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BY
GORM HENRIK FOGH RASMUSSEN

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AALBORG UNIVERSITY
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PHD THESIS

by

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Dissertation submitted

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CV

Gorm Henrik Fogh Rasmussen (GHFR) received his Bachelor's Degree in Sports Sciences in 2015 from Aalborg University and wrote his thesis on kinetics and kinematics of variable resistance in the deadlift exercise. In 2017, he obtained his Master's Degree in Sports Sciences from Aalborg University, with special emphasis on the biomechanics and neurophysiology of movement.

With grants from the Danish Cancer Society and the Harboe Foundation, GHFR was enrolled as a PhD-student at the Doctoral School of the Faculty of Medicine at Aalborg University in 2018. The PhD-project was a collaboration between Aalborg University, Danish Cancer Society and The Society of Cancer Survivor and Late Effects Group.

During his PhD, GHFR gave oral presentations at the 25th and 26th annual virtual Congress of the European College of Sports Science, as well as at the 12th and 13th Annual Meeting of the Danish Society of Biomechanics. In addition, he was invited to give oral presentations at seminars hosted by the Society of Cancer Survivor and Late Effects Group in 2020 and 2022, respectively. He also acted as reviewer for the Journal of Strength and Conditioning Research and Frontiers in Physiology.

ENGLISH SUMMARY

Persistent pain after treatment for breast cancer is a common problem with a complex and poorly understood aetiology. Consequently, there is a lack of effective treatment options available for breast cancer survivors. Resistance training is a promising tool to combat a variety of adverse effects to breast cancer treatment that may provide pain-relieving benefits. Investigating the effects of resistance training on persistent pain after breast cancer treatment could elucidate further on the efficiency of resistance training as a clinical therapeutic tool for pain management.

The overall aim of this thesis was to investigate the short- and long-term effect of resistance training on persistent pain occurring more than 1.5 years after breast cancer treatment through a series of four studies. In study I, the absolute and relative reliability of the experimental assessments employed to measure mechanical pain sensitivity, active range of motion and maximal strength in Study II-IV were assessed and found to range from substantial to excellent, confirming the used experimental assessments would be suitable. Study II examined the effects of persistent pain on shoulder function compared to healthy controls and found a significant decrease in pressure pain thresholds and shoulder function. This highlight that hyperalgesia and shoulder impairment are long lasting adverse effects. Study III aimed to investigate the acute effects of strength training on pain sensitivity and revealed an analgesic response in the ventral region, demonstrating that resistance training could provide a transient analgesic effect. Study IV was a randomized controlled study demonstrating a significant decrease in pain sensitivity, but not pain intensity, following a 12-week resistance training program. This may suggest that regular exposure to resistance training could reduce widespread hyperalgesia and thus, be useful for managing central sensitization.

In summary, the present thesis indicated that common methods for assessing pain, active range of motion and muscular strength can be used reliably in the target population. Furthermore, women with self-reported pain after treatment for breast cancer demonstrate significant reductions in pain thresholds and shoulder function well beyond 1.5 years after treatment. Finally, and importantly, resistance training can decrease mechanical pain sensitivity following both acute and prolonged exposure but may not have systematic effects on self-reported pain intensity.

DANSK RESUME

Vedvarende smerter efter behandling for brystkræft er hyppige og vores nuværende forståelse af den underliggende ætiologi er mangelfuld. Derfor er der mangel på effektive behandlingsstrategier for brystkræftoverlevere med vedvarende smerter. Styrketræning udgør et lovende redskab til at bekæmpe en række bivirkninger ved brystkræftbehandling, og kan muligvis også lindre smerter. Forskning i effekten af styrketræning på vedvarende smerter efter behandling for brystkræft kan derfor bidrage med ny viden om styrketræning som klinisk terapeutisk værktøj til smertebehandling.

Afhandlingens formål var derfor at undersøge styrketrænings kort- og langsigtede effekt på vedvarende smerter mere end 1.5 år efter behandling for brystkræft gennem fire sammenhængende studier. Studie I undersøgte den absolutte og relative pålidelighed af metoderne, der anvendtes til at måle mekanisk smertefølsomhed, aktivt bevægelsesudslag i skulderen og maksimal styrke i Studie II-IV. Pålideligheden spændte fra betydelig til næsten perfekt, hvilket bekræftede metodernes anvendelighed. Studie II undersøgte effekten af vedvarende smerter på skulderfunktion og smertefølsomhed sammenlignet med raske kontrolpersoner og fandt en signifikant reduktion i smertetærsklen over for tryk og skulderfunktionen. Det understreger, at smerteoverfølsomhed og nedsat skulderfunktion er langvarige bivirkninger. Studie III undersøgte den akutte effekt af styrketræning på smertefølsomhed og afdækkede et respons for den ventrale skulderregion, hvilket viser at styrketræning kan have en midlertidig smertelindrende effekt. Studie IV var et randomiseret kontrolleret forsøg som påviste en signifikant reduceret smertefølsomhed, men ikke intensitet efter et 12 ugers styrketræningsprogram. Det kan indikere at regelmæssig styrketræning kan reducere smerte overfølsomhed og således være anvendelig i behandlingen af central sensibilisering.

Samlet set indikerer denne afhandling, at almindelige metoder til måling af smerte, bevægeudslag og muskelstyrke er pålidelige ved anvendelse på målgruppen. Endvidere har kvinder med selvrapporterede smerter efter behandling for brystkræft signifikant forøget smertefølsomhed og nedsat skulderfunktion i langt mere end 1.5 år efter behandlingen. Endelig kan styrketræning reducere mekanisk smertefølsomhed efter både én og flere styrketræningssessioner, men lader til at have en begrænset effekt på selvrapporteret smerteintensitet.

ACKNOWLEDGEMENTS

Completion of the current thesis would not have been possible without the financial support of The Danish Cancer and the Harboe Foundation.

I also wish to thank the representatives of The Society of Cancer Survivor and Late Effects Group for their valuable inputs and aid in popular dissemination of Study I-IV. Watching your commitment and tireless work for bettering the quality of life for cancer survivors has been highly inspiring.

Furthermore, I would like to acknowledge the support and encouragement that I have received from my supervisors. Firstly, I would like to thank Prof. Pascal Madeleine for providing an outstanding example of scientific excellence and integrity, his guidance in project management and his genuine care for my professional and personal development. Secondly, I would like to thank Prof. Michael Voigt for his excellent technical guidance, vast scientific experience, and supreme understanding of human neuromechanics, as well as his boundless curiosity and openness to new ideas. Thirdly, I wish to thank Dr Mathias Kristiansen for his relentless attention to detail, grounded and practical approach to research, his inspiring work ethic and for always holding me to a high scientific standard. Finally, I wish to thank Prof. Manuel Arroyo-Morales for his excellent clinical perspectives, constructive criticism, and enthusiasm for the project. I have gained an immense amount of knowledge and experience from working with you all and I am truly grateful for this experience.

All my outstanding colleagues at the Sport Performance and Technology research group also deserve to be mentioned. You have helped create an amazingly open and informal working environment, which made me feel welcome and made my time in the group fun and immensely enjoyable. Moreover, I wish to thank my friends and family for all your endless love and support. You have not only endured my infinite complaints at times of peak frustration but also expressed immense interest in my work throughout the entirety of this project. Finally, I want to give a special thank you to my girlfriend, Katarina, for being my companion through all the *ups and downs* of this journey. You have celebrated my victories, shared my defeats, and believed in me through all of it.

I could not have done this without any of you.

Sincerely,

Gorm

PREFACE

The present studies were carried out in the period 2019-2021 at the Sports Sciences Performance and Technology Group, Department of Health Science and Technology, Aalborg University, Denmark. The Danish Cancer Society funded the current PhD stipend.

The thesis is based on the following four articles, referred to as Study I, Study II, Study III and Study IV. Full length articles can be found in Appendix.

STUDY I

Rasmussen, G. H. F., Kristiansen, M., Arroyo-Morales, M., Voigt, M., Madeleine, P.: "Absolute and relative reliability of pain sensitivity and functional outcomes of the affected shoulder among women with pain after breast cancer treatment. ". PLoS One 2020;15(6):1–16.

STUDY II

Rasmussen, G. H. F., Madeleine, P., Arroyo-Morales, M., Voigt, M., Kristiansen, M: "Pain sensitivity and shoulder function among breast cancer survivors compared to matched controls: a case-control study". Journal of Cancer Survivorship 2021;15(2):1–10.

STUDY III

Rasmussen, G. H. F., Madeleine, P., Arroyo-Morales, M., Voigt, M., Kristiansen, M. "Resistance training induced acute hypoalgesia in women with persistent pain after breast cancer treatment". Journal of Strength and Conditioning Research. ***Accepted.***

STUDY IV

Rasmussen, G. H. F., Kristiansen, M.., Arroyo-Morales, M., Voigt, M., Madeleine, P. "Effect of resistance training on persistent pain after breast cancer treatment: A randomized controlled trial". ***Submitted.***

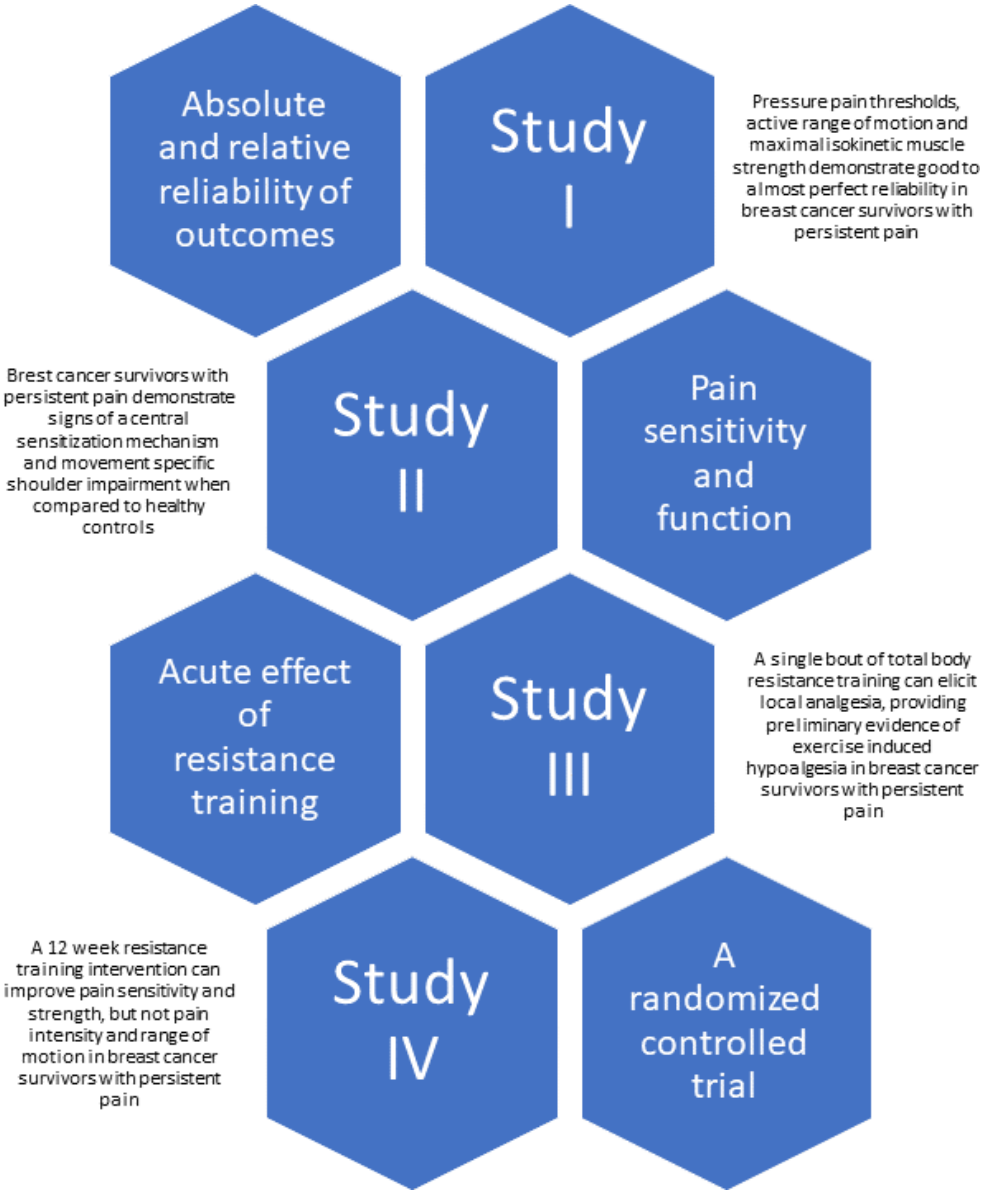
This thesis has been submitted for assessment in partial fulfilment of the PhD degree. The thesis is based on the submitted or published scientific articles, which are listed above. Parts of the articles are used directly or indirectly in the extended summary of the thesis. As part of the assessment, co-author statements have been made available to the assessment committee and are also available at the faculty. The thesis is not in its present form acceptable for open publication, but only limited and closed circulation as copyright may not be ensured.

ABBREVIATIONS

ANTRAC	: Analgesic effect of resistance training after breast cancer
BCS	: Breast cancer survivors
CON	: Control group
EIH	: Exercise induced hypoalgesia
EXP	: Experimental group
ICC	: Intra-class correlation coefficient
IPAQ	: International physical activity questionnaire
MEP	: Movement evoked pain
MIMS	: Maximal isokinetic muscle strength
MRE	: Mental readiness to exertion
MDC	: Minimum detectable change
NRS	: Numeric rating scale
PI	: Pain intensity
PPT	: Pressure pain threshold
PRE	: Physical readiness to exertion
ROM	: Range of motion
RT	: Resistance training
RPE	: Rating of perceived exertion
SEM	: Standard error of measurement
1RM	: One repetition maximum

FIGURES AND TABLES

THESIS AT A GLANCE



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CHAPTER 1. INTRODUCTION

Breast cancer, the most common type of cancer in women, is a major public health problem, with 2,261,419 estimated new cases and 684,966 related deaths according to Global Cancer Statistics (GLOBOCAN) for the year 2020 (173). This corresponds to 11.7% and 6.9% of all registered cancer cases and related deaths in 2020, and demonstrate an alarming increase in breast cancer incidence and related mortality by nearly 8% from 2018 (24). In Denmark, the estimated annual incidence and mortality rates corresponds to 4,826 and 1,090 cases, respectively, according to the most recent data (2015-2019) published by the Association of the Nordic Cancer Registries (NORDCAN) (49).

NORDCAN has predicted an increasing incidence rate over time with an estimate of 5,442 annual breast cancer cases in Denmark by 2034, whereas the annual number of cases on a global scale has been predicted to reach 3.2 million in 2050 (90). Fortunately, the prognosis has improved over time due to new treatments and early detection (24), and the current 1- and five-year survival rates are approximately 90% on average (49). However, breast cancer and its treatments can cause complications and adverse effects are therefore common (148). Consequently, there is a demand for knowledge on how to manage late effects of the treatment as the population of survivors is growing.

This chapter provides an overview of the incidence and burden of persistent pain after breast cancer treatment, factors suggested to influence the underlying aetiology,

available treatment options (or lack thereof) and the rationale for utilizing resistance training as a tool for managing persistent pain in breast cancer survivors (BCS).

1.1. PAIN AFTER TREATMENT FOR BREAST CANCER

Persistent pain after breast cancer treatment is a common problem, affecting 25-60% of all BCS depending on literature (7). The term refers to pain in and around the surgical area lasting more than three months after treatment (130), and is often used interchangeably with “chronic pain after breast cancer”. However, as highlighted by Raffaeli et al. (150), the term “chronic” solely emphasizes temporal pain features, whereas the term “persistent” arguably encompasses the dynamic interaction among biological, psychological and social factors of pain to a greater extent. Consequently, persistent pain after breast cancer is arguably the more appropriate term in this thesis.

In Denmark, the prevalence of persistent pain is roughly 45% and 37% when measured four and eight years after the initial treatment, respectively (65,129). In these studies, pain where most frequently located in the areas of the breast (79-86%), axilla (58-63%), arm (51-57%) and side of body (54-56%), with 22-25% reporting pain in more than one location. Clearly, persistent pain in BCS is a substantial issue with important consequences for the healthcare system (19,20,168). In Europe, the socioeconomic and national healthcare costs of conditions associated with persistent pain amount to billions annually, representing 3–10% of gross domestic product (42,74).

On a personal level, persistent pain in BCS is a predominant cause of upper limb impairments (6) that can limit activities of daily living (81). Pain has also been

associated with increased sensitivity to mechanical stimuli (39) and a reduction in strength and range of motion (ROM) of the affected shoulder (115), which may further exacerbate upper limb impairments (88). The observed mechanical hyperalgesia is widespread and suggested to indicate the presence of central sensitization mechanisms (38,39). Further, kinesiophobia has also been reported as the main contributor to-pain related disability in mid- to long-term BCS (73), implying that performance of physical tasks can trigger a pain response, i.e. movement-evoked pain (MEP). Collectively, persistent pain and related issues can severely impact the patients quality of life (119,147) and cause substantial reductions in perceived physical function (6), which is associated with increased breast cancer-related morbidity and mortality (23,27).

1.1.1. AETIOLOGY & TREATMENT OF PERSISTENT PAIN

The aetiology of persistent pain is complex and poorly understood, but is thought to involve a combination of pre- intra, and post-operative risk factors (7,11,131). The most well established include the surgical procedure to the breast and/or axilla, along with adjuvant radio and/or chemo therapy (7). In particular, the influence of potential damage to nerve pathways from surgery and adjuvant therapy is often discussed (7). For example, the intercostobrachial nerve (i.e. lateral cutaneous branch of T2), highlighted in Figure 1, is particularly vulnerable during operative procedures on the breast and/or axilla (48,118). Further, post-surgical exposure to radiation may cause inflammation that lead to nerve damage due to fibrosis, atrophy, and ulceration of the tissues (53). Similarly, many chemo therapeutic agents used in breast cancer treatment have neurotoxic attributes (7), which may cause structural damage to the peripheral

nerves (152). For these reasons persistent pain after breast cancer is suggested to have a predominantly neuropathic character (79,98), although the neuropathic component appear to be unclear in the majority of cases (i.e., 71%) (97).

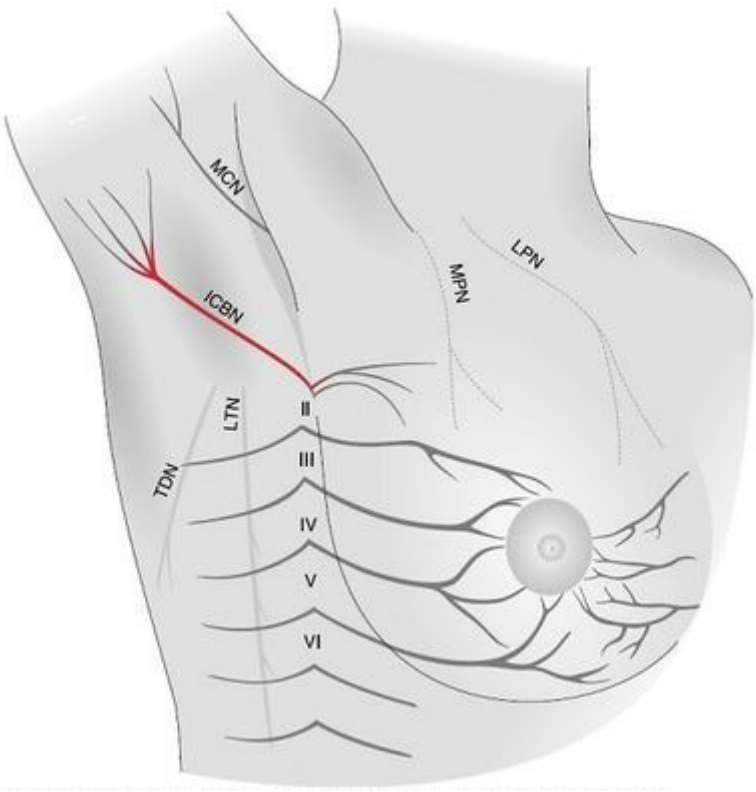

Figure 1: *Peripheral nerve fibers exposed to surgery and adjuvant therapy for breast cancer. Abbreviations: Intercostobrachial nerve (highlighted in red): ICBN, intercostal nerves 2-6: II-IV, lateral pectoral nerve: LPN, long thoracic nerve: LTN, medial cutaneous nerve: MCN, medial pectoral nerve: MPN, thoracodorsal nerve: TDN. Adapted from Wijayasinghe et al. (182).*

Unfortunately, research on managing persistent pain in BCS is limited and there is currently a lack of knowledge on optimal treatment strategies (110). Some pain-relieving medicine (i.e., antidepressants like amitriptyline, venlafaxine) have been

demonstrated to provide an adequate analgesic effect on neuropathic pain in BCS (99,174). Further, autologous fat grafting (i.e., fat injection to the surgical area) have shown promising results in BCS suffering for persistent pain and severe scar retractions (40,124). However, the effect of these approaches may be limited to patients with a clear neuropathic pain component, and each have their own limitations. The medical drugs are associated with serious side effects, e.g. nausea, vomiting, and physical dependence (157), and the outcome of surgery is unknown in women without severe scar retraction (110). Therefore, the development of safe and effective treatment strategies with broader application abilities and limited side effects is of major clinical and societal importance (37).

1.2. ANALGESIC EFFECT OF PHYSICAL EXERCISE

As highlighted by Sluka and colleagues in several studies (114,117,166), physical activity has become a first-line treatment in rehabilitation settings for individuals with persistent pain, and evidence based practice guidelines recommend exercise for a variety of persistent pain conditions (13,25,26,33,34,149). Physical activity and exercise offer numerous general health benefits, including improved physical function (116), mood (89) and decreased risk of secondary health problems such as cardiovascular, metabolic, bone, and neurodegenerative disorders (146). Further, it is well-established that long-term exercise training can provide pain relief across many different persistent pain conditions, including fibromyalgia (13,120), osteoarthritis (86,140), chronic low back pain (132), chronic neck pain (72) and neuropathic pain (51). Finally, precision exercise (i.e., exercise adapted to the an individual) is likely to be associated with minimal adverse effects in comparison to pharmaceutical and

surgical interventions (66). Therefore, the use of exercise for pain management is attractive and has been recognized for its effectiveness in reducing disability and health care costs (91).

Importantly, exercise and physical activity are considered safe at all stages of breast cancer treatment and are strongly recommended for BCS without no medical contraindications to exercise (37,84,161). There is strong evidence to support the efficacy of exercise for reducing risk of cancer specific mortality and recurrence (84), and improving physical function, mental and physical health (37,161). However, as recently highlighted by Campbell et al. (37), there is currently a lack of research on the effect of exercise on cancer-related pain, which limit our understanding of how exercise may benefit BCS with persistent pain. Regardless, survivors may very well be able to exercise with pain that is tolerable (37) and a growing body of evidence demonstrates pain relieving benefits of both aerobic and resistance exercise (44,52), some of which may have an additive effect when paired with pharmacological interventions (44). Moreover, the use of aerobic and resistance training for pain management in cancer survivors was recently recommended by Exercise and Sports Science Australia (84) and thus, there is reason to believe that an exercise-based approach may benefit BCS with persistent pain.

1.2.1. A CASE FOR RESISTANCE TRAINING

Resistance training (RT) confers unique benefits to the musculoskeletal system in common disorders and in healthy people (60,123), and has been associated with a 21% reduction in all-cause mortality (155). Moreover, RT can reduce mortality in breast cancer survivors by 33% (78) and has been shown to improve a variety of adverse

effects to breast cancer treatment such as fatigue scores (76), quality of life (76,144,169), body image (169), psychosocial assessment (144), bone mineral density (181), body composition (122,158), physical function (28,183), shoulder range of motion (ROM) (1) and muscular strength (28,122,165,183), without increasing the risk of developing or exacerbating lymphedema symptoms (2,76,77,159,160). However, little is known about the effects of prolonged exposure to progressive RT on BCS suffering from persistent pain. At the time of this writing, only two randomized controlled trials (RCTs) have reported the effect of progressive RT on persistent pain postoperatively and found no significant decrease in pain (4,46). Importantly, these studies were originally designed to assess the effect influence of RT on breast cancer related lymphedema, employed substantially different RT interventions and utilized pain as a secondary outcome measure. Consequently, there is a need for research to improve our current understanding of RT as a clinical therapeutic tool for long term pain management in breast cancer patients.

There are several potential mechanisms by which RT may provide pain relieving benefits, including up-regulation of endogenous opioids in the brainstem regions important for pain modulation (62–64,170) and reduced levels of painful pro-inflammatory cytokines (69,186). For example, a single bout of RT has been shown to activate endogenous pain inhibitory mechanisms and cause a transient reduction in sensitivity to noxious stimuli known as exercise induced hypoalgesia (EIH) (104,136). This phenomenon has been observed in a myriad of populations and testing conditions (102,103,105,106,108,177,178), and has previously been suggested to occur in breast cancer patients (58). Moreover, RT has been shown to amplify the natural synthesis

and release of anti-inflammatory cytokines such as interleukin (IL)-10 and IL-6 that inhibit pain from pro-inflammation cytokines (69), and has been reported to effectively reduce plasma and tissue-specific inflammation in BCS (163). This is important, because the synthesis and release of pro- inflammatory cytokines such as tumour necrosis factor alpha (TNF- α) is implicated in potentiation of the pain pathways (i.e. peripheral and central sensitization) (44,100) and hence, RT may decrease central sensitization in BCS with persistent pain.

Collectively, the current evidence suggests that RT is a promising clinical therapeutic tool for managing multiple adverse effects to breast cancer treatment. This exercise modality can improve shoulder strength and ROM in BCS, and there is reason to believe RT may provide both a short- and long-term analgesic effect to BCS suffering from persistent pain. However, there is a lack of research on the pain-relieving benefits of RT in this population and thus, our current understanding is limited. Moreover, it is unclear if and how persistent pain after treatment for breast cancer may affect the relative and absolute reliability of common methods for assessing pain and shoulder function such as pressure algometry, goniometric measurements of joint ROM and isokinetic dynamometry. Considering that pain intensity can affect shoulder function (115) and that substantial day-to-day fluctuations can be observed in perceived pain (162), measures of pain sensitivity, strength and ROM may vary considerably within this population. Reliable tools for measuring clinical outcomes are essential to monitor the effectiveness of an RT intervention and consequently, it is necessary to establish the absolute and relative reliability of assessment methods for pain and shoulder function.

1.3. AIM & HYPOTHESES

The overall aim of this thesis was to investigate the effects of resistance training on persistent pain after treatment for breast cancer. Study I was a reliability study to determine the absolute and relative reliability of common methods for assessing mechanical pain sensitivity, range of motion and muscular strength. Study II was a case-control study to compare the mechanical pain sensitivity, muscular strength, and range of motion in the affected shoulder of BCS with persistent pain to healthy controls. Study III was an intervention study to examine the acute effect of a single bout of resistance training on mechanical pain sensitivity. Study IV was a randomized controlled trial to investigate the effect of a 12-week supervised resistance training program on mechanical pain sensitivity, self-reported pain, shoulder range of motion and maximum strength. These studies formed the basis for this thesis and were performed sequentially as illustrated in Figure 2.

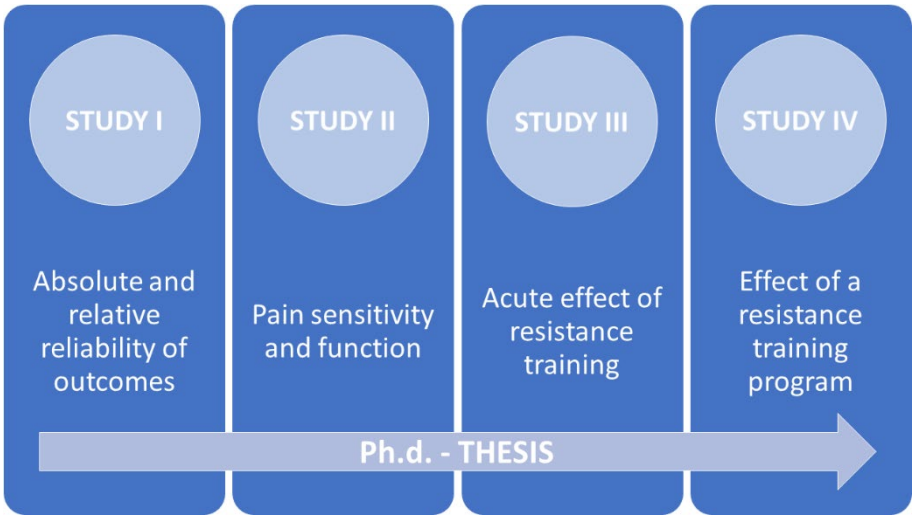

Figure 2: *Study sequence*

It was hypothesized that common methods of assessment could be applied reliably in women with persistent pain after breast cancer (Study I), that persistent pain after treatment would affect mechanical pain sensitivity and shoulder function compared to healthy controls (Study II), and that resistance training would provide both short- and long-term pain-relieving benefits (Study III-IV).

CHAPTER 2. METHODS

This chapter provides a brief overview of the methodological approaches. See Studies I-IV for an in-depth description.

2.1. STUDY OVERVIEW

The protocols of Study I-IV were approved by the local Ethics Committee (N-20180090), registered at ClinicalTrials.gov (NCT04509284), and conducted according to the Declaration of Helsinki. Following a detailed written and verbal explanation of the experimental risks, the participants gave their written informed consent prior to participating in Study I-IV, respectively. All experiments were carried out at the laboratories of the Sports Sciences – Performance and Technology research group at Aalborg University, Aalborg, Denmark, between August 2019 and September 2021. An overview of the specific assessments performed for Study I-IV is presented in Table 1.

	Study I	**Study II**	**Study III**	**Study IV**
Pain intensity during everyday life	✓	✓	✓	✓
Pressure pain thresholds	✓	✓	✓	✓
Movement evoked pain	✓	✓	✓	✓
Active shoulder range of motion	✓	✓	✓	✓
Isokinetic shoulder strength	✓	✓		
One repetition maximum			✓	✓
Rating of perceived exertion	✓	✓	✓	✓
Mental readiness to exertion			✓	✓
Physical readiness to exertion			✓	✓
Arm circumference				✓
IPAQ	✓	✓	✓	✓

Table 1: *Overview of assessments (Study I-IV). Abbreviations: International Physical Activity Questionnaire: IPAQ.*

2.2. RECRUITMENT

The participants of Study I-IV were recruited by means of a database letter through the national database administered by the Danish Breast Cancer Corporate group, and controls for study II were recruited through Senior Sport Aalborg. Volunteers were pre-screened for participation to ensure all inclusion and exclusion criteria were met, and for any contra indications to exercise through the physical activity readiness questionnaire (175). Baseline data for physical activity were obtained through the short-form International Physical Activity Questionnaire (IPAQ) (47). The following inclusion and exclusion criteria were developed in accordance with the guidelines of Andersen & Kehlet 2011 (7) and in collaboration with Prof Niels Kromann (MD, PhD), breast surgery specialist at the Danish Cancer Society.

2.2.1. INCLUSION & EXCLUSION CRITERIA (STUDY I-IV)

Volunteer BCS for Study I-IV were eligible for inclusion if they: I) had a diagnosis of primary breast cancer (grades I-IIIA); II) were adult women at least 18 years of age; III) had completed breast cancer treatment (i.e. surgery and possible adjuvant chemo and/or radiotherapy) at least 18 months before the start of the study; IV) had self-reported pain in the areas of the breast, shoulder, axilla, arm and/or side of body with an intensity of ≥ 3 on a numeric rating scale (0 = no pain, 10 = worst pain imaginable); V) had no signs of cancer recurrence; VI) could read, write and speak Danish. Reasons for ineligibility were as follows: I) breast surgery for cosmetic reasons or prophylactic mastectomy; II) diagnosis with bilateral breast cancer; III) diagnosis with lymphedema; IV) diagnosis with other chronic pain conditions (e.g.,

rheumatoid arthritis) or V) a previous diagnosis of fibromyalgia syndrome. See Study I-IV for greater detail.

Volunteer controls for Study II were asymptomatic (pain-free) females with no previous history of cancer matched to the BCS group as well possible for age and body mass index. Volunteers were eligible for inclusion in the control group if they were as follows: I) adult women at least 18 years of age and II) reading, writing, and speaking Danish. Reasons for ineligibility were as follows: I) pregnancy; II) drug addiction, e.g., continued use of cannabis, opioids, or other substances taken for a non-medical purpose; III) presence of signs or symptoms of musculoskeletal pain; IV) history of persistent pain or trauma in the upper body; V) adverse medical conditions with potential influence on the study (e.g., chronic fatigue syndrome), or VI) participation in other pain trials throughout the study period. See Study I-IV for greater detail.

All participants in Study I-IV were instructed to maintain their normal everyday lifestyle, but avoid physical activity and consumption of alcohol, caffeine, nicotine, or painkillers in the last 24 hours prior to the experimental sessions. This was confirmed verbally upon arrival at the laboratory. See Table 2, Table 3 and Table 4 for demographics, health behaviour and treatment profiles of the participants in Study I-IV

	Study I	Study II		Study III	Study IV	
		BCS	CON		EXP	CON
n	21	21	21	20	10	10
Age, mean (CI: 95%), y	57.4 (54;60.8)	57.4 (54;60.8)	60 (55.5;64.5)	59.7 (56.1;63.3)	58.9 (52.1;65.7)	60.5 (56.3;64.7)
Height, mean (CI: 95%), cm	167.9 (165.5;170.2)	167.9 (165.5;170.2)	165.5 (162.8;168.2)	167.1 (164.2;170)	165.8 (160.6;171.1)	168.4 (164.9;171.8)
Living arrangement, No. (%)						
Living with a partner	17 (81)	17 (81)	15 (71)	16 (80)	8 (80)	8 (80)
Living alone	3 (14)	3 (14)	6 (21)	4 (20)	2 (20)	2 (20)
Other	1 (15)	1 (15)	0 (0)	0 (0)	0 (0)	0 (0)
Education, No. (%)						
Short	6 (26)	6 (26)	4 (19)	2 (10)	0 (0)	2 (20)
Medium	14 (67)	14 (67)	13 (62)	16 (80)	9 (90)	7 (30)
Long	1 (5)	1 (5)	4 (19)	2 (10)	1 (10)	1 (10)
Employment, No. (%)		9				
Full time	11 (52)	11 (52)	10 (48)	7 (35)	4 (40)	3 (30)
Part time	3 (14)	3 (14)	2 (10)	8 (40)	3 (30)	5 (50)
Retired	6 (29)	6 (29)	8 (38)	5 (25)	3 (30)	2 (20)
Other	1 (5)	1 (5)	1 (5)	0 (0)	0 (0)	0 (0)

Table 2: *Participant demographics (Study I-IV). Abbreviations: 95% Confidence interval: CI: 95%.*

	Study I	Study II		Study III	Study IV	
		BCS	CON		EXP	CON
n	21	21	21	20	10	10
BMI, mean (CI: 95%), kg/m^2	27.6 (25.3;29.8)	27.6 (25.3;29.8)	27.1 (24.9;29.2)	26.1 (23.9;28.3)	25.6 (22.1;29.1)	26.7 (23.3;30.1)
BMI, No. (%)						
≤ 25 kg/m^2	8 (38)	8 (38)	7 (33)	11 (55)	6 (60)	5 (50)
>25 - ≤30 kg/m^2	6 (29)	6 (29)	10 (48)	6 (30)	3 (30)	3 (30)
>30 kg/m^2	7 (33)	7 (33)	4 (19)	3 (15)	1 (10)	2 (20)
Menopausal status, No. (%)						
Pre	1 (5)	1 (5)	4 (19)	0 (0)	0 (0)	0 (0)
Peri	4 (19)	4 (19)	4 (19)	1 (5)	0 (0)	1 (5)
Post	16 (76)	16 (76)	13 (63)	19 (95)	10 (90)	9 (90)
Physical activity, No. (%)						
Low	6 (29	6 (29	4 (19)	3 (15)	1 (10)	2 (20)
Moderate	10 (48)	10 (48)	15 (71)	9 (45)	4 (40)	5 (50)
High	5 (24)	5 (24)	2 (10)	8 (40)	5 (50)	3 (30)
Smoking, No. (%)						
Current	1 (5)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Former	11 (52)	11 (52)	7 (33)	11 (55)	5 (50)	6 (60)
Never	9 (43)	9 (43)	14 (67)	9 (45)	5 (50)	4 (40)
Alcohol consumption						
No. units per week, mean (CI:	3.1 (1.5;4.8)	3.1 (1.5;4.8)	5.1 (3.2;7.1)	5 (2.8;7.1)	5.6 (2.5;8.7)	4.3 (0.8;7.8)
None, No. (%)	8 (38)	8 (38)	1 (5)	4 (20)	2 (20)	2 (20)

Table 3: *Participant health characteristics (Study I-IV). Abbreviations: 95% Confidence interval: CI: 95%, Body mass index: BMI.*

	Study I & II	Study III	Study IV	
			EXP	CON
n	21	20	10	10
Histologic stage of malignancy, No. (%)				
I	6 (29)	7 (35)	3 (30)	4 (40)
II	11 (52)	7 (35)	3 (30)	4 (40)
III	4 (19)	6 (30)	4 (40)	2 (20)
Tumour diameter, mean (CI: 95%), mm	17.8 (14.1;21.5)	20.6 (13.5;27.8)	21,2 (6,5;35,9)	20,1 (12,6;27,6)
Surgical protocol, No. (%)				
Breast conserving surgery	17 (81)	15 (75)	7 (70)	8 (80)
Mastectomy	4 (19)	5 (25)	3 (30)	2 (20)
Lymph node protocol No. (%)				
Sentinel lymph node biopsy	15 (71)	14 (70)	7(70)	7(70)
Axillary dissection	2 (10)	1 (5)	2 (20)	0 (0)
Both	4 (19)	5 (25)	1 (10)	3 (30)
No. of lymph nodes dissected, mean (CI: 95%),	4.9 (3.1;6.7)	5.2 (2.9;7.5)	4.9 (1.6;8.2)	5.5 (1.7;9.3)
Dominant limb affected, No. (%)	9 (43)	9 (45)	5 (50)	4 (40)
Adjuvant treatment, No. (%)				
Chemotherapy only	1 (5)	0 (0)	0 (0)	0 (0)
Radiotherapy only	4 (19)	5 (25)	3 (30)	2 (20)
Both	16 (76)	15 (75)	7 (70)	8 (80)
Endocrine therapy, No. (%)				
Currently	10 (48)	14 (70)	6 (60)	8 (80)
Ceased	4 (19)	2 (10)	1 (10)	2 (20)
Receptor status, No. (%)				
Estrogen positive	14 (67)	17 (85)	7 (70)	9 (90)
HER2 positive	6 (29)	6 (30)	3 (30)	1 (10)
Time since treatment, mean (CI: 95%), months	66.1 (51.3;80.8)	70.7 (57.2;84.1)	80.1 (55.6;104.6)	64.9 (44.1;85.7)

Table 4: *Participant treatment profile (Study I-IV). Abbreviations: 95% Confidence interval: CI: 95%, Human epidermal growth factor 2: HER2.*

2.2.2. SAMPLE SIZE ESTIMATES (STUDY I-IV)

Sample size for Study I and II were estimated in agreement with the guidelines of Bujang & Baharum (30). Hence, assuming two observations per participant, an α level of 0.05, a β level of 0.20 and an expected ICC of 0.60, the minimum sample size required for this study was 15 participants. To account for potential dropout, it was decided to enrol 21 BCS. The same BCS group participated in Study II, and an equivalent number of healthy, pain free women matched for age and body mass index were recruited for the control group. In order to detect a significant difference in PPTs collected pre- and post a single bout of RT in Study III, the minimum sample size was determined to be 16, assuming an α level of 0.05, a β level of 0.20 and an effect size of 0.40 estimated from the acute analgesic response reported by Burrows (32). To account for a potential drop out of 20%, 20 participants were enrolled. Regarding Study IV, the minimum required sample size to detect a significant difference in PPTs collected pre-, post and three months after the intervention was determined to be 28. This was done assuming an α level of 0.05, a β level of 0.20 and a moderate effect size of 0.25 (43). To account for a possible drop out of 20%, 34 participants were invited to participate in the study (Figure 3). See Study I-IV for greater detail.

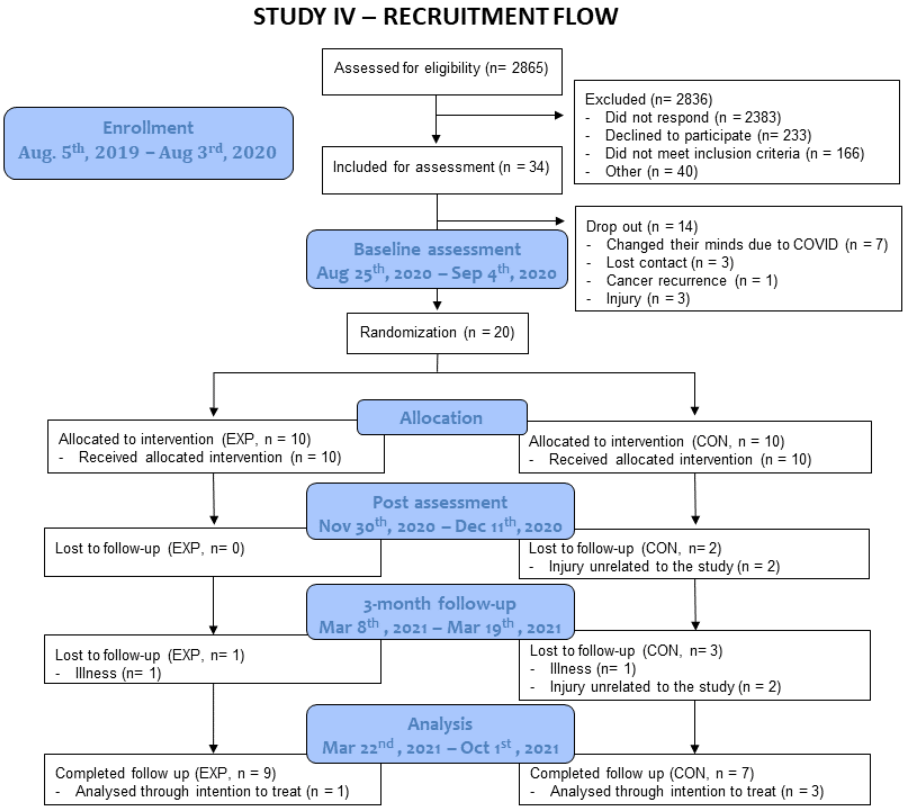

Figure 3: *Enrolment, randomization, and dropout of participants allocated to the intervention group (EXP) or control group (CON). Injury or illness was defined as a change in physical status that altered the outcome of the physical activity readiness. Adapted from Study IV.*

2.3. PAIN ASSESSMENTS (STUDY I-IV)

The methods used to assess pain intensity and sensitivity have been described in detail previously (Study I-IV), however, a brief explanation will be provided. Subjective pain was assessed in two domains: 1) Pain intensity (PI) during everyday life in the chest, shoulder, axilla, arm, and side of body for the past three months and 2) Movement-evoked pain (MEP) during the assessments of maximal strength (Study I-IV). Both domains were rated on a 0-10 numeric pain rating scale (95,Study I-IV),

and cut-off scores used as reference for Study I-IV were: 0 = no pain; 1–3 = mild; 4–6 = moderate; 7–10 = severe pain (125,Study I-IV). For PI, the highest pain intensity rated across locations was reported as peak pain (Study I-IV).

Pain sensitivity in was assessed through pressure pain thresholds (PPT) measured unilaterally across a total of 17 points located on the dorsal and ventral parts of the chest, shoulder and neck regions of the affected side (Figure 4), and at a single reference point located on the ipsilateral tibialis anterior muscle (70,Study I-IV). The assessments were performed twice over two rounds in systematic order and a third time if the point assessed had a coefficient of variance over 20% (14,Study I-IV). This procedure yielded approx. 6-minutes between measurements made over the same point to avoid temporal summation of pain (141,Study I-IV). To obtain a map of the spatial pressure pain distribution of the dorsal and ventral shoulder regions inverse distance weighted interpolation was applied to the measurements (15,Study I-IV). For greater details on PPT mapping, see Alburquerque-Sendin et al. (3).

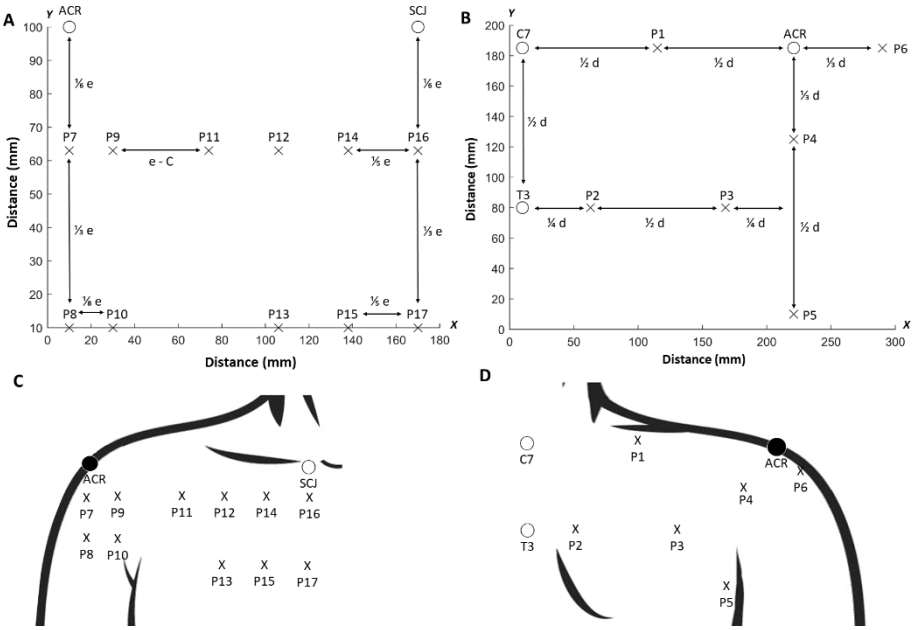

Figure 4: *Pressure pain threshold grids. Schematic representation of the ventral (A) and dorsal (B) grids for pressure pain threshold (PPT) assessments and their approximate anatomical location (C & D). The PPTs of the dorsal region were measured over 6 points located on the trapezius muscle (P1-P2), infraspinatus (P3), posterior deltoid (P4), latissimus dorsi (P5) and lateral deltoid (P6). The PPTs of the ventral region were measured over 11 points located on the anterior deltoid (P7-P10) and pectoralis major (P11-P17). d = distance between the seventh cervical vertebra (C7) and acromion (ACR), e = distance between the sternoclavicular joint (SCJ) and acromion (ACR) and C = the summed distance between P11 and P12, P12 and P14, P14, and P16 on the x-axis. Note that the position of the assessed PPT on figure 5C and 5D were adapted to take in consideration body shape. Adapted from Study I - III.*

2.4. FUNCTIONAL ASSESSMENTS (STUDY I-IV)

Physical measurements in the context of this thesis include active range of motion (Active ROM), maximal isokinetic muscle strength (MIMS) and one-repetition maximum (1RM). The methods applied to perform these assessments have been described in detail previously (Study I-IV), however, a brief overview will be provided here. Active ROM was measured for supine shoulder flexion, supine horizontal shoulder flexion/extension, supine internal/external shoulder rotation, and

seated upright shoulder abduction in agreement with Norkin & White (142,Study I) and Dougherty et al. (54,Study I). Measurements were obtained with a goniometer and performed twice over two rounds in systematic order and a third time if the measurements had a coefficient of variance ≥ 20% (Study I-IV).

Isokinetic dynamometry allows the measurement of angle specific maximal muscle strength at constant angular velocities, thereby enabling maximum force production throughout a prescribed ROM (75). Accordingly, MIMS were performed through the active ROM previously determined for the affected shoulder and measured at a speed of 60º/s using an isokinetic dynamometer (Humac Norm, model 770, Computer Sports Medicine Inc., Stoughton, USA). Each participant performed a brief general warm up (approx. 10-minutes) of various stretching exercises for the prime movers, followed by a series of 10 consecutive contractions with submaximal progressive effort (Study I & II). Participants then performed a series of five consecutive contractions at maximal effort for each muscle group with a 2-minute rest period between series (Study I & II). Rest between strength measures for different movement patterns consisted of the time required for readjustment of the dynamometer (approximately 5 minutes) (Study I & II). The first repetition of each maximal trial was discarded and mean peak torque at a fixed angular position was calculated for the remaining four in accordance with the recommendations of Brown & Weir (29,Study I).

The 1RM can be defined as the greatest weight that can be lifted once and can be considered the gold standard for dynamic assessment of muscular strength (29). As demonstrated by Gentil et al. (67), MIMS and 1RM produce conflicting results when assessing muscular strength following a dynamic RT program with 1RM being more

suitable for determining exercise specific changes in strength. Consequently, the 1RM was the most appropriate strength assessment for the dynamic RT interventions of Study III and IV. In agreement with the recommendations of the American College of Sports Medicine (9) the assessment began with a general warm up, consisting of five minutes of moderate intensity cardiovascular exercise on a rowing ergometer and five minutes of general stretching for the prime movers. This was followed by a specific warm up with two sets of 8-10 repetitions, 3-5 repetitions and 1 repetition with approximately 50%, 70% and 90% of estimated 1RM, respectively. A maximum of five single repetition attempts with load increments of 1-20kg was then performed until a true 1RM was achieved. Incremental rest periods were provided between sets with 1-4 minutes between warmups and 3-5 minutes between 1RM attempts to prevent excessive fatigue. This was identical for all exercises.

2.5. PSYCHOMETRIC ASSESSMENTS (STUDY I-IV)

Rating of perceived exertion (RPE) and mental and physical readiness to exertion (MRE & PRE) are useful subjective measures to compliment physical performance assessments and control for both perceived intensity of effort and perceived readiness to exert effort (83,143). RPE was rated immediately following every set of each exercise every laboratory session on a RT-specific 10-point numeric rating scale based on repetitions in reserve (RIR) (Table 4**)**, where RPE 10 = 0 RIR, RPE 9 =1 RIR and so forth (Study I-IV). This scale has been validated as a subjective measure of intensity in both novice and experienced power lifters (188). Similarly, MRE and PRE were obtained prior to each exercise in every laboratory session on an 11-point

numeric rating scale (Table 5), where 0 corresponded to “no readiness to exertion” and 10 corresponded to “maximum readiness to exertion” (55,Study I-IV).

RPE SCALE		MRE & PRE-SCALE	
RATING	**DESCRIPTION**	**RATING**	**DESCRIPTION**
10	*Maximum effort*	10	*Maximum readiness to exertion*
9.5	*No further repetitions but could increase load*	9	
9	*1 repetition remaining*	8	
8.5	*1-2 repetition remaining*	7	
8	*2 repetitions remaining*	6	
7.5	*2-3 repetitions remaining*	5	
7	*3 repetitions remaining*	4	
5-6	*4-6 repetitions remaining*	3	
3-4	*Light effort*	2	
1-2	*Little to no effort*	1	
0	*No effort*	0	*No readiness to exertion*

Table 5: *RPE, MRE and PRE scales (Study I-IV). RPE scale adapted from Zuordos et al. (188). Abbreviations: PRE: Rating of Perceived exertion, MRE: Mental readiness to exertion, PRE: Physical readiness to exertion.*

2.6. TRAINING INTERVENTIONS (STUDY III & IV)

The acute resistance training intervention in Study III consisted of a general warm up followed by a standardized training protocol based on the study by Burrows et al. (32), who reported exercise induced hypoalgesia in knee osteoarthritis patients following a single bout of submaximal RT (i.e. 3 sets of 10 repetitions with 60% of 1RM).

Accordingly, the participants performed five minutes of self-selected, moderate intensity, aerobic exercise on a rowing ergometer (Concept II, Boston, USA) followed by stretching of the major muscle groups in the upper- and lower body (i.e., pectorals, latissimus dorsi, triceps, biceps, quadriceps, and hamstrings). They then performed three sets of 10 repetitions with 60% of 1RM in five resistance training exercises (i.e., 90º box squat, bench press, trap bar deadlift, bench pull and lateral pulldown), which was preceded by two warm-up sets of 10-12 and 6-8 repetitions with 50% and 70% of the prescribed training weight, respectively. Rest periods were 1-2 minutes between warmups and 3 minutes between training sets.

The ANTRAC intervention in Study IV consisted of a 12-week supervised progressive RT program, with two training sessions per week. Each session consisted of group training with two to four participants per trainer exercising concurrently. Trainers were certified strength and conditioning specialists, educated in the current guidelines for exercise medicine in cancer management (84). The ANTRAC was separated into three distinct phases: 1) 2-4 sets of 10-12 repetitions, 2) 2-4 sets of 6-8 repetitions and 3) 2-4 sets of 2-4 repetitions (Figure 5, A). Each phase had a duration of four weeks, creating a progressive decrease in number of repetitions to accommodate load progression. A 3-5min rest period was provided between sets across all phases. Initial loads were set to 60% of one-repetition maximum (1RM) and were increased each time an individual was able to complete the maximum number of repetitions prescribed (Figure 5, B). Similarly, loads were decreased if an individual failed to complete the minimum number of repetitions prescribed. Further, to account for fluctuations in fatigue, number of sets was adjusted for the individual within and

between sessions, in accordance with the perceived readiness. In agreement with Smith et al. (167), movement-evoked pain during training was not discouraged provided the participants themselves perceived it as tolerable. Hence, training was only adjusted to accommodate movement-evoked pain in case the participants perceived it as too severe to continue as planned. This approach was identical for all exercises (Figure 5, C). Participants randomized to CON were offered to complete the ANTRAC program following the final follow up assessments.

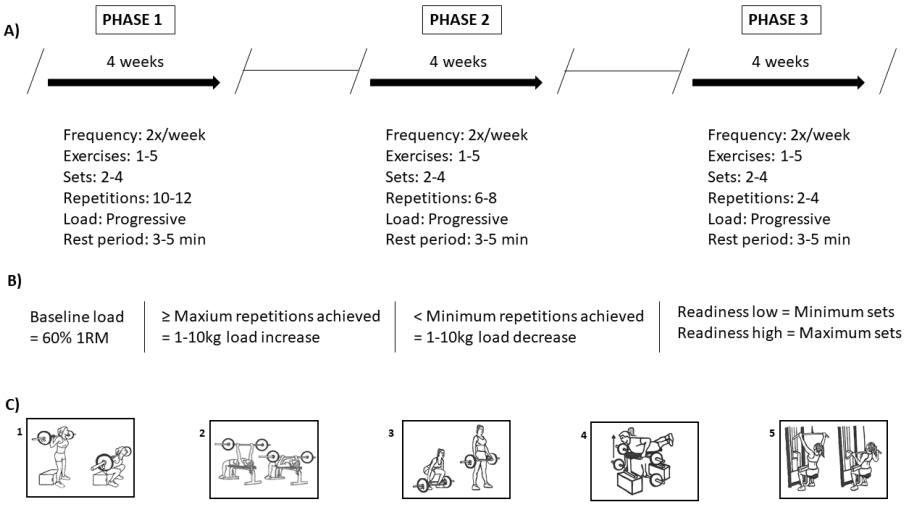

Figure 5: *ANTRAC intervention. Resistance training was performed twice per week for twelve weeks in three four-week phases with a progressive decrease in number of repetitions and a concurrent increase in load (A). Initial loads were 60% of 1RM and were increased or decreased within and between session according to individual performance (B). Number of sets were adjusted within session according to perceived readiness of the individual. This was identical for exercise 1-5: 90º box squat, bench press, trap bar deadlift, bench pull and lat pulldown (C).*

2.7. COMPLIANCE & ADVERSE EVENTS (STUDY I-IV)

Compliance was determined in two contexts: 1) dropout rate and 2) adherence to the ANTRAC intervention. Dropout rate was defined as the percentage of participants

enrolled who decided to withdraw prior to completion of each study. Adherence to the ANTRAC intervention defined as the percentage of supervised resistance training sessions initially planned and effectively achieved by the participants was measured using attendance registration forms by the ANTRAC trainers (8). Adverse events were defined as harmful or negative outcomes associated with the study protocols and collected for each individual study (e.g., injury). Moreover, arm circumference was collected for Study IV to monitor potential signs of lymphedema and determined in agreement with the protocol of Hidding et al. (87). A single tape measure was performed 30cm from the ulnar styloid process for both arms held relaxed and straight at 90º shoulder flexion. A difference in arm volume of ≥10% was considered an indication of lymphedema.

2.8. CHANGES TO THE PROTOCOL (STUDY IV)

As can be inferred from the sample size estimation and the recruitment flowchart (Figure 3), approximately 40% fewer participants were enrolled in Study IV than originally planned which warrant explanation. Data collection for Study IV was performed between August 2020 and March 2021, at the peak of the COVID-19 pandemic in Denmark. Unfortunately, this caused at substantial dropout among the recruited participants prior to the beginning of the study, and we were unable to recruit more during this period. Major reasons for dropout were mental health issues due to the nation-wide restrictions at the time, and fear of infection. Further, nation-wide restrictions severely hampered the logistics of the RT intervention as all gyms were closed, and thus the intervention was relocated to the laboratories of the Department of Health Science and Technology, Aalborg University. In addition, some of the

municipal boundaries of Northern Jutland were closed, causing major confusion and uncertainty among the participants. Hence, it was necessary for the principal investigator to maintain close contact with the authorities and the ANTRAC trainers to support the intervention and ensure compliance with the nationwide and regional restrictions at the time.

2.9. STATISTICAL PROCEDURES (STUDY I-IV)

The statistics in the present thesis and within Study I-IV were made using SPSS 25.0 (SPSS Inc., Chicago, Illinois, USA). Further, data analysis for MIMS assessments in Study I & II were performed in MATLAB R2020a (The MathWorks Inc., Natick, MA, USA). In Study I-III, continuous outcomes were assessed for normality using the Shapiro-Wilk test and were log transformed if the criteria for normality were not met. Mauchly's test of sphericity was used to test for equality of variance in the differences between levels, and the Greenhouse-Geisser correction was applied if the assumption of sphericity was violated (Study I-III). In study IV, Lidl's Missing Completely At Random (MCAR) test was applied to determine if missing data was MCAR. If not, a series of Chi squared tests of association were run to determine potential associations between missing and observed data. Statistical significance in Study I-IV was considered at $P < 0.05$.

In Study I, the aim was to investigate the relative and absolute reliability of PPT, active ROM and MIMS in women with persistent pain after breast cancer treatment. To accomplish this, Intra-class correlation coefficient ($ICC_{2,1}$ for absolute agreement) was computed for all measures to assess the relative variability and interpreted according to Landis and Koch in which an ICC between 0.00 and 0.20 is considered

"poor", 0.21–0.40 is "fair", 0.41–0.60 is "moderate", 0.61–0.80 is "substantial", and 0.81–1.00 is "almost perfect" (109). Absolute reliability of each measure was estimated by computing the standard error of measurement (SEM). SEM was further utilized to calculate minimal detectable chance (MDC), which represents the minimal value for which a difference can be considered as real. See Study I for greater detail.

In Study II, the aim was to compare the PPT, MIMS, active ROM, and MIMS of BCS with persistent pain to healthy, pain-free controls. Potential differences were investigated through a two-way analysis of variance (ANOVA). Outcome (i.e., PPT, MEP, active ROM, and MIMS) were used as dependent factors and PPT location (1-18), movement direction (1-6) and group (BCS/CON) were used as independent factors. Post hoc analyses were performed as univariate analyses with Bonferroni correction for multiple comparisons = α/n. Associations between PPTs and MEP assessments were explored through a Pearson's product-moment correlation analysis or Spearman's rank order correlation. Missing data points were omitted from the above analyses. See Study II for greater detail.

In Study III, the aim was to investigate the acute effect of a single bout of RT on PPTs of BCS with persistent pain after treatment. Separate 2-way repeated measures ANOVAs were performed to investigate the acute analgesic effect of resistance training for the dorsal and ventral shoulder region respectively. PPT was used as dependent factor with anatomical location (P1-17, mean dorsal, mean ventral & reference) and time (PRE, POST) as independent factors. Effect size estimates are reported as partial eta squared (partial η^2), and interpreted according to Cohen (43) in

which ≥ 0.01 – < 0.06 = small, ≥ 0.06 – < 0.14 = moderate, and ≥ 0.14 = large. See Study III for greater detail.

In Study IV, the aim was to investigate the effect of a 12-week supervised RT intervention on PI, PPT, MEP, 1RM and active ROM of BCS with persistent pain. To accomplish this, a linear mixed model (LMM) incorporating two or three fixed effect factors was applied to investigate the effect of resistance training on each outcome using an intention to treat analysis to account for missing data and/or dropouts. PI and BIA estimates were used as dependent factors with group (EXP/CON) and time (PRE, POST & FOLLOW) as independent factors in LLMs with two fixed effects. PPT, MEP, 1RM and active ROM were used as dependent factors with location PPT location, movement direction and exercise, and time (PRE, POST & FOLLOW) as within subject factors, and group (EXP/CON) as a subject factor. See Study IV for greater detail.

CHAPTER 3. RESULTS

The primary findings of Study I-IV are presented in this chapter. Secondary results and additional results only presented orally at scientific conferences, in abstract form or otherwise not included in the studies are not included. For a more detailed description of the primary and secondary results, see Study I-IV.

3.1. PAIN INTENSITY & SENSITIVITY (STUDY I-IV)

Mean (CI95%) PI during everyday life range from 7.2 (6.6;7.9) to 8.1 (6.8;9.4) on the NRS for Study I-IV (Table 6**)**. Peak PI was >7 points on average and 50-75% of each individual participants reported severe PI (i.e., >7 points on the NRS). The most frequent location of pain was the chest and shoulder areas, and most participants reported pain in more than one location. RT did not appear to influence Peak PI as no statistically significant differences was detected following the ANTRAC intervention in Study IV. There was, however, an overall effect of time as PI decreased significantly between assessments (i.e., from PRE to POST to FOLLOW UP) in both groups (Study IV).

Assessments of MIMS for the affected shoulder elicited an MEP response ranging from 3.8 (2.3;5.2) to 4.2 (2.8;5.7) on the NRS in Study I & II, with no significant effect of movement pattern ($P \leq 0.05$). This corresponds to a moderate intensity level (i.e., 4-6 on the NRS) and were inversely correlated with the PPTs for shoulder flexion/extension ($\rho = -0.572$, $P < 0.05$) and shoulder abduction/adduction ($\rho = -0.536$, $P < 0.05$) where lower PPTs = higher MEPs (Study II). Similarly, participants reported MEP ranging from 0.3 (0.0:0.6) to 3.0 (1.5:4.4) during assessments of 1RM

in Study III & IV. There was no significant effect of neither exercise selection, load nor exertion level (Study III). Finally, MEP was not influenced by RT as there was no significant effect of the ANTRAC intervention on the MEP values rated by the participants (Study IV).

	Study I & II	Study III	Study IV					
			EXP				CON	
			Pre	Post	Follow Up	Pre	Post	Follow up
n	21	20	10	10	9	10	7	7
Peak pain intensity, mean (CI: 95%)	7.2 (6.6;7.9)	7.9 (7.1;8.7)	7.7 (6.6;8.8)	7.0 (5.3:8.7)	5,8 (4.4;7.2)	8.1 (6.8;9.4)	6.9 (4.3;9.4)	7.3 (4.9;9.7)
Pain severity, No. (%)								
Light (NRS 1-3)	0 (0)	0 (0)	0 (0)	1 (10)	1 (11)	0 (0)	1 (14)	0 (0)
Moderate (NRS 4-6)	10 (48)	5 (25)	3 (30)	3 (30)	7 (78(	2 (20)	3 (43)	4 (57)
Severe (NRS 7-10)	11 (52)	15 (75)	7 (70)	6 (60	1 (11)	8 (80)	3 (43)	3 (43)
Location, No. (%)								
Chest	17 (81)	12 (60)	7 (70)	7 (70)	5 (56)	5 (50)	4 (57)	5 (71)
Shoulder	8 (38)	14 (70)	7 (70)	9 (90)	6 (67)	8 (80)	5 (71)	5 (71)
Axilla	8 (38)	6 (30)	1 (10)	1 (10)	3 (33)	5 (50)	4 (57)	3 (43)
Arm	4 (19)	12 (60)	4 (40)	3 (30)	4 (44)	8 (80)	5 (71)	5 (71)
Side of body	8 (38)	9 (45)	5 (50)	2 (20)	3 (33)	4 (40)	4 (57)	3 (43)
More than 1 location	11 (52)	19 (95)	9 (90)	7 (70)	5 (56)	10 (100)	5 (71)	5 (71)
Time with pain, mean (CI95%), months	58.9 (42.9;75.0)	67.1 (53.8;80.4)	66.4 (46.9;86.0)	69.4 (49.9;89.0)	74.6 (52.7;96.6)	67.8 (45.1;90.4)	76.7 (42.5;110.8)	79.7 (45.5;113.8)
Pain since treatment No. (%)	15 (71)	17 (85)	8 (80)	8 (80)	7 (77)	9 (90)	7 (100)	7 (100)
Use of pain-relieving medicine. No. (%)	7 (33)	17 (85)	10 (100)	10 (100)	8 (89)	7 (70)	4 (57)	4 (57)
Pain considered biggest problem, No. (%)	10 (48)	14 (70)	9 (90)	7 (70)	8 (89)	5 (50)	7 (100)	5 (71)

Table 6: *Self-reported participant pain profile (Study I-IV). Abbreviations: 95% Confidence interval: CI: 95%, Numeric Rating Scale: NRS.*

As demonstrated by the “almost perfect” (109) ICCS of Study I, ranging from 0.88-0.97, PPTs can be measured reliably in BCS with persistent pain. Moreover, SEM values ranged from 12.0 to 28.2 kPa, while MDC ranged from 33.2 to 78.2 kPa across all anatomical locations (Study I). There was a significant difference in PPTs of BCS when compared to healthy matched controlds in Study II, demonstrating a marked increase in mechanical pain sensitivity for BCS with persistent pain after treatment (Figure 6). In Study III, a single bout of total body RT was sufficient to elicit a significant increase in PPTs located on the ventral shoulder region, but not the dorsal or at the distant reference point, of BCS with persistent pain (Figure 6). Following the ANTRAC intervention in Study IV there was a significant increase in PPTs across all locations when measured at the POST session compared to PRE. However, at the 3 month follow up all values had largely reverted to baseline (Figure 6).

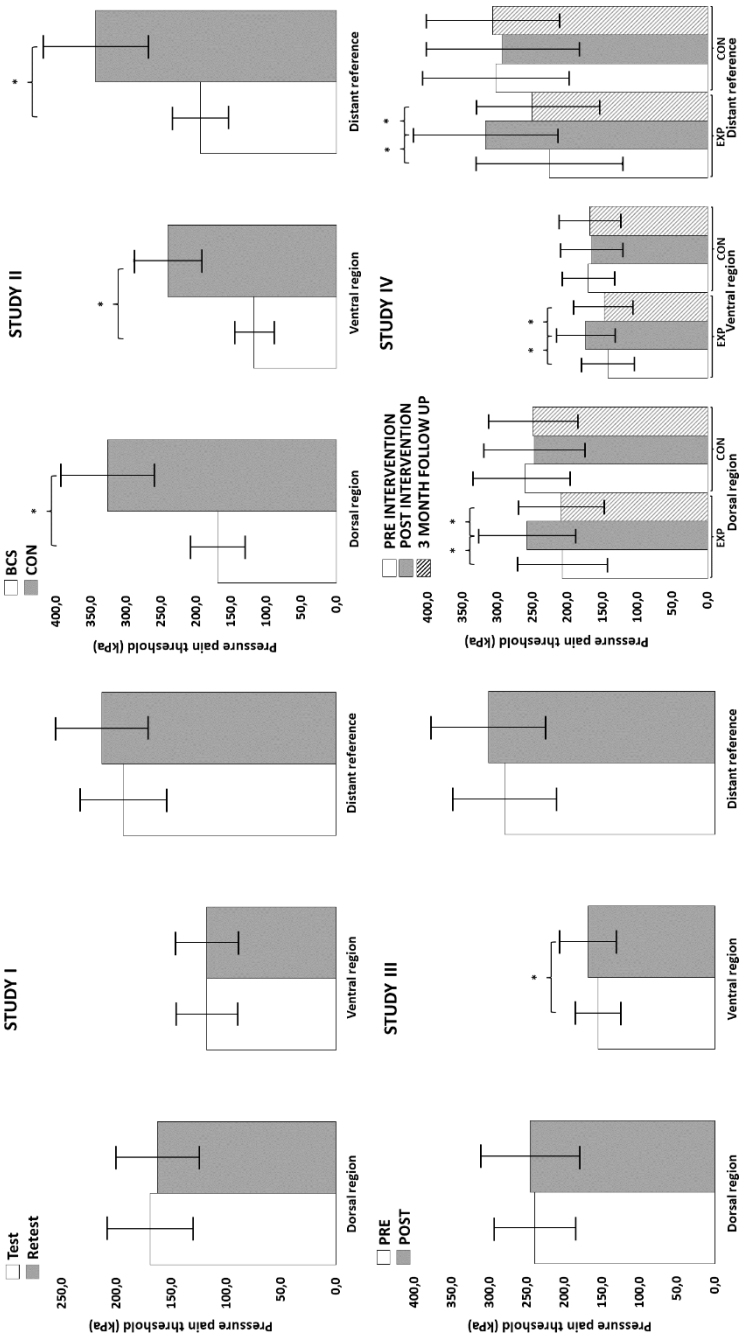

Figure 6: *Summary of mean pressure pain thresholds collected from the dorsal and ventral shoulder regions and tibialis anterior muscles of Study I-IV. Error bars denote the 95% confidence interval. Abbreviations; Breast cancer survivors: BCS, controls: CON, pre intervention assessment: PRE, post intervention assessment: POST. Significant differences (P ≤ 0.05) are indicated by *.*

3.2. STRENGTH & RANGE OF MOTION (STUDY I-IV)

Like PPTs, active ROM can be measured reliably in the target population as indicated by the "substantial" to "almost perfect" ICCs of Study I, ranging from 0.66-0.97. Further, SEM values ranged from 3.0 to 7.5º, while MDC ranged from 8.4 to 20.8º (Study I). When comparing BCS with persistent pain to matched healthy controls in Study II, the former demonstrated movement specific impairments in active ROM for shoulder flexion, horizontal shoulder flexion, shoulder abduction and external shoulder rotation (Figure 7). Active ROM of the affected shoulder was not affected by RT as indicated by the lack of significant differences observed following the ANTRAC intervention in Study IV (Figure 7**).**

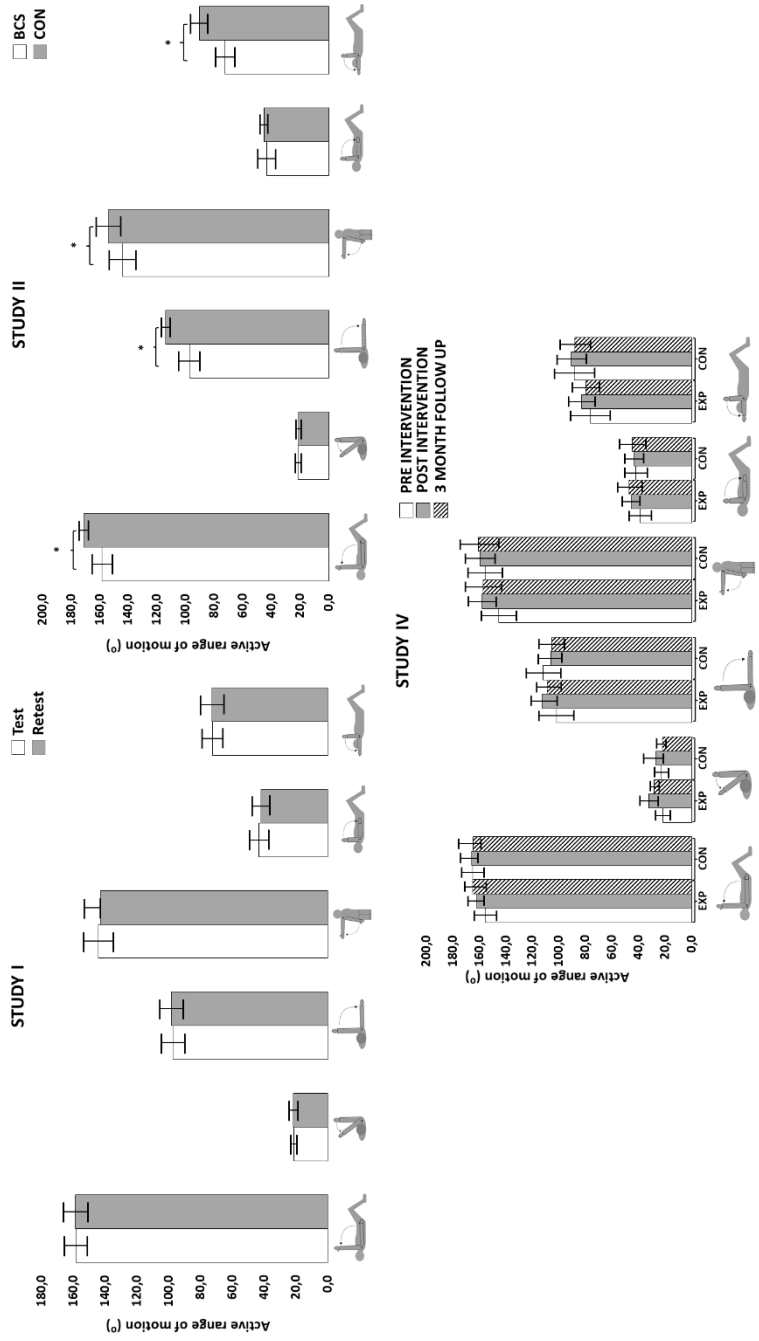

Figure 7: *Summary of mean active range of motion (Active ROM) for shoulder flexion, horizontal shoulder flexion, horizontal shoulder extension, shoulder abduction and internal/external shoulder rotation of Study I, II & IV. Error bars denote the 95% confidence interval. Abbreviations; Breast cancer survivors: BCS, controls: CON. Significant differences ($P \leq 0.05$) are indicated by *.*

As indicated by the “substantial” to “almost perfect” ICC values ranging from 0.62-0.92 for MIMS in Study I, muscular strength can be measured reliably in BCS with persistent pain after treatment. SEM values ranged from 0.03 to 0.07 Nm/Kg FFM, while MDC ranged from 0.09 to 0.19 Nm/kg FFM (Study I). When compared to healthy matched controls in Study II, BCS with persistent pain demonstrated movement specific reductions in muscle strength for horizontal shoulder extension, horizontal shoulder flexion and shoulder adduction **(**Figure 8**).** Further, maximum muscle strength was trainable and increased significantly for all exercises in response to the ANTRAC intervention in Study IV (Figure 8). Moreover, gains in maximal strength were largely maintained following a 3-month period of detraining with no significant decrease in strength **(**Figure 8**)**.

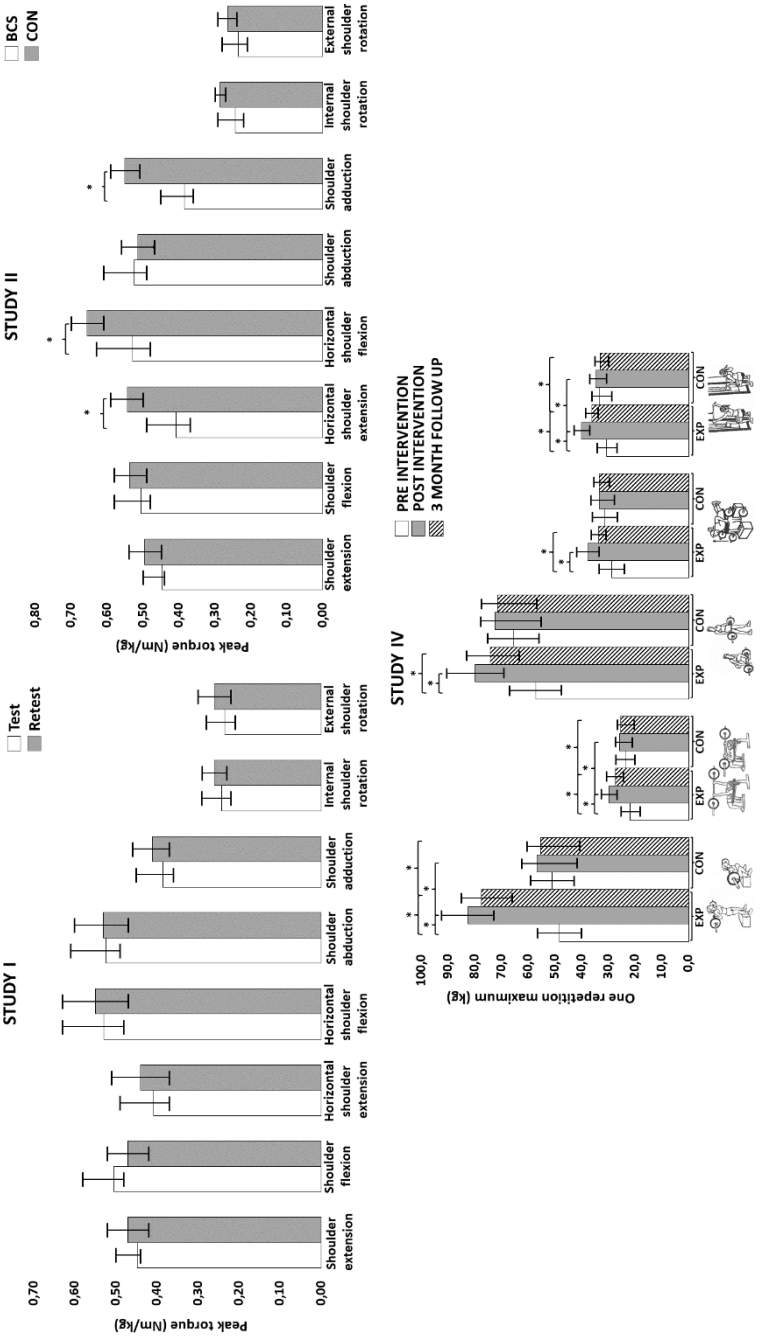

Figure 8: *Summary of mean maximal isokinetic muscle strength (MIMS) in each movement direction for Study I & II, and one-repetition maximum (1RM) in the 90°box squat, bench press, trap bar deadlift, bench pull and lat-pulldown for Study IV. Error bars denote the 95% confidence interval. Abbreviations; Breast cancer survivors: BCS, controls: CON. Significant differences ($P \leq 0.05$) are indicated by *.*

3.3. PSYCHOMETRICS (STUDY I-IV)

The mean (CI95%) RPE rating of the participants ranged from 9.6 (9.2;9.9) to 9.7 (9.4;10) during the assessment of MIMS in Study I & II, and from 9.6 (9.4;9.8) to 10 (9.9;10) during the assessment of 1RM in Study III and IV. The mean (CI95%) MRE rating ranged from 8.7 (8.0;9.3) to 9.7 (9.3;10), while the mean (CI95%) PRE rating ranged from 7.9 (7.3;8.5) to 9.3 (8.8;9.7) prior to the 1RM assessments for each exercise in Study III & IV. Neither movement pattern (Study I & II) nor exercise (Study III & IV) had a significant effect on RPE rating in, and exercise order (Study III & IV) did not influence MRE and PRE ratings ($P \leq 0.05$).

3.4. COMPLIANCE & ADVERSE EVENTS (STUDY I-IV)

There were no dropouts in Study I-III, yielding a participant compliance of 100% in these studies. In contrast, dropout was ≈ 20% in Study IV as indicated by the recruitment flow chart in Figure 3 and described in greater detail in 2.8. Participant adherence to the ANTRAC intervention ranged from 75% to 100% with an average of 89.3% scheduled sessions completed among participants in the EXP group. Assessments of muscular strength elicited a MEP response in Study I-IV, which could be considered an adverse event, but no other undesirable side effects were reported from the protocols. Finally, there was no significant change in arm circumference throughout the ANTRAC intervention in Study IV ($P \leq 0.05$).

CHAPTER 4. DISCUSSION

In this section, the presented results are compared and discussed within Study I – IV and related to existing evidence from the literature. The potential mechanisms underlying the observations in Study I and II, and the effects of RT in Study III and IV are addressed, and the strengths and limitations of the specific studies and the overall thesis are discussed. Finally, a conclusion based on the main findings from Study I – IV is presented in combination with the relevant implications and perspectives.

4.1. PARTICIPANTS (STUDY I-IV)

As indicated by the participant characteristics in tables 2-4, the participant cohorts were reasonably similar between studies. The demographic and health characteristics of Study I-IV are similar to the participants of previous studies (4,5) who argue that their samples reflect the Danish population (i.e., generally well-educated, ethnic homogeneous, and benefiting from a uniform public health care system covering all citizens). Most participants (>70%) had received breast conserving surgery in combination with SLND, a combination of adjuvant chemo- and radiotherapy, and either received or had previously received endocrine therapy. This reflects the nationwide implementation of guidelines for breast cancer treatment provided by the Danish Breast Cancer Corporate Group (94), which is similar to Mejdahl et al. (129) who argue that their sample represents the majority of women who survive breast cancer (>85 %). Moreover, the PI during everyday life of >7 reported by each cohort on the NRS is well beyond the inclusion threshold of ≥ 3. Similarly to the studies of

Gärtner & Mejdahl et al. (65,129) pain was most frequently reported for the breast area with the majority (>50%) experiencing pain in more than one location. Hence, the demographic, clinical and pain characteristics of Study I-IV are arguably a reasonable representation of Danish BCS with persistent pain after breast cancer.

4.2. PAIN

Persistent pain after treatment for breast cancer and its treatments is complex, poorly understood and consequently difficult to treat. Based on the findings of this thesis and previous studies (39,65,70), there are several useful ways to evaluate persistent pain after breast cancer (i.e., PI, PPT and MEP) which may yield different information and increase our understanding of this issue. In contrast to previous studies (4,46), the findings of this thesis also suggest that RT may offer some pain relieving benefits which is partially in support of the thesis hypothesis.

4.2.1. PAIN INTENSITY (STUDY I-IV)

Mean PI in study I-IV ranged from 7.2 to 8.1 on the NRS, which is substantially higher than the 3.5 to 4.7 previously reported by Danish nationwide cohort studies on women with persistent pain after breast cancer (65,97,129). Accordingly, the PI reported by the majority of participants in Study I-IV (52-80%) could be interpreted as severe in agreement with the cut-off scores of McCaffery et al. (125), which is also a greater proportion than previously reported for this population (65,97,129). In contrast, the relative frequency of painful locations reported in Study I-IV was in line with studies by Gärtner et al. (65), Mejdahl et al. (129), and Juhl et al. (97), with pain most commonly reported in the areas of the breast and shoulder (50-80% and 38-80% of participants in Study I-IV, respectively). However, pain was not restricted to one area

as 52% to 100% of participants in Study I-IV reported pain in more than one location, which is also in agreement with the previous observations (65,97,129). Collectively, PI of Study I-IV reinforce the previous observations that persistent pain in BCS most frequently manifest in areas directly affected by the treatment and can linger for a long time (i.e., 58.9 to 67.8 months). In addition, PI of Study I-IV had, on average, higher intensity than previously reported, which further highlight the severity of persistent pain that in BCS that took part in Studies I-IV.

Contrary to what was hypothesized, the ANTRAC trial did not have a significant effect on PI, which is in agreement with the results of Cormie & Ammitzbøl et al. (4,46). Collectively, these results may indicate a limited effect of RT on PI of BCS as any potential benefits could not be differentiated from the reference condition, nor between sessions. In our case, this may be partially explained by pain variability as PI is known to fluctuate over time (187) and the statistical analysis did reveal a significant effect of time. Moreover, baseline pain severity has been demonstrated as an important predictor of pain variability (187) and hence, the severe baseline intensity in this study (i.e. >7 on a 0-10 scale) (125) may have influenced the observed variability. However, like Ammitzbøl et al. the results appear to favour the intervention despite the absence of a statistically significant difference, as 50% of the participants in EXP experienced a decrease of ≥ 2 points in PI on the NRS from PRE to POST which can be considered clinically important (57). Hence, it could be speculated that the sample size originally planned for this study might have yielded the necessary statistical power to detect a difference in PI.

4.2.2. MOVEMENT-EVOKED PAIN (STUDY I-IV)

Despite evidence of shoulder dysfunction and pain after treatment for breast cancer persisting for up to six (164) and eight (129) years, respectively, no other studies have assessed pain perception and shoulder function simultaneously in BCS with persistent pain beyond 1.5 years after treatment. Study II-IV demonstrated, for the first time, MEP during the performance of single and multi-joint assessments of muscular strength. Interestingly, the single joint assessments of shoulder strength in Study II yielded higher MEP values compared to the multi-joint assessments in Study III and IV. This may be related to the discrepancies between test protocols, as Study II utilized isokinetic dynamometry to measure shoulder strength across five max effort concentric repetitions and Study III and IV measured 1RM. A five-repetition maximum is arguably more fatiguing than a 1RM, and fatiguing exercise have been reported to increase pain sensitivity (117). This may be related to the signs of central sensitization (i.e. increased pain sensitivity) observed in Study I-IV as centrally-mediated pain pathways are implicated in MEP (45,Study II). Specifically, discomfort associated with demanding physical activity could intensify perceived pain, or an exacerbation of perceived pain in individuals with signs of central sensitization (Study II). Hence, an exacerbation of central sensitization symptoms from fatigue might potentially facilitate greater intensity of MEP.

The results of Study IV did not indicate any significant effect of RT on the magnitude of MEP in BCS with persistent pain when performing a 1RM. However, it should be noted that the MEP response was not affected by neither exercise order, load, nor exertion level as indicated by Study III. This observation mostly demonstrates that the

protocols of Study III & IV were well tolerated by the participants and therefore suggests that BCS with persistent pain can perform RT at both moderate and high intensities without symptom exacerbation. This is important, because it suggests that clinicians can prescribe a broader range of RT training loads for this population, which may have important implications for the potential benefits of prolonged exposure to RT. For example, systematic variation of volume and intensity is recommended for long-term progression in muscle strength and hypertrophy (151) and thus, most likely advantageous to combat the loss of muscular strength and muscle mass commonly observed in BCS (12,35). Moreover, long-term progression of training intensity may influence the immunological response to RT (36) and thereby, synthesis and release of pain relieving anti-inflammatory cytokines which is upregulated in response to exercise (153). Thus, progressing training intensity based on individual training programme may increase the efficacy of RT for managing loss of muscular strength and size, and enhance the long-term pain-relieving benefits by increasing the anti-inflammatory response.

4.2.3. PRESSURE PAIN THRESHOLDS (STUDY I-IV)

As indicted by Study I, PPT is a reliable measure of mechanical pain sensitivity in BCS with self-reported pain after treatment. The PPT values and distribution observed in Study I-IV were considerably lower across all anatomical locations including the remote reference point over the tibialis anterior muscle when compared to a healthy control group. This is similar to the results previously reported by Caro-Morán et al. (39) for BCS with neck-shoulder pain approximately 20 months after treatment for breast cancer and demonstrate a widespread mechanical hyperalgesia (Study I).

Combined with the marked reduction in PPT measured distant to the surgical area (i.e., tibialis anterior) in Study I-IV, this is suggested to indicate the presence of a central sensitization mechanism in BCS with persistent pain (39,Study I&II). It should be noted that the participants of Study I-IV reported pain in the chest, shoulder, axilla, arm and/or side of body approximately 70 months post treatment. This may imply that sensitization of group III and IV afferents and thus, hypersensitivity to mechanical stimuli is a persistent characteristic of BCS with pain after treatment.

Interestingly, Study I-IV revealed spatial differences within and between ventral and dorsal shoulder region with the most sensitive area located on the pectorals of the ventral region. This area is affected directly by surgery and adjuvant radiotherapy, and therefore more susceptible to nerve injury which may explain relatively lower PPTs observed for the ventral region (50,70) (Study I). However, considering the similar spatial distribution of mechanical pain sensitivity in a healthy control group observed in Study II this may also reflect an otherwise normal spatial difference in mechanical pain sensitivity, which is amplified by alterations in pain-modulatory processes (56). Specifically, a central sensitization mechanism would be analogue to an enhancement in the functional status of neurons and circuits in nociceptive pathways caused by increases in membrane excitability, synaptic efficacy, reduced inhibition or a combination thereof (111). As a result, previously subthreshold synaptic inputs will be recruited to generate an augmented action potential output, thereby producing a state of facilitation, potentiation and/or amplification.

The results of Study III and IV suggest that RT may influence the PPTs of BCS with persistent pain after treatment in the short- and long term. In the short-term, injury to

Aδ- and/or C-fibers in the ventral region from the surgical incisions and/or adjuvant therapy could be a potential explanation for the localized EIH response. Endogenous opioids are known to play a role in EIH (153) and a growing body of evidence suggest that the anti-nociceptive effects of endogenous opioids can be mediated by peripheral opioid receptors located on sensory neurons (171). Hence, treatment related injury to the sensory nerves of the ventral shoulder region might have increase expression of opioid receptors (180), thereby resulting in local EIH by making them more susceptible to endogenous opioids released in response to submaximal RT. In the long-term however, it becomes more speculative, but may be related to neuroplastic changes promoted by exercise which has been theorized to alter pain processing (10). Specifically, evidence from human subjects support modulation of central nervous system function with enhanced inhibition and reduced excitation in response to exercise (85,107,112,117,137,172,176). Hence, considering that the PPTs recorded at baseline are like those reported as indicative of central sensitization in study I and II, the systematic increase in PPTs following RT may suggest neuroplastic changes associated with a reversal of the central sensitization mechanism.

4.3. PHYSICAL FUNCTION

Markers of physical function, such as active ROM and strength of the affected shoulder is reduced after breast cancer treatment and exercise training is known to improve this. In agreement with previous studies (46), the findings of this thesis suggest that RT alone may not produce an improvement in shoulder ROM, but does yield a substantial and robust gain in muscular strength. Collectively, this supports the

hypothesis of impaired shoulder function in BCS with persistent pain but lends only partial support to the functional benefits of RT in this population.

4.3.1. RANGE OF MOTION (STUDY I-IV)

The active ROM values performed by the BCS in Study I-IV were generally lower compared with previous observations in asymptomatic adults (134) and BCS (18,21,41,61,92,154), but only for certain movement patterns like shoulder flexion, horizontal shoulder extension and shoulder abduction when compared directly to matched controls (Study II). In contrast to the general ROM impairments reported in previous research (18,21,41,61,92,154), this suggests that BCS with persistent pain demonstrate movement specific impairments in active ROM of the affected shoulder. As suggested in Study II, this discrepancy may be largely explained by methodological differences as only few case control studies have evaluated shoulder function in BCS (59,80), whereas several have assessed ROM by comparing the affected and unaffected limbs of BCS in a crossover design (96,139,154). The latter approach, while attractive from a statistical perspective (i.e., requires fewer participants), may underestimate the loss of shoulder function as shoulder morbidity after breast cancer can be bilateral (164). Moreover, as noted in Study I, most previous studies have only provided vague descriptions of their procedure for measuring ROM (18,21,41,92,154) and do not specify if ROM was measured actively or passively.

There was no significant increase in active ROM following the ANTRAC intervention (Study IV), indicating no effect of RT on shoulder mobility in BCS with persistent pain. This is in line with Cormie et al. (46), who found little change in shoulder ROM following RT despite a significant increase in strength. A recent study by Özden et al.

(145) reported an association between pain and shoulder ROM, suggesting a pain related inhibition in ROM. Hence, it could be speculated that pain could have influenced the assessments of active ROM in the present study, indicating that measured ROM may only reflect pain-free ROM. Moreover, ROM is improved by factors such as augmented muscle architecture (17), and RT has been suggested to improve ROM through increased fascicle length (1). However, changes in fascicle length are suggested to be associated with mechanical stress and sarcomere lengthening (126), which appear to require large exercise ROM in training (179). Hence, the inherent ROM of the ANTRAC exercise selection in Study IV may have been insufficient to provide the specific stimulus required to facilitate changes such as augmented fascicle length. Of note, many functional tasks require less than maximal active ROM (135) and assessments mimicking daily activities might have revealed an improvement in shoulder function during everyday life as shown for knee osteoarthritis (121). Future studies investigating the effects of RT in activities of daily living involving the shoulder are warranted.

4.3.2. MAXIMAL STRENGTH (STUDY I-IV)

Like active ROM, the MIMS of the participating BCS in Study I and II were generally lower compared to previous observations in healthy individuals (127) and BCS (101), but revealed movement specific impairments when compared to a matched control group (Study II). Time since treatment was considerably higher for participants in Study I and II when compared to previous investigations on shoulder morbidities in BCS (71,80,96,138,154), and greater impairment has been reported closer to treatment (115). Hence, the movement specific impairments of MIMS (and active ROM) in

Study II may be indicative of variable long-term recovery of the tissues affected by the treatment paradigm. Permanent scar tissue formation and fibrosis in the muscle tissues most directly affected by surgery and/or adjuvant therapy (185), such as the pectorals, may reduce contractile strength as scar tissue does not exhibit any contractile function (93). In contrast, muscles such as the rhomboids and trapezii are affected indirectly and might have recovered to normal levels at the time of Study I and II.

It is difficult to compare the 1RM's demonstrated by the participants of Study III and IV to previous studies due to substantial variability in the methodological approach to training and testing. As highlighted by Montaño-Rojas et al. (133) there is a major problem regarding inadequate reporting of the characteristics that make up the exercise program reported in other studies. However, in comparison to the study of Cormie et al. (46) the participants of Study III and IV demonstrated slightly lower 1RM's for the upper and lower body, respectively. This is most likely related to differences in exercise selection as Cormie et al. utilized machines rather than free weights, which may yield different loads and resistance profiles depending on the machine design (16). Greater differences emerge in comparison to the results of Ammitzbøl et al. (4) due to even greater discrepancies in exercise selection and approach to evaluating muscular strength. For example, Ammitzbøl et al. employed a 7RM to assess muscular strength in primarily single joint exercises which can hardly be compared to a 1RM performed in multi joint exercises according to the ACSM guidelines (9), such as in Study III and IV.

There was a marked increase in 1RM strength following the ANTRAC intervention, demonstrating a substantial effect of RT on muscular strength. This is in agreement with the current literature (133,156) and further reinforce that BCS experience substantial strength gains in response to prolonged exposure to RT. Moreover, the insignificant loss of strength from detraining during the follow up period is similar to previous observations in older adults (113) and suggest that gain in muscular strength is a robust and stable adaptation to RT in BCS with persistent pain. This differ from the temporal response pattern of PPT and may suggest that different pathways are responsible for RT mediated improvements in strength and pain sensitivity, respectively. Hence, it could be speculated that potential pain-relieving benefits are not restricted to this modality and underline that additional sensory-motor assessments are necessary to describe and potentially understand the complex interplay between pain and motor function.

4.4. TOLERABILITY OF TESTING & TRAINING (STUDY I-IV)

Testing and training were generally well tolerated by the participants of Study I-IV, as indicated by the low dropout of Study I-III and adherence to the ANTRAC intervention in Study IV. The adherence level of the ANTRAC intervention was higher than recently reported in a review by Bullard et al. (31), indicating that the intervention was well received by the participants. Most missed training sessions were related to the ongoing COVID-19 pandemic (i.e., suspicion of infection, closure of municipality border etc.), which further reinforce that the participants considered the intervention as tolerable. Similarly, the psychometrics (i.e., RPE, MRE and PRE) collected for Study I-IV indicated high levels of exertion and perceived readiness

during assessments of muscular strength, clearly demonstrating that the participating BCS were highly motivated and prepared to perform. In agreement with previous research (82) , there was no change in arm circumference in response to RT (Study IV), which add to the growing body of evidence demonstrating that RT is a safe exercise modality for BCS. Further, the participants were inquired for potential adverse events during and between both experiment and exercise sessions with none reported. Finally, although MEP was reported during evaluation of maximal strength in Study I-IV, this was never perceived as too severe for the assessment to continue and was, arguably not truly an adverse event.

4.5. STRENGTHS & LIMITATIONS (STUDY I-IV)

To the authors knowledge, the series of studies contained in the present thesis is the first to specifically investigate the short- and long-term effects of resistance training on persistent pain after breast cancer treatment, elucidate on pain and functional characteristics of the target population and determine the reliability of common evaluation methods. The well described participant cohort, consistent inclusion & exclusion criteria, and use of well-accepted methods for evaluating pain and physical function provide support to the findings of this thesis. Study I-IV are reported in accordance with current guidelines, thereby ensuring transparency and permitting replication in future studies. Finally, the ANTRAC intervention was designed in agreement with the current exercise guidelines for cancer survivors. Such precision exercise approach accounted for individual variation among the participants. Regardless, a few limitations should be acknowledged.

Firstly, as highlighted in Study I, the cohorts of Study I-IV included participants with great variety in age, time since treatment, and body composition. Moreover, the participating BCS had undergone varying treatment regimens and reported range of different pain intensities for disparate bodily areas. Therefore, the results of Study I-IV are not representative of a specific group of BCS. However, as suggested in Study I, it could be argued that BCS in general are a heterogeneous population due to the highly individual nature of diagnosis, related treatment paradigm, complications, and adverse effects. Consequently, the heterogeneous cohorts of Study I-IV arguably provide the results with a higher level of ecological validity and generalizability for BCS with persistent pain after treatment.

Secondly, inflammation is known to play a role in pain modulation and be susceptible to exercise mediated changes. Hence, the original intent was to assess serum concentrations of inflammatory biomarkers such interleukin 6 and tumour necrosis alpha in the participants of Study I-IV. However, initial results were considered improbable as they barely exceeded detection thresholds and were ultimately omitted from the protocol due to distrust in the outcome. Further, the inclusion of mechanistic outcomes, such as temporal summation (85,107,112,137,172,176) and conditioned pain modulation (68,128), could have provided additional insight into the neuroplastic characteristics of BCS with persistent pain and potential alteration mediated by RT. However, this was beyond the scope of Study I-IV, and the thesis.

Thirdly, pain is associated with psychosocial factors such as depression and catastrophizing and is well known to have a severe impact on quality of life. Hence, the inclusion of questionnaires such as the Major Depression Index, the Pain

Catastrophizing Scale and the European Organization for the Research and Treatment of Cancer quality of life questionnaire could have provided additional insight to the benefits of RT. However, the benefits of RT on psychosocial status and quality of life are reasonably well established (133) and the main interest of Studies I-IV was therefore on the pain related and functional outcomes.

Finally, the ANTRAC trial may suffer from insufficient statistical power and a certain level of recruitment bias which could have influenced the results. The sample size was smaller than originally estimated which, in combination with participant dropout, may have increased the risk of random and systematic error. Further, despite the severity of self-reported pain, most of the participants were employed, reported higher levels of physical activity compared to previous research (22) and still found the time and energy to participate in the study. This indicates a certain level of resourcefulness that may not be representative for the majority of BCS with persistent pain. Further, all participants expected a positive effect of the ANTRAC trial prior to randomization, which can introduce a motivational bias. However, the intention to treat analysis arguably limited the effect of dropout and the observed effect sizes support the results. Moreover, the included sample arguable increase the ecological validity of the trial as unresourceful BCS with little or no positive expectations are unlikely to volunteer for intervention studies and/or training programs (184).

CHAPTER 5. CONCLUSIONS

The overall aim of the thesis was to investigate the effect of RT on persistent pain after treatment for breast cancer by assessing PI, PPTs, active ROM, strength, and evaluating outcomes following a single bout of RT and a 12-week RT intervention.

Based on the work in the present thesis the main conclusions are as follows:

- PPTs, active ROM and MIMS are reliable measures of mechanical pain sensitivity and shoulder function in BCS with persistent pain (Study I).
- In comparison to healthy, pain free controls matched for age and BMI, BCS with persistent pain display signs of a central sensitization mechanism along with movement specific shoulder impairment (Study II).
- A single session of total body RT can elicit a transient analgesic response limited to the ventral region of the affected shoulder of BCS with persistent pain, indicative of localized hypoalgesia (Study III).
- Supervised RT performed 2x/week for 12 weeks can improve PPT and 1RM, but not PI and active ROM in BCS with persistent pain (Study IV).

In addition, it is concluded RT is safe and well tolerated by BCS with persistent pain and can be performed with to moderate to maximal intensity without significant risk of pain exacerbation or breast cancer related lymphedema. Moreover, improvements in mechanical pain sensitivity in response to RT will revert to baseline levels without continuous training exposure, whereas gains in strength are unchanged following a 3-month detraining period.

CHAPTER 6. PERSPECTIVES

The studies presented in this thesis contribute to our understanding of the effects of persistent pain after breast cancer treatment beyond the first 1.5 years after treatment, how we can measure them and provide new knowledge on how we can manage them. Considering that little research has previously addressed the use of RT for managing persistent pain in BCS and even less has addressed the use of RT BCS with pain beyond 1.5 years after treatment, the present thesis may provide a scientific and practical foundation for future studies in this area.

More research is needed to further explore the potential central sensitization mechanism of BCS with persistent pain after treatment, and to elucidate on the neuroplastic changes that might be involved. The global increase in PPTs followed by complete reversal after three months of detraining observed in Study IV may indicate that RT can reduce signs of central sensitization to some extent on a short term but require regular exposure to do so on a long-term basis. Further, the fact that 1RM levels were largely maintained, while PPT reverted to baseline levels following detraining suggest that the improvement in mechanical pain sensitivity may not be associated with gains in strength per se. Rather, it may be a product of the physical activity associated with engaging in RT on a regular basis. Thus, the underlying mechanism may not be unique to RT and could, theoretically, be exploited by a multitude of different exercise modalities. If so, a similar or even greater effect might be derived from aerobic training, or a combination of the two, which would support the current exercise guidelines for cancer survivors. This would, in the authors

opinion, provide clinicians and patients with a greater variety of options and increased chance of success when prescribing an exercise plan for pain management.

The movement-specific impairments observed in Study II suggests a requirement for specialized rehabilitation programs in this population and indicate that it may be beneficial to directly target muscles involved in these movement directions through strengthening exercise, such as RT. Further, the lack of improvements in shoulder ROM observed in Study IV may indicate a requirement for a dedicated stretching program to compliment RT when managing BCS in clinical practice. Alternatively, clinicians should consider selecting exercises that can be performed with a large ROM in training to yield sufficient lengthening of the sarcomeres under tension. It is the authors opinion that a different exercise selection, emphasizing unilateral exercises with large ROM, might further enhance the benefits of RT for BCS with persistent pain after treatment and future studies should investigate this.

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APPENDICES

Appendix 1: STUDY I

Appendix 2: STUDY II

Appendix 3: STUDY III

Appendix 4: STUDY IV

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