beneficial effects of exercise on energy balance control and body weight, it may have a direct effect on tumor. Therefore, exercise may not just be preventive but also therapeutic and hence serve as an important new modality for prevention of cancer.

Despite strong evidence, showing that regular physical activity can protect against BC, it has been shown that only 32% of BC survivors engage in the recommended level of physical activity (Kruk and Aboul-Enein, 2006). Furthermore, several studies demonstrated a 24–67% reduction in the overall risk of deaths and a 50–53% reduction in the risk of BC deaths in women who are physically active after BC diagnosis compared with sedentary women (Beasley et al., 2012), (Volaklis et al., 2013).

1.7. Skeletal muscles

Skeletal muscles are the largest organ in the human body, constituting up to 40% of total body (lean) mass in healthy non-obese individuals (Ehrenborg and Krook, 2009). The tissue that muscle consists of, has extraordinary adaptability and is, therefore, able to respond to variable conditions of functional demands including neuromuscular activity and hormonal signaling to reversibly changing its functionality and structural composition (Mujika and Padilla, 2001). Skeletal muscle function is classically defined by its ability to perform muscular contractions, generating external mechanical force, which makes possible physical activities of daily living and exercise (Correa-de-Araujo and Hadley, 2014).

Furthermore, to the functional role of the movement, skeletal muscle has an important metabolic role in glucose and triglyceride storage and consumption. Muscle contractions are important as an aspect of homeostasis and thermoregulation in heat production and regulation (Díaz and Becker, 2010). Interestingly, in recent years it is being emphasized that the effects of exercise are mediated by various molecules (proteins, lipids, RNAs, metabolites, etc.) secreted

into the circulation by muscle, bone, brain, and other tissues, particularly skeletal muscle has been identified as a secretory tissue that releases numerous myokines, which might be a possible therapy-induced from strength training coping with cancer-induced cachexia (Scheele et al., 2009), (Manole et al., 2018). These molecules can be secreted in a soluble form or packaged into carriers known as extracellular vesicles (Fitzgerald et al., 2018).

Also, skeletal muscle plays a vital role in primary and secondary disease prevention as an essential regulator of metabolic and inflammatory homeostasis (Neufer et al., 2015). Importantly, substantial evidence shows that muscle function, defined as muscle strength or muscle composition (muscle mass or size), have been consistently demonstrated to be predictors of overall survival, disease progression and complications to anti-cancer treatment, including postoperative complications and chemotherapy-induced toxicities in cancer patients (Christensen et al., 2014), (Caan et al., 2018), (Simonsen et al., 2018). Conclusively the immunological and metabolic functions of skeletal muscle further emphasize the importance of maintaining and rebuilding muscle mass for those dealing with cancer (Lonbro, 2014).

1.8. Muscle strength

Maximal muscle strength is one of the main physiological factors that define the performance of daily activities and is commonly expressed as one repetition maximum (1RM); the load that a person can attain during a single voluntary effort in standardized movement (Hoff and Helgerud, 2004). Maximal muscular strength is associated with several health-related factors, for instance, resistance to diseases and recovery time from them (Newman et al., 2006), and muscle strength is typically reduced by most diseases, as well as by aging and inactivity (Kalyani et al., 2014). Moreover, in the situation of a pre-existing deficiency, a substantial loss of muscle mass and strength might contribute to a physical decline below a threshold where recovery of normal function is implausible (Wolfe, 2006). Muscle strength also indicates a strong and independent predictor of both all-cause- and cancer mortality (Ruiz et al., 2008). Typically, muscle strength is largely dependent on two main factors: muscle morphology (myofibers, which differ in respect to size, contractile function, and metabolic phenotype) and neural factors such as firing frequency and motor unit recruitment (Aagaard et al., 2002b), (Unhjem et al., 2015). On the muscular level, muscle fiber composition and size are key contributors to the maximal contractile force that can be generated. Type 1 slow-twitch myofibers are characterized by slow contraction time and high oxidative capacity, while Type 2 fast-twitch myofibers are known for having a faster contraction time, rapid fatigue profile and predominant glycolytic metabolism. All muscles contain a mix of these myofibers, ensuring

that muscles can adapt to both aerobic endurance and strength-based exercises (Hawley et al., 2014). For a skeletal muscle to produce maximal force several factors are important: muscle fiber-dependent force-generating mechanisms, and also from initial position, speed of lengthening and shortening, muscle fiber type, cross-sectional area of the muscle, substrate availability, number of motor units activated at the same time, and impulse frequency (Hoff and Helgerud, 2004).

1.9. Anti-cancer treatment affects physical capacities

Within oncology, interest in muscle function has initially been confined to cancer cachexia, which is characterized by systemic inflammation leading to severe muscle wasting (Argiles et al., 2009). A clinical entity like cancer cachexia is associated with approximately 80% of severe cancer cases and it is responsible for more than 30% of all cancer-related deaths (Donohoe et al., 2011). Emerging evidence shows that decreased muscle mass (sarcopenia) (Cruz-Jentoft et al., 2010) is a prevalent condition in cancer patients regardless of disease stage (Prado et al., 2008) and nutritional status (Martin et al., 2013), and is associated with higher mortality rates in both advanced stages (Tan et al., 2009) and early-stage BC patients (Villasenor et al., 2012).

The majority of clinical studies to report muscle strength have used repetition maximum measurement and collectively, the studies indicate that cancer patients have significant impairments in muscle strength regardless of disease stage, when compared with healthy controls matched by age, sex, BMI, and/or physical activity level. For example, Burden et al. (Burden et al., 2010) found that 54% of newly diagnosed early-stage colorectal patients had an 85% lower strength than the age-matched reference group. In accordance, patients with locally advanced prostate cancer undergoing androgen deprivation therapy, which lowers testosterone, had a 29% lower strength compared with the healthy control group (Soyupek et al., 2008). Furthermore, BC survivors evaluated after completion of primary therapy showed consistently lower muscle strength 20–30% in seven different upper body exercises compared with healthy counterparts (Harrington et al., 2011), and up to 25% lower muscle strength of lower extremities (Klassen et al., 2017).

In the large study reporting data using bone densitometry (DEXA) scan on whole-body muscle mass, reported results from 714 newly diagnosed patients with mixed diagnoses (i. e. lung, gastric, esophagus, colorectal, or pancreas cancer) they found that cancer patients had 0.9 kg lower muscle mass compared with healthy controls, before initiation of antineoplastic therapy (Cao et al., 2010). Additionally, early-stage BC patients during adjuvant chemotherapy

lost 1.3 kg of lean body mass and continued to lose lean body mass after therapy completion (Freedman et al., 2004). In comparison, early-stage prostate cancer patients on long-term (>6 months) androgen deprivation therapy had ~2.5 kg lower muscle mass (reported as 4.5% lower lean body mass) compared with healthy BMI-matched controls (Greenspan et al., 2005), while metastatic prostate cancer patients, who were weight stable during 12 months of androgen deprivation therapy, lost 11.8 kg lean body mass (Reis et al., 2009). Additionally, cancer treatment accelerates bone loss, bone turnover, and unfavorable shifts in body composition. Adjuvant chemotherapy has been associated with a 1–2% loss of bone mineral density (BMD) (Winters-Stone et al., 2011), and chemotherapy-induced ovarian failure accelerates the bone loss to 5–8% per year. These changes place BC patients at higher risk of developing osteoporosis (Chen et al., 2015), (Van Poznak, 2015).

Generally, all cancer patients are exposed to a wide range of cancer-specific and noncancer-specific degenerative factors including; aging, malnutrition, physical inactivity, and factors directly related to disease pathophysiology and therapy toxicity which are all potential causes of muscle dysfunction. As a consequence of inactivity muscle strength is reduced, causing an unfavorable chain reaction affecting bone health.

1.10. Physical inactivity

Alterations in physiological properties and a decline in physical capacities are likely due to insufficient physical activity. Opposite to physical activity, inactivity or disuse has been described as a period of insufficient or reduced body movement that causes contrary adaptations of physical activity (Mujika and Padilla, 2001). Typically, injury or illness/treatment is accompanied by reduced engagement in physical activity, which is a major contributor to physical deconditioning and is associated with diminished physiological functions (Bogdanis, 2012). Strong evidence supports that individuals, not being able to manage recommended levels of physical activity increases the risk of cancer, heart disease, stroke and diabetes by 20–30% and shortens lifespan by 3–5 years (Booth et al., 2012), moreover, physical inactivity task social-economic situation through the growing cost of medical care and loss of productivity (Ding et al., 2016).

As mentioned, patients diagnosed with cancer typically reduce their daily physical activity. Most immensely following major surgery, where prolonged bed rest can cause muscle dysfunction as seen in elderly men, whom following 10 days bed rest had a 16% decline in isokinetic muscle strength and a loss of 1.5 kg whole-body muscle mass, including 1 kg from the lower extremities (Kortebein et al., 2007). Results confirm that the loss of strength might

primarily be attributed to a decreased capacity of the nervous system to excite the muscle (Deschenes et al., 2002). Indeed, the study by Deschenes et al., showed that after 2 weeks of right leg immobilization in a lightweight orthopedic knee brace to six male and four female college students decreased strength by 10%, the velocity of peak torque decrease 17% in quadriceps muscle evaluated by electromyography recordings, muscle biopsy, and total work performed (Deschenes et al., 2002). Additionally, adverse effects like pain, physical weakness, or therapy toxicity can furthermore reduce daily physical activity.

Inverse adaptations to inactivity occur fast, and during the first week of immobilization muscle strength is reported to decline by approximately 4% each day (Suetta et al., 2004). Furthermore, it has been reported that muscle strength reduces 25 to 30% after 6 weeks in a famous bed rest study (Berg et al., 1997). Even though 6 weeks of compulsory bed rest is not typical in early-stage BC, but obtained results show the magnitude and quick muscle adaptive response to inactivity.

A recent study found that patients receiving neoadjuvant chemotherapy or radiotherapy walked ~4000 steps per day, compared with ~9000 steps in healthy counterpart controls (Ferriolli et al., 2012). In accordance, BC patients undergoing adjuvant chemotherapy reduced their daily energy expenditure by 10% measured as kcal, which was associated with a loss of 0.4 kg muscle mass (Demark-Wahnefried et al., 2001). However, the direct effects of cancer disease to impaired muscle strength are not easy to separate from indirect effects, such as detraining or changes in body weight and body composition as a consequence of physical inactivity. Therefore, inactivity that accompanies cancer and anti-cancer treatment can further accelerate muscle wasting, muscle strength and lower physical capacities can significantly increase the risk of being diagnosed with cancer, negatively impacting physical function and HRQoL during and after anti-cancer treatment.

1.11. Aerobic endurance capacity and work economy

Together with muscle strength, another key component of physical capacity is aerobic endurance and it is defined as the ability to perform large-muscle, whole-body exercise at moderate to high intensities (Pate and Kriska, 1984). Aerobic endurance incorporates three main factors, that account for interindividual variance in aerobic endurance performance: maximal oxygen uptake (VO_{2max}), work economy, and anaerobic threshold (Helgerud et al., 2007). VO_{2max} has been defined as the amount of oxygen consumed during maximal exercise intensity that could not be increased despite further increases in exercise workload (Hawkins et al., 2007). Whereas, the work economy is defined as the energy expenditure, typically measured

as oxygen uptake ($\dot{V}O_2$) and heart rate, on a given submaximal workload (Heggelund et al., 2013). The anaerobic threshold is defined as the highest sustained intensity of exercise, whereas the oxygen consumption above (aerobic energy production) is supplemented by anaerobic mechanisms, causing a sustained increase in lactate and metabolic acidosis (Svedahl and MacIntosh, 2003).

In studies of human performance, the term work economy is also frequently used to describe the oxygen uptake needed at a given submaximal work rate, or as the oxygen required per mass unit to cover a horizontal distance (Bassett and Howley, 2000). It has been observed that patients with pulmonary, cardiac, or vascular chronic diseases are documented to have impaired walking work economy (Hoydal et al., 2007), (Karlsen et al., 2009), (Wang et al., 2010).

Importantly, that poor muscle strength of the lower extremities is associated with the reduced walking economy – derives from the work economy when defining activity is performed (Helgerud et al., 2011), and as a consequence – individuals with poor muscle strength may use more energy during walking. For a wide range of patient groups, lower muscular strength and poor walking economy contribute to increased physical fatigue, and this might be a limiting factor for endurance-related activities of daily living including domestic chores, work and leisure time activities (Heggelund et al., 2013), thus further enabling a sedentary lifestyle. Reductions in muscle strength related to disuse may also contribute to reducing blood supply to less active muscles, leading to reduced capillary density, which in turn impairs glucose transport and substrate availability, lower mitochondrial density, and decreased oxidative enzyme activity (Thompson, 2002). Exercise intolerance due to anti-cancer treatment and physical inactivity further intensifies CRF, which is the most prevalent symptom among cancer patients (Nail et al., 1991). The problem afflicts up to 96% of patients receiving chemotherapy, 78% of patients receiving radiation therapy (al-Majid and McCarthy, 2001), (Gandevia, 2001), (Skipworth et al., 2007). As a result, a higher level of oxygen uptake and thus increased heart rate is needed for a given workload (Christiansen et al., 2009), (Ganley et al., 2008).

Both aerobic endurance and strength training has the potential to improve the work economy, and both training modalities may even return the work economy in the elderly to a level similar to young (Wang et al., 2017), and also training-induced effects are evident in patients with reduced work economy, some studies showing a recuperation of work economy to the level of healthy age-matched counterparts (Bronstad et al., 2013), (Karlsen et al., 2009), (Lavie and Milani, 1999). Interestingly, it has been shown that strength training alone has been

used as a training modality to improve the work economy (Sunde et al., 2010), (Wang et al., 2017).

A compelling amount of evidence emphasizes that muscle loading and training volume are essential factors to highlight when seeking improvement of work economy following strength training, especially indicating that explosive type programs with higher loads (85–90% of 1RM) seem to be more effective than more hypertrophic type programs using lighter loads (50–70% of 1RM) and a higher number of repetitions (Aagaard and Andersen, 2010), (Heggelund et al., 2013), (Rønnestad and Mujika, 2014).

1.12. Recommended physical activity level for cancer patients

Currently, most physical activity interventions that have been applied in cancer setting combine aerobic endurance training with strength training, relaxation therapies (body awareness, yoga, massage, etc.), and recreational physical activities in the post-treatment phase to reduce nausea, fatigue and improve HRQoL (Baumann et al., 2013), (Christensen et al., 2018). Exercise in oncology (also referred to as “exercise oncology”) is an emerging field of research, and the current physical activity guidelines developed by The American College of Sports Medicine (ACSM) recommend that cancer patients and survivors perform 150–300 minutes of moderate-intensity aerobic exercise per week. Strength training recommendations include moderate-intensity activities for all major muscle groups, at least twice a week, carefully following to current treatment regime, and a general feeling of a patient (Wolin et al., 2012), (Schmitz et al., 2019). However, the American Institute for Cancer Research and The World Cancer Research Fund encourages to achieve a more intensive ratio of physical activity to specifically reduce the risk of cancer: 60 min of moderate-intensity or 30 min of vigorous-intensity exercise daily (Winzer et al., 2011), (Castello et al., 2015). Thus, the current ACSM guidelines advocating 150–300 minutes of moderate-intensity aerobic exercise weekly, plus two sessions of strength training with intensity 50% of 1RM with 2–3 sets of 5–12 repetitions (Schmitz et al., 2019), (Maginador et al., 2020) from a physiological point of view, these guidelines might be too low to get optimal training effect and may not provide equal benefit for all cancer patients (Lemane et al., 2013). It is uncertain if cancer patients may gain, given their treatment-situation, the same physiological benefits as observed in healthy individuals. As an anti-cancer treatment, particularly chemotherapy, may interfere with the typical adaptations observed following strength training, studies investigating interventions during anti-cancer treatment are warranted.

1.13. Exercise training to improve muscle strength

Muscle strength is determined by a combination variety of morphological and neural factors including muscle cross-sectional area and architecture, musculotendinous stiffness, motor unit recruitment, rate coding, motor unit synchronization and neuromuscular inhibition.

Strength training is a set of actions to purposefully improve maximal strength, to produce maximal muscle power (i. e. force x velocity of contraction), and to improve the rate of force development (i. e. Δ force/ Δ time) (Sapega and Drillings, 1983). Training intensity has been recognized as the key stimulus to produce desirable neuromuscular adaptations. An early review By McDonagh et al., documented that any resistance below 66% of 1RM did not affect maximal strength (McDonagh and Davies, 1984), and thus training intensity > 66% higher than the minimal adaptive threshold might be preferable during strength training to induce sufficient strength improvements, however, this intensity threshold not necessary applies for untrained individuals, elderly and patients, they may even benefit from lower training intensities.

Emphasizing, that intensity is the important part and key stimulus, although low/moderate training intensity may yield strength improvements a threshold of 66–70% 1RM is necessary for moderately trained individuals. However, the untrained individuals or patients may have experience improvements at lower training intensities they will certainly have better improvements at higher training intensities. Concluding, there has been a limited amount of studies on BC patients that include high-intensity strength training, especially during the anti-cancer treatment phase.

Typically, strength training is separated into two main categories: strength training that aims to induce muscle hypertrophy, and strength training that aims to induce neural adaptations (Heggelund et al., 2013).

Conventional training protocols focusing on hypertrophy typically are performed using 8–12 repetitions with a load equivalent of ($\sim$ 60–80% of 1RM), practically performed on a slow to moderate velocity, accompanied by eccentric actions and metabolic stimuli to optimize the hypertrophic effect (Kraemer et al., 2002).

Strength training aiming to induce neural adaptations is typically performed using few repetitions ($\leq$ 5) with a higher intensity ($\sim$ 85–95% 1RM). Resting periods are longer with $\geq$ 3 minutes between sets. Importantly, repetitions should be carried out with maximal intended velocity in the concentric phase (Heggelund et al., 2013), to maximally stimulate the nervous system, despite slow actual movement (Behm and Sale, 1993b). This type of strength training which primarily targets neural adaptations has also commonly been referred to as maximal strength training (MST) (Hoff and Helgerud, 2004).

Notably, the feasibility and safety of MST extend across a variety of populations, including the elderly (Unhjem et al., 2015), (Wang et al., 2017), chronic obstructive pulmonary disease (Hoff et al., 2007), coronary artery disease (Karlsen et al., 2009), peripheral arterial disease (Wang et al., 2010) and osteoporosis (Mosti et al., 2013) patients. However, it is unknown whether BC patients suffering from treatment-induced side effects would exhibit similar improvements to such training.

1.13.1. Morphological adaptations

Gains in strength are due to the broad combination of morphological and neural factors. It has been well documented that strength training can induce morphological adaptations within the trained muscle. Three main factors have been identified to induce hypertrophic adaptations: mechanical tension, metabolic stress and muscle damage (Schoenfeld, 2010). These factors induce anabolic results and an increase in myofibril content, it is achieved when muscle protein synthesis exceeds muscle protein breakdown (Phillips, 2014). Other adaptive factors include steeper muscle fiber pennation angles and changes in muscle fiber type (Folland and Williams, 2007), muscle architecture, myofilament density and increased hormonal factors: insulin-like growth factor 1 (Schoenfeld, 2010).

1.13.2. Neural adaptations

MST with the emphasis on the maximal rate of force mobilization in the concentric phase, has been reported to improve strength, peak force, walking economy and rate of force development (RFD) (Karlsen et al., 2009). In this type of training, strength gains have been attributed primarily to neural adaptations such as selective activation of motor units, synchronization, coordination, motor learning, selective activation of muscles involved, ballistic contractions, increased rate coding (frequency), increased reflex potential, increased recruitment of motor units and increased co-contractions of an antagonist (Almasbakk and Hoff, 1996), (Zijdwind et al., 2003), (Folland and Williams, 2007). Reaching maximal force potential depends on activating as many motor units as possible and increase the high firing rates of motor neurons. Including the size principle of motor unit recruitment, the low threshold slow-twitch motor units are recruited first and then the high threshold fast-twitch motor units, and an early adaptation to strength training is enhanced recruitment of the high-threshold units (De Luca and Contessa, 2012).

Recruitment of the high-threshold motor units is particularly important for maximal force production. These contain the largest size and highest number of muscle fibers, and their

glycolytic properties make them quicker and more forceful. Because of their larger diameter, they need a higher impulse frequency to fire (Henneman, 1957). A broad list of neural factors has been identified in neural adaptations as a response to strength training: improved neural drive to the muscle recognized as increased motor unit recruitment and firing frequency seems to be essential for improving strength (Unhjem et al., 2015), improved reflex potential, synchronization of motor units, impaired co-contractions of antagonists, coordination and motor learning also have been recognized as potential adaptations to training response (Sale, 1988), (Duchateau and Enoka, 2002), (Hoff and Helgerud, 2004).

1.13.3. Rate of force development

One of the most important derivatives from muscle strength is explosive muscle strength or contractile RFD that describes the ability to rapidly develop muscular force. RFD is recognized as highly important in health and sports performance (Andersen and Aagaard, 2006). It takes more than 300 ms for an individual to reach maximal force in maximal voluntary contraction (Thorstensson et al., 1976). In contrast, a time ranging from 50–250 ms is typically required to maintain postural balance and prevent falls (Aagaard et al., 2002a). To reach a higher level of muscle force in the early phase of muscle contraction, RFD is influenced by several physiological factors, which include muscle fiber type, muscle cross-sectional area, maximal muscle strength, viscoelastic properties of the muscle-tendon complex and efferent neural drive to the muscle (Andersen and Aagaard, 2006). It has been well documented that strength and RFD improves more in healthy populations and athletes when higher training intensity was applied (Heggelund et al., 2013).

2. Methods

2.1. Subjects

A 57 of newly diagnosed stage I–III BC patients scheduled for adjuvant treatment at the Oncology Center of Latvia, Riga participated in the study from October 2017 to September 2018 (Figure 2.1.).

Inclusion criteria were females between 18–63 years of age with newly (< 3 weeks) diagnosed stage I–III invasive BC, assigned for treatment with lumpectomy /mastectomy, and adjuvant therapy (radiation therapy and/or adjuvant chemotherapy). Exclusion criteria were verified heart disease (coronary heart disease, angina, myocardial infarction, heart failure, arrhythmia, hypertension, valve disease), diabetes, musculoskeletal disorders of lower extremities (osteoarthritis, sacroiliac pain, knee bursitis, tendonitis, coxarthrosis, gonarthrosis, sprained ankle, stress fractures, meniscal lesions/tear damage, disorders of the hamstring muscle group) or any disorder that prohibited participation in the testing procedures or MST. Patients were randomized into an MST group or control group. Before randomization patients were stratified into 3 blocks based on diagnosed BC stage, stage I, stage II, and stage III respectively, then patients in each block using block randomization were randomized to the MST group or control group. Shortly after inclusion and before randomization, 2 patients (mean age 52 years) dropped out due to family or work circumstances. Therefore, 55 patients (MST group; N=27), (Control group; N=28) were randomized and completed the study (Table 2.1.).

Subjects were informed of potential risks (for example; delayed onset of muscle soreness, fatigue 1–2 days following training sessions) and gave their voluntary written informed consent to participate.

Figure 2.1. Consort diagram of the study progress

2.2. Study timeline

All included patients attended a standardized 1.5-hour testing procedure 2–3 weeks post-surgery. The aim was to initiate MST as soon as possible post-operation, after the surgeon’s approval that the healing process on the operated site was without complications. After this was confirmed, patients were randomly allocated 1:1 to standard treatment with or without 12 weeks of supervised MST. The patients allocated to the MST group started their training 1–2 days after the testing and 1 week before receiving adjuvant therapy, subsequently all patients trained during adjuvant therapy. After 12 weeks, the 1.5-hour testing procedure was repeated (Figure 2.2.). The testing procedure started with measurements of quadriceps femoris muscle mass (Mqf), then patients continued with a battery of functional performance tests. Following a short break, dynamic maximal muscle strength of the lower extremities was assessed, then patients continued with walking economy and time to exhaustion testing. Finally, patients completed HRQoL questionnaires.

Figure 2.2. **Timeline visualization of the study**

2.3. Breast cancer treatment

All included patients were treated according to the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) guidelines. Surgery consisted of oncoplastic lumpectomy or mastectomy and sentinel node biopsy or axillary node dissection. After surgery, patients were scheduled for adjuvant anti-cancer therapy potentially receiving chemotherapy and/or radiation therapy and/or Trastuzumab and/or endocrine therapy. Chemotherapy consisted of 4–8 cycles of doxorubicin ($50\text{--}60\text{ mg} \cdot \text{m}^{-2}$) or epirubicin [$60\text{--}90\text{ mg} \cdot \text{m}^{-2}$] and cyclophosphamide ($600\text{ mg} \cdot \text{m}^{-2}$) administered once every third week. Following the completion of anthracycline, some patients were furthermore scheduled to 4 cycles of paclitaxel ($135\text{--}175\text{ mg} \cdot \text{m}^{-2}$) or docetaxel ($75\text{--}100\text{ mg} \cdot \text{m}^{-2}$) administered once every third week. Patients with HER2-positive tumors were treated with 18 cycles of trastuzumab ($600\text{ mg} \cdot \text{m}^{-2}$) administered once every third week after completion of chemotherapy (Table 2.1.). Some patients received endocrine therapy (aromatase inhibitors and/or tamoxifen) and biphosphates following completion of chemotherapy.

Table 2.1.

Anthropometric parameters and treatment

	MST group (n=27)	Control group (n=28)	P-value
Age (years)	48 ± 7	49 ± 8	0.69
Bodyweight (kg)	77.0 ± 15.2	72.3 ± 17.4	0.29
Height (cm)	170 ± 6	167 ± 6	0.07
Disease stage, TNM classification (%)			0.57
IA, IB	9 (33)	13 (46)	
IIA, IIB	12 (44)	9 (32)	
IIIA, IIIB, IIIC	6 (23)	6 (22)	
Surgery (%)			0.37
Lumpectomy	16 (59)	22 (78)	
SSM	5 (19)	4 (14)	
AB	4 (15)	1 (4)	
MRM	2 (7)	1 (4)	
Adjuvant therapy (%)			
Radiation	23 (85)	26 (92)	0.42
Anthracyclines	25 (93)	24 (86)	0.70
Cyclophosphamides	14 (52)	17 (61)	0.51
Taxanes	16 (59)	16 (57)	0.88
Trastuzumab	3(11)	3(10)	0.99
Endocrine therapy	15 (44)	15 (46)	0.75

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as n (%). SSM; skin-sparing mastectomy; AB = Amputation of the breast; MRM = Modified radical mastectomy.

2.4. Muscle mass measurements

Quadriceps femoris (Mqf) was assessed by the following steps: the volume (V) of the left thigh was estimated using the following equation (Layec et al., 2014):

$$V = L \cdot 12\pi^{-1} \cdot (C1^2 + C2^2 + C3^2) - (S - 0.4) \cdot 2^{-1} \cdot L \cdot (C1 + C2 + C3) \cdot 3^{-1} \quad (2.1.)$$

Utilizing standard measuring tape, the thigh-length (L) was measured from the lateral femoral epicondyle to the greater trochanter. The thigh circumferences were measured at the midpoint (C1) and 10 cm distal (C2) and 10 cm proximal (C3) of the midpoint. Further, at the midpoint three skinfold measures (S) were made: medial, anterior and lateral, and was then averaged for the whole thigh using skinfold caliper (SH5020, Saehan Corporation, MD, South Korea). Quadriceps femoris muscle mass (Mqf) was calculated as $Mqf = 0.307 \cdot V + 0.353$ kg (Radegran et al., 1999).

2.5. Maximal muscle strength measurements

Before all strength measurements, a warm-up procedure, consisting of 2–3 sets of 6–8 repetitions was conducted. Maximal dynamic leg press strength for lower extremities was measured as 1RM in a horizontal leg press apparatus (Cybex Eagle 1040, USA). Starting from a near 180° knee-joint angle, the patients were instructed to move slowly to a 90° knee-joint angle, after which they moved concentrically back to the initial position (Figure 2.3.). The load was increased by 2.5–7.5 kg until the patients were unable to complete the lift. 1RM was defined as the heaviest lifted load and was typically obtained within 3–6 attempts. Rest periods of a minimum of 3 minutes were applied between each lift.

Figure 2.3. One repetition maximum testing and training using dynamic leg press apparatus

2.6. Walking economy

The submaximal walking economy was assessed during the submaximal walking exercise on a treadmill. Before the test patients were familiarized with treadmill walking. Following a 5-minute warm-up at a self-chosen speed, patients continued with a 5 minutes submaximal walking economy test, performed on a motorized treadmill (Spirit CT 100, Jonesboro, USA) at 5% inclination. The speed was calculated to yield a workload of 40 Watt for the individual patient, using the following equation (Høydal et al., 2007):

$$\text{Speed (Km} \cdot \text{h}^{-1}) = \frac{40 \text{ Watt}}{[m_b \cdot N] \cdot \sin \theta} \cdot 3.6 \quad (2.2.)$$

where m_b is the individual patient's body mass, N represents newton converted to kg, and θ is the 5% inclination of the treadmill. Thus patients with different body mass would all walk on a work rate corresponding to 40 Watts, implying different walking speeds. The walking economy was defined as the average heart rate, using a heart rate monitor (Polar Electro FT7, Kempele, Finland) at the last minute of the 5 minutes 40 Watt work rate. Besides, patients were asked to

state their subjective rating of perceived exertion (Borg scale) (6–20) to assess perceived exertion and the end of the fifth minute.

2.7. Time to exhaustion

Following the submaximal walking economy test, patients commenced directly to the measurement of time to exhaustion. The speed was held constant at 3.8 or 4.8 km · h⁻¹, depending on the patient's condition, and the inclination was increased by 2% every minute. If the patient was able to continue after reaching an inclination of 12%, the speed was increased by 0.5 km · h⁻¹ per minute until voluntary exhaustion (Wolthuis et al., 1977). The heart rate and perceived exertion (Borg scale) were recorded immediately after the exhaustion test.

2.8. Functional performance

Battery consisting of three functional performance tests, previously associated with daily tasks, were applied. First, 6 minutes walking distance (6MWD) was measured. The patients were instructed to walk back, forth, and around two cones separated > 20 meters in length, with distance interval markings every 3–5 meters, aiming to walk the longest possible distance in 6 minutes (Dobson et al., 2013).

Second, chair rising ability was assessed by 30 seconds sit-to-stand test. Starting from a seated position with crossed arms, the patients were instructed to rise from a 44 cm high chair as many times as possible in 30 seconds (Guralnik et al., 1994).

Third, the stair climb test, ability to climb stairs was assessed as the time needed to ascend and descend 10 stair steps of 18 cm without the use of handrail support as quickly as possible, best out of two trials were recorded (Fiatarone et al., 1994).

2.9. Level of physical activity

Shortly before the scheduled operation (typically 1–2 days), patients were asked if they engaged in recreational physical activities weekly, applying the short form of the International Physical Activity Questionnaire (IPAQ – SF). The IPAQ aimed to determine the activity level of included patients in the present study. Previously, in The Republic of Latvia, A. Kaupužs (Kaupužs, 2011) used IPAQ in this Dissertation where it has been validated and retested. The IPAQ calculates the average weekly physical activity level by estimating the metabolic equivalent of task (MET) score and accounts for the total number of minutes per week spent

with low, moderate, and vigorous-intensity activities (3.3, 4.0, and 8.0 MET-minutes/week, respectively). The IPAQ has previously been tested and documented to have good validity and reliability (Craig et al., 2003). Additionally, patients were asked whether they specifically were involved in regular strength training for the last 6 months before diagnosis.

2.10. Health-related quality of life measurements

HRQoL was measured by The European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), a 30-item questionnaire (version 3.0), (Appendix 4) and an additional Breast cancer module (QLQ-BR23), (Appendix 3) (Aaronson et al., 1993). Core questionnaire QLQ-C30 is the most commonly used for assessing HRQoL in exercise oncology trials. Also, QLQ-C30 is recognized as valid and reliable to assess CRF (Minton and Stone, 2009) and is sensitive to change when used for cancer patients during chemotherapy (Uwer et al., 2011). Before initiation of the study, confirmation from authors was received to use the QOL-C30 and QLQ-BR23 questionnaires. After this was confirmed authors sent both questionnaires in Latvian and Russian languages as this was requested, additionally scoring manual and other relevant supplementary materials with detailed reference values and proper use of questionnaires.

EORTC QLQ-C30 and QLQ-BR23 is a merged system for assessing HRQoL of cancer patients participating in clinical studies. The QLQ-C30 consists of multi-item scales and single-item measures. These include 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning), 3 symptom scales, a global health status/QoL scale and 6 single items. Importantly that each of the multi-item scales includes a different set of items – no item occurs in more than one scale. Additionally, the QLQ-BR23 module consists of 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy, and hormonal treatment), body image, sexual functioning and future perspective (Aaronson et al., 1993).

All of the scales and single-item measures range in scores from 0 to 100. A high score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status /QoL represents high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems (Fayers P, 2001).

2.11. Maximal strength training

The MST group attended two supervised training sessions per week for 12 weeks. The training was carried at the Breast Surgery Department at the Oncology Centre of Latvia, Riga, Latvia, and was initiated 2–3 weeks' post-surgery. As for the testing, MST was performed as a dynamic leg press in the horizontal leg press apparatus using a 90° knee-joint angle. Following two warm-up sets, the patients performed 4 sets of 4 repetitions at ~90% of 1RM. Emphasis was put on slow velocity in the eccentric phase and maximal intended velocity in the concentric, contraction phase. A marked stop of ~0.5 seconds was applied between the eccentric and concentric contraction phases. Rest periods minimum of 3 minutes were used between sets. The load was increased by 2.5 kg when the patients were able to complete all sets. The patients were trained in groups of 3–5 individuals and all training sessions were supervised. A training session typically lasted for 20 minutes, and each time the patients attended training they were asked if they experienced MST-related discomfort, pain, or other adverse events during or between the MST sessions, except the lifted loads feeling heavy when executed. The control group was instructed to perform 3 sets of 10 chair rises twice a week for 12 weeks. All patients were encouraged to maintain their typical level of physical activity during the study period. It was emphasized for both groups not to engage in additional exercise training during the intervention period. After the study, all patients (MST group and control group) received physical activity recommendations based on ACSM guidelines (Campbell et al., 2019).

2.12. Statistical analysis

Statistical analyses were performed using IBM SPSS (version 25), and figures were made using Graph Pad Prism software (version 8). Data distribution was assessed using Quantile-Quantile plots. The power analysis in this thesis was based on previous MST trials conducted for healthy individuals (Støren et al., 2008), and patients (Karlsen et al., 2009), showing a 1RM increase of 15–60 kg after 24 MST sessions. The power analysis in this study was estimated by setting the standard deviation of a 1RM to 15 kg. Presuming a mean difference of 12 kg between the groups in this study at post-test, we needed a total of 52 patients ($n = 26$ in each group) to maintain statistical power of 0.80 and alpha 0.05. Additionally, 25 patients have set a minimum for the EORTC Health-related Quality of life instrument (Aaronson et al., 1993). To compensate for possible dropouts and a relatively short period for data collection, in total 63 patients were aimed to include in the study.

All independent and dependent variables were approximately normally distributed for each group at the pre-and post-test. Changes in dependent variables were examined using a repeated measure mixed ANOVA, with a group (control, MST) and time (pre, post) as factors. Significant interactions were followed up with independent sample t-tests for between-group differences and paired sample t-tests for within-group differences. Spearman's correlation was used to assess associations between pre- to post-test changes in 1RM and pre- to post-test changes in the walking economy, TTE, QoL, and functional variables for combined groups. For categorical variables, χ^2 or Fisher's Exact test was used to determine the difference between groups. Values are expressed as mean $\pm$ standard deviation in text and tables and as mean $\pm$ standard error in figures.

For the article, assessing the impact of MST on HRQoL, data are expressed as mean $\pm$ standard deviation (SD) for descriptive data and tables. To test for differences in changes of variables from pre-test to post-test between groups, an independent sample t-test was applied. Within-group differences in variables were assessed from pre-test to post-test by paired sample t-tests. The statistical level of significance was set at $P < 0.05$. Cohen's d: value effect, 0.1–0.2 small, 0.3–0.5 medium, 0.6–0.8 large, 0.9–1.10 + extreme large.

3. Results

55 of 57 initially scheduled patients completed the study, additional characteristics of patients who completed the study are presented at (Table 3.1.).

Table 3.1.

Patient characteristics and physical activity level at baseline			
	MST group (n=27)	Control group (n=28)	P-value
Physical activity level (%)			0.59
Low – 3.3 METs	22 (82)	21 (75)	
Moderate – 4.0 METs	3 (11)	6 (21)	
High – 8.0 METs	2 (7)	1 (4)	
Strength training	0	0	<0.99
Smoking status (%)			<0.99
Current	3 (11)	3 (10)	
Former	1 (4)	2 (7)	
Non-smoker	23 (85)	23 (83)	
Married, cohabiting or in a relationship (%)	20 (74)	23 (82)	0.70

Categorical variables are presented as n (%). MST; maximal strength training, MET; metabolic equivalent. Physical activity level was assessed by applying the short form of the International Physical Activity Questionnaire short form.

3.1. One-repetition maximum

No between-group difference was observed in one-repetition maximum (1RM) at the pre-test ($P = 0.187$), (Table 3.2.), (Figure 3.1.).

Table 3.2.

Muscle strength before and after of control period and maximal strength training				
Variables	Baseline Mean $\pm$ SD	After 12 weeks Mean $\pm$ SD	Estimated means difference (95% CI)	<i>P-value and Cohen's d-value after intervention</i>
One repetition maximum (kg)				
Exercise	106.8 $\pm$ 22.8	127.2 $\pm$ 26.4	20.4 (17.3 to 23.6)	0.001 ; (0.9)
Control	98.9 $\pm$ 20.7	89.9 $\pm$ 20.9	-8.9 (-11.0 to -6.9)	0.001 ; (0.5)
<i>P-value and Cohen's d-value between the groups</i>	0.19; (0.3)	0.001 ; (1.6)		

Data are presented as mean $\pm$ standard deviation.

- The MST group completed 23 ± 1 of 24 planned training sessions $96 \pm 4\%$.
- The MST group increased 1RM by $20 \pm 8\%$ ($P < 0.001$) from pre- to post-test.
- In contrast, 1RM decreased by $9 \pm 5\%$ in the control group ($P < 0.001$) from pre- to post-test.
- Resulting in 1RM being higher in the MST group compared to the control group at post-test ($P < 0.001$), (Figure 3.1.).

Figure 3.1. One repetition maximum (1RM) following 12 weeks of adjuvant therapy with and without maximal strength training (MST). Data are presented as mean $\pm$ SE. * $p < 0.05$, within-group increase from pre- to post-test. $^s p < 0.05$, within-group decrease from pre- to post-test. $^{\#} p < 0.05$, the difference between groups from pre- to post-test.

3.2. Quadriceps femoris muscle mass

- In the control group, Mqf decreased ($7 \pm 10\%$) from pre- to post-test ($P < 0.001$).
- No changes were found in the MST group, resulting in Mqf being higher in the MST group than the control group at post-test ($P < 0.001$).
- Changes in Mqf was associated with the training-induced changes in 1RM ($r = 0.45$; $P < 0.001$), (Figure 3.2.).

Figure 3.2. Quadriceps femoris muscle mass following 12 weeks of adjuvant therapy with and without maximal strength training (MST). Data are presented as mean $\pm$ SE. ^{\$} $p < 0.05$, within-group decrease from pre- to post-test. [#] $p < 0.05$, the difference between groups from pre- to post-test.

3.3. Aerobic endurance performance

Walking economy and time to exhaustion are presented in (Table 3.3.) with the group – time interactions for the walking economy, the speed at exhaustion and inclination at exhaustion.

- In the MST group, improvements in 1RM were accompanied by the improved walking economy ($9 \pm 8\%$) and increased time to exhaustion during incremental walking ($9 \pm 8\%$; both $P < 0.01$).
- In contrast, the control group reduced walking economy ($4 \pm 4\%$) and time to exhaustion ($10 \pm 8\%$; both $P < 0.01$).
- Rating of perceived exertion, as can be seen from (Table 3.3.), rating of perceived exertion reported as Borg Score fairly well estimate the relative exercise intensity expressed as a percent of maximal heart rate. During the submaximal walking economy test, intensity corresponding to 40 Watts now requires significantly more exertion compared with the MST group, that perceived intensity as less strenuous. During the time to exhaustion test, patients were able to push themselves till the very hard feeling of exhaustion, both during pre-test and post-test.

Table 3.3.

Endurance performance before and after maximal strength training

	Pre	Post	<i>P</i> -value after <i>intervention</i>	Interactions (Time x Group)
Walking economy				
HR (beats·min ⁻¹)				
Exercise	140 ± 16	128 ± 15	< 0.001	< 0.001
Control	134 ± 12	149 ± 12	0.002	
<i>P</i> – value between groups	0.150	0.009		
RPE (6-20)				
Exercise	12 ± 1	10 ± 2	< 0.001	< 0.001
Control	12 ± 2	13 ± 1	0.184	
<i>P</i> – value between groups	0.289	< 0.001		
Graded walking test				
TE (s)				
Exercise	536 ± 71	571 ± 68	< 0.001	< 0.001
Control	531 ± 73	476 ± 63	< 0.001	
<i>P</i> – value between groups	0.814	< 0.001		
HR _{max} (beats·min ⁻¹)				
Exercise	172 ± 8	172 ± 7	<0.99	0.443
Control	167 ± 11	166 ± 11	0.275	
<i>P</i> – value between groups	0.042	0.013		
E _{speed} (km·h ⁻¹)				
Exercise	4.8 ± 0.4	5.1 ± 0.4	< 0.001	< 0.001
Control	4.8 ± 0.5	4.7 ± 0.3	0.002	
<i>P</i> – value between groups	0.454	0.001		
E _{inclination} (%)				
Exercise	11 ± 1	12 ± 1	0.009	< 0.001
Control	11 ± 1	10 ± 2	0.003	
<i>P</i> – value between groups	0.402	0.010		
RPE (6-20)				
Exercise	17 ± 1	18 ± 1	0.120	0.475
Control	17 ± 1	17 ± 1	0.563	
<i>P</i> – value between groups	0.975	0.372		

Data are presented as mean ± standard deviation. MST; maximal strength training, HR; heart rate, RPE; rating of perceived exertion, TE; time to exhaustion, HR_{max}; maximal heart rate, E_{speed}; treadmill speed at exhaustion, E_{inclination}; treadmill inclination at exhaustion.

3.4. Functional performance

- At post-test, the MST group displayed improvements in all functional performance tests, the 6MWD improved by ($10 \pm 7\%$), chair rising performance by ($30 \pm 20\%$) and stair climbing performance by ($12 \pm 7\%$; all $P < 0.001$), presented at (Figure 3.3.).

Figure 3.3. (A) 6MWD (m), (B) chair rising performance (repetitions), and (C) stair climbing performance (s) after 12 wk of adjuvant therapy with and without maximal strength training (MST). Data are presented as mean $\pm$ SE, * $P < 0.05$, increase within-group from pretest to posttest. $^{\$}$ $P < 0.05$, decrease within-group from pretest to posttest. # $P < 0.05$ difference between groups from pretest to posttest.

- Conversely, in the control group, reductions were found in the 6MWD ($5 \pm 5\%$), chair rising performance ($12 \pm 12\%$) and stair climbing performance ($6 \pm 8\%$; all $P < 0.001$).
- As a result, 6MWD ($P < 0.001$), chair rising performance ($P < 0.001$) and stair climbing performance ($P = 0.004$) were different between groups at post-test.
- The change in 1RM correlated with the change in walking economy ($r=0.754$), time to exhaustion ($r=0.793$), six minutes walking distance ($r=0.807$), chair rising performance ($r=0.808$) and stair climbing performance ($r=0.754$; all $P < 0.001$), presented at (Figure 3.4.).

Figure 3.4. Associations between changes in maximal strength (leg press one-repetition maximum) and changes in (A) 6-minutes walking distance, (B) stair climbing performance, (C) chair rising performance, (D) time to exhaustion during incremental walking and (E) walking work economy following 12 weeks of breast cancer adjuvant therapy with and without maximal strength training (MST).

3.5. Health-related quality of life

Changes in Health-related quality of life using The European Organisation for Research and Treatment of Cancer Core Quality of life Questionnaire-C30 (Table 3.4.) and additional Breast cancer module BR23 (Table 3.5.) for MST group and control group followed 12 weeks of the intervention period.

3.5.1. The core questionnaire; QLQ-C30

No significant differences in baseline values between the groups were observed ($p > 0.05$), (Table 3.4.).

Global health status

- The Global health status/QoL (QoL) improved by 13% for the MST group with a large effect ($P=0.002$, $d=0.6$), but no relevant changes were observed in the control group ($P=0.44$, $d=0.2$). The results obtained from the post-test revealed changes with extreme large effect size in QoL between the groups ($P=0.002$, $d=0.9$).
- The improvements in 1RM correlated with the change in QoL ($r=0.60$; all $P<0.001$), (Figure 3.5.).

Figure 3.5. Correlation between changes in maximal strength (leg press one-repetition maximum 1RM) and changes in Global health status/QoL (QoL) following 12 weeks of breast cancer adjuvant therapy with and without maximal strength training (MST).

Functional scales

- Role functioning for MST group increased by 23% ($P=0.001$, $d=0.7$), social functioning by 12% ($P=0.01$, $d=0.5$), emotional functioning improved by 13% ($P=0.001$, $d=0.5$), while emotional functioning decreased by 11% ($P=0.02$, $d=0.4$) in the control group.
- At post-test, differences with large effect size were observed between groups in emotional functioning ($P=0.005$, $d=0.7$) and social functioning ($P=0.004$, $d=0.9$).
- In other functional scales – physical functioning and cognitive functioning – no changes were observed within groups from pre to post-test, however, physical

functioning was higher with extreme large effect size in the MST group compared to the control group after the intervention ($P=0.003$, $d=0.9$).

Symptom scales

- Cancer-related fatigue (CRF) diminished by 24% ($P=0.03$, $d=0.6$) in the MST group, while it became worse by 25% ($P=0.02$, $d=0.4$) in the control group. Differences between groups after the post-test with a large effect in this variable size were observed ($P=0.01$, $d=0.6$).

Table 3.4.

Changes in The European Organization for Research and Treatment of Cancer using the core questionnaire (QLQ-C30) before and after the intervention

Variables	Baseline Mean $\pm$ SD	After 12 weeks Mean $\pm$ SD	Estimated mean difference (95% CI)	<i>P</i>-value and Cohen's <i>d</i> value after intervention
Global health status / QoL				
Exercise	67.2 $\pm$ 15.6	76.2 $\pm$ 14.3	9.0 (3.6 to 14.3)	0.002 ; (0.6)
Control	66.3 $\pm$ 16.5	63.5 $\pm$ 14.7	-2.7 (-10.0 to 4.4)	0.44; (0.2)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.84; (0.1)	0.002 ; (0.9)		
Functional scales				
Physical functioning				
Exercise	88.6 $\pm$ 8.2	90.6 $\pm$ 6.4	2.0 (-1.0 to 4.9)	0.17; (0.3)
Control	84.2 $\pm$ 14.6	81.6 $\pm$ 13.2	-2.5 (-5.3 to 0.2)	0.07 ; (0.2)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.18; (0.3)	0.003 ; (0.9)		
Role functioning				
Exercise	70.0 $\pm$ 26.7	85.9 $\pm$ 18.2	15.8 (6.7 to 24.9)	0.001 ; (0.7)
Control	69.1 $\pm$ 25.5	77.0 $\pm$ 19.5	7.9 (-2.6 to 18.5)	0.13; (0.4)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.89; (0.01)	0.09 ; (0.01)		
Emotional functioning				
Exercise	72.4 $\pm$ 21.1	82.1 $\pm$ 18.8	9.7 (4.1 to 15.4)	0.002 ; (0.5)
Control	74.4 $\pm$ 23.9	66.3 $\pm$ 21.3	-8.1 (-14.7 to -1.3)	0.02; (0.4)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.76; (0.1)	0.005 ; (0.8)		

Table 3.4. (Continued)

Variables	Baseline Mean $\pm$ SD	After 12 weeks Mean $\pm$ SD	Estimated mean difference (95% CI)	<i>P</i> -value and Cohen's <i>d</i> value after intervention
Cognitive functioning				
Exercise	86.3 $\pm$ 15.4	87.0 $\pm$ 14.1	0.7(-5.9 to 7.4)	0.83; (0.1)
Control	86.2 $\pm$ 18.2	80.8 $\pm$ 19.5	-5.3 (-11.8 to 1.2)	0.11; (0.3)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.99; (0.1)	0.19; (0.4)		
Social functioning				
Exercise	76.4 $\pm$ 24.1	85.7 $\pm$ 16.4	9.2 (2.1 to 16.4)	0.01 ; (0.5)
Control	74.3 $\pm$ 27.3	70.2 $\pm$ 20.9	-4.1 (-11.8 to 3.6)	0.29; (0.2)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.76; (0.1)	0.004 ; (0.8)		
Symptom scales				
Fatigue				
Exercise	33.5 $\pm$ 17.1	25.5 $\pm$ 15.5	-7.9 (-1.0 -14.9)	0.03 ; (0.6)
Control	29.5 $\pm$ 18.5	36.8 $\pm$ 16.7	7.3 (1.4 to 13.1)	0.16; (0.4)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.41; (0.2)	0.01 ; (0.6)		

Data are presented as mean $\pm$ standard deviation.

3.5.2. Breast cancer module; QLQ-BR23

Changes in the EORTC QLQBR23 supplementary model are listed in (Table 3.5.).

Functional scales

- A decrease in body image with medium effect size ($P=0.05$, $d=0.4$) was noticed in the control group at the post-test. This variable did not alter in the MST group but showed a medium effect size ($P=0.2$, $d=0.3$).

Symptom scales

- Systemic therapy side effects worsen with the large effect size for the control group ($P=0.001$, $d=0.8$), while there were no considerable changes for the MST group, indicating medium effect size ($P=0.4$, $d=0.3$). Differences with large effect size ($P=0.04$, $d=0.5$) were observed between the groups at post-test.

Table 3.5.

Changes in the European Organization for Research and Treatment of Cancer using Breast cancer module: QLQ-BR23 before and after the intervention

Variables	Baseline Mean $\pm$ SD	After 12 weeks Mean $\pm$ SD	Estimated means difference (95% CI)	<i>P</i>-value and Cohen's <i>d</i> value after intervention
Functional scales				
Body image				
Exercise	64.9 $\pm$ 25.9	72.1 $\pm$ 24.7	7.1(-3.0 to 18.3)	0.19; (0.3)
Control	72.4 $\pm$ 24.6	62.9 $\pm$ 25.4	-9.5 (-19.4 to 0.3)	0.05 ; (0.4)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.27; (0.3)	0.18; (0.4)		
Symptom scales				
Systemic therapy side effects				
Exercise	24.2 $\pm$ 14.7	21.5 $\pm$ 9.9	-2.6 (-9.5 to 4.3)	0.46; (0.3)
Control	17.1 $\pm$ 14.1	29.3 $\pm$ 17.0	12.2 (5.9 to 18.5)	0.001 ; (0.8)
<i>P</i> value and Cohen's <i>d</i> value between the groups	0.74; (0.5)	0.04 ; (0.6)		

Data are presented as mean $\pm$ standard deviation.

4. Discussion

Adjuvant BC therapy is associated with reduced muscle strength, muscle mass, and amount of physical activity (Irwin et al., 2003), (Klassen et al., 2017), (Mijwel et al., 2018c), contributing to the reduced overall HRQoL (Mijwel et al., 2018a). Despite the well-documented effectiveness of strength training to improve these factors in other patient groups, evidence of the strength training, particularly applying higher intensity, in the important initial phase of BC treatment is very limited.

Therefore, the current thesis sought to investigate the effect of strength training in functionally relevant lower extremities, performed with high loads (~90% 1RM) and few repetitions (4), in newly diagnosed BC patients undergoing adjuvant therapy. The major findings were that three months of MST yielded large improvements in lower extremity maximal muscle strength, walking economy, and functional performance, and maintained muscle mass. Additionally, improved strength contributed to increased HRQoL, and improved role functioning, emotional functioning, social functioning, simultaneously reducing the sense of CRF. Importantly, improvements in body image and reduction in side effects experienced during treatment showed significant changes after the intervention period. Conversely, patients assigned to the control group receiving prescribed treatment alone without any strength training displayed reductions in all assessed variables. The majority of the patients were not physically active starting adjuvant treatment, thus it has been shown that lower physical activity level has the potential to increase the risk of being diagnosed with cancer (McTiernan et al., 2019). The results of the current study add to a growing body of evidence supporting the inclusion of structured strength exercise prescription and advocate that lower extremity MST should be considered as part of BC management post-surgery, preferably starting before initiation of adjuvant chemotherapy to maintain, or even improve, physical and mental health.

4.1. Muscle strength following maximal strength training

Strength training has the purpose of inducing neural and muscular adaptations. Strength training programs for BC patients vary considerably in training volume (the amount of work done: including repetitions per exercise and the total amount of sets per training session), frequency (how often certain exercise is performed/practiced or certain muscle trained) and intensity (percentage of 1RM of weight that has been used during exercise) (al-Majid and McCarthy, 2001), (Campbell et al., 2012).

Most of the strength training interventions in oncology settings apply low to moderate training intensities < 75% of 1RM, using 1–3 sets and performing ≥ 8 repetitions. Typically

training interventions last 4–weeks to even 12 months, carried out in clinical setting or home-based training programs, performing an exercise with a slow movement in concentric action, and initiation of the training commonly starts after completion of primary treatment (Wernbom et al., 2007), (Schmitz et al., 2010), (Hagstrom et al., 2019). Therefore, a need to expand knowledge and contribute to the exercise oncology field, well-defined strength training methods with higher strength training intensity are gaining recognition. To our knowledge, the present study is the first to test the effects of high-intensity strength training in BC patients receiving adjuvant therapy.

In the present study, the control group that received standard adjuvant treatment alone without strength training displayed a 9% decrease in leg press maximal muscle strength, apparent after only 12 weeks of adjuvant therapy, corresponds to more than one decade of typical aging (Lindle et al., 1997), whereas patients in the MST group performed strength training two times a week had ~30% higher maximal muscle strength after three months than the control group. This MST-induced effect is similar to what has been observed after a comparable volume of leg press MST in healthy individuals (Hoff et al., 2002) and other patient populations (Hoff et al., 2007), (Wang et al., 2010), (Helgerud et al., 2011) where leg press MST has been examined in COPD and peripheral arterial disease patients (PAD). Even though the pathology is different, COPD, PAD and BC patients share the condition of being untrained and with lower physical capacities. The strength improvements in the COPD and PAD patients were similar to the improvements observed in the present study with dynamic 1RM. It is striking that MST seems to cause similar improvements in strength across age, level of physical capacities and patient populations when the intensity is kept constant. Importantly, the ~20 kg improvement in leg press 1RM for the MST group in the current study is about 2.5 times larger compared to the ~8 kg 1RM increase observed in a previous study where the patients exercised three times a week with an intensity corresponding to 60–70% of 1RM (Courneya et al., 2007b).

Several mechanisms might explain large strength gains despite receiving adjuvant chemotherapy. The repeated, regular, episodic bouts of muscle contraction associated with strength training stimulate numerous physiological adaptations, altering the phenotype of skeletal muscle; including changes in the contractile apparatus, mitochondrial function, metabolic regulation and intracellular signaling, amount of contractile protein and stiffness of the connective tissue (Wernbom et al., 2007). The adaptations to strength training are generally observed after 8 to 12 weeks (Folland and Williams, 2007), which may result in an increase in muscle size by increasing cross-sectional area, neural adaptations (motor output), and improved muscle strength (maximal force production). Adaptations evident within the neuromuscular system have centered on increases in motor learning through the nervous system and increased

maximal muscle activation by motor unit synchronization, muscle recruitment and increased neural activation (Endo et al., 2020). All of these adaptations play important role in strength increase following effective strength training.

Typically MST has been shown to improve both maximal strength and RFD, generally, RFD improves ranging from 26% to 60%, and is important in functional performance (Heggelund et al., 2013), (Unhjem et al., 2016). Although not measured in the present study, similar improvements in RFD might have been gained for BC that participated in the MST. This is also supported by improved walking economy, which has been mainly attributed to improved RFD (Støren et al., 2008). Contrary, the control group performing chair rises three times per week did not reach the required intensity, thus not ensuring enough stimulus to excite motor units, and muscle strength decreased were accompanied by the reduced walking economy and functional performance.

Reduce muscular strength and RFD have been associated with a higher risk of falls and fractures (Moreland et al., 2004). Increased age, anti-cancer treatment side effects and decreased bone density (Winters-Stone et al., 2013) along with the reduced RFD, put BC patients at higher risk of falls and impaired daily functions.

4.2. Changes in muscle mass

Muscle atrophy or cancer-related muscle wasting also known as cachexia may be triggered as a consequence of many different physiological and pathological processes. Cachexia is the cause of death for approximately 2 million people worldwide and severely reduces HRQoL (Burckart et al., 2010), which is a prevalent side-effect, often occurs as a consequence of anti-cancer treatment and is indicative of worse outcomes and poor participation in daily activities in cancer patients (Mazzuca et al., 2018). Cachexia is associated with approximately 80% of severe cancer cases and it is responsible for more than 30% of all cancer-related deaths (Isaac, Tan et al., 2015).

The molecular mechanisms underlying cancer-related muscle wasting have not been fully elucidated. Available evidence suggests that a notable role is played by increased muscle protein degradation and impaired muscle protein synthesis and insufficient myogenesis. Multiple factors appear to contribute to alterations in muscle wasting, such as several pro-inflammatory cytokines that have been produced by some of the tumor cells: tumor necrosis factor-alpha (TNF- α), interleukin 1 (IL-1 α , β), interleukin-6 (IL-6), interferon-gamma – (IFN- γ), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) (Schneider, Hsieh et al., 2007), (Battaglini et al., 2012). These inflammatory mediators and tumor products limit

anabolism and increased catabolism that contributes to loss of the lean muscle mass that occurs due to decline in protein synthesis and increased protein degradation (Argiles, Costelli et al., 1999), (Yakovenko et al., 2018) if unchecked, these physiological responses/ adaptations lead to a gradual reduction in functionality and thus worse HRQoL. Also, alterations in energy metabolism involving mitochondrial dysfunction have been linked to the cancer-related muscle wasting process (Johns et al., 2013). For example, while the loss of contractile proteins predominantly affects the type II fast fibers during aging or cancer cachexia, causing a rise to a higher proportion of slow type I versus fast fibers (Fanzani et al., 2012). These alterations in combination with anti-cancer treatment and absence of strength training for the control group lead to significantly reduced Mqf by ($7 \pm 10\%$).

Researchers for several years have taken this integrative physiology approach in an attempt to examine the influence of exercise training on mitigating the cachectic effects in cancer patients (Battaglini et al., 2007), (Lira et al., 2011). Importantly the positive influence of physical exercise on protein synthesis in skeletal muscle through an up-regulation of anti-inflammatory cytokines: the interleukin-1 receptor antagonist (IL-1RA), interleukin 4 (IL-4), interleukin 10 (IL-10), interleukin 15 (IL-15), soluble tumor necrosis factor receptors (sTNFR), soluble IL-6 receptor (sIL6R) and acceleration of myoplasticity events (i.e., protein synthesis) within the skeletal muscle have been recognized (Kim et al., 2015), (Suzuki, 2018). Our study supports and demonstrates that BC patients can engage in regular strength training and that physical exercise have the potential to shift the balance of protein turnover towards an anabolic vs. catabolic state (Montalvo et al., 2018). That is, the appropriate amount of strength training facilitates muscle mass retention or even hypertrophy.

However, only a few studies have been able to demonstrate the effect of strength training on muscle mass during anti-cancer treatment (Christensen et al., 2018). Importantly, muscular adaptations to training, first occur at the neural level, before morphological changes, which are dependent on protein synthesis and myofibrillar transformation, thus, taking a relatively longer adaption period (Folland and Williams, 2007). As previously described and typically observed for BC patients following anti-cancer treatment, the control group in the present study, displayed reductions in Mqf, indicating that muscular alterations contributed to the reduction in lower extremity maximal muscle strength. Indeed, our results revealed a tendency for alterations in Mqf to be associated with changes in lower extremity maximal muscle strength. In this perspective, the length of most strength exercise-trials for cancer patients are relatively short (<3 months), suggesting that while the time for morphological adaptations might be too limited to observe large-enough adaptations, but might be adequate for neural adaptations (Egan and Zierath, 2013). Although MST primary is tailored to induce neural adaptations and has a

relatively low metabolic stress, it was effective to maintain Mqf in the current study for the MST group. This may be unsurprising considering a recent study, documenting that MST led to similar improvements in muscle morphology as what is seen following conventional (hypertrophy) training with 10–12 repetitions of moderate-intensity (70–75% of 1RM) in older adults (Wang et al., 2017). Our results show and support previous findings that MST primary is tailored to increase the muscle strength through neural mechanisms, importantly that muscle mass can be maintained during adjuvant treatment, emphasizing that BC can experience both neural and muscle morphological adaptations during adjuvant chemotherapy.

The absence of strength training led to reduced muscle mass in the control group with a Mqf decrease ($7 \pm 10\%$) from pre-to post-test ($p < 0.001$). Emerging evidence supports that chemotherapeutics promote a reduction of muscle fiber size, causing severe depletion of skeletal muscle (sarcopenia) (Guigni et al., 2018). Depletion of muscle mass can lead to chemotherapy toxicity, which in turn may necessitate dose reduction or delayed administration (Prado et al., 2011). Indeed, it has been an important field of interest that patients who continue to be active during anti-cancer treatment and include strength training in their weekly routine can tolerate and enhance treatment efficacy and regain physical function much faster after treatment is completed (Segal et al., 2003), (Campbell et al., 2012), (Courneya et al., 2014), further supporting adding strength training during anti-cancer treatment. Patients diagnosed with BC often reduce daily physical activity, due to adverse effects like pain, physical weakness, or chemotherapy-induced toxicity, also lack information, dialogue with physicians and encouragement to stay physically active during treatment, augment effects of inactivity (Christensen et al., 2014).

Our results further support that incorporation of strength training as a part of the therapeutic regime of cancer treatment can result in skeletal muscle protein synthesis, thus potentially maintaining muscle mass.

4.3. Functional performance

The present study highlights that MST improved functional performance, measured as stair climbing, sit-to-stand test, and 6MWD. Again, a reduction in functional performance was observed in the control group in all measured functional tests. In combination, these findings indicate that the loss of muscle strength and mass during anti-cancer treatment is reflected in reduced ability to perform daily functional tasks, thus potentially having a large negative impact on HRQoL. Since the majority of weight-bearing activities are performed using the legs, strength training of the lower extremities may especially be an advantageous investment for BC

patients during anti-cancer treatment. For this purpose, leg press exercises, tasking the entire stretch apparatus may be a simple and effective strategy to improve the strength of important weight-bearing muscle groups.

4.4. Maximal strength training improves walking economy (endurance-related activities)

After the intervention period walking economy improved the following 24 sessions of MST, by reduced heart rate during the submaximal walking economy test. The increased strength in BC patients led to improved aerobic endurance performance, by improving one of the main components; walking economy.

Several previous investigations have found MST to improve the work economy (Barrett-O'Keefe et al., 2012), (Wang et al., 2017), (Berg et al., 2018) and our study supports these findings adding that MST can effectively improve the work economy measured during submaximal walking also for BC patients. Importantly that training compliance also was high in the current study, indicating that MST appears to be tolerable and feasible. Furthermore, in the present study, the improved walking economy correlated positively with improved muscle strength. This is in accordance with observations from Wang et al. (Wang et al., 2010), strengthening our assumption that the walking economy improvements were indeed related to the improved muscle strength.

The ability to sustain a selected work rate over a longer duration is important in daily life. As most activities in everyday life are carried out at light to moderate intensities, the VO_{2max} is rarely required (Støren et al., 2008). However, with declining VO_{2max} as a result of inactivity or disease, these chores would become increasingly difficult, or the intensity at which they were conducted would need to be reduced (Støren et al., 2008). Also, the absolute metabolic cost of everyday tasks is increased in several patient groups and with aging (Knaggs et al., 2011), further contributing to CRF.

Improvements in the walking economy contributed along with the other measures of physical function (6MWD; stair climbing; sit to stand; time to exhaustion) to an overall consideration that BC patients that had trained MST not only were able to avoid the typical reduction in daily function but were able to improve their performance correspondingly as is seen in healthy.

Contrary, the control group reduced the walking economy. It has been reported that neural mechanisms are responsible for early strength loss to muscle unloading. Indeed, a study by Deschenes et al. (2002) showed that after 2 weeks of right leg immobilization in a lightweight orthopedic knee brace to six male and four female college students decreased strength by 10%, the velocity of peak torque decreases 17% in quadriceps muscle evaluated by

electromyography recordings, muscle biopsy and total work performed. Results confirm that the loss of strength can primarily be attributed to a decreased capacity of the nervous system to excite the muscle (Deschenes et al., 2002).

Alterations in muscle resulting from reduced levels of physical activity may also contribute to a decrease in muscle endurance. These alterations reduce blood supply to less active muscles that leads to reduced capillary density, which impairs glucose transport and substrate availability, lower mitochondrial density, and decreased oxidative enzyme activity, these reverse changes also reduce muscle ability to generate force (Thompson, 2002). Inverse adaptations to inactivity occur fast, and during the first week of immobilization muscle strength is reported to decline by approximately 4% each day (Suetta et al., 2004). Furthermore, it has been reported that muscle strength reduces 25 to 30% after 6 weeks of bed rest (Berg et al., 1997). Work economy is a major determinant of aerobic endurance performance. In real life, these performances may range from professional competitions and daily activities in patients with reduced physical capacities. In cancer patients' work economy, more likely is at a level that challenges the performance of daily activities and may lead to reduced HRQoL. This study advocates MST using heavy loads and explosive movement in concentric action to improve the walking economy. After MST training walking economy improved by ~ 9%. In other words, a person now has the ability to perform more walking or to perform the same amount of work with reduced effort as observed in the present study, were walking at 40 Watts now required less energy. Opposite, reduced walking economy would likely have significant practical implications for control group.

4.5. Tolerance of the high-intensity program

Importantly, while MST may be considered strenuous, the 96% completion rate in the present study indicates that BC patients are, despite suffering adverse side effects of early phase adjuvant therapy, capable of performing strength training of the lower extremities with a targeted intensity ~90% of 1RM. Furthermore, the intervention was completed without any reported difficulties or injuries, indicating that the feasibility and safety of leg press MST during BC treatment should be considered satisfactory.

Of notice, it is only the concentric phase of movement during MST that is carried out with high intensity. The eccentric phase, which is more associated with muscle soreness and microdamage to the muscle (Toien et al., 2018), is carried out in a slow and controlled fashion. This is a likely reason why MST may be safely performed, as the high impact force associated with eccentric muscle action is avoided (Toien et al., 2018). Importantly, again, the concentric

phase may preferably be performed with maximal intended velocity, to maximize neural stimulation (Behm and Sale, 1993a).

The targeted training intensity was met during all training sessions, and the sessions were also executed following the protocol. Included patients completed the study, and except for the repeated lifts typically being perceived as heavy, no patients reported MST-related adverse events during or between the testing or training procedures.

4.6. Health-related quality of life and maximal strength training

HRQoL is part of objective quality of life and attributes to components of quality of life that center upon or are directly and indirectly affected by health condition (treatment side effects, physical, cognitive, emotional, and social functioning, etc.) and as such HRQoL overlaps with the concept of health status (Karimi and Brazier, 2016). HRQoL is persons perceived physical, mental, social, and functional health that is integrated these different domains in a common score, thus the universal goal for exercise trials in oncology seems to be focused on different physiological outcomes, to improve persons HRQoL.

Results in the present study show that 12 weeks of MST contributed to improved Global health status/QoL (QoL) by 13% for the MST group, but no relevant changes were observed in the control group. Importantly, that intervention period induced improvements in role functioning by 23%, emotional functioning by 13%, social functioning by 12%, simultaneously reducing the sense of CRF by 24% for the MST group. Thus, the benefit of strength training on fatigue appears to be not only statistically significant but also clinically relevant, as many BC patients experience fatigue as the most distressing side effect of chemotherapy (Berger et al., 2012).

Similar to our findings, a trial was done by Van Waart et al. (van Waart et al., 2015b), who included moderate to high-intensity aerobic endurance exercise and progressive strength exercise demonstrated that a combined exercise program was effective in counteracting CRF. In contrast, another trial by Mutrie et al. (Mutrie et al., 2007), showed no difference in CRF between participants performing combined aerobic endurance and strength exercises versus a control group at moderate-intensity, concluding that higher intensity/load was required to counteract increases in CRF and that multi-modality of exercise may interfere with typical physiological adaptations from strength training alone. As our study investigated strength training alone without aerobic endurance exercise, therefore our results suggest that MST is an effective type of exercise, likely reducing fatigue with maintained muscle mass and improved physical functioning.

Noteworthy, the control group was not able to counteract a decrease in CRF following the intervention period, CRF worsened by 25%. This indicates how severely disease and treatment without strength training impacts productivity tasks, leisure-time activities, family life and relationships with friends, all of these socially and emotionally important activities now would demand more energy. It seems that intensity is important not only to improve CRF but also to improve HRQoL. In the study by Courneya et al. (Courneya et al., 2007b), a multimodal training intervention did improve physical capacities but did not improve HRQoL, elucidating that strength training with and intensity (60–70% of estimated 1RM) was not sufficient, and 70% adherence of training sessions, have reduced total training volume. In contrast, 96% adherence rate in our study far exceeds the typically observed exercise trial adherence rate (Rejeski et al., 2007), this supports that high intensity indicates large strength gains and has substantially improved CRF, and HRQoL, despite the continuation of adjuvant anti-cancer therapy. In our study, BC patients continued MST with excellent adherence. Additionally, MST was initialized as early as possible, and before receiving the first chemotherapy session patients were familiar with training and already got initial strength improvements that kept them regularly to attend MST.

To our knowledge, this is the first trial to demonstrate the effects of MST on the role, social and emotional functioning in patients with BC during chemotherapy as observed from the EORTC QLQ-C30 questionnaire. Our findings might be explained that being involved in a supervised exercise program can improve both role and emotional functioning, and such positive interaction might potentially give noticeable improvements (McAuley et al., 2000). In our study, training was carried out in small groups of 3–5 patients, thus factors such as social support from the training peers, talking to other BC patients, supervision from an exercise physiologist, traveling to an exercise facility twice a week, and having a positive attitude by becoming proactive, may give an additional role for observed improvements. An increased level of self-efficacy has been suggested as a possible mechanism for improved emotional functioning in the elderly engaged in exercise (McAuley et al., 2000), which in our study may be linked to feelings of being able to carry out the MST and continue to carry out daily activities. Also, results from the EORTC QLQ-BR23 questionnaire reveal that systemic therapy side effects and body image worsen for the control group, while changes in these scales were mitigated for the MST group.

A cancer diagnosis is an especially challenging period for a person, MST has shown to be an effective method and contribute to improve HRQoL and reduce CRF for BC during early anti-cancer therapy. Although the guidelines of the American College of Sports Medicine and the American Cancer Society include strength training in exercise recommendations,

predominantly exercise programs focus on aerobic endurance exercise. Therefore, our results will support raising awareness that strength training is effective and important in addition to aerobic endurance exercises. Importantly, our results support that MST works effectively not only on the physical aspect but also on the psychosocial aspect, thus positively influencing HRQoL.

4.7. Strengths and limitations

Few studies have investigated the effects of strength training in the initial phase of BC treatment. A strength of the present study is the application of effective high-intensity strength training of functionally relevant muscle groups of the lower extremities. MST is time- and cost-efficient, demanding less than an hour of training per week, and patients may train in groups of 3–5 individuals per training apparatus during the same training session. Despite adverse early phase side effects of adjuvant therapy, the patients had a completion rate of 96%, suggesting leg press MST to be a feasible exercise modality in this critical phase of BC treatment. Importantly, the strength training was also carried out without any observed injuries during the training period. Ultimately, the major strength in the current study was that the large improvements in lower extremity muscle strength were strongly associated with improvements in the patient's functional performance and also reduced CRF and improved HRQoL.

A limitation of the current study is the lack of measurements of neural and muscular components. This may have provided important information about the origin of the strength training-induced improvements, and if certain components of adjuvant therapy possibly affected some factors more than others. As BC patients may suffer attenuated bone health, it would also have been beneficial to include musculoskeletal measurements. Increased lower extremity muscle strength has previously been documented to result in enhanced bone formation and bone mineral density (Nygard et al., 2018), and it would have been of great value to investigate if this was also the case in our study. Finally, the relatively short duration of the study also represents a limitation, as information on long-term effects would have provided a better understanding of the role of exercise in breast cancer treatment and survival rate.

4.8. Clinical implications for cancer rehabilitation

The present study demonstrates the importance of counteracting the detrimental effects of adjuvant BC therapy on neuromuscular function. Indeed, while patients commencing leg press MST improved lower extremity maximal muscle strength, walking economy, functional

performance, maintained muscle mass, and improved HRQoL, the control group was subject to reductions in all these variables. Notably, 20 minutes of leg press MST 2 times per week was sufficient to gain lower extremity muscle strength and functionality. Only one exercise, dynamic leg press, was performed. Also, the effort required to lift heavy loads for 4 repetitions might be strenuous, no adverse side effects (increased level of fatigue) were recorded. This opens wide variations of possibilities on exercise type and muscle groups trained, therefore giving adaptive options to include this type of methodology in other cancer diagnoses. Although it would be beneficial to include strength training of other muscle groups, the lower extremities should be prioritized due to their weight-bearing function. Taken together, the findings in the current study certainly support previous suggestions of implementation of strength training in adjuvant BC treatment and extend recommendations to include effective high-intensity MST of the lower extremities. However, when higher training intensities are applied, supervision of trained medical personal should be mandatory to avoid the risk of injuries. Strength training with progression should be accessible and implemented as soon as possible following the BC diagnosis, to maintain or even improves HRQoL.

Conclusion

1. The present study showed that three months of leg press maximal strength training was an effective, safe, and feasible method for improving maximal muscle strength during adjuvant breast cancer treatment.
2. Starting strength training early during breast cancer treatment may prevent impaired muscle mass, maximal strength training ensured sufficient stimulus to maintain muscle mass for breast cancer patients during adjuvant therapy.
3. Improved lower extremity maximal muscle strength in breast cancer patients receiving adjuvant treatment was associated with improvements in the aerobic endurance capacity, by improving walking economy.
4. Maximal strength training on functionally relevant lower extremities improved functional performance.
5. Maximal strength training contributed to improved health-related quality of life, by reducing the sense of fatigue, improving global health status, social factors, and lighting treatment side effects.

These results advocate that lower extremity high-intensity strength training should be considered as part of BC treatment to not only counteract the typically observed decline in lower extremity muscle strength but also to improve physical health, functioning, and HRQoL from the time of diagnosis.

Presentations on the study topic

List of original articles

Article I

1. **Heavy resistance training in breast cancer patients undergoing adjuvant therapy.**

Ceseiko, R., Thomsen, S. N., Tomsone, S., Eglitis, J., Vetra, A., Srebnijs, A., Timofejevs, M., Purmalis, E., Wang, E. (2020). Heavy Resistance Training in Breast Cancer Patients Undergoing Adjuvant Therapy. *Medicine and Science in Sports and Exercise*, 2020;52(6):1239–1247 (Appendix 1).

Article II

2. **The impact of maximal strength training on quality of life among women with breast cancer undergoing treatment.**

Ceseiko, R., Eglitis, J., Srebnijs, A., Timofejevs, M., Purmalis, E., Erts, R., Vetra, A., Tomsone, S. (2019). The impact of maximal strength training on quality of life among women with breast cancer undergoing treatment. *Experimental Oncology*, 41(2), 166–172 (Appendix 2).

Abstracts and presentations at the international conferences

1. **Ceseiko, R.** (2017). 84P - Effective strength training for breast cancer patients: a literature review. *Annals of Oncology*, 28, x23.
doi:<https://doi.org/10.1093/annonc/mdx655.026>. ESMO Asia 2017 Congress, Singapore, Singapore, 17/11/2017–19/11/2017 (Poster presentation).

2. **Ceseiko, R.**, Tomsone, S., Srebnijs, A., Vetra, A., Timofejevs, M., Purmalis, E. & Eglitis, J. (2018). Maximal Strength Training for Breast Cancer Patients Undergoing Adjuvant Treatment. *Journal of Global Oncology*, 4(Supplement 2), 102s-102s.
doi:10.1200/jgo.18.29400. World Cancer Congress held in Kuala Lumpur, Malaysia from 1 – 4 October 2018 (Oral presentation).

Abstracts and presentations in local conferences in Latvia

1. **Cešeiko, R.**, Eglītis, J., Vētra, A., Tomsone, S. Efektīvas spēka treniņa metodes krūts vēža pacientēm: literatūras pārskats. Rīgas Stradiņa universitātes 2018. gada zinātniskā konference, Rīga, Latvija, tēžu grāmata: 119 (Oral presentation).

2. **Cešeiko, R.**, Eglītis, J., Srebnijs, A., Timofejevs, M., Purmalis, E., Tomsone, S. Krūts vēža slimnieču aerobās spējas pirms ķīmijterapijas uzsākšanas. Rīgas Stradiņa universitātes 2018. gada zinātniskā konference, Rīga, Latvija, tēžu grāmata: 97 (Oral presentation).

3. **Ceseiko, R.**, Eglītis, J., Srebnijs, A., Timofejevs, M., Purmalis, E., Vētra, A., Tomsone, S. Maximal strength training for breast cancer patients undergoing adjuvant treatment. Rīga Stradiņš University international conference “Knowledge for Use in Practice”, 1.–3. aprīlis, 2019, Rīga, Latvija, tēžu grāmata: 52 (Poster presentation).

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Appendix

Heavy Resistance Training in Breast Cancer Patients Undergoing Adjuvant Therapy

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ABSTRACT

CEŠEIKO, R., S. N. THOMSEN, S. TOMSONE, J. EGLĪTIS, A. VĒTRA, A. SREBNIJS, M. TIMOFEJEVS, E. PURMALIS, and E. WANG. Heavy Resistance Training in Breast Cancer Patients Undergoing Adjuvant Therapy. *Med. Sci. Sports Exerc.*, Vol. 52, No. 6, pp. 1239–1247, 2020. **Background and Purpose:** Adjuvant breast cancer therapy may reduce maximal muscle strength, muscle mass, and functional performance. Although maximal strength training (MST) has the potential to counteract this debilitating outcome and is shown to be superior to low- and moderate-intensity strength training, it is unknown if it can elicit effective adaptations in patients suffering treatment-induced adverse side effects. **Methods:** Fifty-five newly diagnosed stage I to III breast cancer patients (49 ± 7 yr) scheduled for adjuvant therapy were randomized to MST or a control group. The MST group performed 4×4 repetitions of dynamic leg press at approximately 90% of one-repetition maximum (1RM) twice a week for 12 wk. **Results:** In the MST group, improvements in 1RM ($20\% \pm 8\%$; $P < 0.001$) were accompanied by improved walking economy ($9\% \pm 8\%$) and increased time to exhaustion during incremental walking ($9\% \pm 8\%$; both $P < 0.01$). Moreover, the MST group increased 6-min walking distance (6MWD; $10\% \pm 7\%$), and chair rising ($30\% \pm 20\%$) and stair climbing performance ($12\% \pm 7\%$; all $P < 0.001$). All MST-induced improvements were different from the control group ($P < 0.01$) which reduced their 1RM ($9\% \pm 5\%$), walking economy ($4\% \pm 4\%$), time to exhaustion ($10\% \pm 8\%$), 6MWD ($5\% \pm 5\%$), chair rising performance ($12\% \pm 12\%$), and stair climbing performance ($6\% \pm 8\%$; all $P < 0.01$). Finally, although MST maintained estimated quadriceps femoris muscle mass, a decrease was observed in the control group ($7\% \pm 10\%$; $P < 0.001$). The change in 1RM correlated with the change in walking economy ($r = 0.754$), time to exhaustion ($r = 0.793$), 6MWD ($r = 0.807$), chair rising performance ($r = 0.808$), and stair climbing performance ($r = 0.754$; all $P < 0.001$). **Conclusions:** Lower-extremity MST effectively increases lower-extremity maximal muscle strength in breast cancer patients undergoing adjuvant therapy and results in improved work economy, functional performance, and maintenance of muscle mass. These results advocate that MST should be considered in breast cancer treatment. **Key Words:** EXERCISE ONCOLOGY, CHEMOTHERAPY, STRENGTH TRAINING, WALKING ECONOMY, MUSCLE MASS, NEUROMUSCULAR FUNCTION

Breast cancer is the most frequently diagnosed type of cancer among women, with more than 2 million new cases in 2018 worldwide (1). In combination with surgical resection, adjuvant therapy constitutes the mainstay in the management of breast cancer and is considered a key

contributor to the steadily increasing survival rates. Yet, its widespread application comes at the expense of numerous side-effects that adversely affect patients' health and functional performance, and counteracting strategies are requested to advance current breast cancer treatment.

Breast cancer patients are shown to display lower levels of lower-extremity maximal muscle strength after primary adjuvant treatment compared with healthy age-matched individuals (2). Although the cause of this reduction is uncertain, it may, in turn, lead to the impaired walking economy (3,4) and impede the ability to perform force-demanding everyday activities such as stair climbing and chair rising (5). Further, adjuvant breast cancer treatment has been documented to induce skeletal muscle atrophy (6), potentially affecting tolerability to chemotherapy (7). The reduction in muscle strength observed after

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adjuvant treatment is likely attributable to direct effects of antineoplastic therapeutic agents (e.g., anthracyclines) on skeletal muscle fibers (8) and augmented levels of physical inactivity (9).

Strength training has been suggested as a strategy to counteract cancer treatment-induced reductions in maximal muscle strength, muscle mass, and functional performance (10). Importantly, loading intensity is established as a key determinant of neuromuscular adaptations to strength training, with higher intensity (>85% of one-repetition maximum [1RM]) eliciting superior improvements in muscle strength compared with lower intensity (<75% of 1RM) (11). In accordance with this concept, maximal strength training (MST), using three to five repetitions of high loads (85%–90% of 1RM) and maximal indented contraction velocity in the concentric phase, has been shown to induce large improvements in maximal muscle strength and walking economy, and have the potential to improve functional performance (4). Notably, the feasibility and safety of MST extend across a variety of populations, including elderly (4,12), chronic obstructive pulmonary disease (3), coronary artery disease (13), peripheral arterial disease (14), and osteoporosis (15) patients. We recently documented that MST also has the potential to improve breast cancer patients' quality of life when they undergo primary adjuvant therapy (16). Although MST primarily is tailored to target the neural system, Wang et al. (4) recently documented that MST also induces muscle fiber hypertrophy, suggesting that MST may counteract treatment-mediated reductions in muscle mass.

Despite the well-documented neuromuscular and functional adaptations resulting from strength training, very few studies have, somewhat surprisingly, investigated the effects of strength training in the initial critical phase of breast cancer treatment. Furthermore, the few previous studies that have applied strength training also appear to have applied low to moderate loading intensities (<75% of 1RM) (17–19). However, recognizing the adverse early phase side effects of adjuvant therapy, in particular, due to the impact of anthracyclines, it remains unknown whether high-intensity strength training could yield similar neuromuscular and functional effects as observed in other populations, and whether it is feasible in breast cancer patients shortly after surgery. Therefore, the aim of the current study was to examine if leg press MST yielded a typical impact on lower-extremity maximal muscle strength, walking economy, muscle mass, and functional performance in newly diagnosed breast cancer patients scheduled for adjuvant treatment. Specifically, it was hypothesized that lower-extremity maximal muscle strength, walking economy, muscle mass, and functional performance would be superior after the intervention in patients receiving leg press MST as a part of the adjuvant therapy, compared with standard treatment alone.

METHODS

Patients. The present study was a part of a study investigating the effects of heavy resistance training on functional performance and quality of life (16), in breast cancer patients undergoing primary adjuvant therapy at the Oncology Centre

of Latvia, Riga, Latvia. A total of 55 breast cancer patients were recruited, and inclusion criteria were women between 18 and 63 yr with newly (<3 wk) diagnosed stage I to III invasive breast cancer, assigned for treatment with breast-conserving surgery/mastectomy and adjuvant therapy (radiation therapy and/or chemotherapy). Exclusion criteria were known heart disease, diabetes, musculoskeletal disorders, or any disorder that prohibited participation in the testing procedures or MST. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Rīga Stradiņš University and the Scientific Department of Rīga East University Hospital. Informed consent was obtained from all patients before inclusion.

Study timeline. The patients attended a standardized 1.5-h testing procedure 2 to 3 wk postsurgery. We aimed to initiate MST as soon as possible after operation, after the surgeon had confirmed that the healing process on the operated site was without complications. After this was confirmed, patients were randomly allocated 1:1 to standard treatment with or without 12 wk of supervised MST. The patients allocated to the MST group started their training 1 to 2 d after the testing and 1 wk before receiving adjuvant therapy, subsequently all patients trained during adjuvant therapy. After 12 wk, the 1.5-h testing procedure was repeated. The testing included assessments of dynamic maximal muscle strength of the lower extremities, walking economy, time to exhaustion (TTE), quadriceps femoris muscle mass, and functional performance.

Maximal muscle strength. After a standardized warm-up consisting of eight repetitions at 50% of predicted 1RM and five repetitions at 70% of predicted 1RM, maximal muscle strength of the lower extremities was assessed as 1RM in a horizontal leg press apparatus (Cybex Eagle 1040, USA). Starting from a near 180° knee-joint angle, the patients were instructed to move slowly to a 90° knee-joint angle, after which they moved concentrically back to the initial position. The load was increased by 2.5 to 7.5 kg until the patients were unable to complete the lift. The 1RM was defined as the heaviest lifted load and was typically obtained within three to six attempts. Rest periods minimum of 3 min were applied between each lift.

Walking economy. After a 5-min warm-up at a self-chosen speed, a 5-min submaximal, steady-rate walking economy test was performed on a motorized treadmill (Spirit CT 100; Jonesboro, AR) at 5% inclination. The speed was calculated to yield a workload of 40 W for the individual patient, using the following equation (20):

$$\text{speed (km}\cdot\text{h}^{-1}) = \frac{40 \text{ W}}{[m_b N] \sin \theta} \times 3.6 \quad [1]$$

where m_b is the individual patient's body mass and θ is the 5% inclination of the treadmill. Thus patients with different body mass would all walk on a work rate corresponding to 40 W, implying different walking speeds. The walking economy was defined as the average HR (Polar Electro FT7, Kempele, Finland) at the last minute of the 5-min 40-W

work rate. In addition, the Borg scale (6–20) was used to assess perceived exertion.

Time to exhaustion. After the submaximal walking economy test, the patients commenced directly to the measurement of TTE. The speed was held constant at 3.8 or 4.8 km·h⁻¹, depending on the patient's condition, and the inclination was increased by 2% every minute. If the patient was able to continue after reaching an inclination of 12%, the speed was increased by 0.5 km·h⁻¹·min⁻¹ until voluntary exhaustion. The HR and perceived exertion were recorded immediately after exhaustion.

Functional performance. Functional performance was assessed using three tests. First, the 6-min walking distance (6MWD) was measured. The patients were instructed to walk back, forth, and around two cones separated by 30 m, aiming to walk the longest possible distance in 6 min. Second, chair rising ability was assessed by 30 s sit to stand test. Starting from a seated position with crossed arms, the patients were instructed to rise from a 44-cm high chair as many times as possible in 30 s. Third, the ability to climb stairs was assessed as the time needed to ascend and descend 10 stairs of 18 cm without the use of handrail support. Familiarization was given before all tests.

Anthropometrical measurements. The volume (*V*) of the left thigh was estimated using the following equation (21):

$$V = L \times 12\pi^{-1} \times (C1^2 + C2^2 + C3^2) - (S - 0.4) \times 2^{-1} \times L \times (C1 + C2 + C3) \times 3^{-1} \quad [2]$$

Utilizing standard measuring tape, the thigh length (*L*) was measured from the lateral femoral epicondyle to the greater trochanter, and thigh circumferences were measured at the midpoint (C1) and 10 cm distal (C2) and proximal (C3) to the midpoint. Skinfold measurement was taken at the midpoint of the thigh, using skinfold caliper (SH5020; Saehan Corporation, MD, South Korea). Quadriceps femoris muscle mass (*M_{qf}*) was calculated as $M_{qf} = 0.307 \times V + 0.353 \text{ kg}$ (22).

Level of physical activity. Patients were asked if they engaged in recreational physical activities weekly, applying the short form of the International Physical Activity Questionnaire (IPAQ-SF). The IPAQ calculates average weekly physical activity level by estimating the metabolic equivalent of task (MET) score, and accounts for the total number of minutes per week spent on low-, moderate-, and vigorous-intensity activities (3.3, 4.0, and 8.0 MET·min·wk⁻¹, respectively). The IPAQ has previously been tested and documented to have good validity and reliability (23). The patients were also asked whether they specifically were involved in regular strength training for the last 6 months before diagnosis.

Maximal strength training. The MST group attended two supervised training sessions per week for 12 wk. The training was carried at the Oncology Centre of Latvia, Riga, Latvia, and was initiated 3 wk after surgery. As for the testing, MST was performed as a dynamic leg press in the horizontal leg press apparatus using a 90° knee-joint angle. After two warm-up sets, the patients performed four sets of four repetitions at approximately 90% of 1RM. Emphasis was put on

slow contraction velocity in the eccentric phase and maximal intended contraction velocity in the concentric phase. A marked stop of approximately 0.5 s was applied between the eccentric and concentric contraction phases. Rest periods minimum of 3 min were used between sets. The load was increased by 2.5 kg when the patients were able to complete all sets. The patients trained in groups of three to five individuals and were supervised by an exercise physiologist. A training session typically lasted for 20 min, and each time the patients attended training they were asked if they experienced MST-related discomfort, pain, or other adverse events during or between the MST sessions, with the exception of the lifted loads feeling heavy when executed. The control group was instructed to perform 3 sets of 10 chair rises twice a week for 12 wk. All patients were encouraged to maintain their typical level of physical activity during the study period.

Breast cancer treatment. The patients were treated according to the European Society for Medical Oncology and the National Comprehensive Cancer Network guidelines. Surgery consisted of oncoplastic breast-conserving surgery or mastectomy and sentinel node biopsy or axillary node dissection. After surgery, patients were scheduled for adjuvant radiation and potentially chemotherapy and Trastuzumab. Chemotherapy consisted of 4–8 cycles of doxorubicin (50–60 mg·m⁻²) or epirubicin [60–90 mg·m⁻²] and cyclophosphamide (600 mg·m⁻²) administered once every third week. After the completion of anthracycline, some patients were furthermore scheduled to four cycles of paclitaxel (135–175 mg·m⁻²) or docetaxel (75–100 mg·m⁻²) administered once every third week. Patients with HER2-positive tumors were treated with 18 cycles of trastuzumab (600 mg·m⁻²) administered once every third week after completion of chemotherapy.

Statistical analysis. Statistical analyses were performed using IBM SPSS (version 25), and figures were made using Graph Pad Prism software (version 8). The power analysis in this study was estimated by setting the standard deviation of a 1RM to 15 kg. Presuming a mean difference of 12 kg between the groups in this study at posttest, we needed a total of 52 patients (*n* = 26 in each group) to maintain statistical power of 0.80 and alpha 0.05. Data distribution was assessed using Quantile-Quantile plots. All independent and dependent variables were approximately normally distributed for each group at pretest and posttest. Prechanges to postchanges in the 6-min walking test and the walking economy were approximately normally distributed, whereas changes in 1RM, TTE, thigh volume, and *M_{qf}* were skewed. Changes in dependent variables were examined using a repeated measure two-factor ANOVA, with group (control, MST) and time (pre, post) as factors. Significant interactions were followed up with independent sample *t*-tests for between-group differences and paired sample *t*-tests for within-group differences. Spearman's correlation was used to assess associations between pretest to posttest changes in 1RM and pretest to posttest changes in walking economy, TTE, and functional variables for combined groups. For categorical variables χ^2 or Fisher's exact test were used to determine difference between groups. Values are expressed as

TABLE 1. Anthropometric parameters and treatment.

	MST Group (n = 27)	Control Group (n = 28)	P
Age (yr)	48 ± 7	49 ± 8	0.69
Body weight (kg)	77.0 ± 15.2	72.3 ± 17.4	0.29
Height (cm)	170 ± 6	167 ± 6	0.07
Breast cancer stage (%)			0.57
I	9 (33)	13 (46)	
II	12 (44)	9 (32)	
III	6 (23)	6 (22)	
Surgery (%)			0.37
OBCS	16 (59)	22 (78)	
SSM	5 (19)	4 (14)	
AB	4 (15)	1 (4)	
MRM	2 (7)	1 (4)	
Adjuvant therapy (%)			
Radiation	23 (85)	26 (92)	0.42
Antihormones	25 (93)	24 (86)	0.70
Cyclophosphamides	14 (52)	17 (61)	0.51
Taxanes	16 (59)	16 (57)	0.88
Trastuzumab	3 (11)	3 (11)	0.99

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as n (%).

OBCS, oncoplastic breast-conserving surgery; SSM, skin-sparing mastectomy; AB, amputation of the breast; MRM, modified radical mastectomy.

mean ± standard deviation in text and tables and as mean ± standard error in figures.

RESULTS

Baseline patient anthropometric parameters and adjuvant therapy are presented in (Table 1), and patient characteristics and physical activity levels are presented at (Table 2), and no significant differences between groups were observed for the demographic and clinical factors at baseline. All patients completed adjuvant therapy without interruptions or dose modifications.

Training compliance and adverse events. The MST group completed 23 ± 1 of 24 planned training sessions (96% ± 4%). The targeted training intensity was met during all training sessions, and the sessions were also executed in accordance with the protocol. All included patients completed the study, and except for the repeated lifts typically being perceived as heavy, no patients reported MST-related adverse events during or between the training or testing procedures.

Maximal muscle strength. A group–time interaction was found for leg press 1RM ($P < 0.001$). The MST group increased 1RM by 20% ± 8% ($P < 0.001$) from pretest to posttest. In contrast, 1RM decreased by 9% ± 5% in the control

TABLE 2. Patient characteristics and physical activity level at baseline.

	MST Group (n = 27)	Control Group (n = 28)	P
Smoking status (%)			1.00
Current	3 (11)	3 (11)	
Former	1 (4)	2 (7)	
Nonsmokers	23 (85)	23 (82)	
Married, cohabiting, or in a relationship (%)	20 (74)	22 (79)	0.70
Physical activity level (%)			0.59
Low—3.3 METs	22 (82)	21 (75)	
Moderate—4.0 METs	3 (11)	6 (21)	
High—8.0 METs	2 (7)	1 (4)	
Strength training (%)	0 (0)	0 (0)	1.00

Categorical variables are presented as n (%). Physical activity level was assessed applying the short form of the International Physical Activity Questionnaire short form.

FIGURE 1—A, 1RM and (B) quadriceps femoris muscle mass after 12 wk of adjuvant therapy with and without MST. Data are presented as mean ± SE. * $P < 0.05$, within-group increase from pretest to posttest. $SP < 0.05$, within-group decrease from pretest to posttest. # $P < 0.05$, the difference between groups from pretest to posttest.

group ($P < 0.001$) from pretest to posttest, resulting in 1RM being higher in the MST group compared with the control group at posttest ($P < 0.001$; Fig. 1). No between-group difference was apparent in 1RM at pretest ($P = 0.187$).

Body mass, thigh volume, and quadriceps femoris muscle mass. No group–time interaction was found for body mass ($P = 0.147$). In contrast, there was a group–time interaction for thigh volumes ($P = 0.045$). A tendency toward a pretest to posttest increase (2% ± 4%) was found in the MST group ($P = 0.076$). No changes (0% ± 4%) occurred in the control group ($P = 0.287$). There was a tendency toward a between-group difference at pretest ($P = 0.068$), whereas a between-group difference was found after the intervention ($P = 0.034$). No correlation was apparent between change in thigh volume and change in 1RM ($r = 0.17$; $P = 0.197$).

A group–time interaction was observed for M_{qf} ($P = 0.004$). In the control group, M_{qf} decrease (7% ± 10%) from pretest to posttest ($P < 0.001$). No changes (1% ± 2%) were found in the MST group ($P = 0.683$), resulting in M_{qf} being higher in the

MST group than the control group at posttest ($P < 0.001$; Fig. 1). Changes in M_{gr} was associated with the training-induced changes in 1RM ($r = 0.45$; $P < 0.001$).

Functional performance. Group-time interactions were found for 6-min walking test ($P < 0.001$), chair rising performance ($P < 0.001$), and stair climbing performance ($P < 0.001$). At posttest, the MST group displayed improvements in the 6MWD ($10\% \pm 7\%$; $P < 0.001$), chair rising performance ($30\% \pm 20\%$; $P < 0.001$), and stair climbing performance ($12\% \pm 7\%$; all $P < 0.001$). Conversely, in the control group, reductions were found in the 6MWD ($5\% \pm 5\%$; $P < 0.001$), chair rising performance ($12\% \pm 12\%$), and stair climbing performance ($6\% \pm 8\%$; $P < 0.001$). As a result, 6-min walking test ($P < 0.001$), chair rising performance ($P < 0.001$), and stair climbing performance ($P = 0.004$) were different between groups at posttest (Fig. 2). No differences in 6-min walking test, chair rising performance, and stair climbing performance were observed between the groups at baseline. Changes in 6-min walking test ($r = 0.807$; $P < 0.001$), chair rising performance test ($r = 0.808$; $P < 0.001$), and stair climbing performance ($r = 0.754$; $P < 0.001$) exhibited an association with changes in 1RM (Fig. 3).

Walking economy and TTE. Pretest and posttest walking economy and TTE are presented in Table 3 with group-time interactions for walking economy, speed at exhaustion, and inclination at exhaustion. Prechanges to postchanges in walking economy ($r = 0.754$; $P < 0.001$) and TTE ($r = 0.793$; $P < 0.001$) were associated with prechanges to postchanges in 1RM (Fig. 3).

DISCUSSION

Adjuvant breast cancer therapy is associated with reduced muscle strength, muscle mass, and physical activity (2,6,9). Despite the well-documented effectiveness of strength training to improve these factors in other populations, evidence of the impact of strength training, particularly applying high intensity, in the important initial phase of breast cancer treatment is scarce. Therefore, this study sought to investigate the effect of strength training performed with high loads ($\sim 90\%$ 1RM) and few repetitions (3–5) in newly diagnosed breast patients undergoing adjuvant therapy. The major findings were that 3 months of MST yielded large improvements in lower-extremity maximal muscle strength, walking economy and functional performance, and maintained muscle mass. Conversely, patients assigned to the control group displayed reductions in all assessed variables. The results of the current study advocate that lower-extremity MST should be considered part of breast cancer management postsurgery, starting before initiation of adjuvant therapy, to improve and maintain physical health and functionality.

Maximal muscle strength, adjuvant therapy, and MST. Primary adjuvant treatment, without strength training, resulted in reductions in lower-extremity maximal muscle strength, muscle mass, and functional performance in the current study. The approximately 9% decrease in leg press

FIGURE 2—A, 6MWD (m), (B) chair rising performance (repetitions), and (C) stair climbing performance (s) after 12 wk of adjuvant therapy with and without maximal strength training (MST). Data are presented as mean $\pm$ SE. * $P < 0.05$, increase within-group from pretest to posttest. \$ $P < 0.05$, decrease within-group from pretest to posttest. # $P < 0.05$ difference between groups from pretest to posttest.

maximal muscle strength, apparent after only 12 wk of adjuvant therapy, corresponds to more than one decade of typical aging (24). This is in accordance with several previous studies (2,18), which has documented especially chemotherapy to reduce the main determinants of muscle strength such as muscle

FIGURE 3—Associations between changes in maximal strength (leg press 1RM) and changes in (A) TTE during incremental walking, (B) walking work economy, (C) 6-min walking distance, and (D) chair rising performance after 12 wk of breast cancer adjuvant therapy with and without MST.

fiber cross-sectional area (25) and diminish motoneuron excitability (26). However, strength reductions are not always observed (27–29). Of importance, the latter studies applied single-joint isometric measurements of muscle strength, whereas

we applied dynamic leg press, and the equivocal findings may partly be explained by the application of different measurement techniques. Additionally, a discrepancy between studies may be attributable to type, duration, and dose of chemotherapy. Indeed,

TABLE 3. Endurance performance before and after maximal strength training.

	MST Group (n = 27)			Control Group (n = 28)			Interactions (Time-Group)	Between Groups	
	Pre	Post	P	Pre	Post	P		P	
Walking economy									
HR (bpm)	140 ± 16	128 ± 15	<0.001	134 ± 12	149 ± 12	0.002	<0.001	0.150	0.009
RPE (6–20)	12 ± 1	10 ± 2	<0.001	12 ± 2	13 ± 1	0.184	<0.001	0.289	<0.001
Graded walking test									
TTE (s)	536 ± 71	571 ± 68	<0.001	531 ± 73	476 ± 63	<0.001	<0.001	0.814	<0.001
HR _{max} (bpm)	172 ± 8	172 ± 7	1.000	167 ± 11	166 ± 11	0.275	0.443	0.042	0.013
E _{speed} (km·h ⁻¹)	4.8 ± 0.4	5.1 ± 0.4	<0.001	4.8 ± 0.5	4.7 ± 0.3	0.002	<0.001	0.454	0.001
E _{inclination} (%)	11 ± 1	12 ± 1	0.009	11 ± 1	10 ± 2	0.003	<0.001	0.402	0.010
RPE (6–20)	17 ± 1	18 ± 1	0.120	17 ± 1	17 ± 1	0.563	0.475	0.975	0.372

Data are presented as mean ± standard deviation.

E_{speed}, treadmill speed at exhaustion; E_{inclination}, treadmill inclination at exhaustion.

reductions in muscle strength induced by therapeutic agents typically applied in breast cancer treatment (e.g., anthracyclines) have been shown to be dose-dependent (30).

Compared with the control group that received standard adjuvant treatment, the patients that performed strength training two times a week had approximately 30% higher lower-extremity maximal muscle strength after 3 months. This MST-induced effect is similar to what has been observed after a comparable volume of leg press MST in healthy individuals (31) and other patient populations (3,14,32). The approximately 20 kg improvement in leg press 1RM in the current study is about 2.5 times larger compared with the approximately 8 kg 1RM increase observed in a previous study where the patients exercised three times a week with an intensity corresponding to 60% to 70% of 1RM (17), and even similar to improvements observed after 1 yr of home-based training 4 d·wk⁻¹ (18). Albeit, again, direct comparison between studies should be made with caution due to differences in type, dose, and duration of chemotherapy. Importantly, although MST may be considered strenuous, the 96% completion rate in the present study clearly indicates that breast cancer patients are, despite suffering adverse side effects of early phase adjuvant therapy, capable of performing strength training of the lower extremities with a targeted intensity of approximately 90% of 1RM. Furthermore, the intervention was completed without any reported difficulties or injuries, indicating that the feasibility and safety of leg press MST during breast cancer treatment should be considered satisfactory. Of notice, it is only the concentric phase of movement during MST that is carried out with high intensity. This is a likely reason why MST may be safely performed, as the high-impact force associated with eccentric muscle action is avoided (33).

Muscle mass, adjuvant therapy, and MST. Although breast cancer patients undergoing adjuvant therapy typically are weight stable or gain weight, recent data reveal that chemotherapy may cause muscle fiber atrophy (34). Accordingly, in the present study, the control group displayed reductions in M_{qf} , indicating that muscular alterations contributed to the reduction in lower-extremity maximal muscle strength. Indeed, our results revealed a tendency for alterations in M_{qf} to be associated with changes in lower-extremity maximal muscle strength. Although MST primarily is tailored to induce neural adaptations, it may also cause muscle hypertrophy (4), and thus potentially counteract chemotherapy-induced reductions in muscle mass. In line with this finding, muscle mass was preserved in the MST group. Depletion of muscle mass can lead to chemotherapy toxicity, which in turn may necessitate dose reduction or delayed administration (7).

Endurance performance, adjuvant therapy, and MST. In accordance with previous interventions (4,14), the increments in lower-extremity maximal muscle strength were associated with improvements in the walking economy, one of three major determinants of aerobic endurance (35). When lower-extremity maximal muscle strength is improved, the load imposed by each stride becomes relatively lower and may lead to decreased reliance on the less efficient high-threshold type II muscle fibers and to lower motor unit recruitment (4). The

improved walking economy is likely to have implications for the patients' everyday function as a given submaximal workload now requires less energy compared with before the intervention. In accordance with previous findings (14), the improved walking economy likely also led to the observed improvements in TTE observed in the present study. This implies that the breast cancer patients that had performed leg press MST not only were able to walk with a lower energy cost but also that they increased their maximal walking effort.

Functional performance and MST. Importantly, MST-induced improvements in lower-extremity maximal muscle strength were accompanied by improved functional performance in the current study. Particularly the chair rising performance, stair climbing, and 6MWD tests exhibited strong relationships with the changes in lower-extremity maximal muscle strength. These findings are in accordance with previous observations, documenting changes in muscle strength to occur in conjunction with changes in functional performance. Especially functional tasks involving upward displacement of the body are shown to be susceptible to change with enhanced lower-extremity muscle strength (36). In contrast, low-force activities, such as walking, appear to be less dependent on muscle strength (36). The MST-induced increases in chair climbing performance and chair rising in the current study are in accordance with this notion, whereas the improved 6MWD may to a greater extent be attributable to the improved walking economy. In contrast to their strength training counterpart, the control group displayed impaired functional performance, further consolidating the close relationship between lower-extremity muscle strength and physical functioning.

Strengths and limitations of the study. Few studies have investigated the effects of strength training in the initial phase of breast cancer treatment. A strength of the present study is the application of effective high-intensity strength training of functionally relevant muscle groups of the lower extremities. Maximal strength training is time- and cost-efficient, demanding less than an hour of training per week, and patients may train in groups of three to five individuals per training apparatus during the same training session. Despite adverse early phase side effects of adjuvant therapy, the patients had a completion rate of 96%, suggesting leg press MST to be a feasible exercise modality in this critical phase of breast cancer treatment. Importantly, the strength training was also carried out without any observed injuries during the training period. Ultimately, the major strength in the current study was that the large improvements in lower-extremity muscle strength were strongly associated with improvements in the patients' functional performance. A limitation with the current study is the lack of measurements of neural and muscular components. This may have provided important information about the origin of the strength training-induced improvements, and if certain components of adjuvant therapy possibly affected some factors more than others. As breast cancer patients may suffer attenuated bone health, it would also have been beneficial to include musculoskeletal measurements. Increased lower-extremity muscle strength has previously been documented to result in enhanced bone formation and bone mineral density (37), and it would have been of great value to

investigate if this was also the case in our study. Finally, the relatively short duration of the study also represents a limitation, as information on long-term effects would have provided a better understanding of the role of exercise in breast cancer treatment and survival rate.

Clinical implications. The present study clearly demonstrates the importance of counteracting the detrimental effects of adjuvant breast cancer therapy on neuromuscular function. Indeed, although patients commencing leg press MST improved lower-extremity maximal muscle strength, walking economy, functional performance, and maintained muscle mass, the control group was subject to reductions in all these variables. Notably, 40 min of leg press MST per week was sufficient to gain lower-extremity muscle strength and functionality, and we recently documented that it also improved the patients' overall quality of life (16). In fact, only one exercise, dynamic leg press, was performed. Although it would be beneficial to include strength training of other muscle groups, the lower extremities should be prioritized due to their weight-bearing function. It is noteworthy that MST appears to be safe, despite the heavy loads applied in the training. Of importance, only the concentric phase of movement has a high intensity. The eccentric phase, which is more associated with muscle soreness and microdamage to the muscle (33), is carried out in a slow and controlled fashion. In combination with few repetitions (4) and sets (4), and low actual velocity also in the concentric phase,

this is a likely explanation of why MST can be carried out safely. Taken together, the findings in the current study and the Češko et al. (16) study certainly support previous suggestions of implementation of strength training in adjuvant breast cancer treatment and extend recommendations to include effective high-intensity MST of the lower extremities.

CONCLUSIONS

In conclusion, the present study showed that 3 months of leg press MST effectively improved lower-extremity maximal muscle strength in breast cancer patients receiving adjuvant treatment and that the changes were associated with improvements in walking economy and functional performance. These results advocate that lower-extremity high-intensity strength training should be considered a part of breast cancer treatment to not only counteract the typically observed decline in lower-extremity muscle strength but also to improve physical health and functionality from the time of diagnosis.

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The authors declare that they have no conflicts of interest regarding the publication of this paper. There are no financial conflicts of interest to disclose. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute an endorsement by ACSM.

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THE IMPACT OF MAXIMAL STRENGTH TRAINING ON QUALITY OF LIFE AMONG WOMEN WITH BREAST CANCER UNDERGOING TREATMENT

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Cancer rehabilitation programs mainly involve endurance training while little attention has been paid to strength training. Breast cancer (BC) patients lose muscle strength while undergoing adjuvant treatment, thus affecting daily activities and quality of life. Maximal strength training, with an emphasis on velocity in the concentric phase, improves maximal strength and muscle force development characteristics. However, the effect of maximal strength training on quality of life for BC patients undergoing treatment remains elusive. Consequently, the aim of this study was to evaluate the effectiveness of maximal strength training in Health related quality of life in women with newly diagnosed BC. **Materials and Methods:** 55 BC patients with disease stage I–III were randomized into a training group and control group. The training group performed maximal strength training twice a week for 3 months, whereas the control group followed prescribed treatment without strength training. Overall quality of life was measured by The European Organization for Research and Treatment of Cancer Core Quality of life Questionnaire-C30 and additional BC module BR23 before and after the intervention. **Results:** The results obtained from pre-tests and those obtained after 3 months of intervention revealed that patients in the training group significantly increased one repetition maximum, by 20.4 kg (20%) ($p = 0.001$, $d = 0.9$). Simultaneously, statistically significant alterations were observed in this variable for the control group, one repetition maximum decreased by 8.9 kg (9%) ($p = 0.001$, $d = 0.5$). The overall quality of life improved significantly by 13% for the training group with large effect ($p = 0.002$, $d = 0.6$), but no relevant changes were observed in the control group ($p = 0.44$, $d = 0.2$). Results revealed remarkable changes in overall quality of life after 3-month post-test period between the two groups with large effect ($p = 0.002$, $d = 0.9$). The training sessions had helped in diminishing the sense of fatigue by 24% ($p = 0.03$, $d = 0.6$), while it had got worse by 25% ($p = 0.02$, $d = 0.4$) for the control group. Again, the data on large effect were noticed to differ between the groups ($p = 0.01$, $d = 0.6$). **Conclusion:** Maximal strength training for BC patients was well tolerated, safe and feasible and showed strength improvements that led to improved muscle strength and improved overall quality of life. These data certainly support the therapeutic role for maximal strength training in the treatment of BC.

Key Words: breast cancer, muscle strength, rehabilitation, quality of life, physical activity.

The incidence of breast cancer (BC) increases with age, the median age for diagnosis being 61 years [1]. Studies in the field have indicated the link between improved cancer treatment and prolonged survival — 5 year survival rates for non-metastatic BC exceed 84% [2]. However, the majority of patients are to encounter a wide range of symptoms and side effects. The treatment of cancer and the disease itself are often associated with adverse physical side-effects, the most prominent being muscular atrophy, decreased muscle strength, reduced aerobic capacity, leading towards the decrease of the quality of life [3].

As a countermeasure, exercise training has been increasingly implemented in the oncology for the last 3 decades. Until recently, reduction in the amount of physical activities has been recommended as treatment for fatigue [4]. Such a practice has led to a physiological paradox as the lack of activities induces

muscle catabolism and further deconditioning, which incites even more fatigue [5]. Rehabilitation programs are becoming an important part of the care of cancer patients [5, 6]. Recently, the effect of physical activities in cancer patients has been described in several literature reviews [3, 7–11]. Most of the studies conclude that physical training programs were beneficial for cancer patients' physical or psychosocial capacity. The improvements in muscle strength, body composition, aerobic capacity, the quality of life and fatigue reduction have been noticed [12–16]. However, several intervention studies discussed in the literature proved to have shortcomings. Most of the studies applied aerobic exercises like walking or stationary cycling, while strength training appeared to be a component of a small number of trials [13, 17]. The majority of the interventions correspond to the form of a training complex combining endurance training with strength training and relaxation therapies, making it difficult to evaluate the effect of a training type [18]. Also, training programs usually last no longer than 12 weeks and involve less than 40 participants. The after-treatment exercises are of a light to moderate training intensities. Relevant to the present discussion, the proportion of studies on BC patients being exposed to high intensity strength training is low in spite of muscle atrophy

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Abbreviations used: ACSM – American College of Sports Medicine; BC – breast cancer; CG – control group; EORTC – the European Organization for Research and Treatment of Cancer; MST – maximal strength training; QLQ-BR23 – EORTC Breast Cancer Module; QLQ-C30 – EORTC Core Quality of Life Questionnaire-C30; QoL – overall quality of life; TG – training group; 1RM – one repetition maximum.

being a common problem for this target group [19]. It postulates strength training a relevant choice for the physical training program.

Muscle atrophy originates from a sedentary life-style and prolonged bed rest. Unfortunately, the presence of tumors and side-effects of medication (e.g. glucocorticoids or chemotherapeutic agents) makes it even worse for cancer patients as the skeletal muscle structure and function happens to be affected [5, 10, 20]. Yet even in cases of severe fatigue and muscle atrophy skeletal muscle has indicated considerable adaptability with appropriate training stimuli [5].

Progressive strength training has proved to increase lean body mass, muscle protein mass and contractile force. It improves physical function in healthy, young and elderly people [21]. Higher-intensity training has demonstrated excellent results among patients suffering from Chronic Obstructive Pulmonary Disease (COPD), peripheral artery disease, coronary artery disease and schizophrenia [22–25]. As claimed by Brill *et al.* (2000), a great proportion of evidence suggests that there is a strong connection between the ability to engage in physical task performance in daily activities and the threshold level of muscular strength [26].

Strength training has the potential of targeting muscles. Increased muscle strength may contribute to comprehensive participation in daily life and its quality. However, the optimal type, intensity and frequency of strength training that enhances muscle strength the most is yet unknown. The suggested exercise intensities happen to vary from rather low or moderate, as proposed by the American College of Sports Medicine (ACSM) [27], to more intense as described in recent publication about the fundamentals of resistance training [28]. Therefore, in order to observe strength improvements, it is essential to ensure optimal intensity of training.

Studies have shown that training with high loads — known as maximal strength training (MST) — induces greater adaptations in neural system. Training intensity of 85–90% of one repetition maximum (1RM) has proved to lead towards greater improvement in maximal strength than conventional training programs [29]. To boost maximal strength, it is beneficial to apply a program characterized by loads $\geq 85\%$ of 1RM, few repetitions ≥ 4 , and maximal mobilization of force in the concentric phase with maximal intentional velocity [30] and long resting periods ≥ 3 min [31].

Therefore, the objective of the present study was to investigate the effect of a 12-week MST under supervision in the training group (TG) of BC patients compared to the control group (CG) of BC patients undergoing treatment without strength training. We hypothesized that women with BC undergoing adjuvant treatment benefit from MST in terms of muscle strength and improved overall quality of life (QoL) immediately after the intervention.

MATERIALS AND METHODS

The study was conducted in Oncology Centre of Latvia, Riga. The project was approved by the Ethics

Committee of the Riga Stradiņš University and the Scientific Department of Riga East University Hospital. Oncologists recruited patients and informed consent was obtained from all patients involved.

The criteria for inclusion in the study were: treatment with breast conserving surgery/mastectomy and/or radiation therapy and/or chemotherapy with/without hormone therapy; age 18 to 63 years; patients were newly diagnosed with stage I–III BC. Patients being unable to perform such basic skills as sitting or lying down, having cognitive disorders or severe emotional instability, suffering from other serious diseases that might diminish physical performance capacity (e.g. heart failure, COPD, neurological disorders) were excluded from the study.

57 consecutive patients were initially referred to the study. Patients were randomized into a TG and CG. During the intervention period 2 patients dropped out (mean age 52 years) due to family or work circumstances. Therefore, 55 patients (N = 27 in TG, N = 28 in CG) completed the entire program. Patient characteristics at the beginning of the study are indicated in Table 1.

Training intervention. The participants randomized into the TG received supervised MST twice a week for 12 weeks. The training took place at the BC surgery department and began 2–3 weeks after a breast surgery. Each training session consisted of 2 warm-up sets followed by MST in 4 sets with 4 repetitions in each set applying horizontal dynamic leg press (Figure). The exercise followed the sequence of putting emphasis on stopping the eccentric phase with a 90° in the knee joint, a short pause (~ 1 s), and emphasis on the maximal mobilization of force in the concentric action. The initial workload was set at 85–90% of the individual 1RM and adjusted during the progression of training. The workload was increased by 2.5 kg when the patients were able to complete all sets and repetitions. One training session lasted for approximately 20 min including 3 min of resting periods between the sets. The patients trained in groups of 3–5 people. Safety of the training sessions was ensured by exercise physiologist. The participants' heart rate was continuously monitored with heart rate transmitter (Polar F7, Finland).

Table 1. Patient characteristics and clinical data of the study population

	TG (N = 27)	CG (N = 28)	
Continuous variables	Mean $\pm$ SD	Mean $\pm$ SD	p value
Age (years)	48.2 $\pm$ 6.7	49.0 $\pm$ 8.0	0.69
Weight (kg)	77.0 $\pm$ 15.2	72.3 $\pm$ 17.4	0.29
Height (cm)	170.4 $\pm$ 6.1	167.4 $\pm$ 6.2	0.07
Categorical variables	Number (%)	Number (%)	
Disease stage			
I	9 (33%)	13 (46%)	
II	12 (44%)	9 (32%)	
III	6 (23%)	6 (22%)	
Treatment			
Breast surgery	27 (100%)	28 (100%)	
Chemotherapy	25 (92%)	22 (79%)	
Radiation therapy	23 (85%)	26 (92%)	
Hormone therapy	21 (78%)	17 (61%)	

Note: Data are presented as mean (SD). Stage of cancer: present patient distribution at diagnostic stage. Treatment: number of each treatment type prescribed for the included patients.

The CG was following standard care regime of prescribed cancer treatment supervised by an oncologist. The CG received phone call once a week and advice to perform chair stands twice a week with 3 sets and 10 repetitions, in order to keep them motivated and close to study.

One repetition maximum testing. 2 warm-up sets (8 repetitions at ~50% of 1RM and 5 repetitions at ~70% of predicted 1RM) were performed. Next, the patients were tested for the maximal strength in the lower extremities by 1RM in a dynamic horizontal leg press machine (Cybex Eagle, USA). Starting with an extended leg position, the subjects were instructed to slowly move down until the knee joint angle was positioned at 90°. The movement was followed by a short fraction of the second pause, then by a concentric action with the emphasis on maximal mobilization — the position during which the patients were instructed to focus on maximal intended velocity. Finally, the patients were asked to get back to the starting position [32].

Verbal supervision and encouragement were provided in order to reach the appropriate angle, avoid hyperextension in the knees, and keep the knees and toes on the line to minimize the risk of injury. 1RM was measured in 3–6 trials by successively increasing the load for each lift by 2.5–7.5 kg, until the patients were no longer able to complete the lift. Rest periods of about 4 min were applied between each trial [23].

Measurements of quality of life. The primary outcome measure was the QoL measured by The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and additional BC Module (QLQ-BR23). EORTC QLQ-C30 and QLQ-BR23 is an integrated system for assessing QoL of cancer patients participating in clinical trials. The QLQ-C30 is composed of multi-item scales and single-item measures. These include 5 functional scales, 3 symptom scales, a global health status/QoL scale, and 6 single items. Each of the multi-item scale includes a different set of items — no item occurs in more than one scale [33].

Figure. 1RM testing and training applying horizontal leg press

The QLQ-BR23 module comprises 23 questions assessing disease symptoms, side effects of treatment (surgery, chemotherapy, radiotherapy and hormonal treatment), body image, sexual functioning and future perspective.

All of the scales and single-item measures range in scores from 0 to 100. A high score represents a higher response level. Thus, a high score for a functional scale represents high/healthy level of functioning, a high score for the global health status/QoL represents high QoL, but a high score for a symptom scale/item represents high level of symptomatology/problems.

Tolerance of exercise intervention. Although the training intensity was high, the program was tolerated well by all the patients. None of the patients dropped out claiming the program being too intense; neither had they complained about muscle soreness. The average attendance was 23 of 24 planned training sessions.

Statistics. Data were analyzed using IBM SPSS Statistics (v. 24.0). All values are expressed as mean $\pm$ standard deviation (SD) for descriptive data and tables. To test for differences in changes of variables from pre- to posttest between groups, independent sample t-test was applied. Within-group differences in variables were assessed from pre- to posttest by paired sample t-tests. Statistical level of significance was set at $p < 0.05$. Cohen's d : value effect, 0.1–0.2 small, 0.3–0.5 medium, 0.6–0.8 large, 0.9–1.10 + Extreme large.

RESULTS

Adherence and baseline characteristics. The study was completed by 55 patients. 27 patients from the TG and 28 from the CG were monitored for 12 weeks. There were no significant differences in age, weight and height between the participants from both groups ($p > 0.05$). The patients were exposed to a breast surgery, chemotherapy, radiation and hormone therapy as the treatment for illness.

Effects on muscle strength. Results obtained from pre-tests and those obtained after 3 months of intervention period revealed that patients in the TG significantly increased 1RM, by 20.4 kg (20%) ($p = 0.001$, $d = 0.9$) and statistically significant alterations were observed in this variable for the CG — 1RM had decreased by 8.9 kg (9%) ($p = 0.001$, $d = 0.5$) (Table 2). The analysis of the tests performed at the beginning of the study and after 3 months revealed statistically remarkable difference with extreme large effect ($p = 0.001$, $d = 1.6$). There were no significant changes between the members of both groups in terms of the body weight measured in pre- and post-test ($p = 0.43$).

Effects on HRQOL C-30

Global health status/QoL. Changes in The EORTC C-30 are listed in Table 3. No significant differences in baseline values between the groups were observed ($p > 0.05$). The QoL improved significantly (by 13%) for the TG with large effect ($p = 0.002$,

Table 2. Body weight and muscle strength of BC patients before and after of control period and maximal strength training

Variables	Baseline Mean ± SD	After 12 weeks Mean ± SD	Estimated means difference (95% CI)	p value and Cohen's d value after intervention
Weight (kg)				
Exercise	77.0 ± 15.2	76.7 ± 14.5	−0.4 (−0.8 to 1.5)	0.56 (0.1)
Control	72.3 ± 17.4	73.3 ± 16.5	1.0 (0.1 to 2.2)	0.08 (0.1)
p value and Cohen's d value between the groups	0.29 (0.3)	0.43 (0.2)		
1RM (kg)				
Exercise	106.8 ± 22.8	127.2 ± 26.4	20.4 (17.3 to 23.6)	0.001 (0.9)
Control	98.9 ± 20.7	89.9 ± 20.9	−8.9 (−11.0 to −6.9)	0.001 (0.5)
p value and Cohen's d value between the groups	0.19 (0.3)	0.001 (1.6)		

d = 0.6), but no relevant changes were observed in the CG ($p = 0.44$, $d = 0.2$). The results obtained from the post-test revealed significant changes with extreme large effect size in QoL between the groups ($p = 0.002$, $d = 0.9$) (Table 3).

Functional scales. Noticeable improvements after MST were observed in the TG: role functioning increased by 23% ($p = 0.001$, $d = 0.7$), social functioning — by 12% ($p = 0.01$, $d = 0.5$), emotional functioning improved by 13% ($p = 0.001$, $d = 0.5$), while it decreased by 11% ($p = 0.02$, $d = 0.4$) in the CG. After the post-test, important differences with large effect size were observed in emotional functioning ($p = 0.005$, $d = 0.7$) and social functioning ($p = 0.004$, $d = 0.9$). In other functional scales — physical functioning was significantly higher with large effect size for TG than CG after post test ($p = 0.002$, $d = 0.9$), and cognitive functioning — no statistically significant changes were observed between both groups.

Symptom scales. Fatigue diminished by 24% ($p = 0.03$, $d = 0.6$) in the TG, while it became worse by 25% ($p = 0.02$, $d = 0.4$) in the CG. Differences with large effect size were observed between the groups after post-test ($p = 0.01$, $d = 0.6$). Other symptoms

are not associated with physical training effects rather than with the elapsed period of time after treatment.

QLQ-BR23

Functional scales. Changes in the EORTC QLQ-BR23 supplementary model are listed in Table 4. At the end of the intervention significant decrease in body image with medium effect size ($p = 0.05$, $d = 4$) was noticed in the CG. This variable had not altered in the TG, but showed medium effect size ($p = 0.2$, $d = 0.3$).

Symptom scales. Systemic therapy side effects deteriorated with large effect size for the CG ($p = 0.001$, $d = 0.8$), while there were no statistically considerable changes for the TG indicating medium effect size ($p = 0.4$, $d = 0.3$). Significant differences with large effect size ($p = 0.04$, $d = 0.5$) were observed between the groups after post-test performed after 3 months.

DISCUSSION

This is the first study applying MST in BC patients during adjuvant treatment. The major finding of this study is that MST considerably enhanced strength in patients with BC resulting in (13%) increase in the QoL. In addition, MST indicated improvement in role

Table 3. Changes in the EORTC QLQ-C30 before and after the intervention

Variables	Baseline Mean ± SD	After 12 weeks Mean ± SD	Estimated mean difference (95% CI)	p value and Cohen's d value after intervention
Global health status/QoL				
Global health status				
Exercise	67.2 ± 15.6	76.2 ± 14.3	9.0 (3.6 to 14.3)	0.002 (0.6)
Control	66.3 ± 16.5	63.5 ± 14.7	−2.7 (−10.0 to 4.4)	0.44 (0.2)
p value and Cohen's d value between the groups	0.84 (0.1)	0.002 (0.9)		
Functional scales				
Physical functioning				
Exercise	88.6 ± 8.2	90.6 ± 6.4	2.0 (−1.0 to 4.9)	0.17 (0.3)
Control	84.2 ± 14.6	81.6 ± 13.2	−2.5 (−5.3 to 0.2)	0.07 (0.2)
p value and Cohen's d value between the groups	0.18 (0.3)	0.003 (0.9)		
Role functioning				
Exercise	70.0 ± 26.7	85.9 ± 18.2	15.8 (6.7 to 24.9)	0.001 (0.7)
Control	69.1 ± 25.5	77.0 ± 19.5	7.9 (−2.6 to 18.5)	0.13 (0.4)
p value and Cohen's d value between the groups	0.89 (0.01)	0.09 (0.01)		
Emotional functioning				
Exercise	72.4 ± 21.1	82.1 ± 18.8	9.7 (4.1 to 15.4)	0.002 (0.5)
Control	74.4 ± 23.9	66.3 ± 21.3	−8.1 (−14.7 to −1.3)	0.02 (0.4)
p value and Cohen's d value between the groups	0.76 (0.1)	0.005 (0.8)		
Cognitive functioning				
Exercise	86.3 ± 15.4	87.0 ± 14.1	0.7 (−5.9 to 7.4)	0.83 (0.1)
Control	86.2 ± 18.2	80.8 ± 19.5	−5.3 (−11.8 to 1.2)	0.11 (0.3)
p value and Cohen's d value between the groups	0.99 (0.1)	0.19 (0.4)		
Social functioning				
Exercise	76.4 ± 24.1	85.7 ± 16.4	9.2 (2.1 to 16.4)	0.01 (0.5)
Control	74.3 ± 27.3	70.2 ± 20.9	−4.1 (−11.8 to 3.6)	0.29 (0.2)
p value and Cohen's d value between the groups	0.76 (0.1)	0.004 (0.8)		
Symptom scales				
Fatigue				
Exercise	33.5 ± 17.1	25.5 ± 15.5	−7.9 (−1.0 to −14.9)	0.03 (0.6)
Control	29.5 ± 18.5	36.8 ± 16.7	7.3 (1.4 to 13.1)	0.16 (0.4)
p value and Cohen's d value between the groups	0.41 (0.2)	0.01 (0.6)		

Note: Data are presented as mean (SD).

Table 4. Changes in the EORTC QLQ-BR23 before and after the intervention

Variables	Baseline Mean $\pm$ SD	After 12 weeks Mean $\pm$ SD	Estimated means difference (95% CI)	p value and Cohen's d value after intervention
Functional scales				
Body image				
Exercise	64.9 $\pm$ 25.9	72.1 $\pm$ 24.7	7.1 (–3.0 to 18.3)	0.19 (0.3)
Control	72.4 $\pm$ 24.6	62.9 $\pm$ 25.4	–9.5 (–19.4 to 0.3)	0.05 (0.4)
p value and Cohen's d value between the groups	0.27 (0.3)	0.18 (0.4)		
Symptom scales				
Systemic therapy side effects				
Exercise	24.2 $\pm$ 14.7	21.5 $\pm$ 9.9	–2.6 (–9.5 to 4.3)	0.46 (0.3)
Control	17.1 $\pm$ 14.1	29.3 $\pm$ 17.0	12.2 (5.9 to 18.5)	0.001 (0.8)
p value and Cohen's d value between the groups	0.74 (0.5)	0.04 (0.6)		

Note: Data are presented as mean (SD).

functioning (23%), emotional functioning (13%), social functioning (12%), simultaneously reducing the sense of fatigue by 24% for the TG (according to core questionnaire QLQ-C30). The supplementary module QLQ-BR23 pointed to improvements in body image and reduction in side effects experienced during and after treatment for the TG, while they worsen for the CG.

Strength training in cancer rehabilitation.

General conclusion regarding strength training interventions for cancer patients is that training programs were well tolerated, safe and feasible. They showed improvements in strength leading towards enhanced physical functioning and better quality of life [15, 34].

Recognizing intensity during strength training the key factor for increasing maximal muscular strength, strength training with intensity higher than the adaptive threshold of 66–70% of 1RM may have been preferable to induce great physiological adaptations, thus stimulating faster recovery from specific cancer treatment [35]. There are only several studies discussing higher training intensities for BC patients. ACSM suggests exercise intensities of 50% of 1RM with 2–3 sets of 3–5 repetitions evolving to 10–12 repetitions [27]. As claimed by Kraemer *et al.* (2002) and Kraemer and Ratamess (2004), these might be insufficient for an optimal training effect. A possible reason for the insecurity is the hesitance to expose these patients to risks — muscle and joint injuries — when applying higher intensities. Besides, since cancer patients are subjects to intense psychological and physical stress, the treatment should be gentle, thus patients being exposed to low intensity exercises only. Since the guidelines were developed in 2003 and the knowledge about strength training was only at its very beginnings, such a situation appears to be logical. Studies of healthy subjects have proved strength training programs to be more effective when applying higher intensities. Kraemer and Ratamess (2004) continue by acknowledging that essential benefits in maximal strength and the subsequent hypertrophy can only be attained by recruiting the maximal number of motor units, guaranteeing high training loads. Simultaneously, heavy loads initiate more favorable responses in other tissues, e.g. bone. It is especially vital for BC patients due to the bone material density being lower than normal. Strength training helps preventing further bone loss [36].

Tolerance of the high-intensity program.

The TG performed MST twice a week for 12 weeks, each training session lasting only 20 min. None of the patients dropped out because of overloading or injuries. The adherence rate was 96% which is far above the average indicators for quality of life interventions. High adherence rate could be explained by several reasons: extensive intake procedure by oncologists, individualization of training loads based on pre-test, supervision by exercise physiologist during training. These factors contributed to the safety and efficiency of the program. The training program is found to be motivating as muscle's strength increased by 20% after MST and the results correspond to other studies that have applied MST in healthy subjects and patient groups [22, 23, 31].

Quality of life and clinical relevance.

Even though the benefits of strength training have been adhered in healthy subjects, its role in rehabilitation is hardly explored. In cancer rehabilitation, one of the main goals is to fight the side-effects of the disease and treatment procedure to improve the QoL. The present study proved that MST is capable of improving different aspects of QoL and reducing the sense of fatigue. Various biopsychosocial mechanisms could explain the improvements in BC patients' QoL. They result from strength training, including neuromuscular adaptations, endorphins distraction, mastery achievements, positive feedback, and social interaction [37]. According to EORTC QLQ-C30 core questionnaire, changes in role functioning, emotional functioning and social functioning after intervention have considerably improved and have indicated significant difference between the groups. Patients in TG were more socially active during treatment phase, and that could potentially explain improvement in the QoL. These findings prove that clinical strength training could keep patients socially active during the treatment period. As BC affects women's identities, improved QoL is especially vital for women going through complex treatment. As 1RM improves, other submaximal activities become more cost effective. Improvements in absolute strength indicate reduction in relative effort. Thus, work can be performed at a lower percentage of one's maximum capacity [38]. Due to improved muscle strength patients decide to do more, thus maintaining the life style they practiced prior to the treatment.

Typically, the patients of the study started adjuvant chemotherapy 4 weeks after breast surgery. On average, MST started 2 to 3 weeks after surgery. So, the patients had > 4 training sessions before the first chemotherapy. As a result, the patients already had improved muscle strength when engaging in adjuvant treatment. Our observations verify the positive effect of starting training as early as possible — the muscle strength is upgraded even before the chemotherapy process. The muscle strength improves from 1–3% after every training session [29, 39].

Clinical implications. It is generally acknowledged that reduction in exercise capacity and attenuation in maximal work rate is typical for BC patients. In addition, it cannot be denied that the ability to engage in physical activities is strongly affected by loss of muscle strength and reduction of muscle mass [40, 41]. These factors lead towards inactivity, muscle disuse, and even worse health condition. The current findings indicate that MST is appropriate for patients suffering from BC as the patients of the present study demonstrate 96% compliance and completion of training. The current data show that the inclusion of MST in a BC rehabilitation program could increase muscle strength for about 20%, while the QoL could be improved by 13%. Reduction of therapy side effects and fatigue seem to be logical consequence. The patients are to demonstrate the potential of performing significantly more work or accomplishing the same work with reduced effort.

CONCLUSION

Finally, this study demonstrates a considerable improvement in muscle strength, QoL and reduction of fatigue after 12-week high-intensity strength-training program in BC patients. These findings give a reason for the authors of the study to recommend incorporating high-intensity strength training in cancer rehabilitation, accompanied by careful screening and supervision of patients during training period.

DISCLOSURES

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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