The Effects of Anthracycline/Taxane Adjuvant Chemotherapy and Resistance Exercise on Body Composition, Muscle Strength, Quality of Life and Fatigue in Breast Cancer Survivors

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This work has not previously been submitted for a degree or diploma in any university.

To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Ravin Lal
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Abstract

Adjuvant chemotherapy treatment for breast cancer with the widely used anthracycline/taxane combination has potential myotoxic effects on skeletal muscle. More generally morbidity linked to breast cancer treatment may well be associated with physical deconditioning. Together these factors could lead to reduced muscle strength, increased fatigue and consequent decreases in quality of life. Resistance exercise offers the potential to promote improvements in muscle mass and strength, with related benefits in functional capacity and life quality in this population.

The primary aims of this thesis were to investigate the effects of anthracycline/taxane adjuvant chemotherapy treatment and resistance exercise on body composition, knee muscle strength, quality of life (QoL) and perceived fatigue in women diagnosed with breast cancer. The study was designed:

1. To assess the effects of anthracycline/taxane chemotherapy on the following outcome measures in a group of volunteers following surgery for breast cancer:
   - whole body muscle and fat composition,
   - knee extension/flexion muscle strength
   - quality of life
   - perceived overall fatigue
2. To compare these outcome measures in women post chemotherapy with a group of age-matched sedentary healthy females.

3. To evaluate the effect of an individualised semi home-based 12-week resistance exercise intervention on the above variables in women with breast cancer compared to a non-exercising breast cancer control group.

4. To determine whether the changes in the above variables following the exercise intervention differs between women treated with chemotherapy compared with a healthy control group.

Firstly, 19 breast cancer patients (age of 49.8 ± 7.9 years) were assessed pre- and post-chemotherapy. Following chemotherapy, body mass increased (76.6 vs 78.7 kg; p < 0.05), along with body mass index (BMI) (28.4 vs 29.1 kg/m²; p < 0.05), and muscle cross-sectional area (CSA) (67.5 vs 71.3 cm²; p < 0.05). Muscle strength decreased in all four moments tested: isometric extension (2.02 vs 1.83 Nm; p < 0.05), isometric flexion (0.79 vs 0.65 Nm; p < 0.05), concentric extension (1.16 vs 0.89 Nm; p < 0.05), and concentric flexion (0.59 vs 0.43 Nm; p < 0.05). Chemotherapy was not associated with any change in whole body lean mass (43.6 vs 43.6 kg; p > 0.05) whole body fat mass (35.4 vs 36.2 kg; p > 0.05), fat CSA (97.6 vs 99.1 m²; p > 0.05) or muscle density (73.9 vs 73.7 g/dL; p > 0.05). After chemotherapy there were no changes in any of the 8 quality of life domains except for a decrease in physical functioning (70.0 vs 61.3; p < 0.05); there were no changes in any of the 5 domains of perceived fatigue except for increased motivation (12.8 vs 11.8; p > 0.05).
Following chemotherapy treatment, the breast cancer group \((n = 19; \text{age} = 49.8 \pm 7.9 \text{ years})\), had greater fat CSA \((99.1 \text{ vs } 78.8 \text{ cm}^2; p < 0.05)\) compared to the healthy control group \((n = 27; \text{age} = 46.9 \pm 10.0 \text{ years})\), but there were no differences between the two groups for either body mass \((78.7 \text{ vs } 71.8 \text{ kg}; p > 0.05)\) or body mass index (BMI) \((29.1 \text{ vs } 26.5; p > 0.05)\). Furthermore, there were no differences between the two groups for whole body lean mass \((43.6 \text{ vs } 42.2 \text{ kg}; p > 0.05)\) whole body fat mass \((36.2 \text{ vs } 29.6 \text{ kg}; p > 0.05)\), muscle CSA \((71.3 \text{ vs } 77.0 \text{ m}^2; p > 0.05)\) or muscle density \((73.7 \text{ vs } 74.5 \text{ g/dL}; p > 0.05)\). Muscle strength was greater in the healthy control group compared to the breast cancer group for all four moments tested: isometric extension \((2.1 \text{ vs } 1.8 \text{ Nm}; p < 0.05)\), isometric flexion \((0.8 \text{ vs } 0.7 \text{ Nm}; p < 0.05)\), concentric extension \((1.4 \text{ vs } 0.9 \text{ Nm}; p < 0.05)\), and concentric flexion \((0.7 \text{ vs } 0.4 \text{ Nm}; p < 0.05)\). The healthy women reported better quality of life compared to breast cancer patients who had completed chemotherapy treatment for all 8 domains except for mental health (MH) \((75.8 \text{ vs } 76.3; p > 0.05)\). There were no differences between the breast cancer group following chemotherapy treatment and the healthy control group for any of the 5 domains of perceived fatigue. The decrease in muscle strength in the breast cancer patients, following chemotherapy treatment, suggests potential impacts on functional capacity and well-being.

For the intervention arm of the study, 14 breast cancer patients \((\text{age of } 51.9 \pm 3.6 \text{ years})\) who had been treated with anthracycline/taxane adjuvant chemotherapy were randomly assigned to either an individualised home-based 12-week resistance exercise program or usual care. The previously mentioned outcome measures were compared between
breast cancer groups (Exercise; \( n = 7 \), Non-exercise; \( n = 7 \)) after 12 weeks, and between the breast cancer exercise group and the age-matched healthy women (\( n = 24 \); age of \( 47.1 \pm 2.2 \) years) who had also undertaken the 12-week exercise program. Following the 12-week intervention, the breast cancer non-exercise group showed a higher fat CSA (75.0 vs 129.7 cm\(^2\); \( p < 0.05 \)) compared to the breast cancer exercise group but there were no differences between the breast cancer exercise and non-exercise groups for either body mass (72.8 vs 80.6 kg; \( p > 0.05 \)) or body mass index (BMI) (24.9 vs 29.9; \( p > 0.05 \)). Furthermore, there were no differences between the two groups for whole body lean mass (44.8 vs 45.7 kg; \( p > 0.05 \)) whole body fat mass (32.1 vs 41.7 kg; \( p > 0.05 \), muscle CSA (69.7 vs 74.8 m\(^2\); \( p > 0.05 \)) or muscle density (74.0 vs 74.1 g/dL; \( p > 0.05 \)). Muscle strength was greater in the breast cancer exercise group compared to the breast cancer non-exercise group for three of the four moments tested: isometric flexion (1.0 vs 0.6 Nm; \( p < 0.05 \)), concentric extension (1.4 vs 0.9 Nm; \( p < 0.05 \)), and concentric flexion (0.7 vs 0.5 Nm; \( p < 0.05 \)); isometric extension, was slightly higher in the breast cancer exercise group compared to the breast cancer non-exercise group (2.2 vs 1.8 Nm; \( p > 0.05 \)). There were no differences between the two breast cancer groups in 6 of the 8 domains of quality of life, with Physical Functioning (92.1 vs 64.3; \( p < 0.05 \)) and Role Physical (93.6 vs 62.6; \( p < 0.05 \), showing higher values for the breast cancer exercise group compared to the breast cancer non-exercise group. Surprisingly, the breast cancer exercise group reported higher on the Mental Health domain (12.6 vs 10.9; \( p < 0.05 \)) of perceived fatigue compared to the breast cancer non-exercise group. The breast cancer non-exercise group reported higher on the Reduced Activity domain (13.9 vs 12.1; \( p < 0.05 \)) compared to the breast cancer
non-exercise group. There were no differences between these two groups for the remaining domains of perceived fatigue.

Following the 12-week exercise intervention, the healthy control group showed a higher muscle density (75.4 vs 74.0 g/dL; \( p < 0.05 \)) compared to the breast cancer exercise group. However, the effect of exercise on muscle density was not different between the two groups (\( p > 0.05 \)). There were no differences between the breast cancer exercise and healthy control groups for either body mass (72.8 vs 65.0 kg; \( p > 0.05 \)) or body mass index (BMI) (24.9 vs 24.1; \( p > 0.05 \)). Furthermore, there were no differences between the two groups for whole body lean mass (44.8 vs 41.6 kg; \( p > 0.05 \)), whole body fat mass (32.1 vs 26.1 kg; \( p > 0.05 \)), muscle CSA (69.7 vs 78.9 m\(^2\); \( p > 0.05 \)) or fat CSA (75.0 vs 74.9 cm\(^2\); \( p > 0.05 \)).

Muscle strength was greater in the healthy control group compared to the breast cancer exercise group for three of the four moments tested: isometric extension (2.7 vs 2.2 Nm; \( p < 0.05 \)), concentric extension (1.7 vs 1.4 Nm; \( p < 0.05 \)), and concentric flexion (1.2 vs 0.7 Nm; \( p < 0.05 \)). For isometric flexion, there was no difference between the two groups (1.0 vs 1.0 Nm; \( p > 0.05 \)).

The exercising breast cancer group reported higher scores for three of the QoL scales: Physical Functioning (92.1 vs 91.8; \( p < 0.05 \)), Role Physical (93.6 vs 90.7; \( p < 0.05 \)) and Vitality (74.1 vs 67.6; \( p < 0.05 \)), compared to the healthy exercise control group following the 12-week exercise intervention. There were no differences between these two groups for the remaining five quality of life domains. Furthermore, there were no differences between these two groups on any of the domains of perceived fatigue.
The reduction in fat mass, increase in muscle strength, improvements in quality of life and fatigue in the exercising breast cancer group, compared to the breast cancer non-exercise group and healthy exercising women following the intervention, can be regarded as a beneficial effect of resistance exercise. There was no indication from our data that resistance training arrested loss of lean mass in our exercising breast cancer group, an observation that may be related to the small sample size. The gain in muscle strength in the exercising breast cancer group raises questions about the functional significance of the loss of lean mass. In conclusion, despite our small sample size, we were able to show improvements in muscle strength, quality of life and fatigue in breast cancer patients (treated specifically with anthracycline/taxane adjuvant chemotherapy) following a 12-week progressive resistance training program in a home-setting. These observations support the use of home-based progressive resistance training in this population. Although not the first study to explore the efficacy of a resistance exercise program in breast cancer survivors, the current study has shown definitive (i.e. dynamometry) improvements in muscle strength and body composition associated with a “low-tech” home-based resistance exercise program over a relatively short period. Related improvements in quality of life and perceived fatigue support the promotion of such a program immediately following the completion chemotherapy treatment.
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List of Abbreviations

AACR  Australian Association of Cancer Registries
AC  Adriamycin (doxorubicin) + cyclophosphamide
ACS  Australian Cancer Society
ACSM  American College of Sports Medicine
ADL  activities of daily living
ADR  adverse drug reactions
AESS  Australian Association of Exercise and Sports Science
AIHW  Australian Institute of Health and Welfare
ANOVA  Analysis of Variance
BC  breast cancer group
BCE  breast cancer exercise group
BCN  breast cancer non-exercise group
BMI  body mass index
BP  Bodily pain
BRCA 1 (or 2)  breast cancer susceptibility gene 1 (or 2)
CMF  cyclophosphamide + methotrexate + 5-floururacil
CSA  cross-sectional area
CTC  circulating tumour cells
d  effect size
DHAC  Department of Health and Ageing
DNA  deoxyribose nucleic acid
DXA  Dual energy x-ray absorptiometry
EC  Epirubicin + cyclophosphamide
EORTC QLQ-30  European Organisation for Research and Treatment of Cancer QoL questionnaire
ES  effect size
ESSA  Exercise and Sports Science Australia
FAC  5-flurouracil + Adriamycin (doxorubicin) + cyclophosphamide
FACT-B  Functional Assessment for Cancer Therapy – Breast Cancer
FEC  5-flurouracil + Epirubicin + cyclophosphamide
GF  General Fatigue
GH  General Health
HC  healthy control group
HREC  Health Research and Ethics Committee

HR$_{\text{max}}$  maximal heart rate

IARC  International Agency for Research on Cancer

MF  Mental fatigue

MFI-20  Multi-dimensional Fatigue Inventory

MH  Mental health

MRI  magnetic resonance imaging

$n$  sample size

NBOCC  National Breast and Ovarian Cancer Centre

PF  Physical Functioning

PFat  Physical fatigue

PICF  Patient Information and Consent Form

pQCT  Peripheral quantitative computed tomography

PRT  progressive resistance training

QoL  quality of life

RA  Reduced activity

RE  Role limitations due to emotional problems
RM Reduced motivation

RM repetition maximum

RNA ribose nucleic acid

ROM range of motion

RP Role limitation due to physical health

RR response rate

SD standard deviation

SE standard error

SF Social functioning

SF-36 Medical Outcomes Study Short Form 36

SPSS Statistical Package for Social Sciences

TTP Time (after treatment) to progression

VO$_{2\text{max}}$ maximal volume of oxygen consumption per minute

VT Vitality

WCRF World Cancer Research Fund

WHO World Health Organisation
Chapter 1: Introduction
1.1 Background

Breast cancer is one of the most common malignancies in females and one of the major contributors to morbidity and mortality in the world (Ferlay et al., 2012; WCRF, 2013). Breast cancer is estimated to be the most commonly diagnosed tumour in females in Australia with an estimated 14560 new cases in 2012 (AIHW/AACR, 2012). The incidence of breast cancer is continuously increasing globally, with the highest incident rates occurring in developed regions such as Europe and North America (Ferlay et al., 2012). Incidence rates of breast cancer in Australia increased steadily from 101 cases per 100,000 in 1991 to 114 cases per 100,000 in 2012 (AIHW/AACR, 2012), with this pronounced increase thought to be due to the introduction of the national breast screening program, BreastScreen Australia (AIHW/AACR, 2012).

Despite significant improvements in diagnosis, prognosis and survival, breast cancer remains to be a leading cause of mortality in developing countries due to a less developed screening and treatment programs in these regions (Ferlay et al., 2012). Breast cancer is the second most common cause of cancer-related deaths (after lung cancer) in Australia, with an estimated 2480 deaths in 2010 (AIHW/AACR, 2012). However, due to the availability of quality and effective treatment, management and the implementation of various cancer surveillance programs in Australia, breast cancer has shown to have a 17% increase in the 5-year survival rate for the period of 2006-2010 as compared to the period of 1982-1987 (AIHW/AACR, 2012). The risks of developing breast cancer include damage to genetic material, family history of breast
cancer, old age, changing patterns in childbearing and breastfeeding, exogenous hormonal exposure, westernised lifestyle factors such as obesity, increased alcohol consumption and reduced physical activity (Hartz & He, 2013; Kluttig & Schmidt-Pokrzywniak, 2009).

Treatment for breast cancer initially comprised of surgery and radiotherapy, with chemotherapy treatment later introduced in the 1970’s as an adjuvant treatment modality in the pursuit of complete eradication of the tumour (Nabholtz, Reese, Lindsay, & Riva, 2002). Adjuvant chemotherapy in the treatment for breast cancer has undergone a series of progressive developments by including newer and more effective chemotherapeutic drugs that have significantly improved the treatment and survival in breast cancer patients (Ayoub, Verma, & Verma, 2012). By combining the main classes of chemotherapeutic drugs such as the anthracyclines and taxanes, this combination has shown to be more effective and considered to be the gold standard in the treatment for breast cancer (Cardoso et al., 2009). However, administration of this chemotherapeutic cocktail has resulted in some notable cytotoxic side-effects, besides the beneficial efficacy in the treatment of breast tumour malignancies (Greil, 2009; Mlineritsch, 2009). Improvements in diagnosis of breast cancer over the decades and recent advances in the treatment with chemotherapeutic agents have resulted in increased survival rates and increased life expectancy, although a number of undesirable consequences have dramatically affected various aspects of the patients’ physiological, psychological and psychosocial characteristics including body weight.
changes, muscular atrophy, decreased or loss of muscle strength, depression, fatigue and overall decrease in quality of life (Manir et al., 2012; Prado et al., 2009).

Previous reports show that exercise in elderly and healthy individuals contributed to improvements in cardiorespiratory fitness, physical functioning, body weight, body fat, lean mass, muscle strength, fatigue and quality of life (Caspersen, Powell, & Christenson, 1985; Friedenreich et al., 2011; Hanson et al., 2009). Exercise intervention studies have shown that any form of physical activity or aerobic or strength training exercises have contributed to reproducible and durable significant positive effects on weight loss, fat loss, improvements in muscle mass and strength, improved physical functioning, quality of life and fatigue in a number of medical-related conditions such as diabetes, hypertension, depression and osteoarthritis. (Church et al., 2009; Hubbard, Fallah, Searle, Mitnitski, & Rockwood, 2009; Johnson et al., 2007; Kerksick et al., 2009). Given the beneficial effects of exercise on health-related outcomes in healthy, elderly and clinical populations as discussed above, exercise intervention programs can be effectively used to ameliorate the various side effects of chemotherapy in breast cancer, improve cardiovascular fitness, enhance lean mass and muscle strength, improve quality of life and reduce fatigue.

1.2 What is breast cancer?

Breast cancer describes the pathological condition in which the cells and the tissues of the breast become abnormal and begin to multiply out of control as a result of changes (mutations) in the genetic information (i.e. DNA sequence) of a cell (Grimsey, 2003;
Mohamed, 2007). Breast tissues include lobules that produce milk and ducts that transport milk, surrounded by fatty tissue. Initially, breast cancer begins in the ducts or the lobules and when the cancer cells stay within these areas, it is known as non-invasive breast cancer (Grimsey, 2003; Mohamed, 2007). It is possible that the cancer cells could spread into the surrounding tissues and this is called invasive breast cancer (Grimsey, 2003; Mohamed, 2007). Breast cancer cells, also known as circulating tumour cells (CTCs), can travel in the blood stream or the lymphatic system to other parts of the body, such as the bones or the liver and this is known as metastatic breast cancer (advanced breast cancer) (Dong, Alpaugh, & Cristofanilli, 2012; Mohamed, 2007).

Ductal carcinoma (breast cancer cells localised in the ducts) is the most common type of breast cancer among women (Abdulrahman & Rahman, 2012; Mohamed, 2007). Histologically, mutations of the tumour suppressor genes, breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2), are the main factors leading to increased risk of developing breast cancer (Abdulrahman & Rahman, 2012; Boeri, Canzonieri, Cagioni, Ornati, & Danesino, 2011). Based on various clinical, histopathological and gene expression microarray profiles, breast cancer tumours can be classified into various molecular subtypes with distinct tumour characteristics, treatment responses and prognosis (Gaudet et al., 2011).
1.3 Incidence of breast cancer

1.3.1 Incidence of breast cancer in the world

Breast cancer is the most frequently diagnosed cancer (with its detection facilitated by recent advances and developments in breast cancer screening programs), and one of the major contributors to morbidity and mortality in the world (Ferlay et al., 2013; WCRF, 2013). The International Agency for Research on Cancer (IARC) of the World Health Organisation (WHO), in a recent press release on the latest world cancer statistics, reported 1.7 million new cases of breast cancer in 2012, with an estimated 6.3 million women diagnosed in the previous five years (Ferlay et al., 2013). This recent marked increase in new cases makes breast cancer the world’s most common and frequent cancer among women in 140 out of 184 countries representing 25% of all new female cancer cases. Overall it is the second most common cancer representing about 12% of all new cancer cases (Ferlay et al., 2013). It is further reported that breast cancer incidence had increased by more than 20% since 2008, with increases in mortality by 14% (Ferlay et al., 2013).

The incidence of breast cancer is continuously increasing globally, with the highest incident rates occurring in developed regions such as Europe and North America (Ferlay et al., 2013). Despite significant improvements in diagnosis, prognosis and survival, breast cancer remains a leading cause of mortality in developing countries due to a less developed screening and treatment programs in these regions (Ferlay et
al., 2013). The global burden of breast cancer continues to increase in economically developing countries due to population aging and growth, as well as an increased prevalence of cancer-associated lifestyle behaviours including physical inactivity, obesity, smoking, alcohol consumption and hormonal factors (Jemal et al., 2011). While there has been a remarkable progress in the diagnosis and treatment for breast cancer that has resulted in increasing survival rates, further approaches need to be introduced and adapted to improve the well-being and quality of life amongst the survivors.

In a more comprehensive investigation in the global incidence of all cancers, it was reported that the number of new cases of breast cancer was similar in both more or less developed regions, with slightly more cases (883,000 new cases) in less developed regions than in more developed regions (794,000 new cases) in 2012 (Ferlay et al., 2013). Additionally, it was further noted that incidence rates were higher (96 cases per 100,000 women) in Western Europe and low (27 cases per 100,000 women) in Middle Africa and Eastern Asia (Ferlay et al., 2013). Breast cancer is also found to be the most common cause of cancer-related death among women with 522,000 deaths worldwide in 2012 (Ferlay et al., 2013). Breast cancer-related deaths are more pronounced in less developed countries of the world with 324,000 (14.3% of total) deaths, compared to 198,000 breast cancer related deaths in more developed regions, where it is now known to be the second cause of cancer-related deaths after lung cancer (Ferlay et al., 2013).
It has been suggested that there is a multifactorial basis for the international variation in breast cancer incidence rates which include differences in lifestyle, reproductive and hormonal factors as well as a more advanced screening paradigm in developed nations (Jemal et al., 2011). The risks of developing breast cancer include damage to genetic material, family history of breast cancer, old age, changing patterns in childbearing and breastfeeding, exogenous hormonal exposure, westernised lifestyle factors such as obesity, increased alcohol consumption and reduced physical activity (Hartz & He, 2013; Kluttig & Schmidt-Pokrzywniak, 2009). Reproductive and hormonal factors include early menarche and late menopause (a long menstrual history), late age at first birth, recent use of post-menopausal hormonal therapy and oral contraceptives (Kluttig & Schmidt-Pokrzywniak, 2009). Lifestyle behaviours include alcohol consumption, smoking, poor diet, obesity and physical inactivity (Kluttig & Schmidt-Pokrzywniak, 2009). The recent general worldwide increasing trend of breast cancer in undeveloped/developing poorer regions of the world is indicative of a shift in lifestyle behaviours (involving a number of societal and economic changes), leading to higher incidences in these areas as compared to the developed and richer regions.

Breast cancer-related mortality is high in less developed regions as compared to the more developed regions of the world, and this may be due to lack of clinical advances (including infrastructure, specialised medical personnel/specialists, equipment, and disease management and rehabilitation processes) available for the communities in these regions. The huge inequalities between the richer and poorer regions of the world are probably the main reasons of high mortality rates in less developed regions due to
lack of early detection programs and access to appropriate treatment and/or management facilities and process (Ferlay et al., 2013).

1.3.2 Incidence of breast cancer in Australia

Breast cancer is estimated to be the most commonly diagnosed tumour in females in Australia with an estimated 14,560 new cases in 2012 (AIHW/AACR, 2012). Incidence rates of breast cancer in Australia increased steadily from 101 cases per 100,000 in 1991 to 114 cases per 100,000 in 2012 (AIHW/AACR, 2012), with this pronounced increase thought to be due to the introduction of the national breast screening program, Breast Screen Australia (AIHW/AACR, 2012). Breast cancer is the second most common cause of cancer-related deaths (after lung cancer) in Australia, with an estimated 2480 deaths in 2010 (AIHW/AACR, 2012). However, due to the availability of quality and effective treatment, management and the implementation of various cancer surveillance programs in Australia, breast cancer has shown a 17% increase in the 5-year survival rate for the period of 2006-2010 as compared to the period of 1982-1987 (AIHW/AACR, 2012). In addition to the improvements in the treatment for breast cancer leading to an increased survival rate, further development of management strategies are needed to help improve the quality of life in the survivors of his condition.

Breast cancer is the most commonly diagnosed cancer in females, accounting for 27.0% of all cancer diagnoses in 2009, increasing slightly to 27.2% in 2012 (AIHW/AACR, 2012). As a result, for women, the risk of being diagnosed with breast cancer before
the age of 75 is 1 in 11 compared with 1 in 27 for bowel cancer (AIHW/AACR, 2012). The age-standardised incidence rates of breast cancer in females rose steadily from 101 per 100,000 women in 1991 to 114 per 100,000 women in the general population in 2009, and was predicted to remain stable through to 2012 (AIHW/AACR, 2012). Although breast cancer is primarily a disease that affects older people, a high incidence of breast cancer in females between the ages of 30 and 54 years, makes breast cancer atypical in terms of age distribution (AIHW/AACR, 2012).

Breast cancer is the second most common cause of death in females with 2,680 deaths in 2007, increasing to 2,840 deaths in 2012 (AIHW/AACR, 2012). However, a decrease of 30% in age-standardised mortality rate from 31 per 100,000 women in 1994 to 22 per 100,000 women in the general population in 2010 was observed, thought to be due to an improved quality and availability of a breast screen program known as BreastScreen Australia, and subsequent improved treatment/management processes (AIHW/AACR, 2012). Despite this, the recently estimated age-standardised mortality rate of breast cancer-related deaths in 2012 means that Australia likely has the fourth highest rate of cancer-related mortality in the world (AIHW/AACR, 2012; Ferlay et al., 2010).

Although breast cancer is one of the leading causes of death in Australian women, advances in the clinical management have led to an increase in five-year survival rate, after diagnosis of breast cancer, of around 88.3% between 2000 and 2006 (AIHW/AACR, 2012). Currently, the five-year relative survival rate of breast cancer
in Australia is at 90.0%, and the main aim of treatment is to increase the duration of time free from disease-related symptoms with minimal toxicity (AIHW/AACR, 2012). Optimal treatment is also focused on ensuring the maximum quality of life for the majority of the patients, and is targeted at achieving a maximal benefit with minimal side effects (Johnston & Swanton, 2006).

1.4 Risk factors for breast cancer

As detailed above, numerous epidemiological studies reveal that breast cancer is one the most lethal malignancies worldwide. While the causes of breast cancer are not fully understood (extensive investigations on the exact mechanisms are ongoing worldwide), the likely risk factors that are usually identified include, but are not restricted to, age, obesity, family history, menopause, hormonal therapy, oral contraceptive use, alcohol use, cigarette smoking and lack of physical activity (Kluttig & Schmidt-Pokrzywniak, 2009). Such risk factors, categorised into non-modifiable risk factors and modifiable risk factors based on various genetic, physiological and lifestyle characteristics have been collated from a number of studies and reviews, and are illustrated in Figure 1 (Begum, Richardson, & Carmichael, 2009; Beral, Reeves, Bull, & Green, 2011; Clark, 2004; Flynn et al., 2010; Green, Hankinson, Bertone-Johnson, & Tamimi, 2010; Hartz & He, 2013; Kluttig & Schmidt-Pokrzywniak, 2009; Maccio & Madeddu, 2011; Schreer, 2009).
### Non-modifiable risk factors

- Old age†
- Female gender†
- Race, ethnicity, geographical variation and migration†
- Genetic factors and family history†
  - Early age at menarche†
  - Late age at menopause†
  - Increased breast density†
  - Increased body height* 
- Increased endogenous hormones (oestrogen)†
- Prior history of breast biopsy with benign diagnosis†

### Modifiable risk factors

- Unhealthy diet*
  - Increased alcohol consumption*
- Smoking*
- Decreased physical activity*
- Obesity*
- Older age at first birth, parity and breastfeeding frequency†
- Hormonal replacement therapy/hormonal contraceptives*
- Ionising radiation

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**Figure 1:** Risk factors associated with breast cancer in women

† Major risk factors, * minor risk factors
1.4.1 Non-modifiable risk factors

a) Old age

Increasing age in any given population is usually considered to be one of the main risk factors for many common diseases and illnesses including breast cancer (Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009). Despite being rarely observed before the age of 25 years, and with very low incidence for those under 30, breast cancer incidence increases significantly between the ages of 30 and 50, and continues, albeit at a lower rate, up to the age of 80 years (Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009).

b) Female gender

Being a woman is the most striking risk factor for breast cancer. Although breast cancer affects both men and women, current data indicate a 100-fold higher level in women as compared to men; breast cancer represents less than 1% of all cancers in men worldwide (National Breast and Ovarian Cancer Centre, 2009; Weiderpass, Meo, & Vainio, 2011). The obvious explanation for this disparity is the difference in levels of ovarian and female sex-related hormones, which play an important role in the development of breast cancer (National Breast and Ovarian Cancer Centre, 2009).
c) Race, ethnicity, geographical variation and migration

Incidence and mortality of breast cancer differ amongst various countries around the world, with age-standardised incidence rates at around five-fold higher in developed regions (e.g. Europe and North America) compared to less developed areas (e.g. Africa and certain parts of Asia) (Abdulrahman & Rahman, 2012; Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009).

d) Genetic factors and family history

Family history of breast cancer in previous generations is another important and well-reported risk factor for developing breast cancer (Boeri et al., 2011; Flynn et al., 2010; Gramling et al., 2010; Hartz & He, 2013; Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009; Tazzite, Jouhadi, Saiss, Benider, & Nadifi, 2013). The risk of developing breast cancer increases two-fold in women with an immediate family (mother, sister or daughter) with breast cancer as compared to those with a non-affected first-degree relative (Boeri et al., 2011; Flynn et al., 2010; Mavaddat et al., 2010; National Breast and Ovarian Cancer Centre, 2009; Nelson et al., 2012).
e) Early age at menarche

Age at menarche is referred to as the chronological indicator of the onset of the menstrual cycle, characterised by monthly fluctuations in hormone levels, ovulation and cellular proliferation in the breasts. It is a predictor of ovulatory frequency during adolescence and hormone levels in young adults (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009).

f) Late age at menopause

Menopause is characterised by cessation of the menstrual cycle and ovarian hormone production, associated with decreased cell proliferation and reduction in breast tissue known as involution (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; National Breast and Ovarian Cancer Centre, 2009). Menopause signals reduced exposure to endogenous female sex hormones, and thus the risk of developing breast cancer is lower in post-menopausal as compared to pre-menopausal women.

g) Increased breast density

Breast (mammographic) density has been previously used to detect certain breast diseases, more recently to screen for breast cancer and now considered an important risk factor for the development of breast cancer (Cummings et al., 2009; Green et al., 2010; Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009).
The risk of developing breast cancer is four to six times higher in women in the upper quartile of breast density as compared to women lower quartile (Cummings et al., 2009; Green et al., 2010; Kluttig & Schmidt-Pokrzywniak, 2009; National Breast and Ovarian Cancer Centre, 2009; Schreer, 2009).

h) Increased body height

A number of reports have discussed the relationship between body height and risk of developing breast cancer (Friedenreich, 2001; Kluttig & Schmidt-Pokrzywniak, 2009). Data showed a 7% increase in risk of breast cancer for every 5cm increase in body height (relative risk of 1.07), with this positive association observed for both pre- and post-menopausal women (Kluttig & Schmidt-Pokrzywniak, 2009).

i) Oestrogens

The female sex hormones known as oestrogens are produced by the ovaries, and are actively involved in the reproductive functions of the female. It is now well established that these compounds promote the growth of mammary tumours (Mufudza, Sorofa, & Chiyaka, 2012). Numerous studies have reported that high serum concentrations of endogenous oestrogens are closely linked to increased risks of developing breast cancer (Arslan et al., 2009; Hankinson & Eliassen, 2007; Kluttig & Schmidt-Pokrzywniak, 2009).
j) Prior history of benign or malignant diagnosis

Several reports have suggested that women with prior benign breast disease are at a higher risk of developing further tumours related to breast cancer (National Breast and Ovarian Cancer Centre, 2009; Schnitt, 2001). For women with a prior history of malignant breast cancer, the risk of developing a second primary breast cancer is increased up to two-fold compared to individuals with no such history (National Breast and Ovarian Cancer Centre, 2009).

1.4.2 Modifiable risk factors

a) Unhealthy Diet

Recent reviews and meta-analyses have categorised common dietary patterns as “healthy (low fat diet)” and “unhealthy (consistent with a high fat diet)”, and reported a decreased risk of breast cancer in individuals with a healthy pattern compared to those eating unhealthily (Brennan, Cantwell, Cardwell, Velentzis, & Woodside, 2010; Hauner & Hauner, 2010; MacLennan & Ma, 2010).

b) Increased alcohol consumption

Alcohol consumption is a risk factor for both pre- and post-menopausal women, irrespective of the beverage type (Hamajima et al., 2002; Weiderpass et al., 2011).
c) Smoking

A few reviews have reported that smoking may be associated with a small increase in breast cancer risk, especially in chronic smokers (Khuder, Mutgi, & Nugent, 2001; Morabia, 2002; Terry & Rohan, 2002).

d) Decreased physical activity

A number of studies, reviews and meta-analyses have reported a positive association between physical activity and reduced risk for breast cancer for both pre- and post-menopausal women, compared to sedentary age-matched individuals (Kluttig & Schmidt-Pokrzywniak, 2009; Lahmann et al., 2007; Monninkhof et al., 2007; National Breast and Ovarian Cancer Centre, 2009; Weiderpass et al., 2011).

e) Obesity

It has been reported that in pre-menopausal women, obesity decreases the risk of breast cancer while in post-menopausal women, obesity is closely related to an increased risk (Amadou, Hainaut, & Romieu, 2013; Begum et al., 2009; Friedenreich, 2001; Hartz & He, 2013; Kluttig & Schmidt-Pokrzywniak, 2009; Maccio & Madeddu, 2011; National Breast and Ovarian Cancer Centre, 2009; Weiderpass et al., 2011).

f) Older age at first childbirth/ parity/ breastfeeding frequency

The age of women at their first childbirth, the frequency of childbirths and breastfeeding frequency patterns are considered to be strong risk factors for the

g) Hormone replacement therapy/hormonal contraceptives

Previous evidence has confirmed that women who were given hormonal replacement therapy have a 14% higher risk of breast cancer compared to non-users with the risk increasing by 2.3% for each year of HRT use (Beral et al., 2011).

h) Ionising radiation

Ionising radiation is a well-established breast cancer risk factor and mostly reported in studies of atomic bomb survivors, exposures to radiation from medical imaging, treatment for benign conditions such as acne, medical and dental diagnostic tests, and in occupational settings (Hartz & He, 2013; National Breast and Ovarian Cancer Centre, 2009; Ronckers, Erdmann, & Land, 2005).

While the non-modifiable risk factors may be challenging to control, there could be several possibilities in controlling the modifiable risk factors by implementing and adapting to healthy lifestyles, including improved diet and increased physical activity and exercise.
1.5 Breast cancer treatment

Breast cancer is a heterogeneous disease that has a number of different clinical presentations, ranging from isolated tumours in either single breast lobules through to partial or whole breast metastasis, or spread of the tumour to lymph node sections to even metastatic lesions in other organs of the body. With marked improvements in early diagnosis and prognosis, including the widespread availability of modern systemic therapies, the overall survival of patients with breast cancer is slowly but steadily improving (Chia et al., 2007; Giordano et al., 2004). Treatment of breast cancer requires an integrated approach involving both clinical and rehabilitation services (Figure 2). While the overall approach to the treatment and management of breast cancer is the same in young women as in older women, these two age groups require different specific management and therapeutic approaches. For example, young women are at a particular risk of emotional and psychosocial problems, and require appropriate strategies in age- and disease-specific support, including both psychological and medical therapy (Shannon & Smith, 2003).

Optimal clinical management of breast cancer requires good pathological and prognostic assessment. The primary treatment modality is surgery and this may be supplemented by adjuvant chemotherapy, adjuvant radiotherapy and hormonal therapy (Johnston & Swanton, 2006; Montazeri, 2008; Thomssena & Harbeckb, 2010). Treatment for breast cancer with chemotherapy treatment introduced in the 1970’s as an adjuvant treatment modality was targeted in the pursuit of complete eradication of
Individual breast cancer patients respond differently to treatment and management procedures based on age and pathology, as well as individual characteristics, including genetic, molecular, and immunological factors (Cho, Jeon, & Kim, 2012). Challenges in the treatment of breast cancer include differences in drug responses and associated toxicities, adverse drug reactions, patients’ failure to respond to certain treatments and recurrence of the tumour (Cho et al., 2012). These issues have led to the development of more targeted therapeutic approaches focussed on different patient cohorts or individual patients (Cho et al., 2012). Personalized medicine and treatment for breast cancer usually incorporates categorization of heterogeneous subsets of patients based on their respective responses to therapeutic intervention (Cho et al., 2012). This enables the healthcare systems to provide optimal choices in patient care to maximise the effectiveness of treatment and simultaneously reduce the risks of adverse reactions. In addition to medical treatment for breast cancer, further rehabilitative approaches could be adapted to supplement the treatment process and promote improvements in the treatment and recovery of the survivors aiding towards a return to an active and normal lifestyle.
Breast cancer screening and diagnosis

- Mammography
- Ultrasound
- Biopsy
- Genetic and molecular assay

Surgery

- Lumpectomy
- Lymphadenectomy
- Quadrantectomy
- Mastectomy
  (Any of the above)

Chemotherapy OR Radiation

OR a Combination of both
(Depending on tumour type)

Rehabilitation and Periodic Monitoring

*Figure 2: Screening and treatment modalities in breast cancer*
1.5.1 Surgery for breast cancer

The surgical approaches to breast cancer treatment is determined by the size and the position of the primary tumour and may involve breast-conserving surgery, quadrantectomy (surgical removal of one-quarter of the breast, regarded as a breast-conserving procedure) or mastectomy (surgical removal of one or both breasts) (Harmer, 2003). Surgery for breast cancer is planned after a thorough pre-operative diagnostic work-up including pre-operative histology by image-directed needle biopsy, detailed description of the extent of the suspicious lesion, and in some cases magnetic resonance imaging (MRI) of the breast (Thomssen & Harbeckb, 2010). Surgical removal of the primary tumour by quadrantectomy or mastectomy eradicates the source of further metastatic spread and recurrence (Pagani et al., 2010). For most women, breast-conserving surgery (i.e. compared to mastectomy) is desirable for cosmetic and quality of life considerations (Voogd et al., 2001). Where mastectomy is indicated medically, breast reconstruction surgery can be considered.

1.5.2 Chemotherapy treatment in breast cancer

Increased survival and low mortality rates observed in recent outcomes in the management of breast cancer have been attributed to advances in early detection, treatment and management of the disease (Ayoub et al., 2012). The primary objectives of treatment for breast cancer are focused on survival, alleviation of symptoms and maintenance or improvement of quality of life (Huober & Thurlimann, 2009; Jansens et al., 2011). The primary adjunct to surgical treatment for breast cancer is usually
pharmacotherapy comprising of chemotherapy and endocrine treatments (Lee & Nan, 2012).

A wide range of established and novel pharmacological agents has been shown to significantly improve clinical outcomes for breast cancer. However, such agents commonly have cytotoxic effects which can impact negatively on normal tissues and thereby create new challenges in the management of the disease (Huober & Thurlimann, 2009; Verma et al., 2011).

Anthracyclines are well established as the preferred agent in first-line chemotherapy treatment for breast cancer, resulting in improved clinical responses and longer survival periods, compared with non-anthracycline combinations (A'Hern, Smith, & Ebbs, 1993; Bonneterre et al., 2004). Inclusion of anthracyclines, such as doxorubicin in combination chemotherapy, has signalled a new generation of clinical regimens in the treatment for breast cancer (Carrick et al., 2009).

Adjuvant chemotherapy is an evolving focus for the treatment for breast cancer, and aims to target increased efficacy and reduced toxicity of the chemotherapeutic drugs, reduced risk of cancer recurrence and death (Butters, Ghersi, & Wilcken, 2009). The novel first-line chemotherapeutic formulations in the pharmacotherapeutic management of breast cancer include a number of “gold standard” anthracycline-based regimens including: (1) AC (doxorubicin plus cyclophosphamide), (2) FAC (5-flurouracil, doxorubicin plus cyclophosphamide), and (3) FEC (5-flurouracil, epirubicin plus cyclophosphamide) (Lopez-Tarruella & Martin, 2009). The efficacy of
the anthracycline doxorubicin (adriamycin) in the clinical management of breast cancer is now well established; however, its effective use is limited by its sustained toxicity, particularly affecting myocardial cells, leading to fatal toxic reactions in around 2-7% of treated patients (Saltiel & McGuire, 1983). Adjuvant chemotherapy in the treatment for breast cancer has undergone a series of progressive developments by including newer and more effective chemotherapeutic drugs that have significantly improved the treatment and survival in breast cancer patients (Ayoub, Verma, & Verma, 2012).

Generally speaking, adjuvant chemotherapy involving a combination of anticancer cytotoxic drugs targets a number of different biological pathways that can delay cancer adaptation processes such as cancer cell mutations (Lee & Nan, 2012). By combining the main classes of chemotherapeutic drugs such as the anthracyclines and taxanes, this combination has been shown to be more effective and is considered to be the gold standard in the treatment for breast cancer (Cardoso et al., 2009). Combination chemotherapy also results in synergistic responses resulting in higher therapeutic efficacy and higher target selectivity of the constituent drugs (Huober & Thurlimann, 2009). Combination chemotherapy has also been shown to be associated with a better time to progression (TTP – time after treatment until the disease has progressed) and significantly improved tumour response rates (rates of changes in either uni- or bilateral dimensions of the tumour) (Carrick et al., 2009).

Combining taxanes (namely docetaxel and paclitaxel) with anthracyclines represents the current best practice for adjuvant chemotherapy, and is now widely used in the
treatment for breast cancer (Huober & Thurlimann, 2009; King et al., 2009). A meta-
analysis by Ghersi, Wilcken, Simes, and Donoghue (2005) has shown that taxanes added to a combined adjuvant chemotherapy regimen helped improve overall survival, time to progression (TTP), and overall tumour response rates. The effectiveness of this combination is facilitated by the lack of cross-resistance and limited overlapping toxicities between these two classes of drugs (Tang, 2009).

The literature on the incorporation of taxanes with anthracyclines in the treatment for breast cancer has grown considerably in recent years and this therapeutic approach continues to be widely studied. Chemotherapy treatment by a combination of anthracyclines and taxanes is the most common approach used in the three hospitals used as recruitment sites for participants in this study; however, we were unable to extract any statistics on the number or percentage of patients treated with this modality.

A number of clinical studies have explored the effects of taxanes in combination therapy, either administered concurrently or sequentially, and in addition to or substitution for standard anthracycline chemotherapy. Some of the common anthracyclines and taxanes chemotherapeutic agents used in the treatment of breast cancer are illustrated in Figure 3 (Chu & Sartorelli, 2007).
1.6 Current investigations on the effects of chemotherapy treatment and resistance exercise in breast cancer

The current study has been structured to investigate and report the myotoxic effects of specific chemotherapeutic agents, mainly anthracyclines and taxanes, on skeletal muscle, body fat, muscle strength, health-related quality of life, and self-rated perceived fatigue in breast cancer patients. The focus of the study is to include an assessment of these outcome measures using validated, reliable and well-established instruments and methodologies. The study further investigates the effects of a 12-week supervised progressive resistance training program (PRT), on the same outcome measures. The study includes a breast cancer control (non-exercise) group and a healthy control group in order to make clear observations in the improvements in the outcome measures brought about by the exercise program. The uniqueness of this study was to recruit breast cancer patients who had been specifically treated with...
anthracycline/taxane adjuvant chemotherapy, and administering a resistance exercise program to promote improvements in physical and psychological characteristics. Specific interest was given to anthracycline/taxane adjuvant chemotherapy as this regimen is a common modality of treatment for breast cancer. Patients treated with either additional or different chemotherapeutic drugs were excluded.

Nineteen breast cancer patients (age of 49.8 ± 7.9 years) were assessed for whole body lean and fat mass, muscle, fat cross-sectional area (CSA) and muscle density of the thigh, quality of life and fatigue using standard protocols, before and after their chemotherapy treatment. These post chemotherapy data were compared with data from 27 age-matched healthy women (age of 46.9 ± 10.0 years). Following chemotherapy treatment, the breast cancer group, had greater fat CSA compared to the healthy control group, but there were no differences between the two groups for either body mass or body mass index (BMI). Furthermore, there were no differences between the two groups for whole body lean mass whole body fat mass, muscle CSA or muscle density. Muscle strength was greater in the healthy control group compared to the breast cancer group for all four moments tested: isometric extension, isometric flexion, concentric extension, and concentric flexion. The healthy women reported better quality of life compared to breast cancer patients who had completed chemotherapy treatment for all 8 domains except for mental health (MH). There were no differences between the breast cancer group following chemotherapy treatment and the healthy control group for any of the 5 domains of perceived fatigue. The increases in body mass, BMI and whole body fat mass, without any corresponding increase in lean mass are an indication of the
development of “sarcopenic obesity” associated with chemotherapy treatment. The decrease in muscle strength in the breast cancer patients, following chemotherapy treatment, indicate a negative effect of this therapy on muscle functional capacity and well-being.

14 breast cancer patients (age of 51.9 ± 3.6 years) who had been treated with anthracycline/taxane adjuvant chemotherapy were randomly assigned to either a 12-week resistance exercise program or usual care. The previously mentioned outcome measures were compared between breast cancer groups (Exercise; \(n = 7\), Non-exercise; \(n = 7\)) after 12 weeks, and to 24 age-matched healthy women (age of 47.1 ± 2.2 years) who had also undertook the 12-week exercise program. There were no differences in body composition, quality of life and fatigue between breast cancer groups after the 12-week intervention. However, the exercising breast cancer group demonstrated greater increases in muscle strength than the non-exercising breast cancer group. There were also no differences in body composition, muscle strength and fatigue between the exercising breast cancer group and exercising healthy controls after 12 weeks. However, the exercising breast cancer group exhibited greater improvements for five of the eight QoL scales, compared to the healthy exercise control group following the 12-week exercise intervention.
Chapter 2: Literature Review
2.1 Side effects of chemotherapy in breast cancer

Chemotherapy treatment, either administered as single agents or in a combination regimen, remains the best choice for adjuvant treatment of breast cancer. However, in addition to the desirable therapeutic effect, chemotherapy also causes side effects that limit their clinical efficacy (Arslanagic, Zulic, Musanovic, Softic, & Karamehmedovic, 1990; Greil, 2009). Administration of this chemotherapeutic cocktail has resulted in some notable cytotoxic side-effects, besides the beneficial efficacy in the treatment of breast tumour malignancies (Greil, 2009; Mlineritsch, 2009). Such side effects include cardiac, neurological, musculoskeletal and psychological complications (Arslanagic et al., 1990; Greil, 2009; Mlineritsch, 2009). Current trends indicate that adjuvant chemotherapy is becoming increasingly aggressive with the use of a range of cytotoxic agents administered with various dose regimens to minimise the potential of a relapse of the tumour or the metastasis (Greil, 2009).

Advances in the diagnosis, prognosis and treatment of breast cancer have led to an increase in the number of long term survivors. However, increased survival, both depends on, and leads to greater cumulative exposure to chemotherapeutic drugs with a consequent increase in prevalence of long term side effects and complications (Ganz & Hahn, 2008). For example, for a more effective cytotoxic effect on tumour cells (which is a desirable effect) requires an extended use of anti-hormonal therapies (beyond 5 and 10 years) increasing the occurrence of non-desirable side effects in some patients (Citron et al., 2003). The extended exposure to cytotoxic chemotherapeutic
drugs obviously impacts on healthy cells, resulting in a higher propensity towards cardiac, neurological, muco-epidermal and haematopoietic side effects.

Despite the fact that there exists a positive dose-response relationship for many forms of adjuvant chemotherapy in terms of tumour cytology, the extent to which this can be used to improve anti-tumour efficacy is limited by the increased risk of serious side effects and complications (Fisher et al., 1997; Piccart et al., 2001). For example, elevated doses of cyclophosphamide may increase the risk of leukaemia (Piccart et al., 2001) while higher doses of docetaxel can result in myelosuppression (Nuzzo et al., 2011).

Anthracycline and taxane toxicities remain a challenging issue when these drugs are administered either alone or in combination with other agents (Rafiyath et al., 2012). The risks associated with higher cumulative doses of anthracyclines mainly include cardiotoxicity where toxicity increases due to persistent cumulative peak plasma levels of the agents administered in regular monthly cycles (Harris et al., 2002). The impacts of anthracyclines on cardiotoxicity is of particular concern since it can lead to the development of cardiomyopathy as a result of free radical damage to the cardiac myocytes (Harris et al., 2002). Another common dose-limiting side effect of the anthracycline doxorubicin is redness, tenderness and peeling of the skin on the hands and feet, and can be uncomfortable and painful (O'Shaughnessy, 2005; Rivera, 2003).

Treatment for breast cancer using anthracycline/taxane adjuvant chemotherapy is associated with a number of other physical, physiological and psychosocial side effects,
and these depend on the combination of drugs used, the doses administered and the duration of the treatment (Battaglini et al., 2007b). Some of these symptoms and side effects include surgical complications, wound infections (e.g. when follow-up breast surgery is required), and a host of side effects as shown in Figure 4 (Battaglini et al., 2007b; Berglund, Bolund, Fornander, Rutqvist, & Sjoden, 1991; Bower, 2008; Courneya & Friedenreich, 1999; De Backer et al., 2008; Wagner & Cella, 2004). While breast cancer survivors do receive palliative treatments for these associated symptoms and side effects, there may also be a need to reduce the intensity of chemotherapy, which could increase the risk of breast cancer recurrence (De Backer et al., 2008; Demark-Wahnefried, Aziz, Rowland, & Pinto, 2005).

Improvements in diagnosis of breast cancer over the decades and recent advances in the treatment with chemotherapeutic agents have resulted in increased survival rates and increased life expectancy. However, a number of undesirable consequences have dramatically affected various aspects of patients’ physiological, psychological and psychosocial characteristics; these include body weight changes, muscular atrophy, decreased or loss of muscle strength, depression, fatigue and overall decrease in quality of life (Manir et al., 2012; Prado et al., 2009).

While treatment for breast cancer by surgery and chemotherapy treatment has shown impressive results in breast cancer survival rates, further rehabilitative approaches need to be adopted to contain the debilitating side effects of chemotherapy. These include changes in whole body muscle and fat composition, loss of muscle strength, decreased
quality of life and increased fatigue. It is possible that by implementing a number of lifestyle changes such as improving and promoting a healthy diet and increasing physical activity and exercise could assist in containing, minimising some of these detrimental side effects.

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*Figure 4: Side effects of chemotherapy treatment in breast cancer*

Together with the associated symptoms and side effects, the secondary effects of treatment for breast cancer could also contribute to marked changes in body composition (Courneya, 2003). The effects of treatment for breast cancer on changes
in body composition forms the basis of the current study, and are discussed in detail in the following sections.

### 2.1.1 Effects of chemotherapy on body weight, lean and fat mass

Obesity and being overweight are potential risk factors for post-menopausal women developing breast cancer, and a recent review by (Demark-Wahnefried, Campbell, & Hayes, 2012) reported that women, irrespective of menopausal status, gain weight after diagnosis. Earlier studies have reported that diagnosis of breast cancer and subsequent treatment with chemotherapy causes gains in body weight in pre- and as well as in post-menopausal women (Caan et al., 2008; Demark-Wahnefried et al., 2001; Demark-Wahnefried, Rimer, & Winer, 1997). Weight gains of up to 11kg in 1 of the 4 women receiving adjuvant chemotherapy are typical (Demark-Wahnefried et al., 2012). and appear independent of the type of chemotherapy (Freedman et al., 2004; Gu et al., 2010; McInnes & Knobf, 2001). While the mechanisms associated with weight control during and after chemotherapy treatment in breast cancer are yet to be established, it is believed that this side effect may be mainly due to reduced physical activity during and post-treatment (Demark-Wahnefried et al., 2012). Weight gain after diagnosis and chemotherapy treatment for breast cancer is a commonly reported side effect, and could also be associated with increases in appetite and dietary intake and deterioration of psychological well-being (Yaw et al., 2011). Weight gain in patients during adjuvant chemotherapy could also be dependent on the type of chemotherapy, length of treatment, fatigue and decreased levels of physical activity, increase in energy intake,
decrease in resting energy expenditure and development of amenorrhea and/or menopause (Campbell, Lane, Martin, Gelmon, & McKenzie, 2007; Foltz, 1985; Freedman et al., 2004; Goodwin et al., 1999; Ingram & Brown, 2004; Rock et al., 1999). Other contributing factors worth noting include psychological barriers to exercise (such as clinical depression, anxiety, and coping with chronic illness), physical side effects leading to reduced mobility (e.g. chronic pain, dyspnea, insomnia, nausea), and lack of motivation to adapt healthy diets (Newman et al., 2005; Pierce et al., 2007; Yu, 2009).

Weight gain during and post treatment in breast cancer is often accompanied by changes in body composition, particularly gain in fat mass and total body water, and decreases in muscle mass (Ingram & Brown, 2004). (Aslani, Smith, Allen, Pavlakis, & Levi, 1999; Demark-Wahnefried et al., 2001; Demark-Wahnefried, Rimer, et al., 1997). These changes in body composition and weight gain in breast cancer patients during or post-treatment with chemotherapy could be termed as sarcopenic obesity, characterised by whole body weight gains without any gain, or even a reduction, in lean muscle mass but significant increases in fat mass (Campbell et al., 2007; Demark-Wahnefried et al., 2012; Demark-Wahnefried et al., 2001; Kutynec, McCargar, Barr, & Hislop, 1999). While weight gain is associated with increases in fat mass and decreases in muscle mass, many of these changes are observed in abdominal and visceral adipose deposits (Cheney, Mahloch, and Freeny (1997). Decreases in muscle mass may have effects on functional capacity secondary to reduced muscle strength and mobility (Demark-Wahnefried et al., 2012).
Although the pathophysiological basis of this weight gain is fully understood, it is suspected that the primary factor is related to an imbalance between intake and energy expenditure (Demark-Wahnefried et al., 2012). The decreased energy expenditure could be due to reductions in resting energy expenditure and reduced physical activity (Demark-Wahnefried, Hars, et al., 1997; Demark-Wahnefried et al., 2001). There is also a possibility that caloric consumption increases over baseline levels, contributing to the weight gain (Demark-Wahnefried et al., 2012).

Weight gain in breast cancer patients has a number of detrimental consequences, likely exacerbating the negative psychosocial impact on women who already have a compromised state of self-esteem and may have chronic co-morbidities such as diabetes, hypertension and other cardiovascular diseases and/or orthopaedic disturbances such as osteoarthritis (Demark-Wahnefried, Hars, et al., 1997; Ingram & Brown, 2004; Yaw et al., 2011). Additionally, weight gain in this situation can be negatively associated with risk of breast cancer recurrence and may impact on survival (Campbell et al., 2007; Cheney et al., 1997).

The linked problems of weight gain and increased fat mass, associated with chemotherapy treatment for breast cancer, merits further attention with a view to minimising these undesirable effects. While medical treatment is able to control the growth and spread of the tumour, supplementary measures such as physical activity and exercises could be adapted to better control the weight gain and the increased fat mass in survivors of breast cancer.
2.1.2 Effects of chemotherapy on loss of skeletal muscle

Chemotherapy-induced fatigue, caused by asthenia (weakness or loss in strength) resulting in sustained exhaustion and decreased functional capacity, is one of the most common side effects of adjuvant chemotherapy (Morrow, Andrews, Hickok, Roscoe, & Matteson, 2002; van Norren et al., 2009). A notable side effect of anthracyclines (typically doxorubicin) is impairment of skeletal muscle function secondary to interference with mitochondrial function (Doroshow, Tallent, & Schechter, 1985; van Norren et al., 2009). A steady and involuntary loss in skeletal muscle due to increased exposure to oxidative stress and inflammation during aging and chronic illness was first described by Rosenberg in 1989 (Lang, Streeper, et al., 2010). Studies in breast cancer patients have demonstrated that anthracycline therapy leads to decreased lean body mass via its chemotoxic effect on skeletal muscle myocytes (Aslani, Smith, Allen, Pavlakis, & Levi, 2000; Prado et al., 2009). The cellular and patho-physiological processes involved in loss of muscle mass include nerve fibre damage, mitochondrial dysfunction, inflammatory events and hormonal changes. These typically lead to a set of clinically important outcomes such as decreased muscle strength, decreased mobility and function, increased fatigue, greater risks of falls and reduced energy needs (Lang, Streeper, et al., 2010; Melton et al., 2000; Sakuma & Yamaguchi, 2012a). Not surprisingly, loss of muscle mass has been found to be associated with decreased physical functioning, increased fatigue and frailty and loss of independent living in this population (von Haehling, Morley, & Anker, 2010, 2012; Waters, Baumgartner, Garry, & Vellas, 2010).
While sarcopenia best describes the loss of skeletal muscle mass and strength (often associated with ageing), *cachexia* is a more appropriate term used to describe a complex metabolic syndrome characterised by loss of muscle with or without the loss of fat mass, and specifically associated with a chronic illness such as cancer (Gould, Lahart, Carmichael, Koutedakis, & Metsios, 2012; Lenk, Schuler, & Adams, 2010). It has been suggested that the one of the most likely underlying mechanisms for cancer cachexia is an accelerated level of protein catabolism compared to anabolism. A possible mechanism underlying this phenomenon is increased oxidative stress leading to increased mitochondrial dysfunction and increased myofibril damage (Lenk et al., 2010).

Cancer cachexia is characterised by skeletal muscle atrophy, mostly affecting glycolytic fibres, resulting from the accelerated breakdown of muscle tissues (Julienne et al., 2012). This provides substrates to the tumour and is responsible for the depletion of protein stores and loss of body weight (Julienne et al., 2012; Sakuma & Yamaguchi, 2012b; Tisdale, 2009). Cancer cachexia contributes to physical disability, weakness and decreased capacity of wound healing and reduces responsiveness to chemotherapy (Acharyya et al., 2005; Julienne et al., 2012; Marin-Corral et al., 2010; Sakuma & Yamaguchi, 2012b).

In addition to the terms “sarcopenia” and “cachexia”, a more universal term describing skeletal muscle wasting of clinical relevance due to any illness at any stage of the disease and associated treatment has been proposed as “*myopenia*” (Fearon, Evans, &
Anker, 2011). Myopenia is now used to define a clinically significant degree of muscle wasting, accompanying a particular chronic disease, that is associated with impaired functional capacity and/or with increased risk of morbidity or mortality (Fearon et al., 2011). The term myopenia is also used to describe skeletal muscle loss/wastage during chemotherapy treatment of breast cancer and will be used in this thesis to describe muscle loss. This is consistent with a recent commentary recommending the use of myopenia rather than sarcopenia to refer to muscle loss associated with a specific chronic disease (von Haehling et al., 2012).

The loss of skeletal muscle mass and function in breast cancer patients is a direct clinical consequence of the cancer disease and possibly the use of chemotherapy treatment over a period of time. Myopenia in breast cancer patients, caused by chemotherapy treatment, is likely to lead to impaired functional capacity affecting daily living and possibly increasing morbidity and/or mortality. However, currently, myopenia cannot be defined in precise quantitative terms since the extent and rate of skeletal muscle loss, related to clinical progression, has not been established (Fearon et al., 2011).

2.1.3 Effects of chemotherapy on quality of life

Breast cancer patients, at various stages of their treatment, often experience a number of physical and psychosocial symptoms that have adverse effects on their quality of life, including disturbances in physical functioning, psychological well-being and social support (Perry, Kowalski, & Chang, 2007). Quality of life is defined as an
individual's perception of life, values, objectives, standards and interests within the framework of one's culture, and encompasses the areas of general health, physical functioning, social functioning, emotional well-being, bodily pain and mental health (Ahles et al., 2005). Quality of life is considered to be an important outcome in cancer-related studies, providing critical information for clinical judgements on optimal health care as treatment progresses (Dehkordi, Heydarnejad, & Fatehi, 2009; Montazeri, 2008). Patients are also able to use components of their quality of life responses to adjust to the cancer by shifting their priorities and expectations to align with their actual circumstances (Sharpe, Butow, Smith, McConnell, & Clarke, 2005).

Specific aspects of quality of life, that have been the main areas of concern in many studies investigating effects of adjuvant chemotherapy in breast cancer treatment, include cognitive functioning, physical functioning, sleep disturbances, anxiety, fatigue and depression (Ahles et al., 2005; Brezden, Phillips, Abdolell, Bunston, & Tannock, 2000; Costanzo et al., 2007; Frazzetto et al., 2012; Reid-Arndt, Hsieh, & Perry, 2010; Saquib et al., 2011; Thornton, Carson, Shapiro, Farrar, & Andersen, 2008). An earlier study by Brezden et al. (2000) reported that adjuvant chemotherapy impaired cognition and led to mood disturbances and depression, with residual effects noted after the completion of the treatment. It has been shown that breast cancer survivors treated with anthracyclines had poorer social and physical functioning compared to age matched control subjects (Ahles et al., 2005). Similarly, patients receiving taxanes, scored significantly lower in mental and emotional scales compared
to healthy subjects; it was further noted that recovery from these depressive symptoms took an average of 2 years (Thornton et al., 2008).

2.1.4 Effects of chemotherapy on fatigue

Fatigue is a common side effect of cancer and its associated treatment, negatively impacting on a patients’ quality of life. Cancer-related fatigue is best defined as a feeling of debilitating tiredness or a profound lack of energy that lasts for a period of time and is associated with feelings of weakness/being worn out, nausea, pain and depression (Andrykowski, Donovan, & Jacobsen, 2009; Bardwell & Ancoli-Israel, 2008; Bower, 2008). Fatigue has also been described as an overwhelming, sustained sense of exhaustion, leading to decreased physical and cognitive function work, that is not relieved by rest (Narayanan & Koshy, 2009). Fatigue, in patients treated for cancer, is often experienced as a decrease in strength and physical activity, tiredness, weakness, lack of energy, lethargy, depression, difficulty with concentration, lack of motivation and difficulty with sleeping (Ancoli-Israel, Moore, & Jones, 2001). More specifically patients commonly report difficulties in performing simple daily activities such as climbing stairs, walking short distances and regular domestic tasks (Narayanan & Koshy, 2009).

Cancer-related fatigue is a common symptom in women with breast cancer both before and after adjuvant chemotherapy treatment. It generally improves after the treatment is completed, but could also persist for several months or even years (Andrykowski, Schmidt, Salsman, Beacham, & Jacobsen, 2005; Manir et al., 2012; Richardson, 1995).
For example, it has been reported that an increased level of fatigue persists for at least six months after cessation of chemotherapy treatment (Bower et al., 2000; Jacobsen et al., 2007; Woo, Dibble, Piper, Keating, & Weiss, 1998).

It has been shown that cancer-related fatigue is more commonly reported during adjuvant chemotherapy in comparison with other forms of treatment for breast cancer (Bardwell & Ancoli-Israel, 2008; Blesch et al., 1991; Meyerowitz, Watkins, & Sparks, 1983). For instance, Donovan et al. (2004) demonstrated that patients who received adjuvant chemotherapy for breast cancer reported greater fatigue than patients who received adjuvant radiotherapy. Alongside the occurrence of fatigue as one of the major symptoms associated with breast cancer, deficiencies in the contractile function of skeletal muscle have been reported. Thus an inability to maintain a normal force production with a sustained contraction has been noted in breast cancer patients (Enoka & Duchateau, 2008; Gerber et al., 2011).

2.1.5 Effects of chemotherapy on outcome measures and possible associations

Previous reports show that exercise in elderly and healthy individuals contributes to improvements in cardiorespiratory fitness, physical functioning, body weight, body fat, lean mass, muscle strength, fatigue and quality of life (Caspersen et al., 1985; Friedenreich et al., 2011; Hanson et al., 2009). Exercise intervention studies have shown that any form of physical activity including aerobic or strength training exercises contributes to reproducible and durable significant effects on weight loss, fat loss, improvements in muscle mass and strength as well as improvements in physical
functioning, quality of life and fatigue. Exercise impacts positively on a variety of medical conditions such as diabetes, hypertension, depression and osteoarthritis (Church et al., 2009; Hubbard et al., 2009; Johnson et al., 2007; Kerksick et al., 2009). Given the beneficial effects of exercise on health-related outcomes in healthy, elderly and clinical populations as discussed above, exercise intervention programs should be effective in ameliorating the side effects of chemotherapy in breast cancer by improving cardiovascular fitness, percentage lean body mass, muscle strength, quality of life and fatigue.

The effects of chemotherapy treatment for breast cancer on factors such as body weight and composition, muscle strength, quality of life and fatigue have been previously reported and discussed above. While these outcomes can be considered to be independent of each other and have been reported in separate studies as discussed above. There is the potential that any adverse changes in one particular outcome may affect others, e.g. any change in body composition affecting muscle mass may have potential corresponding effect on muscle strength (Demark-Wahnefried et al., 2012). However such associations or relationships between different outcomes are not the focus of this study and any discussion linking outcomes is thus speculative.
2.2 Exercise for fitness and health

Physical fitness is defined as the physiological state of well-being that allows an individual to meet the demands of daily living (health-related fitness) as well as providing a key basis for improved sport performance (performance-related fitness) (Warburton, Nicol, & Bredin, 2006). It has been further identified that health-related fitness encapsulates cardiovascular fitness, musculoskeletal fitness, optimal body composition and absence of metabolic disorders (Warburton et al., 2006). Physical activity is defined as any combination of bodily movements, facilitated by contractions of the musculoskeletal system, which promotes an increase in energy expenditure above resting levels (Caspersen et al., 1985; Thompson et al., 2010). Exercise is considered as an amount of physical activity that is planned, structured and repeatedly performed to maintain or improve physical fitness (Södergren, Sundquist, Johansson, & Sundquist, 2008). Increased physical activity improves health outcomes in the prevention and management of numerous diseases such as metabolic disorders, cardiovascular, musculoskeletal and pulmonary diseases, including various cancers, and is associated with reductions in mortality and improvements in psychological well-being (Kerksick et al., 2009; Schutgens, Schuring, Voorham, & Burdorf, 2009; Södergren et al., 2008; Warburton et al., 2006). The National Physical Guidelines for Adults program developed by the Department of Health and Ageing (DHAC) of the Australian Government recommends adaptation of a daily 30-minute moderate intensity physical activity for all adults to maintain and improve fitness (DHAC, 1999).
Chronic adaptations to regular physical activity and exercise include various physiological, metabolic and physical improvements in the human body, leading to enhancements in the cardiovascular, pulmonary, metabolic, musculoskeletal, endocrine and immune system function which all together improve a person’s functional capacity (Schneider, Dennehy, & Carter, 2003). Adaptive responses to endurance and resistance exercise interventions help to enhance skeletal muscle function in a number of ways, which includes 1) increases in the number and size of mitochondria, 2) an increase in the amount of myoglobin to increase oxygen delivery to the mitochondria, 3) increase in enzymes required for glucose oxidation, 4) muscle hypertrophy, 5) increased muscle glycogen storage and 6) increased efficiency of muscle cells to utilise fats as a substrate (Schneider et al., 2003).

Regular physical activity and exercise help promote fat metabolism, leading to a reduction in fat and increases in muscle mass (Schneider et al., 2003). A recent study by Irving et al. (2008) demonstrated that exercise training results in a significant reduction in abdominal visceral fat, and suggested that the reduction in body fat is dependent on training volume and training intensity. Another study by Kerksick et al. (2009) showed that regular participation in resistance-based circuit exercise program resulted in marked reduction of body fat mass and improvements in body composition, as well as in cardiovascular and musculoskeletal fitness. Resistance exercise increases muscle mass, strength and endurance by increasing muscle cross-sectional area leading to more efficient muscular contractility and reduced fatigue (Brooks & Faulkner, 1988; Evans, 1996; Kraemer, 1988).
2.3 Benefits of resistance exercise

Strength or resistance based exercises are structured and performed to enhance muscular strength that helps to improve daily functioning with low physiological stress, and helps to maintain functional independence throughout one’s lifespan (Thompson et al., 2010). It is well established that strength and resistance training, over an extended period of time, contributes to improvements in musculoskeletal strength and endurance, enhanced reinforcement of connective tissue, maintenance of a lean body mass, decreased risk of hypertension and diabetes, and can maintain or even increase bone mineral density (Bocalini, Serra, & Dos Santos, 2010; Frimel, Sinacore, & Villareal, 2008; Hanson et al., 2009; Melov, Tarnopolsky, Beckman, Felkey, & Hubbard, 2007; Strasser & Schobersberger, 2011; Sundell, 2011).

Muscle strength declines with advancing age due to a reduction in muscle mass leading to a decline in functional capacity (Frimel et al., 2008; Melov et al., 2007; Sundell, 2011). It has been reported that resistance training increases muscular strength, power and endurance in elderly persons, and it thus has the potential to enhance mobility and functional independence, particularly with respect to activities of daily living (Frimel et al., 2008; Melov et al., 2007; Sundell, 2011). Adults who are obese and avoid physical activity are prone to impaired body fitness, reduced quality of life and frailty brought about by sarcopenia (Frimel et al., 2008). Introduction of an exercise program results in an improvement in fat free muscle mass and muscle strength in obese adults, including post-menopausal women (Church et al., 2009).
2.4 Effects of exercise in breast cancer

Given the well-recognised benefits of exercise in daily living, it is not surprising that its efficacy as a rehabilitative intervention both during and after cancer therapy is being widely investigated (Valenti et al., 2008). Previous studies have shown that physical activity and prescribed exercise in persons with cancer can improve fitness and physical functioning, reduce fatigue, decrease body weight and fat, and improve psychosocial status (Oldervoll, Kaasa, Hjermstad, Lund, & Loge, 2004; Valenti et al., 2008). Studies by Valenti et al. (2008) and Kolden et al. (2002) have demonstrated that physical exercise can be used effectively as supportive therapy for breast cancer survivors associated with improvements in quality of life. A number of studies have shown that exercise results in significant improvements in body weight and lean body mass, accompanied by decreases in fatigue and anxiety, and can lead to improved socialisation and goal setting (Battaglini et al., 2007b; Bicego et al., 2009; Brown et al., 2012; Cadmus et al., 2009; Cheema, Gaul, Lane, & Fiatarone Singh, 2008; Cheema & Gaul, 2006; Chen et al., 2009; Courneya, Mackey, & McKenzie, 2002; Courneya, Segal, Mackey, et al., 2007; De Backer et al., 2007; Ferrer, Huedo-Medina, Johnson, Ryan, & Pescatello, 2011; Galanti, Stefani, & Gensini, 2013; Galvao & Newton, 2005; Rabin, Pinto, Dunsiger, Nash, & Trask, 2009; Winters-Stone et al., 2012).

The American College of Sports Medicine (ACSM) advocates regular exercise as a crucial part of cancer management as it increases the fitness of the whole body along with combating depression and increasing self-confidence (Thompson et al., 2010).
This recommendation further demonstrated published evidence on the safety and efficacy of exercise prescription in cancer survivors and concluded that although there are specific risks associated with cancer treatment, exercise is considered to be safe during and after treatment for cancer and is recommended for all cancer survivors (Schmitz et al., 2010).

The American Cancer Society has also recommended that breast cancer survivors get at least 30 minutes of moderate activity for 5 or more days of the week as a preventive measure for cancer recurrence, at least 150 minutes per week of moderate intensity exercise or 75 minutes per week of vigorous intensity (ACS, 2010; Rock et al., 2012; Visovsky, 2006). In the Australian context, the Australian Association of Exercise and Sport Science (AAESS) has established a position stand on exercise prescription during treatment for and survival from cancer diseases (Hayes, Spence, Galvao, & Newton, 2009). The AAESS has developed these recommendations with reference to the guidelines set by the ACSM panel, which reviewed 70 exercise intervention trials conducted in North America (Hayes et al., 2009; Humpel & Iverson, 2005). The recommendations for aerobic-based exercise prescription for cancer patients and survivors include either treadmill, cycle, swimming or general walking and running exercise about 20 – 30 minutes continuous exercise of moderate intensity (50 - 75% of VO₂ max or 60 – 80% of HRmax), 3 – 5 times per week (Hayes et al., 2009). Recommendations for a resistance-based exercise prescription for cancer patients and survivors include dynamic concentric (lifting and pushing/pulling) and eccentric (controlled lowering/returning) muscle contractions using machine weights, free
weights, body weight and/or tension bands at 50 – 80% of 1-repetition maximum (RM) or 6 – 12 RM per set for 1 – 4 sets per muscle group or 6 – 10 exercises per session, 1-3 times per week with rest days between sessions (Hayes et al., 2009).

While resistance exercise training involving the upper body, trunk and lower body muscle groups is used for developing general health and fitness of many populations, it has been reported that resistance exercise can also lead to significant improvements in full body fitness and quality of life in breast cancer survivors (Cheema & Gaul, 2006). Reports by Cheema and Gaul (2006) showed that both upper body and lower body muscular strength were significantly improved after an 8-week resistance exercise training intervention in survivors of breast cancer. While studies clearly show that both aerobic or the resistance exercise training programs result in improved health outcomes, there is currently no consensus on whether one mode of training is better than the other in this population. Muscle strength is closely related to the various aspects of health-related quality of life whereby supporting activities of daily living, and considerable evidence suggests that the ability to sustain physical tasks require increased muscle mass and improved muscle strength brought about by resistance training (Brill, Macera, Davis, Blair, & Gordon, 2000; De Backer et al., 2007; De Backer et al., 2008; Woods, Iuliano-Burns, King, Strauss, & Walker, 2011).

A randomised controlled trial included a combined aerobic and resistance exercise program and showed improvements in quality of life, fatigue, aerobic fitness and muscle strength in breast cancer survivors after 6 weeks of exercise training (Milne,
Wallman, Gordon, & Courneya, 2008). Other supportive evidences demonstrate that resistance exercise training, or strength training promotes positive changes in body composition and muscle strength in breast cancer survivors, both during and following completion of primary treatment (surgery, chemotherapy and radiation therapy) (Battaglini et al., 2007b; Courneya, Segal, Mackey, et al., 2007; Demark-Wahnefried & Jones, 2008; Demark-Wahnefried et al., 2001; Irwin et al., 2009; Knols, Aaronson, Uebelhart, Fransen, & Aufdemkampe, 2005; McNeely et al., 2006; Winters-Stone et al., 2012).

There have been a number of studies and reviews reporting the effects of exercise intervention on various outcomes in breast cancer survivors, including positive effects on general health and well-being, quality of life and fatigue (Brown et al., 2012; Cadmus et al., 2009; Cheema & Gaul, 2006; Chen et al., 2009; Courneya et al., 2002; Courneya, Segal, Gelmon, et al., 2007; Cramp & Byron-Daniel, 2012; De Backer et al., 2008; Floyd & Moyer, 2009; McNeely et al., 2006; Milne et al., 2008; Ohira, Schmitz, Ahmed, & Yee, 2006; Spence, Heesch, & Brown, 2010; Valenti et al., 2008). A number of studies and reviews reporting the effects of exercise intervention in breast cancer survivors have been focused on cardiopulmonary function, muscle strength, menopausal symptoms, psychosocial factors (including anxiety, depression and distress from disease), sleep quality, quality of life and fatigue (Agil, Abike, Daskapan, Alaca, & Tuzun, 2010; Battaglini et al., 2007b; Cheema & Gaul, 2006; Courneya et al., 2008; Courneya, Segal, Mackey, et al., 2007; De Backer et al., 2008; Demark-
Wahnefried et al., 2001; Galvao & Newton, 2005; Milne et al., 2008; Spence et al., 2010).

Most of these studies have focused on psychosocial factors including anxiety, depression and distress from disease, sleep quality, quality of life and fatigue. While the benefits of resistance exercise in the general population have been well documented, there are limited reports on the effects of exercise intervention on body composition, muscle volume and muscle strength in breast cancer survivors (Visovsky, 2006). It has been reported that there are limited precise standards for the prescription of the type, intensity, duration and progression of the exercises in breast cancer survivors, and these factors need to benchmarked based on various physiological, anatomical and behavioural factors (Kampshoff et al., 2010; Klika, Callahan, & Golik, 2008). Due to challenges in exercise ability in breast cancer patients mentioned above, traditional beliefs and misconceptions have prevented breast cancer patients from participating in various exercises, but recently the perspective towards exercise in breast cancer rehabilitation have changed with increased focus on the introduction and incorporation of exercise programs during and after treatment (Kent, 1996).

The current study has been structured to investigate the myotoxic effects of specific chemotherapeutic agents, mainly anthracyclines and taxanes, on skeletal muscle, body fat, muscle strength, health-related quality of life, and self-rated perceived fatigue in breast cancer patients. The focus of the study is to include an assessment of these outcome measures using validated, reliable and well-established instruments and
methodologies. The study further investigates the effects of a 12-week supervised progressive resistance training program (PRT), on the same outcome measures. The study includes a breast cancer control (non-exercise) group and a healthy control group in order to make clear observations in the improvements in the outcome measures brought about by the exercise program. The uniqueness of this study was to recruit breast cancer patients who had been specifically treated with anthracycline/taxane adjuvant chemotherapy, and administer a resistance exercise program to promote improvements in physical and psychological characteristics. Specific interest was given to anthracycline/taxane adjuvant chemotherapy as this regimen is a common modality of treatment for breast cancer. Patients treated with either additional or different chemotherapeutic drugs were excluded.
2.5 Aims

2.5.1 To assess the effects of:

1) anthracycline/taxane adjuvant chemotherapy treatment, and

2) a 12-week resistance exercise program commencing within four weeks following end of chemotherapy treatment on body composition, knee muscle strength, quality of life and fatigue in women diagnosed with breast cancer.

2.5.2 To compare any observed changes in body composition, knee muscle strength, quality of life and fatigue in breast cancer patients following a resistance exercise program with those observed in a non-exercising breast cancer group and an age-matched healthy control exercising group.

2.6 Hypothesis

2.6.1 There will be no difference in body composition, knee muscle strength, quality of life and fatigue between breast cancer patients prior to commencement of chemotherapy treatment and age-matched healthy control group.

2.6.2 There will be decreased lean mass, knee muscle strength, quality of life, and increased body fat and fatigue in women who have undergone chemotherapy to treat breast cancer compared with 1) the values observed at pre-chemotherapy stage, and 2) those observed in healthy control group.
2.6.3 There will be increased lean mass, knee muscle strength, quality of life, and decreased body fat and fatigue in women who have undergone chemotherapy to treat breast cancer after a resistance exercise program compared with a non-exercising breast cancer group.

2.6.4 There will be similar increases in lean mass, knee muscle strength, quality of life, and similar decreases in body fat and fatigue in women who have undergone chemotherapy to treat breast cancer after a resistance exercise program compared with an age-matched healthy control group undertaking the same exercise program.

2.7 Possible missing links and further research to fill gaps

To summarize, a number of studies discussed above have been conducted to assess the effects and benefits of exercise in breast cancer patients to improve various aspects of health and well-being and these include studies assessing a combination of different cancers and breast cancer where the type of chemotherapy has not been indicated. These studies have reported solely on the effects of exercise and not one single study investigated the effects of anthracycline/taxane adjuvant chemotherapy followed by exercise intervention in a breast cancer population. These studies have also included a combination of different exercise modalities such as simple walking, aerobic and resistance training. These studies have also assessed outcome measures using indirect techniques, such as using a 1-repetition (1-RM) for assessing muscle strength. The
previous studies have reported on either one outcome measure or at the most two outcome measures in any single study.

This current study has reported on four major outcomes in this single study and these include assessment of 1) whole body and thigh muscle/fat composition using dual energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT), 2) muscle strength directly measured from knee extension and flexion manoeuvres, 3) quality of life and 4) perceived fatigue.

Therefore, the purpose of this work was to investigate the effects of specifically (the commonly used) anthracycline/taxane adjuvant chemotherapy on four important outcomes such as the body composition, muscle strength, quality of life and perceived fatigue in breast cancer patients. Additionally, this study investigated the effects of structured resistance exercise on these outcomes measures, with a view to examine if these outcomes were improved in any way following the resistance exercise intervention.

In order to report on specific and detailed aspects of the various outcome measures, this study employed direct and “gold-standard” techniques and procedures such as using the 1) DXA for the whole body composition (instead of skin-fold measurements), 2) pQCT for detailed examination of changes in muscle and fat composition in the thigh cross-sectional area, 3) Biodex isokinetic dynamometer to directly assess muscle strength of the extension and flexion phases of the knee (that can be considered to be an important interpretation of ambulatory functions), 4) SF-36 to evaluate various
aspects of quality life associated with physical, psychological, emotional, social, health and well-being dimensions, and 4) the MFI-20 Fatigue Inventory to evaluate the various dimensions of fatigue.
CHAPTER 3: Systematic Review
The effects of resistance training on body composition, muscle strength, quality of life and fatigue in breast cancer patients – A systematic review

3.1 Abstract

**Purpose:** This study aimed to determine the effects of resistance exercise intervention programs on body composition, muscle strength, quality of life and fatigue in breast cancer survivors by systematically reviewing the literature. **Methods:** Potentially relevant articles were identified by searching electronic databases. Abstracts were included if they described any resistance exercise intervention program in breast cancer patients compared with controls and presented pre- and post-intervention results for changes in body composition, muscle strength, quality of life and fatigue. Identified studies were systematically reviewed for methodological quality. **Results:** Nineteen eligible trials were identified including thirteen randomized control trials and six nonrandomized control trials. The quality analysis revealed eight studies to be of high quality, eight studies to be of medium quality and three studies to be of below-average quality. Most studies used a combination of aerobic and resistance exercises, with some being supervised. Resistance exercise involved 8-10 large muscle groups, with 1-3 sets of 8-12 repetitions. The duration of the resistance exercise programs ranged from 8 weeks to 12 months, with a training frequency of 3-5 sessions per week. The training intensity varied from 50% to 85% of the one-repetition maximum. **Discussion:** In general, overall, there were little or no effects of resistance exercise on lean or fat mass, little effects on upper and lower body strength, little or no effects on quality of life and fatigue. **Conclusion:** Due to most exercise intervention studies in breast cancer survivors utilizing a combination of aerobic and resistance exercises and showing no adverse effects on body composition, muscle strength, quality of life and fatigue, a resistance-only exercise intervention program could promote better
improvements in body composition, muscle strength, quality of life and fatigue in breast cancer survivors.

3.2 Introduction:

Recent advances in the diagnosis and treatment for breast cancer with adjuvant chemotherapy have contributed to increased survival rates, together with a number of undesirable effects that have negative impacts on the physical and psychosocial aspects including changes in body weight and composition, muscle strength, quality of life and fatigue (Greil, 2009; Hwang, Chang, & Park, 2013).

Regular physical activity and exercise have shown to promote improvements in various physiological, physical and psychosocial characteristics in the general population as well as in clinical populations such as in breast cancer patients (Haskell et al., 2007; McNeely et al., 2006). Exercise has shown to be closely associated with a number of improvements including increases in cardiovascular function, muscle strength, bone mineral density and quality of life, with decreases in body weight, fat mass and fatigue (Church et al., 2009; Hacker, 2009; Hubbard et al., 2009; Martin, Church, Thompson, Earnest, & Blair, 2009; Otto et al., 2007; Södergren et al., 2008).

While resistance and strength training have shown to be the most effective mode of exercise to promote improvements in muscle mass and strength, majority of the exercise intervention studies investigating the rehabilitation of breast cancer survivors have used either predominantly aerobic exercise or have combined aerobic with resistance exercise (Courneya et al., 2002; Courneya, Segal, Mackey, et al., 2007; Ingram, Courneya, & Kingston, 2006). More recently, studies are now including resistance exercise to improve outcomes in various
cancer populations, including breast cancer, and this has shown to have a positive effect on the improvement of muscle mass and strength (Demark-Wahnefried & Jones, 2008; Hanson et al., 2009). Studies investigating resistance exercise in cancer have considered mainly quality of life and psychosocial aspects using self-reported questionnaires and tools, and have focused less on physical and physiological outcomes (Bicego et al., 2009; Chen et al., 2009).

The gap in literature on the benefits of resistance exercise on physical and physiological outcomes, and the limited number of resistance exercise intervention studies in the breast cancer population forms the basis of this systematic review which explores methodological quality, exercise methods and outcome measures. Therefore, the aims of this systematic review are to 1) systematically review studies using resistance exercise after treatment for breast cancer, 2) summarize the types of resistance exercise, including type, intensity and duration, 3) report on the effects of exercise on various outcomes, and 4) to provide recommendations for further studies.

3.3 Methods:

3.3.1 Search Strategy

This systematic review was conducted and reported according to the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). One reviewer (RL) searched 7 electronic databases during August 2015 to identify articles in which body composition, muscle strength, quality of life and fatigue were assessed in participants with breast cancer who had undergone a resistance training intervention. These databases were PubMed, the Cochrane Library, CINAHL, Embase, Scopus, Science Direct and Web of Science. The keywords were grouped and searched in the title, abstract and keyword search fields. The search strategy used search terms (using MeSH, subject terms, subject headings) and keywords, to locate the widest
spectrum of articles for consideration (Figure 9). Articles identified from the original search of each database were exported to separate Group sets in a single EndNote X7.0.2 library (Thomson Reuters, ©1988-2013). The various Group sets were then subsequently combined into a single Endnote library and duplicate records were removed.

3.3.2 Inclusion criteria:

Studies were included in this review if they were full journal articles, written in the English language, and assessed body composition, muscle strength, quality of life and fatigue in women with breast cancer who had undergone a resistance training intervention program. Studies including randomised and designs such as cross sectional, which compared exercise intervention and non-exercise groups and/or between a breast cancer group and healthy control, were included. Studies were included if they involved breast cancer patients undertaking resistance exercise after chemotherapy treatment.

A single reviewer (RL) performed the initial screening of titles and abstracts, and articles that did not meet the inclusion criteria were removed. The full paper was inspected if the title and abstract failed to provide sufficient information from which to make a decision. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart summarizing identification, screening and eligibility of the articles is shown in Figure 5. After the full text inspection by one reviewer (RL), the excluded studies were verified by a second reviewer (PM) and any discrepancy was resolved through discussion. All the articles included in the final analysis of this review were screened by title, abstract, and then eventually full-text with a consensus on included full-text articles reached between two authors. A supplementary manual search was made of the reference lists for all the included articles.
Chapter 3

Total number of records identified from electronic database search 
(n = 1073)

PubMed (n = 67)
Cochrane (n = 78)
CINAHL (n = 19)
EMBASE (n = 158)
Scopus (n = 136)
Science Direct (n = 611)
Web of Science (n = 4)

Duplicate records excluded 
(n = 691)

Records retained after duplicates removed 
(n = 382)

Excluded for reasons:
No resistance training intervention (n = 41)
Studies not in breast cancer populations (n = 198)
No evaluation of tested outcomes (n = 81)
Articles were reviews 
(n = 21)

Records retained after title, abstract and primary objectives screening 
(n = 41)

Full text articles assessed for eligibility 
(n = 19)

Records included in qualitative analysis 
(n = 19)

Figure 5: Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow chart. Showing the process to identify resistance exercise intervention trials in breast cancer survivors with body composition, muscle strength, quality of life and fatigue as outcomes in the current review.
3.3.3 Methodological quality assessments

The included articles were assessed using a 25 item CONSORT checklist with the maximum score of 25 points (Moher, 1998) for the methodological quality of included articles (Figure 6). Any discrepancies in the methodological quality assessments between the raters were resolved by consensus.

3.3.4 Data extraction and analysis

Data extraction was performed by a single reviewer (RL). Data extracted included population, age, intervention type, duration, activities and outcome measures (Figure 7). Summary statistics (mean, SDs, sample size and change) of outcome measures were extracted from the included studies. A summary of pre-intervention and post-intervention results for body composition, muscle strength, quality of life and fatigue for breast cancer and control groups are presented in Figure 8.
### Figure 6: CONSORT checklist for methodological quality of included studies

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No.</th>
<th>Checklist item</th>
<th>Validity</th>
<th>Included studies (References)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Participants

| 4a | Eligibility criteria for participants | 1 1 1 1 1 1 0 0 1 1 1 0 1 1 1 |
| 4b | Settings and locations where the data were collected | 1 1 1 1 1 1 1 1 0 1 1 1 0 1 1 |

### Interventions

| 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | 1 1 1 1 1 1 1 1 0 1 1 1 0 1 1 |

### Outcomes

| 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |
| 6b | Any changes to trial outcomes after the trial commenced, with reasons | 1 1 1 1 0 0 0 0 1 1 0 0 1 0 1 |

### Sample size

| 7a | How sample size was determined | 0 0 1 1 0 0 0 0 1 1 0 0 1 0 1 |
| 7b | When applicable, explanation of any interim analyses and stopping guidelines | 1 1 1 1 1 1 1 1 0 1 1 1 0 1 1 |

### Randomization

| 8a | Method used to generate the random allocation sequence | 1 0 0 1 0 0 1 1 1 0 0 1 1 1 1 |
| 8b | Type of randomisation; details of any restriction (such as blocking and block size) | 1 1 0 1 1 0 0 1 1 |

### Allocation concealment mechanism

<p>| 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps | 1 0 1 1 0 1 1 0 0 1 1 0 0 1 0 1 1 1 |</p>
<table>
<thead>
<tr>
<th>Implementation</th>
<th>10</th>
<th>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
</tr>
<tr>
<td></td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
</tr>
<tr>
<td></td>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
</tr>
<tr>
<td>Results</td>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
</tr>
<tr>
<td></td>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
</tr>
<tr>
<td>Recruitment</td>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>Systematic Review</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
<td></td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
</tr>
<tr>
<td>Numbers analysed</td>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
</tr>
<tr>
<td>Harms</td>
<td>19</td>
<td>All-important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
</tr>
<tr>
<td>Discussion Limitations</td>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
</tr>
</tbody>
</table>
## Generalisability

Generalisability (external validity, applicability) of the trial findings

| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

## Interpretation

Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

## Other Information

| Registration | Registration number and name of trial registry | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Protocol | Where the full trial protocol can be accessed, if available | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Funding | Sources of funding and other support (such as supply of drugs), role of funders | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |

### Total Score (out of 25)

| 18 | 12 | 22 | 20 | 12 | 18 | 18 | 13 | 11 | 23 | 24 | 16 | 16 | 20 | 16 | 14 | 20 | 20 | 21 |

### Total Quality in Percentage (%)

| 72 | 48 | 88 | 80 | 48 | 72 | 72 | 52 | 44 | 92 | 96 | 64 | 64 | 80 | 64 | 56 | 80 | 80 | 84 |

Note: Scoring criteria, 1=yes; 0=No or unable to determine. For the purpose of this review, a study was considered of high quality reporting if it scored 75% or more points, 50% or more as medium quality, 25% or more as below average quality and less than 25% as poor quality.
3.4 RESULTS

3.4.1 Database search

The PRISMA flow diagram (Figure 5) shows the results of the electronic search and screening process of articles through reviewing, with reasons for exclusion of studies. Following various database searches, 19 papers were considered relevant of which 13 were randomized controlled trials (RCT’s) while 6 were uncontrolled trials (T’s).

3.4.2 Population demographics

Figure 7 shows an overview of the study population of the 19 included studies, together with the age, exercise or non-exercise group, intervention type, intervention duration, exercise activity and outcome measures. A total number of 1399 breast cancer patients of ages ranging from 41.1 years to 64 years old were included in the 19 studies.

3.4.3 Intervention

The duration of the intervention in these 19 studies ranged from 8 weeks to 12 months and included various exercise modalities including cardiovascular, flexibility, aerobic, resistance. Exercise activities include cycling, rowing, walking, stretching, resistance or weight training of major muscle groups, treadmill running or indoor cycling. Most training programs prescribed 2 to 3 sessions per week and these were either supervised or self-directed.

3.4.4 Outcome measures – Physical

Body composition was assessed in 14 studies and included either lean or fat mass, % of lean and fat mass or body composition by skinfold measurements. Muscle strength was assessed in 12 studies and all of these employed 1-repetition maximum of major exercises such as arm
curls, leg press, leg curls, lateral pull-down and chest press. Other functional tests included cardiopulmonary function, aerobic capacity, 12-minute walk test and sit-and-stand test.

3.4.5 Outcome measures – Psychosocial and Quality of life

Quality of life was assessed in 12 studies by various general and cancer-specific quality of life assessment tools. Fatigue was assessed in 5 studies while depression was assessed in 3 studies.

3.4.6 Data of outcome measures

Figure 8 shows a comprehensive detail of results (mean ± SD) of the outcome measures for the exercise intervention and control groups at the pre- and post-intervention stages (and change in values from pre- to post intervention) in all the 19 studies. While it is encouraging to report quantitative data from all these 19 studies, there were no evidence for any significant effects of exercise training intervention on the various outcome measures.

3.4.7 Methodological quality of the studies

The methodological quality of the studies were assessed primarily based on the CONSORT scale (Figure 6). Based on a 25 point scale, 8 studies were assessed to be of high quality, 8 studies assessed to be of medium quality and 3 studies were assessed to be of below average quality.
**Figure 7: Overview of included studies, experimental groups, intervention specifics and outcome measures**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Participants</th>
<th>Age (mean ± SD)</th>
<th>Intervention</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Battaglini et al. 2007</td>
<td>Breast cancer</td>
<td>Exercise (57.5 ± 23.0 yrs)</td>
<td>Cardiovascular</td>
<td>Body composition by skinfold measurements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (56.6 ± 16.0 yrs)</td>
<td>21 weeks</td>
<td>Walking</td>
</tr>
<tr>
<td></td>
<td>Exercise (n = 10)</td>
<td></td>
<td></td>
<td>Cycling</td>
</tr>
<tr>
<td></td>
<td>Control (n = 10)</td>
<td>Flexibility</td>
<td>Whole body stretch</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Muscles strength using 1-RM of leg extension, seated leg curl, lateral pull down and seated chest press</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resistance</td>
<td>8-10</td>
<td>Exercises for major muscle groups</td>
</tr>
<tr>
<td>Battaglini et al. 2008</td>
<td>Breast cancer</td>
<td>Exercise (57.5 ± 23.0 yrs)</td>
<td>Cardiovascular</td>
<td>Body composition by skinfold measurements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (56.6 ± 16.0 yrs)</td>
<td>21 weeks</td>
<td>Walking</td>
</tr>
<tr>
<td></td>
<td>Exercise (n = 10)</td>
<td></td>
<td></td>
<td>Cycling</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue levels using the Piper Fatigue Scale (PFS)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Systematic Review

<table>
<thead>
<tr>
<th>Control (n = 10)</th>
<th>Flexibility</th>
<th>Whole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

- **Body Stretch**: Whole body stretch

<table>
<thead>
<tr>
<th>Resistance</th>
<th>8-10</th>
<th>Exercises for major muscle groups</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Courneya et al. 2007</th>
<th>Breast cancer</th>
<th>Usual care (49.0)</th>
<th>Resistance</th>
<th>6 months</th>
<th>9 exercises</th>
<th>Cancer specific Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistance Exercise (49.5)</td>
<td>Fatigue using FACT-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usual care (n = 82)</td>
<td>Strength</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resistance Exercise (n = 82)</td>
<td>Body fat %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fat mass</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lean mass</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Courneya et al. 2013</th>
<th>Breast cancer</th>
<th>Aerobic only (49.2 ± 8.4)</th>
<th>Aerobic</th>
<th>6 months</th>
<th>Cycle, Treadmill, Rowing</th>
<th>Physical functioning by SF-36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resistance + aerobic combined (50.5 ± 9.4)</td>
<td>Strength test using 1-RM of horizontal bench and leg press</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aerobic only (n = 96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resist + Aerobic combined (n = 104)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Disease</td>
<td>Intervention</td>
<td>Exercise</td>
<td>Duration</td>
<td>Outcome Measures</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Demark-Wahnefried et al. 2002</td>
<td>Breast cancer</td>
<td>Intervention (42.4 ± 1.8)</td>
<td>Aerobic + Resistance</td>
<td>6 months</td>
<td>Body weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (41.6 ± 6.2)</td>
<td></td>
<td></td>
<td>% Body fat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention (n = 9)</td>
<td></td>
<td></td>
<td>Fat mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n = 36)</td>
<td></td>
<td></td>
<td>Lean mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Leg lean mass</td>
<td></td>
</tr>
<tr>
<td>Demark-Wahnefried et al. 2008</td>
<td>Breast cancer</td>
<td>Exercise + calcium-rich diet (41.9 ± 4.8)</td>
<td>Aerobic</td>
<td>6 months</td>
<td>Body weight</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Body fat %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exercise + calcium-rich diet (n = 29)</td>
<td></td>
<td></td>
<td>Total fat mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium-rich diet only (41.1 ± 5.8)</td>
<td>Resistance bands</td>
<td></td>
<td>Total lean mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium-rich diet only (n = 29)</td>
<td></td>
<td></td>
<td>Quality of life (FACT-B)</td>
<td></td>
</tr>
<tr>
<td>Herrero et al. 2006</td>
<td>Breast cancer</td>
<td>Training (50 ± 5yrs)</td>
<td>Aerobic (cycling)</td>
<td>8 weeks</td>
<td>QOL (EORTC QLQ-C30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Training (n = 8)</td>
<td>Non-exerc control (51 ± 10yrs)</td>
<td></td>
<td>Body mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Resistance (11 exercises of major muscle groups)</td>
<td></td>
<td>Fat mass</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Control Group</td>
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<tr>
<td>Hsieh et al. 2008</td>
<td>Breast cancer</td>
<td>Non-randomised (57.9 ± 10.4yrs) 6 months aerobic + resistance exercise</td>
<td>Non-exerc control (n = 8)</td>
<td>Body fat %</td>
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<td>Bench press (reps)</td>
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<td>Leg press (reps)</td>
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<td>Sit and stand test (s)</td>
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<td>Kolden et al. 2002</td>
<td>Breast cancer</td>
<td>Age (55.3 ± 8.4yrs) 16 weeks aerobic + resistance exercise</td>
<td>Non-randomised (n = 96)</td>
<td>Cardiopulmonary function</td>
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<td>Milne et al. 2008</td>
<td>Breast cancer</td>
<td>Immediate exercise group (IEG) (n = 29) 12 weeks</td>
<td>Immediate exercise group (IEG) (n = 29)</td>
<td>QoL using FACT-B</td>
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<td>Delayed exercise group (DEG) (n = 29)</td>
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<td>Aerobic fitness using API cycle test</td>
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<td>Muscle strength using biceps curl, leg press and chest extension</td>
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### Systematic Review

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<th>Cancer Type</th>
<th>Intervention 1 (Mean ± SD)</th>
<th>Control 1 (Mean ± SD)</th>
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<th>Control Details</th>
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<tr>
<td>Mutrie et al. 2007</td>
<td>Breast</td>
<td>Intervention (51.3 ± 10.3)</td>
<td>Control (51.8 ± 8.7)</td>
<td><strong>Intervention:</strong> 12 weeks exercise, 10 mins warm-up, 20 mins aer + strength per session</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>(Total of 45 mins exerc) 3 sessions per week</td>
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<td><strong>Control:</strong> Usual care</td>
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<td>QoL by FACT-G, Beck Depression Inventory, Physical activity recall, BMI, 12-min walk test</td>
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<td>Ohira et al. 2006</td>
<td>Breast</td>
<td>Intervention (5.3 ± 8.7)</td>
<td>Control (52.8 ± 7.6)</td>
<td><strong>Intervention:</strong> 6 months weight training (3 months supervised) 9 weight training exercises</td>
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<td>(QoL using Cancer Rehab Evaluation system short form (CARES-SF), Depression using Center for Epidemiological Studies Depression Scale (CES-D))</td>
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<td>Schmidt et al. 2015</td>
<td>Breast</td>
<td>RT (53 ± 12.55)</td>
<td>ET (56 ± 10.15)</td>
<td><strong>Intervention:</strong> 12 weeks, 60 min per session, 2 sessions per week</td>
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<td><strong>Control:</strong> Resistance training (n = 21)</td>
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<td>RT = major muscle groups</td>
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### Chapter 3

#### Systematic Review

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<td>Schmitz et al. 2005</td>
<td>Breast cancer</td>
<td>Endurance training (n = 20)</td>
<td>SC (54 ± 11.19)</td>
<td>Fatigue by MFI-20</td>
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<td>Standard care (n = 26)</td>
<td>ET = indoor bike</td>
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<td>Resistance training</td>
<td>Immediate treatment group (n = 40)</td>
<td>ITG (53.3 ± 8.7)</td>
<td>6 months weight training</td>
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<td>Delayed treatment group (n = 41)</td>
<td>DTG (52.8 ± 7.6)</td>
<td>9 major muscle groups</td>
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<td>Simonavice et al. 2014</td>
<td>Breast cancer</td>
<td>Resistance training (n = 12)</td>
<td>RT (64 ± 5)</td>
<td>10 resistance exercises for upper and lower body</td>
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<td>Resistance training + dried plum consumption (n = 11)</td>
<td>RT + DP (64 ± 7)</td>
<td>Chest press (kg)</td>
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<td>Fat mass (kg)</td>
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<td>Outcome Measures</td>
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<td>Turner et al. 2004</td>
<td>Intervention group ONLY (n = 10)</td>
<td>8 weeks exercise, once per week</td>
<td>Total body fat %</td>
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<td>Aerobic capacity (VO2) (ml.kg.min⁻¹)</td>
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<td>Mostly aerobic on all weeks.</td>
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<td>Water-based exercise in Week 4 and 5</td>
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<td>Resistance exercise in only weeks 6-8.</td>
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<td>Winters-Stone et al. 2011</td>
<td>Resistance + impact intervention (POWIR) (n = 36)</td>
<td>12 months, 3 sessions/week, 60mins/session</td>
<td>Body weight (kg)</td>
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<td>POWIR = Resistance exercises + jumps</td>
<td>Bone-free lean mass (kg)</td>
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<td>FLEX = whole body stretching and relaxation exercises</td>
<td>Fat mass (kg)</td>
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<td>FLEX (62.2 ± 6.7)</td>
<td>% Body fat</td>
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<td>Control (FLEX) (n = 31)</td>
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<td>Winters-Stone et al. 2012</td>
<td>Resistance + impact intervention (POWIR) (n = 36)</td>
<td>12 months, 3 sessions/week, 60mins/session</td>
<td>Bench press</td>
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<td>POWIR = Resistance exercises + jumps</td>
<td>Leg press</td>
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<td>FLEX = whole body stretching and relaxation exercises</td>
<td>QoL (SF36)</td>
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<td>FLEX (62.2 ± 6.7)</td>
<td>Schwartz cancer Fatigue scale</td>
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<td>Control (FLEX)</td>
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<td>Winters-Stone et al. 2013</td>
<td>Resistance + impact intervention (POWIR) (n = 36)</td>
<td>12 months, 3 sessions/week, 60 mins/session</td>
<td>POWIR = Resistance exercises + jumps</td>
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<td>POWIR (46.5 ± 5.0)</td>
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<td>Bone-free lean mass (kg)</td>
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<td>FLEX (46.4 ± 4.9)</td>
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<td>Fat mass (kg)</td>
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<td>Control (FLEX) (n = 35)</td>
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<td>% Body fat</td>
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<td>FLEX = whole body stretching and relaxation exercises</td>
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### Figure 8: Results of outcome measures in resistance exercise intervention studies in breast cancer patients

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<th>Author</th>
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<th>Exercise Group</th>
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<tr>
<td>Battaglini et al., 2007</td>
<td>72</td>
<td>Fat mass (%)</td>
<td>20.0 ± 3.4 10</td>
<td>30.1 ± 4.2 10</td>
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<td>% Lean body mass</td>
<td>71.0 ± 3.4 10</td>
<td>69.1 ± 4.2 10</td>
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<td>% body fat</td>
<td>29.0 ± 3.4 10</td>
<td>30.1 ± 4.2 10</td>
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<td>Strength (kg)</td>
<td>269.77 ± 12.77</td>
<td>295.59 ± 22.65</td>
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<td>Battaglini et al. 2008</td>
<td>48</td>
<td>Time versus Group interaction effect of Total Calorie Intake (TCI) and Resistance exercise</td>
<td>Main effect was significant (Exercise group had significantly higher TCI than the control group. (Did not show pre- and post-intervention data but only reported interaction effect)</td>
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<td>Courneya et al. 2007</td>
<td>80</td>
<td>Self-esteem (QoL)</td>
<td>34.1 ± 4.2 82</td>
<td>34.7 ± 4.2 82</td>
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<td>Fatigue</td>
<td>34.3 ± 10.1 82</td>
<td>36.3 ± 9.4 82</td>
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<td>1-RM leg (kg)</td>
<td>24.4 ± 11.2 82</td>
<td>32.8 ± 12.6 82</td>
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<td>1-RM chest (kg)</td>
<td>23.2 ± 7.2 82</td>
<td>31.9 ± 10.8 82</td>
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<td>Body fat %</td>
<td>37.2 ± 9.0 82</td>
<td>37.2 ± 9.0 82</td>
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<td>Fat mass (kg)</td>
<td>26.2 ± 11.7 82</td>
<td>26.9 ± 12.0 82</td>
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<td>Lean mass</td>
<td>40.3 ± 4.6 82</td>
<td>40.9 ± 5.6 82</td>
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<td>Upper body strength</td>
<td>Lower body strength</td>
<td>Lean mass</td>
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<td>Courneya et al., 2013</td>
<td>50.2 6.9 104</td>
<td>48.4 6.9 104</td>
<td>52.2 5.8 96</td>
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<td>Demark-Wahnefried et al. 2002</td>
<td>25.0 8.6 104</td>
<td>30.7 8.4 104</td>
<td>25.0 8.5 96</td>
<td>6.9</td>
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<td>Demark-Wahnefried et al. 2008</td>
<td>87.1 27.4 104</td>
<td>95.7 24.7 104</td>
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<td>Lean mass</td>
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<td>42.2 5.3 104</td>
<td>41.2 5.7 96</td>
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<td>Fat mass</td>
<td>29.7 12.3 104</td>
<td>30.1 12.3 104</td>
<td>26.4 9.8 96</td>
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<td>Body fat %</td>
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<td>39.8 8.4 104</td>
<td>37.7 8.1 96</td>
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<td>Body weight</td>
<td>68.8 4.2 9</td>
<td>67.8 4.7 9</td>
<td>72.2 2.1 36</td>
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<td>% body fat</td>
<td>32.5 2.3 9</td>
<td>31.2 2.2 9</td>
<td>35.4 1.5 36</td>
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<td>Fat mass</td>
<td>22.6 22.9 9</td>
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<td>Lean mass</td>
<td>43.1 1.9 9</td>
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<td>Leg lean mass</td>
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<td>Body weight</td>
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<td>63.7 10.5 8</td>
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## Chapter 3

### Systematic Review

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<th>Year</th>
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<th>Leg press (reps)</th>
<th>Sit and stand (s)</th>
<th>Bench press (submax, lbs)</th>
<th>Leg press (submax, lbs)</th>
<th>QoL (FACT-G)</th>
<th>QoL (FACT-B)</th>
<th>Aer fitness test (Wkg-1)</th>
<th>Bicep curl (kg)</th>
<th>Leg press (kg)</th>
<th>Chest extension (kg)</th>
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<td>Hsieh et al. 2008</td>
<td>52</td>
<td>4.97</td>
<td>16.4 6.6 8</td>
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<td>24 6 8</td>
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<td>7.90 0.8 8</td>
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<td>45.67 223.76</td>
<td>94.05 10.9 40</td>
<td>118.6 9.4 29</td>
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<td>16.8 3.7 29</td>
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<td>Milne et al. 2008</td>
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<td>16.9 5.5 7</td>
<td>7.53 0.49 8</td>
<td>45.67 13.5 40</td>
<td>223.76 70.7 40</td>
<td>74.05 10.9 40</td>
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<td>96</td>
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<td>74.05 10.9 40</td>
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**Hsieh et al. 2008** NO CONTROL GROUP

**Kolden et al. 2002** NO CONTROL GROUP

**Milne et al. 2008**

**Mutrie et al. 2007**
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<td><strong>Schmidt et al.</strong></td>
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**Turner et al. 2004 (No control group)**

- **VO₂ (ml.kg.min⁻¹):**
  - 23.0 ± 7.2
  - 25.0 ± 8.1

- **Lean mass (kg):**
  - 54.7 ± 7.5
  - 56.6 ± 9.6

- **Fatigue:**
  - 4.9 ± 0.9
  - 3.8 ± 1.4

- **Quality of life:**
  - 98.1 ± 17.4
  - 106.9 ± 17.1

**Winters-Stone et al. 2011**

- **Body weight (kg):**
  - 75.6 ± 15.5
  - 76.5 ± 15.6

- **Bone-free lean mass (kg):**
  - 43.4 ± 6.5
  - 44.0 ± 6.7

- **Fat mass (kg):**
  - 30.4 ± 9.4
  - 30.9 ± 9.7

- **% Body fat:**
  - 40.5 ± 5.7
  - 40.5 ± 6.2

**Winters-Stone et al. 2012**

- **Bench press (lbs):**
  - 56.3 ± 12.8
  - 63.3 ± 15.3

- **Leg press (lbs):**
  - 167.9 ± 39.4
  - 201.3 ± 57.4

- **SF36 QoL:**
  - 50.3 ± 5.1
  - 51.7 ± 6.2

- **Fatigue:**
  - 9.9 ± 3.3
  - 10.1 ± 4.7

- **Body weight (kg):**
  - 72.3 ± 13.4
  - 73.6 ± 14.9

**Notes:**

- Turner et al. 2004: No control group
- VO₂ values are reported as mean ± standard deviation.
- Quality of life and Fatigue scores are also reported in the same manner.
- Fatigue scores are further broken down into Mean ± Standard Error.
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This review summarizes the research of previous studies that investigated the effects of a resistance exercise intervention program in breast cancer patients following the completion of their treatment, by focusing on methodological quality, exercise specifics and outcome measures (including physical and psycho-social). From the 19 exercise intervention studies in breast cancer patients following treatment, 12 studies have used some type of aerobic or cardiovascular exercise in addition to resistance exercise (2 of these also included flexibility exercises together with aerobic + resistance), 4 studies utilized only resistance exercises while 3 studies used a combination of resistance and flexibility exercises (as seen in Figure 7). The main outcome measures from these studies included body composition, muscle strength, fatigue, quality of life, sit-and-stand functional test, cardiopulmonary function, flexibility, depression and endurance.

One of the first studies, conducted by Kolden et al. (2002), examined the effects of a 16-week combined aerobic and resistance exercise intervention in a single group of 40 breast cancer patients assigned to a structured group exercise training 3 times per week. The exercise components included aerobic fitness, strength and flexibility, and results demonstrated improved health benefits in aerobic capacity, strength (assessed by 1 repetition maximum (1-RM)). However this study did not have a control group. Although this study utilised simple assessment techniques, such as estimation of body fat using skinfold measurements and measurement of strength using 1-RM of bench and leg press, the results show a decrease in body fat percentage and increase in bench and leg press strengths. Due to this study incorporating both aerobic and resistance exercises, it cannot be clearly ascertained if the decrease in body fat percentage were due to either the aerobic or resistance exercises.

The effect of a 6-month clinic-based exercise program incorporating aerobic activity + strength training + healthful diet was also investigated by Demark-Wahnefried, Kenyon, Eberle, Skye, and Kraus (2002). Nine premenopausal women who had received adjuvant chemotherapy were
assigned to the exercise program and assessed for body composition at baseline and at 6-month follow-up, and compared to 36 historic patient controls. Results demonstrated increases in body weight, % body fat, fat mass and decreases in lean body mass in the historic patient group. The breast cancer intervention group, on the other hand, demonstrated decreases in body weight, % body fat, fat mass and increases in lean body mass. Results from this pilot study suggest that exercise interventions may prevent chemotherapy-induced weight and body composition changes in women with breast cancer and recommended the need of further study utilizing home-based exercise programs as most of women declined participation based on time and travel requirements.

In a pilot project, Turner, Hayes, and Reul-Hirche (2004), examined the effects of an 8-week mixed-type, moderate intensity exercise program in 10 breast cancer patients following treatment and assessed fitness, body composition, fatigue, mood and quality of life. While the results indicated a trend towards reduction in fatigue and improved quality of life, there was no control group to compare these changes. The exercise program mostly composed on aerobic exercise while resistance exercise was only administered in the last two weeks of the exercise program. It has also been suggested the need of further larger randomised studies to confirm the benefit of exercise in women treated with chemotherapy for breast cancer.

Schmitz, Ahmed, Hannan, and Yee (2005) conducted a randomised controlled trial examining the effects of a twice-weekly weight training among 85 recent breast cancer survivors for 12 months. Body weight, body fat, lean mass, body fat % and waist circumference were assessed at baseline and post-test. Results demonstrated significant increases in lean mass, and significant decreases in body fat %. While this study demonstrated that a twice-weekly weight training improved lean mass and body fat % in breast cancer survivors, it has suggested the need for further studies in weight training in breast cancer survivors.
A pilot study by Herrero et al. (2006) examined the effects of a 8-week combined cardiorespiratory and resistance exercise training program on cardiorespiratory fitness, strength endurance, task-specific functional muscle capacity, body composition, and quality of life. Following the training program, quality of life, VO2 peak, leg press performance and sit-to-stand tests improved, with no significant changes in the control group. Since this study concluded that aerobic training together with resistance training could improve quality of life and overall fitness of women breast cancer survivors, it cannot be confirmed that resistance exercise alone contributed to such improvements.

The effects of a 6-month weight training exercise on quality of life and depressive symptoms were examined in a randomised controlled trial by Ohira et al. (2006) in 86 breast cancer survivors. Over the 6 month period, quality of life improved significantly in the treatment compared to the control group.

Battaglini et al. (2007a) examined the effects of a 21-week resistance exercise program on changes in body composition and strength in 10 breast cancer survivors in a randomised controlled trial. The exercise included low to moderate intensity training for 60 minutes on two days per week. The results demonstrated significant improvements in lean body mass, body fat and strength in the training group as compared to the controls.

Courneya, Segal, Mackey, et al. (2007) conducted a randomised controlled trial with 82 breast cancer survivors in a resistance exercise group, 82 in the usual care group and 79 in an aerobic exercise arm for the duration of their chemotherapy treatment (17 weeks). The results demonstrated that resistance exercise was superior to usual care and aerobic exercise groups for improving self-esteem, muscular strength, lean body mass and chemotherapy completion rates, without any significant improvements in quality of life.
The effects of a 12-week supervised group exercise program involving combined aerobic and resistance exercises on functional and psychological benefits in 203 breast cancer survivors were examined by Mutrie et al. (2007) in a randomised controlled trial. Following the intervention, the supervised group exercise provided functional and psychological benefit after a 12-week intervention and these effects were maintained at a six-month follow-up.

In a randomised controlled trial, Battaglini et al. (2008) examined the effects of a combined aerobic and resistance exercise in breast cancer survivors over a 6 month period and assessed a 3-day food diary, % body fat by skinfolds and fatigue. In addition to this study not having a structured exercise program dedicated to resistance training only, it used indirect methods of assessment for common outcome measures, such as the % body fat which was done by skinfolds. The results of this study conclude that any form of exercise may mitigate any side effects of chemotherapy treatment for breast cancer.

Demark-Wahnefried et al. (2008a) examined the effects of a 6-month mixed aerobic and strength training in 45 breast cancer survivors and assessed waist circumference, dietary intake, physical activity and quality of life. The results of this study demonstrate that exercise interventions can help prevent weight gain and adverse body composition changes, and suggests the need for further research in determining optimal training procedures to ensure maximal benefits from exercise.

Hsieh et al. (2008) also examined the effects of a combined exercise program on 22 breast cancer patients and assessed cardiovascular function, quality of life and fatigue. The results demonstrate that cardiovascular function improved significantly, together with quality of life and fatigue. While this study utilised strength training, it did not test for any outcome measure that was directly related to strength training.
A similar randomised controlled trial was conducted by Milne et al. (2008) and these examined the effects of a mixed exercise program on quality of life, fatigue physique and physical fitness. While this study utilised a strength training component in the exercise program, there was no outcome measure tested that was directly related to strength training. The results demonstrate that quality of life improved significantly after a 12-week exercise intervention period.

The effects of a one-year long moderate-intensity resistance training was examined for possible changes in lean mass and fat mass in a randomised controlled trial with 106 women with breast cancer (Winters-Stone et al., 2011). Increases in lean mass and decreases in fat mass were clearly seen in the results of this study.

Winters-Stone et al. (2012) conducted another randomised controlled trial examining the effects of a one-year long resistance training on muscle strength and physical function in 106 post-menopausal women with breast cancer. While this study utilised the indirect method of assessment of strength using the 1-RM, results demonstrate that the women significantly improved in maximal leg and bench press strengths, compared to the control group.

The effects of different exercise types and doses during breast cancer chemotherapy were examined in a multi-centre randomised trial by Courneya et al. (2013) in which 301 breast cancer patients were randomised either to the aerobic, strength or combined group. The endpoints tested in this study were quality of life and physical functioning. The results demonstrate that strength training was superior to aerobic and combined modes in improving quality of life and aspects of physical functioning. This study did not test for any strength outcomes.

In another randomised controlled trial, Winters-Stone et al. (2013) examined the effect of resistance exercise on body composition, hip and spine bone mineral density. 71 breast cancer survivors were randomly assigned either to the resistance exercise group or to the control
group. The exercise sessions were 3 times per week for one year. Results demonstrated that the resistance exercise helped increase bone mineral density at the hip and contributed to improvements in % body fat.

A similar randomised controlled trial was conducted by Simonavice et al. (2014) to examine the effects of a 6-month resistance training on strength, body composition and biomarkers of bone turnover in 12 breast cancer patients. The exercise sessions were conducted over a one year period. The results did not show any notable improvements in body composition and bone mineral density and it has been further suggested that a larger study with a more structured exercise program to be implemented to achieve the expected results.

More recently, Schmidt et al. (2015) examined the effects of strength training in 67 breast cancer patients compared to standard care. The exercise sessions were for 12 weeks and the end point outcome measures were muscular strength, quality of life, endurance and rate of perceived exertion. The results demonstrated that the resistance and endurance exercise groups improved significantly in muscular strength, endurance and quality of life. It has also been suggested physical activity during breast cancer treatment can reduce side effects and improve clinical outcomes,
3.5 Discussion

The primary objective of this systematic review was to present a summary of previously published studies reporting the effects of resistance exercise in the breast cancer population during and after treatment with chemotherapy. While there has been a fair bit of literature on the use of various exercise modes, including a combination of aerobic and resistance training, a number of these studies have certain limitations and these include studies not being randomised control trials, not restricted to resistance exercise only, use small sample sizes, employing indirect methods of assessment of certain variables. However, despite the various shortfalls in these studies, there is considerable evidence that exercise benefits various physiological and psychological aspects during or following chemotherapy treatment. Therefore, this review will aim to identify the missing gaps in the literature with regards to the contributing effects of resistance exercise in the enhancement of physiological and psychological variables such as body composition, muscle strength, quality of life and fatigue in breast cancer survivors.

While the literature demonstrates various benefits of resistance exercise in breast cancer survivors, a number of methodological limitations in these studies warrants further investigations on a number of key research questions. Appropriately designed randomised controlled trials with structured resistance exercise interventions of a reasonable dose and duration, with scientifically-valid direct measurements of various physiological and psychological parameters need to be administered to better report the effectiveness of resistance training as a rehabilitative tool in the management of breast cancer. Data from such defined studies will then assist in the development of appropriate and effective exercise prescription guidelines, and this forms the basis of any future investigations.
It is encouraging to note that ten of the studies included in this review considered randomisation of participants into exercise and non-exercise groups. Nearly half of the studies conducted did not involve any randomisation and provided no comparison to a non-exercising group. While these studies should be able to provide a foundation for the adaptation of resistance exercise prescription as a rehabilitative tool in the management of breast cancer, further research is essential to include a strict guideline in the randomisation process to demonstrate an effective involvement of an exercise and a non-exercise group to clearly affirm the beneficial effects of resistance training in the improvements of the various physiological and psychological parameters. The non-randomised studies contain relevant data and these should form a basis of the development of larger, appropriately designed randomised controlled trials.

The exercise prescription described in these studies are generally not clearly defined and do not specifically include resistance training alone. Only four of the studies have included resistance exercises alone in the exercise prescription while five studies used a combination of cardiovascular, resistance and flexibility exercises. Ten studies incorporated aerobic exercises with resistance training in their design. A number of these studies did not describe the specific exercises performed, with no clear indication of the intensity of the exercises. Further studies investigating the beneficial effects of resistance training should be appropriately defined to clearly demonstrate the duration, frequency, volume, intensity, specific exercises performed, equipment used, exercise venue and training supervision. These data is essential for the development of an effective exercise and training plan for the relevant exercise and clinical professionals involved in the management of breast cancer.

In general, these clinical trials should demonstrate the use of direct measurement methods in the assessment of relevant outcome measures using scientifically-valid and reliable tools in order to relate to various physiological and psychological improvements. While the use of skin-fold measurements to assess body fat, 6-minute/12-minute walk tests to assess functional
capacity, 1-repetition maximum (1-RM) to assess muscle strength are all valid and reliable methods that have been used extensively in many other studies to evaluate physical performances, a more direct approach and employment of direct measurement tools needs to be adhered to for a better analysis and reporting of the various physical, physiological and psychological outcomes. These improvised methods could include computed tomography scans to better report body composition, VO2max tests to better assess aerobic capacity and cardiorespiratory function, and the use of specific dynamometers for measurement of muscle strength.

Additionally, appropriate and complete reporting of all components of any study should form an essential feature of any such clinical trial that has possible positive and valuable impact. This details could include participant characteristics such as age, menopausal status, stage of breast cancer, treatments administered (type, dose, duration), timing of the exercise intervention (during or after treatment) and any side effects due to the exercise intervention. Completion of the exercise intervention and compliance should be the other important factors that need to be reported to describe the efficacy of the intervention that as a number of implications for the implementation and dissemination of such exercise interventions.

3.6 CONCLUSION

Briefly summarising, exercise interventions (particularly resistance training) is widely recommended for various clinical populations with a view of providing a number of health-related benefits. Resistance training, no doubt, has also been widely advocated and implemented to aid in the rehabilitation process in the management of breast cancer, leading to potential health benefits in functional capacity and psychosocial characteristics. However, as described above, there are no clear guidelines in the process and components of this very
important rehabilitative tool. The limited amount of information in the literature has a number of shortfalls in the methodological process and obvious gaps in knowledge are clearly evident. Further studies are required which clearly defines the methodological structures as discussed above to better advance the general knowledge of this important field of study. This is essential to develop a benchmark and guidelines in the construction and implementation of an effective exercise prescription to be used as one of the main rehabilitative tool in the management of breast cancer. The current research and thesis makes an attempt to address these many shortfalls and has successfully incorporated these many components and missing links in the evaluation of the effects of resistance training in breast cancer survivors. The current study has investigated and reported on appropriate participant characteristics and demographics, a clearly defined resistance exercise prescription, the use of specific and direct assessment methods of various physical, physiological and psychosocial outcomes.
**Figure 9: Search terms and strategy**

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<th>Search terms category</th>
<th>Disease (breast cancer)/related term</th>
<th>Intervention/related terms</th>
<th>Outcome 1/related term</th>
<th>Outcome 2/related term</th>
<th>Outcome 3/related term</th>
<th>Outcome 4/related term</th>
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<tbody>
<tr>
<td><strong>Data base specific:</strong></td>
<td>(1) breast cancer OR breast neoplasms OR breast carcinoma OR breast tumors OR cancer of breast OR cancer of the breast</td>
<td>(2) resistance exercise OR resistance training OR strength exercise OR strength training OR weight-bearing exercise program OR weight-bearing strengthening program OR weight-lifting exercise program OR weight-lifting strengthening program</td>
<td>(3) body composition OR muscle mass OR lean mass OR fat-free mass OR fat mass</td>
<td>(4) muscle strength OR muscle contraction</td>
<td>(5) quality of life OR life style OR value of life</td>
<td>(6) fatigue OR lassitude OR asthenia OR muscle weakness</td>
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**Combined searches**

A = 1) AND (2)

B = (1) AND (2) AND (3)

C = (1) AND (2) AND (3) AND (4)

D = (1) AND (2) AND (3) AND (4) AND (5)

E = (1) AND (2) AND (3) AND (4) AND (5) AND (6)
4.1 Ethics Approvals

Ethical approvals for the study were received from the Human Research Ethics Committees (HREC’s) of the Princess Alexandra Hospital (HREC/09QPAH/172), the Mater Adult Hospital (1504E), the Gold Coast Health Services District (M10-963), and Griffith University (PES/12/09/HREC) – (Appendices).

4.2 Study design

This study was designed to recruit breast cancer survivors from two hospitals in Brisbane and one hospital in Gold Coast two weeks post-surgery and prior to the commencement of their chemotherapy treatment. The breast cancer survivors were assessed for body composition, muscle strength, quality of life and fatigue at the a) pre-chemotherapy stage, b) post chemotherapy stage and c) post intervention (exercise or non-exercise) stage. A group of healthy age-matched sedentary controls allowed comparison of 1) post chemotherapy status and 2) response to the exercise intervention. This study (as a whole) is a randomised control trial of a 12-week progressive resistance training (PRT) intervention program for breast cancer patients previously treated with chemotherapy.

4.3 Recruitment

Two groups of participants were recruited for the sub-studies: (1) individuals who had recently been diagnosed with breast cancer and had undergone surgery but were yet to undergo treatment with anthracycline/taxane adjuvant chemotherapy, and (2) age-
matched healthy participants who served as a control group. For the purpose of these studies, “treatment with anthracycline/taxane adjuvant chemotherapy” will be referred to as “chemotherapy treatment” in this thesis. Due to a number of challenges faced during recruitment of breast cancer patients, participants were recruited in a staggered process with an average of one breast cancer patient recruited per month, and not all participants were able to be recruited in a block. Therefore, the breast cancer patients were assigned either to the exercise or to the non-exercise group by simple randomisation in the order of recruitment.

4.3.1 Breast cancer group

Potential participants in the breast cancer group were recruited from the Princess Alexandra, and Mater Hospitals in Brisbane and from the Gold Coast Hospital. Recruitment for potential participants in the breast cancer groups were conducted by the clinicians, mainly the oncologists and cancer care nurses at the Breast Cancer Clinics of these hospitals, as the researchers were not provided any opportunity to conduct any recruitment themselves within the locality of the hospitals. Potential breast cancer patients scheduled for treatment by chemotherapy using anthracyclines and taxanes were approached for participation in the study and this group represented the most common category of breast cancer patients treated at these hospitals. Recruitment flyers were handed to potential participants at the Breast Cancer Clinics of the respective hospitals. The recruitment flyer (Appendix 9.1) included a brief outline of the study, inclusion and exclusion criteria, target volunteers, requirements
and commitments of the participants, outcomes of the study and potential benefit to breast cancer survivors in the future. Interested participants were requested to contact one of the research team listed on the flyer; following this, potential volunteers were sent more detailed information, including an approved Participation Information and Consent Form (PICF) (Appendix 9.2). Screening was performed and a comprehensive summary of all aspects of the study (i.e. risks and benefits, assessment techniques, number of visits, details of intervention program) were provided. Subject to the participant providing informed consent at this point, baseline assessment was performed.

The inclusion/exclusion criteria used to screen potential participants for the study were:

\textit{a) Inclusion criteria:}

- Breast cancer diagnosis within previous 4 weeks, with associated surgery being conducted not less than 2 weeks earlier
- < 75 years old (the study initially planned to investigate only post-menopausal women but due to lack of recruitment numbers, the study population was extended to include all age groups below the age of 75 years)
- Scheduled for, but not commenced, anthracycline/taxane adjuvant chemotherapy
- Prepared to exercise three times per week for 12 weeks
- Prepared to travel to exercise training and assessment venues.
b) **Exclusion criteria:**

- Exercised aerobically for greater than 20 minutes twice weekly or more (Martin et al., 2009) within the past 6 months
- Undertook resistance training within the past 6 months
- Diagnosed and/or self-reported conditions likely to limit adherence to the resistance exercise training program to be used in these studies
- Diagnosed and/or self-reported conditions that may limit the ability to exercise safely (e.g. impaired physical mobility, cardiopulmonary complications, diabetes, hypertension, osteoarthritis and other musculoskeletal constraints)
- Not approved by an oncologist for participation.

### 4.3.2 Randomisation of breast cancer participants

All breast cancer participants were assessed before and following chemotherapy (see below for details). Thereafter, they were randomly assigned to either the breast cancer exercise group (BCE) or the breast cancer non-exercise group (BCN) in an alternating sequence (i.e. with respect to time of first assessment) to ensure equal numbers in each group and avoidance of bias that might be related to the passage of time. The mean age, body mass and BMI of the breast cancer (exercise and non-exercise) groups were crucial in ensuring a clear randomisation of participants into these each groups. These variables demonstrated a fair distribution of breast cancer participants between these two groups, with similar demographic features between these two groups.
4.3.3 Healthy control group

Age-matched healthy women were recruited from the Griffith University community and the general public community in the cities of Gold Coast and Brisbane with the aid of recruitment flyers (Appendix 9.3) circulated via the staff email distribution list and on community notice boards of the various suburbs. The healthy control group was selected from a relatively sedentary population, based on established criteria (Martin et al., 2009) that describes sedentary women not exercising more than 20 minutes on 3 or more days per week, and less than 8000 steps per day assessed over the course of one week, and who had a systolic blood pressure of 120.0 to 159.9 mmHg. Age-matching was achieved by recruiting participants in this group after recruiting breast cancer patients and screening for age to ensure reasonably close matching (± 5 years) of pairs of individuals across the two groups. The inclusion/exclusion criteria used to screen healthy participants for the study were:

a) Inclusion criteria:

- < 75 years old
- Prepared to travel to exercise training and assessment venues
- Prepared to exercise three times per week for 12 weeks
b) *Exclusion criteria:*

- Breast or any other cancer
- Exercised aerobically for greater than 20 minutes twice weekly or more (Martin et al., 2009) within the past 6 months
- Undertook resistance training within the past 6 months
- Diagnosed and/or self-reported conditions likely to limit adherence to the resistance exercise training program to be used in these studies
- Diagnosed and/or self-reported conditions that may limit the ability to exercise safely (e.g. impaired physical mobility, cardiopulmonary complications, diabetes, hypertension, osteoarthritis and other musculoskeletal constraints).

Following a single initial assessment session (see below for details) all subjects in the age-matched healthy group (HCE) undertook the prescribed resistance exercise training program and hence did not require randomisation.

### 4.4 Assessment of primary and secondary outcomes

Participants in the breast cancer group completed three assessment sessions: (1) one week before the commencement of anthracycline/taxane adjuvant chemotherapy, (2) one-to-two weeks after the end of chemotherapy but before 4-6 weeks of radiotherapy (when prescribed), (3) within one week after the completion of the 12-week intervention program. Exercise intervention was only introduced to the breast cancer exercise group after the completion of the chemotherapy treatment (and/or
radiotherapy) as clinicians did not approve of any exercise intervention during treatment for the fear of interference and to avoid any potential complications.

The participants in the age-matched healthy control group (HCE) attended assessment sessions on two occasions: (1) one week before the 12-week intervention program (only 12-week resistance exercise training program), (2) within one week of the completion of 12 week resistance exercise training program.

The primary outcome measures for the intervention efficacy were muscle mass, thigh muscle cross-sectional area and knee flexion/extension strength while the secondary outcomes were body mass, fat mass, quality of life and fatigue.

4.4.1 Primary outcomes

   a) Muscle mass

Muscle (lean) mass was estimated using standard procedure pencil beam dual-energy x-ray absorptiometry (DXA) (Norland XR-800, Cooper Surgical, USA). The DXA provides a reliable (intraclass correlation for total body mass $R = 0.94$, fat mass $R = 0.97$ and lean mass $R = 0.89$) estimate of body composition in comparison with computed tomography (CT) (Glickman, Marn, Supiano, & Dengel, 2004). The DXA scanner was calibrated daily using an anthropometric phantom in accordance with the manufacturer’s recommendations. All scans were performed following established and validated procedures, with the participant lying in supine on the scanning bed with arms and legs extended and, palms downwards and feet apart (Haderslev, Haderslev, &
Staun, 2005; Keller et al., 1998; Knobf, Insogna, DiPietro, Fennie, & Thompson, 2008; Lee & Gallagher, 2008). During the DXA scan, transverse slices, approximately 1cm apart, were captured from head to toe in an automated procedure. Each whole body scan took approximately 10 minutes. Whole body lean muscle mass was derived using the Illuminatus DXA User Interface Software (Norland, Cooper Surgical, USA). While most of the previous studies estimated body fat using skin fold assessments, the novelty of the current study is the use of a gold-standard computed tomography technique to accurately report changes in lean and fat mass.

\[ b) \text{ Thigh muscle cross-sectional area}\]

Thigh muscle cross-sectional area (CSA) was estimated using peripheral quantitative computed tomography (pQCT) (XCT-3000 scanner, Stratec Inc., Pforzheim, Germany). The pQCT demonstrated adequate validity (high coefficient of determination (R2) of 0.979) and a high test-retest reliability (intraclass correlation coefficient = 0.996) when compared with magnetic resonance imaging (MRI) (Cramer, 2007) and therefore was considered to be an ideal tool for the assessment of muscle cross-sectional area in the thigh in this study. To the best of our knowledge, the current study is the first to have engaged the use of a pQCT to investigate and report on the fat and lean mass in the thigh cross-sectional area.

A 2.3 mm-thick single tomographic transverse slice (with a diameter of 270mm) of the thigh at 33% of femur length (from the lateral condyle to the greater trochanter) was scanned while participants were seated on a high chair with their lower extremity
positioned through the gantry rested on a Perspex holder and secured using a Velcro (Figure 4.1), as per the manufacturer’s recommendations (Stratec, Pforzheim, Germany). Muscle cross-sectional area of the thigh were determined using the Thigh Muscle Analysis Software algorithms developed by Bone Diagnostics Inc. (USA), based on threshold ranges of -101 to 40 mg/cm³ for fat, 41 to 101 mg/cm³ for muscle and 102 to 710 mg/cm³ for bone.

Figure 10: Scanning of the thigh using the pQCT scanner
c) **Assessment of knee flexion and extension strength**

Isometric strength is an important variable that can tested to assess muscle strength in the limbs and therefore isometric strength was chosen as a tested outcome to assess muscle strength in this study. Isometric strength is a representative of voluntary strength in individuals and particularly for lower limbs, isometric strength is associated with functional mobility such as gait, speed, balance, stair climbing and chair rising (Sturnieks et al., 2008; Symons, Vandervoort, Rice, Overend, & Marsh, 2005; Wilcock et al., 2008). The resistance exercise employed in this study was targeted at having an effect on the isometric strength that is directly related to voluntary movements associated with functional mobility, which would be an important outcome measured by any study wishing to target improvements in muscle strength associated with functional mobility. Isometric and concentric knee flexion/extension torques were measured using a Biodex isokinetic dynamometer (Biodex System 3, Biodex Medical, Shirley, NY, USA) employing established procedures (Capranica, Battenti, Demarie, & Figura, 1998; Drouin, Valovich-mcLeod, Shultz, Gansneder, & Perrin, 2004; Sturnieks et al., 2008; Symons et al., 2005). The Biodex System 3 was found to achieve trial-by-trial and day-to-day reliability (intraclass correlation coefficient = 0.99 for torque (Nm)) and demonstrated mechanical validity (intraclass correlation coefficient = 0.99 for torque) when compared to a criterion measure of torque (Drouin et al., 2004). With the Biodex system 3 performing with acceptable mechanical reliability, validity, and capable of direct measurements of torque, this system was employed to the measurement of torque in this study.
Strength testing was performed with the participant seated on the Biodex chair with the backrest angle set at 85°. The dynamometer head was oriented such that the dynamometer axis was aligned with the knee flexion/extension axis (i.e., dynamometer head rotation = 90°; tilt = 0°). The length of the dynamometer lever arm (knee attachment) was adjusted to ensure that the ankle cuff strap was immediately superior to the lateral and medial malleoli (Symons et al., 2005). Participants’ lower torsos and dominant thighs were restrained using padded straps to limit movement (Sturnieks et al., 2008). Shoulder and chest straps were not used due to potential discomfort in the breast cancer participants.

The dynamometer seat was orientated and fixed at 90° (Symons et al., 2005). Participants’ knee ranges of motion (ROM) were established at the knee joint with 0° at full extension and to approximately 90° at full flexion (Symons et al., 2005). The mechanical axis of the dynamometer was aligned with the estimated rotational axis of the knee, and the angle of flexion at rest measured using a goniometer. All the chair seat and participant settings were recorded to ensure repeatability on subsequent visits.

The lower limb weight was determined to account for gravity on all measured torques, in accordance with the manufacturer’s specifications. Maximal isometric knee flexion/extension strengths were tested at 45° of knee flexion. Maximal concentric knee flexion/extension strengths were measured from 10° through to 90° of knee flexion at a velocity of 120 degrees.s⁻¹. Prior to each trial, participants were provided with a full description and demonstration of the action to be performed. Participants performed
three sub-maximal (~50% of self-perceived maximal effort) familiarisation trials of each action prior to the maximal trials. The participants then performed four repetitions of knee flexion and extension at each angular velocity, with a 30 second interval in between the flexion and extension manoeuvres. The participants were given a 60 second rest between different actions and a 3 minute rest between the isometric and concentric contractions. The order of the isometric and concentric trial blocks was randomised between participants. Participants were provided with verbal encouragement and visual feedback to encourage maximum voluntary effort. Peak isometric and concentric torques were recorded using the Biodex Software System 3 Pro, Version 3.30 (Biodex Medical Systems Inc., USA) and the maximal peak torque was noted. While previous studies have used 1-repetition (1-RM) to estimate muscle strength and that no study has used the Biodex isokinetic dynamometer to investigate and report on accurate muscle strength parameters, the current study used the Biodex as an accurate and definitive tool in estimating muscle strength of the leg.

4.4.2 Secondary outcomes

a) Body mass

At each assessment visit, all participants were weighed without shoes and wearing light clothing on a calibrated digital column scale (Seca 762, Germany), accurate to within 0.1 kg. Body height was measured to the nearest 0.1 cm after a maximal inhalation using a standard wall-mounted stadiometer. These two parameters were measured twice and the average of each was used as the reported value.
b) Quality of life

Health-related Quality of Life (QoL) was assessed for all participants using the Medical Outcomes Study Short Form-36, Version 2 (SF-36.v2) (Appendix 9.4) (Quality Metric Inc., Lincoln, USA). SF-36.v2 is a validated self-administered, self-reported questionnaire consisting of 36 questions that evaluate the following eight health domains: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health (Costanzo et al., 2007; Gandek et al., 1998; Montazeri, 2008; Perry et al., 2007; Ware et al., 1998). Criterion validity and reliability studies of the SF-36 showed that the results of the analysis of the seven dimensions of the SF-36 evaluating functioning and well-being were strongly associated with patients reports of overall general health (Jenkinson, Wright, & Coulter, 1994). The 36 questions refer to different aspects of health and quality of life, and 2-10 of these questions were combined together to form the eight domains (Gandek et al., 1998; Ware et al., 1998).

We chose to employ the widely used SF-36 questionnaire despite the availability of breast cancer-specific QoL questionnaires as several members of the research team (including research supervisors) were familiar with its use, and also because a number of studies investigating QoL in this clinical population had used this more general QoL instrument (Ahmed, Prizment, Lazovich, Schmitz, & Folsom, 2008; Costanzo et al., 2007; McKenzie & Kakla, 2003; Perry et al., 2007; Segal et al., 2001). The SF-36 is a validated questionnaire designed to study health status in clinical practice and research (Apolone & Mosconi, 1998; Gandek et al., 1998; Keller et al., 1998; Ware et al., 1998;
Chapter 4

Methodology

Ware & Sherbourne, 1992), and is the most frequently administered questionnaire to
long-survivor cancer patients (Apolone, Filiberti, Cifani, Ruggiata, & Mosconi, 1998).
Furthermore, the SF-36 has been demonstrated to have convergent validity with the
European Organisation for Research and Treatment of Cancer Core Quality of Life
Questionnaire C30 (EORTC QLQ-C30), a questionnaire designed specifically for
cancer patients, confirming its validity for use with breast cancer populations (Apolone
et al., 1998).

The SF-36 questionnaire was administered to all participants during visits to the
laboratory for their assessments. The responses to the questions were recorded on an
SF-36 scoring tool (Quality Metric, Health Outcomes Solutions, USA) that calculated
the values in each domain for every participant. The responses of each question were
assigned a numerical value (0-100) and these were averaged to obtain a score on a
standardized 0 to 100 scale for each domain, where a higher score indicated a more
favourable health status (Gandek et al., 1998; Ware et al., 1998). A participant’s scores
for the eight domains were then exported in an Excel format for further analysis.

c) Fatigue

Fatigue was assessed using the Multi-dimensional Fatigue Inventory (MFI-20)
(Appendix 9.5), which is considered to be the gold standard tool for assessing cancer-
related fatigue (Hjollund, Anderson, & Bech, 2007; Horneber, Fischer, Dimeo, Ruffer,
& Weis, 2012; Lewko, Bidgood, & Garrod, 2009; Smets, Garssen, Bonke, & De Haes,
1995; Smets, Garssen, Cull, & de Haes, 1996). The MFI-20 (when compared to the
Rhoten Fatigue Scale) had high Cronbach alphas for the five sub-classes (0.74 to 0.84), indicating a high internal consistency and high correlations ($r = 0.59$) (Schneider, 1998). The MFI-20 consists of twenty items relating to five different dimensions of fatigue (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue). The responses to each item were scored on a five-point scale (ranging from 1 to 5) and summed within fatigue modes, such that a total of 4 indicated no fatigue and a total of 20 indicated maximal fatigue (Smets et al., 1995; Smets et al., 1996).

The MFI-20 questionnaire was administered to all participants during their visits for assessment. The responses to the items in the questionnaire were recorded on an Excel spreadsheet, and a scoring tool was used to collate the items into the five different dimensions.

4.5 Exercise intervention

Individuals assigned to the BCE and HCE groups were prescribed an exercise training program consisting of low-to-moderate intensity resistance exercise performed three times per week for a 12-week period. The individualised resistance exercise program was based on a participant’s age, anthropometric characteristics, exercise history, 1-RM efforts for each exercise and self-reported fitness level. Each program prescription also took account of any relevant medical history, e.g., musculoskeletal constraints, hypertension, and lymphoedema in those with breast cancer. All breast cancer participants commenced the exercise program (or non-exercise control period) within two to three weeks of completion of their chemotherapy and/or radiation treatments.
Patients scheduled for radiation treatment commenced the exercise intervention after the completion of their radiation treatment. Healthy participants commenced exercise training within one week of their pre-intervention assessment.

Participants were prescribed three exercise sessions per week, with one supervised group session (typically comprising 5-20 participants from both groups) either at the Gold Coast campus or the Southbank (Brisbane) campus of Griffith University. The other two sessions were self-directed and home-based and scheduled on alternate days. The individualised resistance exercise program was based on a whole-body approach, modified from other published reports of resistance training in breast cancer patients (Courneya, Mackey, & McKenzie, 2002; De Backer et al., 2008). Each exercise session lasted 60 minutes, including 10 minutes of warm-up and whole-body stretching, 40 minutes of resistance-based exercises, and a 10 minute cool-down period.

The resistance training program consisted of the following dumbbell-based exercises (primary agonist muscles for each exercise shown in parenthesis):

1. Lunges (quadriceps femoris, glutei and hamstrings);

2. Squats (quadriceps, hamstrings, glutei, gastrocnemii and soleus);

3. Dead lifts (latissimus dorsi, erector spinae and hamstrings);

4. Biceps curls (biceps brachii and brachialis);

5. Triceps kickbacks (triceps brachii, deltoids and trapezius);
(6) Lateral bends (internal/external obliques, rectus abdominis and gluteus medius);

(7) Dumbbell rows (latissimus dorsi, trapezius, deltoids and triceps brachii).

The weekly supervised sessions were scheduled depending on the availability of the participants, and all sessions were supervised by one of the three qualified fitness trainers (i.e., Certificate III & IV in Fitness). For each type of resistance exercise, the correct procedure was demonstrated by the trainers during the initial session and subsequently monitored throughout the remainder of the program. Illustrated training guidelines were also provided in the form of both an exercise instruction sheet and a demonstration DVD, developed specifically for this study. The participants were provided with parking access and compensated for their travel to the campuses for each exercise and assessment session.

The dumbbell sets were comprised of 5 pairs of dumbbells, weights ranging from 1 to 5 kg per dumbbell and were provided to the participants at the pre-intervention assessment session. During Week 1 of the intervention, participants performed two sets of 8 – 10 repetitions of each exercise using a weight that enabled completion of the two sets with moderate difficulty. From Week 2 onwards, participants performed three sets of 8 – 15 repetitions of each exercise, with progression of dumbbell weight once 3 sets of 15 repetitions could be successfully completed for a given exercise.
Each BCE and HCE participant was required to maintain a training compliance diary detailing: 1) the number of sessions completed, 2) the exercises, dumbbell weights, numbers of sets and repetitions completed at each session, 3) any adverse effects (such as any exercise-related discomfort or undue exhaustion), and 4) any other issues that influenced their ability to complete the prescribed exercise sessions. During the supervised sessions, exercise trainers also requested participants to report any adverse events and/or issues that affected their ability to exercise. This included any problems associated with the exercise training (e.g., soreness although not delayed-onset muscle soreness), any changes in clinical management (e.g., prescription of symptom medication) or any minor illness (e.g., a cold). Compliance with the exercise program was encouraged through flexible scheduling of facility-based exercise sessions and follow-up phone calls for unexpected missed sessions. Compliance was further facilitated by the social interactions that developed within the group sessions.

Recruitment, and execution of the exercise intervention program for the healthy control group were timetabled to commence once the recruitment of the breast cancer survivors had been completed within the study timeframe to ensure that age-matched healthy individuals were studied at the same time as their breast cancer counterparts.

### 4.6 Control activities

Breast cancer survivors in the non-exercise group were asked to maintain their regular lifestyle and not to engage in any vigorous or intense exercises over a 12 week period corresponding to the exercise intervention. These participants were contacted once
weekly via telephone by the student researcher and asked about their well-being and whether there were any significant health-related issues (i.e. that might impact negatively on outcome measures). As with the exercise-intervention cancer group, this group received usual healthcare from their hospitals and clinics and attended the pre- and post-intervention assessment sessions at which outcomes measures were completed. Following this period, they were offered access to the same 12 week exercise training program undertaken by the other group of cancer survivors.

4.6 Data and statistical analysis

Results were included and considered for statistical analysis only from participants if they were complete for the pre- and post-chemotherapy or intervention stages. Missing data by any attrition either at the pre- or post-chemotherapy stages were not generated using any statistical models. All results were expressed as group means ± SE (or as SD where described), categorised into breast cancer exercise, breast cancer non-exercise and healthy control groups (between-group factor), and stratified into: 1) pre- and post-chemotherapy stages and 2) pre- and post-intervention stages (within-group factor). The effects of chemotherapy (pre- vs post-) on outcome measures within the breast cancer group over time were assessed using paired t-tests, while the comparisons between the breast cancer and healthy control groups were assessed using one-way ANOVA. The effects of intervention (pre- vs post) on outcomes for the exercising breast cancer participants were separately compared to the control non-exercising
cancer and the control healthy group. These comparisons were made using 2-way repeated-measures ANOVA. All statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) with statistical significance set at an alpha level of $p < 0.05$.

To further describe the effect of chemotherapy or intervention on outcome measures, the changes (between pre- and post-chemotherapy or intervention) are presented together with the effect size ($d$)$^1$, comparing (1) the breast cancer group (pre- and post-chemotherapy stages taken separately) with the healthy control group, and (2) the changes in outcome measures within the breast cancer group from pre- to post-chemotherapy stages. Effect sizes are positive when (a) the values in the breast cancer group (either at the pre- or post-chemotherapy stage) are greater than the values in the healthy control group, or (b) the post-chemotherapy values are greater than the pre-chemotherapy values within the breast cancer group. The values of effect size are categorised as follows: Negligible: $d = < 0.20$ (not reported in the Results section); Minimal: $d = 0.20 - 0.49$; Moderate: $d = 0.50 - 0.79$; Large: $d = > 0.80$.

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$^1$ Effect size ($d$) is calculated as follows:

1. Mean (pre- or post-chemotherapy (separately) value for BC) $-$ Mean (value for HC)/ Pooled Standard Deviations (for both groups)
2. Mean (post-chemotherapy value for BC) $-$ Mean (pre-chemotherapy value for BC)/ Pooled Standard Deviations (for both groups)
CHAPTER 5: Effects of anthracycline/taxane adjuvant chemotherapy treatment on body composition, muscle strength, quality of life and fatigue in women treated for breast cancer
5.1 Aims

5.1.1 To compare body composition, knee muscle strength, quality of life and fatigue in women diagnosed with breast cancer with age-matched healthy women (1) prior to the breast cancer patients commencing their chemotherapy treatment and (2) one week following the completion of chemotherapy treatment in breast cancer patients.

5.1.2 To examine the effects of anthracycline/taxane adjuvant chemotherapy treatment on body composition, knee muscle strength, quality of life and fatigue in women diagnosed with breast cancer.

5.2 Hypotheses

5.2.1 Alternative hypothesis 1: There will be (1) no difference in body composition, knee muscle strength, quality of life and fatigue between breast cancer patients prior to commencement of chemotherapy treatment, and age-matched healthy women, (2) decreased lean mass, knee muscle strength, quality of life, and increased body fat and fatigue in breast cancer patients treated with anthracycline/taxane adjuvant chemotherapy compared to those observed in age-matched healthy women.

5.2.2 Alternative hypothesis 2: There will be decreased lean mass, knee muscle strength, quality of life, and increased body fat and fatigue in women who have
undergone anthracycline/taxane adjuvant chemotherapy to treat breast cancer compared with the values observed at pre-chemotherapy stage.

5.3 Materials and methods

5.3.1 Participant recruitment and ethics
Details regarding the recruitment of breast cancer and age-matched healthy participants, and ethical approvals are described in Chapter 4, Sections 4.1 - 4.2. All participants provided their written informed consent prior to participation.

5.3.2 Sample size calculations
This PhD study was powered to detect a difference in lean mass of the breast cancer participants from pre- to post-exercise stages (based on a resistance exercise program discussed in Chapter 6). A priori power analysis using G*Power 3.1 (University of Kiel, Germany) estimated 27 participants per group were required to detect an effect size of 0.5 (in this case considered to be a moderate effect size and considered to be clinically relevant) in the change in lean mass (a representative for all outcome measures) from pre- to post intervention with 80% power (based on exercise intervention studies previously conducted in breast cancer populations) (Courneya, Segal, Mackey, et al., 2007; Herrero et al., 2006; Kilbreath et al., 2006; Milne et al., 2008). In any case should the study have limited power by insufficient sample size, a moderate effect size of 0.5 will be used to define any change to be clinically relevant either (1) within a group (breast cancer OR healthy control) from pre- to post
intervention or (2) between the breast cancer and healthy control groups at post intervention stage.

Lean mass was chosen as the primary measure on which to perform the sample size calculations, based on an expectation that effective resistance training would lead to an increase in this variable, and that this could lead to changes in the other physical and psycho-social outcomes evaluated in this study. An additional consideration was that recruitment of large numbers of participants (as might be needed to power the study for quality of life measures) was not feasible in the context of this PhD project.

5.4 Experimental protocol

Participants in the breast cancer group completed two assessment sessions: (1) one week before the commencement of the anthracycline/taxane adjuvant chemotherapy treatment, and (2) one week after the end of a 4-6 month period of chemotherapy treatment, while healthy controls completed a single session only. For the healthy group, the single assessment data are used twice in comparison with the breast cancer group at their two (pre- and post-chemotherapy) assessment stages (this approach is repeated for all variables assessed). Flow of participants through the study is depicted in Figure 11.
Figure 11: Flow of participants through chemotherapy treatment in the study

5.5 Outcome measures

Body height and mass were measured upon arrival, followed by whole body lean and fat mass measured using pencil-beam DXA (Norland XR-800, Cooper Surgical, USA). Muscle and fat CSA in the thigh region were then measured using a pQCT Scanner (XCT-3000 scanner, Stratec Inc., Pforzheim, Germany). Isometric knee extension/flexion strengths were then measured using a Biodex isokinetic
dynamometer (Biodex System 3, Biodex Medical, Shirley, NY, USA). Finally, health-related quality of life and perceived fatigability were assessed using the SF-36 (Demark-Wahnefried et al., 2008b; Ware & Sherbourne, 1992) and MFI-20 questionnaires (Smets et al., 1995). Additional details regarding these measurements are fully described in Sections 4.4.1 and 4.4.2.
5.6 Results

5.6.1 Body mass and body mass index (BMI)

Body mass and body mass index (BMI) for the breast cancer (BC; \( n = 19 \), age = 49.8 ± 7.9 years, post-menopausal = 16, height = 1.65 ± 0.06m) were 76.6 ± 15.7kg and 28.4 ± 5.8kg/m² respectively at the pre-chemotherapy stage. The body mass and body mass index for the breast cancer group increased to 78.7 ± 15.8kg and 29.1 ± 5.8kg/m² respectively following chemotherapy treatment. In comparison to the breast cancer group at the post chemotherapy stage, the healthy control (HC; \( n = 27 \), age = 46.9 ± 10.0 years, post-menopausal = 14, height = 1.64 ± 0.08m) were 71.8 ± 14.7kg and 26.5 ± 4.1kg/m² respectively.

The breast cancer group (at the pre-chemotherapy stage) was not different from the healthy control for either body mass (\( p = 0.343, d = 0.28 \)) or for BMI (\( p = 0.254, d = 0.39 \)). Following chemotherapy, the breast cancer group exhibited an increase in both body mass (\( p < 0.001, d = 0.32, 2.70\% \) change) and BMI (\( p < 0.001, 2.22\% \) change). The breast cancer group (at the post-chemotherapy stage) was not different from the healthy control group for either body mass (\( p = 0.137, d = 0.45 \)) or for BMI (\( p = 0.086, d = 0.51 \)). Although the mean body mass and BMI were somewhat higher in the breast cancer group (at both pre- and post-chemotherapy stages) compared to the healthy control group, these differences did not reach statistical significance.
5.6.2 **Whole body composition**

Whole body lean and fat mass of the breast cancer (BC; \( n = 19 \)) (pre- and post-chemotherapy) and healthy control (HC; \( n = 27 \)) groups are presented in Figure 12.

The breast cancer group (at the pre-chemotherapy stage) was not different from the healthy control for either whole body lean mass \((p = 0.531)\) or for whole body fat mass \((p = 0.139, d = 0.49)\). After completion of chemotherapy treatment, there was no change in the breast cancer group for both whole body lean mass \((p = 0.879, 0.11\% \text{ change})\) and whole body fat mass \((p = 0.181, 2.22\% \text{ change})\). At the post-chemotherapy stage, there was no statistically significant difference between the breast cancer and healthy control groups for either whole body lean mass \((p = 0.509, d = 0.20)\) or for whole body fat mass which almost reached statistical significance \((p = 0.059, d = 0.56)\).
Figure 12: Pre- and post-chemotherapy data for breast cancer patients, compared with healthy control

Values are in mean ± SD (SE). The breast cancer group at the post-chemotherapy stage were compared to the healthy control group.
5.6.3 Thigh composition

Cross-sectional area (CSA) of muscle and fat, and muscle density in the thigh region (derived from a 2.2mm slice scanned at 33% of thigh length from distal femur) for the breast cancer (BC; n = 19) (pre- and post-chemotherapy) and healthy control (HC; n = 27) groups are presented in Figure 12.

Prior to the commencement of the chemotherapy treatment, the breast cancer group was not different from the healthy control for muscle cross-sectional area (CSA) (p = 0.055, d = -0.58), fat CSA (p = 0.166, d = 0.49) and for muscle density (p = 0.166, d = -0.31). After completion of chemotherapy treatment, there was a significant increase in muscle CSA (p = 0.018, d = -0.26, 5.61% change); however, there was no change for fat CSA (p = 0.550, 1.55% change) or for muscle density (p = 0.681, -0.23% change).

At the post-chemotherapy stage, there was a significant difference between the breast cancer and healthy control groups for fat CSA (p = 0.042, d = 0.55) but there was no difference for either muscle CSA (p = 0.261, d = -0.34) or for muscle density (p = 0.069, d = -0.41).
5.6.4 **Muscle strength**

Peak isometric and concentric knee extension and flexion strengths of the breast cancer participants (BC; \(n = 19\)) (pre- and post-chemotherapy) and for healthy control (HC; \(n = 27\)) group are presented in Figure 12.

**a) Peak isometric strength**

At the pre-chemotherapy stage, there were no differences between breast cancer and healthy control groups for peak isometric knee extension strength \((p = 0.699, d = -0.22)\) and isometric flexion strength \((p = 0.978)\). Following chemotherapy, the breast cancer group showed decreases in peak isometric knee extension strength \((p < 0.001, d = 0.46, -9.82\% \text{ change})\) and isometric flexion strength \((p < 0.001, d = 0.72, -17.30\% \text{ change})\).

At the post-chemotherapy stage, there were significant differences between the breast cancer and the healthy control group for isometric extension strength \((p = 0.032, d = -0.61)\) and for isometric flexion strength \((p = 0.014, d = -0.77)\).

**b) Peak concentric strength**

Prior to the commencement of chemotherapy treatment, there was no difference between breast cancer and healthy control groups for peak concentric knee extension strength \((p = 0.073, d = -0.62)\) and concentric flexion strength \((p = 0.416, d = -0.39)\).

Following chemotherapy, the breast cancer group showed decreases in peak concentric knee extension strength \((p < 0.001, d = -0.87, -23.71\% \text{ change})\) and concentric flexion strength \((p < 0.001, d = -0.81, -26.17\% \text{ change})\). After completion of chemotherapy
treatment, there were statistically significant differences between the breast cancer and the healthy control group for both concentric extension strength ($p < 0.001, d = -1.31$) and for concentric flexion strength ($p < 0.001, d = -1.05$).

### 5.6.5 Quality of life

The mean scores of the responses reported on the eight scales of health-related quality of life (QoL) by breast cancer (BC; $n = 19$) (pre- and post-chemotherapy) and healthy control (HC; $n = 27$) groups are presented in Figure 12. (PF = Physical functioning, RP = Role limiting-physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role limiting-emotional and MH = Mental health). A higher score is associated with an improved state of health (see Methods).

At the pre-chemotherapy stage, overall there were significant differences between the breast cancer and healthy control groups for almost all of the QoL scales, viz, PF ($p = 0.001, d = -1.06$), RP ($p < 0.001, d = -1.67$), BP ($p < 0.001, d = -0.97$), GH ($p = 0.011, d = -0.79$), VT ($p = 0.035, d = -0.58$), SF ($p < 0.001, d = -0.99$), RE ($p = 0.015, d = -0.71$); only MH was not significantly different ($p = 0.508$). Following chemotherapy, the breast cancer group showed no changes in any of the QoL scales (ranging between $p = 0.104, d = -0.44$, -19.07% change for VT to $p = 0.921$, -1.04% change for BP), except for PF ($p = 0.048, d = -0.38$, -12.41% change) which decreased after chemotherapy treatment. Breast cancer patients, after completion of their chemotherapy treatment, reported lower scores for almost all of the QoL scales, viz, PF ($p < 0.001, d = -1.32$), RP ($p < 0.001, d = -1.53$), BP ($p < 0.001, d = -0.89$), GH (p
< 0.001, \( d = -1.05 \)), VT (\( p < 0.001, \ d = -0.96 \)), SF (\( p = 0.001, \ d = -0.89 \)), RE (\( p = 0.002, \ d = -0.91 \)); only MH was not significantly different (\( p = 0.783 \)).

5.6.6 Fatigue

Mean scores on ratings of perceived fatigue for breast cancer (BC; \( n = 19 \)) and healthy control (HC; \( n = 27 \)) groups (pre- and post-chemotherapy) are presented in Figure 12. (GF = General fatigue, PFat = Physical fatigue, RA = Reduced activity, RM = Reduced motivation, MF = Mental fatigue). A higher score indicates a greater level of fatigue (see Methods).

Prior to the commencement of the chemotherapy treatment, overall there were no differences between the BC and HC groups for any of the scales of perceived fatigue (ranging between \( p = 0.384, \ d = -0.36 \) for MF to \( p = 0.987 \) for RA), except for GF which had higher scores for HC group compared to the BC group (\( p = 0.002, \ d = -0.87 \)). For the breast cancer group, there were no changes, from pre- to the post-chemotherapy stage, in any of the scales (ranging between \( p = 0.059, \ d = 0.36 \) for GF to \( p = 0.852 \) for RA), except for RM which had higher scores at the pre-chemotherapy stage compared to the post-chemotherapy stage (\( p = 0.035, \ d = -0.51 \)). The breast cancer patients, at the post-chemotherapy stage, were no different with the healthy control group for any of the scales of perceived fatigue (ranging between \( p = 0.054, \ d = -0.59 \) for GF to \( p = 0.908 \) for RA).
5.7 Discussion

In the present study, we examined the effects of anthracycline/taxane adjuvant chemotherapy treatment in breast cancer survivors on body composition, skeletal muscle morphology, muscle strength, quality of life and perceived fatigue. By measuring key morphometric, physiological and subjective variables following standard clinical chemotherapy treatment, and comparing these with values recorded just before chemotherapy, we were looking to discern any indirect evidence of skeletal muscle damage associated with the administration of these cytotoxic drugs. Furthermore, by comparing these data (both before and after chemotherapy) with measures from age-matched healthy women, we sought to define the extent to which (a) the diagnosis of breast cancer and subsequent surgery and (b) adjuvant chemotherapy per se was related to breast cancer morbidity.

5.7.1 Whole body composition

Our findings indicated that women diagnosed and surgically treated for breast cancer, but yet to commence chemotherapy treatment, were not different from their healthy counterparts with respect to whole body composition. On average the breast cancer group tended to be 7% heavier, with a minimal effect size (BMI also 7% greater), resulting from a 20% greater fat mass with a moderate effect size, and a 3% greater lean mass than the healthy control group. While none of these differences were statistically significant, taken together they may be indicative of reduced physical activity/poor dietary habits associated with diagnosis/surgery. Alternatively, these
differences in body composition between the groups may reflect the fact that lack of physical activity and obesity are both predisposing factors for the development of breast cancer.

In investigating the effect of chemotherapy on body composition, the breast cancer and healthy control groups in the present study were matched only for age. Two other studies that matched treatment and control groups only for age demonstrated, as we have, that the patient groups were heavier and had a higher BMI, with a higher proportion of body fat percentage at baseline as compared to the healthy group (Demark-Wahnefried et al., 2001; Ingram & Brown, 2004).

The observations of significant increases in body mass (2.7%), BMI (2.2%) and increase in fat mass (2.2%, although insignificant), with minimal effect size for body mass, in the breast cancer group following chemotherapy treatment support the hypothesis of the current study. By contrast, there was only a negligible increase (0.2%) in lean mass. The increases in body mass, fat mass and BMI, without any corresponding increase in lean mass are an indication of “sarcopenic obesity”, which refers to weight gain without any significant gains in lean mass (Demark-Wahnefried et al., 2001).

When compared to the healthy group, the breast cancer participants following chemotherapy treatment had a tendency for non-significantly greater body mass (9.6%) and BMI (9.7%), with minimal to moderate effect sizes. Furthermore, following chemotherapy treatment, the breast cancer group tended to have a greater whole body
lean (3.4%) and fat (22.3%) mass compared to the healthy control group, with a moderate effect size for fat mass. While none of these differences were statistically significant, taken together, again they may be indicative of reduced physical activity/poor dietary habits associated with chemotherapy treatment in breast cancer patients. The results of the current study reflect the findings of previous studies of chemotherapy-related trends in weight gain, secondary to increases in fat mass, with no notable increases in lean mass (Campbell et al., 2007; Demark-Wahnefried et al., 2001; Freedman et al., 2004; Ingram & Brown, 2004). This pattern of change in body composition is consistent with a myotoxic effect of chemotherapy treatment on lean muscle tissue. Such an effect of myocyte damage in skeletal muscle fibres has been widely reported (Doroshow et al., 1985; McLoon, Ekern, & Wirtschafter, 1992; Prado et al., 2009; van Norren et al., 2009).

It seems probable that the effects of chemotherapy-induced myotoxicity probably accounts for the associated debilitating increases in fatigue and lethargy noted in these populations. This in turn would likely promote physical inactivity leading to increased accumulation of fat mass over the course of the treatment. The term “sarcopenic obesity” is being increasingly used to describe patterns of body composition changes evident in clinical populations undergoing chemotherapy treatment. These detrimental side effects of chemotherapy are more fully discussed in the literature review chapter of this thesis.
5.7.2 Thigh composition

Our measures of cross-sectional area (CSA) of muscle and fat, together with estimates of muscle density in the thigh, provide us with a more comprehensive analysis of the effects of chemotherapy than the assessment of whole body composition alone. By examining the distribution of muscle and fat in the lower limbs, we aimed for a more specific assessment of the potential myotoxic effects of chemotherapy in areas more directly related to muscle strength, functionality and physical activity. Even before chemotherapy, the lower muscle CSA (14.0%) and higher fat CSA (19.3%), with minimal effect size for fat CSA and moderate effect size for muscle CSA, in the breast cancer group compared to healthy women is consistent with a degree of deconditioning associated with diagnosis/surgery. However, no concomitant difference in muscle density (0.8% lower in breast cancer), with a minimal effect size, was noted. These results are consistent with our findings that the breast cancer population are more obese than their healthy counterparts, even before chemotherapy, and may already be developing sarcopenic obesity presumably due to relative inactivity. While a number of studies investigating body composition in breast cancer populations at diagnosis and after treatment have entirely focused on whole body measurements (Campbell et al., 2007; Demark-Wahnefried et al., 2001; Freedman et al., 2004; Goodwin et al., 1999; Ingram & Brown, 2004), to the best of our knowledge no previous studies, have reported on the distribution of muscle and fat in specific areas related to mobility.

As expected, the breast cancer patients, following chemotherapy treatment, tended to have lower muscle (8.0% - NS) and higher fat (20.5%) CSA in the thigh region, with
minimal effect size for muscle CSA and moderate effect size for fat CSA, compared to the healthy women, however there were no significant differences in muscle density, with minimal effect size, between both groups after the chemotherapy period. Non-significant (1.6%) increases in fat CSA in the thigh of the breast cancer group after chemotherapy treatment is consistent with the hypothesis of the current study. The increase in muscle CSA, coupled with an increase in fat CSA, and tendency for a decrease in muscle density indicates that muscle size (represented by CSA) increased but not muscle tissue. The slight decrease in muscle density demonstrates the true amount of muscle within the muscle CSA did not increase, thus the increase in muscle CSA could be attributed to increases in muscle fat infiltration as intra- and inter-muscular fat. It has been suggested that increases in intra- and inter-muscular fat in healthy or elderly or clinical populations are associated with concurrent losses in muscle volume, possibly due to disuse atrophy, impaired muscle activation and metabolic changes, and consistent with sarcopenic obesity (Beattie, MacIntyre, Ramadan, Inglis, & Maly, 2012; Lang, Cauley, et al., 2010; Ryan, Buscemi, Forrester, Hafer-Macko, & Ivey, 2011). Increases in intra- and inter-muscular fat, without any significant increases in lean mass, contributes to progressive muscle weakness and increased risk of loss of mobility (Beattie et al., 2012; Delmonico et al., 2009).

While previous studies have reported increases in whole body fat mass in breast cancer patients treated with chemotherapy (discussed above and in the Literature Review chapter), to the best of our knowledge, no study has investigated changes in fat or muscle CSA of specific limbs in breast cancer patients after treatment. The results of
the current study, therefore, reflect the general understanding of the myotoxic effects of chemotherapy treatment leading to increases in fat infiltration causing increases in fat and muscle CSA without any meaningful increases in lean tissue represented by muscle density.

5.7.3 Muscle strength

Our findings that individuals with breast cancer recorded statistically similar values to healthy subjects for indices of isometric and concentric muscle strength before chemotherapy suggests they were maintaining reasonably good muscle function at this point. In fact, all peak strength measures were somewhat lower in the breast cancer group but these were not significant (3.8% for isometric flexion, 5.4% for isometric extension; 13.6% for concentric flexion; 16.4% for concentric extension), with minimal effect sizes for isometric extension and concentric flexion strengths, and a moderate effect size for concentric extension strength. These differences indicating poorer strength in the cancer group are consistent with the observed differences in body and thigh composition and could be accounted for by a presumed decrease in physical activity following diagnosis and surgery as already discussed.

Following chemotherapy treatment, the breast cancer group demonstrated significant decreases in all measures of muscle strength (17.3% for isometric flexion, 9.8% for isometric extension; 26.2% for concentric flexion; 23.7% for concentric extension), with minimal effect size for isometric extension, moderate effect size for isometric flexion and large effect sizes for concentric extension and flexion strengths, indicating
a deleterious effect of this therapy on muscle functional capacity. While it might be expected that such decrements in muscle strength would be a consequence of chemotherapy-related muscle loss, there is no specific evidence in this study that sarcopenia occurred. Indeed, there was a small increase (5.6%) in thigh muscle CSA following chemotherapy. As the increase in CSA appears to be related to an increase in the intramuscular fat, the loss of strength appears to be related to non-muscular mechanisms. It is possible that anthracycline/taxane chemotherapy induces some form of central fatigue. This contention is consistent with our observations at the post chemotherapy assessment stage, that participants commonly reported feelings of exhaustion, muscle pain and general malaise. We have not identified any previous studies in a breast cancer population on the effect of chemotherapy on muscle strength assessed by isokinetic dynamometry. However, patients with gastrointestinal or non-small cell lung cancer, experienced chemotherapy-related decrements in muscle strength and increased fatigue albeit with associated loss of muscle mass (Kilgour et al., 2010).

When comparing breast cancer patients, following chemotherapy treatment, with their healthy counterparts, the breast cancer group demonstrated lower peak isometric knee extension (16.4%) and flexion (26.2%) strengths, in addition to lower peak concentric knee extension (51.7%) and flexion (55.8%) strengths, with moderate effect sizes for isometric extension and flexion strengths, and large effect sizes for concentric extension and flexion strengths. These observations are in agreement with the hypothesis of the current study, and might be explained by the debilitating effects of
chemotherapeutic agents on the decline in muscle strength and functionality. We were not able to identify any studies that have compared muscle strength in breast cancer patients after chemotherapy with that in a healthy population. However, Wilcock et al. (2008) reported that 16 patients with thoracic cancer showed lower muscle strength following chemotherapy compared to healthy volunteers. Similarly, Weber et al. (2009) reported reduced muscle strength coupled with lower muscle CSA in 19 patients with gastro-intestinal cancer following chemotherapy compared to healthy volunteers. Thus, as far as reduced muscle strength is concerned, the results of the current study are in agreement with other studies in different cancer types that have focused on the post-chemotherapy stage. While some of these studies have found evidence of chemotherapy-related muscle loss, this was not the case in the present study. Rather, the pre-chemotherapy muscle strength measures were comparable to those in the healthy group despite a lower muscle CSA whereas, following chemotherapy, the poorer muscle strength was not associated with any measurable change in muscle CSA or density.

A previous in vivo study that examined the effects of doxorubicin on skeletal muscle fibres using muscle biopsy in patients with sarcoma showed slight to moderate neuromuscular changes with significant reductions in the diameter of type I and type II muscle fibres, (Bonifati et al., 2000). However, in examining the cytotoxicity of Adriamycin (doxorubicin) on skeletal muscle in the gastrocnemius of male Wistar rats, Zima, Tesar, Richardson, Mantle, and Preedy (2001) showed very little effect on muscle proteases and suggested that this chemotherapeutic agent was not involved in
the specific pathological effects on skeletal muscle tissue. In summarising these studies, Visovsky (2006) has proposed that chemotherapeutic agents are associated with a number of neuromuscular effects, leading to reduced muscle force-generating capacity, muscle weakness and decline in functional capacity and mobility.

### 5.7.4 Quality of life

In investigating the impact of chemotherapy on quality of life in breast cancer survivors, we chose the widely-used 100-point SF-36 questionnaire for reasons already described in Chapter 4, Section 4.4.2.b). We found that before the onset of chemotherapy treatment, the breast cancer group reported significantly lower quality of life in seven of the eight domains (ranging from 12 to 50 points), with moderate effect sizes for General Health, Vitality and Role limiting-emotional, and large effect sizes for Physical Functioning, Role limiting-physical, Bodily Pain and Social Functioning, compared to healthy women. Using just four domains of same instrument Costanzo et al. (2007) also found impaired quality of life in 113 breast cancer patients before chemotherapy compared to healthy population norms. Not surprisingly, these findings provide convincing evidence that the diagnosis of breast cancer and associated surgery has a negative impacts on an individual’s sense of well-being.

Following chemotherapy treatment, the breast cancer group reported further decrements (5 to 10 points) in three (Physical functioning, General health and Vitality) of the eight quality of life domains although only Physical Functioning (9 points, with a minimal effect size) was statistically significant. Using a different QoL assessment
tool, the Functional Assessment for Cancer Therapy - Breast Cancer (FACT-B), Hwang, Chang & Park, (2013) have reported significantly lower levels of quality of life in breast cancer patients as a result of chemotherapy, compared to those who had not undergone this treatment. Similarly, Reid-Arndt et al. (2010), also using FACT-B, showed that breast cancer patients reported lower quality of life as a result of chemotherapy. On the other hand, using another QoL tool (the European Organisation for Research and Treatment of Cancer QoL Questionnaire: EORTC QLQ-C30), Dehkordi et al. (2009) showed that 68% of patients of 200 patients with various cancers reported a fairly favourable level of quality of life following chemotherapy – suggesting that after completion of chemotherapy treatment was associated with subsequent improvements in well-being. While previous studies have reported mixed outcomes on the effects of chemotherapy treatment on QoL in breast cancer patients, the results of the current study indicate relatively minimal further change after chemotherapy following the loss of quality of life accompanying diagnosis/surgery. To an extent this may reflect the fact that while unpleasant, chemotherapy treatment occurs against a background of low life quality such that further decrements are less likely. Moreover, as noted above (Dehkordi et al.), the completion of this treatment may well be associated with a tendency for well-being to improve following a catastrophic life event. An additional factor in the present studies is that most of our breast cancer participants were about to embark on the exercise-training component of the study and this may have had a positive effect on their outlook.
When compared to healthy women, as expected, breast cancer patients after chemotherapy treatment reported significantly lower scores on seven of the eight QoL domains (ranging from 18 to 43 points), with large effect sizes for all domains except for Mental Health. This finding underscores the fact that even though these women have completed their treatment, their sense of well-being remains well below that of their healthy counterparts. An interesting exception is the scores for the Mental health domain which are minimally different between the breast cancer and healthy groups (4 points lower in cancer) and change minimally following chemotherapy (4 point improvement). This may be indicative of the fact that cohort being studied, despite having undoubtedly experienced distress, did not experience any significant psychopathology. Taken together, these QoL findings suggest that additional interventions following standard medical treatment (e.g. participation in a structured exercise program) are indicated with a view to improving well-being into the future.

5.7.5 Fatigue

In exploring the effect of chemotherapy on perceived fatigue in breast cancer patients, we found minimal difference between breast cancer patients and healthy women in four of the five dimensions of perceived fatigue, with minimal effect sizes for Physical Fatigue, Reduced Motivation and Mental Fatigue. The exception, General Fatigue, with a large effect size, was significantly higher (18%) in the healthy group compared to the breast cancer group. Thus, the results are not consistent with our hypothesis that breast cancer patients would report higher levels of fatigue. While we are not able to account for the similar fatigue levels in these two groups, we note that healthy women
were not actively involved in regular exercise and often commented on their wish to improve their fitness by taking part in this study. Indeed, this may explain why the group difference in General Fatigue arose from the healthy subjects reporting higher levels than the cancer group in this domain. Our findings on fatigue levels are not consistent with a recent study (Goedendorp et al., 2012) in 309 breast cancer patients who reported greater fatigue in this group compared to healthy controls. Further comparisons with the literature are not possible because either other studies have not included a non-cancer control group (Andrykowski et al., 2009; Andrykowski et al., 2005) or they have not reported pre-chemotherapy status (Goldstein et al., 2006; Huang, Zhang, Kang, Song, & Zhao, 2010). The study by (Andrykowski et al., 2009) used the Fatigue Symptom Inventory (FSI) and the study by (Huang et al., 2010) used the Visual Analogue Scale (VAS) to assess levels of cancer-related fatigue following chemotherapy treatment. However these studies had no control group to compare the levels of fatigue with and also assessed fatigue only at the post-treatment stage. The current study used the Multi-dimensional Fatigue Inventory – 20, which is a 20 question validated tool assessing five dimensions of fatigue as reported in the results section. The current study assessed levels of fatigue at the pre-chemotherapy stage and also at the post-chemotherapy stage, in an attempt to directly observe the potential effects of chemotherapy treatment on the five dimensions of fatigue. As reported in the results, chemotherapy treatment in breast cancer contributed to some effect on increasing fatigue levels in three of the five dimensions of fatigue. The current study has showed that fatigue levels in breast cancer patients following chemotherapy treatment were higher than age-matched healthy controls for two of the five
dimensions. This method of assessing levels of fatigue using the Multi-dimensional Fatigue Inventory in breast cancer patients before the start of chemotherapy treatment (or any other treatment) and after the completion of this treatment, and comparing these changes with those observed in a control group can be used to understand the impacts of any particular treatment modality for breast cancer or any other clinical condition.

Following chemotherapy treatment, there were no significant changes in four of the five perceived fatigue dimensions. Reduced Motivation decreased significantly (8%) with a moderate effect size, while General Fatigue increased (7%) with a minimal effect size. While these results do not completely support the hypothesis of this study, reduced motivation may be indicative of the debilitating effects of chemotherapy treatment in breast cancer patients. While showing some evidence of fatigue related to chemotherapy, the responses we noted are less pronounced than those noted by others. (Goedendorp et al., 2012) reported increases in ratings of fatigue in breast cancer patients treated with chemotherapy, and these symptoms did not diminish over a subsequent three-year period. Similarly, (Goldstein et al., 2006) reported chemotherapy-induced fatigue, which was associated with morbidity in a number of the subjects whereas (Jacobsen et al., 2007) observed greater fatigue persisting at six months following treatment. Donovan, Jacobsen, Andrykowski, Winters, Balducci et al., (2004) have additionally reported greater treatment-related fatigue in breast cancer patients receiving chemotherapy compared to radiotherapy.
When compared to healthy women, breast cancer patients after chemotherapy treatment, showed no significant differences in the levels of fatigue in any of the five dimensions of perceived fatigue, with minimal to moderate effect sizes. This finding follows from discussed those above which showed minimal difference in reported fatigue between our breast cancer and health groups and only small changes in fatigue associated with chemotherapy.

5.8 Limitations

We recognise that the current study had a low sample size, and that the study was underpowered to demonstrate any significant changes. We conducted a single assessment for the healthy control group, the data are used twice to facilitate comparisons with the breast cancer group at their two (pre- and post-chemotherapy) assessment stages. The investigators were not blinded to the breast cancer and healthy control groups as the study was not able to employ external research assistants to conduct the assessment procedures due to limited resources and funding. One technical issue of concern was the difficulty in positioning obese participants in the pQCT gantry.
CHAPTER 6: Effects of a resistance exercise program on body composition, muscle strength, quality of life and fatigue in women treated for breast cancer
6.1 Aims and objectives

To examine (1) the effects of a 12-week supervised resistance exercise program, commencing within four weeks following chemotherapy treatment, on body composition, knee muscle strength, quality of life and fatigue in women diagnosed with breast cancer, and (2) to compare any changes in these variables with those observed in both a non-exercising breast cancer group and an age-matched group of healthy women following the same exercise protocol.

6.2 Hypotheses

6.2.1 There will be increased lean mass, knee muscle strength, quality of life, and decreased body fat and fatigue in women who have undergone chemotherapy treatment to treat breast cancer after a resistance exercise program, compared with a non-exercising breast cancer group.

6.2.2 There will be similar increases in lean mass, knee muscle strength, quality of life, and similar decreases in body fat and fatigue in women who have undergone chemotherapy to treat breast cancer after a resistance exercise program, compared with an age-matched healthy control group undertaking the same exercise program.
6.3 Materials and methods

6.3.1 Participant recruitment and ethics

Details regarding the recruitment of breast cancer and control participants, and ethical approvals are described in Chapter 4, Sections 4.1 and 4.2. All participants provided their written informed consent prior to participation.

6.3.2 Sample size calculations

The study was powered to detect a difference in lean mass of the breast cancer participants from pre- to post-exercise stages. A priori power analysis using G*Power 3.1 (University of Kiel, Germany) estimated 27 participants per group were required to detect an effect size of 0.5 (in this case considered to be a moderate effect size and considered to be clinically relevant) in the change in lean mass from pre- to post intervention with 80% power (based on exercise intervention studies previously conducted in breast cancer populations) (Courneya, Segal, Mackey, et al., 2007; Herrero et al., 2006; Kilbreath et al., 2006; Milne et al., 2008). In the event that the study be underpowered power due to insufficient sample size, a moderate effect size of 0.5 will be used to define any change to be clinically relevant either (1) within a group (breast cancer OR healthy control) from pre- to post intervention or (2) between the breast cancer and healthy control groups at post intervention stage.

Lean mass was chosen as the primary measure on which to perform the sample size calculations, based on an expectation that effective resistance training would lead to an
increase in this variable, and that this could lead to changes in the other physical and psycho-social outcomes evaluated in this study. An additional consideration was that recruitment of large numbers of participants (as might be needed to power the study for quality of life measures) was not feasible in the context of this PhD project.

6.3.3 Randomisation of participants

Participants in the breast cancer group were randomly assigned alternately to the exercise or to the non-exercise groups as described in Chapter 4, Section 4.3.2. The age-matched healthy group consisted of an exercise cohort only and did not require randomisation.

6.3.4 Experimental protocol

Participants in all three intervention groups (i.e. breast cancer exercise, breast cancer non-exercise and healthy control exercise) completed two assessment sessions: (1) one week before the 12-week exercise intervention program, and (2) within one week after the completion of the exercise intervention (or non-exercise) program. Flow of participants through the study is depicted in Figure 13.
Figure 13: Flow of participants through the resistance exercise intervention study
6.3.5 Intervention protocol for the exercise and non-exercise groups

The 12-week resistance exercise training program and the 12-week non-exercise intervention are described in Chapter 4, Section 4.5.

6.3.6 Outcome measures

Body height and mass were measured upon arrival, followed by whole body muscle and fat mass measurements using pencil-beam DXA (Norland XR-800, Cooper Surgical, USA). Muscle and fat cross-sectional area, and muscle density of the thigh region were measured using a pQCT Scanner (XCT-3000 scanner, Stratec Inc., Pforzheim, Germany). Isometric knee flexion/extension strengths were measured using a Biodex isokinetic dynamometer (Biodex System 3, Biodex Medical, Shirley, NY, USA). Finally, health-related quality of life and perceived fatigability were assessed using the SF-36 (Demark-Wahnefried et al., 2008b; Ware & Sherbourne, 1992) and MFI-20 (Smets et al., 1995) questionnaires. Additional details regarding these measurements are provided in Sections 4.4.1 and 4.4.2.

6.4 Data and statistical analysis

All results were expressed as group means ± SE (or as SD where described), categorised into breast cancer exercise, breast cancer non-exercise and healthy control groups (between-group factor), and stratified into pre- and post-intervention stages (within-group factor). The effects of the intervention (pre- vs post) on outcomes for the exercising breast cancer participants were separately compared to the control non-
exercising cancer and the control healthy group. These comparisons were made using 2-way repeated-measures ANOVA. All statistical analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA) with statistical significance set at an alpha level of $p < 0.05$.

To further describe the effect of exercise on the outcome measures, the changes in outcomes pre- and post-intervention (i.e. 12-week exercise or non-exercise) are presented together with the effect size ($d$)$^2$, comparing the Breast Cancer Exercise group (BCE) with each of the control groups, i.e. Breast Cancer Non-exercise (BCN) or Healthy Exercise (HE). Effect sizes are positive when the response in the BCE group is greater than the response in either control group (i.e. BCN or HE) and are categorised as follows: Negligible: $d = < 0.20$ (not reported in the Results section); Minimal: $d = 0.20$ - 0.49; Moderate: $d = 0.50$ – 0.79; Large: $d = > 0.80$.

---

$^2$ Effect size ($d$) is calculated as follows:

\[
\text{Mean (post-intervention value ─ pre-intervention value for BCE) ─ Mean (post-intervention value ─ pre-intervention value for BCN or HC)/ Pooled Standard Deviations (of above differences)}
\]
6.5 Results

6.5.1 Recruitment

The targeted sample size was not achieved in either of the breast cancer groups with recruitment numbers obtained as follows: Breast cancer exercise (BCE) group, \( n = 14 \) (51.9\% of desired sample size); Breast cancer non-exercise (BCN), \( n = 13 \) (48.1\%).

The flow of breast cancer participants in the exercise and non-exercise arms of the study are depicted in Figure 14. The target sample size was achieved in the healthy control (HC) group, \( n = 27 \) (100\%), following 32 initial expressions of interest to the recruitment flyer. A number \( (n = 5) \) of potential participants declined to proceed after they had been randomly assigned to the non-exercise group, leaving only eight (29.6\% of the target sample size) in the Breast cancer non-exercise group. The main reasons for the low recruitment numbers in the breast cancer groups were: (1) limited awareness of the study by patients attending the breast cancer clinics, especially at the early stages \( (n = 5) \), (2) lack of interest by patients \( (n = 4) \), (3) unwillingness to commit to a 12-week exercise training program \( (n = 4) \), and (4) relative inaccessibility to the assessment site (Griffith University, Gold Coast) or to the training venue \( (n = 2) \).

These reasons, with regards to participation in clinical studies, have been similarly expressed in other oncological studies (Wanger, Foster, Nguyen, & Jatoi, 2014). The common reasons for the healthy individuals not willing to participate (judged from responses to initial “request for volunteers”) included: (1) unwillingness to commit to a 12-week
exercise training program, (2) too busy and/or other commitments preventing them from full engagement with the study.

Figure 14: Flow of breast cancer participants in the resistance exercise intervention study

6.5.2 Completion of intervention, adherence to the exercise program and possible adverse effects

Completion rates of the intervention for each treatment group were as follows: (1) 50.0% \( (n = 7, \text{ out of 14}) \) for the BCE group; (2) 87.5% \( (n = 7, \text{ out of 8}) \) for the BCN
group; (3) 88.9% ($n = 24$, out of 27) for the HC group. For the two exercise groups, participants “dropped out” at different stages for a variety of reasons (see below). We report findings of the analyses “per protocol”, i.e. using data from participants who completed both pre- and post-intervention assessments.

According to the exercise trainers’ verbal reports and the participants’ daily exercise diaries, all exercising participants completed the 60-minute exercise duration at the levels and intensity set by the trainers. For the BCE participants, 4 out of 7 completed all 3 prescribed exercise sessions per week; for the remaining 3, the total numbers of missed sessions (over the 12 weeks) were 3, 6 and 9. For the HC group, 20 out of 24 completed all training sessions; for the remaining 4, the total numbers of missed sessions (over the 12 weeks) were 3, 5, 6 and 9.

There were no major adverse effects from the exercises that prevented the participants from completing the exercise program. The reasons for non-completion of the exercise program by the breast cancer group included symptoms of breast and upper arm lymphoedema, persistent negative effects of chemotherapy treatment (such as nausea and lethargy), gynaecological complications (such as hysterectomy) in one participant, chronic upper-respiratory tract infections in two participants, pre-existing rheumatoid osteo-arthritis in four participants, inability to travel to the campuses for the assessment/supervised exercise sessions, being too busy or no longer interested in the study.
6.5.3 Body mass and body mass index (BMI)

Body mass and body mass index (BMI) for the breast cancer exercise (BCE; \( n = 7 \)), breast cancer non-exercise (BCN; \( n = 7 \)) and healthy exercise (HC; \( n = 24 \)) groups (pre- and post-intervention) are presented in Figure 15.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Breast Cancer Exercise Group</th>
<th>Breast Cancer Non-exercise Group</th>
<th>Healthy Exercise Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-intervention (n = 7)</td>
<td>Post-intervention (n = 7)</td>
<td>Pre-intervention (n = 7)</td>
</tr>
<tr>
<td>Age (years) mean ± SE</td>
<td>51.9 ± 3.6</td>
<td>-</td>
<td>51.9 ± 3.0</td>
</tr>
<tr>
<td>Body mass (kg) mean ± SE</td>
<td>78.7 ± 5.6</td>
<td>72.7 ± 5.1</td>
<td>86.0 ± 7.0</td>
</tr>
<tr>
<td>BMI (kg/m²) mean ± SE</td>
<td>27.0 ± 1.6</td>
<td>24.9 ± 1.5</td>
<td>31.7 ± 2.8</td>
</tr>
</tbody>
</table>

Figure 15: Participant anthropometric characteristics of the breast cancer exercise, breast cancer non-exercise and healthy control groups

BMI = Body mass index.

a) Breast Cancer Group Comparisons

For the cancer groups (exercise and non-exercise), overall (i.e. pre- and post-intervention), there was no statistically significant difference between BCE and BCN groups for changes in body mass (\( p = 0.395, d = -0.2 \)) or BMI (\( p = 0.145 \)). Both groups lost body mass (\( p < 0.001 \)) and BMI (\( p < 0.001 \)) over the 12-week intervention period. Moreover, there was no significant group/time interaction effect for either body mass
(\(p = 0.777\)) or BMI (\(p = 0.649\)), indicating no statistical difference in the response to the 12-week intervention between the two groups for either measure.

\[ b) \textit{Exercising Group Comparisons} \]

For the exercising groups (breast cancer exercise and healthy exercise), overall (i.e. pre- and post-intervention), there was no difference between BCE and HC groups for changes in body mass (\(p = 0.141, d = -0.4\)) or BMI (\(p = 0.563, d = -0.2\)). Both groups lost body mass (\(p < 0.001\)) and BMI (\(p < 0.001\)) over the 12-week intervention period. Moreover, there was no significant group/time interaction effect for changes in body mass (\(p = 0.354\)) or BMI (\(p = 0.470\)), indicating no difference in the response to the 12-week intervention between the two groups.
6.5.4 Whole body composition

Whole body lean and fat mass for the breast cancer exercise (BCE; \( n = 7 \)), breast cancer non-exercise (BCN; \( n = 7 \)) and healthy control (HC; \( n = 24 \)) groups (pre- and post-intervention) are presented in Figure 16.

![Figure 16: Mean (+/- SE) whole body lean and fat mass for BCE, BCN and HC groups at pre- and post-intervention stages](image)

(○) = BCE (Breast cancer exercise; \( n = 7 \))

(●) = BCN (Breast cancer non-exercise; \( n = 7 \))

(▲) = HC (Healthy control; \( n = 24 \))

a) Breast Cancer Group Comparisons

For the cancer groups (exercise and non-exercise), overall (i.e. pre- and post-intervention), there were no difference between BCE and BCN groups for changes whole body lean mass \((p = 0.730)\) or fat mass \((p = 0.221, d = -0.72)\). For these two
groups taken together, the 12-week intervention period was not associated with any significant changes in either lean mass ($p = 0.073$) or fat mass ($p = 0.883$). Moreover, there was no significant group/time interaction effect for either lean mass ($p = 0.810$) or fat mass ($p = 0.410$), indicating no statistical difference in the response to the 12-week intervention between the two groups.

\textit{b) Exercising Group Comparisons}

For the exercising groups (breast cancer exercise and healthy exercise), overall (i.e. pre- and post-intervention), there was no difference between BCE and HC groups for changes in lean mass ($p = 0.248, d = 0.44$) or fat mass ($p = 0.160, d = 0.62$). For these two groups taken together, the 12-week intervention period was not associated with any significant changes in either lean mass ($p = 0.206$) or fat mass ($p = 0.138$). Moreover, there was no significant group/time interaction effect for either lean mass ($p = 0.119$) or fat mass ($p = 0.797$), indicating no difference in the response to the 12-week intervention between the two groups.

\textbf{6.5.5 Thigh composition}

Cross-sectional area (CSA) of muscle and fat, and muscle density in the thigh region (derived from a 2.2mm slice scanned at 33\% of thigh length from distal femur) for the breast cancer exercise (BCE; $n = 7$), breast cancer non-exercise (BCN; $n = 7$) and healthy control (HC; $n = 24$) groups (pre- and post-intervention) are presented in Figure 17.
a) Breast Cancer Group Comparisons

For the cancer groups, overall there was no statistically significant difference between BCE and BCN for changes in muscle CSA ($p = 0.506, d = 0.30$), fat CSA ($p = 0.074, d = -0.90$) or muscle density ($p = 0.991, d = -0.21$) in the thigh region. For these two groups taken together, the 12-week intervention period was not associated with any significant changes in muscle CSA ($p = 0.109$), fat CSA ($p = 0.981$) or muscle density ($p = 0.064$). Moreover, there was no significant group/time interaction effect in muscle CSA ($p = 0.643$), fat CSA ($p = 0.078$) or muscle density ($p = 0.767$), indicating no difference in the response to the 12-week intervention between the two groups.

b) Exercising Group Comparisons

For the exercising groups, overall there was no statistically significant differences between BCE and HC for muscle CSA ($p = 0.342, d = -0.79$), fat CSA ($p = 0.890, d = -0.25$) or muscle density ($p = 0.068$) in the thigh region. For these two groups taken together, the 12-week intervention period was not associated with any significant changes in either muscle CSA ($p = 0.937$) or fat CSA ($p = 0.072$); however muscle density increased significantly ($p = 0.002$). There was no significant group/time interaction effect in muscle CSA ($p = 0.064$), fat CSA ($p = 0.573$) or muscle density ($p = 0.753$), indicating no difference in the response to the 12-week intervention between the two groups.
Figure 17: Mean (+/- SE) thigh muscle cross-sectional area (CSA) and muscle density for BCE, BCN and HC groups at pre- and post-intervention stages

○ = BCE (Breast cancer exercise; n = 7)

● = BCN (Breast cancer non-exercise; n = 7)

▲ = HC (Healthy control; n = 24)
6.5.6 Muscle strength

Peak isometric and concentric knee extension and flexion strengths (adjusted for body mass) for the breast cancer exercise (BCE; \( n = 7 \)), breast cancer non-exercise (BCN; \( n = 7 \)) and healthy control (HC; \( n = 7 \)) groups (pre- and post-intervention) are presented in Figure 18.

a) Breast Cancer Group Comparisons

i) Peak isometric strength

For the cancer groups, overall the BCE group demonstrated a significantly higher mean peak knee isometric flexion strength compared to the BCN group \( (p = 0.016, d = 1.42) \); however, there was no significant difference between the BCE and BCN groups for mean peak knee isometric extension strength \( (p = 0.218, d = 1.06) \). For these two groups taken together, the 12-week intervention period was associated with significant increases in isometric extension strength \( (p = 0.009) \) and isometric flexion strength \( (p < 0.001) \). Moreover, there was a significant group/time interaction effect for isometric extension strength \( (p = 0.039) \) and isometric flexion strength \( (p = 0.001) \), with the BCE group demonstrating greater increases in strength than the BCN group in response to the 12-week intervention.
Figure 18: Mean (± SE) peak knee extension and contraction moments (adjusted for body mass) for BCE, BCN and HC groups at pre- and post-intervention stages

○ = BCE (Breast cancer exercise; n = 7)

● = BCN (Breast cancer non-exercise; n = 7)

▲ = HC (Healthy control; n = 24)
ii) *Peak concentric strength*

For the cancer groups, overall there was no significant difference between BCE and BCN for either mean peak knee concentric extension strength \( (p = 0.079, \, d = 1.27) \) or peak knee concentric flexion strength \( (p = 0.064, \, d = 1.27) \). For these two groups taken together, the 12-week intervention period was associated with increases in concentric extension strength \( (p = 0.001) \) and concentric flexion strength \( (p < 0.001) \). Moreover, there was a significant group/time interaction effect for concentric extension strength \( (p = 0.009) \) and concentric flexion strength \( (p = 0.019) \), with the BCE group demonstrating greater increases in strength than the BCN group in response to the 12-week intervention.

*b) Exercising Group Comparisons*

i) *Peak Isometric strength*

For the exercising groups, overall there was no significant difference between BCE and HC for either mean peak knee isometric extension \( (p = 0.156, \, d = -0.84) \) or mean peak knee isometric flexion strength \( (p = 0.527, \, d = 0.22) \). For these two groups taken together, the 12-week intervention period was associated with increases in isometric extension strength \( (p < 0.001) \) and isometric flexion strength \( (p < 0.001) \). However, there was a borderline significant group/time interaction effect for the isometric extension strength \( (p = 0.050) \) indicating a marginal difference in response to the 12-week intervention between the two groups. There was no significant group/time interaction effect for the isometric flexion strength \( (p = 0.624) \), indicating no difference in the change in isometric flexion strength.
ii) **Peak concentric strength**

For the exercising groups overall, compared to the BCE group, the HC group showed significantly higher mean peak knee strength for both concentric extension \((p = 0.009, d = 0.53)\) and concentric flexion \((p = 0.002, d = -0.72)\). For these two groups taken together, the 12-week intervention period was associated with increases in both concentric extension \((p < 0.001)\) and concentric flexion strength \((p < 0.001)\). However, there was no significant group/time interaction effect for concentric extension strength \((p = 0.216)\) or for concentric flexion strength \((p = 0.092)\), indicating no difference between the two groups in the change in concentric extension and concentric flexion strengths in the response to the 12-week intervention.

### 6.5.7 Quality of life

The mean scores for the responses reported on the eight scales of health-related quality of life (QoL) by breast cancer exercise (BCE; \(n = 7\)), breast cancer non-exercise (BCN; \(n = 7\)) and healthy control (HC; \(n = 24\)) groups (pre- and post-intervention) are presented in Figure 19. (PF = Physical functioning, RP = Role limiting-physical, BP = Bodily pain, GH = General health, VT = Vitality, SF = Social functioning, RE = Role limiting -emotional and MH = Mental health). A higher score is associated with an improved state of health (See Methods).
a) Breast Cancer Group Comparisons

For the cancer groups, overall there were no significant differences between the BCE and BCN for any of the QoL scales (ranging between \( p = 0.062 \), \( d = 0.79 \) for RP to \( p = 0.735 \), \( d = 0.93 \) for MH). Furthermore, there were moderate effect sizes for the scales: PF (\( d = 0.69 \)), VT (\( d = 0.50 \)) and SF (\( d = 0.54 \)), and minimal effect size for RE (\( d = -0.23 \)). For these two groups taken together, the 12-week intervention period was associated with significant increases in the PF (\( p = 0.001 \)), RP (\( p = 0.003 \)), BP (\( p = 0.013 \)), VT (\( p = 0.001 \)) and SF (\( p = 0.024 \)) scales while there were no significant changes in the remaining scales (all \( p > 0.150 \)). There was no significant group/time interaction effect for any of the QoL scales, ranging between MH (\( p = 0.080 \)) to BP (\( p = 0.870 \)), indicating no differences between the two groups in response to the 12-week intervention.
Figure 19: Mean (+/- SE) scores on quality of life scales reported by BCE, BCN and HC groups at pre- and post-intervention stages

○ = BCE (Breast cancer exercise; n = 7), ● = BCN (Breast cancer non-exercise; n = 7), ▲ = HC (Healthy control; n = 24)
b) Exercising Group Comparisons

For the exercising groups, overall the HC group demonstrated significantly higher scores for PF ($p = 0.010$, $d = 1.68$), RP ($p = 0.001$, $d = 1.51$) and GH ($p = 0.006$, $d = 0.45$) compared to the BCE group. Furthermore, there was a minimal effect size for the RE ($d = 0.39$), a moderate effect size for the scale MH ($d = 0.56$), and large effect sizes for the scales: BP ($d = 1.03$), VT ($d = 1.07$) and SF ($d = 0.96$). There were no significant differences between the groups for the remaining QoL scales (ranging between $p = 0.074$, $d = 0.96$ for SF and $p = 0.919$, $d = 0.56$ for MH). For these two groups taken together, the 12-week intervention period was associated with significant increases in all of the QoL scales (ranging between $p < 0.001$ for RP to $p = 0.035$ for BP), except for GH ($p = 0.057$) and RE ($p = 0.163$). There were significant group/time interaction effects for five of the eight QoL scales: PF ($p < 0.001$), RP ($p < 0.001$), BP ($p = 0.014$), VT ($p = 0.011$) and SF ($p = 0.023$), indicating a greater improvement in these measures in BCE compared to HC following the 12-week exercise intervention. There were no significant group/time interactions for the remaining scales: GH ($p = 0.304$), RE ($p = 0.385$), MH ($p = 0.199$), indicating no difference between the two groups in response to the 12-week intervention.
6.5.8 Fatigue

Mean scores on ratings of perceived fatigue for breast cancer exercise (BCE; \( n = 7 \)), breast cancer non-exercise (BCN; \( n = 7 \)) and healthy control (HC; \( n = 7 \)) groups (pre- and post-intervention) are presented in Figure 20. (GF = General fatigue, PFat = Physical fatigue, RA = Reduced activity, RM = Reduced motivation, MF = Mental fatigue). A higher score indicates a greater level of fatigue (see Methods).

\[ \text{a) Breast Cancer Group Comparisons} \]

For the cancer groups, overall there were no significant differences between the BCE and BCN for any of the scales of perceived fatigue (ranging between \( p = 0.075, d = -0.81 \) for RM to \( p = 0.749, d = 0.20 \) for PFat), except for MF which had significantly higher scores for BCE group compared to the BCN group (\( p = 0.025 \)). Furthermore, there was a moderate effect size for the scale: GF (\( d = -0.69 \)) and large effect size for the scale: RA (\( d = -1.00 \)). For these two groups taken together, the 12-week intervention period was not associated with significant changes in any of the scales of perceived fatigue (ranging between \( p = 0.194 \) for PFat to \( p = 0.746 \) for GF). There were no significant group/time interaction effect for any of the scales of perceived fatigue: GF (\( p = 0.209 \)), PFat (\( p = 0.701 \)), RA (\( p = 0.056 \)), RM (\( p = 0.132 \)) and MF (\( p = 0.932 \)), indicating no difference between the two groups in response to the 12-week intervention.
Figure 20: Mean (+/- SE) scores on ratings of perceived fatigue reported by BCE, BCN and HC groups at pre- and post-intervention stages

(○) = BCE (Breast cancer exercise; n = 7), (●) = BCN (Breast cancer non-exercise; n = 7), (▲) = HC (Healthy control; n = 24)
b) *Exercising Group Comparisons*

For the exercising groups, overall there were no significant differences between the BCE and HC groups for any of the perceived fatigue scales (ranging between $p = 0.057$ for MF to $p = 0.952$, $d = -0.62$ for PFat). Furthermore, there were minimal effect sizes for the scales: GF ($d = -0.48$), RA ($d = -0.22$) and RM ($d = -0.46$). For these two groups taken together, the 12-week intervention period was not associated with significant changes in any of the perceived fatigue scales (ranging between $p = 0.101$ for RA to $p = 0.970$ for GF). There were no significant group/time interaction effect for any of the perceived fatigue scales: GF ($p = 0.265$), PFat ($p = 0.153$), RA ($p = 0.602$), RM ($p = 0.288$) and MF ($p = 0.690$), indicating no difference between the two groups in response to the 12-week intervention.
6.6 Discussion

The purpose of the present study was to observe the effects of an individualised 12-week progressive resistance training program on changes in body composition, muscle strength, self-rated health-related quality of life and perceived fatigue in breast cancer patients previously treated with anthracycline/taxane adjuvant chemotherapy. To better assess the efficacy of such exercise, the responses in these patients have been compared to those occurring in two separate control groups: (1) breast cancer patients receiving usual care (i.e. no prescribed exercise intervention), (2) age-matched healthy women subjected to the same individualised resistance exercise intervention.

6.6.1 Whole body composition

A mean reduction in body mass of 6kg in the exercising cancer group, while at first sight encouraging, was not different from a 5.5kg reduction in the non-exercising group, and therefore with this minimal effect size, cannot be regarded as a beneficial effect of the resistance training program. Similarly, both groups experienced equivalent reductions in BMI. In terms of DXA estimates of lean mass, the changes over the intervention period were again not different between the two cancer groups, with both cohorts showing small decreases in this measure (0.9kg and 1.3kg respectively). However, the reduction in fat mass in the exercising group (1.2kg) does contrast with the increase (0.9kg) seen in the control group, accounting for the moderate effect size.
The healthy group and the exercising cancer group again showed similar decreases in body mass and BMI over the course of the resistance exercise program. However, the somewhat greater loss of fat mass in the healthy individuals (1.8kg) did achieve a moderate effect size. There have been a number of studies on the impact of resistance exercise on whole body composition of the breast cancer population treated with CMF (cyclophosphamide + methotrexate + 5-fluorouracil), but none has focused on patients treated specifically with anthracycline/taxane adjuvant chemotherapy. Courneya, Segal, Mackey, et al. (2007), reported a 1.0kg increase in lean mass in 73 breast cancer patients undergoing a 17-week resistance exercise program during treatment, which was significantly greater than the 0.5kg increase by 68 breast cancer patients undertaking an aerobic exercise program. Similarly, Schmitz et al. (2005) reported significant improvements in lean mass (0.9kg) in 40 breast cancer patients undergoing a 13-week resistance exercise program immediately after completion of their treatment, compared to no changes in a cancer control group. On the other hand, Battaglini et al. (2007b) reported no changes in lean and fat mass in 10 breast cancer patients undergoing either 21 weeks of a mixed exercise (aerobic plus resistance) program during treatment or a non-exercising control group. Similarly, Demark-Wahnefried et al. (2008b) did not demonstrate any significant changes in lean mass in 29 breast cancer patients after a 6-month mixed exercise program during chemotherapy or in the same size cancer control group. Herrero et al. (2006) reported increases of 0.7kg increase in lean mass in 8 breast cancer patients after an 8-week mixed (aerobic plus resistance) exercise program following treatment which was significantly greater than 0.3 kg decrease in their control group (n = 8).
In light of the often reported increases in lean mass seen with resistance exercise in healthy populations (Hanson et al., 2009; Visovsky, 2006), it was anticipated that this positive effect would be seen in the breast cancer population in the present study. However, the fact that we did not see this in our participants is perhaps a reflection of our low statistical power which was similar to other studies in this population that have reported modest or no effects as discussed above. It is also possible that, in light of the fact that our healthy control group failed to show any changes in lean mass, our 12 week home-centred training program was not at an intensity/duration sufficient to increase muscle mass.

The non-significant reduction in lean mass in our breast cancer group, not noted in other studies, likely to be related the small sample size, but also the notable (7.5%) reduction in total body mass. The fact that our control cancer group (unlike other similar control groups) also lost a minimal lean mass related to myotoxic effects of anthracycline/taxane chemotherapy used in this but not in other breast cancer/exercise intervention studies. The fact that we also saw the loss of lean mass in the same subjects over the pre- to post-chemotherapy period (see Chapter 4) is consistent with this possibility. If this is the case, there is no indication from our data that resistance training arrested this process.

The effect of resistance training on fat mass in the breast cancer participants, on the other hand, differs from the changes in their non-exercising counterparts. In the latter group a combination of reduced lean mass and increased fat mass appears to continue
a pattern of “sarcopenic obesity” observed over the chemotherapy phase (Chapter 4) whereas following resistance training the loss of lean mass is accompanied by a loss of fat mass.

In further considering the body mass results, the apparent positive impact of resistance training in the cancer group was counterbalanced by an equally beneficial but perplexing weight loss in our control group. These results presented a clear reversal of the weight gain seen over the period of chemotherapy in these same participants, and are not consistent with the typical continuing weight gain seen over time in similar populations (Campbell et al., 2007; Demark-Wahnefried et al., 2001; Freedman et al., 2004; Goodwin et al., 1999; Ingram & Brown, 2004; Wang, Cai, Wang, Zhang, & Zhang, 2014). The most likely explanation for this unexpected finding in our control participants is that it represents a placebo effect secondary to the attention they received, their positive reaction to the prospect of entering the training program at a later stage, or the potential that they in fact began an exercise regime independent of the study activities and did not disclose this to the investigators.

6.6.2 Muscle strength

The most notable findings from the present study were that cancer patients undergoing 12 weeks of resistance exercise, following chemotherapy, demonstrated greater increases in all measures of muscle strength compared with those seen in the non-exercising cancer group. That is, small sample size, notwithstanding, increases in isometric and concentric knee extension and flexion strengths in the exercising group...
were each significantly greater than those seen in the non-exercising group. Moreover, these benefits attained by the cancer survivors were comparable to improvements achieved by the healthy sedentary women of a similar age.

The results of the present study are consistent with the recently reported findings of Winters-Stone et al. (2012), who showed that in 52 post-treatment breast cancer survivors given a one-year resistance and impact training program (compared to a stretching exercise cancer control group), there were improvements in muscle strength (1-RM bench press and leg press) and associated functional tests (e.g. timed stance test and handgrip strength), they did not measure muscle CSA or lean mass for comparisons with our variables. Similarly, De Backer et al. (2008) reported increased muscle strength (1-RM for a range of strength tests) following a post-treatment, 18-week resistance training intervention in 49 breast cancer survivors compared to a usual care control group; these benefits were maintained at one-year follow-up. Ohira et al. (2006) have also reported significant improvements in 1-RM indices of muscle strength (they did not measure muscle CSA or lean mass for comparisons with our variables) following a 6-month resistance exercise program in 79 breast cancer patients during their chemotherapy treatment, although in this study, there was no control group.

Courneya, Segal, Mackey, et al. (2007) compared 82 breast cancer patients undertaking 17 weeks resistance exercise during chemotherapy with 78 patients undergoing an aerobic program and 82 patients in a non-exercise control group. Body strength, assessed by a 1-RM leg and chest press, was significantly improved in the resistance
group compared to the aerobic and control groups. These improvements were maintained at 6-month follow-up (Courneya, Segal, Gelmon, et al., 2007).

A number of studies have investigated the efficacy of combined resistance and aerobic exercise programs in breast cancer patients. Milne et al. (2008) found significant improvements in muscle strength (using a series of 1-RM measures) following 12 weeks of training (involving resistance exercises for all major muscle groups alongside aerobic exercises) in 29 breast cancer survivors compared to a non-exercising control group. In another study, Sprod, Hsieh, Hayward, and Schneider (2010) examined three separate groups of post-treatment breast cancer patients, with one group after 3 months ($n = 29$) and one group after 6 months ($n = 68$) of mixed training (resistance exercise for all major muscle groups together with walking, stepping, cycling or aquatic exercise) compared to a third patient control group ($n = 17$). They reported that body strength (assessed by the leg, bench and shoulder presses, and latissimus pull-downs) was increased significantly in the six-month group but not in the three-month group. Herrero et al. (2006) reported significant improvements in muscle strength (leg and bench press) in eight post-treatment breast cancer survivors following an eight-week mixed exercise program (compared to a non-exercise control group). On the other hand, Battaglini et al. (2007b) failed to show any effect of 21-week mixed exercise training (combining resistance exercise of major muscle groups with ergometer exercise) on muscle strength (assessed with a series of 1-RM manoeuvres) in ten breast cancer survivors compared with a non-exercising cancer control group.
Additional studies utilising mixed training programs have been undertaken, but without the inclusion of a control group. Cheema and Gaul (2006) found that eight weeks of combined aerobic and resistance exercise in 31 breast cancer patients at six months post-treatment significantly improved leg press and bench press strength as well as endurance. Kolden et al. (2002) have also reported significant improvements in leg and bench press measures in 40 breast cancer patients undertaking a combined program for 16 weeks during chemotherapy treatment. Similarly Lane, Jerspersen, and McKenzie (2005) demonstrated significant improvements in bench press strength in ten breast cancer patients participating in a 20-week team rowing (“dragon-boat”) competition.

A strength of the present study is the use of isokinetic dynamometry instead of the usually reported 1-RM measure of particular resistance exercises. Advantages of this approach over commonly-used multi-joint resistance exercises (such as leg press and dead lifts) (Drouin et al., 2004; McCleary & Andersen, 1992; Sturnieks et al., 2008; Symons et al., 2005; Wilcock et al., 2008) is the ability to control inter-session variation by, which results from standardisation of posture, angular velocity and range of angular motion.

Our choice of utilising the knee joint as the primary focus for any intervention-related changes in muscle strength was made on the basis of the functional importance of this joint in completing activities of daily living (ADL). It is the most commonly studied joint movement for strength assessment, and experiences the greatest range of motion across common activities such as walking, sit-to-stand and postural support (Capranica et al., 1998; Eriksrud & Bohannon, 2003; Knapik, Mawdsley, & Ramos, 1983;
McGuigan & Winchester, 2008; Shelburne, Torry, & Pandy, 2006; Symons et al., 2005; Wilcock et al., 2008). The present findings indicate enhanced function in both quadriceps and hamstring muscle groups in the exercising compared to the non-exercising breast cancer group, in that both extension and flexion strength (both isometric and concentric isokinetic) show significantly greater improvement. In particular, the benefits with respect to quadriceps concentric strength alongside analogous improvements in hamstring concentric strength would be predicted to translate into an improved ADL function, with improvements in isometric strength in these muscles leading to better postural support. In addition to these primary knee movement muscles, the gastrocnemius is also involved in the isometric flexion movement of the knee joint. However, by setting the test to a joint angle of 75 degrees (rather than 45 degrees) of knee flexion, our measurement of isometric strength would predominantly reflect hamstring function.

The present study shows that the percentage of training-related improvements in both flexion and extension isokinetic concentric strength of breast cancer patients are greater than those for the corresponding isometric measures. This is consistent with previous findings that have reported that strength gains are specific to training mode (Knapik et al., 1983; Symons et al., 2005) and the fact that most of the exercises in our training program involved concentric exercises (Eriksrud & Bohannon, 2003; Shelburne et al., 2006; Wilcock et al., 2008).
Although the training-related improvements in the breast cancer survivors were statistically not different to those seen in the healthy group, there was a moderate effect size for two of the four measures (isometric extension and isokinetic concentric flexion), indicating greater increases in strength in the healthy group. Thus, in view of the small number of breast cancer survivors recruited into the training study, the present study cannot be definitive on the question of whether resistance training can benefit post-chemotherapy cancer sufferers to the same extent of benefits that can be seen in healthy sedentary individuals. What does appear clear, however, despite small numbers in both cancer groups, is that resistance training does improve muscle strength compared to usual care in breast cancer participants.

6.6.3 Thigh composition

An important design feature of the present study is that we have sought to assess whether improvements in muscle strength, related to resistance training, could be the consequence of changes in muscle morphology rather than simply the result of improved technique. To do this, we employed peripheral quantitative computed tomography (pQCT) of the thigh region (33% distance proximal to the medial condyle of the femur) to determine muscle cross-sectional area (CSA), fat CSA and muscle density in our experimental groups.

The small (2.5%) reduction in muscle cross-sectional area in the cancer group following 12 weeks of resistance training is somewhat surprising, although it is slightly less than the 4% decline observed in the cancer control group, representing a minimal
effect size. By contrast, the 8.8% reduction in the fat cross-sectional area in the trained group compares favourably with the 6.1% increase in the non-exercisers, producing a large effect size which is close to statistical significance ($p = 0.078$). Both cancer groups showed minimal changes in muscle density, suggesting that the primary beneficial effect of training with respect to thigh fat content was confined to the extra-muscular space. It must be noted that the non-exercise group had a much higher thigh fat content (122 vs 82 cm\(^2\)) to begin with, indicating that the randomly allocated control group was more obese than the training group. Indeed, this is borne out by the higher body mass index (BMI) (31.7 vs 27.0) in the control group, and can best accounted for by unintentional sampling bias related to our small group sizes which were matched for age.

Unlike their breast cancer counterparts, the healthy control group did show the expected training-related increase in muscle cross-sectional area (2.5%), resulting in a large effect size. Thus, it is conceivable that prior administration of chemotherapy treatment does limit the ability of peripheral muscle to respond to a strength training stimulus. However, the corresponding reductions in fat CSA were slightly more pronounced in the cancer group (8.8% vs 4.9%) indicating that for this measure, the benefits could be gained from training the both groups. Again, neither group showed any real change in muscle density as a result of training, confirming that in terms of this index of muscle composition, the cancer group responded no differently from the healthy group.
While many studies have investigated the benefits of resistance exercise in breast cancer populations (see above), most have limited their anthropometric analysis to the effect of strength training on whole body composition. By employing the relatively new technique of pQCT, we have been able to make a more direct assessment of thigh composition where strength training-related benefits might be more apparent. By adopting this approach, we have been able to gain greater insight into whether preceding physical de-conditioning and/or potentially myotoxic chemotherapeutic effects have affected the ability of the target organ (skeletal muscle) to respond to a strength training intervention. Overall, the findings indicate that relative to the cancer controls, exercise training constrained muscle wastage in the cancer group, although not appearing to promote muscle growth as seen in the healthy group. In addition, the exercising cancer group did better than the non-exercising cancer group, and as well as the healthy group, in losing fat from the thigh area.

In terms of limb-specific effects of resistance training in breast cancer survivors, while there are no reports on the use of pQCT to assess muscle/fat composition of this population. Other studies have demonstrated increases in thigh muscle CSA in healthy populations (DeFreitas, Beck, Stock, Dillon, Sherk et al., 2010; Jones & Rutherford, 1987; Narici, Roi, Landoni, Minetti & Cerretelli, 1989) and in post-menopausal women with Type-2 diabetes (Cuff et al., 2003) resulting from 12-16 weeks of resistance/mixed training. Two of these studies (Cuff et al., 2003; Jones & Rutherford, 1987) also reported increases in muscle density, an observation not seen in either of our training groups. While our cancer group was small, our healthy group was comparable to that
of Jones and Rutherford (1987) in terms of numbers of subjects, exercise intensity and duration of training, and hence there is no obvious explanation for this discrepancy in our findings, except for inadequate training stimulus.

Because of the small number of breast cancer patients that we were able to recruit, we do not get a clear picture of the extent to which training-related structural changes in the muscle underpin the clear improvements we saw in muscle strength. The reduction in fat CSA in the breast cancer patients is encouraging, but the lack of any definitive evidence of muscle development makes it difficult to implicate increased contractile capacity as an explanation for the strength effects we observed. It is noteworthy, however, that such evidence was also not apparent in the much larger group of healthy subjects who exhibited similar gains in muscle strength. The 2.5% increase in muscle CSA in our healthy middle-aged women was comparable to the 5% noted in a smaller group of younger healthy males (Jones & Rutherford, 1987). However, this small increase in muscle CSA did not correspond with the significant increases in muscle strength. While increases in muscle strength is usually reflected by muscle hypertrophy observed in increases in cross-sectional area of the contractile material (muscles), the significant increases in muscle strength observed in the exercising groups studied (breast cancer participants and healthy women) cannot be accounted for small changes in the muscle CSA.
One possibility is that our exercise intervention was of inadequate intensity or duration to induce much muscle-building and that the strength improvements largely reflected enhanced technique. The learning effect in significant improvements in muscle strength could also be supplemented by increased activation of muscle fibres due to changes in motor unit firing capacities. This seems unlikely to be the whole explanation since, with reference to the healthy group, our intervention was analogous to that used by others who have documented significant effects on both muscle CSA and muscle density (Jones & Rutherford, 1987).

However, against the background of likely underlying cachexia in breast cancer survivors, maintenance of muscle composition might be regarded as a positive outcome. Despite the small, but a consistent decrease in muscle CSA in the exercising cancer group compared to the non-exercise group, the resistance exercise program may have compensated for a small loss in muscle tissue by increasing the amount of fat loss in the muscle and increasing the packing of contractile filaments. The small, albeit insignificant, increase in muscle density in all three groups may well be indicative of disproportionate fat loss with the corresponding packing of contractile elements helping to increase the force per unit area resulting in increased strength.

In the current study, the increase in strength in the absence of any increase in muscle cross-sectional area, indicates that resistance training may induce functional improvement by mechanisms other than via increasing the amount of muscle. One possibility is that there is a “learning effect” perhaps resulting from changes in motor
unit firing patterns. Another possibility would be an increase in muscle fibre and connective tissue attachments to tendons resulting in improved mechanical efficiency at the joint. Jones and Rutherford (1987) suggested that this mechanism probably accounts for the increase in muscle strength within the first 6-12 weeks of resistance training ahead of the subsequent gross muscle hypertrophy. As discussed earlier, we think it less likely that these findings are attributable to improvements in technique related to strength assessment since, unlike the 1-RM protocols, our use of an isokinetic dynamometer should have made this assessment relatively technique independent.

### 6.6.4 Quality of life

In addressing the impact of resistance training on health-related quality of life (QoL) in breast cancer survivors, we employed the widely used SF-36 questionnaire. Despite the availability of breast cancer-specific QoL questionnaires, we chose to use the SF-36 because several members of the research team were familiar with its use, and also because a number of studies investigating QoL in this clinical population had used this more general QoL instrument (Ahmed et al., 2008; Costanzo et al., 2007; McKenzie & Kalda, 2003; Perry et al., 2007; Segal et al., 2001). The SF-36 is a validated questionnaire designed to study health status in clinical practice and research (Apolone & Mosconi, 1998; Gandek et al., 1998; Keller et al., 1998; Ware et al., 1998; Ware & Sherbourne, 1992), and is the most frequently administered questionnaire to long-survivor cancer patients (Apolone et al., 1998). Furthermore, the SF-36 has been demonstrated to have convergent validity with the European Organisation for Research
and Treatment of Cancer Core Quality of Life Questionnaire C30 (EORTC QLQ-C30), a questionnaire designed specifically for cancer patients, confirming its validity for use with breast cancer populations (Apolone et al., 1998).

We found that the 12-week resistance exercise intervention in our breast cancer group improved all eight domains of functioning and well-being, ranging between 10 and 40 points. Overall, this improvement in QoL was greater than that seen in the non-exercising cancer group (-5 to 16 points), with moderate or high effect sizes for physical functioning, role limitation due to physical health, vitality, social functioning and mental health. These findings suggest that while there is a general improvement in quality of life over a 12-week period after chemotherapy, this positive trend is markedly enhanced in those participating in a structured exercise program.

Before the onset of the resistance training program, the breast cancer survivors had poorer quality of life in all eight domains of functioning and well-being compared with their healthy counterparts (-38 to -3 points). However, the benefits associated with participating in the exercise program in the breast cancer group (see above) resulted in them achieving post-training scores equivalent to those of the healthy group for all domains (+7 to -5 points) except for general health (-12 points). Accordingly, there were minimal-to-large effect sizes for physical functioning, role limitations due to physical health, bodily pain, vitality, social functioning, and mental health. These results indicate that our training program not only improved quality of life in the breast cancer group, but also that for almost all of the domains, health-related quality of life
was no different from that reported by a group of healthy individuals following a similar exercise routine.

From the results of this study it is not possible to know the extent to which the observed improvements in QoL measures were related to improvements in physical functioning or psycho-social aspects of engaging with a training intervention. The increases in muscle strength would have likely improved functional capacity, particularly by enhancing the ability to undertake activities of daily living. However, it is probable that the positive benefits of being actively involved in this group activity also contributed to the improved QoL measures. Since, for logistical reasons we were not able to provide a more engaging, non-resistance placebo activity (e.g. yoga) for our control cancer group, and hence it is not possible to discern the relative benefits of the physiological and psycho-social components of our intervention. The less-marked QoL benefits seen in non-exercising group to an extent may reflect our continuing engagement with these participants in the form of weekly telephone conversations, although the passage of time following chemotherapy cannot be discounted as a factor.

Our findings of improved QoL in our exercising cancer group are consistent with most other studies in this population, irrespective of the type of exercise intervention. In assessing these outcomes, investigators have used a variety of instruments, some of which are designed specifically for use in breast cancer populations. Our subjective evaluation does not reveal any great differences in the magnitude of QoL improvements associated with a range of interventions at various stages of treatment.
(Campbell, Mutrie, White, McGuire, & Kearney, 2005; Cheema & Gaul, 2006; Courneya, Segal, Gelmon, et al., 2007; Courneya, Segal, Mackey, et al., 2007; Demark-Wahnefried & Jones, 2008; Herrero et al., 2006; Kolden et al., 2002; Milne et al., 2008; Ohira et al., 2006; Winters-Stone et al., 2012). Of these, only Winters-Stone et al. (2012) used the SF-36 to evaluate perceived QoL but focused specifically on the physical function domain in breast cancer survivors. These investigators reported a 2.8% increase in the physical function score in 36 breast cancer survivors after a 12-month resistance exercise program. This finding is markedly different to 41.8% increase observed in the same domain in the our study. Closer inspection revealed similar pre-intervention scores for the two studies, but very different outcomes in this QoL index. In order to make a broader comparison, we looked at other studies employing resistance training programs in breast cancer survivors using other QoL questionnaires with “Physical Function” subscales. De Backer et al. (2008) reported a 16% increase from a higher baseline resulting in comparable mean post-exercise score compared to our study (84.2 vs 92.1 points) following an 18-week intervention in 49 breast cancer survivors. On the other hand, studied 79 breast cancer survivors for 6 months and found only a 4% increase in the physical function measure from a similar baseline score to the current study. Apart from the greater potential for error in our study, due to a low sample size, we can offer no explanation as to why there was such a marked difference in QoL (physical function) across these four similar studies.
In further attempts to assess the reliability of our QoL outcomes in the exercising cancer group, we have compared our findings with exercise intervention studies in other populations in which SF-36 was used. Brocki et al. (2014) looked at a 4-month mixed (aerobic + resistance) exercise program in 41 lung cancer patients and reported increased scores in most domains (-2 to 30 points), similar in magnitude to the range we observed (10 to 40 points) from equivalent baseline scores. Barrett and Smerdely (2002) reported changes ranging between -3 and +18 points in 40 elderly males following a 10-week progressive resistance training program; this group generally had somewhat higher pre-exercise scores so that the room for improvement was less.

In conclusion, the quality of life improvements associated with a 12-week resistance training in breast cancer survivors were greater than those seen in some studies but comparable to the changes reported by other studies. The relatively low values measured in the pre-exercise condition may explain some of the benefits we observed, and the fact that our control breast cancer group also exhibited some improvement in most domains suggests a possible non-training component in the exercising group. Although our group size was small, we were encouraged to see that their QoL measures were in general equivalent to those reported by our much larger age-matched healthy individuals who had completed a similar program. We are not aware of any previous study that has compared QoL outcomes in breast cancer survivors with those of their healthy counterparts.
6.6.5 Fatigue

In order to better understand the impacts of anti-cancer treatment on symptoms of cancer-related fatigue, we utilised a Multi-dimensional Fatigue Inventory (MFI-20) questionnaire that addresses five different dimensions of the fatigue syndrome, and is commonly used in oncological research (Kuehr et al., 2014; Smets et al., 1995; Smets et al., 1996). Each fatigue dimension is scored between 4 and 20 points, with higher scores indicating a stronger perception of fatigue.

We observed that the 12-week resistance exercise intervention program in the breast cancer exercise group contributed to reductions in four of the five dimensions of perceived fatigue, ranging between -0.4 and -1.0 points; an increase of 0.6 points in the mental fatigue dimension was also observed. These small improvements in perceived fatigue occurred against an increasing fatigue in four out of the five dimensions in the non-exercise group (0.5 to 1.2 points; physical fatigue = -1.3 points) over the same period, accounting for moderate-to-large effect sizes for general fatigue, reduced activity and reduced motivation. Generally, these findings indicate improvements in perceived fatigue in breast cancer patients resulting from the structured resistance exercise program, and associated with the observed improvements in muscle strength and quality of life.

Overall, there was a slight difference in the pre-training fatigue measures between the breast cancer survivors and those reported by healthy women in the same age group (-1.18 to 0.27 points). However, the positive effects of the resistance exercise program
in the breast cancer exercise group resulted in them reporting post-training fatigue scores better than those reported by the healthy group for all the dimensions of perceived fatigue (0.33 to 0.96 points), except for the mental fatigue dimension (-0.32 points) with minimal-to-moderate effect sizes for general fatigue, physical fatigue and reduced motivation. The reported levels of perceived fatigue were similar in both groups before exercise training, and changed relatively minimally in either group as a result of the training program despite improvement in muscle strength resulting from training. This could reflect the fact that the general level of physical activity was increased in our training groups so that an equivalent level of fatigue post-training were associated with improved functional capacity. This in turn could explain the improvements in QoL measures associated with improved strength, but in the absence of any real change in perceived fatigue. However, no measures of physical activity or activities of daily living (ADL) assessment were made in the present study, so this remains speculative. Another possibility is that the instrument we used to assess fatigue lacks sensitivity in populations of relatively sedentary middle-aged women.

The overall increase in perceived fatigue in the non-exercising cancer group, although relatively small over the intervention period, does suggest that there is a gradual decline in vitality in this population following breast cancer diagnosis and chemotherapy treatment, a trend which our results suggest can be arrested with home-centred resistance exercises.
There are no previous reports on the impact of resistance training alone on perceived fatigue in breast cancer survivors with which to compare our results. However, our observations of reduced levels of fatigue in our exercising cancer group are consistent with the trend in a number of other studies in this population group where a mixed aerobic/resistance intervention has been used or with resistance only interventions in other populations (Buffart et al., 2013; De Backer et al., 2008; Hsieh et al., 2008; Kuehr et al., 2014; Kummer, Catuogno, Perseus, Bloch, & Baumann, 2013; Milne et al., 2008; Sprod et al., 2010; Winters-Stone et al., 2012).

Reports by De Backer et al. (2008), using an earlier version of the instrument we used (MFI-20) revealed significant reductions in levels of fatigue in all dimensions, ranging from -0.7 to -4.0 points (corrected to the current version), compared to the minimal reductions in fatigue levels observed in the current study (-0.43 to -1.00 points). The more favourable results observed in the De Backer study may be mainly due to a large sample size of 49 breast cancer survivors undertaking 18 weeks of high-intensity resistance and interval training. Kuehr et al. (2014) reported non-significant increases in levels of all dimensions of perceived function (ranging from 0.0 to 0.6 points) after an 8-week mixed (aerobic + resistance) exercise program in 40 lung cancer survivors. Buffart et al. (2013) demonstrated significant reductions in four domains of perceived fatigue (ranging from -0.7 to -4.8 points; no change in mental fatigue), following 18-week of high intensity resistance exercise in 179 participants with a range of cancers; this study did not have a control group.
6.7 Limitations

The limitations of the current study include having a low sample size, and that the study was underpowered to demonstrate any significant changes. The study was also limited a notable number of dropouts. We failed to include a non-exercising healthy control group due to limitations in resources and funding. The investigators were not blinded to the breast cancer and healthy control groups as the study was not able to employ external research assistants to conduct the assessment procedures due to limited resources and funding. We could not monitor physical activity levels of the participants in the different groups to ascertain the levels of activity the participants have been engaged in, due to resource and funding constraints. We did not monitor changes in diet patterns for any of the participants in the different groups.
CHAPTER 7: General discussion, conclusions and future directions
7.1 Rationale for the study

This research study was designed primarily to investigate the efficacy of a progressive resistance exercise training program in breast cancer survivors who had completed a course of first-line treatment with anthracycline and/or taxane chemotherapy. The widely used treatment is known to be associated with cardiomyopathy (Doroshow et al., 1985; Du et al., 2009; Hershman & Shao, 2009; Korga et al., 2012; Saltiel & McGuire, 1983) and might also impact negatively on skeletal muscles potentially exacerbating sarcopenia sometimes seen in this condition (Prado et al., 2009; van Norren et al., 2009). Certainly, such treatment has been shown to reduce muscle strength (Bower, 2008; van Norren et al., 2009), making progressive resistance training a logical option for breast cancer rehabilitation post chemotherapy. The two main aims of this study were thus: firstly to assess the extent to which anthracycline/taxane chemotherapy negatively impacts skeletal muscle morphology and function and secondly, to explore the therapeutic potential of home-focussed progressive resistance training as a rehabilitative strategy in this clinical population. By using state-of-the-art methodologies to study muscle composition and function, and supplementing those with more widely reported assessments of whole body composition and health-related quality of life, we aimed to gain further insights into the genesis and management of an effective yet debilitating chemotherapy treatment.
Chapter 7  
General discussions, conclusions and future directions

7.2 Study design

7.2.1 Research procedure

We recruited breast cancer patients scheduled for, but yet to undergo, chemotherapy treatment, and an age-matched healthy control group. The following assessments were conducted:

1. Whole body composition for lean and fat mass using Dual-energy x-ray absorptiometry (DXA)
2. Muscle and fat cross-sectional areas and muscle density in the thigh using peripheral quantitative computed tomography (pQCT)
3. Knee extension and flexion strengths using the Biodex isokinetic dynamometer
4. Health-related quality of life (QoL) using the SF-36 questionnaire
5. Perceived fatigue using a MFI-20 questionnaire.

We next investigated the effects of an individualised, home-based progressive resistance exercise program versus usual care and weekly telephone contact. The 12-week progressive program utilised dumbbell kits that we supplied, together with a demonstration DVD for exercising at home. Home sessions were supplemented by a single weekly supervised group session. The breast cancer patients randomised to the exercise group were compared to the non-exercising breast cancer patients and healthy control group who also completed the exercise program.
7.3 Main findings

The primary findings of the study was that, overall, muscle strength in breast cancer patients, before chemotherapy, was no different to that of healthy women, but that it decreased significantly following treatment. As there were no notable associated changes in whole body muscle mass or thigh muscle cross-sectional area, the observed decrease in muscle strength did not appear to be due to a particular sarcopenic effect of chemotherapy. In light of this finding, we have speculated that this chemotherapy-related muscle weakness may be due to central or neural mechanisms, although another possibility is that anthracycline/taxane haemotoxicity could have reduced oxygen delivery to the muscles during activity. Despite marked loss of muscle strength following chemotherapy, we were somewhat surprised that patients reported minimal concurrent loss of quality of life. However, our data show that even before chemotherapy our cancer group had significantly lower quality of life than their healthy counterparts, making further reductions in well-being unlikely, particularly at a time when medical treatment had just concluded.

In regard to the resistance training phase of the study, our findings indicated that the exercising breast cancer group was able to recover their lost muscle strength to a significantly greater extent than the usual-care group, and that the beneficial effects on muscle strength were associated with trends for improvements in whole body and thigh composition. Indeed, in terms of improved muscle strength, our exercising breast cancer survivors gained as much as benefit from the exercise program as did the healthy
sedentary individuals. Moreover, although both cancer groups showed improved quality of life after the completion of chemotherapy, the improvement was more marked in those undertaking the exercise program. In fact, on completion of resistance training, the breast cancer survivors reported equivalent levels of quality of life measures as the healthy individuals.

7.4 Strengths

7.4.1 Compliance and safety

One of the main strengths of this study was the high level of compliance and completion among our participants across all three experimental groups. Although recruitment was problematical (discussed below), most individuals who did volunteer complete the 12-week exercise program and attended the three assessment sessions, despite often having to travel some distance to do this. Similarly, most in the control group stayed engaged with the project even though their participation in the exercise program was delayed. There were no reports of injuries during the course of the progressive resistance training program, apart from the usual exhaustion and muscle soreness experienced after an exercise program. Our experience supports the view that a progressive resistance exercise intervention program can be safely and effectively implemented in a population of breast cancer patients treated with anthracycline/taxane adjuvant chemotherapy.
7.4.2 Resistance training program

The training program was designed to meet the important criteria of duration, specificity, progression and compliance in an attempt to target desired benefits on the muscle. Compliance was optimised by devising exercises that utilised simple equipment, conducted at home and supported by appropriate training and supervised sessions to ensure appropriate progression for each individual.

7.4.3 Definitive quantitative measures (pQCT and Biodex)

An important feature of the present study is the use of sensitive technologies allowing the precise measurement of key structural and functional muscle variables. The use of pQCT enabled us to assess specific body composition changes in target area of interest (i.e. thigh musculature) and has provided novel data in this population to supplement the whole body measures (from the more conventional densitometry techniques) that we and others have made. With this technique, we have been able to show evidence suggestive of peripheral loss in muscle mass in breast cancer survivors (i.e. relative to healthy individuals) secondary to diagnosis/surgery rather than as a result of chemotherapy. Our ability to assess muscle strength using a “gold-standard” isokinetic dynamometer (Biodex) represents a further strength of our study. This has allowed us to more carefully define the functional impact of cancer diagnosis/surgery, adjuvant chemotherapy and targeted training on key ambulatory muscle groups. Previous studies investigating the effects of exercise interventions have mainly used the one-repetition maximum (1-RM) strength test, with dumbbell or free weights to determine whole
body strength in clinical participants after exercise interventions (Courneya, Segal, Mackey, et al., 2007; Kolden et al., 2002; Ohira et al., 2006; Schmitz et al., 2005; Winters-Stone et al., 2012).

### 7.4.4 Experimental groups

The design of the study enabled us to look at the impact of initial treatment for breast cancer (i.e. surgery following diagnosis) by making careful assessments on our participants before their chemotherapy and comparing their status with a group of age-matched healthy volunteers. In studying the effect of training, our design enabled us to assess any benefits for our cancer survivors not only with respect to a non-exercising cancer group but also to a group of healthy sedentary women. This has allowed us to evaluate the capacity of those with cancer to benefit from an exercise intervention.

### 7.5 Weaknesses

The current study had a number of limitations, which have been discussed earlier in this thesis. Paramount among these was our inability to recruit a sufficient number of participants with breast cancer. Although the total number of breast cancer recruits ($n = 20$) did approach our target sample size ($n = 27$), the fact that we subsequently divided this group into exercising and non-exercising cohorts has resulted in that limb of the study being underpowered. In hindsight, it would have been preferable to allocate all participants to the resistance training program and undertake only a comparison between cancer survivors and sedentary healthy women. This limitation was
exacerbated by the disproportionate dropout rate in the cancer patients assigned to the exercise intervention. It would also have been desirable to include a third study in the thesis, maybe looking at long term effects of resistance exercise interventions, such as a 3-month follow-up, etc. However this was not possible within the short tenure of my PhD funding and candidature.

### 7.6 Future directions

The relatively small sample size of breast cancer patients in the current study makes generalisations on the impacts of chemotherapy treatment on various outcome measures in this clinical population difficult, and participant numbers would need to be addressed in any future studies. Any such study would benefit from the considerable experience we have gained in addressing a range of administrative and logistical difficulties that we encountered in progressing this clinical study. Indeed, by the later stages (final 12 months) of this study, recruitment rates were encouraging and the scheduling of assessment and training programs was working very well. Had the PhD support funding been able to continue for a further 12 months, then we predict that we would have been able to reach our target sample sizes.

It is clear from this and other studies that breast cancer diagnosis, associated surgery and chemotherapy treatment impact negatively on body composition, muscle strength, and quality of life. We believe that future research of the type conducted in the present study offers the potential for improved clinical management, in particular in the period immediately following medical interventions. Clearly, the goal should be to rapidly
restore physical and psychosocial capacity to pre-disease levels. In this regard, structured exercise training offers great potential and the value of a home-based, “low tech” resistance exercise program, perhaps supported by rapidly developing e-health initiatives, merits further study. From our experiences, such studies would greatly benefit from clinical and academic institutions fostering stronger and more integrated links between clinicians and clinical investigators.

Although in this study, our exercise intervention was individualised for each participant, we noticed considerable individual variability in response. Indeed, similar variability in response was noted between participants as a result of standardised chemotherapy. In order to provide optimal management for all patients, we suggest that regular and careful measurements of lower limb composition and function, as used in this study, would be a valuable adjunct to the clinical management of breast cancer survivors. Such measurements take about 15 minutes to complete and are straightforward from the patient perspective.

While there are a number of reports on the effects of aerobic or mixed exercise programs on relevant outcome measures in breast cancer patients, there is limited information on the effects of a resistance-only exercise. The current study has revealed a number of potentially beneficial responses to this mode of training, and compliance was overall encouraging. However, further adequately powered studies are needed to establish optimal individualised prescription in terms of mode, frequency, duration, intensity and compliance. In addition, attention needs to be focused on maintenance
strategies to ensure that benefits in body composition and function are sustained over their lifetime.
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9.0 Appendices
Can exercise minimise or eliminate physical side-effects associated with chemotherapy treatment for breast cancer?

Individuals who undergo chemotherapy for breast cancer often experience weight gain, strength loss and fatigue following their treatment. In collaboration with the Princess Alexander, Gold Coast and Mater Adult Hospitals, the School of Physiotherapy and Exercise Science at Griffith University is investigating whether resistance exercise can minimise or eliminate these unwanted side-effects.

We are seeking breast cancer patients under 75 years who are scheduled to undergo chemotherapy as part of their treatment program.

Participants will be allocated either to an exercise group or a non-exercise group. Participants in the exercise group will undertake resistance exercise training following their chemotherapy and radiation treatment. The training will include one supervised session at the PA Hospital and two self-directed exercise sessions at home each week for a 12-week period. All participants will be provided with an exercise kit that includes training equipment, an exercise demonstration video and a training diary. Body composition (fat and muscle mass), strength, and fatigability (the ease at which you fatigue) will be assessed before and after the exercise training program.

All participants will receive a report describing how their results compare with: 1) non-exercising breast cancer patients, and 2) exercising non-cancer patients, of similar ages.

If you are interested in volunteering for this study and/or would like further information please contact:

Prof. Lewis Adams
Griffith University
Ph: (07) 555 28992
E-mail: lewis.adams@griffith.edu.au

Ravin Lal
Griffith University
Ph: 04 0185 4740
E-mail: r.lal@griffith.edu.au
9.2 Participant Information and Consent Form

Participant Information and Consent Form
Griffith University, Gold Coast Campus

Can resistance exercise improve body composition and strength in post-chemotherapy breast cancer survivors?

Principal Researcher:
Professor Lewis Adams, PhD
School of Physiotherapy and Exercise Science, Griffith University, Gold Coast
Tel: (07) 5552 8992, Email: lewis.adams@griffith.edu.au

Associate Researchers:
Dr. Peter Mills, PhD
School of Physiotherapy and Exercise Science, Griffith University, Gold Coast
Tel: (07) 5552 8917, Email: p.mills@griffith.edu.au

Mr. Ravin Lal, MSc.
PhD Candidate
(This research forms an integral part in this candidate’s doctoral research)
School of Physiotherapy and Exercise Science, Griffith University, Gold Coast
Tel: (07) 5552 8281, Email: r.lal@griffith.edu.au

Dr. Tracey Jason, PhD
School of Pharmacy, Griffith University, Gold Coast
Tel: (07) 5552 9230, Email: t.jason@griffith.edu.au
You are invited to take part in our research project which is evaluating an exercise intervention that may improve and restore muscle strength and function in breast cancer patients treated with chemotherapy. You will be provided with a tailored resistance exercise program, designed for breast cancer patients in order to build muscle mass.

This Participant Information and Consent Form tells you about the research project. It explains the procedures involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or healthcare worker.
Participation in this research is voluntary. If you don’t wish to take part, you don’t have to. You will receive the best possible care whether you take part or not.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to participate in the research processes that are described;
- consent to the use of your personal and health information as described

You will be given a copy of this Participant Information and Consent Form to keep.

2. **What is the purpose of this research project?**

The aim of this study is to investigate the effect of exercise program on body composition, muscle strength and muscle function following chemotherapy treatment in breast cancer patients. While previous research has identified that regular strength training can bring about improvements in these factors in other population groups, our knowledge about the effects of exercise in breast cancer patients undergoing chemotherapy is limited.

This study is important because the types and quantity of exercise to optimize post-treatment rehabilitation for breast cancer patients is unknown.

Chemotherapy can have toxic effects on skeletal muscle, and can lead to a trend in decreased lean muscle mass and weight gain in breast cancer survivors. Physical activity and exercise have been associated with cancer prevention, improvement of quality of life during cancer treatment, improved overall cancer survival and decreased risk for cancer recurrence. Evidence to date has established that exercise is safe and beneficial following administration of breast cancer adjuvant therapy.

The significance of this project is to develop an exercise program that will increase skeletal muscle mass and potentially decrease weight gain in breast cancer patients who have received anthracycline-taxane adjuvant chemotherapy. We hope to develop an exercise prescription to optimize post-treatment rehabilitation for breast cancer patients.

There will be 96 participants enrolled in this study; 64 will partake in the exercise sessions at the Princess Alexandra Hospital and at the Griffith University, Gold Coast campus.
There will be 2 groups, one group of 32 women that are aged matched healthy women participating in the exercise sessions (control) and one group of 32 women of breast cancer survivors participating in the exercise sessions. There will be an additional control group of 32 breast cancer survivors treated with chemotherapy that are not prescribed with an exercise program.

Patients from the Princess Alexandra Hospital, Gold Coast Hospital and Mater Adult Hospital will be recruited. All participant tests and scans will be conducted at the Gold Coast campus of the Griffith University.

This is a stand-alone project and is not a follow-up or an extension from any other research.

This project involves collaboration from researchers at Griffith University, oncologists from the PA Hospital, Gold Coast Hospital and Mater Adult Hospital and physiotherapists from the PA Hospital.

The results of this research will be used by Mr. Ravin Lal to obtain a Doctor of Philosophy degree and is partially funded by his AusAID scholarship. Additionally funding has been received from the University Research Committee of the Griffith University.

The results of this research will be used by the researcher Ravin Lal to obtain a Doctor of Philosophy degree.

This research has been initiated by the Principle Investigator, Prof. Lewis Adams and investigator, Dr. Tracey Jason.

This research is being conducted by Griffith University, Gold Coast Campus.

3. **What does participation in this research project involve?**

If you agree to participate in this study you will be asked to complete a 12-week exercise program, involving one, one-hour exercise session each week either at the Princess Alexandra Hospital (PAH) in Brisbane or at the Gold Coast campus of Griffith University, supervised by a physiotherapist and investigator from Griffith University and two self-directed exercise sessions at your home. Patients from Brisbane will attend supervised exercise sessions at the PA Hospital while patients from Gold Coast will attend supervised exercise sessions at Griffith University’s Gold Coast campus. You will also be asked to visit the School of Physiotherapy and Exercise Science at Griffith University’s Gold Coast campus on three occasions for a two hour period for testing of body composition, muscle strength, function and fatigability. These three occasions will be: i) prior to the beginning of chemotherapy, ii) after chemotherapy and iii) at the conclusion of the exercise program.

You will complete a “Quality of Life” questionnaire and a “Measure of Fatigue” questionnaire addressing physical functioning, mental and emotional state, body pain, social functioning and fatigue during the three assessment visits.
Breast cancer participants will be assigned a code which will be used to randomize the participants into those that take part in the exercise sessions and those that do not. Healthy women in identical exercise sessions will act as the control group.

A 12 week personal exercise training program will be provided to you. The program will involve a series of resistance (strength building) exercises to be conducted three times a week. You will be provided with a resistance training kit including dumbbell weights, an exercise diary and an instructional DVD. Each exercise session will last 60 minutes. You will be given choices of scheduled weekly supervised sessions to be held either at the PAH or the Griffith University and you are free to attend any one of these.

Assessment of body composition and muscle volume will be conducted at the School of Physiotherapy and Exercise Science using dual-energy x-ray absorptiometry (DXA) used to estimate bone, muscle and fat composition and peripheral quantitative computed tomography (pQCT) used to measure muscle density and morphology in the forearm.

Full body functional capacity will be assessed using a hand-held pull dynamometer capable of measuring force. You will be required to grasp the dynamometer handles using both hands in a squat position and pull on the dynamometer with maximal strength. You will be required to perform three sets of pulls with the average force considered to be the full body strength.

All muscle assessments will be conducted at the School of Physiotherapy and Exercise Science at Griffith University, Gold Coast Campus. Muscle flexibility, strength and fatigue will be assessed using a Biodex Isokinetic dynamometer (strength measuring device). Participants are required to undergo a series of muscle contractions at the knee and during each contraction the force of the muscles will be recorded.

Follow up for this study will include an analysis of all the factors measured and comparison to both the healthy women on the exercise prescription and the breast cancer survivors that did not exercise. Results will be communicated to the participants at the end of the study.

The participants will be required to take part in the exercise program, which is one hour, three times weekly, for 12 weeks, in addition to measurements and assessments of body composition, muscle mass, strength and fatigability. The testing and assessment sessions at the Griffith University will take two hours to conduct.
You will be reimbursed for any travel, parking, and/or transportation costs that you incur as a result of participating in this research project.

You will not be paid for your participation in this research, but you will be reimbursed for any of the following costs that you incur as a result of participating in this research project: parking and transportation to and from supervised exercise sessions and the assessment sessions at Griffith University.

4. **What will happen to my test samples?**

There will be no collection of tissues in this study.

5. **What are the possible benefits?**

We cannot guarantee or promise that you will receive any benefits from this research, however, possible benefits may include improved muscle strength and function, and decreased fat mass after following an effective strength exercise program and this could be used as a standardised program for other breast cancer patients. There will be no clear benefit to you from your participation in this research.

6. **What are the possible risks?**

Risks can be encountered in all studies, and they should be carefully considered before participation in this study. Possible risks, side effects and discomforts include the risk of muscle strain and delayed onset of muscle soreness associated with performing muscle contractions during exercise. Other risks a minor musculoskeletal discomfort as a result of lying still on a relatively firm examination table for a period of time during the DXA muscle scan. Additionally, during the pQCT scan there could be a minor hamstring (muscles at the back of the thigh) discomfort as a result of sitting with the lower leg outstretched for a period of time. There may also be a slight muscle strain during contractions during assessment of muscle strength using Biodex Isokinetic dynamometer. All muscle strain risks will be minimised by appropriate warm-up, cool down and familiarisation with the exercises and equipment. DXA and pQCT scans are routine clinical tests that are non-invasive and pain-free. However, they expose the body to ionising radiation. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year or nearly 40 times the effective dose for all the scans during this study.

If you become upset or distressed as a result of your participation in the research, the researcher is able to arrange for counselling or other appropriate support. Any counselling or support will be provided by staff who are not members of the research team. In addition, you may prefer to suspend or end your participation in the research if distress occurs.
DXA and pQCT scans are routine clinical tests that are non-invasive and pain-free. However, the body is exposed to ionising radiation. For comparison, natural background radiation to which individuals living in developed countries are exposed is estimated to be around 2.4 mSv per year or nearly 40 times the effective dose for all the scans during this study.

There may be additional risks that the researchers do not expect or do not know about. Tell a member of the research team immediately about any new or unusual symptoms that you get.

7. **What if new information arises during this research project?**

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information and the researcher will discuss how this information affects you.

8. **Can I have other treatments during this research project?**

It is important to tell your doctor and the research staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your doctor about any changes to these during your participation in the research.

9. **Are there alternatives to participation?**

Participation in this research is not your only option. Your other option includes not consenting to participate in the study. Discuss these options with your healthcare worker before deciding whether or not to take part in this research project.

There is currently no standard exercise prescription for breast cancer survivors.

10. **Do I have to take part in this research project?**

Participation in any research project is voluntary. If you do not wish to take part you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your treatment by the Princess Alexandra Hospital, Gold Coast Hospital or the Mater Adult Hospital and will not affect your relationship with any of the healthcare team or your relationship with Griffith University.

11. **What if I withdraw from this research project?**
If you decide to withdraw, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

If you decide to leave the project, the researchers would like to keep the data up until the withdrawal date that has been collected. This is to help them make sure that the results of the research can be measured properly. If you do not want them to do this, you must tell them before you join the research project.

12. Could this research project be stopped unexpectedly?
You will be advised should this project be stopped unexpectedly before the completion of the project. Reasons that this project may be stopped could include unpredictable adverse events.

13. How will I be informed of the results of this research project?
You will receive feedback on the assessments including your body composition, muscle strength, function and fatigability by the Principal researcher and the student researcher in consultation sessions and at the conclusion of the result analysis.

14. What else do I need to know?
• What will happen to information about me?
The questionnaires, together with data on CD-ROMs will be stored in a locked cabinet within the School of Physiotherapy and Exercise Science at the Gold Coast Campus of Griffith University. The data and information is expected to be disposed off after the conclusion of the PhD candidature.

The data from muscle assessments will be re-identifiable (coded) for the purpose of relating drug dosage to muscle changes during the study. The survey questionnaires will be non-identifiable.

The individual questionnaires will be in paper form and any spreadsheet generated from these questionnaires will be stored on CD-ROMs in a safe, secure location at the Griffith University. The Principal Investigator, the associate investigators and the student researcher will have access to the information and will be involved in the analysis of data. The information derived from participants will only be for the sole use of analysis, interpretation and reporting in general terms.
The information and data will be stored for a period of five (5) years to allow the candidature of the student researcher’s PhD program to be completed. The data and information will be disposed off after the conclusion of the PhD candidature.

The participant consent is requested for this project only. The information derived from participants will only be for the sole use of analysis, interpretation and reporting in general terms.

There will be no databank established in this project.

Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at Princess Alexandra Hospital, Gold Coast Hospital or the Mater Adult Hospital for the purposes of this research.

In any publication and/or presentation, information will be provided in such a way that you cannot be identified. The information derived from participants will only be for the sole use of analysis, interpretation and reporting in general terms. Confidentiality will be maintained by assigning a code for each participant.

It is desirable that your local doctor be advised of your decision to participate in this research project. By signing the consent section, you agree to your local doctor being notified of your decision to participate in this research project. Information about your participation in this research project may be recorded in your health records.
• **How can I access my information?**

In accordance with relevant Australian and/or Queensland privacy and other relevant laws, you have the right to access the information collected and stored by the researchers about you. You also have the right to request that any information, with which you disagree, be corrected. Please contact one of the researchers named at the end of this document if you would like to access your information.

• **What happens if I am injured as a result of participating in this research project?**

If you suffer an injury as a result of participating in this research project, hospital care and treatment will be provided by the public health service at no extra cost to you if you elect to be treated as a public patient.

• **Is this research project approved?**

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of the Princess Alexandra Hospital, Mater Adult Hospital and the Griffith University.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)* produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

**Privacy statement**

The conduct of this research involves the collection, access and / or use of your identified personal information. The information collected is confidential and will not be disclosed to third parties without your consent, except to meet government, legal or other regulatory authority requirements. A de-identified copy of this data may be used for other research purposes. However, your anonymity will at all times be safeguarded. For further information consult the University’s Privacy Plan at [www.griffith.edu.au/ua/aa/vc/pp](http://www.griffith.edu.au/ua/aa/vc/pp) or telephone (07) 3735 5585.
15. Consent

I have read, or have had read to me in a language that I understand, this document and I understand the purposes, procedures and risks of this research project as described within it.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Griffith University concerning my disease and treatment that is needed for this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described.

I understand that I will be given a signed copy of this document to keep.

Participant’s name (printed) .................................................................
Signature \hspace{1cm} Date

Name of witness to participant’s signature (printed) ..................................
Signature \hspace{1cm} Date

Declaration by researcher*: I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Researcher’s name (printed) .................................................................
Signature \hspace{1cm} Date

* A senior member of the research team must provide the explanation and provision of information concerning the research project.

Note: All parties signing the consent section must date their own signature.
16. **Who can I contact?**

Who you may need to contact will depend on the nature of your query, therefore, please note the following:

**For further information or appointments:**

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal researcher, Dr. Tracey Jason at 0420809723 or any of the following people:

Name: Prof. Lewis Adams  
Role: Associate Investigator  
Telephone: 0401058458  

OR  
Name: Ms. Suzanne Kuys  
Role: Physiotherapist  
Telephone: 0408198815

**For complaints:**

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Name: Dr. Gary Allen  
Position: Manager, Research Ethics  
Office for Research  
Bray Centre, Nathan Campus  
Griffith University  
Phone: 3735 5585  
E-mail: research-ethics@griffith.edu.au  

OR  
Name: Dr. Peng Tjun Choy  
Position: Manager Research Ethics, Centre for Health Research, Princess Alexandra Hospital  
Telephone: (07) 3176 7672

The Manager, Research Ethics will be promptly notified if any complaints about the ethical conduct of research are received.
9.3 Recruitment flyer – Healthy control participants

Can exercise minimise or eliminate physical side-effects associated with chemotherapy treatment for breast cancer?

Individuals who undergo chemotherapy for breast cancer often experience weight gain, strength loss and fatigue following their treatment. In collaboration with the Princess Alexandra, Gold Coast and Mater Adult Hospitals, the School of Physiotherapy and Exercise Science at Griffith University is investigating whether strength exercise can minimise or eliminate these unwanted side-effects.

We are seeking healthy women 35 to 70 years to participate in this study as a control for women who are scheduled to undergo chemotherapy as part of their treatment program.

This study has been approved by the Griffith University Human Research Ethics Committee: Protocol number: PES/12/09/HREC.

Participants will undertake strength exercise training which will include one supervised session at the School of Physiotherapy and Exercise laboratory at the Gold Coast campus, and two self-directed exercise sessions at home each week for a 12-week period.

All participants will be provided with an exercise kit that includes training equipment, an exercise demonstration video and a training diary. Body composition (fat and muscle mass), strength, and fatigability (the ease at which you fatigues) will be assessed before and after the exercise training program.

All participants will receive a report describing how their results compare with: 1) non-exercising breast cancer patients, and 2) exercising non-cancer patients, of similar ages.

If you are interested in volunteering for this study and/or would like further information please contact:

Ravin Lal
Griffith University
Ph: 04 0185 4740
E-mail: r.lal@griffith.edu.au

Prof. Lewis Adams
Griffith University
Ph: (07) 555 28992
E-mail: lewis.adams@griffith.edu
The Health Survey Questionnaire

Instructions for Completing the Questionnaire

Please answer every question. Some questions may look like others, but each one is different. Please take time to read and answer each question carefully by filling in the bubble that best represents your response.

Example

This is for your review. Do not answer this question. The questionnaire begins with the section *Your Health in General* below.

For each question you will be asked to fill in a bubble in each line:

1. How strongly do you agree or disagree with each of the following statements?
   
<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Uncertain</th>
<th>Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
<td></td>
<td>Disagree</td>
</tr>
</tbody>
</table>

   a) I enjoy listening to music
   
   b) I enjoy reading magazines
Please begin by answering the questions now.

### Your Health in General

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

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very Good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>○₁</td>
<td>○₂</td>
<td>○₃</td>
<td>○₄</td>
<td>○₅</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>○₁</td>
<td>○₂</td>
<td>○₃</td>
<td>○₄</td>
<td>○₅</td>
</tr>
</tbody>
</table>

*Please turn the page and continue.*
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity Description</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b) Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>c) Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>d) Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e) Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>f) Bending, kneeling, or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>g) Walking more than a mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>h) Walking several hundred yards</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>i) Walking one hundred yards</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>j) Bathing or dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or regular daily activities as a result of your physical health?
5. During the **past 4 weeks**, how much of the time 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)?

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Cut down the <strong>amount of time</strong> you spent on work or other activities</td>
<td>○₁</td>
<td>○₂</td>
<td>○₃</td>
<td>○₄</td>
<td>○₅</td>
</tr>
<tr>
<td>b) <strong>Accomplished less</strong> than you would like</td>
<td>○₁</td>
<td>○₂</td>
<td>○₃</td>
<td>○₄</td>
<td>○₅</td>
</tr>
<tr>
<td>c) <strong>Were limited in the kind of work or other activities</strong></td>
<td>○₁</td>
<td>○₂</td>
<td>○₃</td>
<td>○₄</td>
<td>○₅</td>
</tr>
<tr>
<td>d) Had <strong>difficulty</strong> performing the work or other activities (e.g. it took extra effort)</td>
<td>○₁</td>
<td>○₂</td>
<td>○₃</td>
<td>○₄</td>
<td>○₅</td>
</tr>
</tbody>
</table>
6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

9. These questions are about how you feel and how things have been with you during the **past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**….

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b) Have you been very nervous?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>c) Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>d) Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>e) Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>f) Have you felt downhearted and</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
9.0

Appendices

<table>
<thead>
<tr>
<th>depressed?</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>g) Did you feel worn out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>h) Have you been happy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i) Did you feel tired?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>o1</td>
<td>o2</td>
<td>o3</td>
<td>o4</td>
<td>o5</td>
</tr>
</tbody>
</table>

11. How **true** or **false** is each of the following statements for you?

<table>
<thead>
<tr>
<th></th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) I seem to get sick a little easier than other people.</td>
<td>o1</td>
<td>o2</td>
<td>o3</td>
<td>o4</td>
<td>o5</td>
</tr>
<tr>
<td>b) I am as healthy as anybody I know</td>
<td>o1</td>
<td>o2</td>
<td>o3</td>
<td>o4</td>
<td>o5</td>
</tr>
<tr>
<td>c) I expect my health to get worse</td>
<td>o1</td>
<td>o2</td>
<td>o3</td>
<td>o4</td>
<td>o5</td>
</tr>
<tr>
<td>d) My health is excellent</td>
<td>o1</td>
<td>o2</td>
<td>o3</td>
<td>o4</td>
<td>o5</td>
</tr>
</tbody>
</table>
9.5 Multi-dimensional Fatigue Inventory – MF1-20

MULTIDIMENSIONAL FATIGUE INVENTORY

This questionnaire measures fatigue, a symptom commonly experienced by people undergoing treatment for cancer. Using the following statements we would like to get an idea of how you have been feeling lately. There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is entirely true, that indeed you have been feeling relaxed lately, please, place an X in the extreme left box; like this:

| yes, that is true | X | no, that is not true |

The more you disagree with the statement, the more you can place an X in the direction of "no, that is not true". Please, do not miss out a statement and place one X next to each statement.

<p>| 1. I feel fit | yes, that is true | no, that is not true |
| 2. Physically I feel only able to do a little | yes, that is true | no, that is not true |
| 3. I feel very active | yes, that is true | no, that is not true |
| 4. I feel like doing all sorts of nice things | yes, that is true | no, that is not true |
| 5. I feel tired | yes, that is true | no, that is not true |
| 6. I think I do a lot in a day | yes, that is true | no, that is not true |
| 7. When I am doing something, I can keep my thoughts on it | yes, that is true | no, that is not true |
| 8. Physically I can take on a lot | yes, that is true | no, that is not true |
| 9. I dread having to do things | yes, that is true | no, that is not true |
| 10. I think I do very little in a day | yes, that is true | no, that is not true |
| 11. I can concentrate well | yes, that is true | no, that is not true |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>12. I am rested</td>
<td>yes, that is true</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. It takes a lot of effort to concentrate on things</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>14. Physically I feel I am in a bad condition</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>15. I have a lot of plans</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>16. I tire easily</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>17. I get little done</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>18. I don't feel like doing anything</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>19. My thoughts easily wander</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
<tr>
<td>20. Physically I feel I am in an excellent condition</td>
<td>yes, that is true</td>
<td></td>
<td>no, that is not true</td>
</tr>
</tbody>
</table>
9.6 Participant record sheet

### Patient Biodex Record

**Patient Profile**

- **Patient ID:** 
- **Surname:** 
- **First Name:** 

**Patient Vital Data**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Height</th>
<th>Weight</th>
<th>BMI</th>
<th>Blood Pressure</th>
<th>Any other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Biodex parameters**

<table>
<thead>
<tr>
<th>Visit</th>
<th>Date</th>
<th>Seat Length</th>
<th>Seat Height</th>
<th>Knee attachment length</th>
<th>Any other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
9.7 Ethics Approval – Griffith University

GRIFITHE UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

09-Oct-2009

Dear Dr. Jason,

I write further to the additional information provided in relation to the conditional approval granted to your application for ethical clearance for your project “PRIOR REVIEW: Investigation of an exercise intervention to improve skeletal muscle function after anthracycline-taxane adjuvant chemotherapy in breast cancer survivors” (GJ Ref No: FES/12/09/HREC).

This is to confirm receipt of the remaining required information, assurances or amendments to this protocol.

Consequently, I reconfirm my earlier advice that you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

Dr Gary Allen
Manager, Research Ethics
Office for Research
Bray Centre, Nathan Campus
Griffith University
ph: 3735 5365
fax: 3735 7994
email: g.allen@griffith.edu.au
web:

CC:

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9.8 Ethics Approval – Princess Alexandra Hospital

APPROVAL LETTER – PRINCESS ALEXANDRA HOSPITAL

Dear Dr Jason

Research Protocol: HREC/09/QPAH/172

Investigation of an exercise intervention to improve skeletal muscle function after anthracycline-taxane adjuvant chemotherapy in breast cancer survivors

NEAF Version 2.0, dated 18 June 2009
Participant Information and Consent Form Version 1, dated 16 June 2009
The Health Survey Questionnaire Multidimensional Fatigue Inventory

At a meeting of the Metro South Health Service District Human Research Ethics Committee (MSHSD HREC) held on 7 July 2009, the Committee reviewed the above research Protocol. The Metro South Health Service District Human Research Ethics Committee is duly constituted, operates in accordance and complies with the current National Health and Medical Research Council’s National Statement on Ethical Conduct in Human Research 2007.

On the recommendation of the Human Research Ethics Committees approval is granted for your project to proceed. This approval is subject to researcher(s) compliance throughout the duration of the research with certain requirements as outlined in the National Statement on Ethical Conduct in Human Research 2007 and Australian Research Code for the Responsible Conduct of Research.

The following links have been provided for your convenience:

Some requirements are briefly outlined below. Please ensure that you communicate with the PAH HREC on the following:

- Protocol Changes: Substantial changes made to the protocol require HREC approval.
9.9 Ethics Approval – Mater Adult Hospital

MATER HEALTH SERVICES HUMAN RESEARCH ETHICS COMMITTEE

8th June 2010

Dr Tracey Jason
Griffith University
Gold Coast Campus
G16.3.29
Gold Coast QLD 4222

Dear Dr Jason


I write to advise that the Mater Health Services Human Research Ethics Committee considers the above study to meet the requirements of the National Statement on Ethical Conduct in Human Research (2007) and has granted ethical approval for your research proposal. Please accept our very best wishes for the success of this study. In all future correspondence with the Committee please quote the Mater reference number.

Documents reviewed and approved include:
- Correspondence dated 10th May 2010, responding to additional questions raised by Mater HREC members – including Participant Information Sheet and Study flyer – postmenopausal breast cancer patients under 70 years
- Letter dated 14th May 2010, responding to questions raised by Mater HREC members – including Participant Information Sheet and Study flyer – postmenopausal breast cancer patients under 70 years
- Letter dated 29th January 2010, including email correspondence between Griffith University Legal Unit and Rogerscamp and Company
- Correspondence dated 5th August 2009, regarding confirmation of indemnity cover
- NEA* Version 2.0
- Mater Ethics Application Form
- The Health Survey Questionnaire
- Multidimensional Fatigue Inventory
- Study flyer – for postmenopausal breast cancer patients under 70 years
- Study flyer – postmenopausal healthy women under 70 years
- Participant Information Sheet
- Consent Form
- CV for Principal Investigator
- Staff Information Sheet dated 20th January 2010
- Letter dated 3rd August 2004, from Griffith University Human Research Ethics Committee
- Letter dated 20th February 2009, from Griffith University Human Research Ethics Committee
- Budget
- Correspondence dated 13th July 2009, from Princess Alexandra Hospital Research Ethics Committee
- Letter dated 31st July 2009, responding to the questions raised by PAH HREC

Mater Health Services
Exceptional People. Exceptional Care.
9.10 Ethics Approval – Gold Coast Hospital

District Research Governance
24 February 2011

Enquiries to:
Phone: 
Fax:  
Our Ref: 
E-mail:  

Ian Pieper
Queensland Health
(07) 5519 7272
(07) 5519 8718
SSA/11/QGC/9
Ian_Pieper@health.qld.gov.au

Professor Lewis Adams
School of Physiotherapy and Exercise Science
Griffith University Gold Coast Campus
QLD
4222

Dear Professor Adams

HREC reference number: HREC/09/QPAH/172
SSA reference number: SSA/11/QGC/9

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following site(s):

• Gold Coast Health Service District

The following conditions apply to this research proposal. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval.

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project are to be submitted to the HREC for review. A copy of the HREC approval/rejection letter must be submitted to the RGO;
2. Proposed amendments to the research protocol or conduct of the research which only affects the ongoing site acceptability of the project, are to be submitted to the research governance officer;
3. Any proposed amendments to the research protocol or conduct of the research which may affect both the going ethical acceptability of the project and the site acceptability of the project are to be submitted firstly to the HREC for review and then to the research governance officer after a HREC decision is made.

Yours sincerely

Ian Pieper
Research Governance Officer
Gold Coast Health Service District

for Naomi Dryer
District CEO or Delegate
Gold Coast Health Service District
9.11 Radiation Use Licence – Ravin Lal

Radiation Safety Act 1999

Use Licence

Mr Ravin Lal

is, subject to any conditions mentioned in the Act or herein imposed by the Chief Executive, allowed to use:

<table>
<thead>
<tr>
<th>Radiation source</th>
<th>To carry out the radiation practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual energy X-ray absorptiometry radiation apparatus</td>
<td>Estimation of body composition under the guidance and mentorship of a person who holds an unrestricted licence to use DXA radiation apparatus.</td>
</tr>
<tr>
<td>Peripheral quantitative computed tomography radiation apparatus (5mA max)</td>
<td>Estimation of body composition under the guidance and mentorship of a person who holds an unrestricted licence to use peripheral quantitative computed tomography radiation apparatus (5mA max)</td>
</tr>
</tbody>
</table>

Delegated of the Chief Executive Date

16/05/2013 Replcy Date

This licence supersedes and replaces licence no. 2332-8-5618427U which is hereby cancelled.