VARIABILLITY IN PHYSICAL FUNCTION FOR PATIENTS LIVING WITH BREAST CANCER DURING A 12-WEEK EXERCISE PROGRAM

by

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ABSTRACT

OBJECTIVES: The objectives of this study were to describe the variability during weekly performance on common physical function tests during a 12-week exercise intervention for breast cancer patients; to test if the weekly variation surpasses the minimally clinically important difference (MCID) of each test; and to explore if the self-perceived fatigue and energy were associated with weekly physical function performance.

DESIGN: Twenty-five breast cancer patients were recruited in the 12-week individualized exercise program offered in a community-based fitness facility. Physical function was assessed weekly using the 6-minute walk test (6MWT) and the chair stand test before one of the two weekly sessions. A MCID value of 50 meters was used for the 6MWT and two repetitions for the chair-stand test.

RESULTS: A significant average improvement was observed in the 6MWT ($p=.006$) and the chair-stand test ($p<.01$) after the intervention. Individual confidence intervals were wide across all testing measures with only 28% and 8% of participants met or surpassed the MCID for the 6MWT and chair stand test respectively. Correlations between self-perceived energy and fatigue were not significantly associated with the average score of each test during the trial $p > 0.24$.

CONCLUSION: Despite a significant improvement in physical function during the 12-week exercise intervention, the majority of patients did not reach the MCID; could be due to large variability such as treatment-related side effect or measurement bias, but not self-perceived energy and fatigue.

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1.0 Introductory Chapter

Half of Canadian's will receive a diagnosis of breast cancer, while one-quarter of those will die from it. Specifically, breast cancer is the most prevalent cancer diagnosis in Canadian women. The prevalence of diagnosis is increasing, however in recent decades, the number of individuals surviving is also increasing. This means a larger proportion of breast cancer survivors are living in society. A cancer survivor can be defined as anyone with a history of cancer, from the moment of diagnosis until death. This includes individuals who are in active treatment, have been in remission or declared cancer free. Breast cancer is stratified into five stages.

Once diagnosed, breast cancer survivors experience debilitating side effects from potential treatment options such as a decrease in physical function, extreme fatigue, pain, and a decreased quality of life. Evidence suggests that exercise is safe and beneficial for breast cancer survivors, with the ability to mitigate negative side effects due to treatment. Even if exercise is known to benefit patients, the benefits of an exercise intervention can vary from day to day, especially in patients currently in treatment. Typically, the potential benefits from an intervention are only tested pre and post intervention, which can lead to bias and exaggerated improvements in physical function test scores compared to what occurred by not accounting for day to day variability in physical function tests.

The objectives of this study were to describe the variability during weekly performance on common physical function tests during a 12-week exercise intervention for breast cancer patients; to test if the weekly variation surpasses the minimally clinically important difference (MCID) of each test; and to explore if the self-perceived fatigue and energy were associated with weekly physical function performance.

1.1 Cancer

Cancer is a general term for a group of diseases and can be defined as the abnormal growth of cells within the body. A defect will occur within a normal cell, affecting it's function and resulting in abnormal gene expression (Ruddon, 2007). Gene expression can be altered through a direct change to cell DNA, gene mutation and abnormal gene translation, to name a few (Ruddon, 2007). Abnormal cell function will lead to an imbalance in cell death and cell replication, whereas in normal cells there is an equilibrium between both death and replication. This imbalance within tumor cells leads to uncontrollable cell division, growth beyond normal borders, and eventually a tumor or lump (Ruddon, 2007). Cancer can affect almost any area of the body and each form of cancer may require various management strategies (*WHO*, 2019). Cancer is the leading cause of death world-wide and has resulted in 9.6 million deaths in 2018 (*WHO*, 2019).

In Canada, cancer is the number one leading cause of death with half of all Canadians predicted to be affected by cancer and a quarter who will die from the disease (Government of Canada, 2019). For some perspective, there are approximately 37.59 million people living in Canada as of 2019 (Government of Canada, 2017), this means it's predicted 18, 795, 000 people will be diagnosed and 9, 397, 500 of those who will die from cancer. It was predicted that in 2019 alone, approximately 220,400 Canadians will be diagnosed and 81,2000 will die from cancer (Government of Canada, 2019). Due to the Canadian population growing larger and aging at a rapid rate, the annual number of diagnosed cancer cases in Canada is predicted to almost double from 2003-2007 to 2028-2032 (Xie et al., 2015). Cancer can be an expensive disease in comparison to other common chronic conditions and often involves intensive and expensive modes of therapy (Brown et al., 2001). Among Canadian men, prostate, lung and bronchus, colorectal and bladder cancer are the most common diagnoses of cancer (Government of Canada, 2019). Breast, lung and bronchus, colorectal, uterus and thyroid cancer are the most common types of cancer among Canadian women (Government of Canada, 2019).

1.2 Breast Cancer

Breast cancer is the most common cancer among Canadian women, representing an estimated 1 in 8 women who will develop the disease in their lifetime (Breast cancer statistics - Canadian Cancer Society, 2018). The 2019 Canadian Cancer Statistics predict that out of all the new cancer cases that will occur within the Canadian population, approximately 0.2% of of cases that occur in men will be breast cancer, while 25% of new cancer cases for women will be breast cancer (*Breast cancer statistics—Canadian Cancer Society*, 2019)

There are many risk factors associated with the development of breast cancer. These risk factors can be grouped into two categories: uncontrollable and modifiable. Uncontrollable risk factors cannot be controlled by the individual and includes age, family history and genetics and geographical location. The incidence of breast cancer increases as an individual gets older with the risk of developing breast cancer doubling every 10 years from the age 25-29 until menopause, where the rate of increase will then decrease substantially (McPherson et al., 2000). Approximately 10% of breast cancers diagnosis is due to an individual's family history and genetics. Lastly, geographical location can also increase risk of developing breast cancer. For example, mortality from breast cancer in India, China and Japan is significantly lower than in the United States of America, Netherlands and Canada. Individuals living in developed countries are at a higher risk of developing breast cancer than those who are in developing countries (McPherson et al., 2000). Within Canada, incidence rates vary between provinces. An analysis of breast cancer incidence in Canada between 1992 and 2010 was conducted by Lagacé et al., (2019). Their findings suggest Nova Scotia, New Brunswick, Prince Edward Island, Manitoba, British Columbia and Quebec had statistically significantly higher incidence rates than the national average (Lagacé et al., 2019). In contrast, Ontario, Alberta, Newfoundland and Labrador, Yukon, Northwest Territories and Nunavut had statistically significantly lower incidence rates than the national average (Lagacé et al., 2019). The analysis determined differences in incidence rates could be due in part to the percentage of the population that is above the age of sixty-five and the number of nursing care facilities available within the provinces (i.e. women may relocate to areas with available nursing home facilities as they age) (Lagacé et al., 2019). Modifiable risk factors are behaviours or exposures that can increase or decrease the risk of developing a certain disease and can include lifestyle factors such as diet, weight, physical activity, and smoking. Individuals who are living with obesity have a twofold increase in the risk of breast cancer than those who are in a normal weight range (McPherson et al., 2000). Individuals who are sedentary can also have an increased risk in breast cancer (Kerr et al., 2017), while participating in physical activity can have protective benefits and a decreased risk in cancer development (Friedenreich & Cust, 2008). This includes both leisure time and work-related physical activity.

If a patient is diagnosed with breast cancer, the oncology team will work to determine the individual's stage of cancer. Staging is important to determine how large the tumor is, where it's located and if it has spread to other parts of the body. Breast cancer is staged from 0 to 4; the stage of breast cancer an individual is diagnosed with depends on the primary tumour, if the cancer has moved on to lymph nodes and if there is any metastasis (Mahon, 2011).

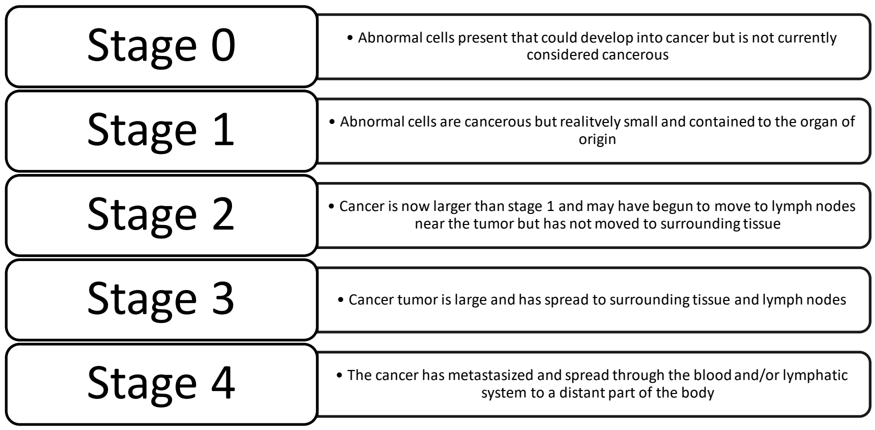

Figure 1: Staging of breast cancer from 1-4 with descriptions (*Government of Canada*, 2018).

Lymph nodes are structures within the body that works to filter out harmful substances; immune cells attack, and fight germs carried through lymph fluid (*American Cancer Society*, 2015). Metastasis refers to the growth of cancer in another site on the body, originating from the primary cancer. This can occur within the body when the cancer cell environment is hostile; lacking the required blood supply, cell death and inflammation from the immune system can stimulate the cancer cells to move around the body, causing metastasis (WANG et al., 2015). Once the baseline information regarding the tumor has been determined, breast cancer will be staged by the oncologist. A higher stage number represents a greater spread of breast cancer through the body and a lower number represents less spread (Peart, 2015). There is limited literature regarding the stage-specific survival rates for Canadian women diagnosed with breast cancer. General guidelines suggest five-year survival rate for stage 0 and 1 is 100%, 2 is 93%, 3 is 72% and 22% for stage 4 (Peart, 2015). Knowing the stage of diagnosis for a breast cancer patient can help the oncology team determine the appropriate treatment plan required. Common treatment options include surgery, chemotherapy, radiation therapy and hormone therapy (Peart, 2015).

1.3 Cancer Treatment

A diagnosis of cancer can lead to many treatment options; the ultimate goal is to eliminate all cancer cells. Breast cancer patients often have a multidisciplinary team including radiation oncology, surgery, medical oncology, oncology nurses, and pharmacists (Strom et al., 2008). Deciding on a treatment plan can depend on many different factors for each individual including the biology and behaviour of the breast cancer. The multidisciplinary team aims to tailor the treatment plan to the patient but there are general guidelines for early or advanced breast cancer. When diagnosed with early-stage invasive breast cancer, oncologists will generally recommend surgery first to remove the tumor and surrounding tissue. After surgery, the team might recommend additional treatment including radiation, chemotherapy, and/or hormone therapy. This is referred to as adjuvant therapy as is prescribed after surgery. These adjuvant therapies can be recommended to reduce risk of recurrence and to eliminate any remaining cancer cells. For larger tumors progressing faster, oncologists might recommend chemotherapy or radiation first and then surgery. This is referred to as neoadjuvant therapy, as it is prescribed before surgery. The neoadjuvant therapy may shrink the tumor and make it safer for removal during surgery (Eggert & Oncology Nursing Society Staff, 2009). A meta-analysis was conducted by Mauri, Pavlidis & Ioannidis (2005) comparing neoadjuvant and adjuvant therapy in breast cancer patients. Results suggest that both neoadjuvant and adjuvant therapy were equal when it came to survival and disease progression (Mauri et al., 2005).

Therefore, the patient and multidisciplinary team will discuss all treatment options including best treatment plan for the disease, possible symptoms and side effects.

Options for surgery include either a lumpectomy or a mastectomy, with different variations per surgery. A lumpectomy is the most breast-preserving option removing only the breast cancer tumour and the surrounding unaffected tissue (Peart, 2015). A mastectomy removes the breast cancer tumour and all of the normal breast tissue from the breast (*Mayo Clinic*, 2019). The most common mastectomy, called a modified radical mastectomy, includes removing the entire breast, nipple/areolar area and some lymph nodes (Peart, 2015). The surgery can take up to 2-3 hours, with a hospital stay of 3-8 days, depending on the patient, (Peart, 2015). The decision between a lumpectomy or mastectomy depends on tumour size, stage of cancer and tumour type (Peart, 2015). Patients who would prefer to save as much breast tissue as possible may opt for a lumpectomy, while some patients who want to try and have a better chance of getting rid of all cancer cells may opt for a mastectomy. Research also suggests older patients can receive the same type of treatment as younger patients, however, some considerations may need to be made using geriatric assessments (VanderWalde & Hurria, 2012). These considerations may include life-expectancy, general fitness and co-morbidities (VanderWalde & Hurria, 2012).

There are 90 different types of chemotherapy drugs that can be used one at a time, or as a combination of different drugs. Chemotherapy can be recommended before surgery to reduce tumour size or after surgery as a continuation of the patient's treatment plan. The goal of chemotherapy is to remove all cancer cells in the breast, to remove cancer cells that may have spread to other parts of the body and to shrink a larger, uncontrollable tumour

(Peart, 2015). Chemotherapy is delivered through the blood stream and effects both unaffected and cancerous cells (Peart, 2015). Typically, oncologists will recommend a longer bout of treatment at a lower dose of chemotherapy, instead of a high-dose drugs with increased adverse effects (Peart, 2015). Chemotherapy as a treatment for cancer varies drastically depending on the patient's health history including tumour size and/or location, general health and ability to handle treatment (Green & Hortobagyi, 2008). The average chemotherapy treatment lasts anywhere from 3 to 6 months, with breaks in between doses. Chemotherapy can cause damage to healthy cells in the body and breaks from chemotherapy treatment allow for those healthy cells to heal. It can be administered intramuscular through shots, orally with tablets, externally with cream or through intravenous via the arm (Peart, 2015). Chemotherapy delivered through shots means the chemotherapy absorbs slower than if it was delivered directly into the blood and therefore side effects can last longer.

Radiation therapy has been used as far back as 1895 and involves exposing the affected tissue in the body to high energy radiation. This is done to kill the cancer cells within that area while still protecting other parts of the body from radiation (Peart, 2015). It can be delivered internally, where the radiation is implanted at the tumour site and administered for 1 to 5 days. It can also be delivered externally, where the radiation beams penetrate the outside of the body at the tumour site, once a day for 6 to 7 weeks (Peart, 2015). External-beam radiation therapy includes high-energy rays that penetrate deep into the tissue to destroy and break down the DNA of cancer cells (Peart, 2015). The delivery of radiation therapy helps target the attack on specific abnormal cancer cells, however, there can be normal cell death within the area due to radiation (Baskar et al., 2012). Areas of the body targeted for breast cancer radiation includes the chest wall, armpit, lymph tissue and breast. External-beam radiation therapy can be administered daily approximately 6 weeks after surgery, for a course of 25-28 days. The treatment only takes a couple of minutes per session (Peart, 2015). Internal radiation involves delivering a high dose of radiation to a specific site in the body for approximately 3 to 5 days (Peart, 2015). It's typically administered twice a day, with 4 to 5 hours in between each session with the radiation working to attack the tumour bed (Peart, 2015).

Hormone therapy is a whole-body treatment used to provide specific biological treatment to individuals with hormone-driven breast cancer. Some breast cancer cells are fueled by naturally occurring hormones in the human body including estrogen and progesterone and are thought to be hormone-driven breast cancers. Receptor positive breast cancer can utilize either estrogen or progesterone to fuel tumor growth. Receptor negative breast cancer is not affected by hormones in the body and won't react to hormone-driven therapy (*Mayo Clinic*, 2019). Different types of hormone therapy drugs can be prescribed depending on the fuel source of the breast cancer. It can be fuelled by estrogen, progesterone or a combination of the two. Aromatase inhibitors is one form of hormone therapy that works to stop the production of estrogen in post-menopausal women and includes Arimidex, Aromasin and Femara. This form of drug works to decrease the amount of estrogen in the body that would stimulate the growth of cancer cells (Eggert & Oncology Nursing Society Staff, 2009). Selective estrogen receptor modulators (estrogen receptor agonists) is another drug available as hormone therapy to block the effects of estrogen in the breast tissue and includes Tamoxifen, Raloxifene and Toremfene. The drug works to allow no room for estrogen to enter or attach, inhibiting the ability for cancer cells to grow and multiply (Eggert & Oncology Nursing Society Staff, 2009). Lastly, gonadotropin-releasing hormone antagonists (GnRH) is a third pharmaceutical option that works to affect hormone production in the anterior pituitary gland to either secrete or not secrete hormones. Prescribed medications include Goserelin, Leuprolide and Triptorelin (Eggert & Oncology Nursing Society Staff, 2009). Determining which hormonal treatment is appropriate for each individual will depend on the stage of breast cancer, health history, pervious response to endocrine therapy and metastasis (Pinder & Buzdar, 2008). Tamoxifen is the oldest and most common hormone therapy medication to be prescribed to patients who have not yet experienced menopause. Tamoxifen has been shown to reduce the recurrence of breast cancer fueled by estrogen, reduce tumours and limit the growth of tumour(s) (Peart, 2015). It is also prescribed to individuals who are at a high risk of breast cancer (age 60+) and is taken once a day, every day for 5 to 10 years (Peart, 2015).

1.3.1 Treatment Side Effects

Treatment for breast cancer is effective at increasing survival rates for patients in Canada but they do not come without consequences. There are many side effects for each treatment of breast cancer and experiences can differ per patient. A summary of these are presented in Table 1. Surgery can present a multitude of side effects including but not limited to muscular weakness, poor posture, skin tightness (on chest and underarm), painful shoulder movement and numbness (Wilson, 2017). It may also include fatigue, limited range of motion, lymphedema, negative body image and pain (Wilson, 2017). Lymphedema occurs when fluid collects in the interstitial space, causing an enlargement of the affected area, usually accompanied by the feeling of breast heaviness (Morrell et al., 2005).

	Short Term	Long Term
Surgery	Pain (Wilson, 2017) Fatigue (Wilson, 2017)	Lymphedema (Wilson, 2017) Limited range of motion (Wilson, 2017) Fatigue (Wilson, 2017)
Chemotherapy	Nausea (Peart, 2015) Diarrhea (Peart, 2015) Hair loss (Trüeb, 2009) Fatigue (Paleville, Topp & Swank, 2007)	Decrease in muscle mass (Paleville, Topp & Swank, 2007) Decrease in functional ability (Paleville, Topp & Swank, 2007) Fatigue (Paleville, Topp & Swank, 2007)
Radiation Therapy	Skin sensitivity (Peart, 2015) Skin burning/swelling (Peart, 2015) Fluid build-up (Peart, 2015)	Fatigue (Peart, 2015) Skin discoloration (Peart, 2015) Lymphedema (Peart, 2015)
Hormone Therapy	Hot flashes (Peart, 2015) Night sweats (Peart, 2015) Mood swings (Peart, 2015)	Secondary cancer development (Peart, 2015) Fatigue (Peart, 2015)

Table 1: Summary of side effects commonly observed during oncology treatments

This can occur after surgery when lymph nodes are disrupted and removed from the axillary area. Severity will depend on the number of lymph nodes removed and will occur in approximately 50% of patients (Morrell et al., 2005). There is currently no cure for lymphedema and it can cause lasting problems for patients including swelling, burning, numbness and tingling in the affected limb (s) (Fu, 2014). The side effects of chemotherapy vary depending on the individual patient and the type of drug(s) administered. Chemotherapy damages hair follicle cells, bone marrow cells, digestive cells and reproductive cells (Peart, 2015). Common side effects from this treatment includes vomiting, nausea, hair loss, diarrhea, loss of appetite, tingling/burning in hands or feet, and low blood cell count (Peart, 2015). Hair loss affects approximately 65% of cancer patients around the world, however, it is generally only temporary (Trüeb, 2009). Other symptoms also include fatigue, decrease in functional ability, decreased quality of life and a decline in muscle mass (Paleville et al., 2007). When completing external-beam radiation therapy, damage can occur to the skin and tissue at the radiation-site. This may include swelling, a burned appearance, fatigue and heaviness of the breast(s) (Peart, 2015). The skin may also be sensitive, the breast tissue can become hard and enlarged due to a build-up to fluid (Peart, 2015). Symptoms may present themselves after 3 to 4 weeks of treatment and disappear within 4 to 6 weeks of completed treatment, however, later effects can develop months or years after radiation and often last forever (Peart, 2015). For example, cancer survivors who have undergone radiation and chemotherapy are at risk for a cardiac event twenty years or longer after initial treatment due to cardiovascular toxicity (Okwuosa et al., 2017). Those who have had radiation near the armpit/axillary area may also experience an increased risk of lymphedema, which currently has no cure and could have effects lasting a lifetime (Warren et al., 2014). Patients who undergo external radiation will not be radioactive, as the dose is immediate. Patients who undergo internal radiation will be radioactive while the radiation is inside their body and are generally secluded in a hospital room for the duration of the treatment (Eggert & Oncology Nursing Society Staff, 2009). Hormone therapy can cause symptoms similar to menopause including hot flashes, mood swings, and night sweats (Peart, 2015). It may also increase the risk for developing other types of cancer such as uterine cancer (Peart, 2015). Side effects of breast cancer treatment are vast and diverse in their nature. Along with psychological and biological side effects, treatment can also have a considerable impact a patient's physical function.

1.4 Physical Function and Cancer

Physical function can be defined as actions essential for maintaining independence (Painter et al., 1999). Some physical function might not be necessary for independence but can affect quality of life and can be associated with falls, hospitalization, loss of independence, nursing home admission and death (Painter et al., 1999). Functional capability is important for coping with daily tasks and challenges including but not limited to stairs, slippery floors and uneven surfaces (Zak et al., 2017). Previous research suggests that treatment for breast cancer including chemotherapy, radiation, surgery and hormone therapy, have a negative effect on a breast cancer survivors' physical function. A systematic review conducted by Neil-Sztramko et al (2014), suggests that aerobic capacity, upper extremity strength, and mobility are generally lower in individuals diagnosed with breast cancer when compared to reported norms for apparently healthy individuals in the same age group (Neil-Sztramko et al., 2014). Therefore, breast cancer patients are already beginning their cancer journey at a lower physical function capacity than the general population. Negative effects on physical function from treatment for breast cancer survivors is in part due to the elements presented in Figure 1 (Galiano-Castillo et al., 2016).

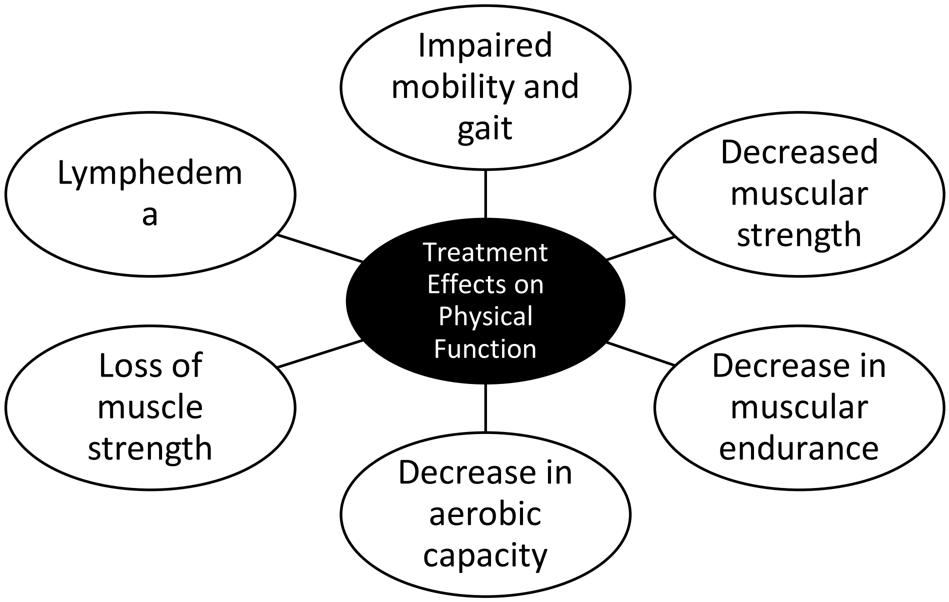

Figure 2: Negative effects on physical function due to breast cancer treatment in patients diagnosed with breast cancer.

A decrease in aerobic function can be due to direct and indirect effects of treatment for breast cancer (Courneya et al., 2007; Neil-Sztramko et al., 2014). Direct effects of treatment can refer to damage to the cardiovascular system. For example, chemotherapy and radiation can impair the hearts pump function, reducing the delivery of oxygen and resulting in a decrease in exercise endurance (Jones, L.W. et al., 2012). In childhood survivors, one strain of chemotherapy can cause a progressive decrease in the systolic left ventricle function, leading to heart failure (Agrawal, 2014; Lipshultz et al., 1991). However it is difficult to clinically distinguish the cause of heart failure in adults, as it can be due to many other factors including cancer treatment, age, any pre-existing cardiac issues and if the patient is an athlete (Agrawal, 2014). Any cancer treatment can also impair the reserve capacity of cardiovascular systems including cardiac, pulmonary, skeletal, blood-vascular and muscle function (Jones, et al., 2012; Jones, Haykowsky, Swartz, Douglas, & Mackey, 2007). The reserve capacity can be defined as the cardiovascular system having the ability to work as an integrative system and be adaptable (Koelwyn et al., 2012). For example, a systematic review conducted by Neil-Sztramko et al (2014) reported $V0_{2peak}$ measures were 22-30% lower than expected in patients diagnosed with breast cancer before, during and after treatment compared to the norms of apparently healthy women aged 50 to 59 (Neil-Sztramko et al., 2014). Indirect effects from treatment can include an overall lower aerobic function from physical deconditioning due to sedentary patterns and fatigue (Drouin et al., 2005). Oncologists may also recommend women undergoing treatment should decrease physical activity and rest, which would lead to a deconditioned state (Drouin et al., 2005). The risk or development of cardiovascular disease can also affect aerobic capacity in breast cancer patients. Women who are age 50 and older have a 40% lifetime risk of developing cardiovascular disease (Lloyd-Jones et al., 2006). Risk factors that increase lifetime risk of cardiovascular disease includes diabetes, being overweight or obese, and increase in blood pressure or total cholesterol (Lloyd-Jones et al., 2006). It can be inferred that at the time of diagnosis, a significant number of breast cancer patients are already living with one or more of the risk factors for developing cardiovascular disease. This may be due to the levels of obesity and physical inactivity in breast cancer patients (Jones, L.W. et al., 2007). Pre-existing risk of cardiovascular disease can be a strong predictor for damage to the cardiovascular system due to treatment in comparison to breast cancer patients with low pre-existing risk of the disease (Jones, et al., 2007). Risk for developing cardiac dysfunction while completing breast cancer therapy includes: high dose of chemotherapy, radiation near the heart, treatment at an older age (>60 years) and more than 2 risk factors for cardiovascular disease (Mehta et al., 2018). Aerobic capacity is an important component of health-related physical fitness and physical function, and therefore, a decrease in aerobic capacity due to treatment could significantly affect physical function for breast cancer patients (Neil-Sztramko et al., 2014). Many activities of daily living require sufficient aerobic capacity and physical function such as walking, climbing household stairs or completing chores. Losing that physical function and aerobic capacity can decrease quality of life and independence for patients.

Breast cancer patients undergoing treatment can experience changes in shoulder, arm and torso musculoskeletal function and structure (Schmitz & Speck, 2010). A systematic review on treatment related impairments in arm and shoulder in patients with breast cancer reported reduced range of motion, pain and lymphedema as common arm and shoulder impairments (Hidding et al., 2014). Other changes can also occur in joint alignment and muscle length and flexibility (Hojan, 2012). These changes in the arm and shoulder upper limb can negatively affect physical function and make simple tasks that allow for independence increasingly difficult for patients. This can include activities such as doing laundry, carrying groceries, and sport and leisure activities.

Breast cancer patients can also experience an excessive reduction in muscle size and strength. A study conducted by Sagen et al (2014) collected arm volume, height, weight, grip strength, functional shoulder tests and self-reported pain before surgery and 2.5 years after surgery from 313 breast cancer patients. From this cohort, 204 underwent axillary lymph node dissection surgery and 187 had a sentinel lymph node biopsy. Axillary lymph node dissection surgery is when multiple lymph nodes are removed from the armpit. Sentinel lymph node biopsy is when the surgical team removes one or two sentinel lymph nodes to determine if it is cancerous. The sentinel lymph node is the first lymph node in a chain or group of lymph nodes that cancer can spread to. The average age of the axillary lymph node group was 55 +/- 10 with an average body mass index of 24. They observed an 11% decrease in grip strength (P<.05) after two and a half years on the affected side of a group who had axillary lymph node dissection surgery, with a similar reduction in the unaffected side (Sagen et al., 2014). In the same study, the loss of handgrip strength 2.5 years after axillary lymph node dissection surgery was a decrease of almost three times more compared to women without a diagnosis of or treatment for breast cancer (Sagen et al., 2014). The Health, Eating, Activity and Lifestyle (HEAL) study included a cohort of 1,183 women diagnosed with stage 1-3 breast cancer and results suggested that women with less muscle strength were three times more likely to die from any cause and two times more likely to die from a breast cancer-specific cause after a nine year follow-up (Villaseñor et al., 2012). Muscle strength is important and should be a target after treatment.

Breast cancer survivors following treatment have a decrease in lower body strength and endurance compared to normative data for the same age and sex groups (Zak et al., 2017). This decrease in strength and endurance puts survivors at a higher risk for falls for those with poor balance (Zak et al., 2017). A study conducted by Winters-Stone et al (2011), suggests that post-menopausal breast cancer survivors have a higher rate of falls compared to population averages for older adults in the community (Winters-Stone et al., 2011). Research also suggests gait speed and risk of falls are correlated, with a higher gait speed decreasing the risk of falls in breast cancer survivors (Zak et al., 2017). It may also be due to impaired mobility and changes in the physiopathology of gait and balance as a common functional impairment in cancer patients (Hojan, 2012). Breast cancer treatment can affect the nervous system and nerves through compression, neurotoxicity from chemotherapy and excessive connective tissue through radiation. It can also negatively affect the musculoskeletal system including muscles, ligaments, bones and tendons (Hojan, 2012). Range of motion and shoulder impairment may occur in patients due to scar tissue from surgery (Crosbie et al., 2010; Hojan, 2012). Treatments (specifically hormone-driven) may cause cancer-treatment-induced bone loss, which puts patients at risk for fractures and breaks (Drudge-Coates et al., 2019). Chemotherapy and radiation may also impact muscles as a result of atrophy or a decrease in force capability (Hojan, 2012). These physiological changes during breast cancer treatment can lead to possible changes in pain, sensory perception, coordination, and motor planning. It can also produce loss of muscle mass, changes in posture, range of motion, flexibility and endurance. This can effect a patient's balance, gait and increase the risk of falls (Hojan, 2012). Research suggests that older adults with cancer have an increased incidence of falls with unique risk factors in comparison to the general population (Wildes et al., 2015). A timed-up and go (TUG) test to assess static and dynamic balance and mobility, is found to be worse in a cancer population compared to a healthy population, partially due to more variations in body sway (Morishita et al., 2018).

Physical function is essential for breast cancer survivors to maintain their independence, complete activities of daily living and have a high quality of life. Individuals who have received a diagnosis of breast cancer and any form of treatment (surgery, chemotherapy, radiation, hormone therapy) can experience low aerobic capacity (Neil-Sztramko et al., 2014), reduced range of motion (Hidding et al., 2014), lymphedema (Hidding et al., 2014), impaired gait and balance (Hojan, 2012) and decreased endurance (Galiano-Castillo et al., 2016). However, research suggests that exercise may be an effective form of adjuvant treatment for survivors and those who exercise throughout their cancer experience can improve their physical function (McNeely et al., 2006).

1.5 Exercise as Adjuvant Treatment

Research suggests that physical activity can help in many aspects for cancer survivors (Burke et al., 2017). Exercise can provide large improvements to physical functioning, physical well-being and quality of life of breast cancer patients during and after treatment (McNeely et al., 2006). Individuals who participate in physical activity during their lifetime before a diagnosis have a 25-30% average risk decrease in developing breast cancer (Friedenreich & Cust, 2008). Research suggests that adherence to an exercise program can vary for breast cancer patients who are undergoing treatment. Breast cancer patients will experience barriers to exercise adherence that are the same as their healthy counterparts including time restraints, lack of enjoyment and support from family and friends. However, patients can experience additional barriers to adherence due to treatment side-effects. Individuals who are completing chemotherapy struggle to adhere as they continue to progress through their treatment sessions, presumably because of an increase in treatment symptoms (Kirkham et al., 2018). Those who are undergoing radiation therapy tend to adhere more than those in chemotherapy, possible due to shorter treatment sessions and manageable side-effects (Kirkham et al., 2018). Exercise has the ability to be a relatively easy risk modifier pre-and-post diagnosis with beneficial outcomes that can change the lives of millions of breast cancer patients (Ibrahim & Al-Homaidh, 2011).

The goal of aerobic exercise during or after a diagnosis of breast cancer is to stop the decline in aerobic fitness, work to restore it to the same level before diagnosis, with the ultimate goal of improving aerobic fitness above the pre-diagnosis level (Stefani et al., 2017). An increase in aerobic fitness may lead to better patient-related outcomes as it can be associated with improved fatigue levels, quality of life, depression and anxiety (Courneya et al., 2007). Aerobic training can include various modes of exercise including walking, biking, jogging or participating in a structured group exercise. Walking is usually the preferred mode of exercise as a result of possible complications due to treatment, however, all modes should be explored (Stefani et al., 2017).

Prevention of breast cancer: An improvement in physical function outcomes through exercise before treatment could increase compliance during the duration of treatment (Silver & Baima, 2013). Research suggests that exercise throughout a lifetime can help protect from cancer through reductions in sex hormones (estrogen and progesterone), inflammatory markers and insulin, which are risk factors related to cancer development (Hojman et al., 2018; McTiernan, 2008)

During treatment: The first steps after a diagnosis of breast cancer typically includes surgery, chemotherapy, radiation and hormone therapy as a form of either primary or adjuvant treatment. Research suggests that using exercise as adjuvant treatment for breast cancer patients can improve physical function including aerobic function, muscular function and balance. For example, a randomized control trial found an average of an 80% reduction in nausea for women participating in a 12-week cycle ergometer programme three times a week at 60-85% maximum heart rate, while undergoing chemotherapy treatment (Kirshbaum, 2007). A systematic review conducted by Fairman et al (2016) reported that a combination of aerobic and resistance training, and other non-traditional modes of exercise including yoga is safe and tolerated by patients currently undergoing chemotherapy or radiation therapy (Fairman et al., 2016). In addition to reducing treatment related side effects, various exercise interventions can provide significant positive outcomes in fitness, psychological and patient reported outcomes for those undergoing breast cancer treatment (Fairman et al., 2016). Alongside functional and psychological improvements, research suggests exercise may also positively effect cell physiology. Research suggests exercise can help increase the effectiveness of cancer treatment. For example, chemotherapy relies on movement of blood through a tumor to deliver the appropriate drugs and immune cells within the cell (Hojman et al., 2018). While exercising, an individual will increase body temperature and movement of blood through the body which can be a key player in improving drug and/or immune cell delivery (Hojman et al., 2018). Similarly, radiation therapy requires adequate oxygen supply for optimal therapeutic effect. Exercise strongly affects oxygen delivery through blood circulation and biophysical adaptations of exercise has the potential to increase the blood travelling through a tumor, promoting cell death (Hojman et al., 2018). Lastly, there is some evidence that pre-operative exercise has the ability to increase immune function, improve metabolic and/or hormonal stress and regulate tumor metastasis; leading to a decreased risk in complications after surgery (Hojman et al., 2018). Similarly, natural killer or NK cells are a class of lymphocytes within the body that have the ability to naturally kill cancer cells (Idorn & Hojman, 2016; Kiessling et al., 1975). Research suggests that exercise performed at the appropriate intensity (i.e. breathlessness, an increased heart rate) can increase NK cell mobilization within minutes (Idorn & Hojman, 2016; Nielsen et al., 1996). An increase in NK cell mobilization, body temperature and blood profusion in cancer patients who exercise has important implications on regulating tumor growth (Idorn & Hojman, 2016).

Fitness professionals who work with cancer patients should have a breadth of knowledge on how to work with this population including common toxicities related to treatment, risk of fractures, neuropathies, and musculoskeletal issues (Schmitz et al., 2010). Treatment-related breast cancer toxicities include fatigue, cardiotoxicity, pain, bone damage, sleep disturbances, metabolic toxicity and psychological distress (Kleckner et al., 2018). Awareness of these toxicities can help fitness professionals understand, address and work towards removing barriers to exercise for breast cancer patients, while also ensuring the exercise is safe (Kleckner et al., 2018). Level of supervision required during exercise participation for cancer patients vary greatly depending on cancer diagnosis (i.e. including stage and type), treatment type, individual factors and cancer experience (Schmitz et al., 2010). A meta-analysis conducted by Floyd & Moyer (2009), suggests that group exercise interventions and individual exercise interventions do not differ in improvements of quality of life. It was suggested, however, that group interventions may still be suggested as they provide more opportunities for social interaction between patients (Floyd & Moyer, 2009). A recent study conducted by Leach et al. (2019), suggested significant increases in physical functions for both group and individual training programs but, improvement in overall quality of life and total physical activity were only significant within patients receiving group sessions (Leach et al., 2019).

Yoga is another mode of exercise that can provide positive psychological and physical benefits to patients who participate (Culos-Reed et al., 2006). The practice of yoga can help alleviate side effects and symptoms due to treatment including quality of life, physical, psychological, and emotional health (Agarwal & Maroko-Afek, 2018). Research suggests yoga can also help improve fatigue, reduce sleep disturbances, and improve health-related quality of life for patients (Cramer et al., 2017).

Contraindications to exercise for cancer patients includes patients who have not had an adequate healing period after surgery (~8 weeks), extreme cancer-related fatigue, anemia, ataxia, cardiopulmonary complications, and/or arm or shoulder complications (Schmitz et al., 2010). Cancer-related fatigue can be defined as “a persistent sense of tiredness that interferes with function, is distressing, and requires monitoring and possibly, treatment.” (Gerber, 2017). Breast cancer patients should be aware of changes in the arm or shoulder including symptoms such as swelling during an exercise program, and consider avoiding upper body exercises or taking a break from an exercise program until they receive medical treatment (Schmitz et al., 2010). Patients with cardiopulmonary complications may need their exercise prescription altered and increased supervision for safety. Patients with bone metastasis may need to alter the exercise prescription including the frequency, intensity, type, and time, due to an increased risk of bone fracture and require increased supervision. Patients who are undergoing chemotherapy or radiation should be aware of their increased risk of infection and precautions should be taken in fitness facilities to reduce risk of infection. Exercise tolerance may also vary session-to-session for patients currently undergoing treatment and care should be taken to modify exercise prescriptions (Schmitz et al., 2010).

After treatment: A systematic review on breast cancer patients during or after chemotherapy and radiation therapy who participated in physical or aerobic exercise reports other benefits from aerobic exercise including reduced fatigue, improvement in mood and quality of life, reductions in subcutaneous fat, improved sleep, and gains in strength and endurance (Kirshbaum, 2007). Once treatment is complete, physical activity is associated with a reduction in body mass index, an increase in peak oxygen consumption, peak power output and quality of life (Fong et al., 2012). Peak oxygen consumption can be determined by the cellular oxygen demand that equals the maximal rate of oxygen transportation, which is then determined by the maximal rate of transport (Albouaini et al., 2007). As oxygen consumption increases with increasing external work, one or more of the determinants of peak oxygen consumption approaches its limit (e.g. heart rate, stroke volume) and peak oxygen consumption versus work rate can plateau (Albouaini et al., 2007). This plateau has been used as evidence of peak oxygen consumption (Albouaini et al., 2007). Peak power output is sustaining a high workload for approximately 2 to 3 minutes during an exercise protocol that gradually increases in intensity until exhaustion (Hawley & Noakes, 1992). Physical activity after treatment of breast cancer can reduce breast cancer mortality by approximately 30% and decrease all-cause mortality by 41% (Ibrahim & Al-Homaidh, 2011).

Strength training or resistance training can offer similar benefits to breast cancer survivors when compared to a general population and can include increased muscular endurance and muscular strength (Lite & Mejia, 2010). Benefits from resistance training for breast cancer survivors also includes the ability to maintain performance of activities of daily life, control of body weight and return to exercise done prior to diagnosis (Lite & Mejia, 2010). Through strength training, an emphasis should be on posture, mobility and whole body stability with a focus on movements made to help increase performance of activities of daily living (Lite & Mejia, 2010).

At the cellular level, participation in exercise can help with prevention in relapse and mitigate long-term adverse effects through increased immune and improved metabolic function (Hojman et al., 2018).

Overall, the research suggests exercise can provide a multitude of benefits to breast cancer patients before, during and after their cancer diagnosis. This includes increasing physical function such as muscular endurance and strength, aerobic capacity and balance. Determining specific improvements in physical function requires reliable and valid methods of testing physical function that are specific to the breast cancer population.

1.6 Measuring Physical Function

Physical function can be defined as actions that are required to maintain independence (Painter et al., 1999). Physical function can be determined through a combination of physical fitness (cardiorespiratory, muscle strength and endurance), clinical condition (i.e. fatigue, cognitive function) and environmental (level of education, support, access), sensory (vision, hearing) and behavioural (perception and preference of exercise, nutrition) factors (Painter et al., 1999). Due to the complexity of physical function, there are multiple tests that are available for use. It's important to tailor physical function tests to targeted populations and characteristics of participants of interest (Painter et al., 1999). Research suggests reliable and valid physical function tests for the breast cancer population include the 6-minute walk test and the chair stand test to measure aerobic capacity and strength all associated with the ability to perform activities or daily living.

1.6.1 Aerobic Capacity

The 6- minute walk test (6MWT) is a sub-maximal exercise test to assess aerobic capacity and endurance that has been validated with clinical populations, including breast cancer survivors. Castillo et al. (2016), found significant relationships between the 6MWT and quality of life, body composition, health-related fitness, cancer-related symptoms, pain and cognitive performance (Galiano-Castillo et al., 2016). Participants are required to cover as much distance (in meters) as possible in 6-minutes, taking as many breaks as they need to. No specific equipment is required; however, the test is usually performed in a flat and straight 20-meter hallway. The 6MWT is a reliable acute clinical assessment, and research has shown breast cancer survivors had about 40% shorter covered distance during the test when compared to healthy individuals in their age group (Galiano-Castillo et al., 2016). Distance travelled on the 6MWT has also been reported to correlate significantly with VO_{2peak} (r=0.67) (Schmidt et al., 2013).

1.6.2 Muscle Strength

The chair stand test is an exercise test used to assess leg strength. A study conducted by Jones et al. (1999), found that the thirty second chair stand has the ability to service a wide range of levels and their results suggested a good test-retest reliability ($0.84 < R < 0.92$) with a valid indication of lower body strength ($0.71 < R < 0.78$) (Jones et al., 1999). Individuals are required to sit on chair with their arms crossed on their chest and feet flat on the floor. When instructed, the individual must rise to a full standing position and sit back down again. They will repeat this movement as many times as possible in thirty seconds and the number of times they stand will be recorded. A study conducted by Ortiz et al (2018) analyzed baseline data from a physical activity intervention for Latina breast cancer survivors. There were 89 breast cancer survivors recruited with a mean age of 55 +/- 10 years, an average body mass index of 31.0 +/- 6.5 kg/m^2 and a minimum of three months post-treatment (surgery, chemotherapy and/or radiation). Results from the chair stand tests showed an average of 11.6 (8.5-14.7) reps in thirty seconds for breast cancer participants. This is a lower performance score compared to apparently healthy individuals aged 60-64 with scores of 12-17 reps in thirty seconds (Ortiz et al., 2018).

1.6.3 Benefit of Exercise on Physical Function Tests

Physical function tests are important clinical measurement for breast cancer patients and exercise can improve scores on these functional tests. Research suggests the 6-minute walk test is associated with quality of life, symptoms, pain, fitness and body composition in breast cancer patients and is therefore an important measure of physical function and overall health (Galiano-Castillo et al., 2016). A systematic review suggested that both home and community based physical activity interventions anywhere between 12-weeks and 12-months, showed a mean difference of a 27.5-meter increase in the 6-minute walk test (Swartz et al., 2017). This suggests physical activity improves scores on the 6-minute walk test and therefore can improve quality of life, pain and more. A randomized controlled trial conducted by Oldervoll et al (2011), recruited cancer patients with less than two years to live, a mean age of 62.6+/- 11.3 who were 66.9% male. One group participated in a physical exercise program with a warm-up, circuit training (focused on balance, aerobic training and lower/upper body strength training and stretching) while the other group acted as a control group, receiving usual care. Results suggest clinically and statistically significant improvements in physical performance for the group who participated in the physical exercise program (Oldervoll et al., 2011). A single-arm pre-post study conducted by Foley & Hasson (2016), enrolled 52 breast cancer survivors to participate in a 12-week exercise program twice a week for 90-minutes per class with aerobic conditioning, resistance training and balance and flexibility training (Foley &

Hasson, 2016). Results suggest there were significant improvement on balance outcomes including the one-leg stance test (p=<0.001) after the 12-week exercise intervention (Foley & Hasson, 2016). The literature suggests that exercise can improve scores on common physical function tests including the 6-minute walk test and chair stand test. However, properly interpreting these improvements is crucial for determining true change in clinical populations.

1.7 Variability in Physical Function Improvements

In a clinical setting, the minimally clinically important difference (MCID) is the smallest benefit of value to the patient (Ibrahim & Al-Homaidh, 2011). Observed changes are not just based off of statistical significance, but also meaningful to the patient (McGlothlin & Lewis, 2014). Jaeschke, Singer & Guyatt (1989), defined the minimally clinically important difference as "the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patients management" (Jaeschke et al., 1989).

There is limited to no literature reporting on the minimally clinically important values for many physical function tests in the breast cancer population. Few studies have reported minimally clinically important values for the 6-minute walk test, however, they are based off of small sample sizes. For example, a study with breast cancer survivors suggested an MCID value of 62 meters (Foley & Hasson, 2016), while another study for cancer survivors suggested improvements of 55 meters was significant (Mina et al., 2017). After a search through the literature, there is currently no value for the minimally clinically significant difference for the 30-second chair stand test in the breast cancer population.

While these minimally clinically important values are rarely reported in the breast cancer population, they can provide important information on meaningful improvement to patients that goes beyond simple statistical importance.

Although research suggests functional benefits for breast cancer patients, the range of improvement is extremely wide and maybe not clinically important partially due to the variation in side effects across treatments and individuals' characteristics prior to treatment. For example, 12-51% of patients experienced pain one year or more after treatment (Rietman et al., 2003) or 2-51% of patients issues with range of motion and 6-43% report oedema (Rietman et al., 2003).

The benefits of exercise on physical capacities might be biased by the fact that the tested improvements are limited to pre-post testing and often does not adjust for energy, mood or treatment schedule (Kiwata et al., 2017). As a result, there is a need for an increase in repetitive measures in vulnerable populations including breast cancer patients. Many research studies also only consider the average change of participants during an intervention and do not consider individual response to exercise. Research suggests large interindividual differences in response to a standardized exercise program or intervention (Ross et al., 2019). Not all individuals are going to respond to exercise the same way; some individuals may experience significant improvements, while others may experience minor or no improvements. This may be due to genetics, sleep patterns, nutrition intake, training status and motivation (Swinton et al., 2018). Single pre-post measurement study designs can only provide a valid estimate on interindividual response if there is no random error and no difference between pre-post changes without the intervention, which never occurs within research (Ross et al., 2019). It can only provide an estimate of pre-post changes, including typical error and random error that may occur. True or typical error can include any error that is expected and uncontrollable (i.e. genetics), while random error can include measurement error or variables the researcher may have more control (Ross et al., 2019). A study design with multiple measurements over time can allow for the random error to be estimated, allowing for the true error free variability of the pre-post change to be isolated (Ross et al., 2019).

1.8 Gap in Literature - Research Questions

A search through the literature suggests that studies evaluating physical function after an exercise program use strictly pre-post measures. As a result, previous research suffers from many biases such as variations in weekly performance on physical function tests, especially when dealing with clinical populations. A bias is defined as a trend, tendency or opinion that can be preconceived or unreasoned (*Dictionary, Bias definition*, 2019). Within research, bias can also be defined as a systematic error into testing that may favor or encourage one outcome over another ("Merriam-Webster Dictionary, Bias definition," 2019). Bias can occur during all stages of research including pre-trial, during a trial and after a trial (Pannucci & Wilkins, 2010). Selection or assignment bias can occur before the trial, where the cohorts to be compared before and after are not equal (Ho et al., 2017). This can be especially important for cancer patients who are at different stages of their diagnosis. During a trial, instrumentation or measurement bias can occur when instruments are not properly calibrated or measurements are not reliable and valid (Ho et al., 2017). Response-shift bias can occur when participants report inaccurate pre-test ratings, which can affect the pre-post measure results (Kaushal, 2016). Once the trial is complete, citation bias may inhibit researchers from publishing unfavorable results and therefore, only positive results are typically published (Pannucci & Wilkins, 2010). External validity can also lead to bias through generalizability of study results to other groups or populations. There may be differences from the population researchers aimed to study and the population the researchers studied (Pannucci & Wilkins, 2010).

Research studies looking at physical function and breast cancer patients may not take these important potential biases into consideration which could influence reported improvements in physical function. As a result, there is a possibility that the current belief that exercise leads to physical improvement could be overestimated. This leaves a gap in the literature regarding variability in physical function improvements and response to exercise. The objectives of this study were to describe the variability during weekly performance on common physical function tests during a 12-week exercise intervention for breast cancer patients; to test if the weekly variation surpasses the minimally clinically important difference (MCID) of each test; and to explore if the self-perceived fatigue and energy were associated with weekly physical function performance.

2.0 References – Introductory Chapter

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3.0 Article

VARIABILITY IN PHYSICAL FUNCTION FOR PATIENTS LIVING WITH BREAST CANCER DURING A 12-WEEK EXERCISE PROGRAM

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Soucy, C[1,2]: Acquisition of subjects, data collection, data interpretations and manuscript preparation.

Contribution of paper:

- Large individual confidence intervals suggest variability in weekly performance on physical function tests
- Less than 30% of participants met or surpassed the minimally clinically important difference in both the 6-minute-walk-test and chair stand test
- Energy and fatigue levels may affect performance on physical function tests and should be considered

Keywords: Breast cancer; Physical Function Performance; Exercise; Interindividual Variability

3.1 Abstract

OBJECTIVES: The objectives of this study were to describe the variability during weekly performance on common physical function tests during a 12-week exercise intervention for breast cancer patients; to test if the weekly variation surpasses the minimally clinically important difference (MCID) of each test; and to explore if the self-perceived fatigue and energy were associated with weekly physical function performance.

DESIGN: Twenty-five breast cancer patients were recruited in the 12-week individualized exercise program offered in a community-based fitness facility. Physical function was assessed weekly using the 6-minute walk test (6MWT) and the chair stand test before one of the two weekly sessions. A MCID value of 50 meters was used for the 6MWT and two repetitions for the chair-stand test.

RESULTS: A significant average improvement was observed in the 6MWT ($p=.006$) and the chair-stand test ($p<.001$) after the intervention. Individual confidence intervals were wide across all testing measures with only 28% and 8% of participants met or surpassed the MCID for the 6MWT and chair stand test respectively. Correlations between self-perceived energy and fatigue were not significantly associated with the average score of each test during the trial $p >0.24$.

CONCLUSION: Despite a significant improvement in physical function during the 12-week exercise intervention, the majority of patients did not reach the MCID; could be due to large variability such as treatment-related side effect or measurement bias, but not self-perceived energy and fatigue.

3.2 Introduction

Cancer is the second leading cause of death worldwide with approximately 9.6 million deaths occurring in 2018 (*WHO*, 2019). Breast cancer is the most prevalent cancer diagnosis among women, responsible for approximately two million cases in 2018 (*WHO*, 2019). The prevalence of cancer diagnoses is increasing, however, in recent decades, the proportion of survivors has also increased (Government of Canada, 2019). Side effects from breast cancer treatment such as physical function are observed (Drouin et al., 2005; Hidding et al., 2014; Hojan, 2012; Koelwyn et al., 2012; Neil-Sztramko et al., 2014; Sagen et al., 2014; Zak et al., 2017). Physical function can be defined as physical actions essential for maintaining independence (Painter et al., 1999; Zak et al., 2017). Exercise can provide large improvements to physical functioning for breast cancer patients during and after treatment (Foley & Hasson, 2016; Galiano-Castillo et al., 2016; McNeely et al., 2006; Oldervoll et al., 2011; Swartz et al., 2017). Although research suggests there are functional benefits for breast cancer patients (Courneya et al., 2007; Mina et al., 2017; Oldervoll et al., 2011; Swartz et al., 2017) the range of improvement is extremely wide and maybe not clinically important. The benefits of exercise on physical function may vary due to measurement variation because of the precision in the measure, energy and fatigue levels, motivation or treatment schedule (Kiwata et al., 2017). As a result, there is a need for an increase in repetitive measures to capture more precisely the change in outcomes. The objectives of this study were to describe the variability during weekly performance on common physical function tests during a 12-week exercise intervention for breast cancer patients; to test if the weekly variation surpasses the minimally clinically important difference (MCID) of each test; and to explore if the self-perceived fatigue and energy were associated with weekly physical function performance.

3.3 Methods

Participants

The eligibility criteria for this study includes patients who have received a diagnosis of breast cancer, are age 19 and older, have been cleared by their medical team to participate in exercise, and have the intention to exercise for the duration of the program

Recruitment

Patients were screened and recruited through the hospital to ensure eligibility. Patients were informed of the study during an education day offered to all cancer survivors at a local fitness facility. The education day consisted of a six-hours of information on various topics related to cancer. These topics included nutrition, sexuality and intimacy, exercise, spirituality and treatment side-effects. For breast cancer patients who expressed interest in the research study, a consent form was explained by the research assistant and signed by participants.

Intervention

Participants gathered at a local fitness facility twice a week, for one hour each session. During each session, they had the support of a physiotherapist, nurse oncologist and two research assistants. Participants had limited social interaction with each other as the exercise sessions were constructed individually. Participants also had full access to the fitness facility for the duration of the 12-week intervention to exercise on their own. Attendance was collected from the fitness facility, using a swipe card, and represented the number of times participant accessed the facility. Due to this, some participants may have more than 24 sessions of attendance.

An exercise prescription for each individual participant was created by the physiotherapist, structured around their ability, previous physical activity level, and goals. Other considerations include timing of surgery, timing of treatment, the presence of lymphedema, and if they had bone metastatic disease. Exercise recommendations were based off of the exercise guidelines to accumulate 150 minutes of moderate-to-vigorous aerobic physical activity per week with two days of strength training (Schwartz et al., 2017). It was not expected that all participants were able to reach these guidelines during the program, but education and guidance was provided to work towards this goal long-term. For strength training, full body exercises were recommended to be completed in two to three sets of 10-12 repetitions. Participants were encouraged to take rest periods up to a minute between each set. There was also a rest period of about two to five minutes as a transition period in between each exercise as participants were required to clean their equipment and move on to the next exercise. Gradual strength training of the upper body was encouraged. Free weights were encouraged for the upper body to prevent compensatory patterns including preferential use of the unaffected side. This could include elbow and shoulder flexion imbalances. For lower body exercises participants were asked to use various apparatus (e.g., leg press, leg curl and leg extension). Participants also had access to a variety of equipment for aerobic exercising including treadmills, stationary bicycles and an arm ergometer. They were expected to do a minimum of 10 minutes of exercise at a time and work towards increasing the duration during the 12-week program, with the goal to perform a 30-45-minute block.

Outcome

The exposure variable was physical function. The two physical function tests (6-minute walk test and chair stand test) were performed at the beginning and the end of the 12-week intervention and once per week. Participants met the research staff 30 minutes prior to the exercise session to test physical functions. Generally, they would first be tested on the chair-stand and then the six-minute walk test. The 6-minute walk test was used to assess aerobic capacity and endurance. The 6-minute walk test is a reliable test for clinical populations (Galiano-Castillo et al., 2016). For this test, participants were required to walk as much distance as possible in six minutes up and down a 20-meter hallway, taking as many breaks as needed. No warm-up or practice session was provided, as per testing protocol. The research assistant kept track of how many meters the participant covered during the test.

There is limited research regarding the minimally clinically important difference for the 6MWT with the breast cancer patient population. For example, a study with breast cancer survivors suggested an MCID value of 62 meters (Foley & Hasson, 2016), while another study for cancer survivors suggested improvements of 55 meters was significant (Mina et al., 2017). After a review of the literature, it was decided that an MCID of 50 meters would be used for this study.

The chair stand test was used to assess leg strength. The chair stand test has moderately high reliability ($0.84 < R < 0.92$) and validity ($0.71 < R < 0.78$) (Jones et al., 1999). The chair stand test was compared to weight-adjusted leg-press and supported the validity of the chair stand as a measure of lower body strength (Jones et al., 1999). Participants were asked to sit on chair with their arms crossed on their chest and feet flat on the floor. When instructed, the participant rose to a full standing position and sat back down again. They repeated this movement as many times as possible in 30 seconds. Research assistants recorded how many times the participant sat for the duration of the test.

There is no known literature regarding a chair stand minimally clinically important difference with breast cancer patients. A study conducted with patients having Chronic Obstructive Pulmonary Disease suggested a change in at least two repetitions might be clinically important to the patient (Zanini et al., 2018). Another study with hip osteoarthritis patients suggested an improvement of 2.1 repetitions would be clinically important (Wright et al., 2011). After a review of the available literature with chronic condition patients, it was decided an MCID of two repetitions would be used for this analysis.

For both the 6MWT and chair stand, weekly scores were averaged every two weeks for each participant. This was to account for anyone who missed a weekly testing session. Then, the group average for every two weeks was calculated and plotted to display the average distance on the physical function tests over the 12-week intervention. The same procedure was completed for reported weekly energy and fatigue levels.

Other variables of interest included physical activity levels which were recorded objectively using the PiezoRxD pedometers (Steps Count, CA); participants were asked to wear the pedometer all day for seven days during the first week of the twelve-week intervention. This tool has been validated in steps ($r = 0.88$) and physical activity intensity ($r > 0.70$) when compared to accelerometry (O'Brien et al., 2018). This tracked their steps per day, and moderate to vigorous minutes of physical activity based on walking cadence: 100 and 120 steps per minute for moderate and vigorous physical activity respectively (Tudor-Locke & Rowe, 2012). Energy and fatigue levels were collected by research assistants every week before the physical function testing session. Participants were asked how much energy they feel they have that day with 0 being "no energy" and 10 being "full energy". They were also asked how much fatigue they were experiencing with 0 being "no fatigue" and 10 being "extreme fatigue". This tool has not been validated, however, it has been used in other work with cancer patients (Ross Zahavich et al., 2013).

Descriptive variables collected at baseline include age (years), weight (kg), cancer stage, and treatment history were all collected from hospital system files. Height (cm) ans waist circumference (cm) was collected by research assistants. Participant treatment history was reported as percentage of those who completed the treatment, with some individuals who completed more than one type of treatment (e.g., both chemotherapy and surgery)

Statistics

The distribution of variables was tested for normality. Then, descriptive data [e.g. median (25-75th) or mean (standard deviation)] was reported for taken measures. A paired t-test was conducted for pre-post values for both 6MWT and chair stand test. Individual linear regressions were developed for every participant who completed the exercise program and were used to develop a response estimate. The response estimate was the slope of an individual's regression line of measured values, versus time (Hecksteden et al., 2018). The intercept and slope of each linear regression was used to determine the estimated value of each variable (i.e. intercept + slope). Then, the observed value was subtracted from the estimated value and squared. Once the squared difference of each value is completed, the sum of the squared differences is computed and divided by the degrees of freedom (10). This was based on number of testing sessions (12) subtracted by two. Finally, the square root of the sum of squared differences divided by the degrees of freedom was calculated. For time, the numerical time value is divided by the total number of timepoints available and the mean time value is also calculated. Then, the time value is subtracted from the mean time value and squared. Similar to above, the sum of all squared differences will be computed and then the square root will be taken. Lastly, the TEslope (error in linear regression) will be calculated by the square root of sum squared differences of the variable divided by the square root of sum squared differences of time. Individual confidence intervals are calculated by adding or subtracting the individual slope to (1.96 x TEslope). The TE slope and confidence intervals were then plotted for each participant as proposed by Bonafiglia et al (2018).

Exploratory statistics were conducted to determine if there was a relation between performance (above or below MCID based on raw pre-post measures) and participant characteristics. A logistic regression was conducted to compare participants who met or surpassed the MCID for each respective physical function test, for baseline and changes in variables (e.g. age, attendance, MVPA, BMI, and waist circumference).

Lastly, Pearson-correlation was conducted to compare the average group scores of every two-week for physical function tests and the average group scores every two-weeks for reported energy and fatigue levels.

3.4 Results

Descriptive results for participants who completed the intervention is presented in Table 1. There was only one male who participated in the study and the group had a median age of 56 years. The average body mass index was 30.5 kg/m^2 and the median waist circumference was 101.0 cm. The average attendance was 20 sessions the median MVPA was 100 minutes per week. Many participants had more than one treatment that was completed or ongoing.

Figure 1A and 1B present information on average group performance on the 6MWT and the chair stand test, along with the self-reported energy and fatigue levels every two weeks. There was a significant difference between baseline and post-testing values for the 6MWT ($p=0.006$) and the chair stand test ($p<0.001$) but the correlations between the average self-reported energy and fatigue and the performance on these two tests was not significant ($p >0.24$).

Based on Figures 2A and 2B depicting the expected change by a participant based on the repeated measures and the area where the score might be when performing the tests. The estimates are wide with no participant completely above the MCID for each test.

Baseline characteristics (i.e. age, BMI, waist circumference, attendance and physical activity level) were tested between those who either did or did not improve the average MCID for the 6MWT and the chair stand test. Waist circumference was predictive of 6MWT performance ($p=0.04$).

3.5 Discussion

Many studies have reported improvements in physical functions following an exercise intervention in oncology settings. The objectives of this study were to describe the variability during weekly performance on common physical function tests for breast cancer patients; to test if the weekly variation surpasses the minimally clinically important difference (MCID) of each test; and to explore if the self-perceived fatigue and energy were associated with weekly physical function performance. Despite a significant improvement in physical function during the 12-week exercise intervention, the majority of patients did not reach the MCID; could be due to large variability, but not self-perceived energy and fatigue.

As previously studies suggested (Mina et al., 2017; Ortiz et al., 2018) a significant improvement was observed when testing the improvement in physical functions. While average change is important and useful, individual response to an exercise program can vary (Hecksteden et al., 2015; Swinton et al., 2018) and is starting to draw attention (Gurd et al., 2015; Hecksteden et al., 2018; Ross et al., 2019).

Wide variability in physical functions results was observed with many patients not reaching the MCID established for these tests. A wide variability in functional testing is consistent with previous research suggesting that this could partially due to long-term side effects of treatments and large variation in baseline individuals' characteristics. For example, a study by Rietman et al. (2003), found that 12-51% of patients experienced pain one year or more after treatment, or 2-51% of patients issues with range of motion and 6-43% report oedema (Rietman et al., 2003). This could be the case in the current study as many patients went through many treatments possibly because this current cancer might not be their first. Also, the variability in baseline characteristics was noted with the physical activity being estimated to be none to five hours per week.

Another factor impacting the large variability in outcomes could be due to measurement variability as suggested previously (Ho et al., 2017). Previous research on the validity and reliability of the 6MWT have reported a strong correlation between spiroergometry on a cycle ergo-meter in cancer patients (r=0.67) and high reliability (r=0.93) (Schmidt et al., 2013) with less accuracy as the mean distance increased (Schmidt et al., 2013). The current sample observed a reliability correlation of (r = 0.47) between week one and week two. Samples between the two studies varied in sex, cancer diagnosis and treatment which may have presented differences in correlations. Lastly, correlations conducted between two separate trials may not display the possible variability that can occur over the course of an intervention, especially if participants are undergoing current treatment and/or changes in diagnosis.

Research is limited with the validity of the chair stand test with cancer patients; however, work has been done with community-dwelling older adults. This work suggests a test-retest reliability of (r=0.89) for both men and women with 95% confidence intervals of (0.79-0.93) and reasonable validity (Jones et al., 1999). The sample for this study was apparently healthy older adults, specifically 42 women and 34 men with a median age of 70.5 (Jones et al., 1999). This differs greatly from the current study population with a median age of 56, living with a breast cancer diagnosis and the majority being women. The same study also found nonsignificant changes in scores from one day to another, suggesting stable performance (Jones et al., 1999). The current study found a similar correlation (r=79) as Jones et al. (1999) between week one and two. It is notable that weekly testing may show instability in performance that is not captured when only being tested twice. However, more work would need to be done to explore the validity of this measure with cancer patients.

When comparing those who surpassed the MCID for the 6MWT and baseline characteristics (e.g. age, attendance, MVPA, BMI, and waist circumference), all results were non-significant except for waist-circumference, which is suggested to be predictive of performance. When the same comparison was done for the chair stand test, no significant differences were found between any characteristics. These findings are surprising based off of the sample, as it was expected that those who began the intervention at an older age, with lower levels of MVPA, high fatigue levels and a higher BMI would be more likely to improve above the MCID. Previous research was done with older adults between the ages of 65 and 75 years who participated in an evidence-based physical activity program for sixty-minutes per session, three times a week for sixteen weeks. Physical function tests observed was the arm curl test, chair stand and the 8-foot-up-and-go test. Findings suggest that those who were female, had a lower level of physical activity at baseline, fair or poor health and older than 75 years was associated with less improvements in physical function (Fishleder et al., 2019). While the current sample differs from previous work, it may suggest greater improvements are not seen with those beginning at a lower level. As for waist circumference, a study conducted with adults aged sixty-years and older from a longitudinal osteoarthritis initiative explored the impact of waist circumference on physical activity and function. Findings suggest that older adults with higher waist circumference values had increased mobility issues or functional impairments over time (Batsis et al., 2014). Another study conducted with adults aged sixty-five years and older diagnosed with heart failure explored the influence of waist circumference and body mass index on physical function. Findings suggest that participants with a moderate waist circumference had an increase in physical function compared to those with a low waist circumference (Prince et al., 2008). It can be suggested that there is a relationship between waist circumference and physical performance as seen in this cohort and previous studies. Those who have a higher waist circumference may exhibit greater physical function impairments, and there for greater improvements.

Lastly, correlations were conducted to explore if the self-perceived fatigue and energy is associated with physical function performance. It was expected, based on our sample that participants who had increased levels of fatigue perceived there was an increased effort required for the physical function tests, specifically for the 6MWT, due to its duration and endurance compared to the chair stand test. Previous research has explored the effect on fatigue and physical performance on apparently healthy adults. A systematic review suggests that physiological variables (e.g., heart rate, cardiac output) and strength or power were not directly affected by fatigue, however, duration and intensity might be affected by fatigue due to the perception in required effort by the participant (Van Cutsem et al., 2017). Another study exploring potential correlations between physical performance and fatigue in cancer patients suggests that physical performance is independent of fatigue (Dimeo et al., 1997). Our findings are consistent with previous research, suggesting that there are no correlations between physical performance and fatigue or energy levels.

3.6 Limitations

Despite the strength of testing physical function weekly some limitations should be considered. This includes the limit of descriptive analysis and the study design with a lack of control group. Compliance was not measured related to the amount and intensity of exercise that was completed by participants. Participants, especially those under treatment might have not felt like being evaluated weekly.

3.7 Impacts/Conclusion

Despite a significant improvement in physical function during the 12-week exercise intervention, the majority of patients did not reach the MCID; could be due to large variability, but not self-perceived energy and fatigue. The present study raises awareness for professionals working with cancer patients the considerable amount of variability in the weekly test scores and call for multiple measurements of outcomes.

Funding

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Ethical Approval

Ethical approval was received from Horizon Health (#2018-2567).

Conflict of Interest

None.

4.0 References – Article

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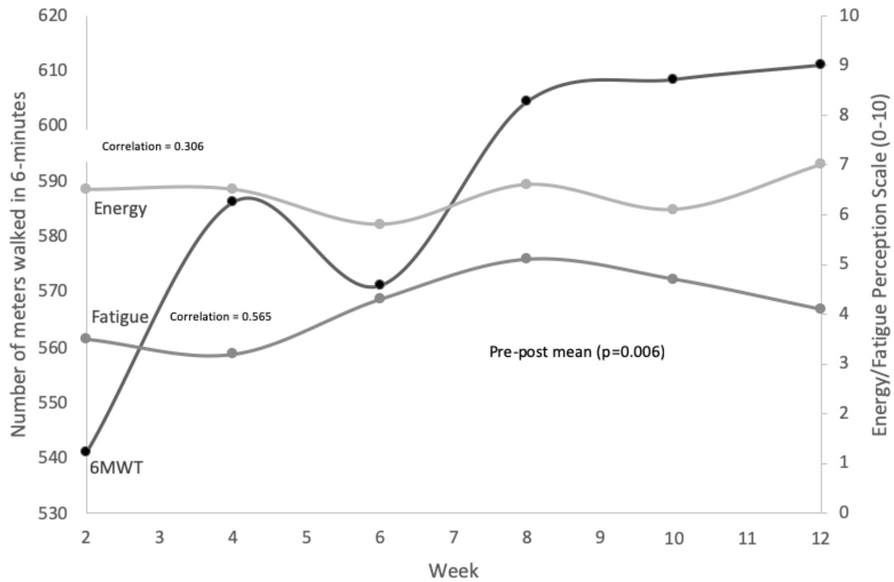
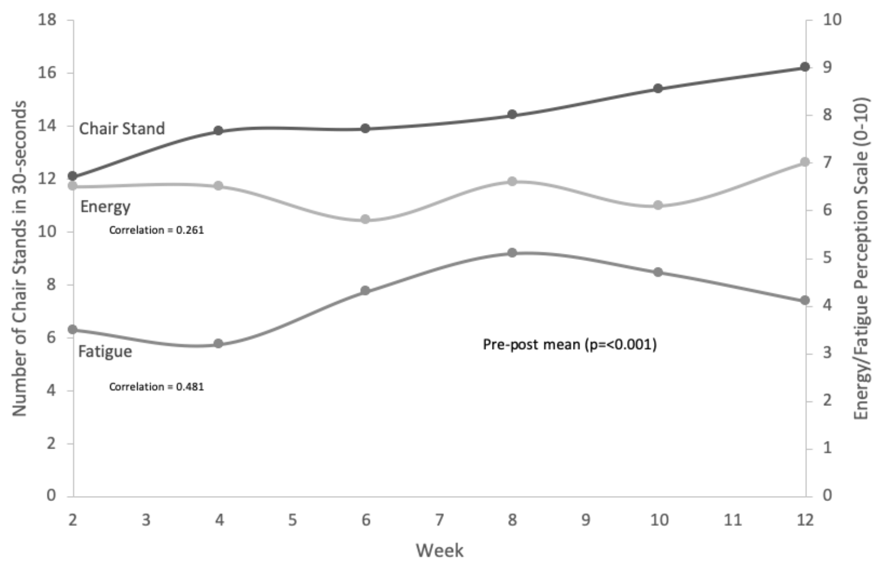
Variable	N=25
Age (years)	56 (31-74)
Sex (Women)	24 (96)
Body mass index (kg/m^2)	30.5 (22.2-43.1)
Waist circumference (cm)	101.0 (75.0-130.0)
Attendance (# of sessions during the 12 weeks)	19.6 (8-44)
Physical Activity level (moderate to vigorous minutes per week)	99.9 (2.0-305.5)
Type of Treatments	
Chemotherapy	19 (76)
Hormone therapy	18 (72)
Radiation	14 (56)
Surgery	19 (76)
Stage of Cancer	
Stage I	5 (20)
Stage II	8 (32)
Stage III	9 (36)
Stage IV	3 (12)

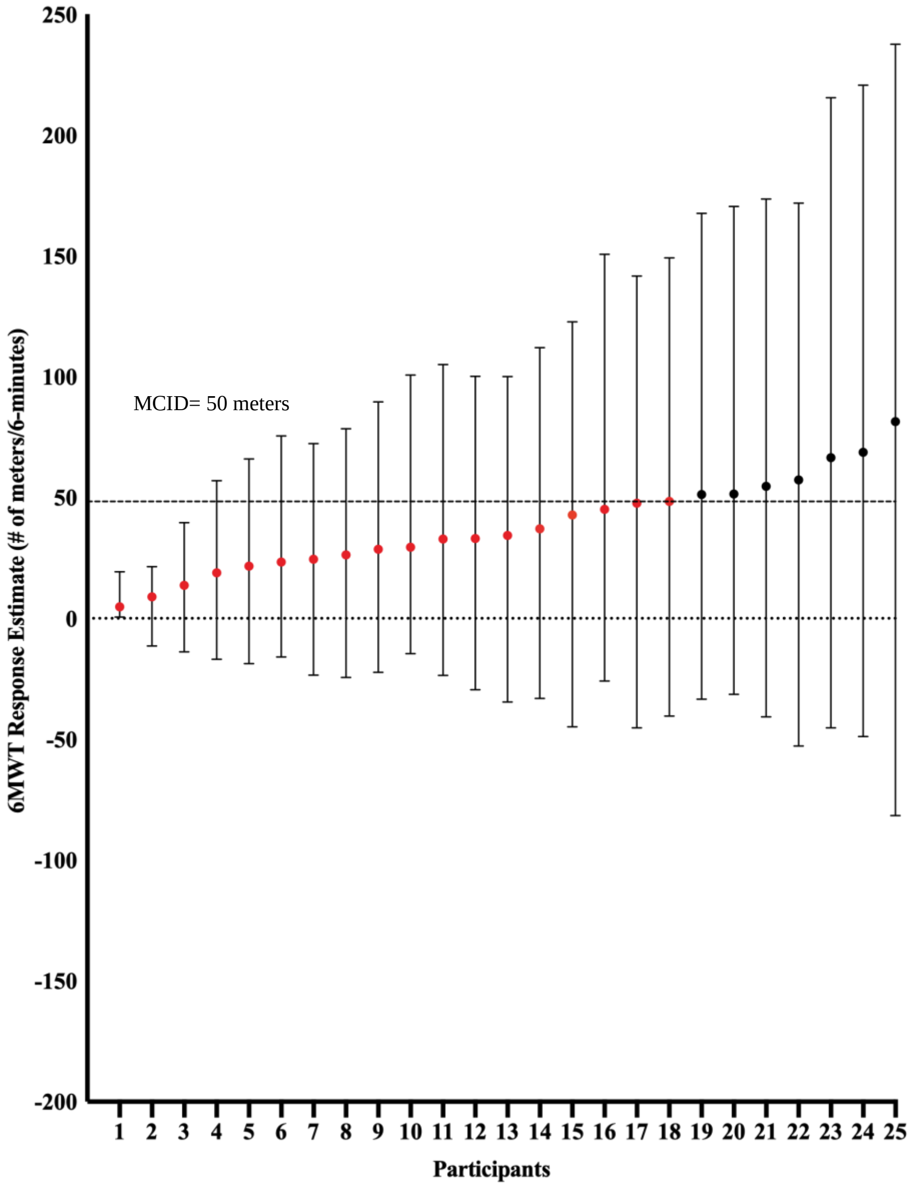
Note. Data shown as median ($25\text{-}75^{th}$) or N (%).



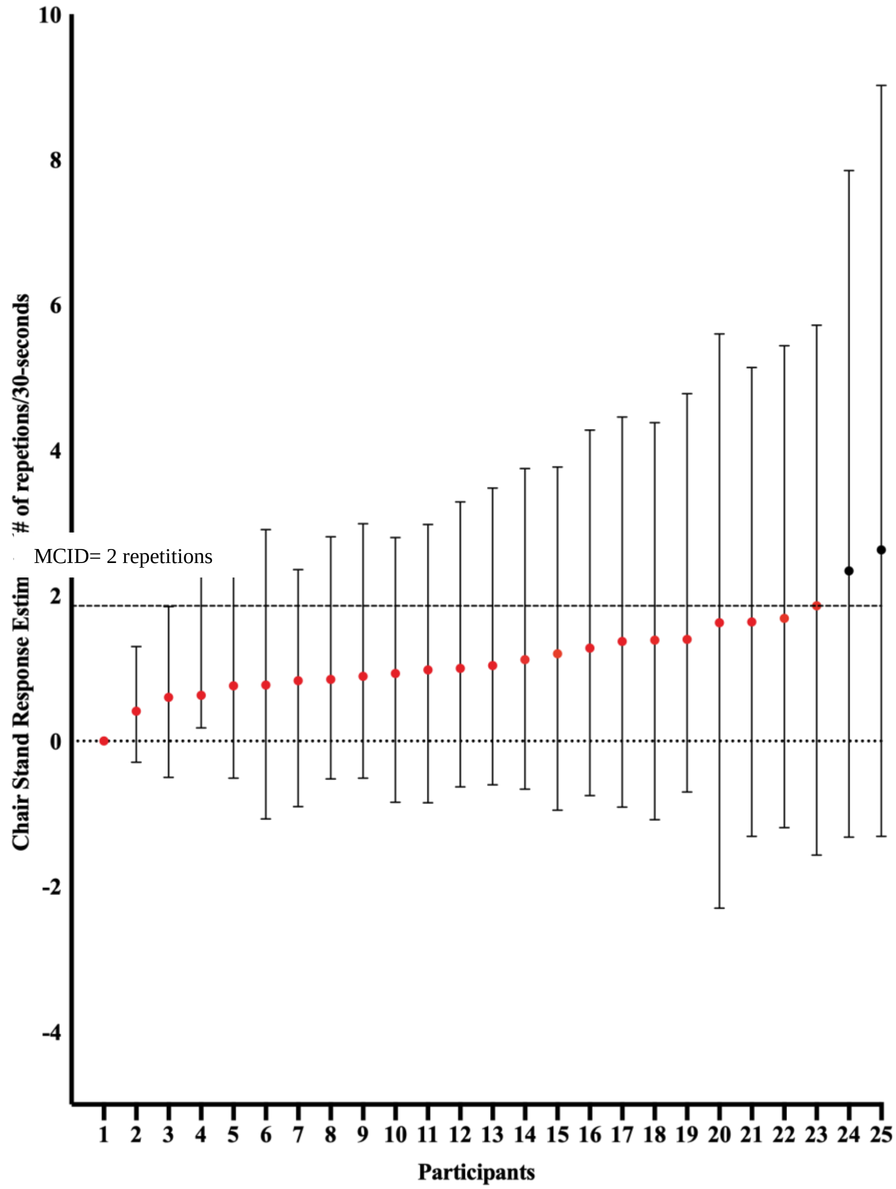
Number of meters walked in 6-minutes
Energy/Fatigue Perception Scale (0-10)
Correlation = 0.306
Energy
Fatigue
Correlation = 0.565
Pre-post mean (p=0.006)
6MWT
Week



Number of Chair Stands in 30-seconds
Energy/Fatigue Perception Scale (0-10)
Chair Stand
Energy
Correlation = 0.261
Fatigue
Correlation = 0.481
Pre-post mean (p=<0.001)
Week



250
200
150
100
50
0
-50
-100
-150
-200
6MWT Response Estimate (# of meters/6-minutes)
MCID= 50 meters
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Participants



Chair Stand Response Estim # of repetions/30-seconds
MCID= 2 repetitions
10
8
6
4
2
0
-2
-4
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
Participants

Table 1. Participant characteristics

Figure 1A. Average distance on 6MWT plotted over the 12-week intervention

Figure 1B. Average number of chair stands in 30 seconds plotted over the 12-week intervention

Figure 2A. Estimated change expected from individual responses estimate for the 6MWT.

Figure 2B. Estimated change expected from individual responses estimate for the chair stand test.

APPENDIX I : CURRICULUM VITAE

Candidate's full name:
Courtni Soucy

Universities attended (with dates and degrees obtained):
Bachelor of Science in Kinesiology, University of New Brunswick 2018

Conference Presentations:
Variability in Physical Function Test Scores for Patients Living with Breast Cancer During a 12-Week Exercise Program. New Brunswick Kinesiology Association Annual Conference and AGM, 2019

Variability in Physical Function Test Scores for Patients Living with Breast Cancer During a 12-Week Exercise Program. New Brunswick Health Research Foundation Conference, 2019

Variability in Physical Function Test Scores for Patients Living with Breast Cancer During a 12-Week Exercise Program Atlantic Provinces Exercise and Scientists and Socioculturalists (APES+), 2019

Variability in Physical Function Test Scores for Patients Living with Breast Cancer During a 12-Week Exercise Program. New Brunswick Health Research Foundation Conference, 2018