Breast cancer survivor functional changes immediately following treatment: quantifying mechanisms of strength deficits and compensatory kinematic and muscular strategy adaptations

by

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Author's Declaration

I herby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Breast cancer is prevalent among Canadian women, but treatments may cause functional impairments among survivors. Over 22,000 Canadian women join the survivor population yearly (Brenner et al., 2020). Despite this substantial number, minimal research has approached the challenges faced by this population after primary treatment. Particularly, decreases in strength, range of motion and shoulder-related quality of life are widely reported (Harrington, Padua, Battaglini, & Michener, 2013; Lee, Kilbreath, Refshauge, Herbert, & Beith, 2008; Rietman et al., 2004). These factors, linked with changes in kinematics and muscular activation may result in further complications (Brookham, Cudlip, & Dickerson, 2018a, 2018b). Variability in previous studies, in both the population sampled and results make it difficult to isolate potential mechanism disrupting function. Further, this complicates the determination of key deficits to target in the early years of survivorship. Therefore, the purpose of this dissertation was to determine which factors affect breast cancer survivors in the first two years following the conclusion of treatment, if these factors translate to differences during low load functional tasks, and to investigate the feasibility of increasing strength (as a surrogate for function) to help mitigate these factors and increase function.

Study 1 and 2 shared an *in vivo* experimental collection, with Study 3 using input from the collection in an *in-silico* approach. Briefly, 35 breast cancer survivors within two years since the conclusion of their treatment participated in the experiment. Participants completed a general questionnaire about their diagnosis, three shoulder-related quality of life questionnaires, and a Godin-Shephard leisure-time physical activity questionnaire, followed by a dual energy x-ray absorptiometry (DXA) scan. Eight muscles were monitored on the affected limb (pectoralis major (sternal and clavicular), deltoids (anterior, middle and posterior), infraspinatus, supraspinatus, and latissimus dorsi). Six maximal isometric strength trials were completed (flexion, extension, abduction, adduction, internal rotation and external rotation). Kinematics of the affected limb were collected for the remaining trials. These consisted of 6 maximal range of motion trials (flexion, extension, abduction, scapular abduction, internal rotation and external rotation), as well as 8 activities of daily living.

Study 1 clustered participants into two distinct groups, the low score cluster (LSC) and high score cluster (HSC). The variance in treatment, force production, range of motion, body composition and shoulder-related quality of life is well documented in literature, however there is no distinguishing characteristics that separate survivors who may need rehabilitation following treatment. This study determined, through feature reduction, that internal rotation force production, active extension range of motion and 3 shoulder related quality of life variables (energy/fatigue, social functioning and pain) separated survivors within 2 years of treatment into two clusters (LSC and HSC). The LSC participants had higher self-reported disability, role limitations (health and emotion), fatigue, and lower self reported physical well-being, along with lower abduction, adduction, extension and flexion force production ($p<0.001$). Several other factors differed between groups ($p<0.05$); the HSC group had more lean mass of the affected arm, internal and external force production and active flexion range of motion. These factors highlight potentially important factors to address in a rehabilitation program, as survivors finish treatment, specifically that lower force production likely corresponds to lower self-reported shoulder-related quality of life.

Study 2 contrasted the muscular activation and kinematics of the LSC and HSC during various activities of daily living. The selected low load functional tasks can indicate survivors' ability to complete daily tasks and return to work. The LSC used lower range of angles, and increased muscular activation. Range of angles differed 6.5-16.1° across elevation angle, axial rotation and plane of elevation during the shelf reach, forward reach, pitcher pour and tray transfer tasks. Additionally, the LSC had 0.89-12.73% MVC more muscular activation than the HSC across all muscles and tasks. At least one muscle differed between groups during each of the 8 tasks investigated.

Finally, study 3 simulated various treatment scenarios to find a maximal producible force and the internal muscle forces required to produce that force in a compromised system with an in-silico approach. Beginning with the force from the LSC, and increasing capacity of muscles based on given treatment scenarios (permanent damage of a subset of muscles from radiation, or overall reduction in capacity due to chemotherapy, or a combination of both), 70-80% of strength in adduction and internal rotation is recoverable if retraining of muscles can be achieved. Specifically, for adduction rhomboid (major and minor), upper trapezius, subscapularis (lower), and triceps (long), latissimus dorsi (upper and lower), pectoralis minor, middle deltoid, middle trapezius and biceps (short) increased during the various simulations to increase force output compared to the LSC group. During internal rotation, latissimus dorsi, rhomboid (major and minor), upper trapezius, posterior deltoid, subscapularis (middle and lower), triceps (long), pectoralis minor, middle deltoid, and middle trapezius estimation increased from the LSC group levels in each of the simulations. Although no scenario reached reference control population force levels, achieving 70-80% of force would be meaningful for enabling daily task performance, returning to work and enhancing physical self-efficacy.

Taken together, these studies point towards novel strategies and valuable considerations in creating rehabilitation foci that enable improved arm function for breast cancer survivors.

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Dedication

For the women who gave their time to this project;
Your time and efforts don't go unnoticed, this work is dedicated to you
and a better future for those to come.
Thank you.

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Chapter I - Introduction

1.1 Motivation

Breast cancer is prevalent in Canadian women, but treatments often compromise upper extremity strength and range of motion. Over 22,000 Canadians join the breast cancer survivor population every year, and although this population continues to grow, minimal research focuses on the challenges in this population post treatment. Glenohumeral range of motion is decreased in 1-67% of survivors (Lee et al., 2008), 9-40% of survivors have weakness in their upper extremity (Rietman et al., 2004), survivors have a reduced shoulder-related quality of life (Harrington et al., 2013), and muscular activation and glenohumeral motion differ in this population from a reference population during daily life tasks (Brookham et al., 2018b, 2018a). However, much of the existing data derived from a diverse cross-section of survivors in terms of treatment types, and time since the conclusion of treatment. Extensive variability in the survivor populations (spanning time since treatment and treatment type) previously evaluated makes it difficult to isolate mechanisms of dysfunction in survivors and how these individuals differ from a reference population immediately following treatment.

1.2 Global Objective

This dissertation incorporated three linked studies that employ both experimental and modelling approaches. The global objective was to determine which factors affect breast cancer survivors immediately post treatment, and to investigate the feasibility of increasing strength (as a surrogate of function) in breast cancer survivors. The proposed studies delineated factors that mitigate differences between cohorts of breast cancer survivors, (Study 1), described differential kinematic and muscle activation across these cohorts (Study 2), and explored the muscular implications of various treatments on the potential to increase strength during adduction and internal rotation strength trials using an *in-silico* approach (Study 3).

1.3 Outline

The three studies were conceptually linked (Figure 1), with a linear flow that provided progressive insight into the breast cancer survivor population. Specific study objectives and hypotheses are detailed in subsequent sections of this dissertation. Study 1 clustered participants into several different cohorts, and identified the differences in these groups. Study 2 contrasted these groups with one another with a specific focus on muscular activation and kinematics during activities of daily living. Study 3 focused on replicating various treatment scenarios, determined the necessary internal muscle forces required to produce maximum force in a compromised system and determined the potential capacity of the system to restore strength (such as with a strength training protocol) with an *in-silico* approach.

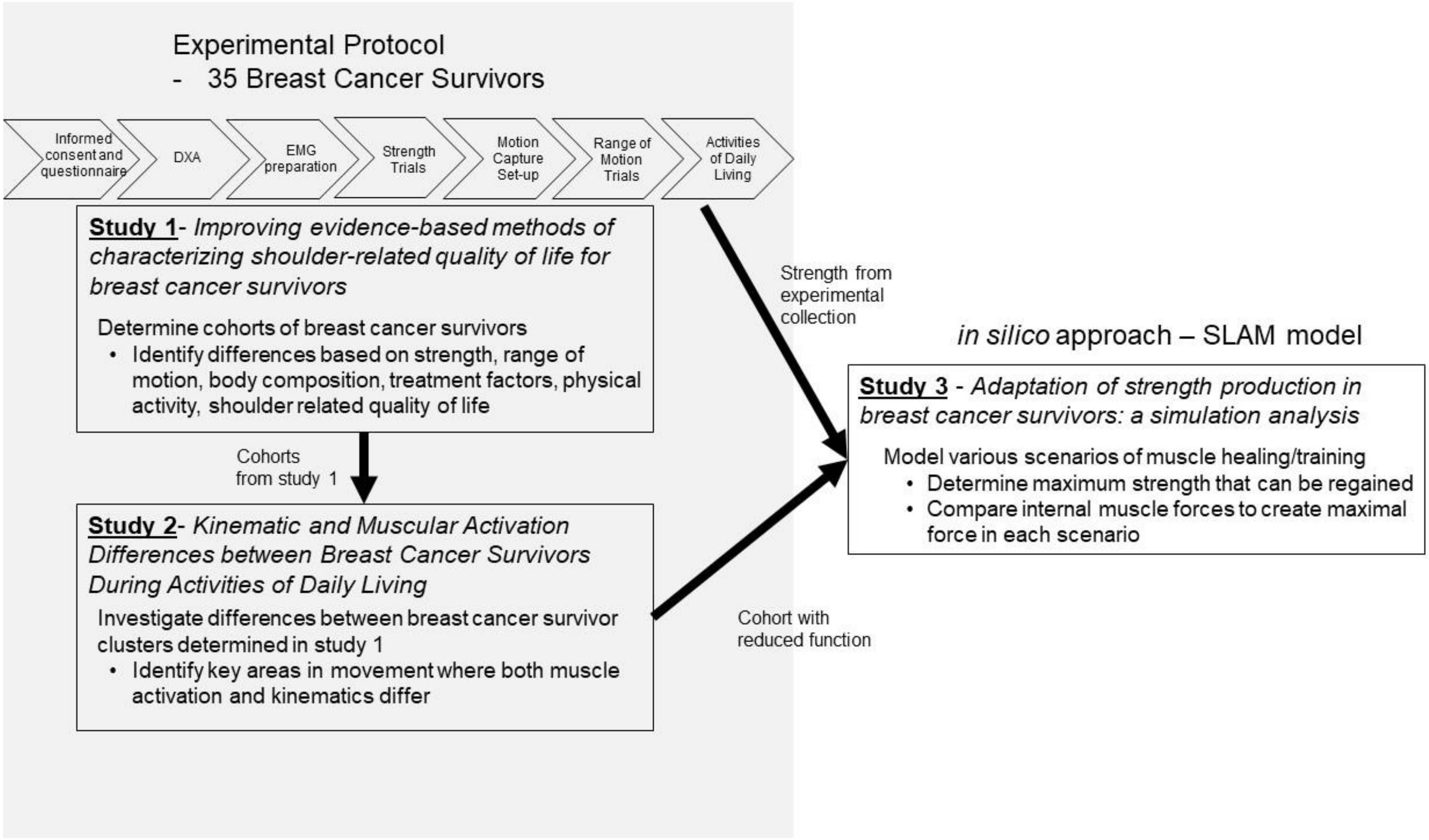


Figure 1: A flowchart outlining each of the three studies contained within this research. Data collected in the experimental protocol is used to create cohorts of survivors in study 1, and subsequently used for comparison in study 2. Baseline strength production in study 3 is based on strength measures collected in the experimental protocol.

Chapter II - Literature Review

2.1 Overview of Breast Cancer

2.1.1 Prevalence

Breast cancer is a common form of cancer among women, with increasingly positive outlooks for survival. 1 in 8 Canadian women will be diagnosed with breast cancer in their lifetime, representing 25% of new cancer cases in 2018, and 6.1% of all cancer deaths (Brenner et al., 2020; Canadian Cancer Society, 2020). Due to improved awareness and detection times, 80% of cases are diagnosed early (stage I or II), with less than 5% at stage IV. This results in a 5-year survival rate of 87% (Canadian Cancer Society, 2020). With approximately 27,400 new cases reported in Canada each year, there will be 22,880 individuals joining the survivor population (Brenner et al., 2020). Although much less common, 1% of all breast cancer diagnoses are in men. A total of 240 men will be diagnosed with breast cancer in Canada each year (Canadian Cancer Society, 2020). As the survivor population continues to grow, this thesis will focus on cisgender women, acknowledging that both men and women experience breast cancer diagnoses and potential complications which arise from treatment.

2.1.2 Disease diagnosis

The tissues affected, cell appearance, hormone influence on the tumour and the genetic makeup of the tumour specify breast cancer diagnosis. Diagnosis first considers the location where the tumour began (Table 1). The tumour often begins in the milk ducts, milk-producing lobules, or connective tissues (Figure 2). In addition to the original location, the invasiveness (spread) of the tumour is determined and allows for the type to be diagnosed (Table 1). Finally, cancerous cells are examined and the difference between healthy cells and cancerous cells are graded from 1-3 (Mayo Clinic, 2019). Generally, a lower grade (grade 1) indicates cancer cells that resemble normal cells and are slow growing, grade 2 grow faster than normal and do not look like normal cells, and finally grade 3 cancer cells are abnormal, aggressive and spread much more quickly than normal healthy cells.

Table 1: Types of Breast Cancer (Canadian Breast Cancer Network, 2019).

Type	Description
Ductal Carcinoma in Situ (DCIS)	• Abnormal cells within the ducts (Figure 2) • Does not spread beyond ducts (non-invasive) • Generally early and could spread beyond
Lobular Carcinoma in Situ (LCIS)	• Abnormal cells in milk-producing glands (lobes) (Figure 2) • Usually does not spread beyond lobes • Increased risk of invasive re-occurrence
Invasive Ductal Carcinoma	• Begins in ducts (DCIS) • Spreads to surrounding breast tissue
Invasive Lobular Carcinoma	• Begins in milk glands (LCIS) • Spreads to breast tissue
Metaplastic	• Rare (less than 1%) • Begins as one type of cancer cell and changes to another
Inflammatory Breast Cancer	• Rare • Cancer involves lymph nodes (Figure 2) and surrounding tissues • Breast appears red, swollen and tender

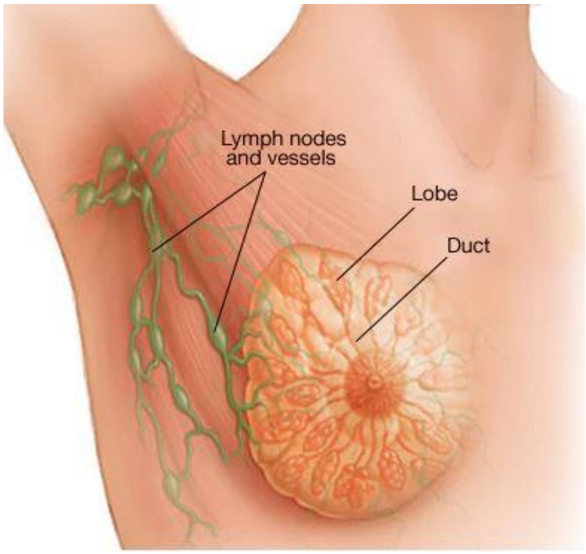


Figure 2: Anatomy of breast tissue (Mayo Clinic, 2019).

Subtype definition considers the hormone sensitivity and genetic makeup of the tumour. Various tumours are sensitive to different hormones and are known as estrogen or progesterone receptor positive. Thus, they use naturally occurring hormones (estrogen, progesterone) for continued growth. If the tumour is insensitive to hormones it is identified as hormone receptor negative (Mayo Clinic, 2019). Basal-like and erbB2+ subtypes are both estrogen receptor negative tumour types, with laminal subtypes being estrogen receptor-positive (Table 2). ErbB2+ subtypes are estrogen receptor negative, but have an over-representation of the HER2 gene, which is a growth-promoting protein (Mayo Clinic, 2019).

Table 2: Subtypes of Cancerous Cells (Perou et al., 2000).

Subtype	**Description**
Basal-Like	• Estrogen receptor negative • Shortest survival times • More likely to relapse
erbB2+	• Estrogen receptor negative • HER-2 overexpression • Less favourable clinical outcomes
Laminal	• Estrogen receptor positive • Favourable clinical outcomes

Along with these characteristics, a stage is assigned during diagnosis. The stage is dependent on the rating of the tumour, nodes and metastases (‘TNM’) (Table 3). Each characteristic is given a score and from 0-4. Known combinations of the tumour, nodes and metastases dictate the severity of the breast cancer diagnosis (Table 4). Stage I tumours are classified as $T_1N_0M_0$, and stages range to any diagnosis with M_1 (indicative of metastases elsewhere in the body) as stage IV (Sainsbury, Anderson, & Morgan, 2000). These diagnoses allow for description of the tumour and provides insight into the type of treatment available for the specific diagnosis.

Table 3: Description of Stage Characteristics (Edge et al., 2010; Hammer, Fanning, & Crowe, 2008; Sainsbury et al., 2000)

Characteristic	**Description**
Tumour (T)	• Tumour size • Invasive (spreading beyond the ducts) vs non-invasive (remaining with the ducts) • Subtype (Table 2)
Nodes (N)	• Any spreading (micro-metastases or tumours) in the lymph nodes
Metastases (M)	• Any metastases detected elsewhere in the body

Table 4: Criteria for staging of breast cancer diagnoses (TNM). Modified from table 1 of (Hammer et al., 2008)

	Primary Tumour (T)	**Regional lymph node status (N)**	**Distant Metastasis (M)**
Stage 0	Carcinoma in situ	No evidence of cancer in nearby nodes	No
Stage I	Tumour ≤ 2cm	No evidence of cancer in nearby nodes	No
Stage IIA	No evidence of primary tumour	Metastasis to 1-3 nodes	No
	Tumour ≤ 2cm	Metastasis to 1-3 nodes	No
	Tumour > 2cm but ≤ 5cm	No evidence of cancer in nearby nodes	No
Stage IIB	Tumour > 2cm but ≤ 5cm	Metastasis to 1-3 nodes	No
	Tumour > 5cm	No evidence of cancer in nearby nodes	No
Stage IIIA	No evidence of primary tumour	Metastasis to 4-10 nodes	No
	Tumour ≤ 2cm	Metastasis to 4-10 nodes	No
	Tumour > 2cm but ≤ 5cm	Metastasis to 4-10 nodes	No
	Tumour > 5cm	Metastasis to 1-3 nodes	No
	Tumour > 5cm	Metastasis to 4-10 nodes	No
Stage IIIB	Tumour of any size with direct extension to chest wall or skin	No evidence of cancer in nearby nodes	No
	Tumour of any size with direct extension to chest wall or skin	Metastasis to 1-3 nodes	No
	Tumour of any size with direct extension to chest wall or skin	Metastasis to 4-10 nodes	No
Stage IIIC	Any tumour designation	Metastasis to >10 nodes	No
Stage IV	Any tumour designation	Any lymph node designation	Yes

2.2 Treatment of Breast Cancer

Several treatments exist to respond to breast cancer. Surgical treatments are often used as an initial intervention to remove the tumour. These procedures include mastectomy, breast conserving therapy or axillary lymph node dissection. Following surgery, an adjuvant therapy (or several) are often recommended in an attempt to ensure no cancerous cells remain. These therapies may include any combination of radiation, chemotherapy and/or hormone therapy.

2.2.1 Surgical Treatment

Three major surgeries are used in breast cancer treatment: mastectomy, breast conserving treatment and axillary lymph node dissection. The choice between mastectomy and breast conserving treatment depends on the tumour location and size (Sainsbury et al., 2000), available technology, and patient choice, while dissection is only used for tumours that have invaded the lymph nodes. In stage I/stage II cancer diagnoses breast conserving treatment is most frequent (61% of cases in the United States, vs 34% mastectomy) (American Cancer Society, 2019a). In stage III, mastectomy is dominant with 68% of patients receiving this surgery, and only 20% receiving breast conserving therapy. Axillary lymph node dissection is the most involved surgery and is used when the cancer spreads beyond the breast tissue into the lymphatic system.

2.2.1.1 Mastectomy

Mastectomies are a common surgical treatment used to remove tumours in breast cancer patients. Both radical mastectomies and modified radical mastectomies are highly effective. The Halsted mastectomy, known as the radical mastectomy, was the original surgery used to remove tumours and involved removal of all of the breast tissue, chest wall muscles below the breast tissue, and lymph node dissection (Bland, 1981). However, by 1981, less than 3% of surgeries were the radical mastectomy (Hammer et al., 2008). As adjuvant therapies were improved and imaging systems advanced, tissues were able to be spared from complete removal. The modified radical mastectomy was introduced allowing the pectoral major muscle to remain after surgery (Patey & Dyson, 1948). Within the modified radical mastectomy there are skin-sparing, nipple-sparing and conventional subtypes. However, the pectoral fascia is still traditionally removed to ensure no cancerous tissue remains. Some surgeons will spare the pectoral fascia as well, but this results in an increased risk of chest wall recurrence (Dalberg, Krawiec, & Sandelin, 2010).

With a high survival rate, it is important to consider shoulder-related quality of life and function following these surgeries, and how it is influenced by time. Individuals who received mastectomy were 6 times more likely to have shoulder restrictions and functional limitations compared to breast conserving therapy (Vidt et al., 2020). These limitations led to decreases across many domains of shoulder-related quality of life, specifically increased perceived disability. However, adjuvant therapy often accompanies surgery and it becomes difficult to delineate which effects occur due to surgery, or to additional treatment. Patients with above average function (as described through FACT-B questionnaires), were approximately 22 months post-surgery, whereas below average function survivors were 8 months post-surgery (Huang & Chagpar, 2018b). Beyond functional limitations survivors may experience body image issues following mastectomy. As time passes, patients who receive a full mastectomy see improvements in body image and function (Huang & Chagpar, 2018a). Body image was below average in the first year following treatment, but improved beyond 1 year since surgery.

2.2.1.2 Breast conserving therapy

Breast conserving therapy, also known as lumpectomy, is a surgical intervention used in western countries with the intention to preserve more tissue without compromising treatment. Breast conserving therapy is more common in western countries due to advances in technology allowing for early diagnosis and therefore smaller, less spread tumours (Newman & Sabel, 2003). The breast conserving therapy surgery involves removing only the cancerous tissues, and sparing as much breast tissue as possible (no more than 25% total reduction) to ensure good cosmetic outcomes (Hammer et al., 2008).

It has been hypothesized that upper limb function and shoulder-related quality of life would be improved following breast conserving therapy, versus a mastectomy. By avoiding lymph node involvement, there is a reduction in the occurrence of lymphedema, and therefore less detrimental on function (Nesvold, Dahl, Løkkevik, Marit Mengshoel, & Fosså, 2008). However, studies have found mixed results. A series of studies have found no difference between function after each of the surgeries (Kuehn et al., 2000; Lauridsen, Overgaard, Overgaard, Hessov, & Cristiansen, 2008), and another set of studies found less impairment in survivors who reserved breast conserving therapy compared to mastectomy (Nesvold et al., 2008; Sugden, Rezvani, Harrison, & Hughes, 1998). The heterogeneous nature of the populations included in each of these studies likely lead to the differences in conclusions, such as differing adjuvant therapies, secondary symptoms and stage of diagnosis. A recent study of breast cancer survivors in India found overall shoulder-related quality of life 5 years post treatment was relatively similar between the two surgery types, with a slight advantage to those receiving breast conserving therapy (Bhat, Roshini, & Ramesh, 2019a). Generally, patients who received breast conserving therapy felt more complete, and had less difficulty completing everyday activities, whereas an equal number of survivors in each group (breast conserving therapy and mastectomy) felt they had not regained their full strength (Bhat, Roshini, & Ramesh, 2019b).

2.2.1.3 Axillary Lymph Node Dissection

Axillary lymph node dissection is the third, and most involved surgical treatment for breast cancer. This surgical intervention is used when the cancer has spread beyond breast tissue and involves the lymphatic system. Lymph nodes in the axilla are often involved once the tumour has reached 5mm, and therefore lymph node dissection is recommended (Silverstein et al., 1994). Due to the invasive nature of this surgery, it is more likely that complications may arise. As the number of nodes dissected increases, so does the likelihood of developing lymphedema (Hack et al., 2010). Patients who receive this surgery have an increased shear elastic modulus of the pectoralis major, indicating stiffer muscle post treatment compared to breast conserving therapy; however, there was no effect on overall joint integrity (Lipps et al., 2019). Additionally, 62.9% of survivors reported having mild pain after surgery, with 29.8% reporting moderate discomforting pain (Hack, Cohen, Katz, Robson, & Goss, 1999). 17.7% of survivors reported weakness, and 63.1% reported numbness following axillary lymph node dissection (Hack et al., 1999). Reductions in pain, disability and overall well-being scores are often seen in survivors who have exercise interventions (M. Kim et al., 2019). However, the format of exercise intervention affects survivors differently. Tools, such as therapeutic exercise balls, have been suggested to help ease pain and discomfort early after surgery before introducing conventional self-lead stretching programs. Once patients are able to reduce pain exercise programs can be introduced to increase function in survivors who received axillary lymph node dissection. (M. Kim et al., 2019).

2.2.2 Radiation Treatment

Radiation treatment is often used as a localized treatment after surgical intervention. In some instances, radiation follows the conclusion of chemotherapy. 49% of patients in Stage I-II will receive radiation as an adjuvant therapy (American Cancer Society, 2019a). Only 16% of patients in stage III opt to receive radiation, as often they undergo full mastectomy (American Cancer Society, 2019a). For tumours that are diagnosed early (stage 1-2, or less than 3 lymph nodes involved), radiation is effective for increasing survival rates (Shi, Luo, Zhao, Huang, & Pang, 2019). The radiation is applied to a localized area in order to damage the DNA of the cells directly through the release of free radicals, thereby controlling or killing cancerous cells (Mayo Clinic, 2018a). Radiation therapy can be either external (a beam external to the body applies radiation treatment) or internal (an implanted device delivers the radiation near the tumour site), but in both scenarios one specific region is targeted. Although localization of the treatment allows for a specific region to be targeted, often other cells are damaged due to the proximity of local healthy cells to the radiation (Courneya, Mackey, & McKenzie, 2002; Lipps, Sachdev, & Strauss, 2017; Mayo Clinic, 2018b). The damage to the local cells can cause numerous side effects such as fatigue, skin erythema, lymphedema, cardiac and pulmonary toxicities, and brachial plexopathy (Truong, Olivotto, Whelan, & Levine, 2004). Specifically, pectoralis major, pectoralis minor, latissimus dorsi, and teres major receive enough radiation in most regimens to promote future morbidity (Lipps et al., 2017). Lymphedema is a common side effect of radiation and is caused by damage to the lymphatic nodes in the axilla, which then hinders proper drainage of the limb (Hack et al., 1999; Truong et al., 2004). Lymphedema is covered more in depth in section 2.3.2.

As the most common adjuvant therapy, radiation is highly effective in treating breast cancer. However, combining surgical interventions with radiation often causes scar tissue formation. Frequently, adhesions form between the musculature in the radiation zone, effecting the glenohumeral joint. This causes joint stiffness, and limits range of motion (Lauridsen et al., 2008; Markes, Brockow, & Resch, 2006). Tellingly, up to 2/3 of breast cancer survivors who received radiation reported some restriction or pain, and 1/4 reported weakness (Lee et al., 2008).

2.2.3 Chemotherapy Treatment

Chemotherapy is a cancer treatment often chosen to manage micro-metastases in patients. In early stages (stage I-II), chemotherapy is less frequently used with 16% of patients receiving this treatment, increasing to 56% of stage III patients (American Cancer Society, 2019a). Often chemotherapy is delivered intravenously, but can also be taken orally. Treatment is completed in durations of cycles (often between 4 and 8) over the course of several months (2-6) (American Cancer Society, 2019b). Due to the nature of the drugs, chemotherapy may attack non-cancerous cells. The drug is designed to kill cells that are dividing. As cancerous cells divide more rapidly than normal cells, these are often the target of the drug. However, normal cells still divide and therefore may be targeted and damaged, leading to additional side-effects.

Although an effective treatment for cancer, chemotherapy side-effects are well documented. Fatigue, nausea, weight gain, decreased strength and range of motion, and overall decrease in shoulder-related quality of life are often cited (Markes et al., 2006). In addition, chemotherapy patients are less likely to participate in exercise or rehabilitation, perpetuating decreases in physical function resulting from treatment (Courneya et al., 2016; Markes et al., 2006; Tiezzi et al., 2016). As chemotherapy affects the entire body, secondary symptoms are not localized to the affected upper extremity. Klassen et al (2017) investigated strength in the lower and upper extremity of breast cancer survivors following chemotherapy treatment. Survivors had 25% lower extremity strength, and 16% lower upper extremity strength compared to reference participants (Klassen et al., 2017).

2.2.4 Hormone Therapy

Hormone therapy, often surgical or oral treatment, is a targeted treatment used for estrogen receptor positive tumours. 83% of breast cancer patients present with a tumour that is estrogen receptor positive (American Cancer Society, 2019a) (Table 2, page 6). In these tumours, estrogen promotes tumour growth and therefore it is imperative to slow or stop the estrogen production to ensure the tumour does not grow (National Cancer Institute, 2017a). Several measures can be taken to attempt to limit a second occurrence of the tumour by limiting the estrogen production. A double mastectomy, ovary removal, or hormone therapy are all methods to decrease likelihood of reoccurrence (National Cancer Institute, 2017b). Surgical interventions provide peace of mind to the survivors, however can affect confidence and self-esteem.

Hormone therapy (also known as endocrine therapy) is an oral medication used to stop the production of estrogen. This drug is taken daily for the lifetime of the survivor and may avoid extra surgery. However, hormone therapy has several known side effects such as fatigue, weight gain and early menopause (Courneya et al., 2002). Cognitive dysfunction has been reported in survivors 12-18 months after the start of hormone therapy (Ferreira et al., 2019; Joly, Lange, Santos, Vaz-luis, & Meglio, 2019; Shilling, Jenkins, Fallowfield, & Howell, 2003). Additional side effects have included self reported pain, musculoskeletal symptoms (including 'joint aches'), insomnia, depression, and decreases in sexual, role and social functioning (Cazzaniga et al., 2021; Ferreira et al., 2019; Garreau et al., 2006). Younger patients have been said to suffer more with these self reported symptoms (specifically sexual functioning and depression) (Cazzaniga et al., 2021). Severe medical side effects such as hypertension, diabetes and osteoporosis have also been reported after using hormone therapy (Cazzaniga et al., 2021;

Hamood, Hamood, Merhasin, & Keinan-Boker, 2020). With the many side effects that come with this treatment, 37-47.5% of patients decide to stop treatment (Garreau et al., 2006).

2.3 Functional Effects of Treatment

Following the conclusion of treatment, survivors often experience difficulties adapting to life as a survivor. This includes, but is not limited to adopting the term 'survivor', primary care concerns, strength, range of motion, shoulder-related quality of life and kinematic and muscular adaptations.

2.3.1 Survivorship

Cancer survivorship is complex. There are many different interpretations of survivorship, and more importantly there are different challenges within these populations. Patients in active treatment are cared for diligently, but following treatment 'survivorship' is vague and not well understood. Individuals struggle with the term 'cancer survivor' as they are unsure if they deserve the title, especially with cancers of breast or prostate that have high rates of survival (Khan, Harrison, Rose, Ward, & Evans, 2012). The struggle also comes with the reality that their disease may reoccur or that their identity does not revolve around their diagnosis (Khan et al., 2012). However, many accept the term as they have in fact been diagnosed, and completed treatment for cancer. A cancer 'survivor' in the past was a term held for individuals beyond 5 years from treatment, but this was a time where the 5-year survivor rate was 50%, and as the survivor rate increases, this time frame is not as relevant (Breaden, 1997). This time immediately following treatment may also be referred to as 'transitional cancer survivorship' which may more accurately refer to the season of change a survivor may experience, but still includes the term 'survivor' (Miller, Merry, & Miller, 2008). For the purposes of this dissertation, the term 'breast cancer survivor' will be used to refer to this population, with acknowledgment that this term is not universally accepted, but clearly encapsulates the time once treatment concludes (excluding additional hormone therapy if necessary), and that the individual is designated cancer-free. Regardless of the term, the needs of these individuals change once treatment has ended. A shortage of oncologists has lead to care being shifted to primary care physicians once the individuals move from ‘patient’ to ‘survivor’ (once an individual is deemed cancer free and course of treatment has ended), however these physicians may not be well versed in the medical complications that may arise due to treatment (ranging from medical side effects, to a loss of function, and secondary side effects) (Bodai & Tuso, 2015).

2.3.2 Primary care

Breast cancer survivors are often taxed with additional medical side effects post treatment. In Korea, where the 5-year survivorship for breast cancer is 93%, individuals who have completed treatment are transitioned to primary care (Kang, Park, & Lee, 2019). This is not common practice in all countries unless immediately necessary. Two primary care issues that may arise are diabetes and osteoporosis (Kang et al., 2019). The increased prevalence for diabetes in this population, also coincides with an increase in the reoccurrence of breast cancer (Kang et al., 2019). Hormone therapy may cause early menopause and thus accelerate the development of osteoporosis – affecting bone resorption, increased bone loss and ultimately increasing fractures (Courneya et al., 2002; Poznak, 2015). Bone mineral density decreases exist in up to 38.5% of breast cancer survivors (Pillai et al., 2019). Finally, cardiac dysfunction (2%) and hypothyroidism (14.47%) are medical morbidities frequently present in this population (Pillai et al., 2019).

2.3.3 Strength

Shoulder dysfunction, often referring to decrease in strength or range of motion, is variable in the breast cancer survivor population. Decreases in strength have been reported in 9-40% of survivors (De Groef et al., 2020; Harrington et al., 2011; Hidding, Beurskens, Van Der Wees, Van Laarhoven, & Nijhuis-van Der Sanden, 2014; Lauridsen et al., 2008; Lee et al., 2008; Pillai et al., 2019; Rietman et al., 2003, 2004). These decreases span grip strength and shoulder specific measures of strength. Shoulder specific strength is not commonly measured, as it is difficult to obtain in a clinical setting. Decreases in abduction & upward rotation, depression & adduction, flexion, external rotation, internal rotation, scaption and horizontal abduction exist compared to non-cancer reference groups (Harrington et al., 2011; Ribeiro, Camargo, et al., 2019). During targeted strength testing infraspinatus, supraspinatus and upper trapezius had decreased strength on the affected side (Brookham et al., 2018b). Further, shoulder extensors, protractors and retractors were at least 20% weaker on the affected side of breast cancer survivors in up to 27.5% of participants (Merchant, Chapman, Kilbreath, Refshauge, & Krupa, 2008).

Several techniques have been used to contextualize strength in breast cancer survivors, such as grip strength, bench press and chest press tasks. Grip strength is often used in clinical settings as it is simple, inexpensive and quick. A clinically significant difference in grip strength reduction is represented by 6.5kg or a difference of 19.5% (J. K. Kim, Park, & Shin, 2014). When comparing to a non-cancer reference group, De Groef et al (2020), found that grip strength in this population was on average 19.1-22.6 kg less. Using the guidelines by Kim et al (2014) they determined 12-13% of these participants were impaired compared to a reference population (De Groef et al., 2020). Decreases in handgrip strength were larger when the non-dominant limb was the affected limb (Perez et al., 2018). However, grip strength is an imperfect surrogate for shoulder strength. One rep maximum (1RM) of bench press is considered a better representation of upper limb strength. Rogers et al (2017) investigated the ability of hand grip strength to predict 1RM of a bench press in breast cancer survivors. The breast cancer survivors in this study had handgrip strength of 23.5kg (range of 9-43kg), and a 1RM of a bench press task of 18.2kg (range 2.2-43kg) (Rogers, Brown, Gater, & Schmitz, 2017). It was concluded that each measure tests distinct components of strength, and that handgrip over estimates 1RM of bench press by 4.7kg (Rogers et al., 2017). Finally, Hagstrom et al. quantified the difference in survivors during a unilateral chest press exercise prior to an exercise program and the affected limb produced 150.96N (±27.72N), whereas the unaffected limb produced 161.36N (±29.51N) of force (Hagstrom, Shorter, & Marshall, 2019). The complex nature of strength makes it difficult for any singular strength measure to be representative of all motion at the shoulder.

2.3.4 Range of motion

Range of motion deficits are a variable contribution to shoulder dysfunction in breast cancer survivors. Impairments related to range of motion have been reported in 1-67% of breast cancer survivors (De Groef et al., 2020; Ernst, Voogd, Balder, Klinkenbijl, & Roukema, 2002; Lauridsen et al., 2008; Lee et al., 2008; Nesvold et al., 2008; Pillai et al., 2019; Rietman et al., 2003, 2004; Tengrup, Tennvall-Nittby, Christiansson, & Laurin, 2000; Voogd et al., 2003). However, the definition of impairment is imprecise, and therefore this measure is variable. Impairment has been variously defined as a decrease in 15° of range of motion (De Groef et al., 2020; Tengrup et al., 2000), a decrease of 20° of range of motion (Ernst et al., 2002; Voogd et al., 2003), or any significant differences between arms or groups. Further, examining decreases between affected and unaffected arms is not a perfect comparison, as individuals often receive chemotherapy, which has full body effects (Klassen et al., 2017). Yet this comparison is often used as it is the most accessible.

Frequently, impairments in flexion, extension, abduction, horizontal abduction and external rotation are reported in this population (Bendz & Fagevik Olsén, 2002; De Groef et al., 2020; Harrington et al., 2011; Ibrahim et al., 2018; Ribeiro, Camargo, et al., 2019). Within two weeks of surgery reductions of up to 58° of flexion, 79° of abduction and 24° of external rotation were present in breast cancer survivors (Bendz & Fagevik Olsén, 2002). The decrease in range of motion continues to vary by motion after adjuvant treatment concludes. Reported flexion decreases range between 10.7-32° (Harrington et al., 2011; Ibrahim et al., 2018), abduction decreases from 10.7-41° (Ibrahim et al., 2018; Pillai et al., 2019), external rotation decreases between 1-11.4° (Harrington et al., 2011; Ibrahim et al., 2018; Pillai et al., 2019), internal rotation and horizontal abduction decreases of 1-8.5° (Ibrahim et al., 2018), and finally extension decreases of 6.2° (Harrington et al., 2011). Absolute values of impaired affected limb flexion are between 129-141°, and abduction values of 119-124° (De Groef et al., 2020; Tan & Wilson, 2019).

Range of motion decreases are associated with several factors and may have implications on shoulder-related quality of life and task completion. Survivors are more likely to have a decrease in range of motion if they have had an axillary lymph node dissection, have more than 15 lymph nodes removed, stage II cancer, increased age, or a BMI greater than 25 (Lauridsen et al., 2008; Levy et al., 2012). Range of motion explains 12% of self-reported variability in shoulder-related quality of life measures, with pain contributing up to 60% (Rietman et al., 2004). It has been suggested that these impairments may combine to an overall reduction in shoulder-related quality of life, and may lead to further rotator cuff diseases (Ebaugh, Spinelli, &

Schmitz, 2011). Additionally, individuals who have limitations in their range of motion are 2.5 times more likely to report a reduction in capacity to complete tasks (Quinlan et al., 2009).

2.3.5 Shoulder-related quality of life

Shoulder-related quality of life provides insight into individual's daily living and is dependent on several factors. For this dissertation, shoulder-related quality of life refers to aspects of an individual's daily living, such as perceived disability, emotional, physical and social well-being as well as physical activity, as affected by shoulder function. Primarily, increased time since treatment is associated with improvements in shoulder-related quality of life, and treatment type, where patients who received breast conserving therapy have better shoulder-related quality of life compared to individuals who had more invasive treatment (Arndt, Stegmaier, Ziegler, & Brenner, 2008; Chopra & Kamal, 2012; Kaur, Gupta, Sharma, & Jain, 2018a; Kessler, 2002; Rietman et al., 2006). Although shoulder-related quality of life increases as time since treatment passes, their shoulder-related quality of life ratings do not reach that of a reference population (Harrington et al., 2011; Kaur, Gupta, Sharma, & Jain, 2018b). However, breast cancer survivors report having a greater positive outlook on life compared to a reference population (Kessler, 2002). The presence of lymphedema also decreases overall shoulder-related quality of life (Kwan et al., 2002), but with intensive treatment targeted to reduce lymphedema this can be recovered (De Vrieze et al., 2020a). Younger age at diagnosis has also been correlated with decreased shoulder-related quality of life (Andersen et al., 2018; Chopra & Kamal, 2012; Howard-Anderson, Ganz, Bower, & Stanton, 2012). Younger breast cancer survivors are likely to have increased weight gain, and increased physical inactivity which perpetuate further decrease of shoulder-related quality of life (Howard-Anderson et al., 2012).

Dysfunction is largely associated with shoulder-related quality of life decreases. Pennsylvania shoulder score (PSS) is used to determine function at the shoulder. Harrington et al (2013) correlated these scores with various measures of function. PSS is related to both range of motion and strength measures. Specifically, active flexion and external rotation were related to PSS, where participants with decreased range of motion also had decreased shoulder-related quality of life (Harrington et al., 2013). PSS was also decreased when decreased strength in abduction & upwards rotation, adduction & depression, flexion, internal rotation, scaption and horizontal adduction were apparent (Harrington et al., 2013). If these factors of dysfunction are improved and participants are able to return to work, a larger increase in shoulder-related quality of life is seen in breast cancer survivors (Colombino, Sarri, Castro, Paiva, & da Costa Vieira, 2020).

2.3.6 Kinematic Changes in Breast Cancer Survivors

Aside from range of motion, activities of daily living are often used to investigate functional movements and determine which cause difficulty or pain. Activities of daily living span tasks such as reaching, washing, putting on a seatbelt and many more. When possible, it is recommended to provide a goaled, or functional task, or use props, opposed to simulating a task as this provides a more accurate and reliable representation of the individuals abilities (Taylor, Kedgley, Humphries, & Shaheen, 2018). These tasks are often variable regardless of whether they are simulated or functional, making comparisons difficult. Several studies have used a series of activities of daily living to investigate breast cancer survivors. Compared to a non-cancer reference group, scapulothoracic and glenohumeral angles were similar during overhead tasks (Spinelli, Silfies, Jacobs, & Brooks, 2016). However, there exists a low/moderate relationship between increased upward rotation of the scapula during functional tasks and pain in breast cancer survivors (Spinelli et al., 2016). Lang et al (2019) investigated whether breast cancer survivors with impingement pain had differences in movement. At extreme postures, survivors with impingement pain had decreased humeral abduction and internal rotation, consistent with movements at high risk of rotator cuff disease (Lang, Dickerson, Kim, Stobart, & Milosavljevic, 2019). To avoid pain in general, it has been suggested that breast cancer survivors use less range of motion on their affected side, with 6.7° plane of elevation, 2.3° less elevation angle, and 7.1° axial rotation used during various reach and rotation tasks, respectively (Brookham et al., 2018a). In addition to functional tasks, work related tasks are often investigated. Difficulty with raising objects and lifting and/or loading a 5kg object are associated with survivors unable to return to work (de Souza Cunha et al., 2020).

2.3.7 Muscular Activation Changes in Breast Cancer Survivors

Muscular activation during functional tasks have been compared to a reference population. In a comparison of breast cancer survivors to reference participants, survivors generally require increased activation for the same tasks (Brookham & Dickerson, 2016; Galiano-Castillo et al., 2011; Shamley, Lascurain-Aguirrebeña, Oskrochi, & Srinaganathan, 2012). During a low load, functional desk work task, the sternocleidomastoid activation of the affected side was 31% higher than reference participants. During the same task, the upper trapezius muscle was 20% more active on the affected side of breast cancer survivors compared with reference participants, and 4% more active on the unaffected side (Galiano-Castillo et al., 2011). These differences may depend on surgery type. Patients who received mastectomy had greater increases in activation compared to patients who received breast conserving therapy (Shamley et al., 2012). Brookham et al (2015) completed internal and external rotation tasks and found that breast cancer survivors required 3.8-16.9% MVC more during internal rotation tasks, and 4.3-16.3% MVC more during external rotation tasks compared to a non-cancer reference group (Brookham & Dickerson, 2016). However, co-activation ratios remained similar between breast cancer survivors and reference participants (Brookham & Dickerson, 2014, 2016). The increased activation in this population may influence fatigue development and other morbidities.

Often, affected side muscle demands are compared to the unaffected side within a survivor. Prior to an exercise intervention, Hagstrom et al (2019) investigated EMG during strength trials. Before the exercise intervention began both the unaffected and affected side had similar activation during maximal strength trials (Hagstrom et al., 2019). During work tasks, total muscle effort was 5.1% higher on the affected side compared to the unaffected side in survivors (Brookham et al., 2018b). During activities of daily living the posterior deltoid, supraspinatus, upper trapezius and serratus anterior required more muscular activation in the affected side, while the pectoralis major was lower on the affected side (Brookham et al., 2018b). Similarly, although this data was not normalized, breast cancer survivors activated upper trapezius and rhomboid less on the affected side during an arm elevation task (Shamley et al., 2007). Ultimately, these studies provide insight that differences post treatment are not localized to the immediate area of treatment, but that muscles outside of this field may also be altered.

2.4 Secondary Effects of Treatment

Breast cancer primary treatments are associated with many additional co-morbidities. Surgical and adjuvant therapies often are linked to tissue changes, axillary web syndrome, lymphedema, fatigue, depression, numbness and pain. Survivors may not develop any of these side-effects, but often will experience one or more.

2.4.1 Tissue changes

Several types of lesions can form after breast cancer. Changes such as skin thickening, rashes, deformity, architectural distortion of muscle and bone, parenchymal scars, and capsular contracture are present in these individuals. Within architectural distortion, changes such as fibrous stranding in the muscle has been observed, as well as a change in tissue interfaces, and disordered trabecular pattern (Sickles & Herzog, 1981). Parenchymal scars are spiculated masses (a lump of tissue with spikes or points on the surface) and may be observed following the conclusion of treatment. Immediately following treatment 95% of patients displayed skin changes, and 83% developed architectural distortion. This percentage reduces to 55% and 35% at two years post treatment, respectively. 3 years following treatment 26% of individuals still display skin changes, and 16% retain architectural distortion (Sickles & Herzog, 1981). These remain even 10 years post treatment. The reduction between 0 and 3 years post treatment indicate levels of healing within the first few years after treatment ends (Sickles & Herzog, 1981). However, individuals who still display these changes 3 years post treatment are not likely to experience any more natural healing. These tissue changes may also lead to tightness surrounding the joint, limiting range of motion (E. J. Yang et al., 2010). Capsular contracture is a side effect that may occur following any type of breast surgery (mastectomy, reconstruction or augmentation). However, having a history of breast cancer increases the risk of this complication. A capsular contracture is identified as excessive tissue formation and contraction of the fibrous capsule, leading to deformation/distortion of the breast, pain or tenderness, and hardness (Bachour et al., 2018).

2.4.2 Axillary Web Syndrome

Axillary web syndrome, or cording, may be present in survivors following axillary lymph node dissection. A cord (or cords) develops starting at the axillary scar and may extend down the arm or into the chest wall and may thicken over time and become visible under the skin. The cords often appear within the first month following surgery, and are palpable during abduction (Lauridsen, Christiansen, & Hessov, 2005; Moskovitz et al., 2001). In women who had axillary lymph node dissection, (35.9-85.4%) develop axillary web syndrome, however it can occur in patients with no axillary involvement (Harris, 2018; Koehler et al., 2015; Leidenius, Leppanen, Krogerus, & von Smitten, 2003; Yeung, Mcphail, & Kuys, 2015). After 8-12 weeks axillary web syndrome was resolved in half of those that developed this symptom (Baggi et al., 2018; Koehler et al., 2015). The cording usually resolves within three months, but for those with persistent cording, 74% present with severe restriction in range of motion, specifically in abduction (less than 90°) , but restrictions in flexion may also occur (Koehler et al., 2015; Tilley, Thomas-MacLean, & Kwan, 2009; Yeung et al., 2015). Following surgery, 70% of patients who received axillary lymph node dissection presented with cording, and 86% had restricted range of motion (as determined by their physiotherapist), opposed to 20% presenting with cording and 45% having restricted range of motion in the group with no axillary involvement (Leidenius et al., 2003). Pain was also persistent in those with cording, rating 8.8/10 on a VAS scale (Lacomba et al., 2009). Risk factors for developing cording may include extensiveness of surgery, younger age, lower body mass index, ethnicity and healing complications (Harris, 2018; Yeung et al., 2015).

2.4.3 Lymphedema

Lymphedema is a common side effect following breast cancer treatments and is defined as a retention of fluid in the arm, ultimately causing swelling of the ipsilateral arm. Commonly, lymphedema occurs after an axillary lymph node dissection or radiation treatment as damage to the lymph nodes located in the axilla has occurred (Shah & Vicini, 2011). However, volume of irradiated axilla, older survivor age, larger numbers of dissections, and higher BMI are also associated with an increased occurrence of lymphedema (Gross et al., 2017; Hack et al., 2010; Sakorafas, Peros, Cataliotti, & Vlastos, 2006).

Lymphedema presence and onset varies among survivors. Prevalence has been reported from 6 to 42% in survivors (Ahmed, Thomas, Yee, & Schmitz, 2006; DiSipio, Rye, Newman, & Hayes, 2013; Norman et al., 2009; Petrek, Pressman, & Smith, 2000; Rietman et al., 2003; Sakorafas et al., 2006; Schmitz et al., 2010; Sugden et al., 1998; Swedborg & Wallgren, 1981; Zou et al., 2018). The variability in this measure can be attributed to measuring techniques, reporting rates, and follow up intervals. Survivors often do not report follow up symptoms as the focus is on preventing reoccurrence rather than secondary symptoms and upper limb dysfunction (Sakorafas et al., 2006). Importantly, lymphedema may occur up to 20 years post-operative , however it often occurs within 3-5 years of treatment (Breast Cancer.org, 2019; Norman et al., 2009).

Commonly, lymphedema is measured clinically in one of two ways. In both scenarios, the affected arm is compared to the non-affected arm. The first technique requires the clinician or researcher to measure the circumference of various parts of the arm, and compare the two arms. A difference greater than 2cm is indicative of lymphedema (Ahmed et al., 2006). The second method involves measuring the volume of the arm by using displacement of water. An increase in volume greater than 20% indicates the presence of lymphedema (Sakorafas et al., 2006; Swedborg & Wallgren, 1981). Dual energy x-ray absorptiometry (DXA) has been identified as a superior method to circumference or water displacement (Gjorup, Zerahn, & Hendel, 2010). By monitoring individuals from the onset of treatment, an increase in volume of 3-5% (not due to weight change – determined by measuring the non-affected limb as well) is indicative of early stage lymphedema (International Society of Lymphology, 2016). Not only is DXA a more exact way to determine the presence of lymphedema, it can also determine differences in body composition that may be a consequence of this secondary symptom (International Society of Lymphology, 2016).

Depending on the severity lymphedema may affect activities of daily living, and reduces overall shoulder-related quality of life. Lower shoulder-related quality of life has been reported in survivors with clinically diagnosed lymphedema, specifically with scores in mental health and overall pain (Lovelace, McDaniel, & Golden, 2019; Pusic et al., 2013; Taghian, Miller, Jammallo, Toole, & Skolny, 2014; Velanovich & Szymanski, 1999). The swelling and pain that characterizes lymphedema may cause daily tasks to be difficult. Particularly the increased weight of the arm causes reduction in range of motion, increased fatigue, and makes it more challenging to lift the arm to complete everyday tasks (Lovelace et al., 2019; Pusic et al., 2013). Compression sleeves work to counteract this swelling and reduce lymphedema in some participants, but more importantly improve shoulder-related quality of life in those that show clinically significant lymphedema (Ochalek, Partsch, Gradalski, & Szygula, 2019). However, these sleeves may worsen lymphedema symptoms as they are often ill-fitting, and in many circumstances may cause the fluid build up to occur in the hand.

2.4.4 Fatigue and Depression

Fatigue is often reported during, and following cancer treatment. Cancer related fatigue presents in 50-75% of cancer patients at diagnosis, 80–96% of patients undergoing chemotherapy and 60–93% of patients receiving radiotherapy (Hsieh et al., 2008; Levy et al., 2012; Mock et al., 2005; Stasi, Abriani, Beccaglia, Terzoli, & Amadori, 2003). Fatigue in breast cancer survivors is increased with increased age, increased body fat percentage, fewer years since diagnosis, decreased strength and physical activity and more treatments (Winters-Stone et al., 2011). It is important to consider fatigue, as it is indicated as a preventative agent for completing daily tasks by 91% of cancer survivors. However, although levels of fatigue during radiation therapy were at their peak halfway through treatment, they returned to pre-treatment levels for most patients 6 months following treatment (Irvine, Vincent, Graydon, & Bubela, 1998).

Of survivors who report severe, and persistent fatigue, a correlation has been shown relating their fatigue to severe pain and depression (Bower et al., 2000). Depression was most strongly correlated with fatigue, where patients who developed depressive symptoms post diagnosis reported higher levels of fatigue. The mean value of reported depression was within the clinically relevant scores. Further, it is difficult to determine which of these factors causes the other. Individuals with depression often report fatigue, and fatigue may cause depression as it limits the ability to complete activities of daily living, participate in leisure or return to work (Bower et al., 2000). This further relates to a decline in shoulder-related quality of life, and although only prevalent in a small portion of the survivor population, it is an important factor to consider.

2.4.5 Numbness and Pain

Numbness appears in breast cancer survivors and is often described as pins and needles, burning or a complete loss of sensation. This numbness is often associated with post-mastectomy pain syndrome, which is pain in the axilla, chest wall or ipsilateral arm persisting beyond 3 months from surgery (natural healing times) (E. J. Yang et al., 2010). 65% of survivors report numbness, with up to 15% of survivors reporting moderate to severe pain (Bosompra, Ashikaga, O'Brien, Nelson, & Skelly, 2002). Pain has been reported in 31-61% of breast cancer survivors, with a mean pain score of 4-6/10, indicating that pain is present but generally not debilitating (Lauridsen et al., 2008; Levy et al., 2012; Tasmuth, von Smitten, Hietanen, Kataja, & Kalso, 1995). These symptoms were more often reported with a combination of lymphedema (4% reported pain without lymphedema, and 24% with lymphedema; 8% reported numbness without lymphedema and 21% had numbness with lymphedema) (Kwan et al., 2002; Lauridsen et al., 2008; Shamley et al., 2012; Tasmuth et al., 1995). Survivors who do not meet the physical activity guidelines, and those that are overweight are more likely to report clinically significant pain, than those who are regularly active and at a normal weight (Forsythe et al., 2013). Additionally, it has been suggested that the younger patients have greater neural disruption which increases pain (Downing & Windsor, 1984). These factors lead to an overall decrease in shoulder-related quality of life when persisting past 2 years following surgery, even with mild – moderate pain (reported by up to 60% of patients) (Rietman et al., 2004).

2.5 Biomechanical Modelling

Biomechanics research uses EMG, kinematics, and kinetics to make inferences about underlying mechanisms in the human body. Unfortunately, it is difficult, and sometimes impossible to collect comprehensive data sets of all contributing muscles and underlying structures. Moreover, experimentally accessible data are only indirect measures of the system and are not direct surrogates of important tissue forces within the body (muscle force, bone on bone forces etc). Biomechanical models can help compensate for these issues. These models solve for unknown forces within the system and calculate loads on the body or system performance based on modifications to system behaviors. Modelling allows insight into tasks and forces that may be difficult to explore in an experimental setting and allows additional control of the data input and removes mitigating factors (such as environmental factors). Forces internal to the system (inaccessible during experimental techniques) are variously estimated using both inverse and forward dynamics (Buchanan, Lloyd, Manal, & Besier, 2004).

Two types of models are frequently applied in practice: Digital human modelling and computational musculoskeletal models. Digital human models such as Siemens Jack TM (Siemens Industry Software Inc., Germany) and Santos Pro TM (SantosHuman Inc., USA) are used in both research and ergonomic settings. These software packages allow the user to develop environments and tasks completed in practice, and often output joint loads to analyze loads on the body (Polášek, Bureš, & Šimon, 2015; Santos, Sarriegi, Serrano, & Torres, 2007). Computational musculoskeletal models are typically more customized tools, and are most typically used to solve for internal forces within the body (generally muscle forces) (Dickerson, Chaffin, & Hughes, 2007). These models include physiological information on muscles (moment arms, cross-sectional area, and origin/insertion), subject and task information, and muscle geometry. Several assumptions are made (and differ between models) in order to solve for unknown forces (Crowninshield & Brand, 1981; Dul, Johnson, Shiavi, & Townsend, 1984). Optimization is a common technique to solve for these forces in computational musculoskeletal models.

2.5.1 Optimization

The human body can produce movements through an infinite combination of muscle activations making it difficult to determine which muscles contribute to each movement. The solution is indeterminate as there are too many unknowns in the system for the available equations to solve. Optimization is a mathematical technique that can solve these types of problems. It imposes an objective function (goal for the system), to reward an optimal result within the range of possible solutions, and thus provides a possible solution to the redundancy problem that generates an optimal value for the objective function. These objective functions can be a variety of measures including minimizing muscle force, or muscle stress (Crowninshield & Brand, 1981; Dul, Johnson, et al., 1984). In many optimization solutions the “best” muscle (the muscle with the most advantageous features in terms of the objective function (i.e. moment arm, cross sectional area etc.)) is used first, and antagonistic contraction is negated as it is counterproductive to the movement at hand (Collins, 1995). Imposing muscle bounds can help improve the biofidelity of the output. These bounds are employed to keep muscle stress at levels proportional to the cross sectional area of each given muscle (the upper bound is represented by $\sigma > Fi/PCSAi$) (Prilutsky & Zatsiorsky, 2002). This ensures the solution for each muscle occurs within these bounds and thus forces remain physiologically realistic (Challis, 1997).

2.5.2 SLAM Model

The Shoulder Loading Analysis Modules (SLAM) model is a musculoskeletal model used to evaluate tissue and joint demands during movement of the shoulder joints. Input data for this model include task specific motion capture and force demands as well as subject specific data (height, weight, sex) (Figure 3). The model includes three modules: shoulder geometry constructor, external dynamic moment calculator, and the internal muscle force prediction module (Dickerson et al., 2007). The model outputs dynamic joint moment and forces, positions and orientations of the defined segments, the line of action and moment arms of each element and the muscle forces for each of the 38 muscle elements in the model.

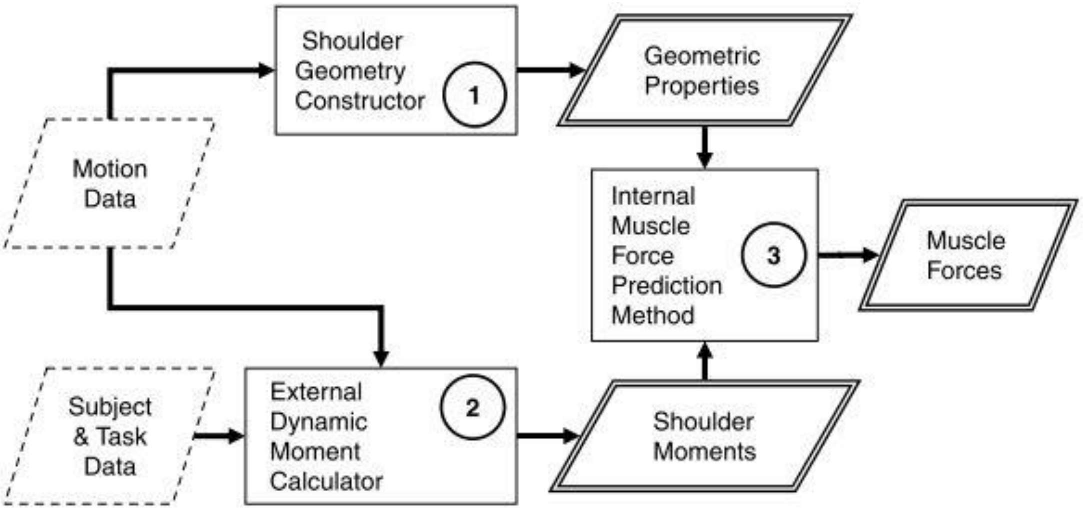


Figure 3: Schematic of SLAM model (Dickerson et al., 2007)

The musculoskeletal geometry module includes relevant anatomy of the upper extremity and torso. The torso, humerus, clavicle, scapula and forearm (ulna and radius) are all modelled in SLAM (Dickerson et al., 2007). Each segment is scaled to the participants height based on previously published data (Hogfors, Karlsson, & Peterson, 1995; Hogfors, Peterson, Sigholm, & Herberts, 1991; Hogfors, Sigholm, & Herberts, 1987; Karlsson & Peterson, 1992; Makhsous, Ho, Siemien, & Peterson, 1999). Two contact sites between the scapula and ribcage are modelled, located at the superior and inferior angles of the scapula (Makhsous et al., 1999). These sites transmit force from the ribcage to the scapula. Ligaments are also modelled, however they do not produce any force in the current state of the model, as ligaments at the shoulders generally contribute force only at end range of motion, and muscles are the primary contributors to force production (Crowninshield & Brand, 1981; Jinha, Ait-haddou, Binding, & Herzog, 2006). All joints of the shoulder (sternoclavicular, acromioclavicular and glenohumeral) are modelled with three degrees of rotational freedom, but no translational movement. The shoulder rhythm (interaction between the scapula and the humerus) used in SLAM is adapted from previous literature (Karlsson & Peterson, 1992; Makhsous et al., 1999). Once the shoulder rhythm is applied constraints are placed to accommodate captured motion data inputted into the model. The inferior and superior angles of the scapular are constrained to minimal movement from the ribcage. The final element of the geometry module is the muscles. 23 muscles (38 total elements) were modelled in SLAM (Dul, 1988). The muscles modelled, and their associated elements are levator scapulae (1), omohyoid (1), pectoralis minor (1), rhomboid major (1), rhomboid minor (1), sternocleidomastoid (1), stenohyoid (1), subclavius (1), coacobrachialis (1), supraspinatus (1), teres major (1), teres minor (1), brachialis (1), brachioradialis (1), latissimus dorsi (2 elements), serratus anterior (3), trapezius (4), subscapularis (3), infraspinatus (2), pectoralis major (2), deltoid (3), biceps (2), and triceps (3) (Dickerson et al., 2007). The origin and insertion of each muscle is modelled, and connected via the muscle elements based on previous literature (Van Der Helm, 1994). However, this may model inappropriate lines of action, through structures such as bones. Therefore, additional conditional wrapping and collision alterations are placed on the elements to ensure proper lines of action (Charlton & Johnson, 2001; Van Der Helm, 1994). The geometric proprieties from this module feed into the internal muscle force prediction module (Figure 3).

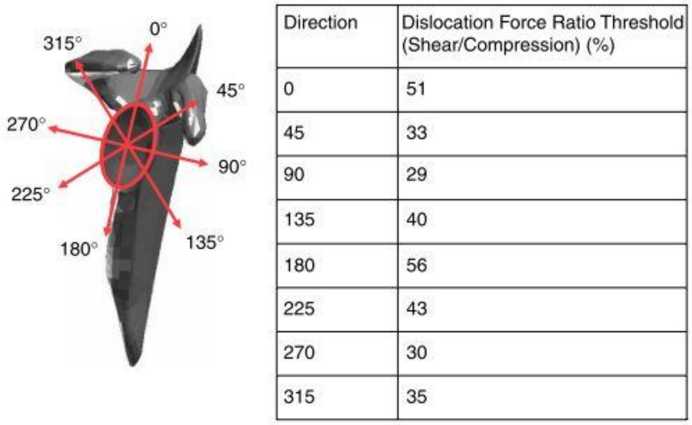
The second module is the external dynamic joint moment module. Subject, task and motion data are all inputs into this module. Segment properties such as segment mass and moment of inertia are calculated based on published proportions and the individual's sex, height, and weight (Zatsiorsky & Seluyanov, 1993). Joint centres are calculated for glenohumeral, elbow and wrist based on published literature from the motion capture data (Nussbaum & Zhang, 2000). Data is filtered at 6Hz, and then linear velocity and acceleration of joint centres are calculated through differentiation and double differentiation, respectively. Joint coordinate systems are calculated based on previously published standards (Hogfors et al., 1987). Angular kinematics are determined using joint coordinate system techniques (Nigg & Herzog, 1994). The orientation of the upper arm and forearm are defined using equation 1. The hand has a different neutral orientation and therefore uses a different rotation sequence [Eq. 2]. The first and second derivatives of the Euler angles are then calculated to determine the angular velocity and acceleration (Vaughan, Davis, & O'Connor, 1992). The final portion of this module calculates net joint forces and torques. The joint load is calculated at the proximal end of the segment, and is influenced by the movement and mass of the segments and hand-held weight. The general equation used in the model for joint force equilibrium (using reaction forces) is found in equation 3. Finally, external moments are calculated using the rate of change of segmental angular momentum (using segmental moments of inertia and the corresponding segment velocity and acceleration). Specifically, the sum of each force crossed to their moment arm is used to determine the external torque at the proximal end of each segment.

$$\begin{Bmatrix} x \\ y \\ z \end{Bmatrix} = \begin{bmatrix} \cos\psi\cos\theta & \sin\psi\cos\theta & -\sin\theta \\ (-\sin\psi\cos\phi + \cos\psi\sin\theta\sin\phi) & (\cos\psi\cos\phi + \sin\psi\sin\theta\sin\phi) & \cos\theta\sin\phi \\ (\sin\psi\sin\phi + \cos\psi\sin\theta\cos\phi) & (-\cos\psi\sin\phi + \sin\psi\sin\theta\cos\phi) & \cos\theta\cos\phi \end{bmatrix} \begin{Bmatrix} X \\ Y \\ Z \end{Bmatrix} \qquad \text{[Eq. 1]}$$

$$\begin{Bmatrix} x \\ y \\ z \end{Bmatrix} = \begin{bmatrix} \cos\psi\cos\theta & \sin\theta & -\sin\psi\cos\theta \\ (\sin\psi\sin\phi - \cos\psi\sin\theta\cos\phi) & \cos\theta\cos\phi & (\cos\psi\sin\phi + \sin\psi\sin\theta\cos\phi) \\ (\sin\psi\cos\phi + \cos\psi\sin\theta\sin\phi) & -\cos\theta\sin\phi & (\cos\psi\cos\phi - \sin\psi\sin\theta\sin\phi) \end{bmatrix} \begin{Bmatrix} X \\ Y \\ Z \end{Bmatrix} \qquad \text{[Eq. 2]}$$

$$\sum F = m_{segment} \times \alpha_{COM\ segment} \qquad \text{[Eq. 3]}$$

The final module of the SLAM model is the internal muscle force prediction module. The outputs from the first two modules are used as inputs into the internal muscle force prediction module, specifically, shoulder moments and geometric properties. Optimization, as previously described, is used to solve for the infinite combinations of muscle forces possible to complete a given task. In the SLAM model, the default objective function is to minimize the sum of cubed muscle stresses. This objective function encourages force sharing between muscles instead of choosing the most mechanically advantageous muscle (moment arm or cross-sectional area). By using muscle stress, it also ensures consideration of both the moment arm and cross-sectional area when assigning forces to muscles. Force bounds are placed on each muscle, as well as 19 mechanical constraints. Muscles forces were bound by zero as minimum, and a maximum that is proportional to the physiological cross-sectional area of the muscle. Each individual muscle's physiological cross sectional area was obtained from a cadaver study (Hogfors et al., 1987), and the specific tension was set to 88Ncm^{-2} (Wood, Meek, & Jacobsen, 1989). Eighteen equilibrium equations constrain the sternoclavicular, acromioclavicular and glenohumeral joints. Three equations define linear equilibrium and 3 equations define angular equilibrium of each of the 3 aforementioned joints. The final equilibrium equation constrains the elbow flexion/extension moment. Three additional constraints are placed based on directional glenohumeral joint dislocation force ratios based on cadaver data (Lippitt & Matsen, 1993). These thresholds were placed in 8 equally spaced compass locations on the glenoid (Figure 4).



Direction	Dislocation Force Ratio Threshold (Shear/Compression) (%)
0	51
45	33
90	29
135	40
180	56
225	43
270	30
315	35

Figure 4: Directional shear to compressive force tolerance for each of the 8 directions included in the SLAM model (Dickerson et al., 2007)

Overall, the SLAM model solves for 60 unknown variables. The force output of 38 muscle elements, 9 joint contact forces, 2 scapulothoracic contact forces, 8 directional dislocation force ratio coefficients, and when applicable 3 ligament forces.

The SLAM model has been used in several settings to investigate internal shoulder exposures, including fundamental science (Chopp-Hurley, Langenderfer, & Dickerson, 2014), ergonomic investigations (Fischer, Brenneman, Wells, & Dickerson, 2012; Steele, Merryweather, Dickerson, & Bloswick, 2013; Vidt et al., 2019) and clinical studies (Chopp-Hurley, Brookham, & Dickerson, 2016).

There are three main limitations to the SLAM model. Although the body parameters are scalable by sex, internal muscle capabilities do not account for sex differences. These capabilities are based on previous literature that derived from exclusively male participants. Secondly, muscle mechanics (length-tension and force-velocity) are not considered in this model, which may be important for fast movements or those involving long excursions. Finally, antagonistic muscles are largely underestimated in many optimization solutions as objective functions are based on mechanical efficiency, and muscles not directly contributing to achieving the required net joint moment increase the physiological cost and are therefore not recruited. However, the SLAM model partially accounts for antagonist muscles by enforcing activation to maintain the stability of the glenohumeral joint.

2.6 Gaps in Literature

With a large number of breast cancer patients entering the survivor population every year, increased attention should be paid to individuals following treatment. As previously described (*2.3.1 Survivorship),* once survivors' complete treatment their care may be transitioned and primary medical concerns are addressed (*2.3.2 Primary care*). Functional concerns may not appear immediately and may go unnoticed. Although previous research has identified that these issues occur (*2.3 Functional Effects of Treatment* and *2.4 Secondary effects of treatment*), often there isn’t an understanding on which survivors may experience specific deficits, and how this affects daily tasks. Research has begun to identify rehabilitation programs to mitigate these issues, but without specific aim on early deficits this can be difficult. As some survivors experience more severe deficits, and some experience none, results can be washed by high variability in a diverse cohort, and the true challenges faced by some individuals may be misunderstood. The current thesis aims to study survivors immediately after the conclusion of treatment (and up to two years post treatment), in order to identify which factors more strongly influenced function, and are important to survivors (identified through self-reported shoulder-related quality of life). Further, how these deficits manifest in the context of low load, daily tasks. Finally, the work uses an *in-silico* approach to determine which muscles should be targeted in a rehabilitation program to mitigate these challenges for a subset of survivors, and how much strength may be reasonably targeted considering possible damage from treatment.

Chapter III – Improving evidence-based methods of characterizing shoulder-related quality of life for breast cancer survivors

3.1 Introduction

Investigation into specific difficulties for breast cancer survivors immediately after treatment has been limited. Further, the sparse research features heterogeneous populations, complicating direct conclusions on which factors influenced function after treatment. Firstly, no time limit is generally enforced in inclusion criteria for time since treatment and therefore extra mitigating factors may be introduced during that time. The time since treatment studied ranges from less than a year to 19 years past treatment (Brookham et al., 2018b; Kaur et al., 2018b). Treatment types also differed drastically between survivors. The type of surgery, and adjuvant therapy all differ, as well as the length of treatment and medication taken by patients. Current literature spans all treatment types, but minimal research has attempted to define each treatment's individual effects on physical function in breast cancer survivors, as it is difficult to find a cohort receiving only one type of treatment. Additionally, and similar to many research areas, differing research techniques, foci, and data reduction/interpretation approaches complicate comparisons and generalizable conclusions. Research has presented differences in groups with interventions and standard care (De Vrieze et al., 2020b; Kaur et al., 2018b), between affected and unaffected limbs (Brookham et al., 2018b; Hagstrom et al., 2019; Merchant et al., 2008) and between reference participants and survivors (Brookham & Dickerson, 2016; Galiano-Castillo et al., 2011; Kaur et al., 2018b). Foci have included exercise interventions (De Vrieze et al., 2020b; Hagstrom et al., 2019; Pillai et al., 2019; Ribeiro, Moreira, et al., 2019), and breast cancer reconstruction methods (Browne et al., 2017; Leonardis et al., 2019; Sowa et al., 2017; Yun, Diaz, & Orman, 2018) despite lacking a thorough understanding of the deficits immediately following treatment. The greatest difficulty with research on this population is its vast inherent variability. True deficits in some individuals are obscured by individuals who have no difficulties following treatment. The variability in various datasets shows the range in this population. All of these factors make it difficult to accurately represent the population, or determine an individual’s potential risk for disability post treatment. Investigating the potential for each factor to differentiate survivors, in the context of others, allows a more focused overview of function.

Multivariate analyses are frequently applied to distinguish important factors in large sets of data. Particularly, principal component analysis, multivariate regression and cluster analysis are common in biomechanics. Regressions assume that a correlation exists between data points, and has been used to determine the relationship between range of motion and strength to shoulder-related quality of life measures (Harrington et al., 2013). Principal component analysis is used to determine a new variable (or component) that sufficiently captures the variation in the original variables, whereas cluster analysis searches for natural groupings among variables (Chau, 2001). Neither principal component analysis nor cluster analysis assume variables are related, and therefore are ideal for characterizing large sets of data. Particularly, cluster analysis demonstrated utility in classifying chronic pain subgroups (Almeida, George, Leite, Oliveira, & Chaves, 2019), as well as regional peak plantar pressure distributions (Bennetts, Owings, Erdemir, Botek, & Cavanagh, 2013). In cluster analysis, data is not forced into assumed relationships analogous to regressions analysis. The analysis determines if pieces of data are more like one another than data in another group (or cluster). By finding subgroups in each of these populations, targeted interventions could be determined. This research aims to use cluster analysis to determine cohorts of breast cancer survivors and characterize factors that differentiate them. This enables an in-depth view into which factors most influence the variability in dysfunction found in this population.

3.2 Objective and Hypotheses

The objective of study 1 was to classify the different function of various groups of breast cancer survivors, and to determine factors that differed across groups of survivors.

The following hypotheses were posed for study 1:

1. Two clusters of breast cancer survivors will be formed based on physical activity, time since treatment ended, internal rotation force production, flexion range of motion, and perceived disability.
2. Between the two groups of survivors one group will have significantly lower measures of shoulder-related quality of life, particularly increased perceived disability (quantified with the DASH questionnaire) compared to the other group. This group will also have decreased physical activity levels (quantified through the GODIN questionnaire), increased arm volume differences (indicative of lymphedema), and decreased lean muscle mass, strength and range of motion.
3. Between the two groups there will be a higher percentage of participants with more invasive treatments (lymph node dissection surgery and radiation), and more advanced diagnosis stage in the group with lower measures of shoulder-related quality of life.

3.3 Methods

3.3.1 Participants

Thirty-five breast cancer survivors (Stage I – IIIa) participated (Figure 5). All participants were women, however we acknowledge that men also experience breast cancer, but at a reduced frequency (Canadian Cancer Society, 2020). Survivors must have undergone any form of surgical procedure for breast tumour removal, as well as radiation and/or chemotherapy treatment. Survivors were within 3 months – 2 years post treatment. Waiting 3 months post treatment to enroll in the study allowed time to heal from surgery and recovery of immune system function from compromises during adjuvant treatment. The upper cut off was 2 years to mitigate external factors (such as seeking physiotherapy to assist with function) and because radiation therapy may affect tissues for up to two years following treatment (American Cancer Society, 2019c). Delimiting a time window since treatment enabled a more targeted examination of effects from treatment. Exclusion criteria included confounders such as prior upper extremity injuries, bilateral cancer, metastases elsewhere in the body, a barium swallow within 3 weeks of participation, and suspected or confirmed pregnancy.

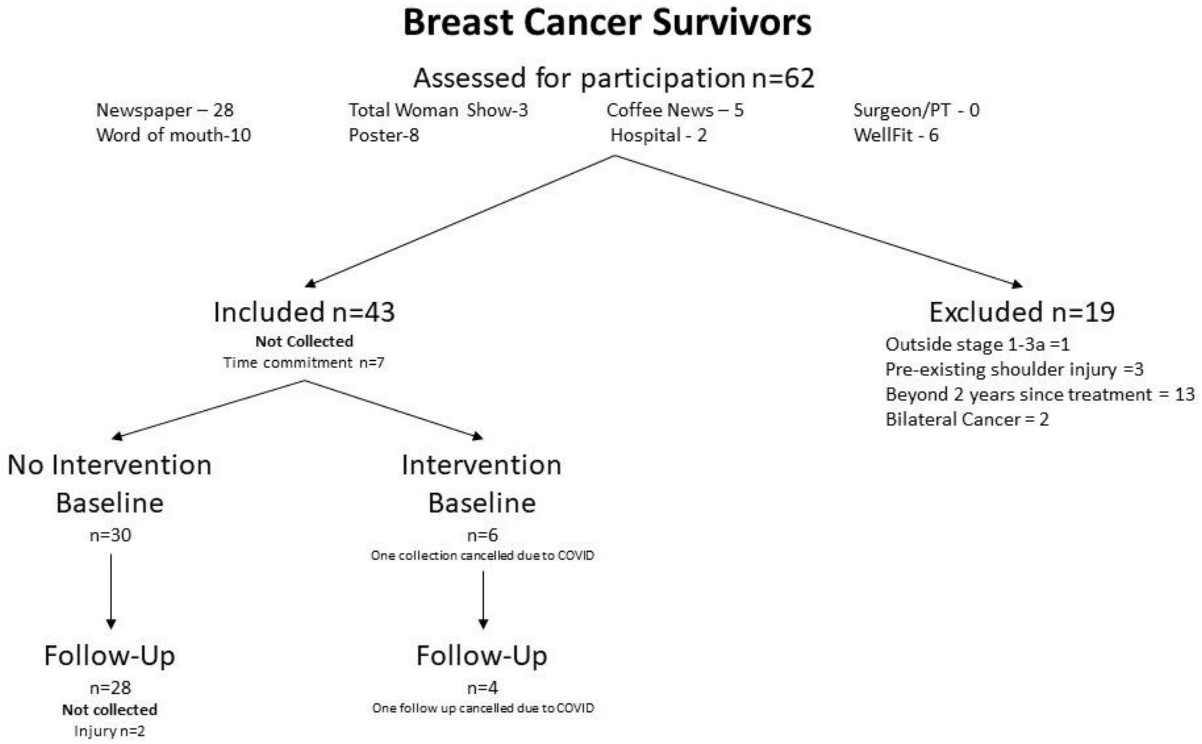


Figure 5: Consort diagram outlining recruitment and retention of participants in the study. The data for this thesis was collected in conjunction with an intervention study, but only baseline data was included in data analysis.

3.3.2 Motion Capture Instrumentation

Kinematic data was collected at 50 Hz using 12 VICON MX20 cameras (VICON, Oxford, UK). The collection space was calibrated prior to the participants' arrival. The global origin was set so that all experimental movements occur in the positive quadrant. The measurement global coordinate system was transposed into ISB standards (Wu & Cavanagh, 1995), where +Y was directed up, +X was directed forward, and +Z was to the right of the origin, defined by the right-hand rule. Twenty-three reflective markers were placed on the torso and both upper extremities over bony landmarks, following ISB standards (Wu et al., 2005) (Figure 6). The anatomical landmarks were the suprasternal notch, xiphoid process, cervical vertebrae 7, thoracic vertebrae 8, lumbar vertebrae 5, and bilaterally on; anterior and posterior superior iliac spine, acromioclavicular joint, lateral and medial epicondyle of the humerus, ulnar and radial styloid processes, and the distal end of the 2nd and 5th metacarpals. Four marker clusters (affixed to ridged plates) were placed on segments (bilaterally on the upper arm and forearm). A static calibration frame was taken with the participant in anatomical position to establish a relationship between anatomical landmarks and each cluster. Clusters were used to reduce skin movement artifact, in comparison to anatomical landmarks (Leardini, Chiari, Della Croce, & Cappozzo, 2005).

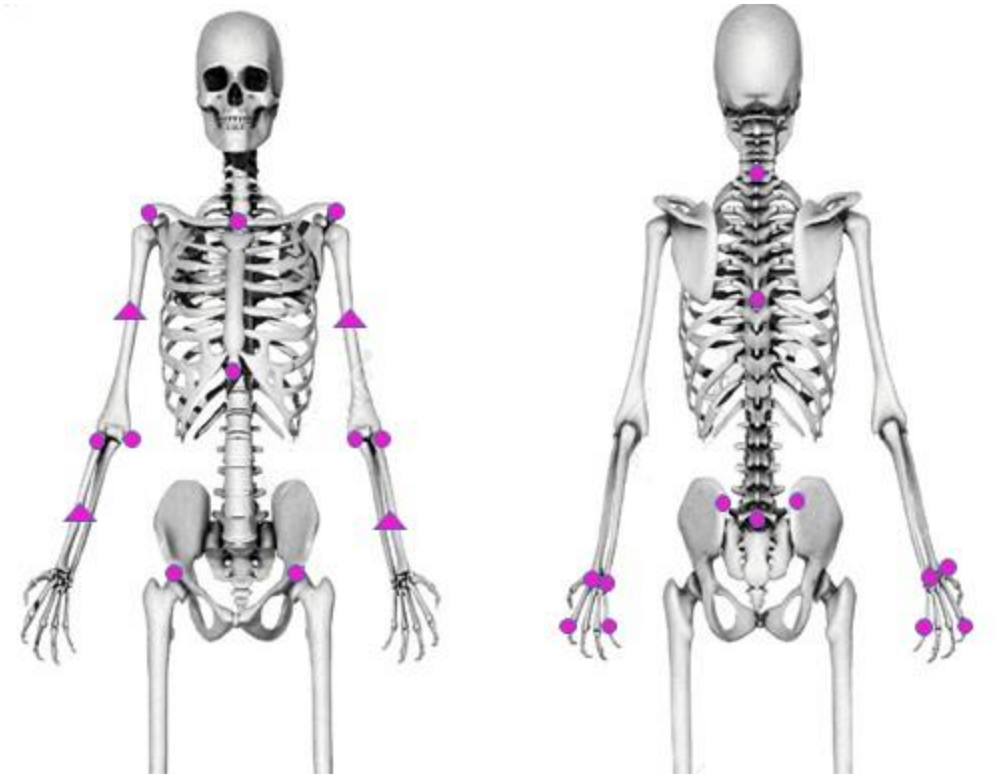


Figure 6: Placement of markers on bony landmarks (pink circles) as well as marker cluster sets (pink triangles)

3.3.3 Force Equipment

Force data was collected at 1500Hz using a 6 degree of freedom force transducer (MC3A, AMTI, Watertown, MA, USA). A cuff was placed on the participant's upper arm, with a chain attached to the force cube to direct force application. The force cube was positioned to ensure that the chain was pulled tight and force exerted was in the transducer z-axis, while the x and y axis forces were minimized (Figure 7).

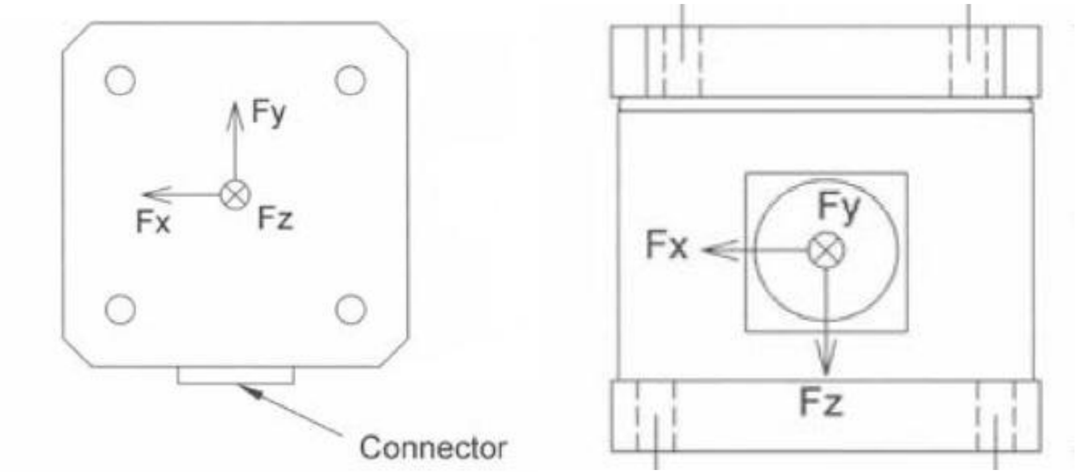


Figure 7: Axis orientation of the force transducer (AMTI – MC3A)

3.3.4 Experimental Protocol

Individuals were in the lab for approximately a 4-hour collection (Figure 8). Initially, participants were given the opportunity to ask questions about the informed consent and all activities were outlined. Following informed consent sign-off, participants had a DXA (Dual-energy x-ray Absorptiometry) scan for body composition. A general health information form (documenting diagnosis, treatment, symptoms) was then filled out (Appendix A), followed by several questionnaires (Appendix B). Within the general health information form, participants were asked to detail diagnosis, treatment types and length, current physical activity levels, co-morbidities, present medications, and history of upper extremity discomfort prior to diagnosis. Experimental set up and collection were completed as outlined below (Figure 8) following questionnaire completion. Prior to experimental tasks, participants were outfitted with surface electromyography (sEMG) and completed muscle specific MVCs. This data was used in Study 2 and is outlined in section 4.3.3 (page 80). Strength measures were collected first to ensure a rested state. Two minutes of rest separated exertions, with extra time upon request. A total of 12 exertions were completed (6 force directions, on both the affected and unaffected limb – Section 3.3.4.3). Reflective markers were placed on the participant. Then, 12 active maximal range of motion trials were completed (6 fundamental shoulder movements, on both the affected and unaffected limb – Section 3.3.4.4). The experimental protocol concluded with activities of daily living tasks, which were subsequently analyzed in Study 2 (outlined in Section 4.3.4.1, page 83).

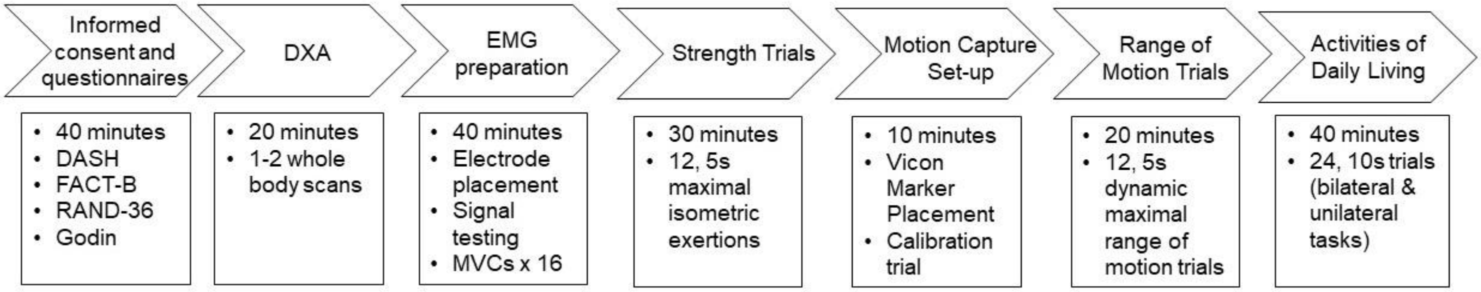


Figure 8: Overview of full lab collection with all components included (EMG and activities of daily living outlined in Chapter IV)

3.3.4.1 Questionnaires

A series of questionnaires (Appendix B) provided insight into survivor's daily lives. Four questionnaires were administered, the Functional Assessment of Cancer therapy – Breast Cancer (FACT-B) (Brady et al., 1997), Rand-36 Health Survey Short Form (RAND 36) (Hays, Sherbourne, & Mazel, 1993), the Disabilities of the Arm, Shoulder and Hand (DASH) (Hudak, Amadio, & Bombardier, 1996), and a modified version of the Godin Leisure Time Activity questionnaire (Godin & Shephard, 1985). Each questionnaire targeted different facets of return to life, and overall shoulder-related quality of life (disability, mental, physical, etc). FACT-B is a cancer specific questionnaire, targeting physical well-being of survivors. RAND 36 is a questionnaire that includes multiple sections including mental well-being, physical well-being, physical functioning, energy/fatigue and pain. The DASH questionnaire is specific to the upper extremity, and its main focus is addressing specific disabilities and hardships due to the dysfunction of the hand, arm or shoulder. The Godin questionnaire details physical activity levels of survivors and an additional question was added to capture any physical therapy/other therapies individuals may have sought out in the past week.

3.3.4.2 Dual-energy x-ray absorptiometry

Dual-energy x-ray absorptiometry (DXA) is a non-invasive whole-body scan used for body composition measurements. DXA scans can be used for bone density measures, whole body composition and segmental measurements (Mazess, Barden, Bisek, & Hanson, 1990). Participants received a full body DXA scan (Hologic Discovery QDR 4500, Hologic, Toronto, ON) completed by a Certified Medical Radiation Therapist. In scenarios where the participant did not fit within the limits of the scanning table, a second scan was obtained. One full body scan emits 1.5mR of radiation in 6.8minutes. Each upper extremity was extracted from the individual scan that contained that limb, and all other regions (head, trunk and legs) were averaged across the two scans. Scans were segmented by a Certified Medical Radiation Therapist using the Hologic software (version 13.2).

3.3.4.3 Strength

Isometric strength trials were collected aligning with several fundamental planes of shoulder motion. Maximal isometric force trials were collected for each posture. Each participant sat in a chair, against a backrest, and were instructed to remain upright for each isometric force trial. Arm positions were chosen to align with previous research (Hughes, Johnson, O’Driscoll, & An, 1999; Stobbe, 1982) (Table 5). A cuff was placed on the upper arm, just above the elbow for all force directions, except internal and external rotation. By placing the cuff above the elbow, participants were required to produce force from the shoulder for each motion. The cuff was attached to the force cube with a chain, pulled tight to maintain the correct position. The chain was aligned to pull force through the z axis of the force cube, and minimize off axis forces (Figure 7, page 44). Participants had 5 seconds to reach maximum force and were given 2 minutes of rest between exertions to minimize fatigue. A recollection took place if the researchers witnessed any movement of the upper arm from the initial position, any lean of the torso used to produce compensatory or additional force, if a plateau in the force was absent (i.e., a definite maximum was not achieved), or if the participant indicated they were unable to produce a maximal force. Of the 192 strength trials collected, 9 recollections occurred. Two each of the internal rotation, external rotation and abduction trials, and 3 flexion trials were recollected due to posture or because there was an indication that maximal force was not achieved.

Table 5: Arm positions for maximal isometric strength forces (Hughes et al., 1999; Stobbe, 1982)

Force Direction	Position
Flexion	- Humerus abducted 30° in the sagittal plane
Extension	- Humerus abducted 60° in the sagittal plane
Abduction	- Humerus abducted 30° in the coronal plane
Adduction	- Humerus abducted 60° in the coronal plane
Internal Rotation	- Humerus abducted 90° in the coronal plane, elbow flexed 90°, forearm neutral
External Rotation	- Humerus abducted 0° in the coronal plane, elbow flexed 90°, forearm neutral

3.3.4.4 Range of Motion

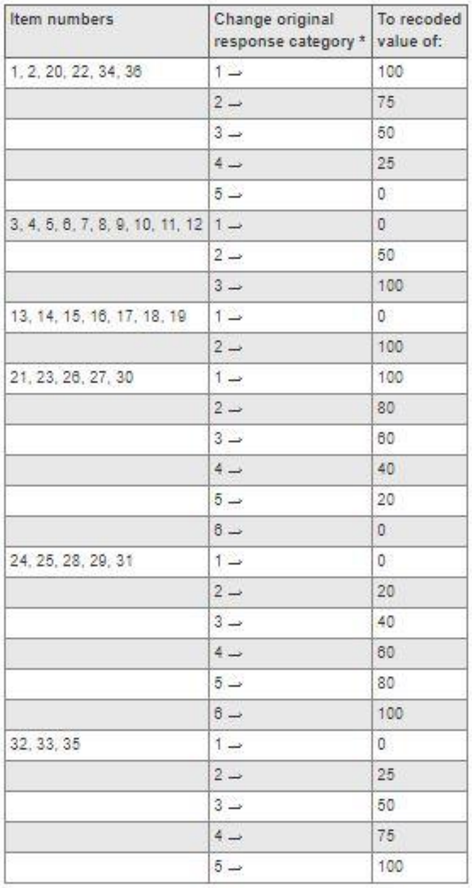
Maximal range of motion trials ensued for various movements about the shoulder. Trials were completed with both upper limbs. Participants began with their arm by their side, in a neutral position, and moved to their maximal end range for each motion. Five seconds were given for the participants to reach end range of motion, and this position was held until the end of the trial. The fundamental shoulder movements completed were flexion, extension, abduction, scapular abduction, internal rotation and external rotation. A small pole was placed for the participant to follow during flexion, abduction and scapular abduction tasks to ensure proper movement. Participants were instructed to limit trunk twist during the extension task, and were monitored closely. Any movement of the trunk resulted in a recollection of this task.

3.4 Data Analysis

This study involved data analysis of questionnaires, dual-energy x-ray absorptiometry (DXA), peak force output and range of motion. The following sections describe how each data set was processed prior to statistical analyses.

3.4.1 Questionnaires

Each questionnaire was scored as instructed by the creator of the individual questionnaire. Each questionnaire (Appendix B) had multiple sections and the ways they are scored are outlined below in Tables 6-8. The Godin questionnaire was scored by using the following equation: Weekly leisure activity = (9 X strenuous) + (5 X moderate) + (3 X light) (Godin & Shephard, 1985).



Item numbers	Change original response category *	To recoded value of:
1, 2, 20, 22, 34, 36	1 ⇀	100
	2 ⇀	75
	3 ⇀	50
	4 ⇀	25
	5 ⇀	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 ⇀	0
	2 ⇀	50
	3 ⇀	100
13, 14, 15, 16, 17, 18, 19	1 ⇀	0
	2 ⇀	100
21, 23, 26, 27, 30	1 ⇀	100
	2 ⇀	80
	3 ⇀	60
	4 ⇀	40
	5 ⇀	20
	6 ⇀	0
24, 25, 28, 29, 31	1 ⇀	0
	2 ⇀	20
	3 ⇀	40
	4 ⇀	60
	5 ⇀	80
	6 ⇀	100
32, 33, 35	1 ⇀	0
	2 ⇀	25
	3 ⇀	50
	4 ⇀	75
	5 ⇀	100

Figure 9: Recoding of RAND 36 responses (Hays et al., 1993)

Table 6: Scoring for each section of the RAND 36 Questionnaire (Hays et al., 1993)

Physical functioning	• Average questions 3-12 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
Role Limitations due to physical health	• Average questions 13-16 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
Role limitations due to emotional problems	• Average questions 17-19 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
Energy/Fatigue	• Average questions 23,27,29,31 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
Emotional well-being	• Average questions 24-26,28,30 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
Social Functioning	• Average questions 20,32 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
Pain	• Average questions 21-22 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life
General Health	• Average questions 1,33-36 after recoding (Figure 9) • Higher score indicates higher shoulder-related quality of life

Table 7: Scoring for each section of the DASH Questionnaire (Hudak et al., 1996)

Disability/Symptom score	• [(sum of n responses)/n -1] X 25 • n is the number of completed responses • Lower score is optimal
Work module	• [(sum of responses)/4 -1] X 25 • Lower score is optimal
Sports/performing arts module	• [(sum of responses)/4 -1] X 25 • Lower score is optimal

Table 8: Scoring for each section of the FACT-B Questionnaire, where n is the number of responses, and a higher scores represents higher shoulder-related quality of life (Brady et al., 1997)

Physical Well-Being (PWB)	• Each score from this section must be subtracted from 4 • [(Sum revised scores) * 7]/n • Score ranges from 0-28
Social/Family Well-Being (SWB)	• [(Sum scores) * 7]/n • Score ranges from 0-28
Emotional Well-Being (EWB)	• Each score from this section must be subtracted from 4, with the exception of question GE2 • [(Sum revised scores) * 6]/n • Score ranges from 0-24
Functional Well-Being (FWB)	• [(Sum scores) * 7]/n • Score ranges from 0-28
Breast Cancer Subscale (BCS)	• Each score from this section must be subtracted from 4, with the exception of question B4 and B9 • [(Sum revised scores) * 10]/n • Score ranges from 0-40
FACT-B Trial Outcome Index (TOI)	• PWB score + FWB score + BCS score • Score ranges from 0-96
FACT-B Total score	• PWB score + SWB score + EWB score + FWB score + BCS score • Score ranges from 0-148

3.4.2 Dual-energy X-ray Absorptiometry

Body composition measures were extracted from the scan for analysis. Body fat percentage, as well as total fat mass and total lean mass were all extracted from the report.

Additionally, lean mass, fat mass and percentage fat were exported for the left/right arm, left/right leg, trunk and head. The difference between the total mass of the left and right arm was used as a basis to identify the presence of lymphedema ($\geq$ 10% volume difference is indicative of lymphedema). Therefore, the parameters that were used for analysis were lean and fat mass and fat percentage of the unaffected and affected limb, as well as a lymphedema measure -volume difference between limbs expressed as a percentage.

3.4.3 Peak Force Output

Peak force data were extracted from each isometric strength trial. Two-point calibration was used to convert raw voltage from the system into force data. Raw force data were smoothed using a low pass, second order, dual pass Butterworth filter, with a cut-off frequency of 4Hz (adjusted to 5Hz (4/0.802) to account for the dual pass filter). This cut-off was chosen to remove high frequency noise as human movement occurs between 0-6Hz, and the strength tasks are isometric (Winter, 2009), and thus would be at the lower end of that range. Peak force was extracted from each trial using a custom MatlabTM R2020a program (Mathworks Inc., USA). These outputs represent a measure of isometric strength in each fundamental shoulder motion (flexion, extension, abduction, adduction, internal rotation, external rotation).

Raw force production (in N) was chosen intentionally. Often handheld dynamometers are used in clinics, which provide clinicians direct force measures (often in N, but can also be expressed in kg or lbs). Therefore, force production was reported, as opposed to normalized strength or shoulder moments, to provide clinical relevance. This enhances translation of the study results to rehabilitation settings. Additionally, force in newtons is an input to the model used in Study 3, so for consistency this is reported here (Dickerson et al., 2007). Finally, often force is normalized to bodyweight. This is common in lower-limb research as they are weight bearing limbs; however, it is less relevant in relation to upper-limb research.

3.4.4 Kinematic Data - Range of Motion

3D markers during range of motion tasks were tracked in VICON Nexus 1.8.5 (Vicon, Oxford, UK) and further filtered for use in calculating joint angles. Kinematic markers were labelled, and the marker trajectory of missing markers (20 frames or less than 0.4s) were pattern filled using present markers in the trial, using the Nexus software. Marker trajectories were exported for further processing. Kinematic data was dual pass filtered with a second order, low pass Butterworth filter with a cut off frequency of 4Hz (adjust to 5Hz for the dual pass filtering), as human movement occurs between 0-6Hz (Winter, 2009).

Local coordinate systems were calculated from the exported marker trajectories following defined recommendations (Wu et al., 2005) (Table 9). In order to calculate the upper arm segment, the humeral head (joint centre of the glenohumeral joint) was located. The humeral head was located by subtracting 60mm from the acromion marker along the y-axis of the torso segment (which connects the centre of SS and C7 and the centre of XP and T8) (Nussbaum & Zhang, 2000). The joint centre of the elbow is necessary for the upper arm local coordinate system and is defined as the midpoint between the lateral and medial epicondyles. The static calibration trial collected was used to develop an anatomical rotation matrix, describing the anatomical landmarks of the trunk and upper limb within the cluster coordinate systems to decrease skin motion artifact (Leardini et al., 2005; Winter, 2009). Segment rotation matrices between the anatomical and cluster axis systems were calculated using the segment cluster system relative to the anatomical local coordinate system. This relationship (between the cluster and anatomical local coordinate systems) was assumed to remain constant during all tasks.

Table 9: Segment coordinate systems, as defined by ISB standards (Wu et al., 2005)

Axis	**Torso**	**Upper Arm**
Y-axis	The line created by the centre of C7 and SS and the centre of T8 and XP, pointing upwards	The line created between the humeral head and the joint centre of the elbow, pointing upwards
Temporary axis	Temporary x-axis: line formed between SS and C7, pointing forwards	Temporary z-axis: line formed between the lateral and medial epicondyles, pointing to the right
Z-axis	Cross multiplication of the temporary x-axis and the y axis, pointing to the right	(Formed after x-axis) cross multiplication of the x and y axes, pointing to the right
X-axis	Crossing the Y and Z axes, pointing forwards	Cross multiplication of the y axis and the temporary z axis, pointing forwards

A direction cosine matrix was calculated for each time point, followed by decomposition and extracting appropriate angles. To begin a time varying rotation matrix from the global coordinate system to the local cluster system was created by using the position data from the cluster on the humerus. The final local coordinate system was found by multiplying the time varying rotation matrix by the constant relationship of the anatomical system to the cluster system. The direction cosine matrix was calculated by multiplying the transpose of the distal segment local coordinate system (humerus) by the proximal local coordinate system (thorax). These matrices were decomposed using Euler rotation sequence of Y-X-Y' (Wu et al., 2005) (Eq. 4). The rotations are described in Table 10. For each range of motion trial maximum and minimum angles for each rotation were extracted using a custom Matlab TM R2020a program (Mathworks Inc., USA). The range of motion was determined by subtracting the minimum angle from the maximum angle (Hall, Middlebrook, & Dickerson, 2011) in the relevant rotations (for abduction, scapular abduction, flexion, extension elevation angle was used, for internal and external rotation, axial rotation was used).

$$R = R_Y(\gamma)R_X(\beta)R_{Y'}(\gamma_2) \quad \text{[Eq. 4]}$$

$$R = \begin{bmatrix} (\cos\gamma\cos\gamma_2 - \sin\gamma\cos\beta\sin\gamma_2) & \sin\gamma\sin\beta & (\cos\gamma\sin\gamma_2 - \sin\gamma\cos\beta\cos\gamma_2) \\ \sin\gamma_2\sin\beta & \cos\beta & \cos\gamma_2\sin\beta \\ (\sin\gamma\cos\gamma_2 + \cos\gamma\cos\beta\sin\gamma_2) & -\cos\gamma\sin\beta & (-\sin\gamma\sin\gamma_2 + \cos\gamma\cos\beta\cos\gamma_2) \end{bmatrix}$$

Where, γ is plane of humeral elevation, β is humeral elevation, and γ_2 is humeral internal/external rotation.

Table 10: Humerothoracic rotation descriptions for rotation sequence (Y-X-Y’) (Wu et al., 2005)

Rotation	**Description**
e1 (γ) – Plane of Elevation	Glenohumeral plane of elevation (0 is pure abduction, 90 is forward flexion)
e3 (γ_2) – Axial Rotation	Internal rotation (positive); external rotation (negative)
e2 (β) – Elevation Angle	Elevation angle (negative), rotation will be expressed as positive for ease of understanding

3.5 Statistical Analysis

Prior to any statistical analysis a Grubb’s test was completed to identify outliers and these data points were removed (Grubbs, 1950). With 47 observations per variable (Table 11) and a confidence interval of 95%, a critical z-score was set at 2.87. Means and standard deviations were calculated, and a z-score was calculated for each point. Any points beyond the critical z-score threshold were removed as outliers. Two participants were removed due to missing more than 5 data points, and one participant was removed as an outlier (more than 5 data points were beyond the critical z-score).

Table 11: Dependent variables for input in cluster analysis. Variables Marked with * remained following the low variance filter. Variables bolded and marked with a $^{+}$ remained following backward feature elimination.

	Dependent Variables
General Health	• Time since treatment ended * • Age • Height • Weight • BMI
Questionnaires	• Physical activity (GODIN) * • Physical well-being (FACT-B) • Social well-being (FACT-B) * • Emotional well-being (FACT-B) • Functional well-being (FACT-B) * • Trial Outcome Index (TOI) (FACT-B) • Full Score (FACT-B) • Breast cancer subscale (FACT-B) • Disability score (DASH) * • Physical functioning (RAND-36) * • Role limitation health (RAND-36) * • Role limitation emotion (RAND-36) * • **Energy/Fatigue (RAND-36)** * $^{+}$ • Emotional well-being (RAND-36) • **Social functioning (RAND-36)** * $^{+}$ • **Pain (RAND-36)** * $^{+}$ • General Health (RAND-36) *
DXA	• Body fat percentage • Total fat mass * • Total lean mass • Lean mass (affected/unaffected limbs, trunk) • Fat mass (affected limb*, unaffected limb, trunk*) • Percentage fat (affected/unaffected limbs, trunk) • Volume difference (lymphedema score)
Peak force (affected limb)	• Abduction force * • Adduction force * • Flexion force * • Extension force * • **Internal rotation force** * $^{+}$ • External rotation force *
Active shoulder range of motion (affected limb)	• Abduction range of motion • Scapular abduction range of motion • Flexion range of motion • **Extension range of motion** * $^{+}$ • Internal rotation range of motion * • External rotation range of motion *

3.5.1 Feature Reduction

Several important factors must be identified to use cluster analysis: the observations to be included, clustering method, similarity measure, and procedure for determining the number of clusters (Blashfield, 1980). Observational features for the cluster analysis performed in this work were strength measures (6), active range of motion (6), time since treatment (1), body composition (13), age (1), height (1), weight (1), physical activity (as determined through the GODIN questionnaire) (1), and shoulder-related quality of life (as determined by questionnaire results) (17) (Table 11). Prior to completing the cluster analysis, the number of dependent variables were reduced. To begin, all data was normalized. For each dependent variable, the maximum observed in the study was determined, and each data point was divided by that maximum value. Following this a low variance filter was completed. Any variable with variance less than 0.03 was removed from inclusion into the cluster analysis. After the low variance filter, 24 of the original observations remained (Table 11). The observations removed were: age, height, weight, BMI, FACT-B (Physical well-being, emotional well-being, TOI, and full score), RAND-36 (Emotional well-being), body fat percentage, total lean mass, lean mass (affected and unaffected limbs, and trunk), fat mass of the unaffected limb, fat percentage (affected and unaffected limbs, and trunk), lymphedema score, and abduction, flexion and scapular abduction active range of motion.

The 24 variables that remained were inputted into backward feature elimination as predictors, with the response variable set as role limitation, health. This variable had the greatest variance of questionnaire results and allowed for the backward feature elimination to be run. The 5 dependent variables that were most predictive of the group of data remained for the cluster analysis (Table 11). These variables were internal rotation force production, extension range of motion, and three questionnaire variables, all from the RAND-36 questionnaire (energy/fatigue, social functioning and pain).

3.5.2 Cluster Analysis

These 5 observations were inputted into a k-means clustering method using a custom Matlab^{TM} R2020a program (Mathworks Inc., USA). k-means clustering seeks to reduce the distance between each data point and the centroid of its respective cluster, and is commonly applied to larger biomechanical data sets (Fraley & Raftery, 1998). Two to nine clusters were investigated for this thesis. Nine clusters were the maximum considered as nine possible treatment combinations exist (3 surgery types – mastectomy, breast conserving therapy/lumpectomy, lymph node dissection, and 3 surgery types – chemotherapy, radiation and a combination of the two). The silhouette method was used to determine the appropriate number of clusters (Everitt, Landau, Leese, & Stahl, 2011). The average silhouette was calculated for 2-9 clusters, and the highest average was considered the best fit. Average silhouette represents how well a point is clustered. This measure determines how similar a point is to its own cluster, compared to other clusters. Values closer to 1 represent points are in the correct cluster, where negative values represent data that is likely placed in the incorrect cluster. Average silhouettes below 0.2 are considered weak and lack evidence, whereas values above 0.5 are considered strong (Kaufman & Rousseeuw, 1990). The average silhouette for two clusters was the largest of all scenarios (0.326773), and therefore two clusters were used for analysis for this study (Table 12). Silhouette values for all data points in the two clusters are depicted in Figure 10. Final cluster results are depicted in Figure 11. Sixteen participants were allocated into each cluster.

Table 12: Average silhouette values for 2-9 clusters, where values closer to 1 indicate data is accurately clustered.

Clusters	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Average Silhouette	0.326773	0.229525	0.245196	0.204399	0.195422	0.193502	0.166886	0.216219

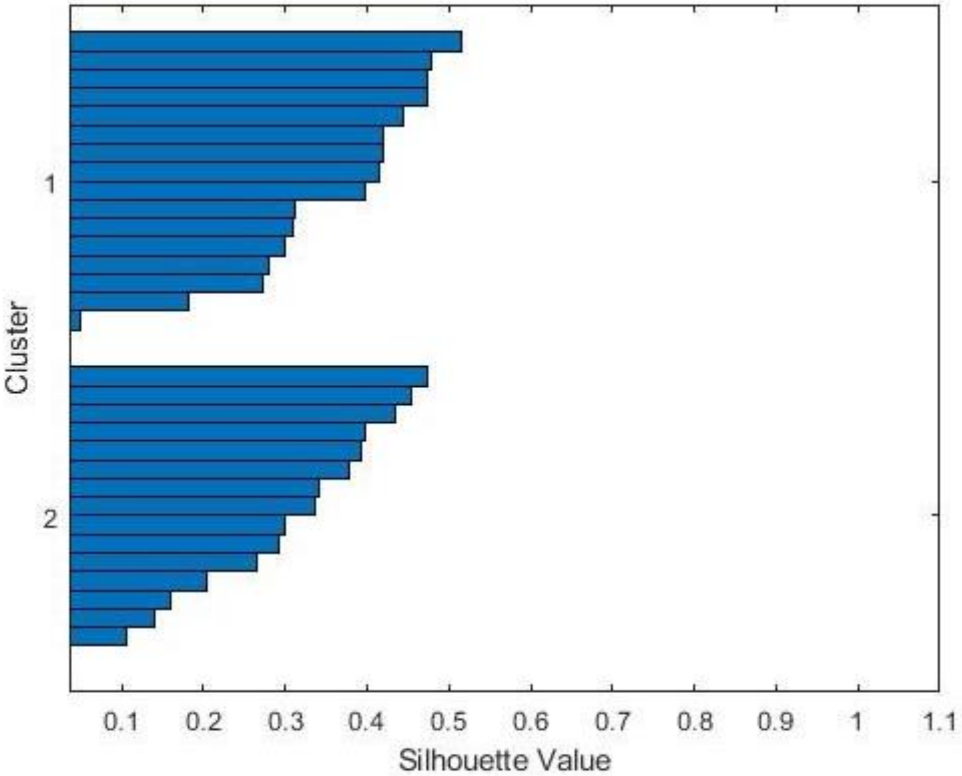


Figure 10: Silhouette scores for each data point in each of the two clusters. Values closer to one represent accurately clustered data, and negative values indicate data that is likely in the wrong cluster.

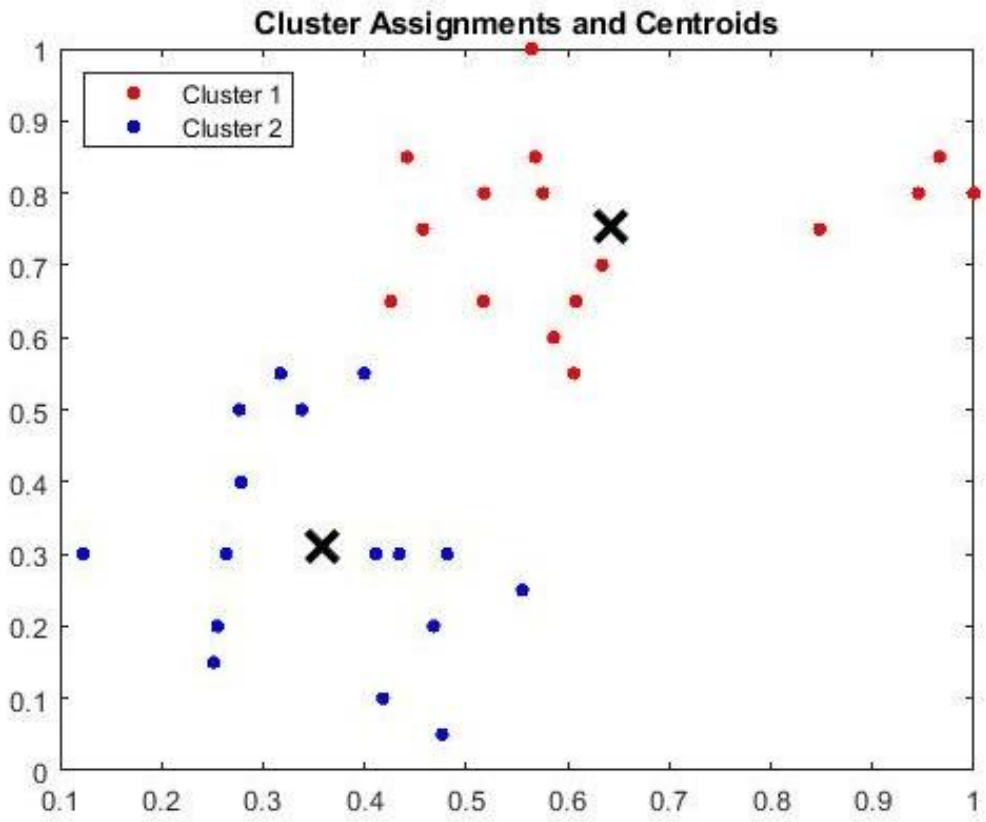


Figure 11: Cluster Analysis results where red indicates the subject is allocated to cluster one, and blue indicates cluster two. The centroid of each cluster is marked within the figure.

3.5.3 Cluster Comparison

The similarity between clusters was tested to determine the factors that separate the groups, and factors of treatment and diagnosis are listed in a table for comparison (Table 13). 47 two-tailed t-tests were used to determine the differences of each group based on strength measures, range of motion, time since treatment, body composition, age, physical activity (as determined through the GODIN questionnaire), and shoulder-related quality of life (as determined by questionnaire results) (Table 14). Significance was set at $p<0.05$. A bonferroni correction was implemented to correct for multiple comparisons (α/n) and adjusted to $p<0.001$ (0.05/47). As this study is exploratory in nature, both levels of significance are discussed to provide a clearer picture of important variables. Descriptive statistics (means and standard deviations) were determined and reported for all dependent variables. For variables where means and standard deviations were not applicable, counts are reported. All quantitative statistical analyses were completed using a custom Matlab^{TM} R2020a program (Mathworks Inc., USA).

3.6 Results

After data reduction techniques, 5 dependent variables were used to complete the cluster analysis and 2 clusters of breast cancer survivors emerged. Three participants were removed from analysis as outliers, leaving 32 participants. The diagnosis information for participants of each cluster, as well as self reported difficulties experienced by survivors in each group (Table 13). 21 of the 47 variables were significantly different between the 2 clusters with $p<0.05$, and 12 were significantly different between the clusters with $p<0.001$. Individuals in cluster one tended towards less fat mass, higher lean muscle mass, higher shoulder-related quality of life, lower perceived disability and higher force production and range of motion (Table 14-16). Absolute percent difference varied from 0.25% to 110.69% between the two clusters. Cluster one will be referred to as ‘High Score Cluster (HSC)’ and cluster two will be referred as ‘Low Score Cluster (LSC)’.

Table 13: Counts for each diagnosis variable, and self-reported difficulties in survivors.

	High Score Cluster (n=16)	**Low Score Cluster (n=16)**
Dominant /Non-Dominant	10/6	8/8
Surgery (Mastectomy/ Lumpectomy/ Lymph Node Removal)	6/8/2	3/11/2
Stage (1/2/3)	9/4/3	7/7/2
Radiation Therapy	13	16
Chemotherapy	11	8
Hormone Therapy	10	10
Shoulder Tightness	6	9
Shoulder Pain	2	6
Pain	8	12
Swelling	5	7
Self-Reported Decreased ROM	7	12
Self-Reported Weakness	5	13
Cording	5	1
Numbness	7	9
ADL difficulty	4	13
Self reported Lymphedema	5	7

There were no significant differences between the two clusters with respect to age, height and weight, as well as months since treatment (Table 14). Eight shoulder-related quality of life variables were significantly different ($p<0.001$) between the two clusters. HSC had 19.5-102.2% greater shoulder-related quality of life measures (Figure 12-14) and 110.7% less perceived disability than that of participants in the LSC (Figure 14). The HSC also participates in 34% more physical activity than the LSC (Table 14) ($p<0.05$).

Table 14: Comparison of HSC and LSC for general health measures and questionnaire results. Higher scores of GODIN, FACT-B and RAND-36, and a lower score for DASH, indicate higher shoulder-related quality of life. Variables with p<0.05 are marked with *.

	HSC (n=16)	**LSC (n=16)**	**p-value**
Months Since Treatment (months)	11.56 ± 7.81	11.53 ± 6.10	0.99
Age (years old)	56.88 ± 6.12	56.73 ± 9.00	0.96
Weight (kg)	72.81 ± 14.48	75.88 ± 14.40	0.56
Height (cm)	165.85 ± 4.09	164.77 ± 6.12	0.56
BMI (kg/m^2)	26.45 ± 5.10	27.93 ± 5.04	0.42
Physical activity (GODIN)	45.63 ± 21.69	30.07 ± 18.73	0.04 *
Physical well-being (FACT-B)	25.26 ± 2.61	19.93 ± 3.26	<0.001 *
Social well-being (FACT-B)	23.06 ± 6.97	20.53 ± 7.77	0.35
Emotional well-being (FACT-B)	20.69 ± 3.03	17.73 ± 3.45	0.02 *
Functional well-being (FACT-B)	23.13 ± 6.93	17.87 ± 3.64	0.01 *
Breast cancer subscale (FACT-B)	26.13 ± 4.73	21.47 ± 5.76	0.02 *
Trial Outcome Index (FACT-B)	74.81 ± 8.67	59.27 ± 9.15	<0.001 *
Full (FACT-B)	118.56 ± 15.98	97.53 ± 15.07	<0.001 *
Disability score (DASH)	8.18 ± 5.44	28.44 ± 14.53	<0.001 *
Physical functioning (RAND-36)	89.69 ± 10.87	60.00 ± 17.63	<0.001 *
Role limitation health (RAND-36)	87.50 ± 22.36	28.33 ± 33.89	<0.001 *
Role limitation emotion (RAND-36)	97.92 ± 8.33	60.00 ± 33.81	<0.001 *
Energy/ Fatigue (RAND-36)	75.31 ± 11.47	31.00 ± 16.06	<0.001 *
Emotional well-being (RAND-36)	74.75 ± 9.32	67.20 ± 10.92	0.05 *
Social functioning (RAND-36)	91.41 ± 14.94	70.83 ± 19.29	0.002 *
Pain (RAND-36)	77.34 ± 14.50	57.17 ± 26.51	0.01 *
General Health (RAND-36)	76.88 ± 15.48	54.33 ± 20.25	0.002 *

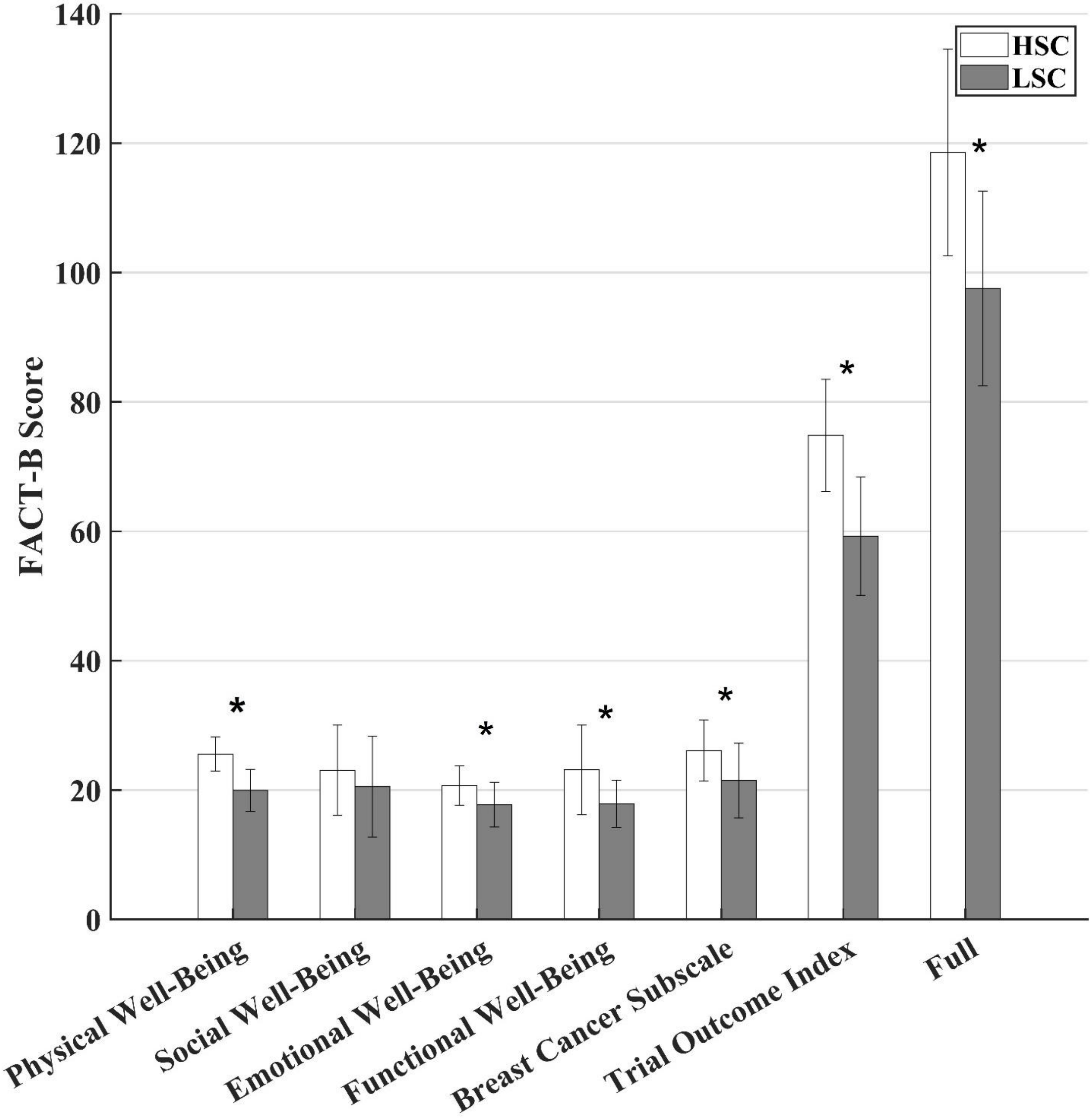


Figure 12: FACT-B scores for HSC and LSC. An * represents significant variables with a p<0.05.

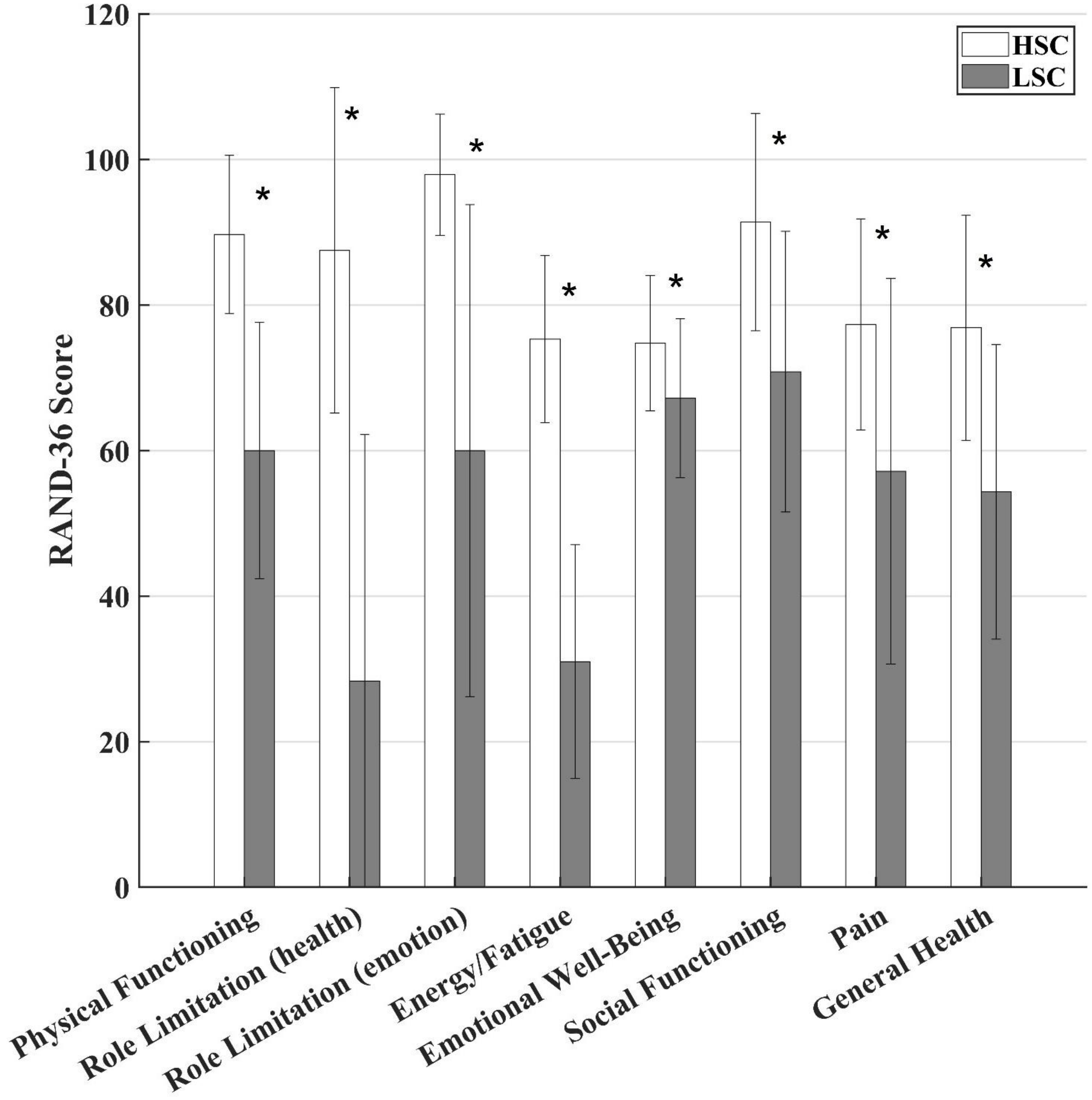


Figure 13: RAND-36 scores for HSC and LSC. An * represents significant variables with a $p<0.05$.

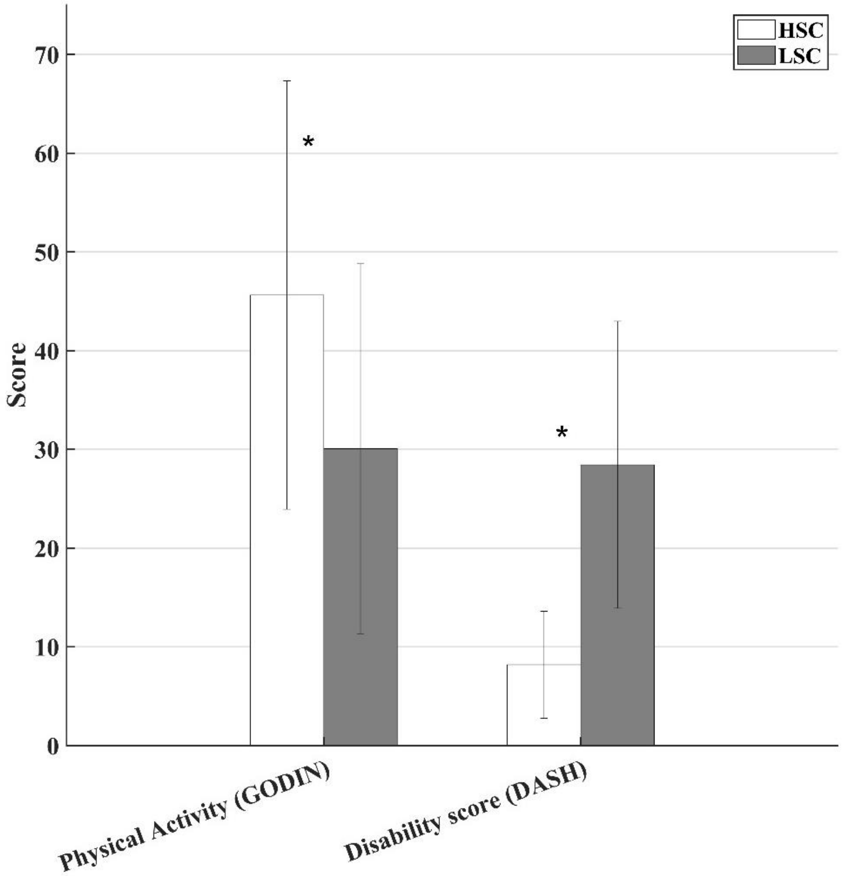


Figure 14: Scores for HSC and LSC for the GODIN and DASH surveys. An * represents variables with a $p<0.05$.

There were no body composition variables that differed between HSC and LSC at $p<0.001$; however, lean mass of the affected arm was significantly different between the two clusters ($p<0.05$). HSC tended to have less fat mass, and increased lean mass compared to LSC (Table 15). Lean mass of the affected arm was 11.50% larger in HSC compared to LSC ($p<0.05$).

Table 15: Comparison of HSC and LSC for body composition results from DXA scan. Variables with a $p<0.05$ are marked with *.

	HSC (n=16)	**LSC (n=16)**	**p-value**
Body fat Percentage (%)	38.57 ± 7.20	43.27 ± 8.04	0.10
Total fat mass (kg)	29.19 ± 11.80	35.60 ± 12.82	0.16
Total lean mass (kg)	39.66 ± 3.75	39.26 ± 3.80	0.77
Fat mass trunk (kg)	12.69 ± 5.82	15.27 ± 5.74	0.23
Lean mass trunk (kg)	20.42 ± 2.66	19.97 ± 2.18	0.61
Fat percentage trunk (%)	35.94 ± 8.88	41.15 ± 8.18	0.10
Fat mass affected limb (kg)	1.64 ± 0.59	2.03 ± 0.84	0.14
Lean mass affected limb (kg)	2.06 ± 0.32	1.84 ± 0.24	0.04 *
Fat percentage affected limb (%)	41.59 ± 8.87	48.66 ± 10.78	0.06
Fat mass unaffected limb (kg)	1.70 ± 0.63	2.17 ± 0.86	0.09
Lean mass unaffected limb (kg)	1.96 ± 0.29	1.89 ± 0.27	0.49
Fat percentage unaffected limb (%)	43.52 ± 8.19	49.95 ± 12.08	0.09
Volume Difference (Lymphedema measure) (%)	7.82 ± 5.28	8.64 ± 6.31	0.70

The two clusters differed significantly in all isometric force production measurements, and for one of the ranges of motion measurements. HSC participants produced 47.8-57.4% more force than participants in the LSC (Table 16). For force directions that were significantly different ($p<0.001$) (abduction, adduction, flexion and extension), absolute difference was largest in adduction force (82.6N), and smallest in abduction force (72.2N) (Figure 15). The other two isometric force production measures and one range of motion measure were significant at $p<0.05$. External rotation and internal rotation force were 47.8 and 53.4N larger in HSC compared to LSC, respectively. Flexion range of motion was 17.8° greater in participants in HSC, compared to LSC (Figure 16).

Table 16: Comparison of HSC and LSC for force production and range of motion (ROM) results. Variables significant with a p<0.05 are marked with *.

	HSC (n=16)	LSC (n=16)	p-value
Abduction Force (N)	161.87 ± 41.25	89.64 ± 41.32	<0.001 *
Adduction Force (N)	201.45 ± 44.66	118.89 ± 31.19	<0.001 *
Extension Force (N)	201.55 ± 50.82	123.80 ± 37.05	<0.001 *
External Rotation Force (N)	131.73 ± 45.41	83.96 ± 41.14	0.005 *
Flexion Force (N)	185.55 ± 54.95	105.77 ± 33.31	<0.001 *
Internal Rotation Force (N)	130.01 ± 56.50	76.62 ± 40.59	0.005 *
Abduction ROM (°)	160.36 ± 13.09	145.71 ± 31.70	0.10
Extension ROM (°)	54.24 ± 29.36	50.14 ± 25.60	0.68
External Rotation ROM (°)	47.66 ± 22.41	45.36 ± 15.82	0.75
Flexion ROM (°)	162.18 ± 18.01	144.46 ± 25.71	0.03 *
Internal Rotation ROM (°)	47.36 ± 15.26	40.82 ± 16.15	0.26
Scapular Abduction ROM (°)	156.35 ± 13.03	147.90 ± 26.28	0.26

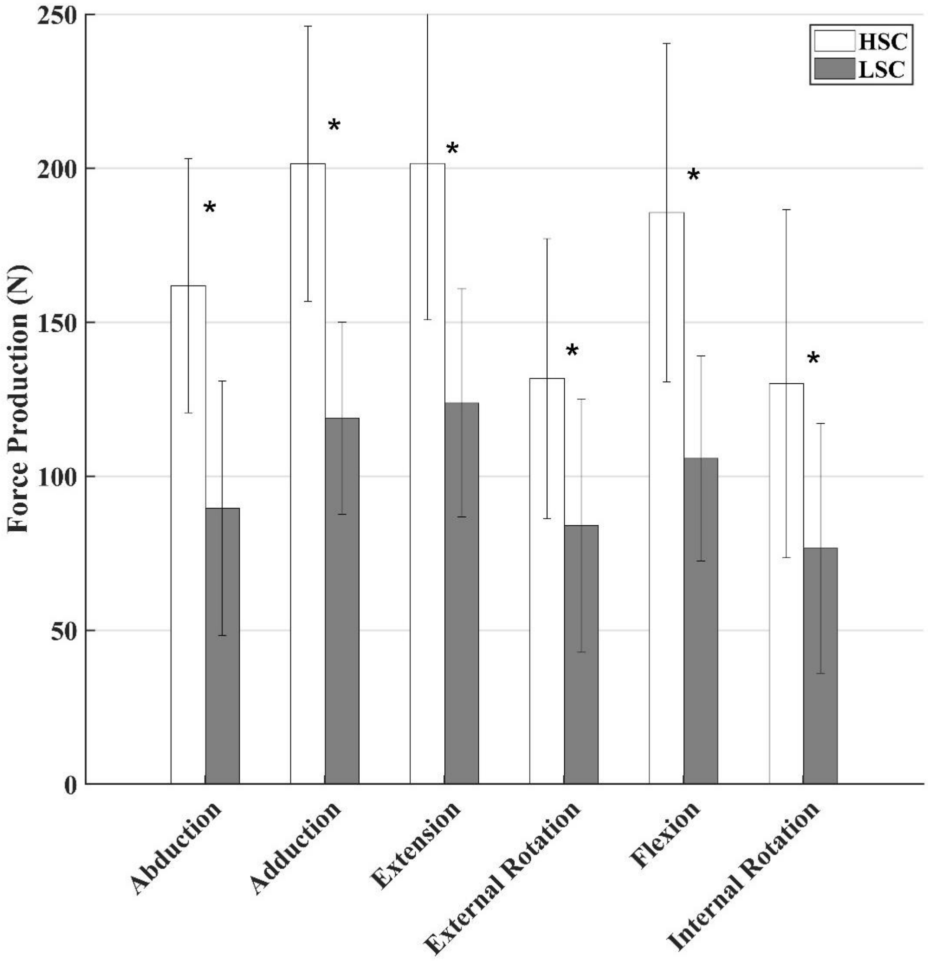


Figure 15: Isometric force production for HSC and LSC in all 6 positions. An * represents significant variables with a p<0.05.

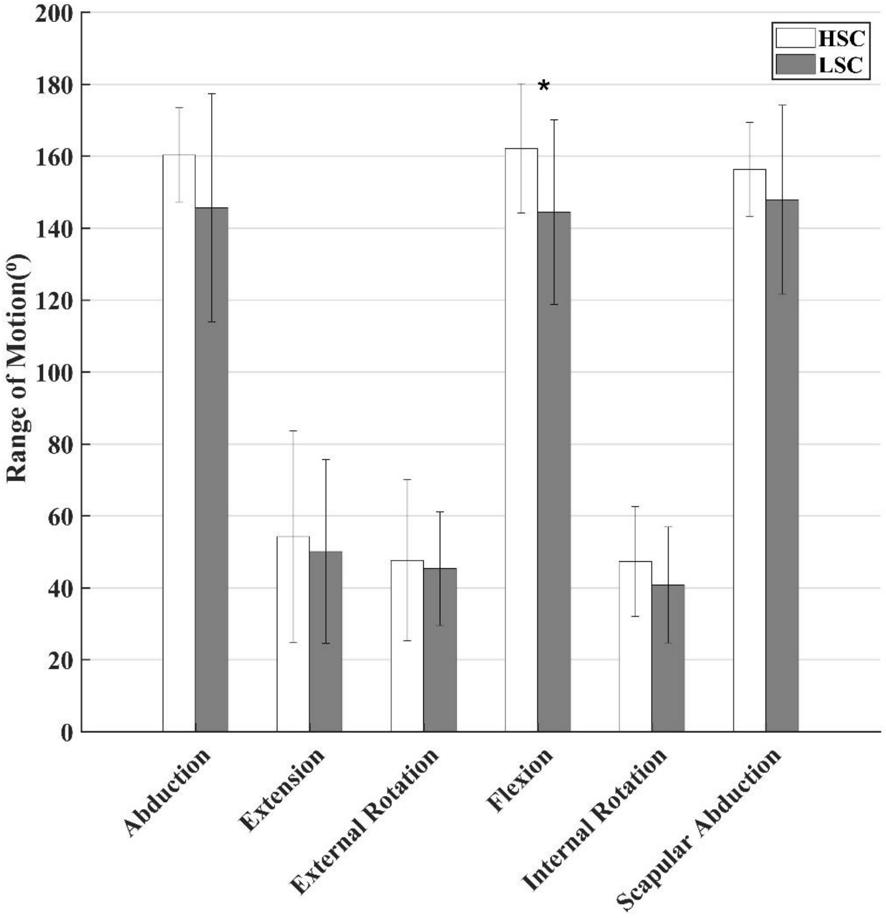


Figure 16: Range of motion for HSC and LSC in all 6 motions. An * represents variables with a p<0.05.

3.7 Discussion

This study classified breast cancer survivors into two groups (referred to in this study as HSC and LSC). The novel classification determined which measures of function (physical activity, perceived disability, strength and range of motion) were more predictive of a lower shoulder-related quality of life.

3.7.1 Classification Features

It was hypothesized that two clusters would be formed, based on physical activity, time since treatment ended, internal rotation force production, flexion range of motion, and perceived disability. Two groups were formed, however the five variables that remained after feature reduction were internal rotation force production, active extension range of motion, and 3 variables from the RAND-36 questionnaire (energy/fatigue, social functioning and pain).

Internal force production was identified as an important factor in this cluster analysis. The pectoralis major is an internal rotator (as well an adductor). Therefore, it was expected that internal rotation strength would be decreased in breast cancer survivors. The pectoralis major may be damaged through both surgery and radiation (Lipps et al., 2017). With the accumulation of damage from treatment, pectoralis major may show deficits, including loss of strength. To measure this factor, the current study investigated force production. Once the 47 factors were reduced, internal rotation force production was left as one of five variables that clustered participants into one of two clusters. A reduction in internal rotation force production following damage to the pectoralis major is expected due to its function. The HSC had 69.68% greater internal force production than the LSC. Literature supports the notion that internal rotation force could be reduced in this population (Harrington et al., 2011; Ribeiro, Camargo, et al., 2019). The current study confirmed that internal force production may be an important factor in determining whether an individual will have a higher, or lower shoulder-related quality of life.

Extension range of motion was determined as another predictor variable in this cluster analysis. One of the many functions of the pectoralis major is to assist in extension (Brown, Wickham, McAndrew, & Huang, 2007). The damage from treatment may cause scar tissue to form in the muscle affecting function and resulting in pectoral tightness (Hayes et al., 2012). Literature reports modest decreases in extension, between 5 and 10° (Harrington et al., 2011; Serra-añó, Inglés, Bou-catalá, Iraola-lliso, & Espí-lópez, 2019). Although this decrease is modest, it is indicative of the underlying tightness from the damage (Serra-añó et al., 2019). Interestingly, although this variable was identified as an important variable to cluster participants, there was no significant difference in extension between the final clusters in the current study.

Energy/fatigue (from the RAND-36 questionnaire) is the first of three variables that emerged from self reported measures. Energy, and more specifically fatigue is often cited following cancer treatment. Although most often cited following chemotherapy, fatigue from radiation returns to pre treatment levels up to 6 months following treatment (Irvine et al., 1998). Energy and fatigue routinely act as an important aspect in survivorship as up to 91% of cancer survivors report fatigue as the reason they are unable to complete daily tasks (Irvine et al., 1998). With such a large impact on daily life, energy and fatigue is logically a suitable predictor variable. Energy and fatigue scores were 142.9% higher in the HSC group (which translates to higher shoulder-related quality of life; less effects of fatigue and more energy).

The second questionnaire variable was pain (from the RAND-36 questionnaire). Pain is a commonly indicated symptom in survivors. It is reported in 31-61% of survivors, and although it may be rated as mild-moderate, its presence is still persistent and affects daily life of survivors (Lauridsen et al., 2008; Levy et al., 2012; Rietman et al., 2004; Tasmuth et al., 1995). Self reported pain occurred in 12/16 participants in the LSC (and in 8/16 in the HSC). There was a 35.3% difference in pain scores in the current study, where the HSC reported higher scores (indicating lower pain). As pain is commonly reported in survivors, it is probable that more severe pain is an indicator of reduced strength and shoulder-related quality of life, but even mild pain persists in over half of survivors that are within two years of treatment.

The final variable left after feature reduction was social functioning. Social functioning was 29.1% higher in the HSC. Social support is an important factor during cancer treatment; however, it can become complicated during and even after treatment. The main factors involved in social functioning include abilities to fulfil social roles (spouse, parent, student, employee etc.) or “household, family, social and community, self-care and occupational activities” (Bourjolly, Kerson, & Nuamah, 1999). Routine follow ups end after five years following the conclusion of treatment, and a decline is seen in both self reported social and physical functioning (predominantly in younger survivors) as there is a deficit in support (Koch et al., 2013). This decline in social functioning persists at 10 years, especially in survivors who received chemotherapy or hormone therapy (Ganz et al., 2002). The decline in support, and mounting social roles are a continued presence long after treatment ends, and are a defining element of survivorship.

It should also be noted that although these five parameters were the remaining variables, this does not mean that other variables may not be important. Rather, due to the low variance filter, and backward elimination, variables that would predict similarly are removed. It is redundant for these similar variables to be kept for the analysis, so the best predictor remains. This does not infer that these variables are unimportant, but that there may be overlapping facets of survivorship expressed within another variable.

3.7.2 Functional differences in survivors

The second hypothesis was that one group would have lower measures of shoulder-related quality of life, particularly increased perceived disability (DASH), decreased physical activity levels (GODIN), increased arm volume differences (indicative of lymphedema), and decreased lean muscle mass, strength and range of motion. Several measures of shoulder-related quality of life were indeed significantly lower in the LSC; Physical well-being and the full FACT-B scores, physical functioning, role-limitation (health and emotion), and energy/fatigue RAND-36 scores, DASH scores, and abduction, adduction, extension and flexion force production. There were minimal significant differences in active range of motion or body composition measures (flexion range of motion, and lean mass of the affected limb).

Force production is an important functional parameter in survivorship. As previously stated, force production significantly differed between the two clusters, specifically in abduction, adduction, extension and flexion. Range of motion, which is often also cited as an important factor in survivor health, did not significantly differ between the clusters. This suggests that weakness, or decreased strength had the largest effect on survivors after the conclusion of treatment. A difference of strength greater than 63.7N (6.5kg) is deemed a clinically important difference (J. K. Kim et al., 2014). Although this is based on grip strength, the exact number is not applicable, it provides a guideline for clinically measurable differences in strength. Differences between HSC and LSC in abduction, adduction, extension and flexion in the current study ranged from 72.23-82.56N, meeting this criterion. Decreases in strength have been previously linked to a decrease in shoulder-related quality of life, especially compared to non-cancer reference populations (Bertoli et al., 2020; Zabit & Iyigun, 2019). These decreases in strength may be more evident after a year following treatment (Maciukiewicz, Hussein, Mourtzakis, & Dickerson, n.d.). Differences in force production led to difficulties completing daily tasks and a return to work in a similar capacity to before treatment.

The second functional parameter investigated was range of motion. Range of motion differences were modest in the current study, below 15° for all planes of motion excluding flexion. As 15° is the smallest difference cited as clinically significant (Tengrup et al., 2000), there were no other clinically meaningful differences between the two groups. However, flexion was significant ($p>0.05$) and had a difference of 17.7° between the HSC and LSC, which may indicate importance of this movement. Decreases in range of motion have been investigated in the workplace, and lead to a loss of productivity (Quinlan et al., 2009). However, like the current study range of motion differences are complex in this population. There are clear restrictions in the breast cancer survivor population, however it is largely variable. After one year from the end of treatment only flexion and scapular abduction experienced a decrease, in comparison to individuals within one year from the end of treatment (Maciukiewicz et al., n.d.). Differences have also been cited to occur between breast cancer survivors and reference populations (Harrington et al., 2011; Lang et al., 2019; Ribeiro, Moreira, et al., 2019), however the current study indicates these differences are likely not as imperative to segregate survivors and unlikely to correspond to a decrease in shoulder-related quality of life. This is not to say that restrictions in range of motion are un-important in this population, but that strength is the more important functional parameter in this population.

Body composition differences were minimal between the HSC and LSC participants. In a review article, the impacts of treatment for breast cancer were not definitive (Sheean, Hoskins, & Stolley, 2012). There was no consistent weight increase, and any changes in weight did not relate to adipose or lean mass changes in participants. However, there was a negative impact on body composition with the use of hormone therapy (Sheean et al., 2012). Similar to range of motion, there are participants who experience these adverse effects of treatment, but the literature is equivocal regarding which participants this may affect. The current study anticipated body composition group differences, specifically decreased lean muscle mass in the affected arm of the LSC, and a decrease in force production was also hypothesized. Lean mass of the affected limb was 2.06 ± 0.32kg in the HSC, and 1.84 ± 0.24kg in the LSC (p=0.04). Overall, with no other differences in body composition, the current study supports the notion that breast cancer survivors have no discernible physical changes. As the current study had similar treatments in each group, potential treatment-derived differences are indistinguishable.

3.7.3 Treatment and self-reported deficits

The third hypothesis stated a higher percentage of participants in the LSC would present with a more invasive treatment and more advanced diagnosis stage. The participants in the LSC and the HSC had similar counts of treatment type and stage. The majority of both groups received a lumpectomy (11 and 8, respectively), and both groups had few participants diagnosed as stage 3 (2 and 3, respectively). Most participants (29/32) received radiation treatment while 50% of the LSC group, and 68.75% of the HSC received chemotherapy. Each group had 10 individuals receiving hormone therapy. The difference in counts emerged most prominently in self reported weakness, shoulder pain and ADL difficulty (Table 13). Literature is inconclusive on the effects of each treatment type on self-reported outcomes and the perceived impact of these treatments can lead to a great range of issues for survivors. Weakness is reported by survivors who have received chemotherapy and radiation (Lee et al., 2008; Markes et al., 2006). Even in the HSC in this study, individuals reported weakness and decreased range of motion although the measured data did not corroborate this. This can be attributed to the variety of force production for each of these measures, as self reported weakness is not specific to any one plane of motion. However, the LSC had larger numbers of self-reported weakness and range of motion and increased pain. Participants in the LSC also had worse shoulder-related quality of life, specifically in physical functioning (33.1%), role limitation (38.7% emotional, 67.6% health) and energy/fatigue (58.8%). They also reported more difficulties with activities of daily living. This supports the notion that survivors who perceive weakness or restriction in their affected arm feel they cannot complete tasks that affect their ability to fulfill important roles in their lives (work and home life) (Lee et al., 2008; Markes et al., 2006). A rather low association between shoulder-related quality of life and range of motion was identified in literature (Rietman et al., 2003). Although there were associations between difficulties completing daily tasks and morbidity of the upper arm, clinical significance was absent and therefore could not be attributed to range of motion. This supports the current finding that range of motion did not differ between groups. Although these restrictions are apparent in this population, range of motion is not the most important factor that quantitatively relates to overall shoulder-related quality of life. The current study results suggest weakness (both measured and self-reported) is more important to differentiate shoulder-related quality of life amongst survivors. Previously, strength of the shoulder girdle related to decreases in shoulder-related quality of life (Harrington et al., 2011, 2013). Overall, these associations support that weakness after treatment could be an important factor in survivorship.

3.7.4 Comparison to non-cancer population

Aging affects the musculoskeletal system in several ways. The population in the current study had an average age of ~ 57 years of age (56.9 and 56.7 for the HSC and LSC, respectively). Studies on younger populations often focus on participants under 40, and aging population studies on individuals over the age of 65, placing the current study population in between. It can be inferred that aging had some affect on our participants, but the loss of strength due to aging may not be overwhelming. Median muscle mass loss over the age of 45 is approximately 0.37% per year (and accelerates over 75 years) (Mitchell et al., 2012). Strength is lost 2-5 times faster than mass in the aging population (Mitchell et al., 2012). A loss in skeletal muscle mass and strength is associated with functional impairment and disability, especially in women (compared to men) (Avin, Tumuluri, Looft, & Frey-Law, 2015; Janssen, Heymsfield, &

Ross, 2002). The difference in strength in 40 and 60 year old women ranged from 32.8-50.0% (Hughes et al., 1999). In the current study the difference between the two clusters ranged from 47.8-57.4% (Table 16). The participants in the current study ranged in age from 35 to 74 years old, but averaged at 57 years old. Unfortunately, due to the COVID-19 pandemic, an age-matched non-cancer reference population was infeasible to collect. Further research is needed to determine whether the HSC in the current study approximates a non-cancer reference population, or deficits exist for all survivors following treatment.

3.8 Limitations

Study results should be considered within the context of several limitations. First, the study had a relatively small sample size. A larger sample may have decreased the variability and increased the difference between the two cohorts. Additionally, variability within each treatment (drugs used, doses given, surgeon completing the surgery) may cofound the results of the current study. However, the heterogeneity of this population can also be considered a strength to determine which factors have a larger influence on survivors' lives. Further, no repetitions were completed for range of motion or strength trials, unless deemed necessary by a researcher (deviation in posture, force did not plateau), or participants (maximum was not reached). This was controlled to avoid any unnecessary pain, or any fatigue that may mitigate results in this population.

3.9 Conclusions

Breast cancer survivors have different experiences after treatment. Wide variance typifies treatment types, force production, range of motion, body composition and shoulder-related quality of life. However, the relationship between these variables, and more importantly which variables might distinguish which survivors may need more rehabilitation remains unclear. The feature reduction in the current study determined that internal rotation force production, active extension range of motion, and 3 variables from the RAND-36 questionnaire (energy/fatigue, social functioning and pain) successfully distinguished survivors within 2 years of treatment into two clusters. Several factors differed between the two clusters or groups. The HSC participants had lower self-reported disability, role limitation (health and emotion), fatigue, and higher self reported physical well-being, along with increased abduction, adduction, extension and flexion force production ($p<0.001$). Several other factors differed significantly ($p<0.05$), including lean mass of the affected arm, physical activity, internal and external force production and active flexion range of motion. This explorative investigation is helpful to clinicians and physiotherapists to assist in determining individuals to target rehabilitation efforts. This study determined that participants with lower self-reported shoulder-related quality of life likely also produce lower maximal force. These associated with more reported difficulties with ADLs, and therefore should be factors that are addressed in a rehabilitation program. Little research has been completed on these factors and their affect on low load daily tasks in this population, prompting the work described in the next chapter (Ch. IV) of this dissertation.

Chapter IV - Kinematic and Muscular Activation Differences between Breast Cancer Survivors During Activities of Daily Living (ADLs)

4.1 Introduction

Functional activities performed by clinical populations are often characterized with discrete data points, neglecting additional information that may be contained in considering the entire movement. Statistical parameter mapping (SPM) enables multi-dimensional time-series biomechanical data analysis as opposed to discrete data. Friston et al (1991) began using this technique in image data by comparing pixels of brain scans to one another to determine regional differences (Friston, Frith, Liddle, & Frackowiak, 1991). This technique has garnered much attention recently in biomechanics as it allows comparison of time-series data. Although it appears to have a multiple comparison problem, by using gaussian random field theory SPM corrects p-values for the entire volume of the data set (Worsley, Evans, Marrett, & Neelin, 1992). Hughes-Oliver et al (2019) used SPM to locate portions of a stop-jump task that differed between limbs in a group of participants with anterior cruciate ligament reconstruction. Discrete data may often indicate differences, however SPM more specifically identified bilateral differences at the ankle during the landing phase of the jump task, where the surgical limb had increased peak eversion (44.7%), but decreased peak inversion (67.3%) compared to the non-surgical limb (Hughes-Oliver, Harrison, Williams, & Queen, 2019). Similarly, during early weight acceptance in a stair descent task differences existed during hip flexion/extension and abduction/adduction between participants who received reconstruction for ACL injuries vs individuals who only received physiotherapy (Sole, Pataky, Tengman, & Häger, 2017).

Investigations in breast cancer survivors have generally focused on discrete data points during various tasks. Recent reports indicate that during various activities of daily living breast cancer survivors used less elevation and rotation on their affected side (Brookham et al., 2018a). Further, during ADLs, breast cancer survivors experienced higher muscular demand than reference participants (Brookham & Dickerson, 2016; Galiano-Castillo et al., 2011; Shamley et al., 2012). Differences in total muscular effort vary substantially across ADLs and work tasks. Generally, discrete data showed similar muscular effort, but during some tasks differences occurred between the affected and unaffected limbs (Brookham et al., 2018b). However, these discrete points did not explain the temporality of these differences during the movement, making clean comparisons difficult. Lang et al. (2019) reported discrete data points during functional tasks comparing breast cancer survivors and reference participants, and accompanied these with plots to describe when these differences were occurring. At extreme postures, survivors with impingement pain had decreased humeral abduction and internal rotation (Lang et al., 2019). As these postures could have serious implications for potential injury mechanisms, it is important to consider when these occur during daily tasks to help identify potential risks for survivors.

4.2 Objective and Hypotheses

The objective of study 2 was to determine if differences existed in kinematic strategies and muscular activation patterns in two a priori defined groups of survivors (by study 1).

The following hypotheses were posed for study 2:

1. Differences will exist between the two clusters of breast cancer survivors during activities of daily living in elevation angle and plane of elevation specifically that the higher functioning score cohort (per study 1) will use more elevation angle

and plane of elevation during tasks (particularly during tasks with external weights)

2. Muscular activation will differ for muscles of the affected arm throughout various ADL tasks between groups of breast cancer survivors. Specifically:
    a. The lower functioning cohort (per study 1) will activate pectoralis major and latissimus dorsi more to completed the same task, due to damage of these muscles (Lipps et al., 2017)
    b. The lower functioning cohort (per 1) will increase activation of muscles less likely to be damaged by radiation (deltoids, supraspinatus, infraspinatus) during ADL tasks (particularly tasks with external weights)

4.3 Methods

4.3.1 Participants

Data generated within study 1 (Chapter III, Section 3.3.1, page 40) contributed to study 2. The results from study 1 formed the two groups of survivors analyzed in study 2.

4.3.2 Motion Capture Instrumentation

Motion capture instrumentation was identical to that described in study 1 (Chapter III, Section 3.3.2, page 41).

4.3.3 Surface Electromyography Instrumentation

Eight upper extremity muscles were collected bilaterally (total of 16 muscles) with the Noraxon T2000 telemetered system (Noraxon, Arizona, USA). Prior to placement of electrodes, the skin overlaying each muscle was shaved and cleansed with alcohol to reduce impedance (Cram & Kasman, 1998). Noraxon bi-polar Ag-AgCl dual surface electrodes with a fixed 2cm inter-electrode spacing was placed over the muscle belly of each muscle based on published standards (Table 17). Specifically, anterior, middle and posterior deltoids, pectoralis major (clavicular and sternal insertions), infraspinatus, supraspinatus, and latissimus dorsi were monitored. A ground electrode was placed over the clavicle. Surface EMG was recorded at 1500Hz within the VICON Nexus 1.8.5 software (VICON, Oxford, UK). Following electrode placement, isometric maximal voluntary contractions (MVCs) for each individual muscle was performed. Participants performed specific exertions in postures that elicit the greatest isometric activity for each muscle as outlined in Table 17 (Cram & Kasman, 1998; Daniels & Worthingham, 1986). Raw EMG signals were band pass filtered from 10-500Hz and differentially amplified (common-mode rejection ratio >100 dB at 60Hz, input impedance 100MΩ) to generate maximum signal amplification. EMG signals were A/D converted at 1500 samples/second using a 16-bit A/D card with a ±3.5V range.

Table 17: Electrode placement and MVC postures (Cram & Kasman, 1998; Daniels & Worthingham, 1986)

Muscle	Placement	MVC Posture
Anterior Deltoid	4 cm below the clavicle, on the anterior aspect of the arm, parallel to the muscle fibers	Seated, Shoulder flexed forward to 90º, elbow fully extended, participant pushes upwards
Middle Deltoid	Lateral aspect of the upper arm, and approximately 3 cm below the acromion, parallel to the muscle fibers	Seated, Shoulder abducted to 90º, elbow fully extended, participant pushes upwards
Posterior Deltoid	2 cm below the lateral border of the spine of the scapula and angled on an oblique angle toward the arm	Subject lays prone, shoulder is abducted 90º, externally rotated, participant pushes upwards
Pectoralis Major (clavicular insertion)	Placed on the chest wall at an oblique angle toward the clavicle, approximately 2 cm below the clavicle, just medial to the axillary fold	Subject lies supine, elbow and shoulder are flexed to 90º, participant exerts upwards and inwards
Pectoralis Major **(sternal insertion)**	Medial to the axillary fold with the arm medially rotated, horizontally on the chest wall, over the muscle mass 2 cm out from the axillary fold	Subject lies supine, elbow and shoulder are flexed to 90º, participant exerts upwards and inwards
Infraspinatus	4cm below, and parallel to the spine of the scapula, on the lateral aspect of the infrascapular fossa	Elbow bent to 90º; participant externally rotates
Supraspinatus	Directly above the spine of the scapula on the distal lateral aspect, over the suprascapular fossa	Participant lays on their side, elbow fully extend, shoulder abducted 10º, participant abducts arm
Latissimus Dorsi	Approximately 4 cm below the inferior angle of the scapula, half the distance between the spine and the lateral edge of the torso, oriented slightly oblique at approximately 25°	Seated, shoulder is abducted to 90º and elbow flexed to 90º, participants adducts arm

4.3.4 Experimental Protocol

The experimental protocol for study 2 was implemented within the collection for study 1. Prior to the aforementioned strength trials, electrode placement took place for both the affected and unaffected limbs. Participants performed MVCs for each muscle, for a total of 16 exertions (Table 17). There was a minimum of two minutes of rest between each exertion to avoid fatigue (Chaffin, 1975). Extra time was given between trials at the participant's request.

Participants completed the collection protocol by performing ADLs (following all tasks for Study 1). These tasks were completed with both the affected and unaffected limb; however, some tasks required both limbs. Each trial was completed twice, for a total of 24 trials. For the purposes of this thesis, only the affected limb is analyzed.

4.3.4.1 Activities of Daily living

Eight ADL tasks (Table 18) were assessed to provide an overview of function in ADL tasks. Where possible, targets and props were used to help decrease variability and increase realism in tasks (Taylor et al., 2018). The various tasks spanned both general tasks and those more frequently performed by women. More challenging tasks were not targeted to avoid fatigue effects in these individuals. Each task began with the participants' hands placed on a table in front of them. The trial ended with the participants' hands returning to the resting position. Five second trials were collected to allow the participant enough time to fully finish the motion and return to a resting position. Data was cut to begin and end when the participant is in motion, to allow for comparison of the active motion of the trial. Kinematic data was filtered first (described below in Section 4.4.1) and then used to crop the time-series joint angles, and EMG data. The mean and standard deviation of acceleration of the wrist (the midpoint between the ulnar styloid and radial styloid) during static trials was calculated. Three standard deviations from the mean was set as the threshold for movement. Once movement acceleration was greater than this threshold, movement had begun, and once the acceleration was less than this, the trial had ended. These time points were exported for each trial to use to cut both the kinematic and EMG data.

Table 18: Description of activities of daily living

Activity	Explanation
Hand to ipsilateral back pocket (unilateral task)	In a resting seated posture, the participant reached and touched the ipsilateral back pocket and return to resting
Reach to shelf at shoulder height (unilateral task)	In a seated posture the subject grasped a weighted object, lift it to the shelf at shoulder height, release, and then return it to resting position. The subject completed this with a weight of 1kg.
Forward reach (unilateral task)	In a seated posture the subject grasped a weighted object, reached to 80% of arm length, released, and then returned to a resting position. The subject completed this with a weight of 1kg.
Lift shopping bag (bilateral task)	From a standing position, subjects reached to the ground to lift a weighted (5kg) shopping bag from the floor to a table, then returned it the floor.
Pour from pitcher (unilateral task)	In a seated posture the subject started with the hand resting on the table, then reached for the handle of a pitcher, filled a cup, set the pitcher down and returned to the resting position.
Reach with weighted tray (bilateral task)	From a standing position, the subject started at rest, reached out and lifted a weighted (2kg) tray from a table, turned a quarter turn and placed the tray on a shelf below. The subject lifted the tray and returned it to the resting position.
Bra fasten (bilateral task)	In a seated posture the subject reached with both arms behind the torso to touch where the bra fastens in the back, then returned the arms to the starting position.
Put on necklace (bilateral task)	In a seated posture subjects picked up an unfastened necklace, reached behind the neck and fastened the necklace then returned the arms to the starting position.

4.4 Data Analysis

4.4.1 Kinematic Data Processing

Kinematic data were tracked and filtered for the ADL trials in the same fashion as the range of motion trials in Study 1 (outlined in section 3.4.4, page 52). Segment coordinate systems were calculated following ISB recommendations (Wu et al., 2005) (section 3.4.4, Table 9, page 53). The difference in processing occurred in calculating the joint angles. Once the direction cosine matrix was calculated (multiplying the transpose of the distal segment (humerus) by the proximal segment (thorax)), the matrices were decomposed using an XZY rotation sequence (Eq.5) to avoid common gimbal lock at 0° when using ISB standard YXY’ (Phadke, Braman, LaPrade, & Ludewig, 2011; Šenk & Chèze, 2006) (Table 19). This mimics previous studies looking at kinematic motion in clinical populations (Lang et al., 2019). Time series joint-angles for all three rotations were exported for further analysis. Data was cut as described in Section 4.3.4.1.

$$R = R_x(\alpha) R_z(\beta) R_y(\gamma) \tag{Eq. 5}$$

$$R = \begin{bmatrix} \cos\gamma\cos\alpha & (\cos\gamma\sin\alpha\cos\beta + \sin\gamma\sin\beta) & (\cos\gamma\sin\alpha\sin\beta - \sin\gamma\cos\beta) \\ -\sin\alpha & \cos\alpha\cos\beta & \cos\alpha\sin\beta \\ \sin\gamma\cos\alpha & (\sin\gamma\sin\alpha\cos\beta - \cos\gamma\sin\beta) & (\sin\gamma\sin\alpha\sin\beta + \cos\gamma\cos\beta) \end{bmatrix}$$

Where, α is humeral elevation, β is plane of elevation and γ is axial rotation.

Table 19: Humerothoracic rotation descriptions for rotation sequence (XZY) (Phadke et al., 2011; Šenk & Chèze, 2006)

Rotation	**Description**
e1 (α) – Humeral Elevation	Axis fixed to the thorax and coincident with the X-axis of the thorax system; elevation (+); depression (-)
e3 (γ) – Axial Rotation	Axial rotation around Y-axis of the humerus; internal rotation (+); external rotation (-)
e2 (β) – Plane of Elevation	Common axis perpendicular to e1 and e3 (the rotated Z-axis of the humerus; horizontal flexion (+); horizontal extension (-)

4.4.2 sEMG Processing

EMG was analyzed in the time domain. Resting bias was removed from the signal of each muscle by subtracting the mean of the raw trial from each time point. A high pass, second order, dual pass Butterworth filter, with a cut-off frequency of 30Hz was applied to reduce heart rate contamination from all trials (Drake & Callaghan, 2006). The signal was full wave rectified and low pass filtered using a second order, single pass Butterworth filter, with a cut-off frequency of 2.5Hz (Brookham & Dickerson, 2016). sEMG was normalized to muscle specific maximums. Each trial was visually inspected to ensure the signal was clean from any noise, or other adverse events. Data was cut with the time points exported as described in Section 4.3.4.1. For all ADL tasks, time-series data was exported as %MVC using a custom Matlab^{TM} R2020a program (Mathworks Inc., USA) for use in analysis.

4.5 Statistical Analysis - Statistical Parameter Mapping

SPM was used to compare the groups determined in study 1 (Section 3.5). SPM one-way ANOVAs were used to identify potential differences between groups over the entire duration of each trial. Open source code previously used in biomechanical data was used to complete the statistical analysis (Pataky, 2012). All 3 thoracohumeral rotations (plane of elevation, elevation angle and axial rotation) along with 8 muscles (anterior, middle and posterior deltoids, pectoralis major (clavicular and sternal insertions), infraspinatus, supraspinatus, and latissimus dorsi) of the affected side were investigated for each ADL. Kinematic and EMG data were time normalized, where the start of the trial was set to 0, and the end was set to 1 to avoid bias in the signal due to shifts in timing of events. Each time point was divided by the total time to represent the relative time for each data point. The p value was set at $p<0.05$ for each comparison. Z-scores were outputted for each time point during each task for comparison. A critical Z-score was determined for each trial, where data beyond this score were considered statistically significantly different at the corresponding time point.

4.6 Results

Results are presented across all 8 activities of daily living, by ADL. Kinematic data is presented for each of the three planes of thoracohumeral motion. In all trials 0° of plane elevation (also referred to as horizontal abduction) indicates pure abduction, and 90° is in front of the body (flexion), positive elevation angles indicate elevation, and positive axial rotations indicate internal rotation. sEMG data is presented for 8 muscles – pectoralis major-clavicular insertion (PEC(C)), pectoralis major-sternal insertion (PEC(S)), anterior deltoid ((A)DEL), middle deltoid ((M)DEL), posterior deltoid ((P)DEL), infraspinatus (INFRA), supraspinatus (SUPRA), and latissimus dorsi (LATS).

4.6.1 Pocket

Both groups performed similarly when reaching to the ipsilateral back pocket. Plane of elevation, elevation angle and axial rotation were statistically the same through the entire task (Figure 17). Plane of elevation remained on average between 50 and 70° for both groups. Elevation angle ranged from 30 to 65°, and axial rotation ranged from 50 to 60° (Figure 17). As participants reached back elevation increased to allow the hand to reach back, and remained in an internally rotated posture.

PEC(C), PEC(S), (M)DEL, and (P)DEL were similarly activated through the entirety of the task (Figure 18). All four muscles were, on average, less than 20% MVC while reaching to the ipsilateral back pocket. SUPRA and LATS were statistically similar for both the HSC and LSC (Figure 18). However, the LSC had a greater amount of variability for these muscles, with 1SD reaching as high as 40% MVC (Figure 18). In two instances, INFRA was statistically more activated in the LSC than the HSC (between 21.5-32.2% of the task, and 69.9-83.8%). During these times, the LSC participants required 3.50-5.41% MVC, and 3.19-5.04% MVC more activation than the HSC participants (Figure 18). Similarly, (A)DEL was statistically different from 16.8-25.1% and 28.1-36.4% of task completion (Figure 18). At these times the LSC required 2.32-3.06% MVC and 1.89-2.62% MVC more than the HSC participants (Figure 18).

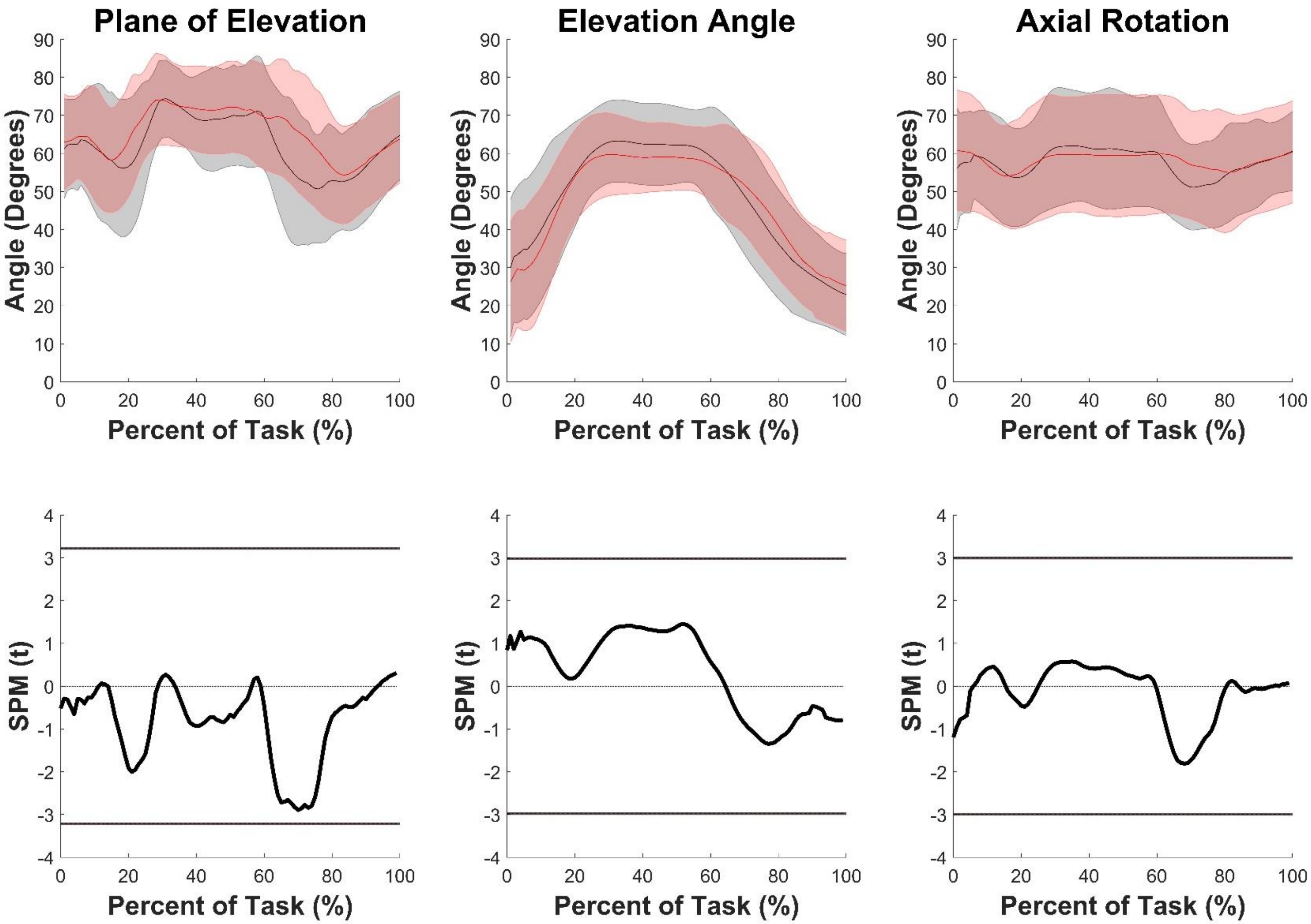


Figure 17: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the reach to back pocket task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

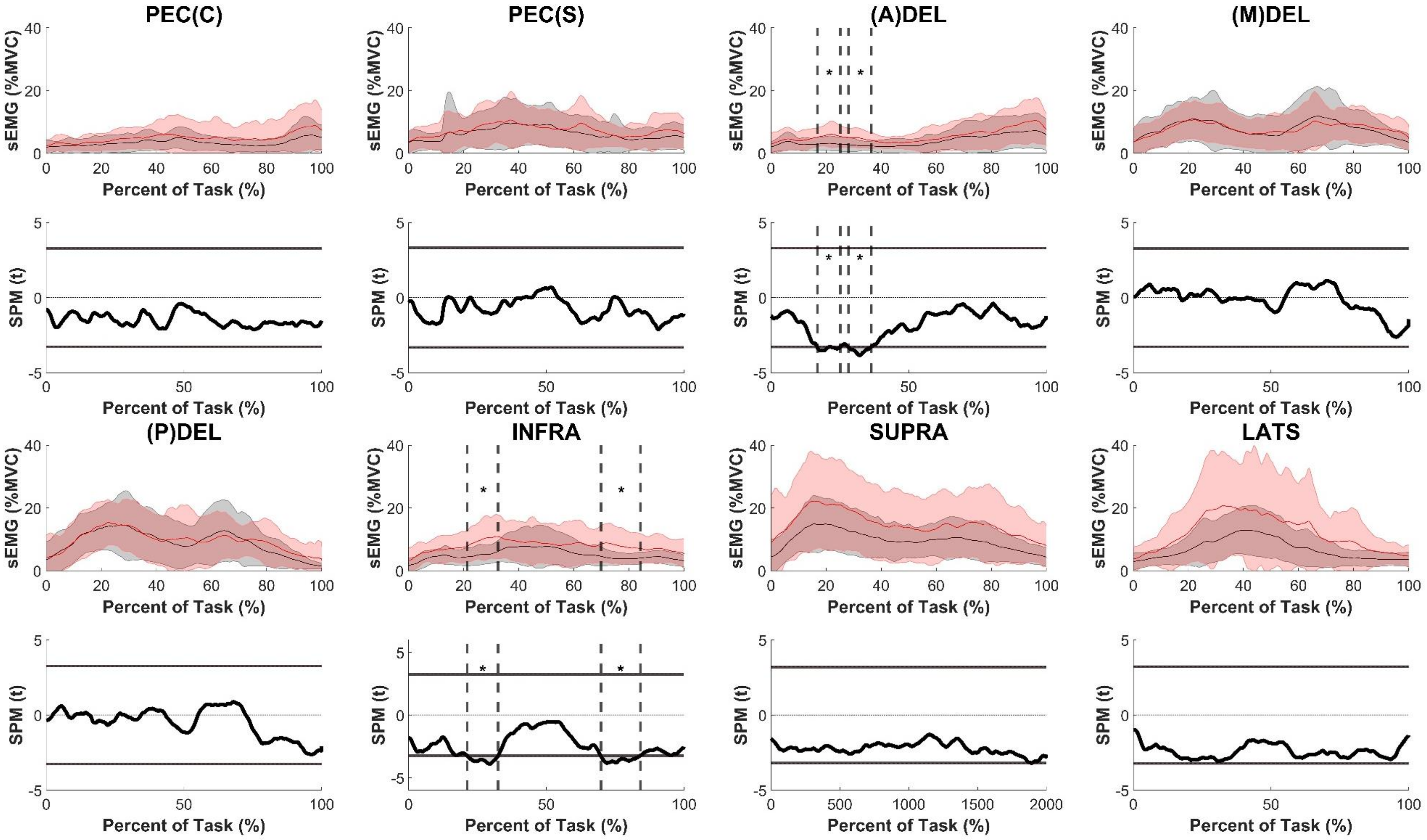


Figure 18: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the reach to back pocket task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.2 Shelf Reach

In plane of elevation and elevation angle, the HSC and LSC groups performed similarly (Figure 19). Participants remained within 25-70° (on average) in plane of elevation, and 20-80° of elevation angle (Figure 19). Although not significant, the LSC exhibited a reduced range in both plane of elevation and elevation angle, compared to the HSC. From 28-37% of task completion, there was a difference of 11.5-12.7° in axial rotation between the HSC and LSC (Figure 19). Similarly, to plane of elevation, and elevation angle, the LSC used a smaller range of axial rotation, compared to the HSC, where the HSC externally rotated closer to a neutral position (although both groups remained internally rotated).

Muscular activation of 4 muscles were statistically similar across the entirety of the reach up to the acromion level shelf (Figure 20). (M)DEL, (P)DEL, INFRA and SUPRA were the same in LSC and HSC across the entire task. On average (M)DEL and (P)DEL were below 20% MVC for the entire task (Figure 20). Although not statistically different, the LSC had variability of the INFRA and SUPRA muscles, while still remaining less than 20% MVC for the task (Figure 20). PEC(C) was statistically more activated in the LSC than the HSC between 57.3-59.7% of the task, requiring 4.96-5.46% MVC more activation than the HSC participants (Figure 18). Similarly, LATS was statistically different from 96.8-100% of task completion requiring 3.35-5.43% MVC more from the LSC participants than the HSC (Figure 18). In three instances the PEC(S) was more activated in the LSC group (44.4-49.1%, 82.2-83.9%, and 96.2-100% of task completion). (Figure 18). During all 3 areas, the LSC required 3.35-4.7% MVC more activation than that of the HSC (Figure 18). Finally, (A)DEL differed in four instances (39.5-45.9%, 49.7-71%, 73.3-76.8% and 80.1-86.7% of task completion). At these times the LSC required 7.87-12.73% MVC more activation than the HSC to complete the lift of a 1kg bottle (Figure 18).

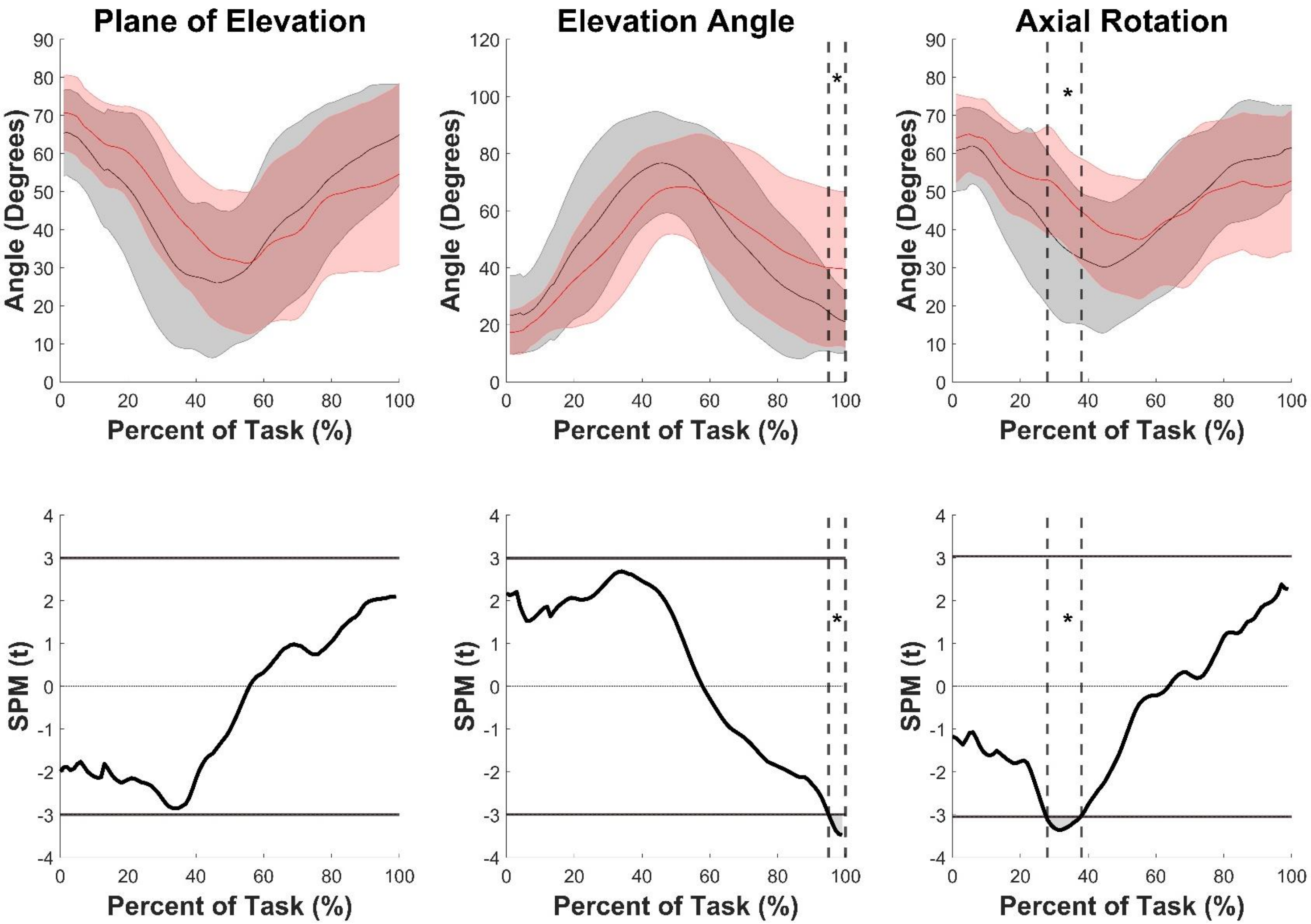


Figure 19: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the shelf reach (with 1kg weight) task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

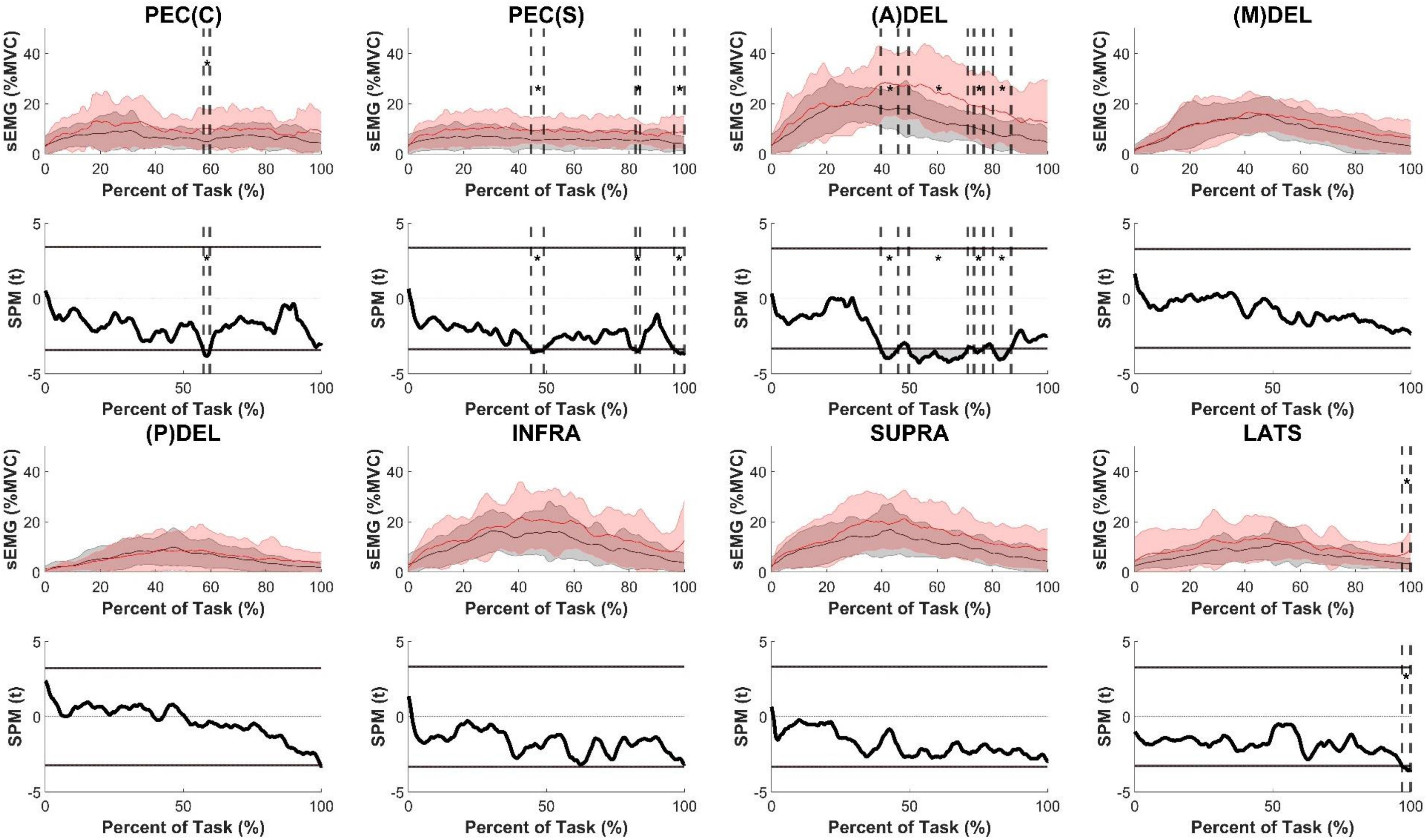


Figure 20: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the shelf reach (with 1kg weight) task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.3 Forward Reach

Plane of elevation, and axial rotation were relatively unchanged throughout the reach forward and back with a 1kg weight (Figure 21). As this task was a reach forward and back, limited changes were anticipated for these angles. Plane of elevation remained between 60-70° for both the HSC and LSC (the bottle was placed to the side of the participant, not directly in front) (Figure 21). Axial rotation also remained between 60-70° for both the HSC and LSC, indicating participants remained in an internally rotated posture (Figure 21). From 59-90% of task completion, the LSC had higher elevation than the HSC (Figure 21). The LSC was 7.5-11.4° higher than the HSC (at 26.1-38.7° and 18.4-28.2°, respectively).

Muscular activation of PEC(C) and PEC(S) were statistically similar during the entire forward reach task (Figure 22). Though not statistically different, the LSC had greater activation and variability across the entire task for both muscles (Figure 22). (A)DEL was statistically different from 43.1-86.3% of task completion, where HSC was activated 3.97-14.98% MVC, while the LSC was activated 11.31-23.46%MVC (Figure 22). (M)DEL differed from 54.7-82.3% of task completion, with LSC activated 3.11-7.29%MVC more than the HSC (Figure 22). (P)DEL differed in two instances, from 0-8.4% and 69.2-75.7% of task completion, where the LSC required 0.89-2.38%MVC more muscular activation than the HSC (Figure 22). Similarly, the LATS differed from 0.5-6.2% and 58.6-63% of task completion, with 2.97-3.59% more activation of the LSC than the HSC (Figure 22). INFRA differed on three instances, 0-9.3%, 37.8-50% and 54.3-85.7% of task completion, differing 3.11-8.69% MVC between clusters (Figure 22). Finally, SUPRA differed on three instances, 1.2-8.1%, 69.5-72.8% and 78-82.5% of task completion where the LSC required 3.51-6.53% MVC than the HSC participants (Figure 22).

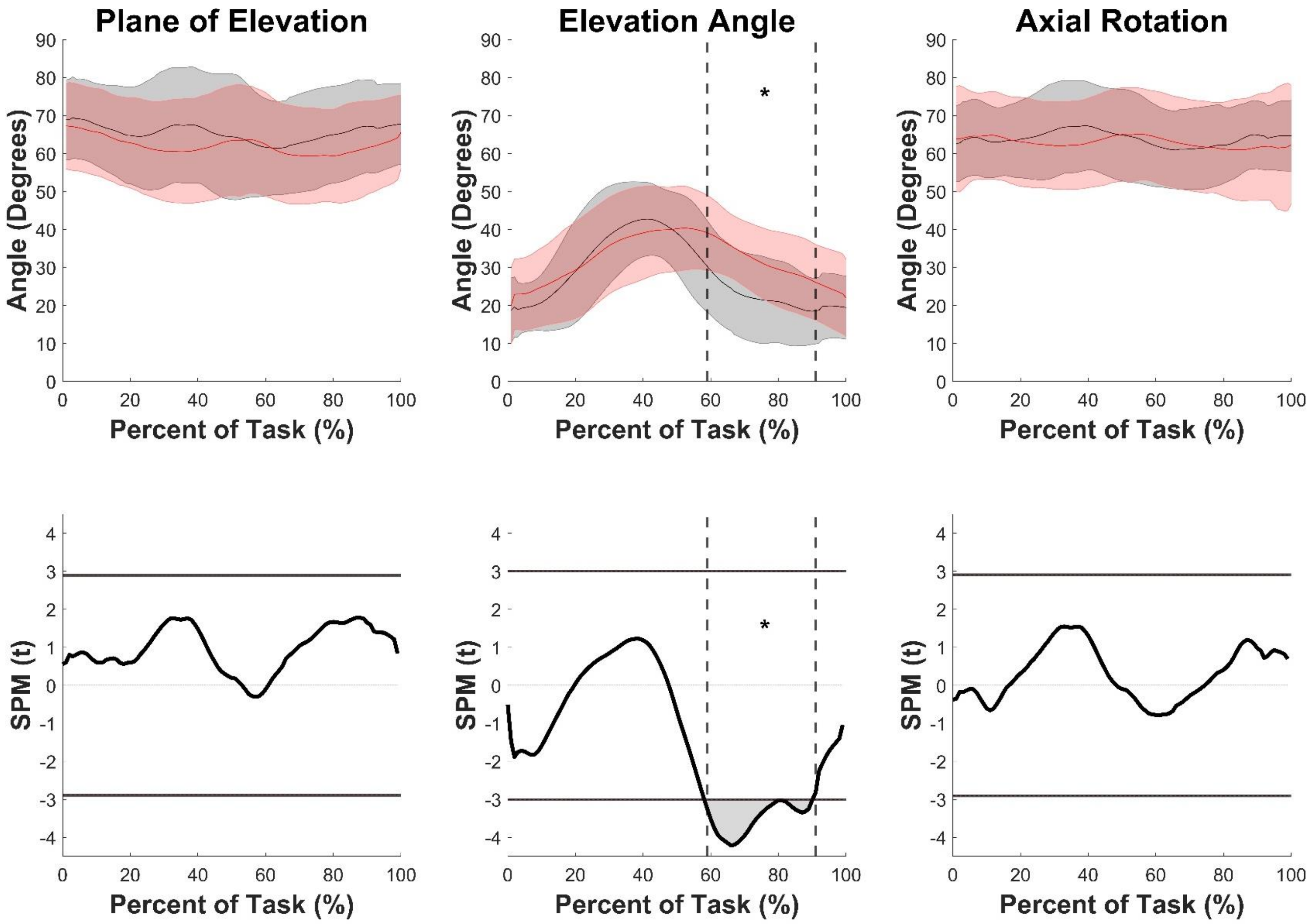


Figure 21: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the forward reach (with 1kg weight) task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * (p<0.05).

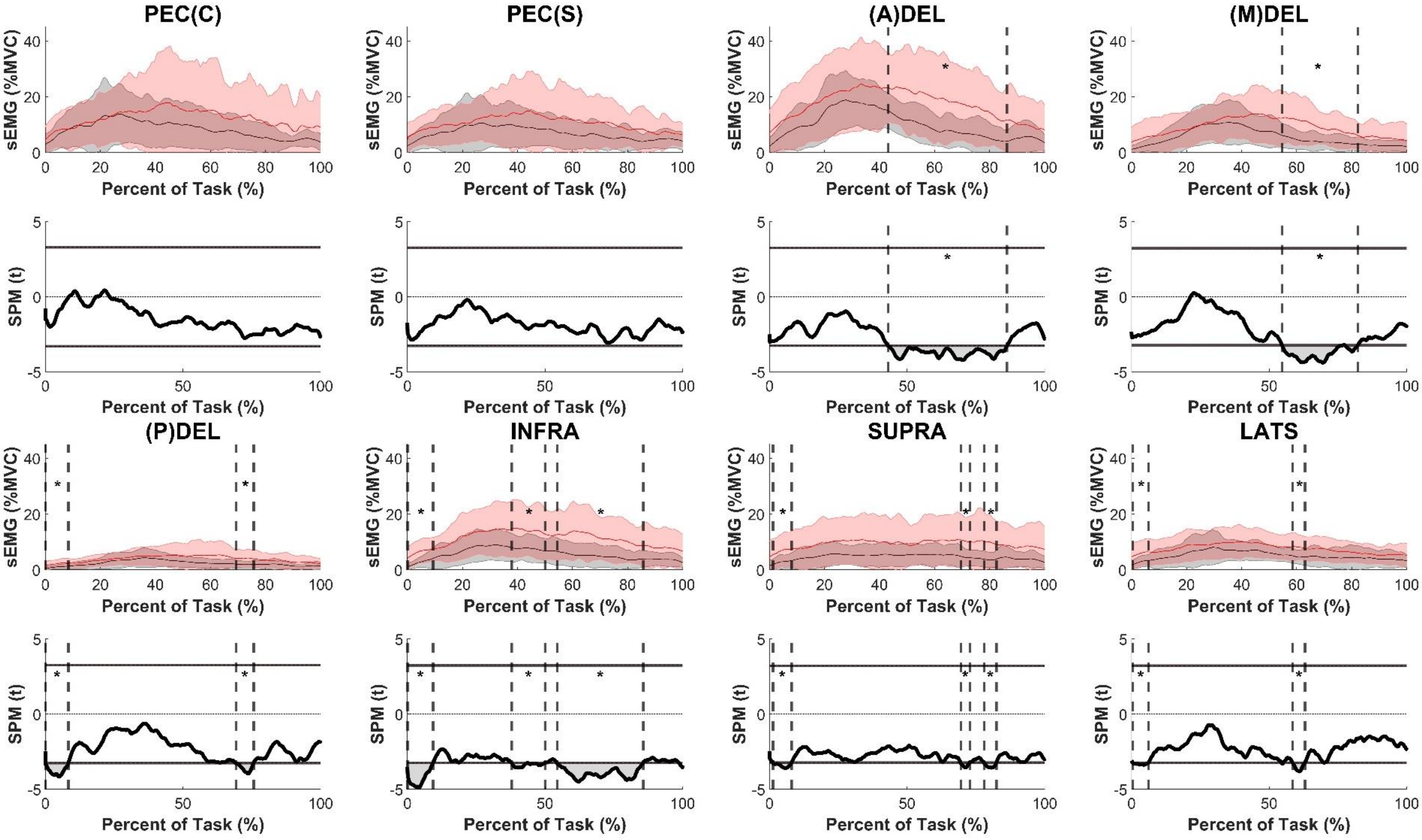


Figure 22: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the forward reach (with 1kg weight) task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.4 Lift a Shopping Bag

Plane of elevation, elevation angle and axial rotation were all similar for the HSC and LSC groups (Figure 23). During the lift of a 5kg bag from the floor to a hip level surface, plane of elevation began at 80° for both clusters, and ended at 60°, within one SD participants remained between 40-90° (Figure 23). Both the HSC and LSC used minimal elevation angle, remaining within 20-40°, although within one SD this ranged from 10-70° (Figure 23). Axial rotation for both the HSC and LSC was variable, but stable across the trial, remaining in internal rotation for the entire bag lift (50-60°) (Figure 23).

Muscular activation of 4 muscles were statistically similar during the bag lift (Figure 24). (P)DEL, (M)DEL, PEC(C) and PEC(S) were the same for the LSC and HSC across the task. (P)DEL was minimally activated during the task (less than 10% MVC). (M)DEL was activated below 20%MVC, however divergence between the two groups began at 75% of task completion (Figure 24). PEC(C) and PEC(S) had greater variability in the LSC, and although statistically similar, the LSC was higher throughout the whole trial in both muscles, and reaching 25% MVC during the task (Figure 24). (A)DEL was statistically different from 8.5-11.6% of task completion, where HSC was activated 3.22-3.63% MVC, while the LSC was activated 8.82-9.77%MVC (Figure 24). SUPRA differed from 0.9-4.5% of task completion, where HSC was activated 1.73-2.75% MVC, while the LSC was activated 4.23-5.78%MVC (Figure 24). INFRA differed at two instances 1-15.2% and 20.3-26.7% of task completion, where the LSC activated 1.64-4.41% MVC more than the HSC (Figure 24). Finally, LATS differed at three instances, 5.2-7.9%, 31.4-34% and 98.9% of task completion, during these times LATS was activated between 9.48-18.86%MVC in the LSC, where the HSC required 4.80-9.02%MVC for the same task (Figure 24).

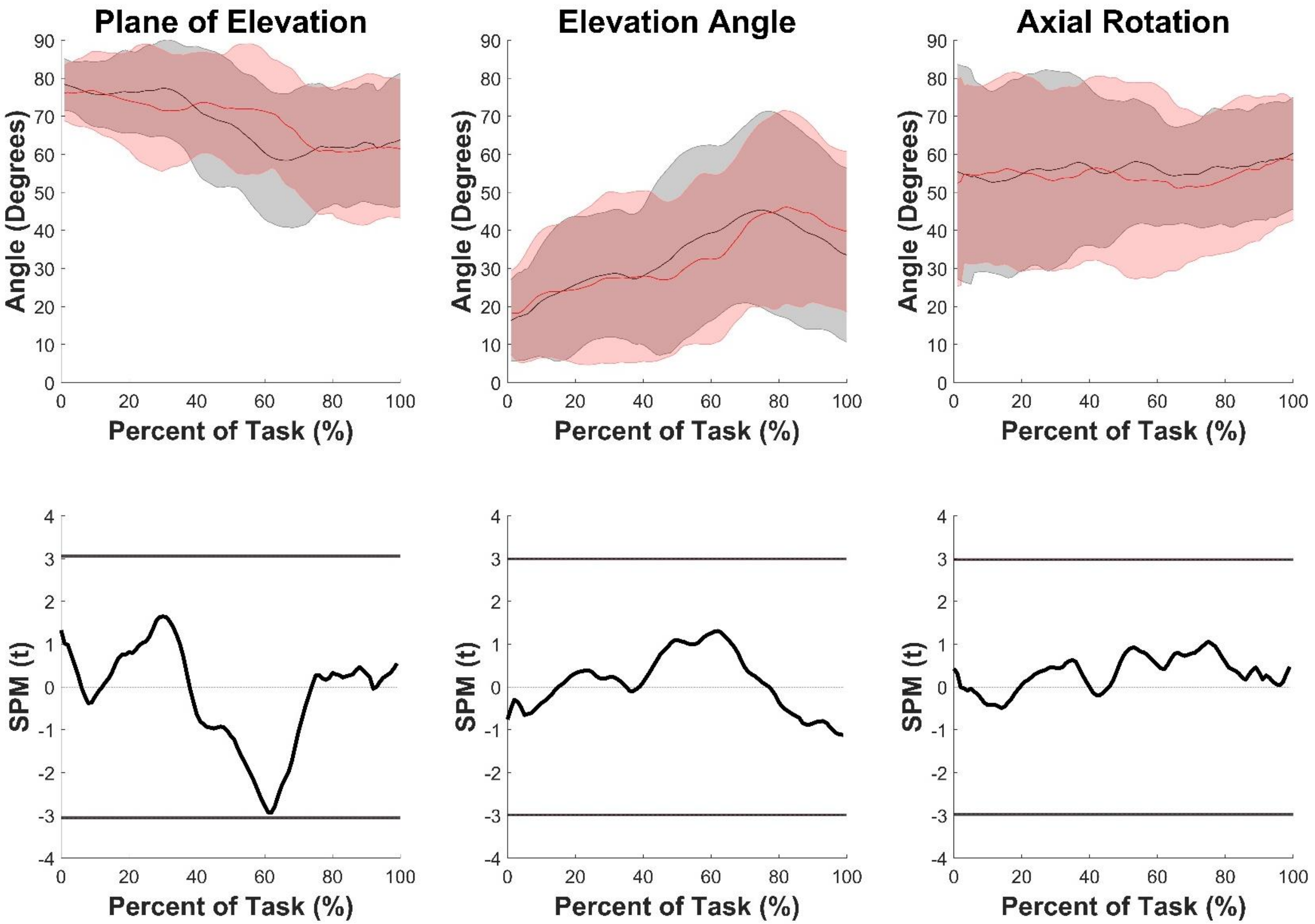


Figure 23: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the 5kg bag lift task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

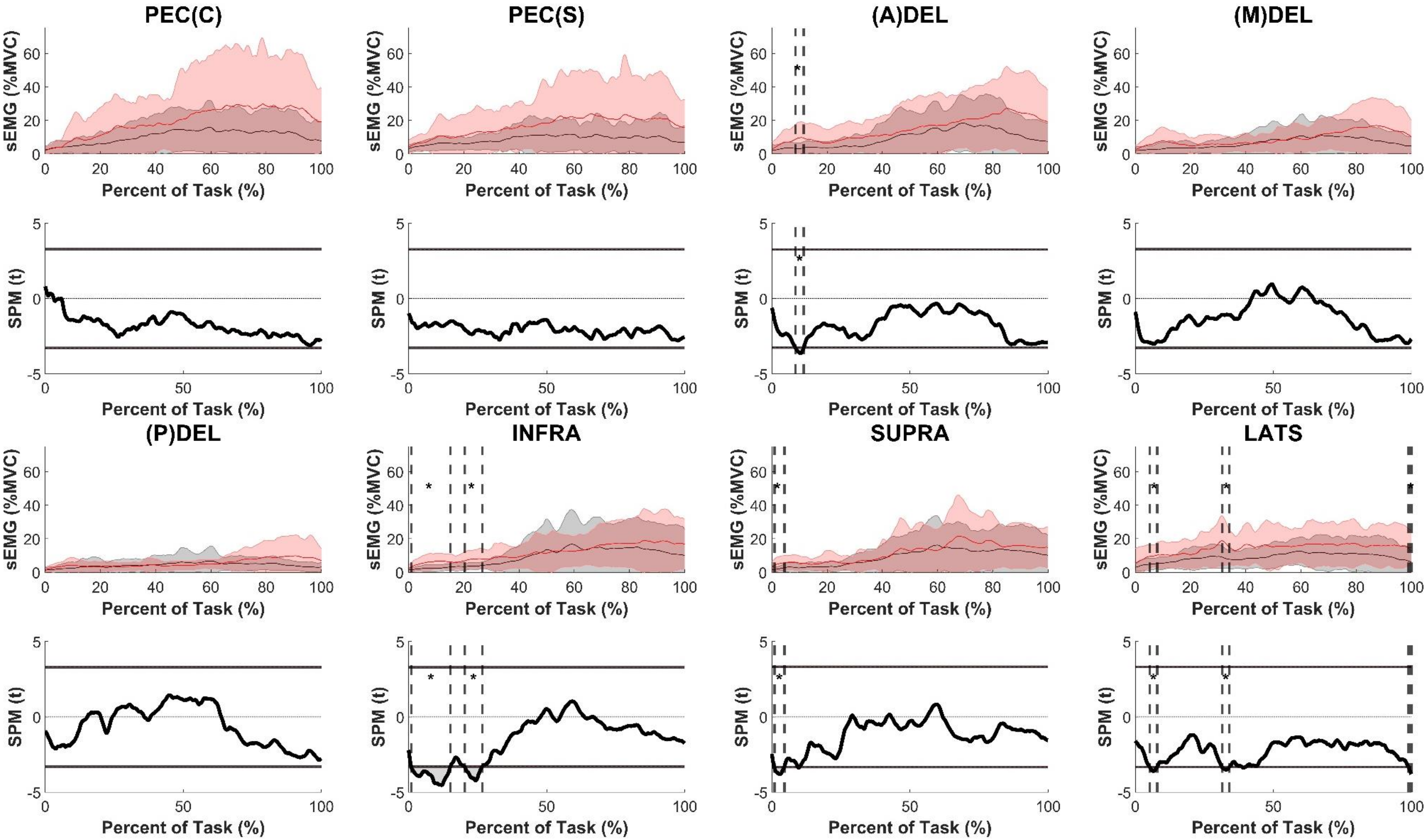


Figure 24: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the 5kg bag lift task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.5 Pour from a Pitcher

All three angles differed while pouring from a pitcher (Figure 25). Plane of elevation was 13.0-16.1° higher in the LSC from 29-47% of task completion (Figure 25). Overall, plane of elevation was higher in the LSC as this group used a smaller range of plane of elevation during this task. Elevation angle was 8.9-9.8° higher in the HSC participants from 31-40% of task completion (Figure 25). Again, the HSC used a greater range of elevation angle. Finally, axial rotation was 10.0-10.8° different between the clusters, from 33-43% of task completion (Figure 25). Although the rotation happened later for the LSC, this group, once again used a smaller range of motion.

All muscles displayed differences while pouring from a pitcher, excluding PEC(C) (Figure 26). PEC(S) was 5.18-6.16%MVC higher in the LSC from 88.7-95.7% of task completion, at 10.60-11.69% MVC (Figure 26). Although (P)DEL was statistically different, it was minimally activated during this task, and thus likely clinically insignificant. At 67.8-100% of task completion, the (P)DEL of the HSC was activated 1.64-3.21%MVC, compared to 3.69-5.74%MVC in the LSC (Figure 26). Similarly, LATS was different from 88.8-93.3% of task completion, where a difference between clusters of 3.18-3.47%MVC occurred (Figure 26). Small differences were also seen in the (M)DEL, where the clusters differed 3.28-4.63%MVC from 65-71.2% and 74.4-100% of task completion (Figure 26). Differences in (A)DEL occurred from 56.1-70% and 80.9-100% of task completion (Figure 26). During these times the HSC was activated 8.10-14.64%MVC, while the LSC was activated 17.69-22.21%MVC (Figure 26). INFRA differed from 53.3-73% and 76.7-100% of task completion, with differences ranging from 4.4-7.37%MVC (Figure 26). Finally, SUPRA differed from 75.1-81.1% and 97-100% of task completion with the LSC requiring 3.59-4.93%MVC more than the HSC (Figure 26).

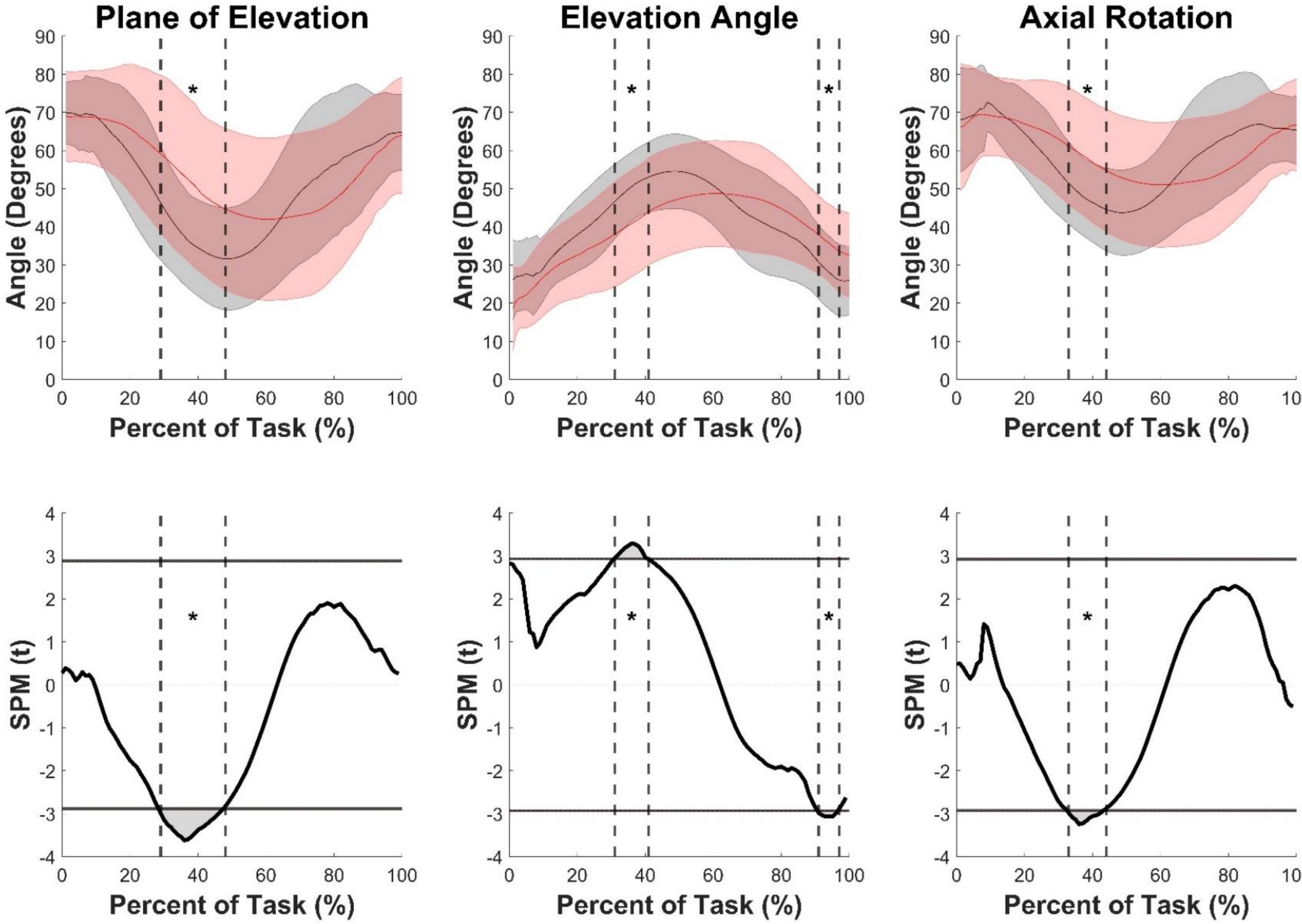


Figure 25: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the pour from the pitcher task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

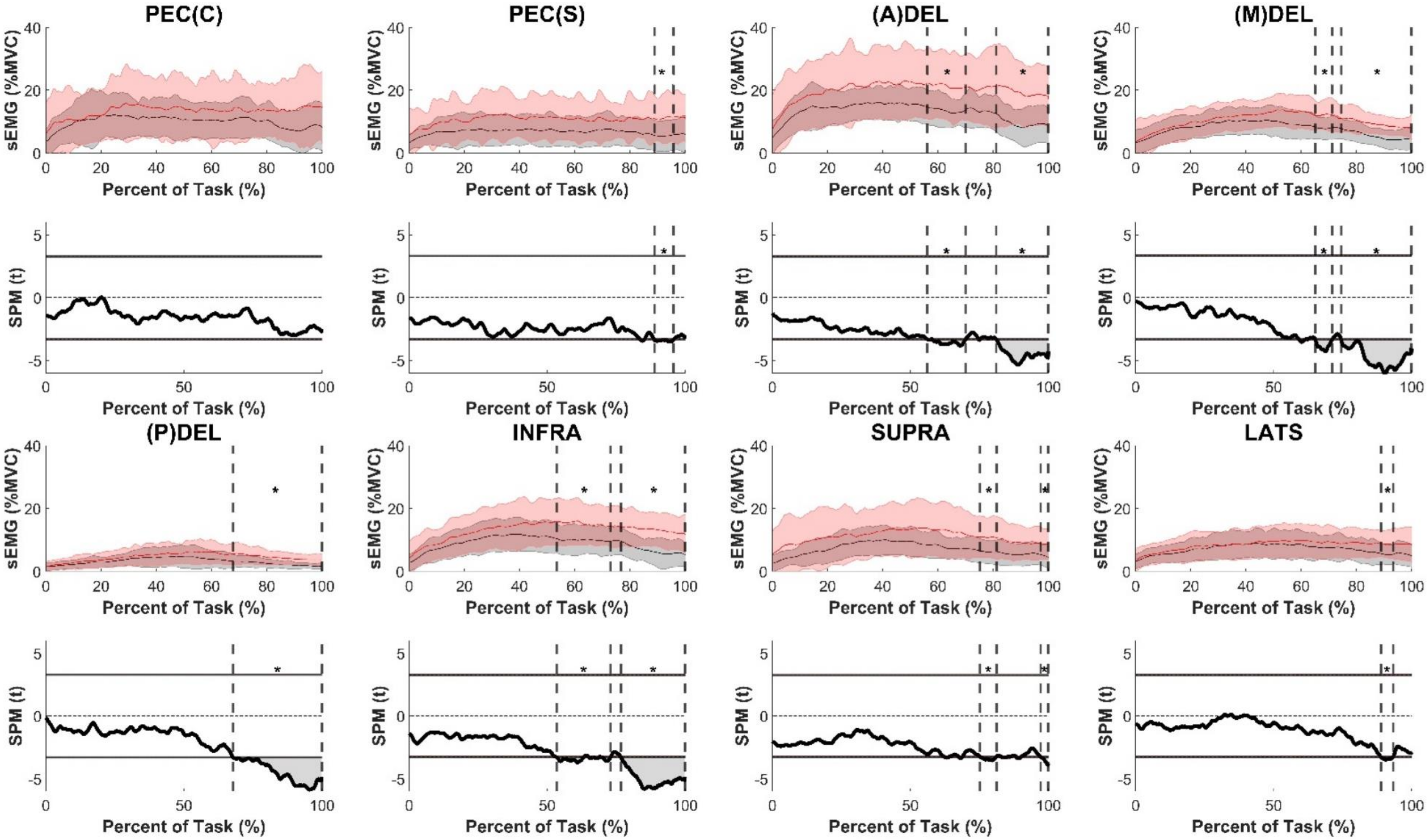


Figure 26: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the pour from the pitcher task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.6 Lift a Weighted Tray

Plane of elevation and axial rotation differed through the 2kg tray transfer task (Figure 27). Plane of elevation differed at 66-69% of task completion, with a difference between 6.5-6.8° between the HSC and LSC groups (Figure 27). The HSC remained at ~78° plane of elevation, where the LSC remained at ~72° during this time. Although statistically different, this minimal difference is not clinically significant. During axial rotation, the two clusters only differed between 86-88% of task completion, with a difference of 15.1-15.9° (Figure 27). The HSC returned to ~65° of internal rotation, where the LSC was at ~50° of internal rotation. Elevation angle was minimally involved in this task, remaining at ~15° in both the HSC and LSC through the entire task.

Most muscles were statistically similar through the trial, excluding INFRA and LATS (Figure 28). During the tray transfer task, the LSC was 1.97-3.79% MVC more activated than the HSC from 3.5-23.7%, 25.1-29.7%, 44.9-48.2%, 49.3-52%, 55.9-63.2%, 64.7-73.4% and 84-86% of task completion (Figure 28). However, INFRA was minimally activated in this task, at ~2.0 and 5.5% MVC for the HSC and LSC, respectively (Figure 28). LATS differed from 43.1-47.2% of task completion, with the HSC activating 3.44-3.82%MVC and the LSC activating 6.17-6.75%MVC (Figure 28). PEC(S), (A)DEL, (M)DEL, (P)DEL, and SUPRA were all below 15% MVC during the entire trial (Figure 28). Although PEC(C) was statistically similar between the two clusters, the LSC had increased variability, reaching 40%MVC within 1 SD (both clusters, on average reached ~20% MVC) (Figure 28).

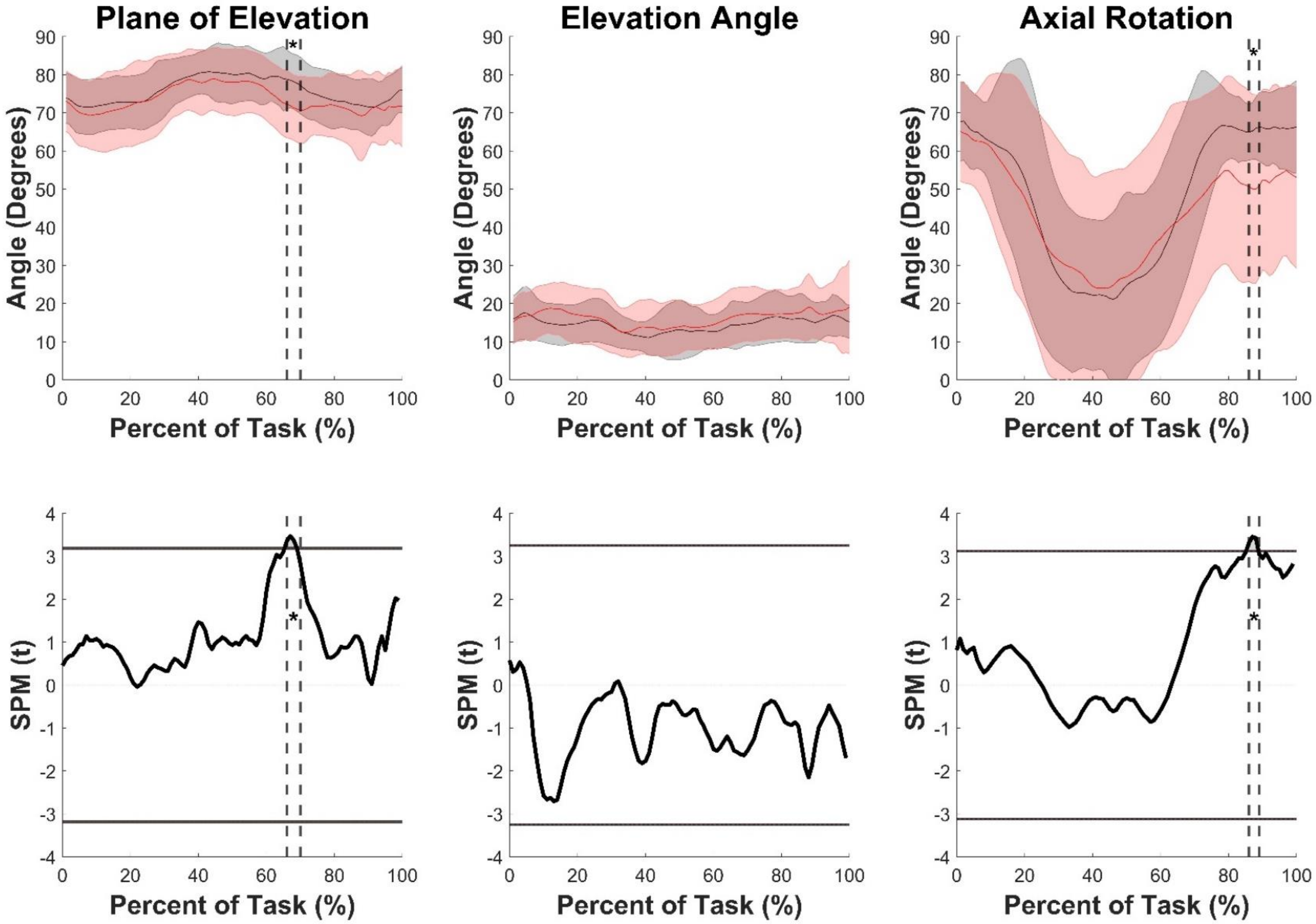


Figure 27: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the weighted tray transfer task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

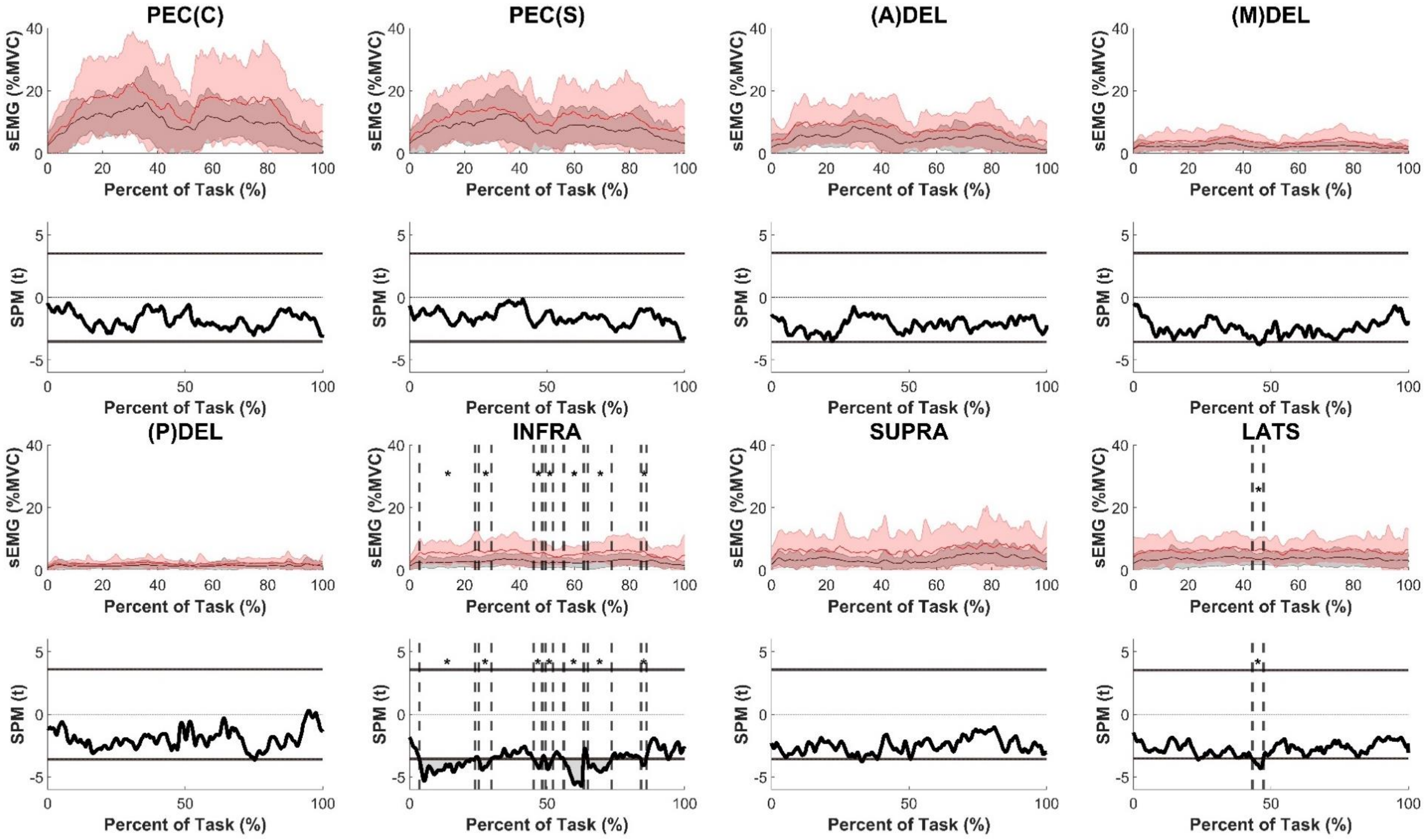


Figure 28: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the weighted tray transfer task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.7 Fasten a Bra

All three angles were similar for the HSC and LSC while reaching back to where a bra is fastened. For both clusters, plane of elevation remained between 45-65°, however within one SD this range increased to 40-80° (Figure 29). Participants used notable elevation to complete this task, ranging, on average, from 30-75° (Figure 29). Within one SD elevation angle range increases to 15-80°. Axial rotation remained within 40-60° for both the HSC and LSC during the bra fasten task (Figure 29).

Muscular activation of all muscles were statistically similar during the bra fasten task, except (A)DEL (Figure 30). (A)DEL remained below 10%MVC for both groups for the majority of the trial (Figure 30). The two clusters differed from 12.9-28.3%, 31.6-36.4%, 41.7-48.4% and 53.57.9% of task completion (Figure 30). The LSC required approximately twice as much muscular activation as the HSC, requiring 3.92-6.56%MVC more activation (Figure 30). PEC(C), PEC(S), (P)DEL and INFRA remained similar across the trial, where PEC(C) was below 10% MVC, and PEC(S), (P)DEL and INFRA were below 25% MVC (Figure 30). (M)DEL, SUPRA and LATS, although statistically similar, the LSC trended towards higher activation throughout the trial, and overall had increased variability with a larger range within one SD (Figure 30). These muscles all remained below 25%MVC, on average (Figure 30).

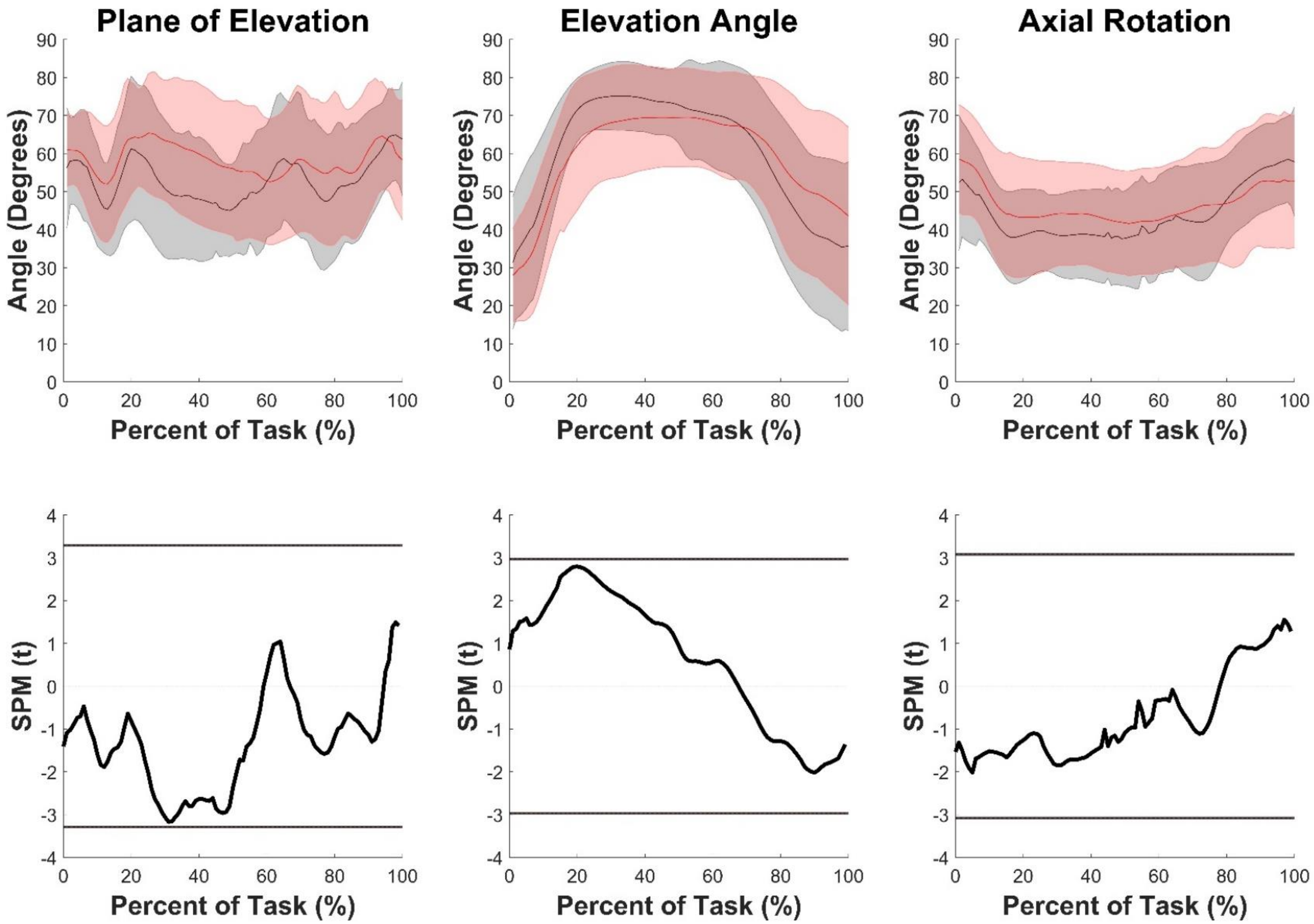


Figure 29: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the bra fasten task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * (p<0.05).

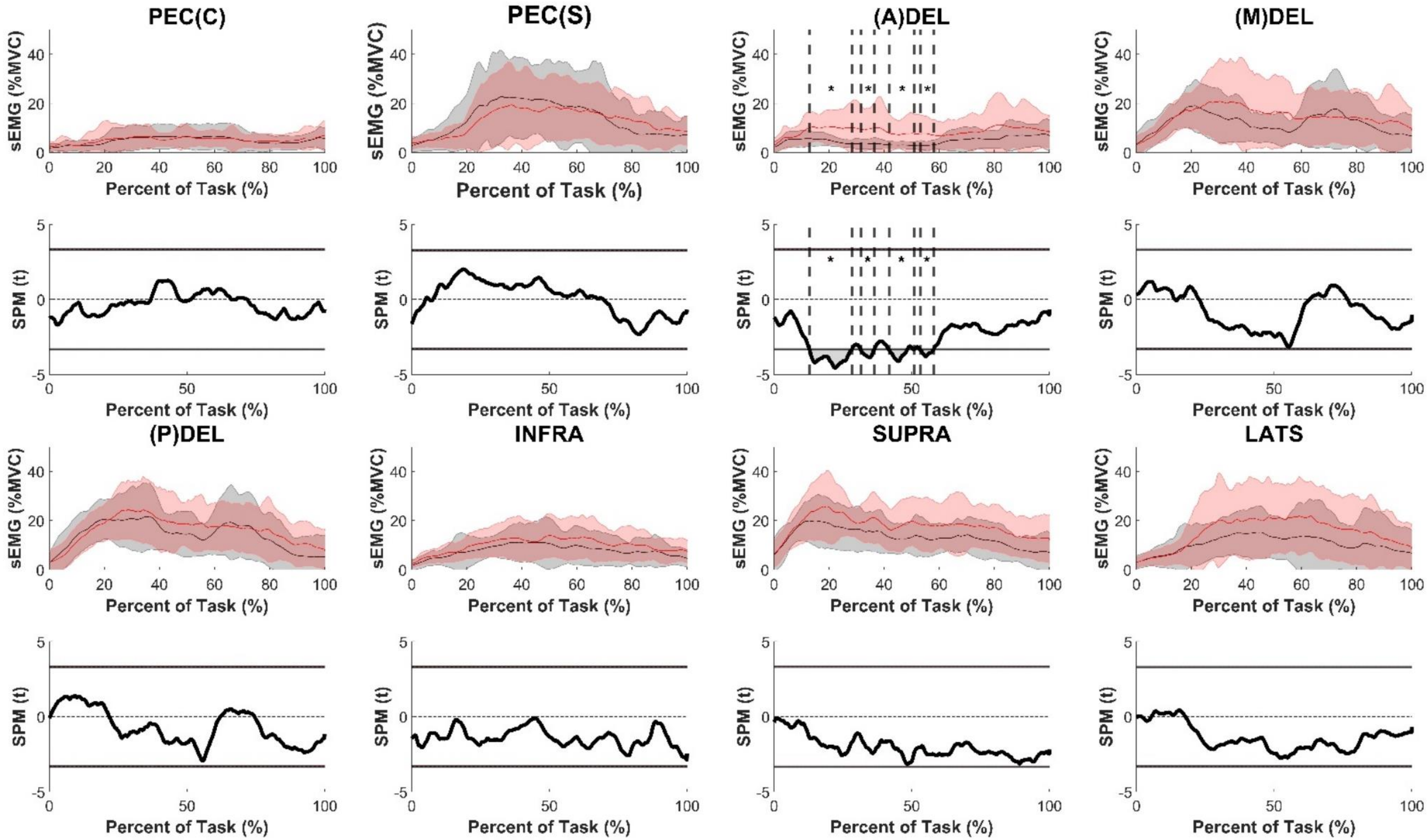


Figure 30: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the bra fasten task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.6.8 Put on a Necklace

Plane of elevation, elevation angle and axial rotation were similar for the HSC and LSC while putting on a necklace (Figure 31). During this task, plane of elevation and axial rotation were stable for both clusters, remaining within 65-75°, and 50-60°, respectively (Figure 31). Elevation angle began near 20°, and reached approximately 90° on average (Figure 31). The HSC had a higher variability, within one SD reaching 120° of elevation (Figure 31).

All muscular activations were statistically similar across this task, except PEC(C) (Figure 32). PEC(C) differed between the two clusters from 59.8-60.5% and 65.6-68.3% of task completion (Figure 32). During these times the LSC required approximately twice as much activation at 9.76-11.43% MVC compared to 5.04-5.89% MVC in the HSC (Figure 32). PEC(S), (P)DEL, INFRA, SUPRA, and LATS were all below 15%MVC for both the HSC and LSC while clasping a necklace (Figure 32). (A)DEL and (M)DEL although statistically similar between the two clusters, the LSC trended towards higher muscular activation, and had increased variability across the trial (Figure 32). These muscles, on average, remained below 30 and 20%MVC, respectively (Figure 32). (A)DEL reached 50%MVC within one SD of the LSC (Figure 32).

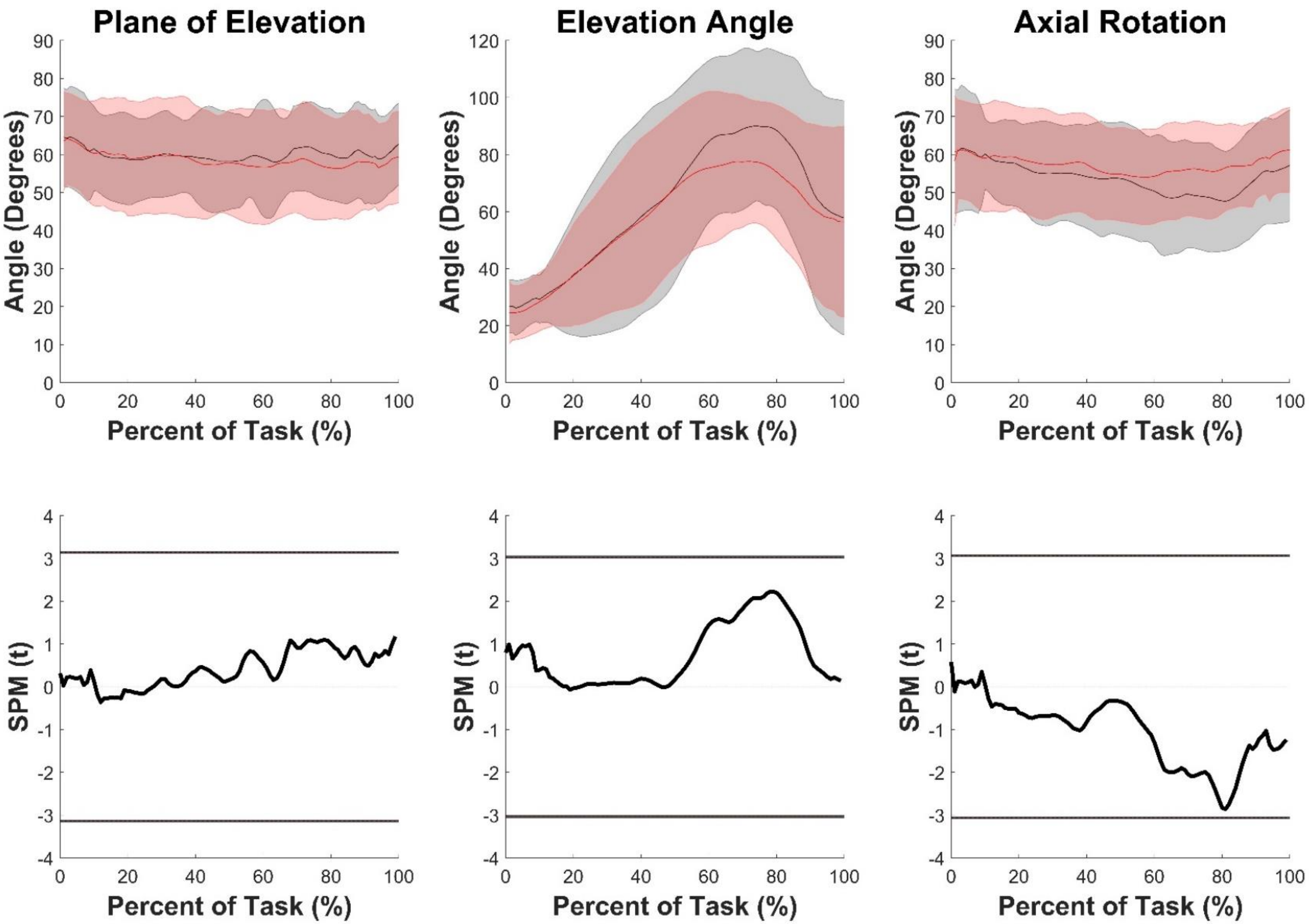


Figure 31: Average affected limb thoracohumeral plane of elevation (left), elevation (middle) and axial rotation (right) angles for the HSC (black) and LSC (red) during the put on a necklace task. Each angle is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines . Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * (p<0.05).

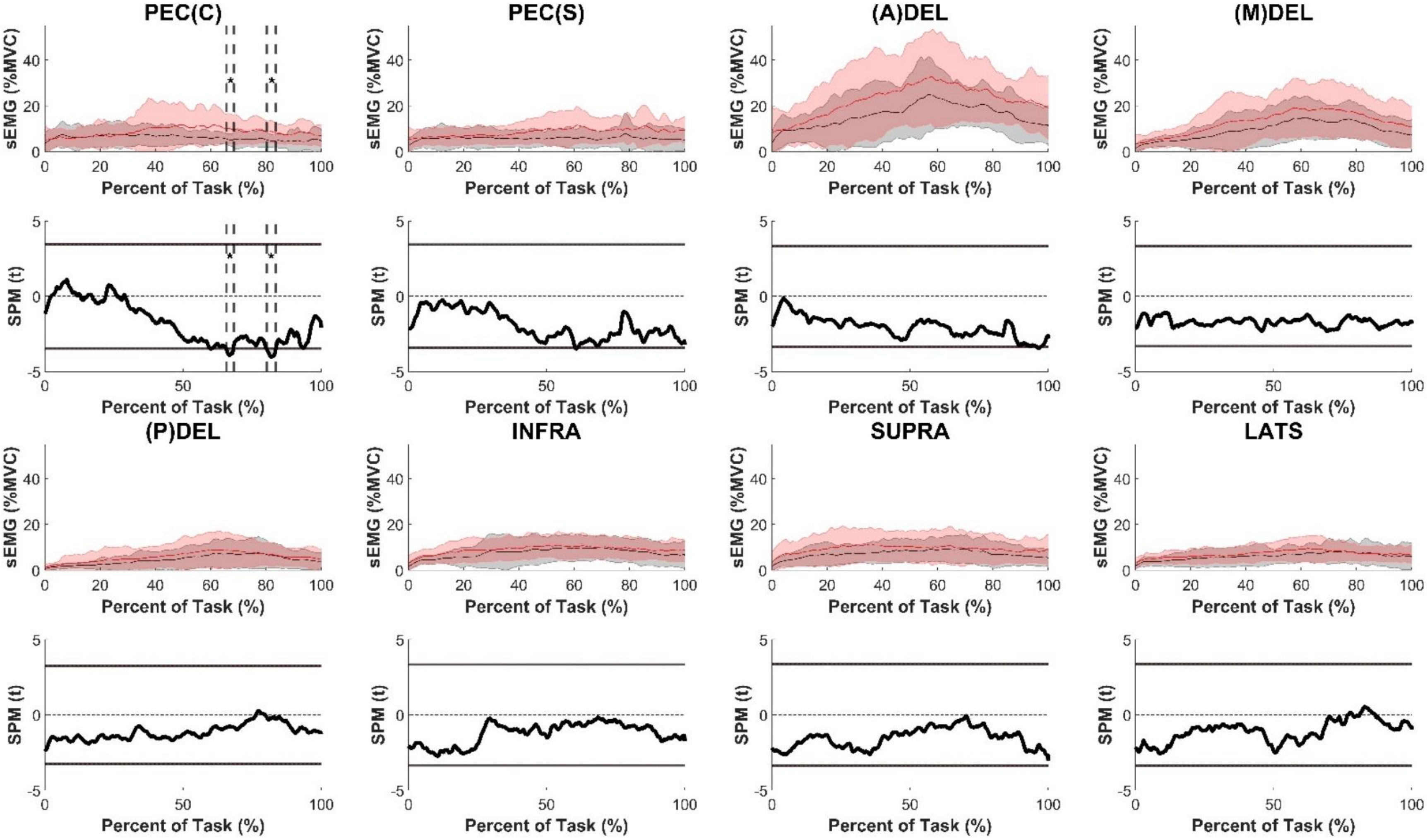


Figure 32: Average affected limb sEMG for the eight muscles recorded for the HSC (black) and LSC (red) during the put on a necklace task. Muscular activation is time normalized to % of task. One standard deviation for each group is represented by the shaded area in each corresponding colour. Associated SPM z-scores are reported below, with critical z-scores denoted by horizontal solid black lines. Z-scores that exceed the critical value represent significant differences between groups, and are marked with an * ($p<0.05$).

4.7 Discussion

Differences in kinematics, muscular activation, or both, existed for all eight activities of daily living. Four tasks (shelf reach, forward reach, pour from a pitcher and tray transfer) had group differences for at least one plane of motion, and all tasks had group differences in muscular activation for at least one muscle. These differences indicate that the performance of even low load ADL tasks are sensitive to treatment effects.

4.7.1 Kinematics during daily tasks

The first hypothesis was that the higher functioning cohort (HSC in study 1) would use more range of elevation angle and plane of elevation (horizontal abduction) during activities of daily living (particularly with external weights- shelf reach, forward reach and the bag lift tasks). This hypothesis was partially accepted, as differences occurred for plane of elevation (pour from a pitcher and tray transfer) and elevation angle (forward reach, pour from a pitcher). Additionally, although no changes were hypothesized, differences emerged in axial rotation (shelf reach, pour from a pitcher and tray transfer). Generally, the HSC used a larger range of each of the angles. Differences in angles ranged from 6.5-16.1°, 7.5-11.4° and 10.0-15.9° for plane of elevation, elevation angle and axial rotation, respectively. Previous research with breast cancer survivors reported that breast cancer survivors use narrower ranges than that of a reference population (Brookham et al., 2018a). The HSC is likely more similar to a reference population with the larger ranges used during ADLs. Simulated tasks (bra fasten task in the current study) have increased variability compared to completing tasks with props, or specific guides (all other tasks in the current study), which may render it less biofidelic (Taylor et al., 2018).

Focus is often placed on the ability for individuals to complete daily tasks, however all survivors in the current study were able to complete all 8 ADLs with differing kinematics. Previous research indicated that breast cancer survivors can complete ADLs, although there are likely some compensations that could lead to the pain felt in this population (Spinelli et al., 2016). In reference populations overheard reach occurred at 72.6° of plane of elevation (closer to forward flexion than abduction), and needed a maximum of 121.4° of elevation, and 60.6° of axial rotation (Magermans, Chadwick, Veeger, & Van Der Helm, 2005). Breast cancer survivors in the current study completed the shelf reach at a similar plane of elevation (30-70°) and axial rotation (30-65°), but decreased elevation angle (20-80°), however the shelf reach was not quite overhead (the shelf was at acromion height). During a 4kg bag lift, reference populations use 63.6° of elevation, and 47.7° of axial rotation, and the task occurred at 79.2° plane of elevation (Magermans et al., 2005). The two clusters in the current study demonstrated similar plane of elevation (60-80°), and axial rotation (50-60°) but lower elevation (20-40°) than the aforementioned reference population. Pouring from a pitcher required on average 8.22-27.2° of abduction, -12.32-23.38° of axial rotation, and occurred from 1.52-35.92° of plane of elevation in a reference population (Doğan, Koçak, Onursal, Ayvat, & Sütçü, 2019). Breast cancer survivors differed in the current study while pouring from a pitcher, where HSC used a larger range in each of the three motions. Overall, the ranges were 30-70° of plane of elevation, 20-55° of elevation, and 40-70° of axial rotation. These ranges were similar in the current study (~30° of each motion), however these ranges were more indicative of the HSC than the LSC (as their ranges were smaller), and plane of elevation angle was closer to forward flexion in the current study, whereas the reference population was closer to abduction. Further, to complete the task the elevation angle and axial rotation were greater than the reference population. Reaching to a back pocket occurred from -37.85-21.52° plane of elevation (where a negative number refers to extension), -21.77-20.97° of axial rotation, and 9.28-22.7° of abduction in a reference population (Doğan et al., 2019). Breast cancer survivors in the current study used 55-75° plane of elevation, 30-60° elevation, and 50-60° of axial rotation. Elevation angle was greater in the current study, compared to the reference population, likely to compensate for the reduction in both axial rotation and plane of elevation.

The current study identified kinematic differences in ADLs between the two clusters of breast cancer survivors, and further that these kinematics also differed from a reference population. Generally tasks were completed similarly; however, the postures were more internally rotated, with lower plane of elevation (horizontal abduction) and with increased elevation, compared to reference populations (Doğan et al., 2019; Magermans et al., 2005). The kinematics of these tasks are also important in return-to-work scenarios. Nearly half of women who receive treatment for breast cancer, regardless of age, reduce their working time, or retire from working early (Schmidt, Scherer, Wiskemann, & Steindorf, 2019). Individuals who have pain or difficulties raising objects overhead, or lifting objects of 5kg or heavier often are unable to return to work, or must return in a limited capacity (de Souza Cunha et al., 2020). Although breast cancer survivors are able to complete the tasks, in the long term the differences while completing these tasks may provoke long term complications. In functional return to work tasks, breast cancer survivors exhibited similar movement patterns to individuals who develop rotator cuff disorder (Lang et al., 2019), which is further supported in the current study. The individuals in that study, similarly to the current study, used smaller ranges of motion. Lang et al. showed decreases in internal rotation, whereas the current study showed decreases in overall range of axial rotation in several tasks. The author suggested this may be a compensation to avoid impinging the supraspinatus tendon, and avoid potential impingement pain (Brossmann et al., 1996; Lang et al., 2019). Additionally, rotator cuff disorders may be perpetuated by the decreases in elevation angles and plane of elevation (Ebaugh et al., 2011; Lang et al., 2019). Participants may exhibit these movement patterns to avoid pain, or due to tightness or weakness experienced after treatment. Therefore, it is important to continue to investigate a wider range of daily tasks (and return to work tasks), as even minimal differences to compensate for restriction can lead to disorders causing long term pain.

4.7.2 Muscular Activation during daily tasks

The second hypothesis was that muscular activation will differ between the groups of breast cancer survivors. Specifically, that lower functioning breast cancer survivors (LSC in study 1) would activate muscles that may be damaged by radiation more (Lipps et al., 2017), and activate the other muscles more to compensate. Similar to hypothesis 1, this was partially accepted, as differences existed in a subset of tasks. In muscles that are likely to be damaged due to radiation (pectoralis major (clavicular and sternal insertions) and latissimus dorsi) there were some statistical differences between the HSC and LSC clusters during the shelf reach, forward reach, bag lift, pitcher pour, and tray transfer tasks. All of these tasks had external weights ranging from 1-5kg. Differences between the clusters for PEC(S) ranged from 3.35-6.16%MVC during the pour from a pitcher and shelf reach tasks. Similarly, the LSC used 4.96-5.55%MVC more activation than the HSC while putting on a necklace and shelf reach tasks. Finally, LATS were 2.52-9.85% MVC more activated in the LSC compared to the HSC during the forward and shelf reach, tray transfer, bag lift and pour from a pitcher tasks. However, this hypothesis was rooted in the thought that the LSC would have a higher percentage of participants receiving radiation. This was not the case as 13/16 participants in the HSC received radiation and 16/16 in the LSC. In the current study, activation of pectoralis major (both insertions) and latissimus dorsi remained between 5-25% MVC for both the HSC and LSC in ADL tasks. As these tasks were low load, daily activities this range is expected. However, previously reports indicated that in low load functional and work tasks pectoralis major decreased activation compared to the unaffected side (Brookham et al., 2018b; Shamley et al., 2007). This decrease in activation was also accompanied by a decrease in size in at least 15.7% of individuals (Gyedu, Kepenekci, Alic, & Akyar, 2009; Shamley et al., 2007). It is possible that the decrease in muscle size alters function, and may contribute to the decrease in activation. The current study did not compare to a reference (either population or unaffected limb), but the overall low activation of pectoralis major and latissimus dorsi during these tasks aligns with prior literature. Further research should explore whether a decrease in muscle size beyond the affected pectoralis major exists, and whether those who experience decrease in muscle size experience increased activation during tasks to complete even low load daily tasks, such as seen in the LSC during these ADLs.

The partially accepted portion of hypothesis two was infraspinatus, supraspinatus, anterior deltoid, middle deltoid, and posterior deltoid would have increased activation in the lower functioning cohort (determined to be LSC in study 1) to potentially compensate for the less effective damaged pectoralis major and latissimus dorsi. The anterior deltoid required 1.89-11.99%MVC more activation of the LSC, compared to the HSC in all tasks except the tray transfer and put on a necklace tasks. Infraspinatus was also affected in more than half of the trials, requiring 1.64-8.69%MVC more activation from the LSC in all tasks except the bra fasten, shelf reach and necklace clasp tasks. Modest differences occurred in the supraspinatus, middle and posterior deltoid muscles, with the LSC group requiring 0.89-7.29%MVC more activation than the HSC. These differences occurred in the forward reach and pour from a pitcher tasks (as well as the bag lift task for the supraspinatus). Total muscle effort increased by 5.1% on the affected side of breast cancer survivors during functional work tasks (Brookham et al., 2018b) in an earlier investigation. In functional and daily tasks higher activation of muscles on the affected side outside the radiation field occurred compared to the unaffected side (Brookham et al., 2018b; Hagstrom et al., 2019) and compared to a non-cancer reference population (Brookham & Dickerson, 2016; Galiano-Castillo et al., 2011; Shamley et al., 2012). This higher muscular activation is accompanied with pain for many survivors (Galiano-Castillo et al., 2011). Lower activation of the irradiated muscles is likely due to a diminished capacity of the muscles due to treatment, caused by both radiation and chemotherapy (Klassen et al., 2017; Lipps et al., 2017). The diminished capacity is evident by the decrease in strength in this population (Brookham et al., 2018b; Ebaugh et al., 2011; Maciukiewicz et al., n.d.; Perez et al., 2018). With a 10% increase in activation, survivors further from treatment exhibited between 19-42% lower force production (Maciukiewicz et al., n.d.). These factors all combine to cause identical tasks to require more effort from survivor populations, whether it be a low load functional work or daily task, or a full-strength exertion. In study 1, the LSC had lower strength, and in the current study, the LSC muscles were consistently more activated than the HSC muscles across all ADLs. This supports the concept that after treatment, diminished capacity may exist for some individuals, making even low load functional tasks more challenging and increases the possibility to induce fatigue through task performance.

4.8 Limitations

Limitations from study 1 also influence the results of the current study. Additionally, only one MVC trial was completed for each muscle, to mitigate pain or fatigue that is evident in this population. Pain is an important consideration in this population. It is feasible that pain may interfere with participants reaching their true maximum during MVCs. Although there is potential that it wasn't a true maximum, it is that individual's maximum in their current state – and is important to consider. Likely, pain led to the greater variability in the LSC sEMG measures. Two repetitions of each ADL tasks were completed, to minimize variability often five or more repetitions are recommended, as well as using tools whenever possible (Taylor et al., 2018). This was generally infeasible given the weakness in the participant population. Additional muscles around the shoulder may compensate during these tasks, but were unmonitored. Compensation may have been manifested as trunk or neck motions, but were also not investigated. Finally, differences were modest, especially in muscular activation. It is difficult to determine what the minimum clinically important difference is without specific criteria for each scenario (Copay, Subach, Glassman, Polly, & Schuler, 2007). However, tasks that elicit activation below 20% MVC are thought to be ideal in early rehabilitation of shoulder related function following injury or surgery (Uhl, Muir, & Lawson, 2010). As the ADL tasks studied generally remained below this threshold, small changes in activation in these tasks are likely more impactful, compared to small changes tasks with higher demands. Time to complete each task and cumulative load were not considered in the current investigation, but could also contribute greatly to the demands in these individuals.

4.9 Conclusion

Activities of daily living are an important element of survivorship. Although most breast cancer survivors can complete these low load daily, functional or work tasks, the manner of completion was relatively unknown. The current study investigated 8 daily living tasks, and how performance of these tasks differed between two groups of breast cancer survivors. During the, upwards reach to a shelf, forward reach, pour from a pitcher and tray transfer tasks breast cancer survivors with lower shoulder-related quality of life and less strength (LSC) used lower ranges of angles. In all tasks, at least one muscle displayed significantly increased activation of this same group of survivors. These differences ranged from 6.5-16.1° and 0.89-12% MVC. The differences between these groups may be due to diminished capacity of the muscles leading to increased muscular activation. This, combined with changes in kinematics may predispose these individuals for increased injuries, including rotator cuff disorders. This work can be useful in determining tasks that may be troublesome for some individuals. Expanding this work to include work tasks may assist in appropriate return to work strategies. More importantly, knowing these differing strategies exist, physiotherapists may work to correct movement patterns for individuals to avoid potential injury.

Chapter V – Adaptation of strength production in breast cancer survivors: a simulation analysis

5.1. Introduction

Often, physical training protocols are introduced in breast cancer survivors to increase shoulder range of motion or overall strength as a means to decrease dysfunction. Training programs vary in the types of exercises, the intensity, outcome measures, duration and the timing of the start of the program, and the participants who partake (De Groef et al., 2015; McNeely et al., 2010; Ribeiro, Moreira, et al., 2019). Commonly, resistance training programs succeed in regaining some strength and range of motion in survivors, but often impairments in daily life persist. Tissues recover from treatments (specifically chemotherapy and radiation) differently and therefore likely respond to these exercise programs differently following disparate damage from treatment. It is often infeasible (or untimely) to find a large population of survivors with similar deficits who received the same adjuvant therapy to test the efficacy of resistance training on those specific deficits due to that form of treatment.

As previously stated, models are often used to provide insight into problems that are difficult or inaccessible with experimental data, such as modelling clinical populations. Clinical populations pose a particularly difficult problem as it is often challenging to recruit a substantial number of participants to investigate the many questions researchers pose. Although there is over 22, 000 patients joining the breast cancer survivor population in Canada every year, additional barriers may deter them from participating in intervention studies, such as reduced immunity from treatment, or the time commitment after already taking time off work for treatment (Brenner et al., 2020; Canadian Cancer Society, 2020; Courneya et al., 2016; Markes et al., 2006). On the other hand, models are often based on reference populations (although if cadaver measurements are used these are often from older adults) (Dickerson et al., 2007; Veeger, Yu, An, & Rozendal, 1997). However, adjustments can be made to existing models to account for challenges clinical populations face, such as altered kinematics or compensation via differing muscular activation (Brookham & Dickerson, 2014; Chopp-Hurley et al., 2016; Lang, Kim, Milosavljevic, & Dickerson, 2020). Often a combination of both techniques can help enlighten researchers to underlying issues in these populations.

Two areas that have used biomechanical models to explore clinical populations are individuals with rotator cuff pathologies and manual wheelchair users. Models were first adapted to the specific population, and then used to investigate research questions (Bolsterlee, Veeger, & Chadwick, 2013). Saul et al (2011) used a previously published model to investigate rotator cuff pathologies. Postures during rotator cuff surgery can dictate post-operative success, where more abducted postures helped during surgery, to ensure closure of larger gaps, but may not lead to post-operative success (Saul, Hayon, Smith, Tuohy, & Mannava, 2011). Dubowsky et al (2008) worked with an existing model to create patient specific musculoskeletal wheelchair models. By altering the existing model for specific patients, the model was able to better predict experimental derived muscle forces (and reducing the error between the model driven results and experimental), with a future goal of prescribing the appropriate wheelchair choice (and particularly axle placement) to reduce joint forces for manual wheelchair users (Dubowsky, Rasmussen, Sisto, & Langrana, 2008).

Pectoralis major is often affected by treatment in breast cancer survivors, and therefore modifications to its typical capabilities have been modelled in several scenarios. Stegink-Jansen et al. (2011) modelled 3 portions of the pectoralis major and the mechanical strain in each portion during a series of exercises aimed to target breast cancer survivor rehabilitation. Single-axis motions, and motions overhead did not uniformly lengthen all 3 portions of the muscles (Stegink-Jansen, Buford, Patterson, & Gould, 2011). Targeting combined movements, specifically with extension and external rotation were deemed ideal lengthening exercises for pectoralis major, and when tolerated adding abduction should provide the greatest benefits. However, it is possible that the muscle may not produce full force and that the tissues may not fully recover. Chopp-Hurley et al (2016) modified the previously described SLAM model (Dickerson et al., 2007) to investigate the influence of reduced pectoralis major capability on muscular strategies for internal and external rotation tasks. By including a pectoralis-specific capability constraint, the dysfunction in pectoralis major reflected the population more accurately (Chopp-Hurley et al., 2016). Force capability was modelled for 0% (total disability), 25%, 50%, 75% (partial capabilities) and 100% capability. Muscle force was underestimated compared to measured muscle activations during submaximal efforts, however when co-activation and 25% pectoralis major capabilities were enforced, these differences were lower than other models of levels of pectoralis capability, indicating this population is likely working with a reduced capability in at least the pectoralis major (Chopp-Hurley et al., 2016). Additional muscles surrounding the shoulder are also commonly affected by treatment, both directly (radiation) or indirectly (chemotherapy) and the effects of exercise on these compromised muscles in terms of overall function, such as regained strength, should be considered. Simulating the effects of surrogate “training” scenarios on specific muscles or muscle groups may provide further guidance on preferred muscles to target to regain strength in a compromised system.

5.2 Objectives and Hypotheses

The objectives of study 3 are to:

1. Alter the muscle capacities within an existing model to replicate the strength outputs of the breast cancer survivor population (at a corporate level)
2. Determine maximum recoverable force outputs from survivors given various scenarios for regained muscle function potential (radiation damage, chemotherapy damage, combination treatment) and across two maximal isometric strength positions (adduction and internal rotation).
3. Determine the internal muscle forces associated with generating each maximal force output (baseline force and maximum recoverable force) and compare these to a non-cancer reference group with an *in-silico* approach

The hypotheses for this study are as follows:

1. The maximum recoverable force will be less than a reference population for each of the fundamental strength measures (adduction and internal rotation) in most scenarios. Specifically:
    a. The combined treatment scenario will have the lowest recoverable force output.
    b. Radiation and chemotherapy scenarios will recover similar levels of force, but will be less than the scenario with no restrictions
2. Muscle forces will differ between scenarios across conditions.
    a. The radiation scenario will yield decreased muscle force from internal rotators and antagonist muscles to this action, without the contribution of pectoralis major and latissimus dorsi

        i. Although muscle activation may increase in tasks (Brookham & Dickerson, 2016; Galiano-Castillo et al., 2011; Shamley et al., 2012), the ability to produce force will decrease with reduced capacity (compared to reference)

    b. The chemotherapy scenario will result in overall decreases in muscle force to achieve maximal force out of these simulations

5.3 Methods

5.3.1 Inputs

The SLAM model was used in this study and required input of both subject and task data. Average anthropometrics (body weight and height) for the LSC group of survivors were inputted into the SLAM model (Table 20). Due to COVID-19 an age and sex matched non-cancer reference groups was not assessed. Previously collected data (Lulic, 2020) was used as a surrogate. Participants in this study were young women (Table 20), and multiple maximal force trials were completed. Maximal force trials collected in the same position as the current study were used for this thesis and filtered as in section 3.4.3 (page 51). Peak force (N) from those trials were used as non-cancer reference force (Table 21). Peak force from the LSC (detailed in Study 1) was used as the breast cancer survivor force (Table 20).

The final SLAM input was kinematic (postural) data. A static trial was taken in each of the humeral postures for isometric strength trials completed during the experimental collection (adduction and internal rotation) (Table 5, page 47). The joint locations from this representative trial were used as the postural input.

Table 20: Population demographics and peak force as inputs for SLAM model

	Non-Cancer Reference Population	**Breast Cancer Survivor LSC Group**
Age (years)	22.4 ± 2.3	56.73 ± 9.00
Height (cm)	164.4 ± 7.7	164.77 ± 6.12
Weight (kg)	62 ± 4.6	75.88 ± 14.40
Adduction Force (N)	212.22 ± 55.35	118.89 ± 31.19
Internal Rotation Force (N)	171.2 ± 44.15	76.62 ± 40.59

5.3.2 Alterations of the SLAM model

The first alteration of the model was adjusting the location of force production. Historically, the model accepted three-dimensional forces at the grip surface of the hand. For the internal rotation trial, this was true and remained unaltered. Adduction forces were exerted above the elbow with the cuff, and therefore the model was altered to add the force at this location.

Several other alterations to the SLAM model preceded simulations in the current study. To begin, the average peak force of the reference group was input into SLAM, with no alterations. The model was unable to converge on an optimized solution. The SLAM model was developed with the use of PSCA from 3 cadavers (ranged from 55-71 years old), a correction factor was placed on these values in the original development of the model, however this was still insufficient to produce the force of a younger, reference population. To correct for this, the correction factor was increased from 2 to 3, where the model was able to sufficiently produce the force exerted by the reference population in the current study. The average force of the non-cancer reference group was used as the upper bound, or target force (Figure 33).

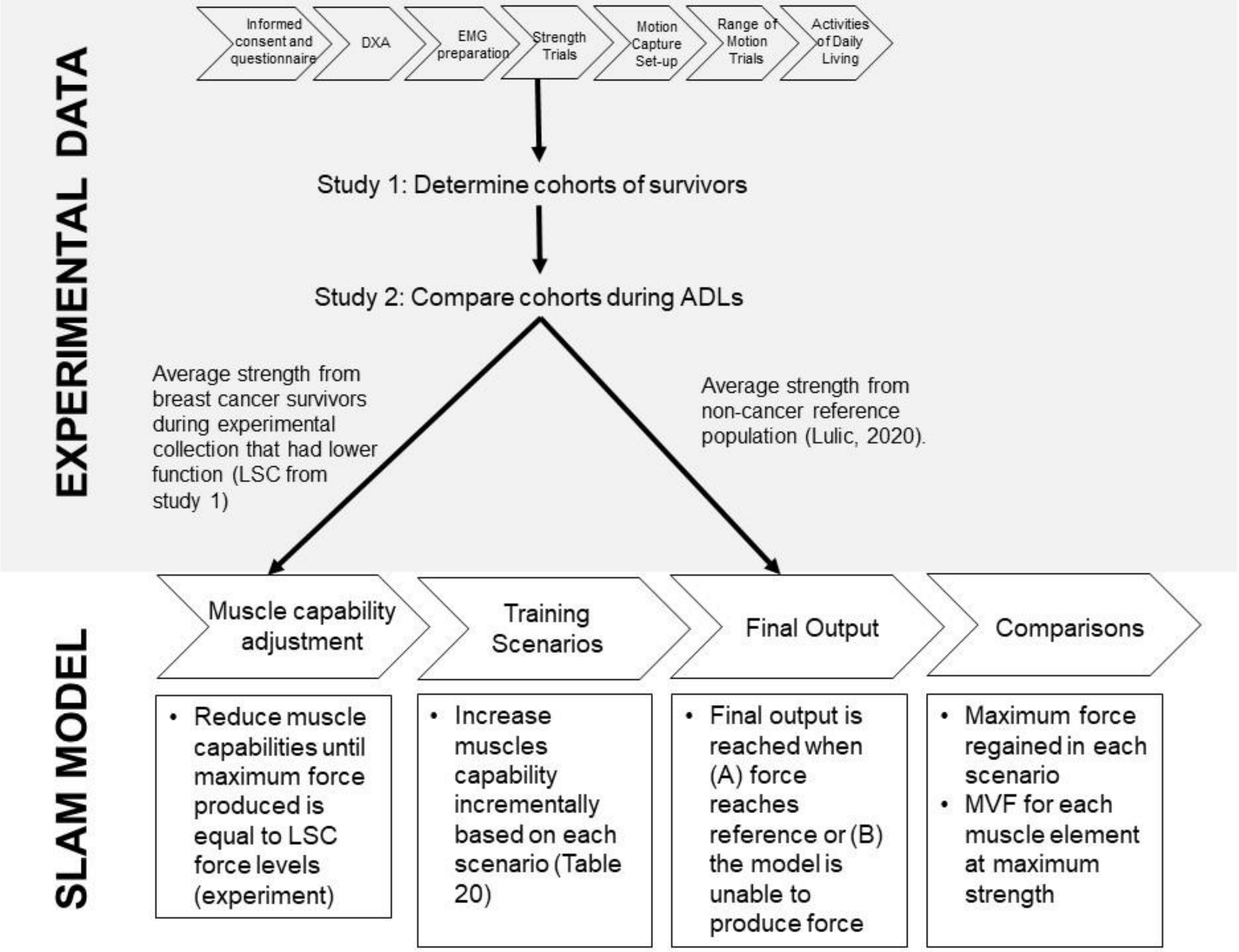


Figure 33: Flowchart outlining study 3. Force inputs to the model are dictated by strength trials collected in the experimental protocol, whereas the cohort of survivors modelled is determined in study 2.

The SLAM model was then altered to produce the force levels of the LSC group of breast cancer survivors (Table 20). Capacity of each muscular element was altered, similarly to (Chopp-Hurley et al., 2016) until the maximum force output from the model (without failing) matched that of the average LSC group breast cancer survivor peak force output collected during isometric strength trials in study 1 (Figure 33). A failure was determined when the model was unable to successfully converge on an optimal solution that minimized cubed muscle stress while satisfying the constraint equations. The capacity of all muscles were altered using equation (6), where F_m is the force output from a given muscle, $PCSA_m$ is the cross-sectional area from each individual muscle, T is the muscle specific tension (87.9 N/cm^2), and C is the capability of the muscle (0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1.0).

$$F_m = PCSA_m * T * C \qquad \text{[Eq. (6)]}$$

The capability of all muscles were altered together, as a simplification of the overall capacity for breast cancer survivors. Altering muscles individually was considered, but many combinations of muscle capacity could lead to the decreased force in the LSC group of breast cancer survivors, and uncertainty would persist for any selected strategy. Therefore, it was decided to decrease the capacity as a whole, to mimic atrophy and a 'worst case scenario'.

After each alteration, simulations were run to determine whether the modifications matched the breast cancer survivor group (until the maximum force capable equalled that of the breast cancer survivor group). To ensure no over, or under correction was completed when the model failed, the capability was increased by 0.01 until the model converged on an optimal result for the given force. When this was achieved, these modifications became the baseline for a compromised system (Figure 33, Table 22). This was completed for both isometric strength trial posture.

5.3.3 Scenario Simulations

Following the acceptance of altered muscle capacity, various training scenarios were used to determine the maximum force output that could be achieved through retraining certain muscle groups to a priori defined states of capability. Each scenario is outlined in Table 21. The capability of all muscles were altered to the maximum that could be trained based on each given scenario. All muscles were 'fully trained' based on each scenario, and the final capabilities were established (Table 22). Maximal force output for each scenario was determined at the maximum capabilities for each muscle, for each scenario. Force was input starting at the LSC breast cancer survivor level, and increased by 10% for each iteration until the model was unable to produce force at the given level with the current muscle capacities modelled. It was proposed that if the configuration was able to produce the force of the reference population, the minimum capabilities to produce that force would be determined. However, in all scenarios, the muscles trained maximally were unable to reach the reference population force. Each scenario was completed for both of the aforementioned isometric strength trials ((reference population + baseline +3 scenarios) X 2 strength trials = 10 total).

Table 21: Training scenarios used to govern increases in force capabilities (each treatment represents a worst-case scenario where full effects of treatment on the various muscles occur)

Training Scenarios	Description
Scenario A “Chemotherapy”	• All muscles are able to be trained, however muscles can only regain 25% of reference capability from the reduced level to represent the inability for PCSA to increase similarly to normal muscle after damage from chemotherapy (Christensen et al., 2014)
Scenario B “Radiation”	• All muscles damaged by radiation are unable to be trained- pectoralis major, pectoralis minor, teres major, latissimus dorsi (Lipps et al., 2017)
Scenario C “Combination”	• All muscles damaged by radiation (pectoralis major, pectoralis minor, teres major, and latissimus dorsi) are unable to be trained • All other muscles are only trained up to 25% from their baseline

Table 22: Capacity of all muscles through each training scenario

Muscle Elements	**Adduction**				**Internal Rotation**			
	Baseline	**Scenario A**	**Scenario B**	**Scenario C**	**Baseline**	**Scenario A**	**Scenario B**	**Scenario C**
Latissimus Dorsi Upper 1	0.53	0.78	0.53	0.53	0.41	0.66	0.41	0.41
Latissimus Dorsi Lower 2	0.53	0.78	0.53	0.53	0.41	0.66	0.41	0.41
Levator Scapulae 3	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Omohypoid 4	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Pectoralis Major Sternal 5	0.53	0.78	0.53	0.53	0.41	0.66	0.41	0.41
Pectoralis Major Clavicular 6	0.53	0.78	0.53	0.53	0.41	0.66	0.41	0.41
Pectoralis Minor 7	0.53	0.78	0.53	0.53	0.41	0.66	0.41	0.41
Rhomboid Major 8	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Rhomboid Minor 9	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Serratus Anterior Upper 10	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Serratus Anterior Middle 11	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Serratus Anterior Lower 12	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Sternocleidomastoid 13	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Sternohyoid 14	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Subclavius 15	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Trapezius Middle 16	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Trapezius Lower 17	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Trapezius Upper 18	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Trapezius Clavicular 19	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Deltoid Middle 20	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Deltoid Posterior 21	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Deltoid Anterior 22	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Coracobrachialis 23	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Infraspinatus Upper 24	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Infraspinatus Lower 25	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Subscapularis Upper 26	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Subscapularis Middle 27	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Subscapularis Lower 28	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Supraspinatus 29	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Teres Major 30	0.53	0.78	0.53	0.53	0.41	0.66	0.41	0.41
Teres Minor 31	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Biceps Long 32	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Biceps Short 33	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Triceps Long 34	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Triceps Medial 35	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Triceps Lateral 36	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Brachialis 37	0.53	0.78	1	0.78	0.41	0.66	1	0.66
Brachioradialis 38	0.53	0.78	1	0.78	0.41	0.66	1	0.66

5.4 Data Analysis

A total of 10 training scenarios were simulated (3 training scenarios (and baseline and reference) by 2 isometric strength trials). Maximum force is reported for each scenario. Additionally, resultant shoulder torque was extracted for each scenario. In addition, percentage of maximal force (%MVF) was extracted for each muscle element at the baseline and maximal force output for each training scenario. The muscle elements are as follows: levator scapulae (1), omohyoid (1), pectoralis minor (1), rhomboid major (1), rhomboid minor (1), sternocleidomastoid (1), sternohyoid (1), subclavius (1), coacobrachialis (1), supraspinatus (1), teres major (1), teres minor (1), brachialis (1), brachioradialis (1), latissimus dorsi (2), serratus anterior (3), trapezius (4), subscapularis (3), infraspinatus (2), pectoralis major (2), deltoid (3), biceps (2), and the triceps (3). %MVF is expressed as a percent of the reference population capability to allow comparisons between scenarios.

To examine the agreement of the model with EMG data, the results were compared to empirically measures EMG measures of the LSC breast cancer survivor group. For this comparison %MVF was also exported as a percent of the given scenario's maximal capacity for the 8 muscle elements in which %MVC can be reported. These muscles are the pectoralis major (sternal and clavicular insertions), latissimus dorsi (lower), deltoid (anterior, middle, posterior), infraspinatus (lower), and supraspinatus. sEMG was filtered and analyzed as in section 4.4.2 *sEMG Processing* (page 85). Unlike Study 2, peak sEMG was extracted from strength trials for comparison. The differences between the maximum for each scenario were calculated and reported (Chopp-Hurley et al., 2016; Lang et al., 2020).

5.5 Statistical Analysis

Descriptive outputs were created for all scenarios. Forty variables were thus extracted for 10 simulations run (2 known force levels (baseline and reference) and 3 training scenarios (radiation damage, chemotherapy damage, combination treatment damage) for 2 isometric strength trials (adduction and internal rotation). The 40 variables that are reported are peak force, peak shoulder torque, and %MVF (as a percentage of reference force capacity) for each muscle element (latissimus dorsi (2), serratus anterior (3), trapezius (4), subscapularis (3), infraspinatus (2), pectoralis major (2), deltoid (3), biceps (2), triceps (3), levator scapulae, omohyoid, pectoralis minor, rhomboid major, rhomboid minor, sternocleidomastoid, sternohyoid, subclavius, coacobrachialis, supraspinatus, teres major, teres minor, brachialis, brachioradialis). Each variable is reported within strength trials, to allow for visual comparison across the scenarios.

Additionally, %MVF, expressed as a percent of reduced capacity, was exported for all 10 simulations for comparison to experimentally derived %MVC for the LSC group of breast cancer survivors. Only 8 muscle elements were compared, as those were the only muscles experimentally collected (latissimus dorsi, pectoralis major (sternal and clavicular), deltoid (anterior, middle and posterior), infraspinatus and supraspinatus).

5.6 Results

The two force exertions investigated were adduction and internal rotation. Maximal force outputs for each scenario (reference population, LSC breast cancer survivor, chemotherapy simulation, radiation simulation, and combination of chemotherapy and radiation simulation) as well as percentage of full capacity muscle force are reported for both force directions. A representation of each simulation can be seen in Figure 34.

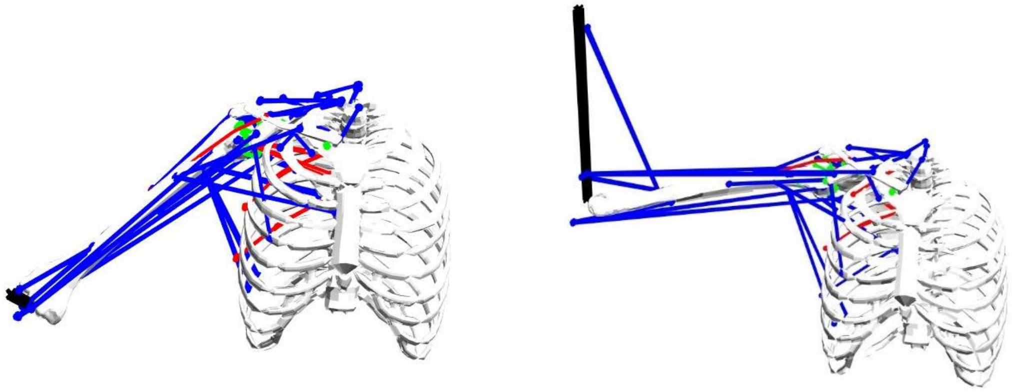


Figure 34: Isometric positions for adduction (left) and internal rotation (right). These model outputs are representative simulations, but the posture remained across all scenarios.

5.6.1 Adduction

With full training of all available muscles, the LSC group of breast cancer survivors were unable to reach the full force output of the non-cancer reference population (Table 23, Figure 35). To begin, the LSC had 55.6% of the maximal force producible of the reference group (Figure 35). The maximal force producible for the chemotherapy and radiation simulations were 77.9 and 80.1% of the reference group (Figure 35). Finally, the maximal recoverable force for the combination simulation was 69.5% of the reference population (Figure 35). As determined in Study 1, the HSC produced an average of 201.45N, in contrast to the 212.22N of the reference population (Table 16, page 64). Similarly, the LSC group had shoulder moment values that were 52.5% of the reference population (Table 23, Figure 35). The three scenarios fell between with chemotherapy and radiation groups 75.1 and 78% of the reference population (Figure 35). The combination treatment scenario had the lowest shoulder moment of the scenarios, at 19.94Nm, or 66.4% of the reference population (Figure 35).

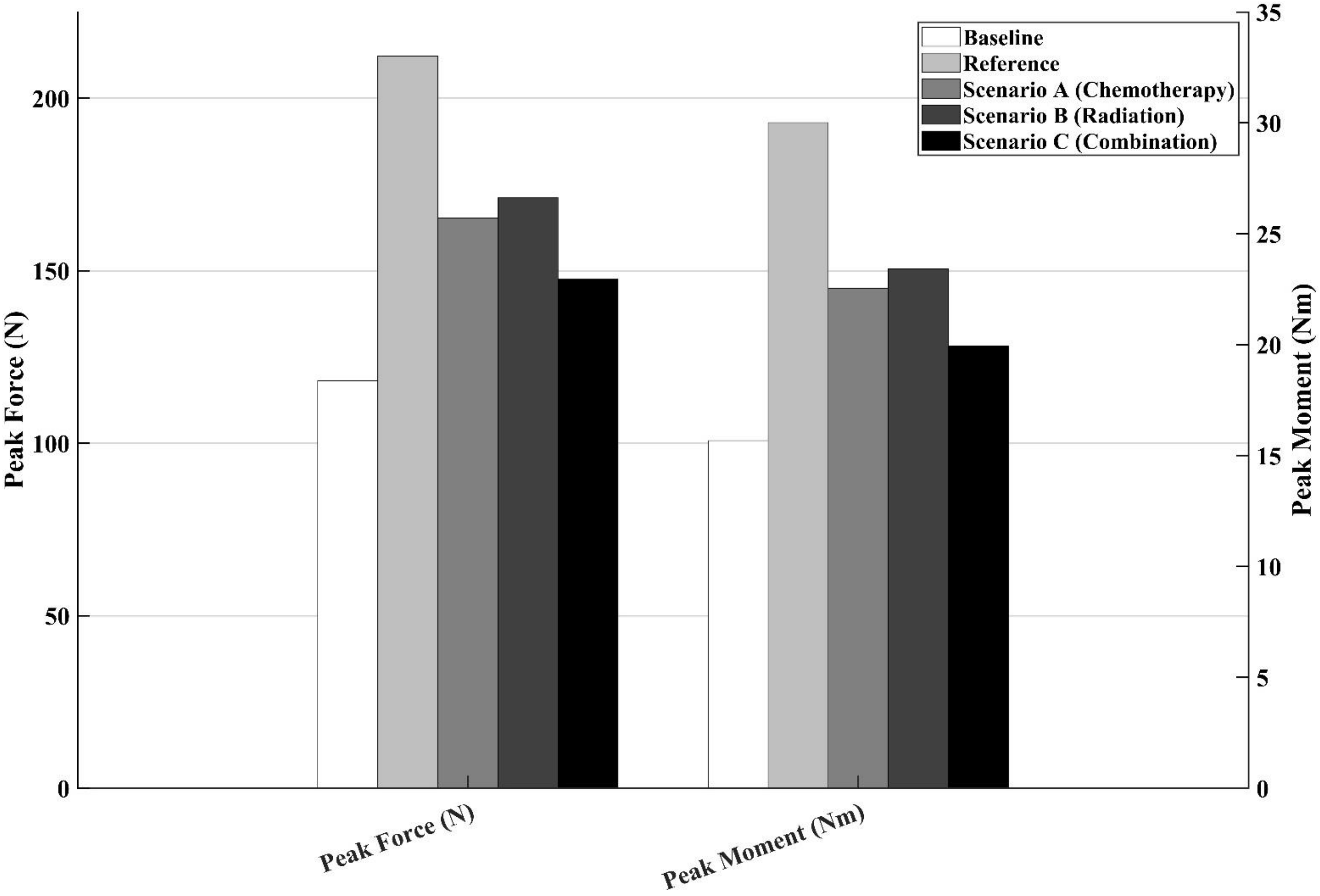


Figure 35: Peak force (input) (N) and peak moment (Nm) during each of the 5 adduction simulations run: baseline (LSC from Study 1), reference (non-cancer reference population), and the 3 scenarios (chemotherapy, radiation and the combination of both chemotherapy and radiation)

The muscles with the biggest differences were scapular stabilizers, adductors and some antagonist abductors (Table 23, Figure 36). Generally, a lower percentage of maximal force production was used in scenario simulations compared to the reference population simulation. %MVF is representative of a full capacity muscle (normalized to reference population capacity for comparison), and therefore these values are necessarily below that of the reference population, as the input force is less and the capacity of the muscle is decreased. The LSC group estimated 10.9-47.1% MVF less than the reference group for the latissimus dorsi (upper and lower), levator scapulae, omohyoid, rhomboid (major and minor), trapezius (upper), deltoid (middle), subscapularis (lower), teres major, biceps (long) and triceps (long) (Table 23, Figure 36). The chemotherapy simulation predicted 16.9-25.6% MVF less than the reference group for the latissimus dorsi (upper and lower), levator scapulae, omohyoid, rhomboid (major and minor), trapezius (upper), deltoid (middle), subscapularis (lower), biceps (long) and triceps (long (Table 23, Figure 36)). The radiation simulation estimated 16.96-70.64% MVF more for the pectoralis minor, sternocleidomastoid, trapezius (middle), teres major and biceps (short), compared to the reference simulation (Table 23, Figure 36). Additionally, this simulation predicted 17.8-45.9% MVF less of the latissimus dorsi (upper and lower), deltoid (middle), subscapularis (lower), and biceps (long), compared to the reference group (Table 23, Figure 36). Finally, the combination simulation estimated 16.7-48.6% MVF more for the pectoralis minor, sternocleidomastoid, trapezius (middle), and biceps (short) compared to the reference (Table 23, Figure 36). This simulation also estimated 19.9-45.9%MVF less compared to the reference for the latissimus dorsi (upper and lower), levator scapulae, rhomboid (major and minor), trapezius (upper), deltoid (middle), subscapularis (lower), biceps (long) and triceps (long) (Table 23, Figure 36).

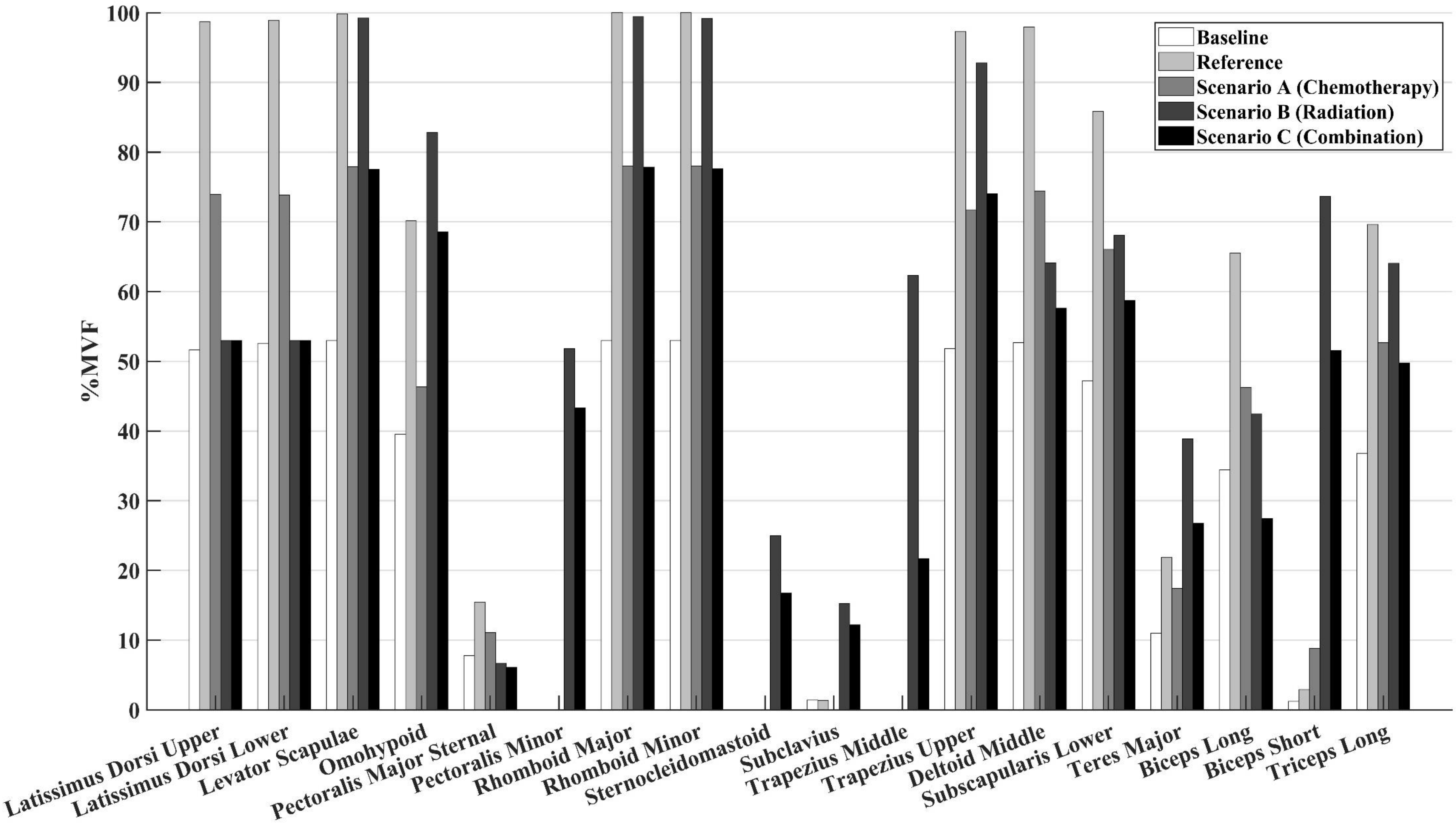


Figure 36: Predictions of each muscular elements with %MVF that differed during each of the 5 adduction simulations run (baseline (LSC from Study 1), reference (non-cancer reference population), and the 3 scenarios (chemotherapy, radiation and the combination of both chemotherapy and radiation). %MVF represents percentage of maximal force of the capacity of muscles in the reference trials.

Table 23: Model outputs for peak force and muscle elements (%MVF is percentage of each muscles full capacity as dictated by reference population) for adduction scenarios

	Baseline (LSC)	**Reference**	**Scenario A**	**Scenario B**	**Scenario C**
Peak force (input) (N)	118.02	212.22	165.22	171.12	147.52
Peak shoulder moment (Nm)	15.67	30.01	22.54	23.41	19.94
Latissimus Dorsi Upper (%MVF)	51.63	98.73	73.94	53.00	53.00
Latissimus Dorsi Lower (%MVF)	52.56	98.92	73.87	53.00	53.00
Levator Scapulae (%MVF)	53.00	99.82	77.91	99.23	77.52
Omohypoid (%MVF)	39.53	70.18	46.35	82.84	68.59
Pectoralis Major Sternal (%MVF)	7.76	15.48	11.08	6.69	6.12
Pectoralis Major Clavicular (%MVF)	0.00	0.00	0.00	0.00	0.00
Pectoralis Minor (%MVF)	0.00	0.00	0.00	51.83	43.30
Rhomboid Major (%MVF)	53.00	100.00	78.00	99.43	77.87
Rhomboid Minor (%MVF)	53.00	100.00	78.00	99.19	77.61
Serratus Anterior Upper (%MVF)	0.16	0.16	0.16	0.16	0.16
Serratus Anterior Middle (%MVF)	0.16	0.16	0.16	0.16	0.16
Serratus Anterior Lower (%MVF)	0.16	0.16	0.16	0.16	0.16
Sternocleidomastoid (%MVF)	0.00	0.00	0.00	25.00	16.74
Sternohyoid (%MVF)	0.00	0.00	0.00	2.58	2.10
Subclavius (%MVF)	1.41	1.33	0.00	15.25	12.19
Trapezius Middle (%MVF)	0.00	0.00	0.00	62.33	21.71
Trapezius Lower (%MVF)	0.00	0.00	0.00	0.00	0.00
Trapezius Upper (%MVF)	51.82	97.33	71.72	92.82	74.03
Trapezius Clavicular (%MVF)	0.05	0.05	0.00	0.00	0.00
Deltoid Middle (%MVF)	52.68	97.97	74.45	64.14	57.64
Deltoid Posterior (%MVF)	0.46	0.00	0.00	0.00	0.00
Deltoid Anterior (%MVF)	0.00	0.00	0.00	0.00	0.00
Coracobrachialis (%MVF)	0.00	0.00	0.00	0.00	0.00
Infraspinatus Upper (%MVF)	0.00	0.00	0.00	0.00	0.00
Infraspinatus Lower (%MVF)	0.00	0.00	0.00	0.00	0.00
Subscapularis Upper (%MVF)	0.00	0.00	0.00	0.00	0.00
Subscapularis Middle (%MVF)	0.01	0.11	0.51	0.00	0.13
Subscapularis Lower (%MVF)	47.16	85.86	66.06	68.09	58.74
Supraspinatus (%MVF)	0.00	0.00	0.00	0.00	0.00
Teres Major (%MVF)	11.00	21.91	17.43	38.87	26.76
Teres Minor (%MVF)	0.00	0.00	0.00	0.00	0.00
Biceps Long (%MVF)	34.45	65.55	46.23	42.43	27.42
Biceps Short (%MVF)	1.23	2.91	8.79	73.68	51.53
Triceps Long (%MVF)	36.76	69.64	52.69	64.08	49.78
Triceps Medial (%MVF)	0.00	0.00	0.00	3.00	0.00
Triceps Lateral (%MVF)	0.00	0.00	0.00	0.00	0.00
Brachialis (%MVF)	0.00	0.00	0.00	0.00	0.00
Brachioradialis (%MVF)	0.00	0.00	0.00	0.00	0.00

Muscle force production varied greatly from experimentally collected muscle activation. Pectoralis major (clavicular activation), infraspinatus, supraspinatus, and the anterior and posterior deltoid were not activated in the simulation (0% MVF) (Table 24). Pectoralis major (clavicular insertion) however, was largely activated in the experiment, averaging 45.3%MVC (Table 24). The supraspinatus and posterior deltoid were relatively inactive experimentally (less than 10%MVC) and therefore well represented in the simulation (Table 24). The infraspinatus and anterior deltoid were moderately active experimentally (16.6 and 15.9% MVC, respectively), and were therefore underestimated in the model (Table 24). The middle deltoid was the furthest from accurate with activation predicted at 56.3-91.6% MVF larger than that of the 7.8%MVC experimentally measured (Table 24). The latissimus dorsi was relied on heavily in the simulation, and overestimated the activation by 63.8-69.1% MVF compared to the 30.89%MVC of the LSC (Table 24). Of the muscles that were activated in the model (and experimentally monitored), the pectoralis major (sternal insertion) had the closest agreement. The model underestimated this muscle by 27.1-31.1%MVF (at 11.6-15.5% MVF) compared to the experimentally derived 42.6%MVC of the LSC group of breast cancer survivors (Table 24).

Table 24: Comparison of muscle elements and experimental sEMG for each scenario during adduction strength simulations. %MVF in this table represents percent of reduced capacity

Muscle Elements	Baseline (LSC) (%MVF)	Reference (%MVF)	Scenario A (%MVF)	Scenario B (%MVF)	Scenario C (%MVF)	Experimental (LSC) (%MVC)	Experimental (HSC) (%MVC)
Latissimus Dorsi Lower	99.17	98.92	94.71	100.00	100.00	30.89 ± 10.92	19.65 ±14.07
Pectoralis Major Sternal	14.65	15.48	14.21	12.63	11.55	42.60 ± 13.02	35.84 ± 14.72
Pectoralis Major Clavicular	0.00	0.00	0.00	0.00	0.00	45.30 ± 8.89	37.25 ± 14.44
Deltoid Middle	99.39	97.97	95.45	64.14	73.90	7.82 ± 4.91	6.65 ± 3.67
Deltoid Posterior	0.87	0.00	0.00	0.00	0.00	6.97 ± 5.93	4.49 ± 2.27
Deltoid Anterior	0.00	0.00	0.00	0.00	0.00	16.57 ± 5.93	14.48 ± 10.71
Infraspinatus Lower	0.00	0.00	0.00	0.00	0.00	15.87 ± 9.02	13.05 ± 6.45
Supraspinatus	0.00	0.00	0.00	0.00	0.00	8.73 ± 6.55	6.54 ± 4.46

5.6.2 Internal Rotation

In all training scenarios, the LSC group of breast cancer survivors did not reach the full force output of the non-cancer reference population (Table 25, Figure 37). The LSC produced 44.5% of the force of reference group, and 40.2% of the shoulder torque, at 76.14N of force, and 26.04Nm of torque (Table 25, Figure 37). As a comparison, the HSC produced 130.01N of internal rotation force (Table 16, page 67). When all muscles were fully trained, the chemotherapy and radiation simulations were able to reach 68.9 and 75.5% of the reference group's force, and 65.9 and 72.9% of shoulder moment, respectively (Table 25, Figure 37). Finally, the maximal recoverable force for the combination treatment simulation was 60.0% of the reference population, and 56.6% of the reference population shoulder moment (Table 25, Figure 37).

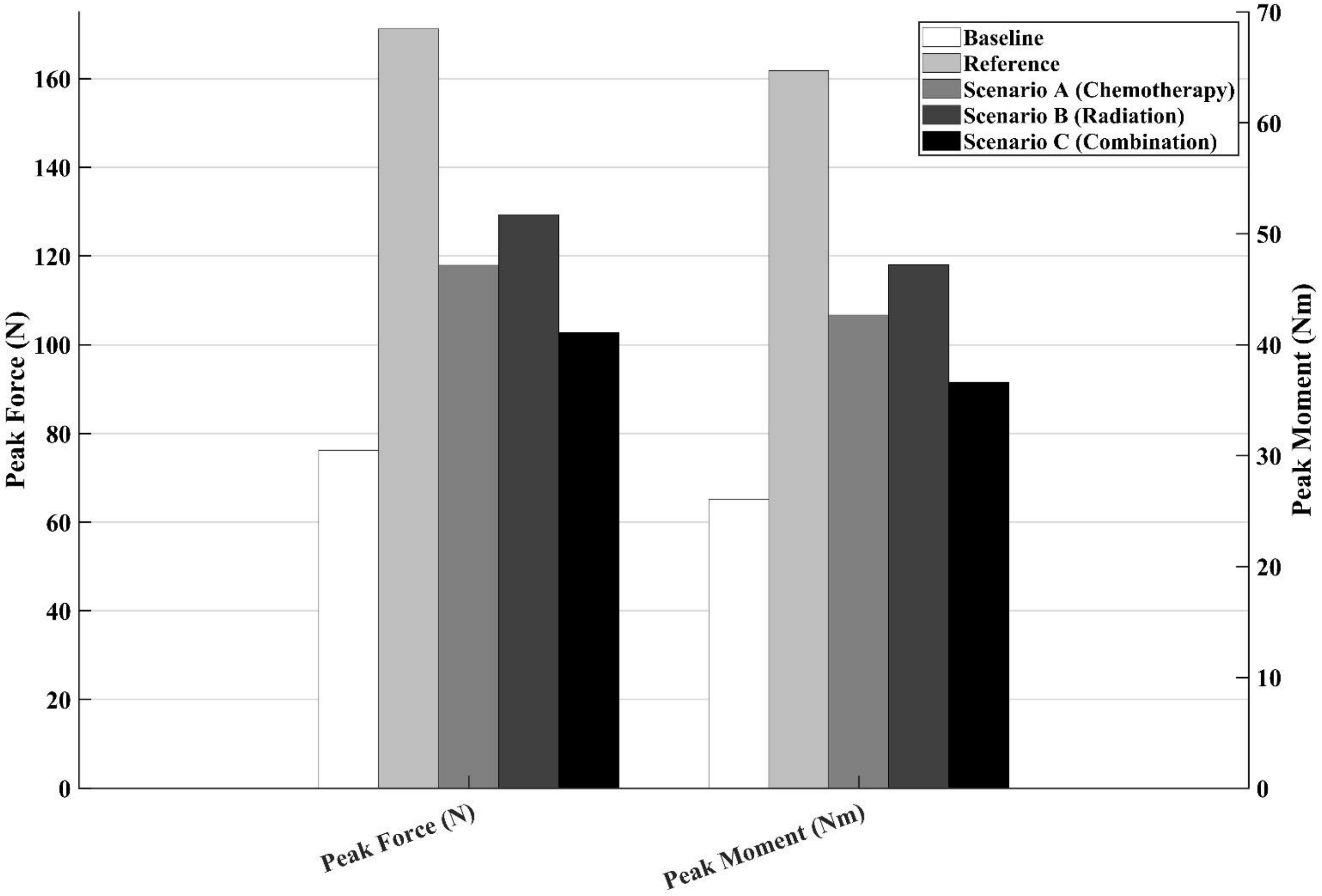


Figure 37: Peak force (input) (N) and peak moment (Nm) during each of the 5 internal rotation simulations run: baseline (LSC from Study 1), reference (non-cancer reference population), and the 3 scenarios (chemotherapy, radiation and the combination of both chemotherapy and radiation).

Internal rotators and scapular stabilizers were affected by the training simulations (Table 25, Figure 38). Generally, maximal voluntary force in the simulations was lower than the comparison reference group (Table 25, Figure 38). In the radiation, and combination simulations some muscles predicted increased %MVF compared to the reference group (Table 25, Figure 38). The baseline group (based on LSC force production) used 16.0-53.0% MVF less than the reference group for the latissimus dorsi (upper and lower), levator scapulae, omohyoid, rhomboid (major and minor), trapezius (upper), deltoid (middle and posterior), subscapularis (middle and lower), biceps (long and short) and triceps (long) (Table 25, Figure 38). In the chemotherapy simulation, a prediction of 13.0-30.4% MVF less of the latissimus dorsi (upper and lower), levator scapulae, omohyoid, rhomboid (major and minor), trapezius (upper), deltoid (middle and posterior), subscapularis (middle and lower), biceps (long) and triceps (long) were estimated, compared to the reference simulation (Table 25, Figure 38). During the radiation simulation, 10.3-46.1% MVF more of pectoralis minor, sternocleidomastoid, trapezius (middle), teres major and biceps (short) (Table 25, Figure 38). Additionally, this simulation predicted 7.8-47.3% MVF less of the latissimus dorsi (upper and lower), trapezius (middle), deltoid (middle), subscapularis (middle and lower), biceps (long) and triceps (long) (Table 25, Figure 38). Finally, the combination treatment simulation predicted 11.1-15.8%MVF more from pectoralis minor and trapezius (middle) (Table 25, Figure 38). This simulation also estimated 12.6-47.3%MVF less of the latissimus dorsi (upper and lower), levator scapulae, omohyoid, rhomboid (major and minor), trapezius (upper), deltoid (middle and posterior), subscapularis (middle and lower), biceps (long) and triceps (long) (Table 25, Figure 38).

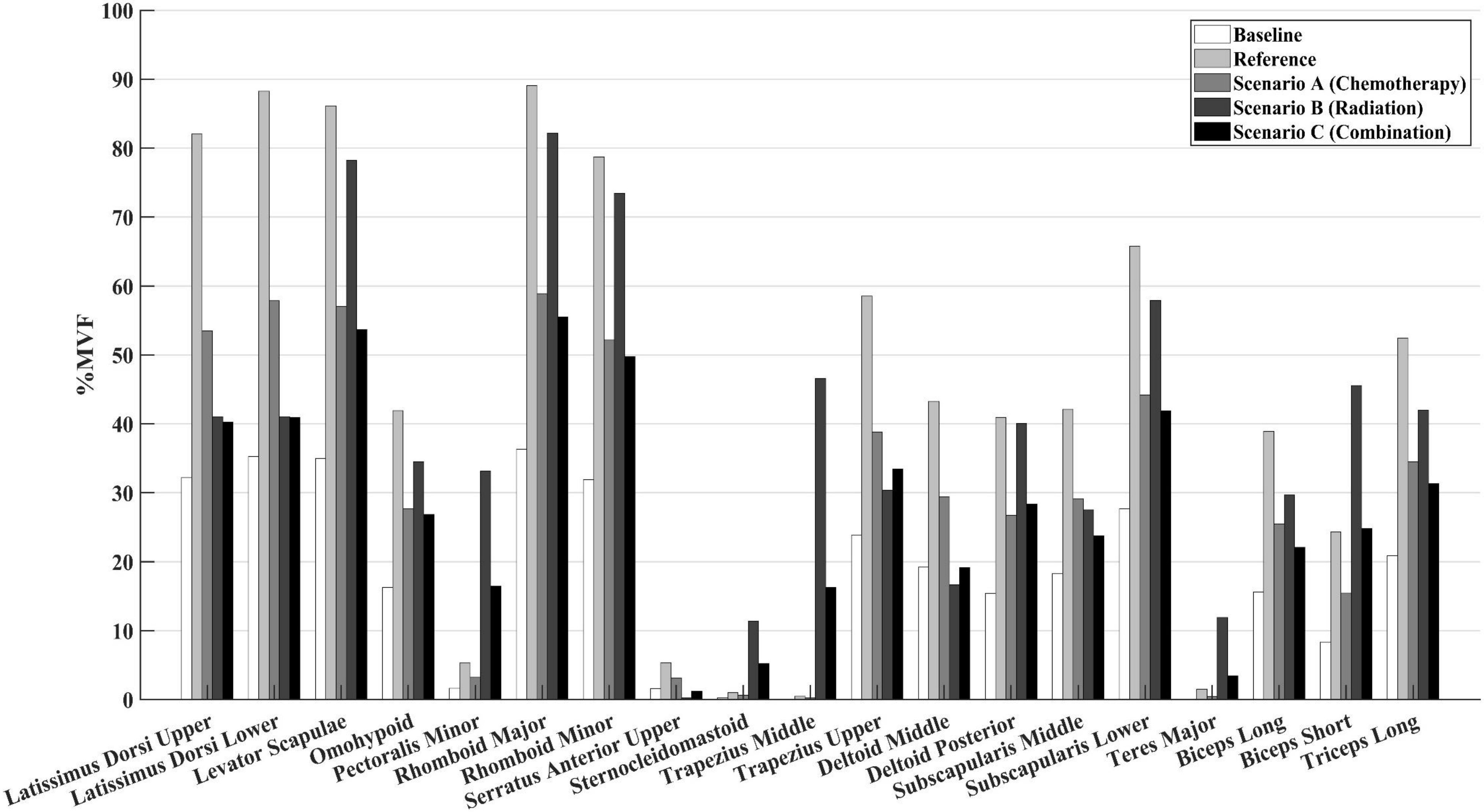


Figure 38: Predictions of each muscular elements with %MVF that differed during each of the 5 internal rotation simulations run (baseline, reference, and the 3 scenarios (chemotherapy, radiation and the combination of both chemotherapy and radiation). %MVF represents percentage of maximal force of the capacity of muscles in the reference trials.

Table 25: Model outputs for peak force and muscle elements (%MVF is percentage of each muscles full capacity as dictated by reference population) for internal rotation scenarios

	Baseline (LSC)	**Reference**	**Scenario A**	**Scenario B**	**Scenario C**
Peak force (input) (N)	76.14	171.20	117.94	129.34	102.74
Peak shoulder moment (Nm)	26.04	64.72	42.67	47.21	36.62
Latissimus Dorsi Upper (%MVF)	32.24	82.05	53.52	41.00	40.24
Latissimus Dorsi Lower (%MVF)	35.27	88.27	57.86	41.00	40.92
Levator Scapulae (%MVF)	34.97	86.15	57.03	78.26	53.66
Omohypoid (%MVF)	16.28	41.93	27.66	34.48	26.88
Pectoralis Major Sternal (%MVF)	0.37	3.82	1.70	0.69	0.78
Pectoralis Major Clavicular (%MVF)	0.00	0.00	0.00	0.00	0.00
Pectoralis Minor (%MVF)	1.64	5.32	3.28	33.14	16.45
Rhomboid Major (%MVF)	36.32	89.06	58.91	82.20	55.50
Rhomboid Minor (%MVF)	31.90	78.74	52.19	73.44	49.78
Serratus Anterior Upper (%MVF)	1.59	5.33	3.11	0.24	1.20
Serratus Anterior Middle (%MVF)	0.24	0.24	0.24	0.24	0.24
Serratus Anterior Lower (%MVF)	0.24	0.24	0.24	0.24	0.24
Sternocleidomastoid (%MVF)	0.27	1.06	0.65	11.38	5.21
Sternohyoid (%MVF)	0.04	0.09	0.05	0.52	0.55
Subclavius (%MVF)	0.29	2.29	1.71	4.80	3.96
Trapezius Middle (%MVF)	0.00	0.51	0.27	46.58	16.28
Trapezius Lower (%MVF)	0.00	0.00	0.00	0.00	0.00
Trapezius Upper (%MVF)	23.88	58.54	38.82	30.40	33.44
Trapezius Clavicular (%MVF)	0.00	0.05	0.04	0.00	0.00
Deltoid Middle (%MVF)	19.21	43.28	29.42	16.66	19.18
Deltoid Posterior (%MVF)	15.44	40.92	26.75	40.09	28.36
Deltoid Anterior (%MVF)	0.00	0.00	0.00	0.00	0.00
Coracobrachialis (%MVF)	0.00	0.00	0.00	0.00	0.00
Infraspinatus Upper (%MVF)	0.00	0.00	0.00	0.00	0.00
Infraspinatus Lower (%MVF)	0.00	0.00	0.00	0.00	0.00
Subscapularis Upper (%MVF)	2.46	2.87	2.60	0.29	1.92
Subscapularis Middle (%MVF)	18.26	42.12	29.09	27.54	23.77
Subscapularis Lower (%MVF)	27.72	65.74	44.20	57.93	41.89
Supraspinatus (%MVF)	0.00	0.00	0.00	0.00	0.00
Teres Major (%MVF)	0.02	1.52	0.48	11.91	3.47
Teres Minor (%MVF)	0.00	0.00	0.00	0.00	0.00
Biceps Long (%MVF)	15.60	38.89	25.49	29.67	22.09
Biceps Short (%MVF)	8.36	24.33	15.47	45.58	24.83
Triceps Long (%MVF)	20.90	52.47	34.52	41.99	31.36
Triceps Medial (%MVF)	0.06	0.00	0.00	2.22	0.64
Triceps Lateral (%MVF)	0.00	0.00	0.00	0.00	0.00
Brachialis (%MVF)	0.00	0.00	0.00	0.00	0.00
Brachioradialis (%MVF)	0.00	0.00	0.00	0.00	0.00

Muscle force production varied from the experimentally derived muscle activation in many cases. In the simulations, pectoralis major (clavicular insertion), anterior deltoid, infraspinatus and supraspinatus were not activated (all were 0% MVF) (Table 26). Both the infraspinatus and supraspinatus were activated at 10%MVC or less in the experiment, however the pectoralis major (clavicular insertion) and anterior deltoid were both activated above 20% MVC (Table 26). The sternal insertion of pectoralis major was underestimated in the simulation (0.9-3.8% MVF) compared to 32.8% MVC in the experiment (Table 26). The latissimus dorsi was overestimated by 69.0-83.0%MVF compared to 17.0%MVC collected for the LSC group. The middle deltoid of the radiation simulation was the most accurate, only overestimated by 7.5% MVF, compared to19.9-37.6% MVF during the other simulations.

Table 26: Comparison of muscle elements and experimental sEMG for each scenario during internal rotation strength simulations. %MVF in this table represents percent of reduced capacity

Muscle Elements	Baseline (LSC) (%MVF)	Reference (%MVF)	Scenario A (%MVF)	Scenario B (%MVF)	Scenario C (%MVF)	Experimental (LSC) (%MVC)	Experimental (HSC) (%MVC)
Latissimus Dorsi Lower	86.0	88.27	87.67	100.00	99.81	16.99 ± 6.91	9.76 ± 5.19
Pectoralis Major Sternal	0.9	3.82	2.58	1.68	1.89	32.78 ± 14.22	28.31 ± 10.46
Pectoralis Major Clavicular	0.00	0.00	0.00	0.00	0.00	38.07 ± 15.46	28.54 ± 12.16
Deltoid Middle	46.84	43.28	44.58	16.66	29.06	9.21 ± 6.17	7.42 ± 3.74
Deltoid Posterior	37.66	40.92	40.54	40.09	42.97	7.08 ± 7.40	4.36 ± 2.60
Deltoid Anterior	0.00	0.00	0.00	0.00	0.00	20.05 ± 10.19	14.85 ± 8.82
Infraspinatus Lower	0.00	0.00	0.00	0.00	0.00	7.24 ± 4.21	6.34 ± 3.02
Supraspinatus	0.00	0.00	0.00	0.00	0.00	10.01 ± 4.76	8.56 ± 8.12

5.7 Discussion

The results of the simulations indicate that the focus in training for regaining strength following breast cancer treatment should not be placed solely on the agonist movers, but also glenohumeral stabilizers. The simulations represented common treatment scenarios, and included known reduced force capability effects on several muscles. Although multiple configurations of muscle forces are capable of producing a given external force, a representative, and conservative, approach was taken to model the average force of each given group. The purpose of this study was to determine the maximal recoverable force outputs for 3 treatment scenarios, while also investigating the internal muscle force patterns associated with producing those forces as estimated by a modified shoulder biomechanical model. It was hypothesized that the combination treatment scenario would have had the lowest recoverable force in both force directions, and that muscle forces would decrease in all muscles represented as having reduced capacity. The combination treatment simulation did produce the least force, however in the radiation and combination simulations several muscles were predicted to require increased muscle force, translating to increased demand, and thereby more rapid fatigue likelihood. Most muscles, however, were estimated to contribute less muscle force than the reference population to produce maximal forces (which is less than the reference force).

5.7.1 Rehabilitation Implications

Simulating training with the damage expected from treatment, can help to infer important rehabilitation considerations and refine or complement contemporary practice. The current study demonstrated the importance of considering muscles outside the radiation field (if radiation was used), and glenohumeral and scapular stabilizing muscles during adduction and internal rotation when improving strength. Reaching 70-80% of reference group strength (in all scenarios except the combination scenario in internal rotation), would allow survivors to sufficiently return to many daily tasks (de Souza Cunha et al., 2020). During adduction simulation, 16.95-48.62% MVF less muscle force was estimated from levator scapulae, omohyoid, rhomboid (major and minor), upper trapezius, subscapularis (lower), and triceps (long) compared to the reference, for all three simulations (Figure 36). During the chemotherapy simulation latissimus dorsi (upper and lower) was also relied on. In the radiation and combination simulations pectoralis minor, middle trapezius and biceps (short) were more heavily relied on compared to the LSC group. The middle deltoid was also predicted as contributing more force during the chemotherapy and radiation only simulations compared to the LSC group. Similarly, during internal rotation, muscle force was predicted to be 7.80-47.34% MVF less from latissimus dorsi, levator scapulae, omohyoid, rhomboid (major and minor), upper trapezius, posterior deltoid, subscapularis (middle and lower) and triceps (long) compared to the reference, for all three simulations (Figure 38). Pectoralis minor and middle trapezius were also recruited during radiation and combination simulations. The middle deltoid was predicted as producing more force in the chemotherapy simulation compared to the LSC group, and less in the radiation group. With the results of this simulation, to increase adduction force it is recommended to focus on both strengthening muscles that historically are thought to contribute to adduction (latissimus dorsi, triceps, teres major and pectoralis major), as well as muscles that work to stabilize the scapula (rhomboid major and minor), and stabilize the glenohumeral joint as antagonist muscles to adduction motion (upper trapezius and middle deltoid) (Moore, Dalley, & Agur, 2010). In internal rotation focus should be placed on increasing strength of subscapularis, latissimus dorsi, anterior deltoid and pectoralis major, as well as muscles that work to stabilize the scapula during rotation (posterior deltoid, middle trapezius and rhomboids). Due to the nature of optimization models (discussed further in section 5.7.4 *Model Comparison to experimental data*) antagonist muscle predictions often do not include all probable or possible muscles, but rather larger antagonist muscles are recruited due to the chosen cost function (cubed muscle stress) (Dul, Johnson, et al., 1984). The importance of these muscles to maintain stability of the joint is still apparent with increased force production during all simulations, compared to the LSC group.

In traditional exercise programs, focus is placed on targeting primary movers (agonists) of particular actions. As observed in study 1 of this dissertation, strength is a more informative measure than range of motion (in terms of functional measurements) and therefore it is important to consider this measurement to address shoulder-related quality of life in breast cancer survivors. Several review studies have concluded that resistance training programs often combine several simple upper body and lower body exercises (bicep curl, rowing, chest press, lateral raises, squats, calf raises) as well as active stretching (De Groef et al., 2015; Lopez et al., 2020; Ribeiro, Moreira, et al., 2019). Although the majority of these studies showed effectiveness in increasing strength, there is no specific focus on stabilizing the entire glenohumeral joint, instead focus is on the major muscle groups of all joints throughout the body. Stan et al (2016) investigated the use of yoga vs traditional resistance training in breast cancer survivors. Yoga combines both active stretching and can strengthen individuals, while using only body-weight (making implementation simpler). However, the goal of this program was to reduce cancer-related fatigue and strength changes were not considered (Stan et al., 2016). Schmitz et al (2019) focused on lymphedema mediation in breast cancer survivors by implementing a full year intervention focusing on facets of resistance training and weight loss. Weight loss intervention, alone or in combined with a resistance training program did not improve lymphedema for either group (Schmitz et al., 2019). Each exercise program aimed to target an adverse symptom experienced by breast cancer survivors. Although resistance training increases the strength of those muscles, more focus should be placed on ensuring that not only the primary movers are targeted, but also on increasing the strength of stabilizing muscles to improve function of breast cancer survivors following treatment to improve both function and shoulder-related quality of life.

5.7.2 Complexities of treatment

The effects of treatment, however, are not uniform for individuals who undergo these treatments. Immediately, participants in the HSC and LSC received similar treatment types, yet their maximum force production levels differed greatly (Table 16, page 67). In fact, the HSC force production was closer to that of the reference group in adduction, and the radiation simulation during internal rotation (Tables 23 and 25). Currently, it is difficult to prospectively predict whether survivors will be more similar to the LSC or HSC. The current simulation study modelled the ‘worst case scenario’ beginning with the force production of the LSC and assuming that muscles cannot be trained if damaged from radiation, and that chemotherapy will result in a finite capacity increase if properly trained. It is clear with the ability of the HSC group of breast cancer survivors that individuals who receive treatment can regain or maintain strength. In the development of the scenarios, the effects of treatment were considered. Mainly, that several muscles (latissimus dorsi, pectoralis major/minor and teres major) had received greater radiation during treatment, and were thus damaged during the process (Lipps et al., 2017). The effect of radiation lingers in the muscle, and scar tissue may form; though it may not be permanent. In this study a conservative approach was taken and the assumption was made that the damage was permanent and these muscles cannot be trained to produce more force (Lauridsen et al., 2008; Markes et al., 2006). Chemotherapy results in a reduced strength capacity in all muscles, as this is not a targeted treatment (Klassen et al., 2017). In this study, muscles were able to be trained to increase force capacity by only 25% to mimic the inability for capacity to continue to increase similarly to a normal muscle (Christensen et al., 2014). Again, this was a conservative approach to mimic a worst-case scenario. The combination scenario yielded the lowest recoverable force output for both adduction and internal rotation (Tables 23 and 25). With this logic, 17 of the 32 participants in study 1 would belong in the LSC, and have force less than 147.52N and 102.74N in adduction and internal rotation, respectively. However, this is not the case as there are 8 survivors in the LSC and 9 in the HSC who received both chemotherapy and radiation.

The force production of each group may be modulated by several factors such as age, surgery, reconstruction, side of diagnosis, strength before treatment, rehabilitation after treatment, and the differing regimens of each treatment (length of radiation, type of chemotherapy drug). The effect of age on strength are discussed in the following section (5.7.3 *Aging Effects on Strength*). As previously discussed, mastectomy, breast conserving therapy and axillary lymph node dissections are the three main surgeries used for treatment. Mastectomy and axillary lymph node dissection patients are 6 times more likely to have shoulder restrictions or functional limitations (which includes both range of motion and strength deficits), compared to breast conserving therapy (Vidt et al., 2020). Due to the removal of tissue in mastectomies force imbalances may occur between the affected and unaffected limbs (Crosbie et al., 2010). Higher invasiveness of surgery may exacerbate residual impairments, as well as additionally surgeries as is necessary in reconstruction. No participants in the current study had undergone reconstruction at the time of participation and therefore considering the additional consequences of these procedures is beyond the scope of this thesis, but it is important to consider that the various reconstructive surgeries may also modulate the ability of survivors to regain their full-strength following treatment. Further, a more pronounced difference occurs when the affected side is the non-dominant limb (Perez et al., 2018). Right-handed individuals have significantly greater grip-strength on their dominant side and therefore dominance should be considered (Incel, Ceceli, Durukan, Erdem, & Yorgancioglu, 2002). The simulations completed in this *in-silico* study were completed as the right limb, and all participants in study 1 and the reference population were right hand-dominant. There was a mix of left and right affected limbs in the LSC, so it is not likely this had an effect on the force production of this group. However, the laterality of diagnosis may have an affect for individual survivors and if the non-dominant side is the affected side may lead to a lower capacity to begin with, and therefore more difficulty achieving a given strength level. From pre-surgery to 1-5 years post surgery, strength is decreased, specifically 13.6-38.7% of survivors experienced continued loss in internal rotation strength, of an average of 1.39kg, coupled with an increase in arm volume (Belmonte, Messaggi-Sartor, Ferrer, Pont, & Escalada, 2018). Individuals who are active prior to surgery are 85% more likely to report limited disability 3 weeks following surgery (A. Yang, Sokolof, & Gulati, 2018), suggesting potential benefits of 'prehabilitation'. Similarly, as discussed in the previous section, rehabilitation and exercise programs completed will have differential outcomes for individuals. Finally, differences in the regimens of each treatment (length of radiation, type of chemotherapy drug) will also affect the musculature and each individual differently. No research has been completed on the biomechanical repercussions of individual treatment regimens, but it is likely that more intense chemotherapy drugs, and longer radiation regimens would lead to more damage and a reduced capacity to regain strength. Combined, all of these factors make it complex to assume that the scenarios simulated in this study capture all of the areas that would prevent muscle capacity gains. Rather, this study illuminated that even in the worst-case scenario, emphasis should not be placed on just the primary movers, or the muscles most often damaged by radiation, but also muscles responsible for stabilization of the scapula and glenohumeral joint.

5.7.3 Aging Effects on Strength

As previously discussed in section *3.7.4 Comparison to non-cancer population* (page 75), aging affects the musculoskeletal system. As stated, over the age of 45, muscle mass is lost at a rate of 0.37%, and strength is lost 2-5 times faster than mass (and these effects accelerate over the age of 75 (Mitchell et al., 2012). The reference population in the current study was 22.4 years old, while the LSC breast cancer groups was 56.7 years old. If the strength loss begins at 45, and conservatively we assume its 5 times faster than mass loss, a 22.2% strength loss may occur by the age of 57 (Mitchell et al., 2012). In similar postures to those evaluated in the current study strength loss is 4.8% in adduction between 20-29-year old's and 50-59-year old's, but 46.2-52.6% in internal rotation for the same age groups (Hughes et al., 1999). The difference between the reference population and LSC breast cancer group in this study was 56.4 % in adduction and 76.3% in internal rotation. Even conservatively, these differences exceed age-related effects, and therefore can at least partially be attributed to treatment or the disease itself. Ideally, an age-matched reference population would serve as an additional comparison group in this study, but COVID-19 resulted in the suspension and ultimate termination of collections before this data could be acquired. The HSC breast cancer group had similar strength to the reference population in adduction (201.45N and 212.22N, respectively). This is comparable to the 5% loss due to aging previously cited (Hughes et al., 1999). The difference between the reference population in the current study and internal rotation strength of the HSC is larger (27.3%), but again can be considered plausible within aging effects (Hughes et al., 1999; Mitchell et al., 2012). In adduction, therefore, the addition of an age-matched reference group would have had minimal difference, and would likely have fallen between the radiation treatment maximal recoverable force (171.1N) and the reference group (212.2N). In internal rotation, the effects of aging are less predictable. The HSC breast cancer group force output was 130.0N, which was comparable to the radiation treatment maximal recoverable force (129.3N). Given the effects of aging and strength previously described, it would be expected that the HSC breast cancer group was within the range of strength expected of an aged-matched reference population (Hughes et al., 1999; Mitchell et al., 2012). With this comparison, strength may be recoverable up to 90.7 and 99.5% in the chemotherapy and radiation treatment scenarios, respectively. The combination treatment scenario would reach 79.0% of the age-matched control force output. With these results, and comparisons to age-matched reference values, it may be realistic to assume that strength may be recoverable to 70-80% even with a combination of treatments, and accompanying worst-case damage. These simulations, however, did not account for damage from surgery or secondary symptoms (such as lymphedema or chording), and these should be taken into consideration for future studies as they would potentially increase dysfunction.

5.7.4 Model Comparison to experimental data

The SLAM model has been used in the breast cancer survivor population in several situations, however not with maximal exertions. The model was initially designed to assess a reference, non-clinical population, and although there was difficulty predicting magnitude of antagonistic muscles during static holds (a common outcome with optimization models), the correct muscles were recruited during targeted reaching tasks (Dickerson, Hughes, & Chaffin, 2008). Previously, breast cancer survivor population was simulated with the SLAM model during submaximal internal and external rotation tasks, with hand forces at 19.6N and 40N (Chopp-Hurley et al., 2016), and under 10N during functional tasks (Lang et al., 2020). In both of these studies predicted muscle forces underestimated empirically collected values (13.4-30.4% and 7.3-31.6%, respectively) (Chopp-Hurley et al., 2016; Lang et al., 2020).

The larger discrepancies in the current study (6.10-91.57% in adduction, and 7.24-83.01% in internal rotation) likely emerge due to several factors. Firstly, co-contraction is not well represented in optimization models, although the inclusion of a stability constraint increases the recruitment of some glenohumeral antagonist stabilizers, it is not a perfect solution (Dickerson et al., 2007, 2008). The sum of the cubed muscle stress (the cost function of SLAM) leads to load sharing between muscles, but still preferentially recruits larger muscles to limit stress (Dul, Townsend, Shiavi, & Johnson, 1984). Beyond this, the model is a single average musculoskeletal geometry. Both the input of height and weight to scale the model are an average of the group, and the shoulder rhythm included represents a population average (Dickerson et al., 2007). Segments and coordinate systems are based on published proportions (Hogfors et al., 1987; Makhsous et al., 1999). These proportions are guided by height (as described), and an input of experimentally collected bony landmarks from one representative individual. The shoulder rhythm included in the study is again, a representation modified from previously reported rhythms (Hogfors et al., 1991; Karlsson & Peterson, 1992; Makhsous et al., 1999). However, in SLAM these are modified to support the bony landmarks experimentally collected (Dickerson et al., 2007). The combination of these factors, and average muscle attachment sites leads to a model that represents one particular geometry, and not the breadth of individuals included in our average values.

Secondly, experimentally measured data has inherent, well known limitations. MVCs may not be accurate, and represent population averages. MVCs completed in different postures may lead to inaccurate muscle activation representation (Maciukiewicz, Lulic, MacKay, Meszaros, & Dickerson, 2019). In addition to potentially inaccurate representation, EMG measures come with variability in collection and output (De Luca, 1997; Maciukiewicz et al., 2019; Winter, 1991). If we consider the variability in EMG to account for these differences, most of the model predictions are within two standard deviations of experimental data (Table 24, 25). Beyond inherent issues with EMG, it is challenging to ensure accurate MVCs with a clinical population, due to physical limitations, and pain avoidance (Lindstroem, Graven-Nielsen, & Falla, 2012). If a true maximal effort is not achieved, muscle activation may be overestimated when normalized to this maximum. In the current study %MVF is calculated based on both full capacity (of the reference population) to allow comparison between simulations (Tables 23 and 25), and for the capacity of each given scenario to allow comparison to measured %MVC (Tables 24 and 26). However, %MVC is not a perfect representation of %MVF. Muscle activation and muscle force magnitudes are qualitatively and conceptually similar, but they are not linearly related. %MVC does not necessarily correspond to the exact proportion of %MVF, but it is the closest approximation currently available (Disselhorst-klug, Schmitz-rode, & Rau, 2009). Validity, as a concept, involves checking all aspects of the model, and is a continual process (Lewandowski, 1981). SLAM has been tested in various scenarios and tasks and has relatively good agreement in predicting inactivity of muscles that are not recruited, as well as for primary movers in given tasks (Chopp-Hurley et al., 2016; Dickerson et al., 2008; Lang et al., 2020). Although it has not been investigated in maximal tasks, the results from the current study align with the prediction of primary movers. An important part of construct validity or appropriateness is interpreting the results (Lewandowski, 1981), where the utility of using the model is not for prediction of exact %MVF of each muscle, but the patterns of muscles used when capacity limitations exist, as well as the recoverable force output of the compromised system.

The final component, load sharing between muscles, combines model and physiological factors. The ability for SLAM to accurately load share can be influenced by several factors, mainly co-activation, moment arm and size of the muscle. Physiologically, we do not activate one muscle at a time, rather several muscles to complete the same task and to maintain glenohumeral and scapular stability. Previously, a co-activation constraint was investigated during internal and external rotation tasks (Chopp-Hurley et al., 2016). By enforcing known co-activation relationships the fidelity of the model improved, and lowered the differences between the predicted forces and experimentally collected data by an average of 6% (Chopp-Hurley et al., 2016). As the co-activation ratio was specific to the posture and task, it was not used in the current study, however this could improve future estimates. Further, with the use of the cubed muscle stress cost function larger muscles with larger moment arms are preferentially recruited (Dul, Johnson, et al., 1984). The internal rotation and adduction positions used in the current study created an ideal situation for latissimus dorsi (a large muscle) to be effective in both internal rotation and adduction, respectively and therefore attractive to the mathematical minimization routine. Rhomboid major was also largely recruited as a scapular stabilizer, with the largest moment arm and PCSA. The pectoralis major with its small size and moment arm was too costly to activate and therefore not required or desired to contribute in the simulation. Further research should include extra partitions of this muscle, as well as co-activation constraints to better represent the pectoralis major and further understand the effects of treatment on this muscle.

5.8 Limitations

There are several limitations that delimit this work. Although the cubed muscle stress is a common and established cost function, it is difficult to predict exactly which cost function best represents an individuals neuromuscular task completion approach (Dul, Johnson, et al., 1984). It is possible that after undergoing treatment, a different cost function, such as pain avoidance via limiting muscle excursion or lengthening, or drastically avoiding specific muscle use, may better represent this population. However, this likely differs between all participants and cannot be easily quantified (such as a reduction of pain). Beyond the limitations of modeling and more specifically SLAM, the scenarios are worst-case representations, and therefore the experiences of individual breast cancer survivors could vary greatly from the proposed scenarios. Along these lines, the training of muscles was not based on a specifically defined rehabilitation program, but rather on the ability to train all muscles to a similar extent and increasing the capacity of the muscles uniformly in a stepwise manner. There is no direct evidence to suggest this is possible.

5.9 Conclusions

Muscle capacity is affected by breast cancer treatment. The current study determined that even with the challenges posed by given treatment scenarios (permanent damage of a subset of muscles from radiation, or overall reduction in capacity due to chemotherapy, or a combination of both), 70-80% of strength is recoverable if retraining of muscles can be achieved. The simulations showed that proper attention should be taken to strengthen not only the primary movers, but also provide stabilizing muscles of the scapula and glenohumeral joint. Specifically, for adduction rhomboid (major and minor), upper trapezius, subscapularis (lower), and triceps (long), latissimus dorsi (upper and lower), pectoralis minor, middle deltoid, middle trapezius and biceps (short) were recruited during the various simulations to increase force output compared to the LSC group of breast cancer survivors. During internal rotation, latissimus dorsi, rhomboid (major and minor), upper trapezius, posterior deltoid, subscapularis (middle and lower), triceps (long), pectoralis minor, middle deltoid, and middle trapezius recruitment increased from the

LSC group levels in each of the simulations. Although no scenario reached the levels of the reference group, the increase in achieved forces produced would be meaningful for enabling daily task performance and enhancing physical self-efficacy if achieved. It is important to increase the force output of breast cancer survivors, as having adequate strength capability is an important element in enhancing shoulder-related quality of life. The current study will be helpful to inform potential strategies for rehabilitation, and to set reasonable goals with known limitation of musculature. Ideally, this work will also be considered when considering treatment and reconstruction options – to limit damage where possible.

Chapter VI - Research Outcomes and Future Directions

6.1 Summary of Research

This thesis has contributed novel findings to the current state of breast cancer research, and specifically in the area of arm function in survivors. In Study 1, a cluster analysis identified two distinct groups of breast cancer survivors within two years of the conclusion of treatment, where one group had less overall function (parameterized by strength and range of motion) and shoulder-related quality of life. The five features identified to split the two groups were internal rotation force production, active extension range of motion, and 3 variables from the RAND-36 questionnaire (energy/fatigue, social functioning and pain). The two groups differed significantly in self-reported disability, role limitation (health and emotion), fatigue, and physical well-being, physical activity, lean mass of the affected arm, active flexion range of motion, as well as abduction, adduction, extension, flexion, internal and external force production.

Study 2 examined the effect of these differences on daily living tasks, and whether there were discernible differences in kinematics or muscular activation between the groups. In 8 daily living tasks (reach to back pocket, pour from a pitcher, forward reach, shelf reach, bra fasten, put on a necklace, tray transfer and bag lift), all 8 muscles monitored experienced differences between the two groups, where the group with more self-reported disability and lower function required greater muscular activation to complete the same tasks. Additionally, this group used less range of motion for all three planes of motion for half of the tasks.

Study 3 focused on determining how much force, and which muscles are predicted to contribute to that force when damage from treatment is modelled. To recover 70-80% of force, strengthening programs should focus on not only primary movers, but also stabilizing muscles of the scapula and glenohumeral joints during movement. The three studies combined to determine that strength is an important facet of survivorship, and can influence performance of even low load tasks. Strength deficits can be recovered up to 70-80% which may help mitigate reduced shoulder-related quality of life, but depends on the level of damage to important tissues.

6.2 Clinical Implications of Research

This dissertation made several principal contributions to the research on breast cancer survivors, with clinical relevance.

1) Determination of factors that define breast cancer survivor function following treatment

In study 1, 5 factors were determined to separate the group of high and low scoring breast cancer survivors. These factors (internal rotation force production, active extension range of motion, and self-reported energy/fatigue, social functioning and pain) defined which group a breast cancer survivor belonged to. These groups differed in many self-reported shoulder-related quality of life factors, as well as all force production measures. By identifying the most important factors to determine which group a survivor belongs in, monitoring can be more targeted. Further, focus on encouraging rehabilitation in the lower scoring individuals may help rectify functional deficits and improve shoulder-related quality of life.

2) Identification of muscle and movement patterns in breast cancer survivors during low load daily tasks

In study 2, different muscular and kinematic strategies existed between the HSC and LSC groups of breast cancer survivors. Particularly, the LSC group more highly activated muscles (and displayed increased variability) when completing all the low load daily tasks. Further, this group also used a smaller range of motion in all planes, during a subset of tasks. This is an important finding, recovering full strength or range of motion is a common clinical target, but patterns adopted by individuals, possibly for compensation, may be equally as important to consider. With this information, attention should be paid to regain maximal function (which may mitigate these differences), but also on how daily tasks are completed. These compensations may increase fatigue, or lead to rotator cuff disorders (such as impingement of the supraspinatus tendon) and further hinder function in these individuals.

3) **Strength recovery of up to 70-80% was possible when accounting for damage to certain muscles from treatment.**

Study 3 investigated the feasibility of increasing strength with several damage scenarios faced by breast cancer survivors. By modelling a reduction in capacity of all muscles (chemotherapy) or a subset of muscles (radiation), 70-80% of strength was recoverable, and that both the primary movers for an action and accessory muscles that stabilize the scapula and glenohumeral joint have importance. Clinically, this study paves the way for targeting rehabilitation driven by specific muscles and acknowledging the limitations that muscles may face from treatment. Combining the knowledge from study 1 and 2, this targeted approach could lead to improved shoulder-related quality of life, and in turn influence daily tasks completion.

6.3 Future Directions

This thesis lays a foundation to better understand treatment effects in breast cancer survivors immediately following treatment, but further work can extend this initial progress and potentially yield more benefits for the breast cancer survivor population. Collection of an aged matched reference population would help determine which changes relate variously to aging and treatment type and status. An expansion of the activities of daily living tasks (including more challenging tasks, and more work specific tasks) would also extend the current research. These could identify tasks that may be challenging for a subset of survivors, and tasks that may put survivors with lower function at risk for injury. It is well documented that pectoralis major is damaged during treatment. To better quantify the effect of treatment on pectoralis major, additional partitions of the muscle should be modelled to increase the fidelity of SLAM. Following this investigation, an intervention study should be completed to determine the effectiveness of targeting specific muscles driven by an *in-silico* approach. Finally, reconstruction is another facet of survivorship. The effect of the various reconstruction surgeries on the factors discussed in this thesis are not fully understood. Study 3 identified latissimus dorsi as an important muscle in adduction and internal rotation strength recovery, even if damaged with radiation treatment. However, a popular reconstruction technique involves altering the latissimus dorsi, which in turn modifies the function and strength of this muscle (Leonardis et al., 2019). By adding in another factor, a more complete understanding of life after treatment can be explored. Many of these research extensions could instigate improved arm function in numerous survivors, and extend independence following breast cancer treatment.

6.4 Overall Conclusion

No two individuals experience the effects of breast cancer treatment equally. This dissertation determined that several factors can help differentiate survivors, and guide which individuals may experience challenges following treatment. More so, that these differences do not exist solely through maximums and functional tasks, but also daily living tasks. Survivors with decreased strength and shoulder-related quality of life also completed tasks in a manner which may predispose them to rotator cuff disorders, furthering any existing issues from treatment related effects. Although it may not be possible to fully recover the damage in tissues from treatment (specifically chemotherapy and radiation), 70-80% of strength is achievable when accounting for these tissue changes, as well as aging effects. Recovering strength may mitigate the need for kinematic compensations, increased muscular activation and improve shoulder-related quality of life. Completing an intervention study with focused rehabilitation to increase strength of primary movers, and shoulder/glenohumeral stabilizers may provide insight into the feasibility of these changes.

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Appendix A: Information Consent and Participant Information

Title of Project: Longitudinal evaluation of upper limb functional capacity and body composition in breast cancer survivors

Investigators:
Marina Mourtzakis and Clark Dickerson, PhD
Department of Kinesiology, University of Waterloo
(519) 888-4567 Exts. 38549 and 37844

Student-Investigator:
Jackie Maciukiewicz, MSc., PhD Student, Department of Kinesiology
Research Assistant:
Alicia Nadon, MSc., Department of Kinesiology

Purposes of this Study:

While 5-year breast cancer survivorship is 88% in Canada, up to 72% of breast cancer survivors (BCS) have upper limb impairments that remain following treatment. This can severely diminish shoulder-related quality of life, reducing the ability to complete activities of daily living (ADL) and successfully return to work. It is currently unknown which ADL tasks and arm postures pose the biggest problem for BCS, as prior studies have focused on coarse clinical measures. A refined definition of these deficits will provide critical information to aid in the development of targeted survivorship programs. In this project, we will assess functional impairment by measuring body composition, shoulder-related quality of life, and shoulder strength, range of motion, joint movement and muscular demands during ADL. This is one of the first studies that objectively looks at and quantitates shoulder function in breast cancer survivors. Understanding upper limb impairment in BCS will allow development of more specific and effective strategies to improve short- and long-term outcomes for BCS. These evidence-based strategies will be incorporated into existing survivorship guidelines for breast cancer patients and clinical decision makers. The purpose of this study is:

- to describe the upper limb impairment of breast cancer survivors in terms of body composition, kinematics, muscle activation and strength, and to relate these physical measures with objective and subjective measures of function and shoulder-related quality of life during ADL and work
- finger prick to determine HbA1c (glycated haemoglobin) will allow for investigation into changes in average blood sugar levels over a period of 3 months.
- Compare the body composition, kinematics, muscle activation and strength of breast cancer survivors to healthy aged matched controls

Who Can Participate:

Two groups of participants will be recruited into this study.

Group 1: Breast Cancer Survivors

Participants in this study should be more then 3 months, but less than two years post-treatment. They may have had Stage I to IIIa cancer, received any form of radiation therapy or chemotherapy, have undergone any form of surgical procedure for breast cancer removal, and have had any form of breast cancer pathology. Participants cannot have had bilateral cancer, metastases, barium swallow within previous 3 weeks of participation, women who are or suspect they are pregnant, or have had upper arm dysfunction prior to cancer treatments. Please note, only the female gender are being recruited for this study, as breast cancer is very rare among men (~1% prevalence) and the potential impairments we are describing have different characteristics across genders.

Group 2: Age-Matched Control Group

Participants in the control group should not have had any upper arm dysfunction in the past 2 years. Additionally, women will be excluded if they are, or suspect they are pregnant.

Procedures Involved in this Study:

The total in-lab time commitment for the participants in the breast cancer survivor group will amount to approximately 6-8 hours; two 3-4 hour collections are required, with a 16 week duration between each.

The total in-lab time commitment for the participants in the control group will be 3-4 hours, with only one lab visit required.

Intervention period

During the 16 week duration, participants in the breast cancer survivor group will participate in regular exercise classes (performed in junction with the Stay Fit classes in the UW WellFit program). A volunteer will monitor exercises and record weights, reps and heart rate during all sessions. All fees related to the exercise program, including parking, will be covered as part of the research study.

Exercise classes will take place at the Toby Jenkins building:

CCCARE
University of Waterloo
Toby Jenkins Applied Health Research Building
340 Hagey Blvd.,Waterloo, Ontario N2L 6R6

Each lab session (regardless of group) will be identical and include all of the following procedures.

Participant Information and Body Composition

- ✓ Medical History: cancer type, treatment (surgery, chemotherapy, radiation and hormonal therapy), chronic conditions, medications, and any musculoskeletal injury that may limit performance

- ✓ Anthropometric Measures (10 minutes): Measurements of standing height, weight and waist circumference will be taken.

- ✓ FACT-B quality-of-life survey (10 minutes): This survey asks you to respond to questions using a rating scale for such things as your physical well-being (e.g., I have a lack of energy, I have nausea, I have pain). *You may, at any time, choose not to answer some or all of the questions by leaving them blank.*

- ✓ RAND 36-Item Health Survey Questionnaire (10 minutes) : This survey asks you to respond to questions using a rating scale for such things as your physical well-being and your physical functioning (e.g., During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?)

- ✓ DASH Questionnaire (10 minutes): This questionnaire asks you to respond to questions about symptoms related to your arm, shoulder, and hand as well as your ability to perform certain activities in the past week. (e.g. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder, or hand problem?)

- ✓ DXA- Dual-Energy X-Ray Absorptiometry (20 minutes): The DXA will be used to precisely measure lean tissue mass as well as body fat for the whole body and for specific regions of the body. There is a very low dose of radiation emitted, which is 200 times less than the limit for exposure to the general public (i.e. the radiation emitted from the scanner is 0.012 mSV/DXA scan, where the maximal trivial dose is 5mSV/year for the general public. This is a very low dose of radiation emitted which is 200 times less than the limit for trivial exposure (and less than the amount of radiation you would be exposed to on a transatlantic flight). This test requires that you put on a hospital gown, remove all jewellery and lie on an X-ray bed. A certified Medical X-Ray Technologist (MRT) will conduct the scan. If you have had barium swallow in the past 3 weeks, you will not be eligible for the DXA scan. You will be asked if you are taking oral contraceptives and if you are pregnant or if you suspect that you are pregnant. The potential risks associated with radiation exposure to an unborn fetus are unknown. Thus, if you are pregnant, you will not be eligible for this assessment or study.

- ✓ Bioelectrical Impedance Analysis (BIA) (5 minutes): To measure your body composition, you will be asked to void your bladder before the assessment. Two disposable adhesive electrodes will be placed on your foot (one above the middle toe and one on the ankle) and 2 on your hand (one on the middle finger and one on the wrist). The skin will be cleaned with rubbing alcohol before placing the disposable electrodes. If you are allergic to rubbing alcohol, please indicate this to the researcher and the skin will be cleaned with water instead. The 4 electrodes will be connected to the cables where the signal is sent and received. If you have a pacemaker; this test will not be performed. Otherwise, there are no risks involved in this assessment.

- ✓ HbA1c Finger Prick (3 minutes): To measure your average blood glucose levels over the previous few months, we will do a finger prick analysis for glycolated haemoglobin using the HbA1c test. A trained phlebotomist (wearing disposable nitrile/vinyl gloves) will perform the test, in which you will provide one finger to prick. The finger will be wiped with rubbing alcohol, and pricked with a small device containing a lancet. If you are uncomfortable the procedure and/or allergic to alcohol wipes, you do not have to participate. In some cases, bruising or discomfort can result from the finger prick.

Physical Activity and Rehabilitation Frequency Assessment

- ✓ Godin Leisure Time Activity Questionnaire (5 minutes): In addition to each lab collection, you will receive (via preferred method – email or phone) this questionnaire once per month, which asks you to describe your level of physical activity in the 7 days prior. Four additional questions will evaluate the frequency of your rehabilitation visits.

Biomechanical Shoulder Assessment

- ✓ Biomechanical Shoulder Assessment (120 minutes): In order to systematically evaluate your shoulder function to describe upper limb capacities and dysfunctions in breast cancer survivors, we will perform a biomechanical assessment of your upper arm. This assessment includes arm motion, muscle coordination, and strength during activities of daily life and work activities. The preparation and testing protocol that will be done in the laboratory is outlined below.

Participant Preparation

It is recommended that participants are dressed in comfortable athletic or workout attire. A sleeveless shirt is required for the biomechanical shoulder assessment. Participants should avoid wearing clothing that has any metal or reflective pieces on it.

EMG Preparation

EMG preparation will be performed by a female graduate student with 3 years of experience with surface EMG. She has had both apprenticeship training from her supervisor as well as formal course training in a UW graduate program.

Prior to electrode placement, any hair in the placement area is shaved. The removal of hair enhances the signal and makes the removal of the electrode easier. A new disposable razor is used for each participant. Over 1000 participants have undergone this procedure in the Kinesiology department, and to date no participants have been cut. All shaving and electrode placements will be done by females. The skin areas for electrode placement are wiped with isopropyl alcohol and then the electrodes are placed on the skin.

Eight surface adhesive bipolar electrodes will be placed on the skin over 8 muscles on each arm (therefore 16 muscles total). One additional electrode will be placed on the sternum as a ground electrode. On occasion the electrodes can leave a mark after removal. Usually, these marks disappear within hours or within two days. Should the irritation/redness last longer than 3 days, please contact your physician.

You will then be asked to perform 14 maximal exertions that require full muscular effort for a total of five seconds each. Two rounds of each of these maximal voluntary muscle exertions will be performed for each muscle group. There will be 2 minutes rest in between each MVC in order to prevent fatigue. You will then be asked to lie down on a bench while remaining as relaxed and still as possible. This resting EMG trial will be used to remove bias in the signal. On completion of the session the electrodes are removed and the skin is rubbed with isopropyl alcohol to remove any residual gel or adhesive material left behind from the electrodes.

Motion capture preparation

Three-dimensional kinematics will be recorded using an 8-camera (2 MP) optoelectronic Vicon MX20+ motion tracking system (sampling rate 50 Hz) (Vicon, Oxford, UK). Thirty-nine reflective markers will be placed on the skin (adhesive backing) over the upper limbs, scapulae, thorax, head, and pelvis. The cameras will track these reflective markers, and these will be used to calculate joint angle. Some participants may experience mild skin irritation/redness from the tape used to attach the instrumentation to the skin. This is similar to the irritation that may be caused by a bandage and typically fades within 1-3 days. Should the irritation/redness last longer than 3 days, please contact your physician.

Experimental Protocol

Strength Trials

We will then measure isometric joint moment positions of the shoulder. Maximal voluntary force will be assessed at the hand using a 6 degree of freedom force transducer (FS6-500, AMTI); three 5 second trials will be performed for a total of 24 per participant. You will be pushing against a force transducer that will record how hard you push with your arm in four different positions. We will repeat the trials for both arms. At least two minutes rest will be given between trials to avoid fatigue.

Shoulder Range of Motion (ROM)

You will then be asked to move through a selection of active shoulder ROM positions. Movement (abduction, flexion, extension, and rotation of the shoulder) in each anatomical plane will be recorded using motion capture cameras.

Performance of Activities of Daily Living

You will then be asked to perform a series of activity of daily living (ADL) tasks (12 in total). Examples of these are bra fasten, pour water from pitcher, push/pull, and forward reach. You will perform each task twice with both arms, however some require both hands and will only need two trials. You will be given at least two minutes rest between trials to avoid fatigue. A total of 40 trials will be collected.

Rating of Perceived Exertion

Following the completion of each ADL task, you will be asked to rate your perceived exertion (RPE) on a calibrated, modified continuous Borg CR-10 scale for the neck, as well as each shoulder, elbow, wrist, and hand.

At any point during the study, participants should advise the researcher if any of the movements or activities are causing discomfort or pain.

Incidental Findings

DXA: In addition to providing us with a measure of fat mass and lean mass, the DXA scan also estimates whole body and regional bone mineral content. The procedure for the DXA scan that we perform is not meant to accurately assess bone mineral density, however, the bone mineral density results that we collect from the DXA scan may provide a crude indication of potential measures of bone mineral density (i.e. whether one may have lower bone mineral density than for someone their age). It is your decision if you would like to be notified if we find that your bone mineral density if below what is considered normal. After receiving notification of your bone mineral density, we encourage you to share this information with your physician to discuss whether you should undergo a bone scan to more accurately measure your bone mineral density.

Do you wish to be notified if we find your bone mineral density to be below what is considered normal?

☐ I do wish to be notified if my bone mineral density is below what is considered normal.
☐ I do not wish to be notified if my bone mineral density is below what is considered normal.

Confidentiality and Security of Your Information and Data:

To ensure the confidentiality of your data, you will be identified by a participant identification code known only to members of the research team. Your information will be stored in a locked office at the Lyle Hallman building (0603) and Burt Matthews Hall (1404 and 1044) at the University of Waterloo. The information will be stored for a minimum of 25 years. Data will also be encrypted and stored on a password-protected computer and server.

The data may need to be inspected from time to time for quality assurance (to make sure the information being used in the study is accurate) and for data analysis (to do statistical analysis that will not identify you). The following organizations may do this inspection: the University of Waterloo Research Ethics Committee and other members of the research team (including monitors or auditors) as required, ensuring the safety of participants and the quality of data.

Photographs and video recordings will be taken during the study, if you give consent to do so. These photographs or video recordings will be focused on the upper body and arm, but will not be focused on facial features. These photos and recordings are useful to verify the movement information recorded by the researchers, and may be helpful in teaching purposes such as when presenting the study results in a scientific presentation or publication. Any facial features or other distinguishing features that are visible in photos or recordings used for these above mentioned purposes will be blotted out to remove distinguishing features and maintain your confidentiality.

Questions and Ethics Clearance: If you have any further questions or want any other information about this study, please feel free to contact:

Marina Mourtzakis, PhD, Department of Kinesiology 888-4567 Ext.38459

Clark Dickerson, PhD, Department of Kinesiology 888-4567 Ext. 37844

This project has been reviewed by, and received ethics clearance through, a University of Waterloo Research Ethics Committee (ORE # 21124). If you have any questions, you may contact the Chief Ethics Officer, Office of Research Ethics, at 519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca.

Remuneration:

Breast cancer survivor participants will be provided with a $50 gift card in appreciation for their participation in this study. Participants in the control group only attend one lab session and therefore will be remunerated $25.The amount received is taxable. It is your responsibility to report this amount for income tax purposes.

Changing Your Mind about Participation

Participation is voluntary. You may withdraw from the study at any time without penalty. To do so, indicate this to a member of the team by saying, “I no longer wish to participate”. You may choose to have your data destroyed, or with your permission, your data will be used for the study. Please note, if you choose to withdraw at any time during the first session or before the start of the second session, you will receive a $25 gift card as part of remuneration.

The StayFit program is available for individuals outside this research study. Therefore, if participants chose to withdraw from the study they are able to continue exercising in the program. Please note, if you chose to withdraw from the study and want to continue exercising in the StayFit program, you would be expected to pay for the remainder of the session.

Consent to Participate By signing this consent form, you are not waiving your legal rights or releasing the investigators (Professor Marina Mourtzakis and Professor Clark Dickerson) or involved institution (University of Waterloo) from their legal and professional responsibilities.

☐ I agree to take part in a research study being conducted by Professor Marina Mourtzakis and Professor Clark Dickerson of the Department of Kinesiology, University of Waterloo.

☐ I consent to the finger prick (HbA1c) test

I have made this decision based on the information I have read in the Information letter. All the procedures, any risks and benefits have been explained to me. I have had the opportunity to ask any questions and to receive any additional details I wanted about the study. If I have questions later about the study, I can ask one of the researchers (Professor Marina Mourtzakis, 519-888-4567 Ext. 38549; Professor Dickerson, 519-888-4567 Ext. 37844).

I understand that I may withdraw from the study at any time without penalty by telling the researcher.

This project has been reviewed by, and received ethics clearance through, a University of Waterloo Research Ethics Committee (ORE # 21124). If you have any questions, you may contact the Chief Ethics Officer, Office of Research Ethics, at 519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca.

Printed Name of Participant   Signature of Participant

Dated at Waterloo, Ontario   Witnessed

Consent to Use Video and/or Photographs

Sometimes a certain photograph and/or part of a video recording clearly shows a particular feature or detail that would be helpful in teaching or when presenting the study results in a scientific presentation or publication. If you grant permission for photographs or video recording in which you appear to be used in this manner, please complete the following section. Please note that any facial features will be blotted out so that you will not be identifiable.

I agree to allow video and/or photographs to be used in teaching or scientific presentations, or published in scientific journals or professional publications of this work without identifying me by name. I understand that I retain the right to withdraw my consent to be video recorded or photographed at any time, and that existing video or photos may be destroyed at my request. There will be no penalty to me if I choose to refuse this consent.

Printed Name of Participant   Signature of Participant

Dated at Waterloo, Ontario   Witnessed

UW WellFit Participants Only: Consent to Use Previous Data (ORE 18987)

Some of the questionnaires (specifically those related to shoulder-related quality of life and arm function) used in this study replicate those in ORE 18987. For participants who have completed those in the last two weeks, if you grant permission, those results can be shared with the researchers of the current study to reduce replication.

I agree to allow the researchers to view my results from ORE 18987. I understand that I retain the right to withdraw my consent at any time. There will be no penalty to me if I choose to refuse this consent.

Printed Name of Participant   Signature of Participant

Dated at Waterloo, Ontario   Witnessed

Participant Information Form

Participant ID: ___________________

DIAGNOSIS INFORMATION

Date of Diagnosis: ____

Type of Breast Cancer: ____

Stage of Breast Cancer: ____

TREATMENT INFORMATION

Radiation Therapy:

a. Start date: ___________________________________

b. Frequency (i.e. everyday, every other day etc): ______________________________

c. Duration of therapy: _______________________

d. Date of last radiation dose: ________________

Surgery:

a. Date of surgery(ies):_____________________

b. Type of surgery (lumpectomy vs mastectomy vs other): _______________________

c. Side (R, L or both): _____________________________

Chemotherapy*:*

a. Start date:__________________________________

b. Total cycles:_________________________

d. Date of treatments (e.g. Every Wednesday for 6 weeks):

____

____

e. Chemotherapy Drugs (if known):____

____

f. Did you have a PICC or port-a-cath? ____

g. If yes, when was it removed? ____

h. Did you experience any pain or discomfort with it?

____

Other treatment information (immune therapy, hormonal therapy, etc.):

____

____

____

PHYSICAL ACTIVITY

Are you currently physically active? (meet Canada’s P.A. Guidelines) ☐Yes ☐ No

Current Physical Activity

i.e. lifting weights, cardiovascular activity, recreational or other unstructured physical activities that are part of daily life/job?

-
-

Previous Physical Activity
List any activities/exercise performed in the past. How long ago? Give brief details regarding activity.

-
-

Physiotherapy and Exercise Prescription
Have you ever been to a physiotherapy or other allied health professional for treatment regarding your arm or shoulder? ____

If yes, how long did you receive treatment? ____________________________________
What did the treatment involve? ____

Have you ever received an exercise program specifically for your arm or shoulder? _____
If yes, how long did you do the program for? _____________________________________
Are you still currently doing the program? _______________________________________

Do you have any difficulty in completing daily tasks? Yes / No
a. If yes, what tasks di you have trouble doing (e.g., reach overhead, lifting)?:
____
Do you often feel tightness in the chest or shoulder of your affected arm? Yes / No
If yes:
Does this occur at a certain time of day or after a certain activity (i.e., morning, night, after exercise)?
____
Does anything help ease the tightness (i.e., certain exercises, medications)?
____
Do you experience the following in the chest/shoulder/arm of affected side?
1. Pain________
2. Swelling________
3. Decreased range of motion________
4. Weakness________
5. Cording________
6. Numbness________
7. Other? Please describe.

Did you have any shoulder or arm injuries before cancer? Please describe.

CHECKLIST FOR SIGNS AND SYMPTOMS OF DISEASE

Condition	Yes	No	Comments
Cardiovascular			
Hypertension	☐	☐	____________________
Hypercholesterolemia	☐	☐	____________________
Heart Condition	☐	☐	____________________
Fainting/dizziness	☐	☐	____________________
Chest pain	☐	☐	____________________
Pulmonary			
Asthma	☐	☐	____________________
Bronchitis	☐	☐	____________________
Emphysema	☐	☐	____________________
METABOLIC			
Diabetes	☐	☐	____________________
Excess weight changes	☐	☐	____________________
Thyroid disease	☐	☐	____________________
MUSCULOSKELETAL			
Osteoporosis	☐	☐	____________________
Arthritis	☐	☐	____________________
Low back pain	☐	☐	____________________
Swollen joints	☐	☐	____________________
Orthopedic pain	☐	☐	____________________
Artificial joints	☐	☐	____________________

OTHER

____________________ ______________________________

____________________ ______________________________

____________________ ______________________________

____________________ ______________________________

____________________ ______________________________

PRESENT MEDICATIONS (name, dose, frequency: i.e. Aspirin/325 mg/ 1 daily)

Name	Dose	Frequency	Comments

Appendix B: Questionnaires

FACT –B

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	**A little-bit**	**Somewhat**	**Quite a bit**	**Very much**
	Physical Well-Being					
GP1	I have a lack of energy	**0**	**1**	**2**	**3**	**4**
GP2	I have nausea	**0**	**1**	**2**	**3**	**4**
GP3	Because of my physical condition, I have trouble meeting the needs of my family	**0**	**1**	**2**	**3**	**4**
GP4	I have pain	**0**	**1**	**2**	**3**	**4**
GP5	I am bothered by side effects of treatment	**0**	**1**	**2**	**3**	**4**
GP6	I feel ill	**0**	**1**	**2**	**3**	**4**
GP7	I am forced to spend time in bed	**0**	**1**	**2**	**3**	**4**
	Social/Family Well-Being					
GS1	I feel close to my friends	**0**	**1**	**2**	**3**	**4**
GS2	I get emotional support from my family	**0**	**1**	**2**	**3**	**4**
GS3	I get support from my friends	**0**	**1**	**2**	**3**	**4**
GS4	My family has accepted my illness	**0**	**1**	**2**	**3**	**4**
GS5	I am satisfied with family communication about my illness	**0**	**1**	**2**	**3**	**4**
GS6	I feel close to my partner (or my main support)	**0**	**1**	**2**	**3**	**4**
GS7	I am satisfied with my sex life (if you prefer not to answer, skip this question)	**0**	**1**	**2**	**3**	**4**
	Emotional Well-Being					
GE1	I feel sad	**0**	**1**	**2**	**3**	**4**
GE2	I am satisfied with how I am coping with my illness	**0**	**1**	**2**	**3**	**4**
GE3	I am losing hope in the fight against my illness	**0**	**1**	**2**	**3**	**4**

		Not at all	A little-bit	Somewhat	Quite a bit	Very much
GE4	I feel nervous	**0**	**1**	**2**	**3**	**4**
GE5	I worry about dying	**0**	**1**	**2**	**3**	**4**
GE6	I worry that my condition will get worse	**0**	**1**	**2**	**3**	**4**
	Functional Well-Being					
GF1	I am able to work (include work at home)	**0**	**1**	**2**	**3**	**4**
GF2	My work (include work at home) is fulfilling)	**0**	**1**	**2**	**3**	**4**
GF3	I am able to enjoy my life	**0**	**1**	**2**	**3**	**4**
GF4	I have accepted my illness	**0**	**1**	**2**	**3**	**4**
GF5	I am sleeping well	**0**	**1**	**2**	**3**	**4**
GF6	I am enjoying the things I usually do for fun	**0**	**1**	**2**	**3**	**4**
GF7	I am content with the quality of my life right now	**0**	**1**	**2**	**3**	**4**
	Additional Concerns					
B1	I have been short of breath	**0**	**1**	**2**	**3**	**4**
B2	I am self-conscious about the way I dress	**0**	**1**	**2**	**3**	**4**
B3	One/both of my arms are swollen or tender	**0**	**1**	**2**	**3**	**4**
B4	I feel sexually attractive	**0**	**1**	**2**	**3**	**4**
B5	I am bothered by hair loss	**0**	**1**	**2**	**3**	**4**
B6	I worry that other members of my family might someday get the same illness I have	**0**	**1**	**2**	**3**	**4**
B7	I worry about the effect of stress on my illness	**0**	**1**	**2**	**3**	**4**
B8	I am bothered by a change in weight	**0**	**1**	**2**	**3**	**4**
B9	I am able to feel like a woman	**0**	**1**	**2**	**3**	**4**
P2	I have certain parts of my body where I experience pain	**0**	**1**	**2**	**3**	**4**

Godin Leisure-Time Exercise Questionnaire

1. During *the past 7 days (week),* how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time (write appropriate number on each line).

Times per Week

a) STRENUOUS EXERCISE ____________

(HEART BEATS RAPIDLY)

(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE
EXERCISE ____________
(NOT EXHAUSTING)

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD
EXERCISE ____________

(MINIMAL EFFORT)

(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snowmobiling, easy walking)

2. During *the past 7 days (week),* in your leisure time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)? Please check one.

1. Often _______ 2. Sometimes ______ 3. Rarely/Never _______

Rehabilitation Assessment

1. Do you have an additional health practitioner or rehabilitation specialist (chiropractor, physical therapist, naturopath, other)?

____

2. If yes, how often did you visit a health practitioner or rehabilitation specialist in the past 7 days (week)?

____

3. Do you continue to do exercises prescribed by a specialist in your own home?

____

4. If yes to # 3, how many times in the last 7 days (week) did you perform those exercises?

____

The Rand SF 36 Quality of Daily Living Questionnaire

The following questionnaire asks questions to gain insight into a picture of your daily health. For each question, please **circle one number** that most appropriately describes your situation.

1. In general, would you say your health is :

Excellent	1	Very Good	2	Good	3
Fair	4	Poor	5		

2. Compared to one year ago, how would you rate your health in general, now:

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	1	Slightly	2	Moderately	3
Quite a bit	4	Extremely	5		

21. How much **bodily** pain have you had during the **past 4 weeks**?

None	1	Very mild	2	Mild	3
Moderate	4	Severe	5	Very severe	6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	1	A little bit	2	Moderately	3
Quite a bit	4	Extremely	5		

These questions are about how you feel and how things have been with you **during the past 4 weeks**. How much of the time during the **past 4 weeks** . . .

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	1	Most of the time	2	Some of the time	3
A little of the time	4	None of the time	5		

How TRUE or FALSE is <u>each</u> of the following statements for you.

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

DASH Questionnaire

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response

	No Difficulty	Mild Difficulty	Moderate difficulty	Severe Difficulty	Unable
Open a tight or new jar	1	2	3	4	5
Write	1	2	3	4	5
Turn a key	1	2	3	4	5
Prepare a meal	1	2	3	4	5
Push open a heavy door	1	2	3	4	5
Place and object on a shelf above your head	1	2	3	4	5
Do heavy household chores (wash walls, wash floors)	1	2	3	4	5
Garden or do yard work	1	2	3	4	5
Make a bed	1	2	3	4	5
Carry a shopping bag or briefcase	1	2	3	4	5
Carry a heavy object (over 10lbs)	1	2	3	4	5
Change a lightbulb overhead	1	2	3	4	5
Wash or blow dry your hair	1	2	3	4	5
Wash your back	1	2	3	4	5
Put on a pullover sweater	1	2	3	4	5
Use a knife to cut food	1	2	3	4	5
Recreational activities which require little effort (card playing, knitting etc)	1	2	3	4	5
Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5
Recreational activities in which you move your arm freely (e.g., playing Frisbee, badminton).	1	2	3	4	5
Manage transportation needs (getting from one place to another).	1	2	3	4	5
Sexual activities	1	2	3	4	5

	Not at all	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	**1**	**2**	**3**	**4**	**5**
	Not limited at all	**Slightly limited**	**Moderately limited**	**Very limited**	**Unable**
During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	**1**	**2**	**3**	**4**	**5**
Please rate the severity of the following symptoms in the last week.	**None**	**Mild**	**Moderate**	**Severe**	**Extreme**
Arm, shoulder or hand pain	**1**	**2**	**3**	**4**	**5**
Arm, shoulder or hand pain when you perform any specific activity	**1**	**2**	**3**	**4**	**5**
Tingling (pins and needles) in your arm, shoulder or hand	**1**	**2**	**3**	**4**	**5**
Weakness in your arm, shoulder or hand	**1**	**2**	**3**	**4**	**5**
Stiffness in your arm, shoulder or hand	**1**	**2**	**3**	**4**	**5**
	No Difficulty	**Mild Difficulty**	**Moderate Difficulty**	**Severe Difficulty**	**I can’t sleep**
During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand?	**1**	**2**	**3**	**4**	**5**
	Strongly Disagree	**Disagree**	**Neither agree or disagree**	**Agree**	**Strongly agree**
I feel less capable, less confident or less useful because of my arm, shoulder or hand problem.	**1**	**2**	**3**	**4**	**5**
Indicate work/job ability (if you do not work skip section) Job:_____________________________	**No Difficulty**	**Mild Difficulty**	**Moderate difficulty**	**Severe Difficulty**	**Unable**
Using your usual technique for your work?	**1**	**2**	**3**	**4**	**5**
Doing your usual work because of arm, shoulder or hand pain?	**1**	**2**	**3**	**4**	**5**
Doing your work as well as you would like?	**1**	**2**	**3**	**4**	**5**
Spending your usual amount of time doing your work?	**1**	**2**	**3**	**4**	**5**
Indicate sport/instrument (if you do not play sports or an instrument skip section): ________________________	**No Difficulty**	**Mild Difficulty**	**Moderate difficulty**	**Severe Difficulty**	**Unable**
Using your usual technique for playing your instrument or sport?	**1**	**2**	**3**	**4**	**5**
Playing your musical instrument or sport because of arm, shoulder or hand pain?	**1**	**2**	**3**	**4**	**5**
Playing your musical instrument or sport as well as you would like?	**1**	**2**	**3**	**4**	**5**
Spending your usual amount of time practising or playing your instrument or sport?	**1**	**2**	**3**	**4**	**5**