Effect of resistance training on natural killer cell activity in women treated for breast cancer treatment: Findings from a randomised controlled trial

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Acknowledgements and Dedications

It feels like this process has been such a significant chunk of my young adult life that I’m not sure where to begin as there are so many people to thank. My PhD journey began a year and a half prior to the enrolment of this PhD. I had an amazing job, but a feeling that I wanted to continue on into academia. Meeting and developing a project with an incredible inspirational supervisor gave me the confidence to give up my job and come back to study. I am so grateful to Dr Johann Edge for encouraging me and for helping me reignite the post-masters passion for research. One day I hope to be able to finish the research we had planned. Rest in Peace Hans.

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**Statement of authentication**

The work presented in this thesis is to the best of my knowledge, my own original work, except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Amanda Dairne Hagstrom
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<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>ACSM</td>
<td>American College of Sports Medicine</td>
</tr>
<tr>
<td>BMD</td>
<td>Bone Mineral Density</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CTL</td>
<td>Cytotoxic Lymphocyte</td>
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<tr>
<td>CTAK</td>
<td>Cutaneous T-cell Attracting Chemokine</td>
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<tr>
<td>FAB-Q</td>
<td>Fear Avoidance Beliefs Questionnaire</td>
</tr>
<tr>
<td>FACIT fatigue</td>
<td>Functional Assessment of Chronic Illness Therapy - Fatigue</td>
</tr>
<tr>
<td>FACT-G</td>
<td>Functional Assessment of Cancer Therapy - General</td>
</tr>
<tr>
<td>FACT-G PWB</td>
<td>Physical well-being</td>
</tr>
<tr>
<td>FACT-G EWB</td>
<td>Emotional well-being</td>
</tr>
<tr>
<td>FACT-G SWB</td>
<td>Social well-being</td>
</tr>
<tr>
<td>FACT-G FWB</td>
<td>Functional well-being</td>
</tr>
<tr>
<td>FACS</td>
<td>Fluorescence-activated cell sorting</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>HIF1-α</td>
<td>Hypoxia-inducible factor one alpha</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>ISAK</td>
<td>The International Society for the Advancement of Kinanthropometry</td>
</tr>
<tr>
<td>JNK</td>
<td>c-Jun N-terminal kinase</td>
</tr>
<tr>
<td>NF-κB</td>
<td>Nuclear Factor Kappa-light-chain-enhancer of activated B cells</td>
</tr>
<tr>
<td>NK</td>
<td>Natural Killer Cell</td>
</tr>
<tr>
<td>NKT</td>
<td>Natural Killer T-Cell</td>
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<tr>
<td>NKCA</td>
<td>Natural Killer Cell Activity</td>
</tr>
<tr>
<td>QOL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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<tr>
<td>SAA</td>
<td>Serum Amyloid A</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form - thirty six</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>Short form - thirty six Physical Component Summary</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>Short form - thirty six Mental Component Summary</td>
</tr>
<tr>
<td>STAT3</td>
<td>Signal Transducer and Activator of Transcription three</td>
</tr>
<tr>
<td>T(_{H1})</td>
<td>Type one helper T-cell</td>
</tr>
<tr>
<td>T(_{H2})</td>
<td>Type two helper T-cell</td>
</tr>
<tr>
<td>TNF-(\alpha)</td>
<td>Tumour necrosis factor-alpha</td>
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ABSTRACT

Background: Previous research has shown that traditional cancer treatments such as surgery, chemotherapy and radiotherapy have a negative impact on immune system functioning. Aerobic exercise has been shown to be beneficial in improving immune function in this population; however, to-date no study has examined isolated resistance training on the markers of immune function and inflammation in this cohort. The purpose of this study was to determine the effect of resistance exercise on the function of natural killer cells in breast cancer survivors. A secondary objective of this study was to determine the effect of resistance training on additional immunological and inflammatory variables, quality of life variables, strength, and body composition. The final objective of this study was to explore potential relationships between primary and secondary outcome measurements.

Methods: Thirty-nine breast cancer survivors were randomly assigned to an exercise (n = 20) or a control (n = 19) group. The exercise group trained three times per-week for 16 weeks in a supervised resistance training laboratory gym. The control group did not perform resistance training. The primary outcome for this study was immune function measured through makers of natural killer cell function. Secondary outcomes were additional measurement of inflammation (serum TNF-α, IL-6, IL-10, and CRP), as well as changes in body composition, strength, quality of life, and fatigue. Statistical analysis consisted on the primary outcome consisted of paired and independent T-tests (α < 0.05) conducted according to intention to treat.
principles. Correlations were utilised to assess relationships as dictated in the third objective.

**Results:** Thirty four women completed the study. Baseline characteristics did not differ between groups except that more women were Caucasian in the control group and more women were taking Arimidex in the exercise group. Intention to treat analysis revealed a significant difference between groups for change in natural killer cell expression of TNF-α ($p = 0.004$, ES = 1.01). Median CRP concentration in the exercise group reduced -0.5mg/L (IQR -0.35 to 0.08). Median CRP concentration in the control group remained constant (0.00mg/L change, IQR -0.10 to 1.10) There were no other significant differences between groups in any other marker of immune function or inflammation. Intention to treat analysis also revealed significant between group differences for change in QOL as measured by the Functional Assessment of Cancer Therapy - General ($p = 0.018$, ES 0.79), and fatigue as measured by the Functional Assessment of Cancer Therapy - Fatigue scale ($p = 0.011$, ES 0.86), and all markers of strength ($p <0.001$ ES ranging from 1.48 to 1.83). No between group changes were observed in the SF-36, percentage body fat, and body weight or body mass index.

**Discussion and Conclusion:** These data demonstrates that resistance training has a beneficial effect on the natural killer cell expression of TNF-α. It remains to be elucidated whether this change has clinical implications. A potential mechanism has been proposed linking alterations in muscle mass with changes in immune functioning and inflammatory profiles. These data also demonstrates the benefit of resistance training for improving quality of life, fatigue and muscular strength. The significant reduction of natural killer
cell expression of TNF-α in combination with a clinically significant reduction in CRP demonstrates that resistance training may be beneficial in improving the inflammatory profile in breast cancer survivors. In addition, the significant improvement in QOL, perceived fatigue, and muscular strength, highlight the wide reaching benefits of resistance training.
1 INTRODUCTION

1.1 Background

Breast cancer is the most commonly diagnosed invasive cancer in women [1]. According to the American Cancer Society, over 1.3 million women worldwide are diagnosed with breast cancer each year [1]. In Australia, an estimated 15,000 new cases are diagnosed annually and this number is projected to rise significantly in the future [2]. The incidence of breast cancer continues to increase in both developed and developing countries [1], and while marked improvements have been noted in 5-year survival [2], mortality rates remain high. In Australia, breast cancer ranks behind only cardiovascular disease, dementia, and lung cancer as the leading cause of death in women [2].

It has been suggested that there are six essential alterations, collectively known as hallmarks of cancer, in cell physiology that must occur mutually for tumour growth to occur [3]. The combination of self-sufficiency in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, limitless potential to replicate, sustained angiogenesis, and tissue invasion and metastasis are all required simultaneously [3]. In addition to these six alterations, Colotta and colleagues proposed that inflammation be included as the seventh commonality of cancer [4]. These authors defined the key features of cancer related inflammation to include the infiltration of white blood cells, the presence of cytokines such as Tumour Necrosis Factor alpha...
(TNF-α), Interleukin six (IL-6), and interleukin one (IL-1), and the incidence of tissue remodelling and angiogenesis [4]. Recently Hanahan and Weinberg [5] updated their previous review to include two new additional emerging hallmarks of cancer: reprogramming of energy metabolism, and evading immune destruction [5]. These authors also concluded that inflammation was not a hallmark of cancer, rather an enabling characteristic. Along with tumour promoting inflammation, the authors identified genomic instability and mutation as an addition enabling characteristic [5]. Each of these changes in cellular physiology represent successful penetration of the body’s anticancer defence mechanism [3].

Specific cells within the immune system and individual markers of inflammation have previously been targets of exercise interventions. Natural killer (NK) cells are specialised lymphocytes within the innate immune system that serve as the first line of defence against cancerous and virus-infected cells and tumours [6, 7]. NK cells, therefore, play a critical role in the prevention of cancer recurrence [8, 9]. Signalling mechanisms, which involve interferons, cytokines, and both inhibitory and activating cell receptors (e.g. CD158b, CD94, CD107a), tightly regulate natural killer cell activity (NKCA) [7, 10]. Activating signalling mechanisms trigger binding of the natural killer cell to the target cell, which upon activation allow the NK cell to kill the target cell by directed exocytosis of secretory lysosomes, also called cytotoxic granules, such as granzyme B and perforin. NK cells also trigger adaptive immune system responses via secretion of many cytokines and chemokines [11].
Individuals diagnosed with cancer exhibit lower NKCA than the general population [6, 12-17] and the level of immunosuppression is most severe in advanced cases [13, 17-19]. Clinical trials have consistently shown that women with breast cancer suffer from low NKCA [14, 16]. Contributing factors include the tumour itself, and the use of invasive and cytotoxic therapies, including surgery [20, 21], chemotherapy [21-23], and radiotherapy [13]. Impairment of NKCA renders these individuals more susceptible to infections and contributes to longer disease durations [17].

The secretion of various cytokines by immunological cells, including NK cells, forms another important part of the immune response. Cytokines mediate the immune and inflammatory responses [24] and hence establish the cancer microenvironment. Common cytokines involved in the immune response to breast cancer include IL-6, IL-10, and TNF-α, one of the key mediators in the inflammatory response in cancer [25]. Elevated levels of TNF-α are present in many pre-cancerous and malignant diseases, including breast cancer, when compared to serum and tissue of healthy controls [25, 26]. In breast cancer patients, high TNF-α levels are correlated with node involvement and larger tumour sizes [27].

Aerobic exercise has been demonstrated to be an effective stimulus for improving immune function in breast cancer survivors [28, 29]; however, little is currently known regarding the effectiveness of resistance training to alter immune function and markers of inflammation in this population. Evidence from other populations, particularly ageing individuals, who also suffer from
chronic low grade inflammation [30], demonstrates the anti-inflammatory and beneficial immunological effect of resistance training [31-34]. While the mechanism eliciting the change in the inflammatory profile is currently unknown, it has been hypothesised that IL-6, released from contracting skeletal muscle [35] mediates many of exercises health related benefits including the inhibition of key pro-inflammatory cytokines such as TNF-α [35, 36]. Higher levels of TNF-α have been linked with reduced muscle mass, reduced muscular strength, and lower levels of protein synthesis [32, 37], and as such observing a reduction would be an important endpoint in resistance training studies. In addition, the reduction of inflammatory markers, increased muscle protein synthesis, and improved glucose metabolism have also been suggested to be contributing factors in the alteration of NKCA [38], suggesting a common mechanism contributing to both the inflammatory and immunological change.

Resistance training is a highly efficacious exercise modality that can counteract the effects of ageing and chronic disease by eliciting a distinct spectrum of physiological adaptations that cannot be achieved with other modes of exercise training. Documented benefits of resistance training in women recovering from breast cancer treatment include the improvement of upper-body muscular strength and endurance, range of motion [39-41], self-esteem [42], bone mineral density [43, 44] and body composition [39, 40, 45].

Resistance training is the preferred exercise modality for increasing lean muscle mass via net protein synthesis accretion, and empirical evidence
suggests that resistance training normalises circulating hormonal and pro-inflammatory cytokine levels in women with breast cancer and other clinical cohorts [40]. Hence, there is a physiological rationale for evaluating the effect of isolated resistance training on NK cell function and the inflammatory profile in women recovering from breast cancer. The enhancement of NK cell function following resistance training may be accompanied by many other clinically meaningful health-related adaptations, further, interventions that improve NK cell function and the inflammatory profile may enhance survival in women recovering from breast cancer treatment [46].

1.1.1 Statement of the problem

Breast cancer survivors often demonstrate marked immunosuppression in the period following cancer treatment. While aerobic exercise has demonstrated positive benefits, and potential mechanisms have been identified, the exact way in which exercise modulates the immune and inflammatory profile remains unclear. The promising evidence from aerobic exercise, combined with evidence examining resistance training and the inflammatory response in other clinical populations provides solid rationale to examine the effect of resistance training in breast cancer survivors which has yet to be explored. Identifying a relationship between resistance training and the immune system will be beneficial as it may lead to more appropriate rehabilitation programs following cancer treatment.
1.1.2 Experimental hypothesis and objectives

The objectives of this study were threefold. Firstly, the primary objective of this study was to implement a 16-week randomised controlled trial to evaluate the effect of resistance training on markers of natural killer cell function in women recovering from breast cancer treatment. I hypothesised that those individuals randomised to the resistance training intervention would show improvements in markers of natural killer cell function at the end of the trial.

A secondary objective of this study was to determine the effect of resistance training on additional markers of immune function and inflammation, quality of life, fatigue and muscular strength in this population. I hypothesised that resistance training would lead to improvements in the inflammatory profile, QOL, fatigue, and muscular strength.

The final objective of this study was to explore the relationships between primary and secondary objective outcomes. I hypothesised that improvements in immune function would be related to improvements in body composition, strength and QOL. I also hypothesised that improvements in strength would be related to improvements in body composition, QOL, and fatigue.
1.1.3 Significance of the study

The proposed research contributed to the literature in the field of exercise immunology. This study is the only study at present to examine the effect of resistance exercise on the function of natural killer cells in breast cancer survivors. It may be an important step in helping to develop multi-disciplinary approaches to cancer rehabilitation.
2 LITERATURE REVIEW

2.1.1 An overview of the immune system

The immune system is a complex system comprised of a multitude of interactive cells, cytokines, humoral factors, and lymphoid organs [47]. The immune system is divided into two sections; the innate immune system, and the adaptive immune system [47]. The innate immune system is responsible for the rapid reaction to a stimulus and includes neutrophils, monocytes, macrophages, cytokines [47]. The second component, the adaptive immune system, acts through T and B lymphocytes to provide an antigen specific response, and as such, takes longer to develop than the innate response [47]. Both the adaptive and innate immune system play a part in the response to tumour development [48]. These separate components are discussed below with specific regard to breast cancer development and progression.

2.1.2 Breast cancer development and progression

Cancer represents an umbrella term for a myriad of conditions occurring as a result of excessive and uncontrolled cellular division. Alteration of the genome that affects the function or expression of genes that control cell growth is thought to be the main cause of cancer [49]. In their seminal publication Hanahan and Weinberg [3] proposed six hallmarks of cancer
development: Self-sufficiency in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, limitless potential to replicate, sustained angiogenesis, and tissue invasion and metastasis [3]. Recently, over a decade later, this publication has been updated to include the addition of two new emerging hallmarks; the reprogramming of energy metabolism, and evading immune destruction [5]. In addition to the two new emerging hallmarks, these authors also defined two key enabling characteristics; tumour promoting inflammation, and genome instability and mutation [5]. Colotta and colleagues [4] defined the key features of cancer related inflammation to include the infiltration of white blood cells, the presence of cytokines such as Tumour Necrosis Factor alpha (TNF-α), Interleukin six (IL-6), and interleukin one (IL-1), and the incidence of tissue remodelling and angiogenesis [4].

Two pathways have been proposed to link inflammation with cancer development (Figure 1). Firstly the extrinsic pathway which is triggered by inflammation or infections and is responsible for approximately 15% of all cancers [50]. The second pathway, the intrinsic pathway is activated by oncogenes [51]. While a definitive progression model for breast cancer development is yet to be established [52], there seems to be no direct inflammatory link involved in the initial development of breast cancer [51]. Therefore the probable pathway involved in the development of breast cancer likely involves oncogene activation as occurs in the intrinsic pathway [51].
Figure 1: The link between extrinsic and intrinsic pathways in the development of cancer related inflammation and subsequent cancer development.

Diagram adapted from Mantovani et al (2008) [51]. This diagram demonstrates the two known pathways in cancer development. Regardless of which initial pathway causes a tumour to arise, inflammation plays a significant role in the microenvironment and in the progression of the disease.
The extrinsic pathway is activated via infection or inflammation. Examples of infections or inflammation that lead to cancers include Hepatitis virus (B and C) which have been linked with an increased risk of liver cancer [53], some strains of human papilloma virus, which are known to cause cervical cancer [54] and the chronic condition, inflammatory bowel disease, which is linked with a dramatically increased risk of colon cancer [55].

The intrinsic pathway is dictated by genetic events and may be activated in response to an inactivation of tumour suppressor genes, chromosomal rearrangement or amplification, or the activation of oncogenes via mutation [51]. Even in tumours that develop as a result of oncogene activation there is inflammation in the microenvironment of these tumours unrelated to an initial inflammatory condition [4, 56]. For example, signs of inflammation are present in breast cancer, even though a direct causal inflammatory link has not been recognized [51]. This inflammation in the tumour environment causes many pro-tumorigenic effects including aiding the proliferation and survival of cancer cells, promotion of angiogenesis, inhibition of the immune responses [51] and metastasis [51, 56].

The initiation of either pathway causes transcription factors such as Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB), Signal Transducer and Activator of Transcription three (STAT 3) and Hypoxia-inducible factor one alpha (HIF-1α) to become activated in tumour cells.
These transcription factors are then involved in the production of inflammatory mediators including cytokines and chemokines [51]. These inflammatory mediators then activate the same transcription factors in inflammatory cells and tumour cells, resulting in further production of the inflammatory mediators and the creation of an inflammatory microenvironment (as seen in Figure 1) [51]. The microenvironment contains cells from the innate immune system including natural killer cells and neutrophils, in addition to cells from the adaptive immune system such as T and B lymphocytes [53]. These immune cells interact with the tumour cells and surrounding stroma in a complex fashion via direct contact or the production of cytokines and chemokines. In turn, these cytokines and chemokines act in an autocrine or paracrine way to control tumour progression [53]. The inflammatory response can cause local immunosuppression, effecting immune surveillance [53] and promoting metastatic spread [53].

While the underlying causes of the oncogene activation in breast cancer remain to be fully elucidated, there are many documented risk factors for the development of this disease [57] many of which are related to alterations in the hormonal profile. The hormonal profile is important in breast cancer development and progression due to its relationship with tumour type. Approximately 70-80% of breast cancers are oestrogen receptor positive [58, 59], meaning these tumours use hormones (oestrogen and/or progesterone) to fuel their growth. Hormone positive and hormone negative breast cancers
are recognised as two separate and distinct cancers [60] and thus likely have two different evolutionary pathways.

Early menarche, late menopause and obesity are all known risk factors for the development of breast cancer [57]. Both early menarche and late menopause increase the risk due to the increase in time of exposure to oestrogens. Obesity also increases oestrogen exposure via an increase in aromatization of oestrogens that occurs in adipose tissue (Please refer to section 2.2.1 for a detailed explanation of this interaction).

Reductions in the risk of breast cancer development also relate to hormonal changes. Surgically induced menopause (via oophorectomy) causes a reduction in breast cancer risk due to the decreased exposure to oestrogen. Further, the younger a woman is when the ovaries are removed, the greater the reduction in risk of developing breast cancer [61].

While there is strong evidence to support a hormonal link in breast cancer, there is also emerging research linking the alteration in the hormonal profile with inflammatory changes, connecting two of the most researched factors involved in cancer development and progression [51].
2.1.3 The immune system and cancer

According to Vesely and colleagues [62], the immune system plays three major roles in the prevention of cancer. First, the immune system can prevent virus-induced tumours (extrinsic pathway) by eliminating the viral infection. Secondly, the prompt elimination of pathogens can prevent the foundation of an inflammatory microenvironment helpful to tumourgenesis. Lastly, the immune system can identify and eliminate tumour cells based on the expression of tumour specific antigens. This final process is known as immune surveillance or immune-editing [62]. Immuno-editing involves the interaction of both the innate immune system and the adaptive immune system (described below).

The immune system is composed of two main components: the innate immune system and the adaptive immune system. The innate immune system is the first responder and contains cells such as macrophages, dendritic cells, natural killer cells, and natural killer T cells that form the first line of defence [63]. The adaptive immune system is comprised of T and B lymphocytes and their cytokines. Both the innate and adaptive components of the immune system are thought to play integral roles in the cancer fighting anti-tumour response [64].
2.1.3.1 *The innate immune system (Natural killer cells: The first line of defence)*

Natural killer (NK) cells are specialised lymphocytes that are the first line of defence against tumour and virus development [6, 7]. NK cells appear to be recruited to inflammatory sites [65] and their activity is regulated by a combination of interferons, cytokines and cell receptors [7, 10, 65]. Perforin and granzyme B induced apoptosis make up the primary pathway used by cytotoxic cells (cytotoxic lymphocytes, NK cells) to kill virus and tumour infected cells [66]. This pathway causes the NK cell to bind to the target virus or tumour cell releasing cytotoxic substances which induce apoptosis [67]. In addition to the initial eradication of target cells, NK cells play an important role in the development [68], growth and metastatic spread of tumours. Increased expression of perforin and granzymes on activated NK cells was significantly correlated with reduced tumour growth and metastatic spread in a mouse model [8]. Further demonstrating this link, several mice studies have demonstrated an enhanced growth and spread of multiple tumour types when NK cells are eliminated in vivo [69].

Individuals diagnosed with cancer exhibit lower natural killer cell activity (NKCA) than the general population [6, 12-17] and this has consistently been demonstrated in women with breast cancer [14, 16]. The level of immunosuppression is most severe in patients with metastases [17-19]. Contributing factors include the cancer itself, and the use of invasive and cytotoxic cancer therapies such as surgery [20, 21], chemotherapy [21-23]
and radiotherapy [13]. Impairment of NKCA causes these individuals to become more susceptible to infections and contributes to longer disease durations [17]. Interventions that improve NKCA may enhance survival and quality of life in women recovering from breast cancer treatment (Please refer to table 1 for a summary of the effects of breast cancer on immune function) [46].
Table 1: Selected examples of research demonstrating the effect of breast cancer on relevant markers of immune function and inflammation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participants (n)</th>
<th>Healthy/benign control comparison</th>
<th>Biomarker (s) measured</th>
<th>Effect of cancer on biomarker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham-Rundles et al. [14]</td>
<td>1981</td>
<td>83</td>
<td>Y</td>
<td>NKCA</td>
<td>↓ NKCA</td>
</tr>
<tr>
<td>Garner et al. [18]</td>
<td>1983</td>
<td>33</td>
<td>Y</td>
<td>NKCA</td>
<td>↓ NKCA. NKCA correlated with size of tumour and with metastasis</td>
</tr>
<tr>
<td>Levy et al. [70]</td>
<td>1991</td>
<td>90</td>
<td>N</td>
<td>NKCA</td>
<td>NKCA at follow up predicted disease free survival. ↓NKCA predicted higher chance of recurrence</td>
</tr>
<tr>
<td>White et al. [16]</td>
<td>1982</td>
<td>81</td>
<td>Y</td>
<td>NKCA</td>
<td>↓ NKCA. No correlation between NKCA and tumour size</td>
</tr>
<tr>
<td>Leek et al. [27]</td>
<td>1998</td>
<td>93</td>
<td>N</td>
<td>TNF-α</td>
<td>↑TNF-α</td>
</tr>
<tr>
<td>Heikkila et al. [71]</td>
<td>2009</td>
<td>4286</td>
<td>Y</td>
<td>IL-6, CRP</td>
<td>— CRP, ↑ IL-6</td>
</tr>
<tr>
<td>Kozlowski et al. [72]</td>
<td>2003</td>
<td>70</td>
<td>Y</td>
<td>IL-6</td>
<td>↑IL-6, ↑ IL-8, ↑ IL-10 levels also correlate with stage of disease</td>
</tr>
<tr>
<td>Pierce et al. [73]</td>
<td>2009</td>
<td>734</td>
<td>N</td>
<td>CRP</td>
<td>↑CRP and SAA associated with reduced survival</td>
</tr>
</tbody>
</table>

Abbreviations used: NKCA, Natural Killer Cell Activity; TNF-α, Tumour Necrosis Factor alpha; CRP, C- reactive protein; IL, interleukin; SAA, Serum Amyloid A.
2.1.3.2 The adaptive immune system (T lymphocytes)

The main type of cell involved in the adaptive immune response is the T lymphocyte. These cells are comprised of two subtypes, CD8+ cytotoxic T lymphocytes (CTL) and CD4+ helper T lymphocytes (T\textsubscript{H}) [63].

Cytotoxic T-lymphocytes (CTL) play an essential role in immune defence against viruses and cancer [63]. Once activated CTL produce cytokines and effector molecules including IFN-\gamma, perforin and granzyme B which are directly cytolytic to their target cells [63] and hence play an integral role in the immunosurveillance of cancer [63].

Helper T cells may be polarized to two different phenotypes (T\textsubscript{H}1 and T\textsubscript{H}2) depending on which cytokine they have been exposed to. T\textsubscript{H}1 cells predominantly secrete IFN-\gamma, TNF-\alpha, and IL-2 [63]. These cytokines secreted by the T\textsubscript{H}1 cells help antitumor immunity directly and via the subsequent activation and regulation of the cytotoxic T cells. This up-regulation of the CTL further helps due to increased perforin and granzyme availability for cytolytic activities [63]. Conversely, T\textsubscript{H}2 responses may enhance tumour growth and in fact inhibit antitumor immunity [63].
Innate immune responses often present as inflammatory responses which are essential for the initiation of adaptive immune responses [51]; however, the immune response may cause chronic inflammation, which then in turn helps the tumour grow through the change in the microenvironment and enhancement of factors such as angiogenesis [74]. Chronic inflammation has been suggested to provoke a change from the T\(_{H1}\) to the T\(_{H2}\) dominant microenvironment and hence enhance tumour progression [75]. The complex interaction of factors means that it is difficult to define which cells and cytokines are strictly pro or anti-tumorigenic [63]. The functional properties of these cells vary depending on mode of differentiation and on the influence of different cytokines in the tumour microenvironment [63].

2.1.3.3 Cytokines and inflammation

Cytokines are glycoproteins usually secreted by immune cells such as macrophages and activated T cells [76, 77]. They may act in a paracrine or autocrine manner [64]. These cells act on multiple different target cells and can affect the growth and function of immunocompetent cells [77]. This ability to activate or modulate antitumor responses may cause tumours to grow or to become inhibited [77]. In combination with T cells, cytokines mediate the immune and inflammatory responses [24] and hence establish the cancer microenvironment. Common cytokines involved in the immune response to breast cancer include TNF-\(\alpha\), IL-6, and IL-10. Levels of multiple
circulating cytokines have been shown to be significantly higher in survivors of breast cancer than in healthy controls [78].

2.1.3.3.1 Tumour Necrosis Factor alpha (TNF-α)

TNF-α is a central cytokine involved in human immune function and inflammatory responses [79] and was initially named 30 years ago due to its ability to cause destruction to tumour cells [26]; however, TNF-α is rarely cytotoxic to tumour cells unless additional treatments are provided [25]. In fact, TNF-α is one of the key mediators in the inflammatory response in cancer [25].

Activated macrophages are the primary source of TNF-α although they can also be produced by multiple other cell types including NK cells, T cells and tumour cells [25, 75]. The previously mentioned “hallmarks of cancer” [3] outlined multiple processes required for the successful growth of tumours. Chronic production of TNF-α is responsible for sustaining many of these processes [3]. Hence it is not surprising that elevated levels of TNF-α are present in many pre-cancerous and malignant diseases, including breast cancer, when compared to serum and tissue of healthy controls [25, 26]. In breast cancer patients, high TNF-α levels are correlated with node involvement and larger tumour sizes [27]. When patients of the same tumour type have been compared, higher TNF-α levels have also been correlated
with advanced tumour stage, shorter survival time and larger paraneoplastic complications [75].

The downstream signalling cascade that follows subsequent to TNF-α binding to its receptor is extremely complex and multifaceted. In vitro research has demonstrated increased invasiveness of breast cancer tumour cells following co-culture with macrophages. Macrophage production of TNF-α causes activation of two separate pathways (NK-KB and c-Jun N-terminal kinase (JNK)) leading to the increased invasive capacity of the tumour cells [80]. Further, multiple animal models have demonstrated increased cancer development and spread when the tumour microenvironment of TNF-α has been manipulated [25].

2.1.3.3.2 Interleukin-6

Interleukin-6 (IL-6) like most cytokines is a pleiotropic cytokine that has both tumour promoting and tumour inhibiting effects [64]. As most cytokines, macrophages and lymphocytes are responsible for the majority of the secretion of IL-6; however, adipose tissue also produces IL-6 [81]. The level of adipose tissue production of IL-6 increase with increasing levels of adiposity [81].
Elevated levels of IL-6 are linked with increased risk of developing breast cancer [71], although as of yet there is no evidence that this link is causal, rather it may linked to breast cancers relationship with adiposity [71]. Individuals with cancer often exhibit higher levels of circulating IL-6 than healthy populations [72, 82] with these levels being utilised as a negative prognostic indicator in breast cancer patients [64]. IL-6 has also been implicated in the regulation of oestrogen synthesis through its stimulatory actions on aromatase activity [83]. These functions of IL-6 fit with the previously proposed possible interaction of adipose tissue and oestrogen production in the development and progression of breast cancer.

2.1.3.3.3 Interleukin-10

Like TNF-α and IL-6, Interleukin-10 (IL-10) is also a pleiotropic hormone exhibiting both tumour inhibitory and promoting capabilities [84]. In contrast to these other cytokines, the predominant role of IL-10 is inhibitory with previous research in mouse models demonstrating the inhibition of growth and metastasis [85] and the rejection of tumours [86]. Higher levels of IL-10 have been observed in patients with lower levels of IL-6 and IL-8 [72]. Increased levels of IL-10 are often observed in the serum of breast cancer patients [84].
2.1.3.3.4 C-reactive protein

C-reactive protein (CRP) is an acute phase protein and a marker of systemic inflammation. Elevated levels of CRP are associated with increased risk of a variety of conditions including diabetes [87], hypertension [88], stroke [89], and some cancers [71, 90].

Average levels of CRP have been shown to be similar in women both with and without cancer [71]; however, if levels of CRP are elevated there is an equal association with decreased survival in both women with and without cancer [71]. Further, in those diagnosed with breast cancer, elevated levels of CRP are associated with decreased survival [73, 91].

2.1.3.3.5 Interferon gamma

Interferon gamma (IFN-γ) is a cytokine predominantly produced by NK and NKT cells. IFN-γ promotes the host immune response to tumours [92] and plays a part in inhibition of angiogenesis [92]. NKT cell production of IFN-γ is reduced in advanced cancer patients [93].
2.2 The detrimental effects of cancer

There are many detrimental effects of cancer including reductions in immune function [14, 16, 18] and increased markers of inflammation [27, 72, 73]. In addition to the cancer, its treatments have many negative effects such as alterations in body composition [94, 95], reductions in bone mineral density [96-98], reductions in immune function [13, 20], fatigue [99], quality of life [100], and strength [101, 102] that may persist after the completion of primary treatment. Negative shifts in body composition and bone mineral density losses are common. Reductions in strength, function, and impaired quality of life are also frequently observed.

2.2.1 Detriments in body composition

Breast cancer patients and survivors commonly experience adverse shifts in body composition as a consequence of specific cancer treatments [94, 95]. These negative shifts in body composition are often multifaceted with losses of skeletal muscle mass [94, 95, 103-105] and a concomitant increase in adiposity [95, 103, 106-108]. Changes in body composition may occur even in the absence of weight change. These two factors, low muscle mass (sarcopenia) and obesity, together comprise a specific condition known as sarcopenic obesity [109]. It is hypothesised that the negative effects of gains
in adiposity and losses in muscle mass may combine to maximise disability, morbidity, and mortality [110]. Both of these factors have separate and distinct consequences to health.

Although changes in body composition have been identified to be multifaceted, the exact mechanisms of these shifts remain largely unknown and may be a complex interaction of factors. Obesity, specifically central obesity, directly effects inflammation including the elevation of levels of CRP and IL-6 [111, 112]. It has been hypothesised that the up-regulation of proinflammatory cytokines associated with gains in fat mass may negatively affect muscle strength and contribute to the development of sarcopenic obesity [111]. This is reiterated by research showing that higher cytokine levels are associated with reduced muscle mass and strength in healthy older persons [37].

Along with the inflammatory processes, numerous treatment specific effects have been identified. The use of tamoxifen [113] and systemic chemotherapy [94, 114-116] contribute to weight gain. Resting metabolic rate declines during chemotherapy, as do physical activity levels [117] potentially contributing to the negative shift in body composition. In premenopausal women, treatment induced early onset menopause may also account for some of the changes in body composition [94, 114]. The shifts in body composition that occur as a result of treatment are characteristic of the
normal ageing process [118]; however, they are condensed into a period of approximately six months [94].

Increased adiposity has negative consequences specific to breast cancer survivors. It has been shown that increased fat mass results in higher rates of breast cancer development [119], recurrence, and mortality [120-122]. If the relationship between body mass index (BMI) and cancer is causally associated then estimates of breast cancer deaths attributed to overweight and obesity range from 30-50% [123]. Adipose tissue contains high levels of aromatase which is responsible for the conversion of androgens to oestrogens [124]. Obese post-menopausal women have an increased production of oestrogens [125] that play a role in the development and progression of breast cancer [124]. Exercise reduces adiposity, hence lowering the capacity for aromatization of androgens to oestrogens, lowering circulating oestrogens levels [126]. Women involved in heavy and moderate aerobic physical activity have a reduced frequency of breast cancers [127], likely associated with reductions in body fat and circulating oestrogens [126].

Losses of skeletal muscle mass can occur as a consequence of the cancer itself as well as treatments such as chemotherapy [95, 128], or as a result of the aging process. Current estimates suggest that approximately 16% of breast cancer survivors may suffer from sarcopenia [129]. Sarcopenia can be defined according to many differing cut-off points in a variety of outcomes including measures of muscles mass, strength, and physical performance.
A commonly utilised method is the skeletal muscle mass index (appendicular skeletal muscle mass/height$^2$). Cut-off points vary with respect to gender, with females having a lower cut-off point than males ranging from 5.5 to 7.26 kg/m$^2$ [130]. Sarcopenia causes a change to muscle quality, mass, and function [131] with the likely hood of functional impairment rising with increasing muscle wastage, particularly in women [132]. Decreases in muscle mass can also have negative consequences with losses of strength predicting reductions in future function and increasing disability in ageing populations [133]. An additional potential cause of muscle mass loss in this population is cancer cachexia. Cachexia is a multifaceted syndrome manifesting with anorexia, muscle wasting and weight loss, fatigue, weakness, and impaired immune function [134]. The syndrome is hypothesised to come about due to a combination of metabolic, hormonal, and cytokine related abnormalities which lead to inflammation and in turn cachexia; however, the exact aetiology and pathophysiology of this syndrome are not well understood [134]. A unique trait of cachexia is that it is unresolved by forced caloric intake [134]. Cytokines TNF-α, IL-6, IL-1 and IFN-γ have been implicated in the development of cachexia; however this is also not yet conclusive [134, 135]. The incidence of cachexia varies across tumour types and is a negative prognostic indicator. Breast cancer patients exhibit a comparatively low frequency of cachexia with only 31-40% of patients suffering from significant weight loss [134] compared to 83-87% of pancreatic and gastric cancer patients [134].
2.2.2 Detriments in musculoskeletal strength and function

Reductions in musculoskeletal strength and function are frequently reported following breast cancer and its treatments [136, 137] which is not surprising given the treatment, cancer, and ageing related atrophy discussed in the previous section.

Specific strength detriments attributed to cancer treatments include chemotherapeutic effects such as myotoxicity and neurotoxicity ultimately leading to reductions in force generating capacity of the muscle [138]. Reductions in strength are also frequently exhibited following surgery [102] and radiotherapy [101].

A significant portion of breast cancer survivors fit into the demographic of ‘ageing populations’ and hence undergo a further age dependent decrement in strength that is independent of cancer burden. Annual losses of strength in the otherwise healthy ageing population are in the magnitude of approximately 3% in those aged 70-79 years [139] and may be as high as 20–40% overall loss by these decades [140]. It has also been demonstrated that total losses of skeletal muscle cross sectional area are in the magnitude of 40% between 20 and 60 years of age [140]. In ageing populations losses of muscular strength are linked with future disability [141] and an increased risk of falls [142, 143]. When these age related changes in quality and quantity of muscle occur in conjunction with the negative effects of treatment,
significant limitations may occur. As mentioned in the previous ‘detrimental
effects on body composition’ this loss of muscle mass is often accompanied
by increases in fat mass [94, 144] further exacerbating the loss of functional
strength due to the ratio of muscle to fat.

Breast cancer survivors frequently report limitations in the use of their
surgical limb. Breast cancer survivors tend to report significant limitations in
upper body strength in the months following treatment [101] with many breast
cancer survivors reporting shoulder pain and disability [145]. In addition,
recent research demonstrates that between 9 and 28% of survivors
experience arm weakness [145] with muscular strength at the shoulder
decreased six months after cancer treatment [102], and the surgical side
weaker than the opposite untreated healthy limb [136, 137]. Consequences
of these reductions in strength and mobility include impacts on quality of life
[146] and limitations in activities of daily living [147].

2.2.3 Fatigue

Fatigue is a common and chronic problem for cancer patients and survivors.
Fatigue, as a symptom, has been defined as feelings of weakness, becoming
easily tired and lacking energy [148]. Cancer related fatigue has been
defined as “a common, persistent and subjective sense of tiredness related
to cancer or to treatment for cancer that interferes with usual functioning” [149]. Fatigue experienced by the general population and cancer related fatigue have been acknowledged to be separate and distinct conditions [150], likely with differing pathophysiology. Although definitions are now clear, the aetiology and pathophysiology of cancer related fatigue are not well understood.

The prevalence of fatigue varies, particularly with respect to treatment phase. A recent review across multiple cancer types concluded that at diagnosis 50-75% of patients suffered from fatigue. During chemotherapy this proportion went up to 80-90% of patients. The effects suffered during radiotherapy were more variable with 60-93% of patients suffering from fatigue [99]. Following cessation of treatment, levels of fatigue tend to decline; however, Bower and colleagues [151] demonstrated that one third of breast cancer survivors who were on average three years post treatment continued to report significant fatigue [151].

Multiple factors have been suggested to contribute to the development of cancer related fatigue including anaemia, cachexia, sleep disorders, and dysregulated cytokine production [152]. There is a shared commonality among these potential contributions with evidence suggesting that all of these factors contain an element of cytokine dysregulation with frequently elevated levels of IL-6 and TNF-α exhibited in all of these conditions [152]. In support of the link with cytokines, it has been demonstrated that fatigued
breast cancer survivors have significantly higher serum markers of proinflammatory activity [153], in particular IL-6 [154]. An alternative hypothesis is that the activation of the immune system in response to the tumour or treatments may be the cause of this fatigue [153].

Fatigue is commonly assessed in breast cancer survivors using a questionnaire called the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT). In a previous study on a variety of cancer populations, the average FACIT score was 36.76 ± 10.49 (range 6-52) out of a possible 52 [155]. In a subsequent study comparing cancer patients (n = 2405) with the general population (n = 1010), it was found that the general population averaged 43.6 ± 9.4 out of 52, an anaemic cancer group averaged 23.9 ± 12.6 and a non-anaemic cancer group averaged 40.0 ± 9.8 [150].

2.2.4 Quality of Life

Quality of life (QOL) is multidimensional concept and encompasses physical, psychological and social functioning [156]. Following breast cancer and its treatments, a large number of women are left with psychological and quality of life (QOL) impairments. These impairments in QOL vary greatly in nature and severity. The variations appear to be due to differences in time along the treatment continuum and age at diagnosis.
A recent systematic review found that approximately half of studies examining QOL in long term (> 5 years) breast cancer survivors reported a reduced QOL compared to healthy controls [100]. Higher QOL was likely found in those individuals who did not need chemotherapy, lack comorbid diseases and those who received emotional support from family and friends [100].

QOL is extremely variable and varies at differing points along the treatment continuum. One year after diagnosis, after acute treatment side effects have subsided, it has been demonstrated that the overall QOL of many breast cancer survivors does not differ from the general population [157]; however, a sub group of women, young breast cancer survivors, still tend to experience reductions in some domains of QOL at this time point [157]. Women who are diagnosed with breast cancer at a younger age are more likely to suffer from detriments to QOL [157-159] than both older women diagnosed with breast cancer and age matched members of the general population. In addition these deficits may last years after diagnosis [158].

Newly diagnosed and recurrent cancer patients exhibit the biggest negative impact on QOL [160]. This is in contrast to breast cancer survivors at the end of primary treatment, who report good emotional functioning but still suffer from impaired physical function [146]. This impaired physical functioning seems to be relatively chronic with fatigue, pain, arm problems
and sleep disturbances being reported 18 months following treatment [161]. Women with breast cancer report significantly larger reductions in self-reported QOL during aging compared to healthy women (measured by the SF-36) [162] which may persist even at ten years post diagnosis [162].

Quality of life is in breast cancer survivors is commonly measured in by the use of two separate questionnaires. The first scale, the Short Form 36 (SF-36) is a generic health questionnaire consisting of two subscales: The Physical Component Summary (PCS) and Mental Component Summary (MCS). Mean scores for the general population for both the PCS and MCS subscales are approximately 50 [163, 164]. Research utilizing this questionnaire in breast cancer survivors (average 3.5 years post diagnosis) found the PCS subscale average to be 50.8 and the MCS subscale average 49.6 [165] demonstrating similar results to the population norms. The second commonly utilised tool for assessing quality of life in breast cancer survivors is the Functional Assessment of Cancer Therpay General (FACT-G). The FACT-G consists of four subscales; Physical Wellbeing (PWB), Functional Wellbeing (FWB), Social Wellbeing (SWB), and Emotional Wellbeing (EWB). Across a variety of cancer types the average scores have been reported to be 81.92 ± 15.87 [166]. Changes of 2-3 raw scale points in subscales PWB and FWB [166] and an overall change of 5-7 raw scale points on the FACT-G have been suggested to be clinically meaningful [166].
2.2.5 Bone mineral density

The prevalence of osteoporosis in the general population is significant with almost 30% of otherwise healthy postmenopausal women sustaining an osteoporosis related fracture, and one third of these women sustaining multiple fractures [167]. Breast cancer treatments such as chemotherapy [96, 97, 168], chemotherapy related early onset menopause [98] and the use of aromatase inhibitors [168, 169] have been shown to accelerate bone loss. As a combined result of aging and breast cancer treatment, post-menopausal breast cancer survivors have been shown to be at an increased risk of fracture compared to age matched women [170, 171].

2.3 Exercise and Cancer

2.3.1 Exercise and its effects on immune function and inflammation

Aerobic exercise training has been investigated as a therapeutic adjunct to breast cancer treatment for nearly three decades. Studies that have prescribed aerobic training both during and following the completion of adjuvant therapies have demonstrated exercise can improve many aspects of recovery. Significant adaptations have included the improvement of cardiorespiratory fitness, cancer related fatigue, body composition, QOL, and
depression [21, 172-174]. The evidence also suggests that exercise training can cause multiple changes in immune functioning in cancer survivors (please refer to Error! Reference source not found. and Error! Reference source not found.).
Table 2: Findings from previous research examining exercise immunology outcomes in breast cancer patients and survivors

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Tumour type</th>
<th>Participants</th>
<th>Study design</th>
<th>Exercise modality</th>
<th>Exercise duration</th>
<th>Biomarker(s) measured</th>
<th>Effect in exercise group (↑↓↔)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutnick et al. [175]</td>
<td>2005</td>
<td>Breast</td>
<td>Women (n = 49)</td>
<td>Controlled</td>
<td>Combined</td>
<td>6 months</td>
<td>CD4⁺CD69⁺ #, production of IFN-γ and IL-6, Plasma IL-6, soluble IL-6 receptor, soluble gp130, IFN-γ</td>
<td>↑ % CD4⁺CD69⁺ activation. ↔ plasma markers</td>
</tr>
<tr>
<td>Peters et al. [29]</td>
<td>1994</td>
<td>Breast</td>
<td>Women (n = 24)</td>
<td>Observational</td>
<td>Aerobic</td>
<td>7 months</td>
<td>NKCA, NK#</td>
<td>NK# ↔, NKCA ↑</td>
</tr>
<tr>
<td>Nieman et al. [176]</td>
<td>1995</td>
<td>Breast</td>
<td>Women (n = 16)</td>
<td>RCT</td>
<td>Combined</td>
<td>8 weeks</td>
<td>NKCA, NK#</td>
<td>↔</td>
</tr>
<tr>
<td>Fairey et al. [28] [177]</td>
<td>2005</td>
<td>Breast</td>
<td>Women (n = 53)</td>
<td>RCT</td>
<td>Aerobic</td>
<td>15 weeks</td>
<td>NKCA, mononuclear cell phenotypes, production of IL-1α, TNF-α, IL-6, IL-4, IL-10, TGF-β1 by mononuclear cells, stimulated and unstimulated lymphocyte proliferation, CRP</td>
<td>NKCA ↑, unstimulated lymphocyte proliferation ↑,all others ↔</td>
</tr>
<tr>
<td>Gomez et al. [178]</td>
<td>2011</td>
<td>Breast</td>
<td>Women (n = 16)</td>
<td>RCT</td>
<td>Combined</td>
<td>8 weeks</td>
<td>46 Different cytokines</td>
<td>↑CTACK, ↔ all others</td>
</tr>
</tbody>
</table>

Abbreviations used: NKCA, Natural Killer cell activity; NK#, number of Natural Killer cells; TNF-α, Tumour Necrosis Factor alpha; CRP, C- reactive protein; IL, interleukin; TGF- β 1, Transforming Growth Factor Beta One; sTNF, serum Tumour Necrosis Factor alpha; CTACK, cutaneous T-cell attracting chemokine; Combined, combined modality exercise consisting of aerobic plus resistance;
### Table 3: Findings from previous research examining exercise immunology outcomes in 'other cancer patients and survivors

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Tumour type</th>
<th>Participants</th>
<th>Study design</th>
<th>Exercise modality</th>
<th>Exercise duration</th>
<th>Biomarker(s) measured</th>
<th>Effect in exercise group (↑↓↔)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimeo et al. [172]</td>
<td>1997</td>
<td>Varied</td>
<td>Male/Female  (n = 70)</td>
<td>RCT</td>
<td>Aerobic</td>
<td>Duration of hospitalisation .Not specified</td>
<td>Complete blood count</td>
<td>↓ neutropenia, thrombopenia duration</td>
</tr>
<tr>
<td>Battaglini et al.[179]</td>
<td>2009</td>
<td>Leukaemia</td>
<td>Male/Female  (n = 10)</td>
<td>Uncontrolled</td>
<td>Combined</td>
<td>3 -5 weeks</td>
<td>IL-6, IL-10, IFN-γ</td>
<td>↔</td>
</tr>
<tr>
<td>Hayes et al. [180]</td>
<td>2003</td>
<td>Varied</td>
<td>Male/Female  (n = 12)</td>
<td>Controlled</td>
<td>Combined</td>
<td>12 weeks</td>
<td>Cell counts of CD3+,CD4+, CD8+,CD3+ cell function</td>
<td>↔</td>
</tr>
<tr>
<td>Galvao et al. [181]</td>
<td>2008</td>
<td>Prostate</td>
<td>Male          (n=10)</td>
<td>Observational</td>
<td>Resistance</td>
<td>20 weeks</td>
<td>IL-6, IL-8, IL-1ra, TNF-α, CRP</td>
<td>IL-8↑, all others ↔</td>
</tr>
<tr>
<td>Galvao et al. [182]</td>
<td>2010</td>
<td>Prostate</td>
<td>Male          (n=57)</td>
<td>RCT</td>
<td>Combined</td>
<td>12 weeks</td>
<td>CRP</td>
<td>CRP↓</td>
</tr>
<tr>
<td>Shore et al. [183]</td>
<td>1999</td>
<td>Leukaemia</td>
<td>Children      (n=6)</td>
<td>Case series</td>
<td>Aerobic</td>
<td>12 weeks</td>
<td>Cell counts, cytolytic activity, cell proliferation</td>
<td>↔</td>
</tr>
<tr>
<td>Na et al. [184]</td>
<td>2000</td>
<td>Stomach</td>
<td>NS            (n=35)</td>
<td>RCT</td>
<td>Aerobic</td>
<td>2 weeks</td>
<td>NKCA</td>
<td>NKCA ↑</td>
</tr>
<tr>
<td>Allgayer et al. [185]</td>
<td>2004</td>
<td>Colorectal</td>
<td>Male/Female  (n=23)</td>
<td>Prospective / controlled</td>
<td>Aerobic</td>
<td>2 weeks</td>
<td>IL-1ra, IL-1b, IL-6, TNF, IL-1, sTNF I and II</td>
<td>IL-1ra↓, all others ↔</td>
</tr>
</tbody>
</table>

**Abbreviations used:** IFN-γ, Interferon gamma; NKCA, Natural Killer cell activity; TNF-α, Tumour Necrosis Factor; CRP, C-reactive protein; IL, interleukin; IL-1ra, Interleukin one receptor antagonist; CTACK, cutaneous T-cell attracting chemokine; sTNF, serum Tumour Necrosis Factor Alpha; Combined, combination of aerobic and resistance exercise training.
The information in table 2 and 3 reveals a large variability in multiple aspects of the methodology in exercise immunology and cancer studies. Aspects which vary between studies include research design; cancer type; participant number; duration, modality, frequency, and intensity of exercise; and immunological parameters studied.

Table 2 illustrates that only five previous studies have been conducted in breast cancer survivors, with 158 participants in total. Of these five studies, three utilised aerobic training and two mixed modality (a combination of resistance and aerobic exercise) training. Sample sizes in general have been small (16-24 participants) with only two RCT’s conducted with larger samples of approximately 50 participants. Both of these RCT’s had significant findings in the exercise group; however, overall interpretation of the efficacy of exercise to modulate immune function and inflammation in this population must be done with caution.

Evidence from other tumour types adds little more knowledge to the field. Eight additional studies in a variety of tumour types were identified. Similar to the research focused solely on breast cancer survivors, a significant limitation of these studies was small sample size. Four of the eight studies had sample sizes equal to or smaller than 12 participants.
In addition to the small sample size, there have been a variety of differing interventions utilised. Previous studies have utilised study durations ranging from 2 – 24 weeks [175, 185], exercise frequencies ranging from twice per week to daily [182, 185], and aerobic intensities ranging from low to high [180, 185]. As a result, at present there is no consensus on the required exercise dose, frequency, intensity, or duration of exercise required to elicit a positive adaptation.

Unsurprisingly, given the scarce research, the causal mechanism eliciting the effect of exercise on immune function in cancer survivors remains unclear. A variety of mechanisms have been hypothesised including flow on effects from reductions body fat and insulin levels [186]; however, more research is required in this area in order to elucidate both the direct, and indirect mechanisms by which exercise modulates the immune and inflammatory profile [186]. One particular area that has demonstrated promise is that of NKCA. Three of the higher quality studies detailed in table 2 and 3 found an improvement in this marker following exercise training. A more thorough discussion about NKCA and exercise, including potential mechanisms, is provided below.
2.3.1.1 Exercise and natural killer cell activity (NKCA)

A commonality between three of the studies that elicited a positive adaptation in the literature cited in Table 2 and 3 is that they all measured change in NKCA, highlighting the potential of this marker for exercise induced alteration.

The mechanisms underlying the exercise-induced modulation of NKCA remain to be fully elucidated with no previous research directly examining this mechanism; however, multiple reviews [38, 187] speculate possible mediators could include the enhancement of neuroendocrine status, inflammatory markers, blood cell production, protein synthesis, and glucose metabolism. These potential mediators such as the inflammatory markers (i.e. CRP) also relate to morbidity and have been shown to be improved via exercise training [177].

Peters et al. [29] were the first to evaluate the effect of aerobic exercise training on NKCA in women recovering from breast cancer treatment. Twenty-four women diagnosed with stage I and II breast cancer, aged $49 \pm 6$ years and $> 6$ months post-surgery, performed cycle ergometer training two to five times per week for seven months. Baseline data indicated significantly lower NKCA in the breast cancer survivors versus a healthy, age-matched control group ($p < 0.05$). Following the intervention period, the exercising survivors experienced a significant improvement in NKCA activity. In fact, NKCA increased to the levels noted in the healthy control group [29]; however, this trial was limited by the small sample size, the lack of inclusion
of a non-treatment breast cancer control group, and inadequate description of the exercise intervention.

More recently, Fairey et al. [28] conducted a randomised controlled trial that evaluated the effect of aerobic exercise training on NKCA in 53 postmenopausal women aged 59 ± 6 years who had been treated for stage I to IIIA breast cancer within the previous 14 months. Participants randomised to the experimental group (n=25) performed cycle ergometer training three times per week for 15 weeks at an intensity of 70-75% of peak oxygen consumption, while the control group (n=28) did not exercise. Duration of each training session progressively increased from 15–35 min throughout the intervention period. Intention-to-treat analyses revealed that NKCA, measured via percent specific lysis and lytic activity per cell, was significantly increased in the experimental group versus the control group (n = 28) (p < 0.05) [28].

Several studies have evaluated the effect of aerobic training methods (e.g. cycling, treadmill, etc.), prescribed from 2–28 weeks on NKCA in healthy adult and elderly cohorts [28, 29, 184, 188, 189]; however, the findings in these populations remain equivocal. Some trials have documented increased NKCA [28, 29, 184, 188, 189] while others have noted no effect [190, 191]. The lack of agreement between trials may be the product of methodological heterogeneity. Specifically, quantification of NKCA, as well as the modalities and dosages of exercise prescribed (i.e. duration,
frequency, and intensity of training) varied considerably between trials. Further, all studies that failed to demonstrate a positive effect were implemented in apparently healthy participants. Accordingly, an attempt to improve NKCA in a cohort that is not suffering from marked immunosuppression may be difficult, given limited potential for adaptation.

Only one trial examining the effect of exercise training on NKCA in breast cancer survivors has failed to elicit a positive finding [176]. Nieman et al. [176] completed a pilot study involving 12 breast cancer survivors, six of whom were randomised to an eight week exercise program involving both aerobic and resistance training components performed three times per week, while the other six received no intervention. No significant difference in NKCA was noted between the two groups post intervention. Potential explanations for the lack of change may include the low sample size (n = 12) and relatively short duration of training (i.e. eight weeks) versus trials documenting a significant effect (i.e. 15 weeks [28] and 7 months [29]). The cohort enrolled by Nieman et al. [176] may have also been relatively healthy. For example, time post treatment averaged 3.0 ± 1.2 years and NKCA in the total cohort at baseline was not significantly different versus comparative data collected from 29 young healthy men. To my knowledge, only three studies have evaluated the effect of exercise training on NKCA in breast cancer patients and survivors, and only one of these studies was a robust randomised controlled trial [28].
2.3.2 Resistance training

The gold standard intervention for the improvement of muscular strength is resistance training as it induces positive anatomic and metabolic adaptations in muscle [192] and bone [193]. Resistance training involves the repeated use of force to move an object, whether that be an exercise band, a dumbbell, barbell, or purpose built resistance training machine. Musculoskeletal strength is one component of musculoskeletal fitness, which also includes power, hypertrophy and local muscular endurance [194]. Musculoskeletal strength refers to the amount of force a muscle can produce and its adaptation is related primarily to two factors, increased cross-sectional area and the enhanced ability of the nervous system to activate the muscle [195, 196].

2.4 Resistance training, inflammatory markers and immune function in apparently healthy individuals

Significant cross-sectional evidence exists demonstrating the link between physical inactivity and inflammation [197-200]; however, empirical research, related to resistance training and inflammation is limited. The majority of research examining the immune and inflammatory response to exercise is based on endurance and aerobic exercise and therefore the effect of
resistance training on the immune function and inflammatory profile of healthy individuals is currently unclear. As ageing is associated with increased low grade inflammation [30], research in this population has provided important evidence regarding the relationship between resistance training and inflammation (Table 4: Previous research findings from studies examining resistance exercise immunology outcomes in healthy adult female populations). Multiple studies in elderly populations have demonstrated reductions in inflammatory markers and improvements in immune function following resistance training [31-34] supporting the notion that resistance exercise appears to exert anti-inflammatory effects [32].

The physiological rationale for the exploration of resistance exercise’s effect on immune function and inflammation stems from the roles of individual cytokines and immune markers. It has been hypothesised that IL-6 may mediate some of the health benefits of exercise. As IL-6 is a pleiotropic cytokine, it can exert both pro and anti-inflammatory effects [64]. During acute exercise IL-6 levels rise [36] as it is produced in contracting muscles [35]. As such, this mechanism may relate to both aerobic and resistance exercise. IL-6 has multiple actions including inducing lipid oxidation, stimulating the production of key anti-inflammatory cytokines, and inhibiting low grade TNF-α production, hence providing an anti-inflammatory effect in this context [35, 36].
An expansion of the IL-6 hypothesis surrounding resistance exercises ability to alter immune and inflammatory profiles arises from subsequent alterations in muscle mass following training. Higher concentrations of inflammatory markers in elderly people are associated with lower levels of muscle mass and muscular strength [37], supporting a direct relationship between levels of inflammatory cytokines and muscle mass [37]. In addition, muscle protein synthesis in elderly following resistance training has been demonstrated to be inversely related to the level of TNF-α protein [32]. It is not known whether the increased levels of TNF-α observed in aging populations are mediated by the aging process independently, or rather by the chronic diseases associated with ageing [32]. Regardless, IL-6 release from contracting skeletal muscle may blunt low grade inflammation, leading to a reduction in TNF-α.

Adding further evidence to the potential relationship between muscle mass and inflammation, Kohut et al. demonstrated that exercise reduces multiple serum inflammatory markers in elderly [201]. These authors demonstrated that serum concentrations of CRP, IL-6 and IL-18 decreased only in response to aerobic exercise, not in response to resistance exercise. Conversely, TNF-α concentration reduced in response to both modalities of exercise, highlighting a potentially different mechanism of change for TNF-α. These authors postulated that a potential explanation for this finding was that TNF-α concentration in the serum may have some association with muscle mass [201]. Their theory was based on the possibility that the greater degree of muscle mass allowed for a greater uptake of TNF-α by the increased TNF-
α (R1) receptor [201], based on Heled and colleagues research that demonstrated that exercise increases the expression of TNF-α and its receptor TNF (R1) in rat muscle [202]. Greiwe et al. [32] demonstrated that muscle protein synthesis is inversely related to levels of TNF-α in muscle, leading Phillips et al. to hypothesise that the reduction in circulating TNF-α may have contributed to the observed strength gains in their study [34].

Not all research in this population has produced positive results; however, studies that have failed to elicit a positive response have had small sample sizes [203] or have been conducted in young women [204]. If an individual is deemed healthy, then they are unlikely to have elevated levels of inflammatory markers, or compromised functioning of immunological markers. Hence, the scope for adaptation would be limited in a healthy cohort.

Additional research supporting the use of resistance training as an anti-inflammatory stimulus is provided from multiple clinical populations. Chronic low grade inflammation, defined by increased levels of inflammatory cytokines including TNF-α, CRP, and IL-6, is linked with, or observed in many diseases such as Type 2 diabetes [205], atherosclerosis [206], insulin resistance [207, 208], obesity [207, 208], and dementia [209]. Emerging evidence suggests resistance training provides beneficial reductions in inflammation in type 2 diabetics [210], and those with chronic kidney disease [211]. Resistance training has also led to the improvement of cardiovascular risk factors in obese individuals [212]. In addition, there is research
demonstrating resistance trainings ability to alter CRP concentration in multiple clinical populations [210, 211, 213]. As mentioned previously, cancer and inflammation are intricately linked, and as cancer is an age related disease [214, 215], individuals with cancer may also suffer from chronic age related low grade inflammation. This inflammatory milieu may respond to the anti-inflammatory effects of resistance training; however, as yet few studies have examined the effect of this exercise modality on these biomarkers in breast cancer survivors.
Table 4: Previous research findings from studies examining resistance exercise immunology outcomes in healthy adult female populations

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Participants (age)</th>
<th>Groups</th>
<th>Exercise duration</th>
<th>Biomarker(s) measured</th>
<th>Effect in exercise group (↑↓↔)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordova et al. [31]</td>
<td>2011</td>
<td>Women (71.3 ± 6.3y)</td>
<td>Resistance adapted (n = 28) Sedentary control (n = 26)</td>
<td>8.6 ± 0.3 months</td>
<td>IL-6, TNF-α, IFN-γ</td>
<td>↓ IL-6, TNF-α, IFN-γ</td>
</tr>
<tr>
<td>Flynn et al. [216]</td>
<td>1999</td>
<td>Women (Ex 72.6 ± 3.5, C 72.9 ± 4.9y)</td>
<td>Exercise (n = 15) Control (n = 14)</td>
<td>10 weeks</td>
<td>Mononuclear cell number, lymphocyte proliferative response to mitogen, NKCA</td>
<td>No change</td>
</tr>
<tr>
<td>Griewe et al. [32]</td>
<td>2001</td>
<td>Women (81 ± 1y)</td>
<td>Exercise (n = 4) Control (n = 3)</td>
<td>3 months</td>
<td>TNF-α mRNA and protein levels in skeletal muscle</td>
<td>↓ TNF-α mRNA and protein levels</td>
</tr>
<tr>
<td>McFarlin et al. [33]</td>
<td>2005</td>
<td>Women (Ex 71.8 ± 6.5, C 73.1 ± 6.0)</td>
<td>Exercise (n = 19); Control (n = 6)</td>
<td>10 weeks</td>
<td>Leukocytes, NKCA</td>
<td>No change leukocytes, ↑ NKCA</td>
</tr>
<tr>
<td>Miles et al. [204]</td>
<td>2002</td>
<td>Women (18-30y)</td>
<td>Exercise (multiple groups) (n = 64) Control (n = 7)</td>
<td>6 months</td>
<td>Lymphocytes subsets (T cells, NK cells, B cells), mitogen stimulated proliferation</td>
<td>Transient increase in NK concentration at 3 months. No change in any variable at 6 months</td>
</tr>
<tr>
<td>Philips et al. [34]</td>
<td>2010</td>
<td>Women (72 ± 6.1y)</td>
<td>Exercise (n = 28) Control (n = 7)</td>
<td>10 weeks</td>
<td>IL-6, IL-1β, TNF-α, LPS stimulated whole blood</td>
<td>↓ serum TNF-α, ↓ stimulated production of IL-6, IL-1β, TNF-α</td>
</tr>
<tr>
<td>Prestes et al. [217]</td>
<td>2009</td>
<td>Women (mean 63 ± 4.8 y)</td>
<td>Exercise (n = 35)</td>
<td>16 weeks</td>
<td>Plasma TNF-α, IL-6,IL-15, leptin, resistin concentration</td>
<td>IL-6, leptin, resistin ↓, no change all other markers</td>
</tr>
<tr>
<td>Rall et al. [203]</td>
<td>1996</td>
<td>Women (Ex 70.3 ± 5.0, C 68.8 ± 2.9y))</td>
<td>Exercise (n = 8) Control (n = 6)</td>
<td>12 weeks</td>
<td>Mononuclear cell subpop, cytokine and prostaglandin E2 production, proliferative response, delayed type hypersensitivity skin response</td>
<td>No change</td>
</tr>
</tbody>
</table>

Abbreviations used: NKCA, Natural Killer cell activity; TNF-α, Tumour Necrosis Factor alpha; CRP, C-reactive protein; IL, interleukin; IFN-γ, interferon gamma
2.4.1 Resistance training and breast cancer

Initial research surrounding exercise for breast cancer patients and survivors predominantly focused on aerobic modalities such as walking and cycling [218-220] as previous recommendations actively discouraged participating in resistance training due to fears of lymphedema exacerbation. In recent years, several trials published data demonstrating that resistance training exercise does not induce or exacerbate lymphedema [41, 221-224]. Recently, the position stand has been updated to reflect current research [225] and now encourages the use of resistance training supporting the notion that resistance training is safe and beneficial for breast cancer survivors.

The limited previous research examining the effect of resistance training in breast cancer survivors has focused on a range of differing outcomes such as bone mineral density, QOL, and lymphedema. Little research has focused on the effect of resistance training on the immune function and associated biomarkers in this population.

2.4.1.1 Benefits of resistance training

According to the American College of Sports Medicine (ACSM), there are a multitude of physiological, metabolic, psychological benefits attributed to resistance training [226]. Specifically, improved muscular strength is
associated with reductions in cardiometabolic risk factors, lower all-cause mortality, less risk of cardiovascular events and reductions in blood pressure. In addition metabolic improvements include improved insulin sensitivity and blood glucose levels. Musculoskeletal benefits of resistance training include enhanced muscular strength, improvements in bone strength and prevention of osteoporosis, along with improvements in body composition. Psychological benefits include improvements in depression and anxiety, increased energy, and reductions in fatigue [226].

2.4.1.1.1 Improvements in strength

Strength has been shown to increase in multiple studies utilising resistance training [40, 42, 45, 223, 227-230] in breast cancer survivors (Error! Reference source not found.5). The magnitudes of strength gains observed following standard resistance training interventions in this population range in magnitude from 12-40% over a period of 12 weeks to 24 months [42, 45, 221, 227, 231].
<table>
<thead>
<tr>
<th>Author/Study</th>
<th>Year</th>
<th>Participants</th>
<th>Study design</th>
<th>Exercise intervention</th>
<th>Duration</th>
<th>Strength outcome measures</th>
<th>% upper body improvement</th>
<th>% lower body improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musanti et al. [42]</td>
<td>2012</td>
<td>42</td>
<td>Uncontrolled trial</td>
<td>Exercise band, RPE progression from 3-5 to 7-8 on a 0-10 scale. One set of 10-12 full body exercises.</td>
<td>12 weeks, 3 x pw</td>
<td>6 RM chest press, leg press and seated row</td>
<td>26</td>
<td>NR</td>
</tr>
<tr>
<td><strong>WTBS</strong> Ahmed et al. [221], Schmitz et al. [40] and Ohira et al. [39]</td>
<td>2005, 2006</td>
<td>45, 85, 86</td>
<td>RCT</td>
<td>Machine and free weights, 9 full body exercises. 3 sets of 8-10 repetitions</td>
<td>12 months, 2 x pw</td>
<td>1RM leg press, bench press</td>
<td>39</td>
<td>28</td>
</tr>
<tr>
<td>Winters-Stone et al. [44, 227]</td>
<td>2011, 2012</td>
<td>106</td>
<td>RCT</td>
<td>1-3 sets of 9 exercises, 8-12 reps at 60-70% 1RM. Free weights, full body.</td>
<td>12 months, 3 x pw</td>
<td>1RM leg press, 1RM chest press</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td><strong>PAL</strong> Schmitz et al. [223, 230] Speck et al. [224]</td>
<td>2009, 2010</td>
<td>295 (154/141)</td>
<td>RCT</td>
<td>3 sets of 10 exercises. Full body machine based and free weights exercises.</td>
<td>12 months, 2 x pw</td>
<td>1RM leg press, 1RM bench press</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Author/Study</td>
<td>Year</td>
<td>Participants</td>
<td>Study design</td>
<td>Exercise intervention</td>
<td>Duration</td>
<td>Strength outcome measures</td>
<td>% upper body improvement</td>
<td>% lower body improvement</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>----------------------------------------------------------------------------------------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Waltman et al [43]</td>
<td>2010</td>
<td>223</td>
<td>RCT</td>
<td>Initial 9 months home based with hand and ankle weights. Months 10-24 full body machine based exercises. 2 sets of 8-12 repetitions</td>
<td>24 months, 2 x pw</td>
<td>Biodex peak torque (knee, hip, wrist)</td>
<td>48</td>
<td>21</td>
</tr>
<tr>
<td><strong>START</strong> Courneya et al [45]</td>
<td>2007</td>
<td>242</td>
<td>RCT</td>
<td>2 sets, 8-12 repetitions, 9 full body free weight and machine exercises at 60-70%1RM</td>
<td>~17 weeks, 3 x pw</td>
<td>8RM bench press, 8RM Leg extension</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Schwartz et al [228]</td>
<td>2007</td>
<td>66</td>
<td>RCT</td>
<td>Exercise band, 2 sets 8-10 repetitions, 8 full body exercises</td>
<td>6 Months, 4 x pw</td>
<td>1RM (no mention what)</td>
<td>16</td>
<td>25</td>
</tr>
</tbody>
</table>

**Abbreviations:** PAL: Physical activity and Lymphedema trial; WTBS: Weight training for breast cancer survivors study; START: Supervised trial of aerobic versus resistance training.
Improvements in body composition are best achieved via a combination of diet modification and exercise [232, 233]. Traditionally aerobic exercise has been utilised as the modality of choice for reduction of body fat [233]; however, resistance exercise is a unique exercise modality which can elicit a broad spectrum of physiological and psychological adaptations including the reduction of fat and gain in muscle to prevent the changes seen in sarcopenic obesity. Body composition changes that have been demonstrated as a result of resistance training in breast cancer survivors include preservation of bone mineral density [43, 44], increases in skeletal muscle mass [40, 45], and reductions in body fat [230].

It is well-acknowledged that resistance training is the modality of choice for inducing muscle hypertrophy, even in elderly and postmenopausal women [234-236]. Both aerobic and resistance training are beneficial in the prevention of sarcopenia, though resistance exercise is likely superior [237]. A review of studies using resistance training as a treatment for sarcopenia in healthy populations has found a unanimous positive effect [237].

To date, only a handful of trials prescribing isolated resistance training in breast cancer survivors have evaluated outcome variables related to body adiposity, including BMI, waist circumference, and sum of skinfolds. Whilst most studies reported no change, these studies primarily looked at BMI or
weight change, rather than specific measures of composition [223, 228, 230].

Three studies that examined specific body composition measures have demonstrated decreases in percentage body fat ranging from 1.15-1.3% [40, 238].

Changes in muscle cross sectional area have been less frequently reported although three recent studies have demonstrated significant improvements in lean muscle mass [40, 45, 238]. These changes ranged from 0.1–1.0 kilograms over periods ranging from 15 weeks to 6 months.

2.4.1.1.3 Improvements in bone mineral density

The effects of resistance training on bone health are well established [239]. Numerous investigations have shown that resistance training can preserve or significantly increase bone mineral density (BMD) in apparently healthy women prior to [240, 241] and following the onset of menopause [242, 243].

Two recent randomised controlled trials (RCT) have examined the effect of resistance training on bone mineral density in breast cancer survivors [43, 44]. The interventions were both over a year in duration and consisted of 2–3 training sessions per week. Both studies demonstrated a greater maintenance of BMD in the exercise group when compared to control (P=0.001 [44] and P = 0.03 [43]).
Clinically, a one standard deviation loss in bone density has been shown to cause an approximate double risk of fractures [244]. The above studies demonstrate that resistance training even that at a low intensity can reduce bone mineral density loss and have large clinically significant implications. While the research at present is still limited initial results are positive, showing resistance exercises ability to help preserve BMD in breast cancer survivors [43, 44].

2.4.1.1.4 Improvements in fatigue

Severe fatigue has been shown to be a problem for up to 40% of breast cancer survivors [245]. Combined resistance and aerobic exercise programmes have been shown to reduce fatigue in breast cancer survivors [246, 247]; however, in this population the evidence regarding resistance exercise alone has been inconclusive with trends for decreases in fatigue that have not reached significance [45]. Research has been limited in other cancer cohorts, although research in prostate cancer is promising. Resistance exercise has been shown to reduce fatigue in a group of men receiving androgen deprivation therapy [248] or radiation therapy [249] for prostate cancer. The reduction in fatigue was attributed to significant increases in both upper and lower body strength.
Exercise improves health related QOL in breast cancer survivors [250]. Specifically, resistance exercise has been shown to improve both physical and psychological QOL scores in breast cancer survivors [39], this improvement has been attributed to result from an increase in strength and muscle mass [39]. Further, resistance exercise has been shown to be superior to other modalities (aerobic and flexibility) in improving self-esteem [42] and is even beneficial when undertaken during treatment [45]. Improvements in self-perception of appearance, sexuality, health, relationships and social functioning were also observed following resistance exercise in this demographic [224].

Not all studies have found resistance exercise to be beneficial for QOL. Recently Courneya et al found no change in QOL in response to a resistance training intervention; however, self-esteem, muscular strength and lean body mass were all still improved as a result of the intervention [45]. This finding was replicated by Speck and colleagues who found QOL did not significantly improve (as measured by SF-36) as a result of resistance training; however these levels were close to normative data and hence less susceptible to change [224].
2.4.1.2 Exercise prescription recommendations

ACSM’s general recommendations for resistance training prescription for novices includes performing two to four sets of each exercise at between 60–70% of 1RM for 8–12 repetitions. These exercises should be performed two to three times a week for optimal gains [226]. The ACSM recently conducted a roundtable and produced guidelines specifically relating to exercise prescription for cancer patients and survivors [251]. Recommendations for breast cancer survivors vary slightly from that of the general population. Prescription should be progressive in nature, especially with respect to upper body training, with no eventual upper limit on weight lifted [251]. Close monitoring should also be undertaken with regards to arm symptoms and exercise reduced if any symptoms occur [251]. While the prescription is slightly varied, the roundtable emphasised that resistance exercise is safe and beneficial for breast cancer survivors [251].

2.5 The links between Cancer and Exercise

There are multiple theories surrounding exercises ability to modulate the immune system. Most of the proposed mechanisms link multiple physiological pathways. A key proposed mechanistic link is the link between adiposity and immune functioning.
2.5.1 A link mediated by obesity?

It is well documented that obesity and cancer are intricately linked. A 2003 review by Calle et al. estimated mortality from cancer to be 52% higher for men and 62% higher for women with a BMI of at least 40 kg/m² compared to that of normal weight men and women [252]. Further, it has been estimated that obesity accounts for 14-20% of all deaths from cancer in the United States [252]. A recent systematic review revealed that the incidence of cancer is linked with increasing BMI with risk ratios ranging from 1.1–1.6 depending on the type of cancer [253]. Increased risk of postmenopausal breast cancer is one of the specific cancers that have been linked with obesity [253, 254].

There are multiple systemic changes associated with obesity including alterations in inflammation, concentrations of sex hormones, insulin, and adipokine secretions which may have a direct influence on the tumour microenvironment [255]. Visceral adipose tissue contains a wealth of inflammatory cells including macrophages and T cells. This abundance of inflammatory cells creates systemic inflammation and consequently a pro-tumorigenic environment [255].

Visceral adipose tissue acts as an endocrine organ and performs multiple functions including metabolic and immunological functions. Increased adipose tissue has been linked with chronic low grade systemic inflammation.
Specific markers of inflammation include increases in TNF-α and IL-6, along with an increased infiltration of the adipose tissue by macrophages [256]. The macrophages of a lean individual activate differently, in a M2 or alternative activation pattern which is characterised by the production of the anti-inflammatory cytokine IL-10. Conversely, the macrophages in an obese individual are classically activated M1 macrophages which are characterised by increased production of the pro inflammatory cytokines TNF-α and IL-6 [256].

NK cell number and phenotype also differ in obese individuals. Obese individuals can have metabolic function similar to a healthy weight individual; conversely obese individuals can have altered metabolic function and be metabolically unhealthy. At present there is no consensus on a definition of metabolic obesity [257]. Insulin resistance, blood glucose levels, blood pressure, and inflammatory markers are all utilised as measures of metabolic health. Obese individuals have significantly lower circulating NK cell numbers than lean controls and metabolically healthy obese [258]. In addition the metabolically unhealthy obese NK cells express a significantly greater number of markers of activation (CD69), which are rarely expressed on NK cells in healthy participants and a significantly greater number of markers of inhibition (CD158b, NKB1) [258]. The presence of CD69, demonstrating that the NK cells have been activated and the increase in inhibitory markers, suggests that although activated these NK cells are inhibited from killing [258]. Further research has also demonstrated that the
cytotoxic capability of NK cells in obese individuals is significantly lower than that of healthy lean controls [259].

This issue of obesity and the inflammatory environment is further complicated by the related increased exposure to oestrogens as discussed previously (2.2.1). Empirical evidence suggests that resistance training favourably alters glucose metabolism [260] and can help normalise circulating hormonal and pro-inflammatory cytokine levels in breast cancer survivors and other cohorts [40]. Although previous research is limited there is a sound rationale for exploring the effect of resistance exercise on various markers of immune function and inflammation in this cohort.

Breast cancer and its treatments cause a variety of health related detriments that may last years following treatment. Of specific concern, is the negative impact on immune function and the potential implications that immunosuppression may have on subsequent illnesses and the potential for recurrent cancers. Non pharmaceutical interventions have begun to be examined, with promising evidence surrounding aerobic exercise and subsequent immune modulation. As established in the previous section, resistance training offers a distinct spectrum of physiological adaptations, many of which are relevant to breast cancer survivors. In addition, the potential mechanism suggested to be responsible for immune modulation in aerobic activity, also applies to resistance training. This review identified a gap in the research for a large sample robust randomised controlled trial
examining the effect of resistance training on immune function in this population.
3 METHODS

3.1 Study design

This parallel-arm randomized controlled clinical trial compared the outcomes of breast cancer survivors assigned to an experimental treatment group (RT) with those assigned to a waitlist control group. The primary outcomes were natural killer cell cytotoxic activity markers granzyme B and perforin and the expression of immunoregulatory cytokines including TNF-α and IFN-γ using multiparametric flow cytometry. Secondary outcomes include additional measures of immune cell function of NKT-like cells and analysis of serum cytokines TNF-α, IL-6 and IL-10.

The resistance training intervention period was 16 weeks, and the assessment of primary and secondary outcomes was completed prior to, and following, the intervention period (week 0 and week 17). Both groups continued to receive usual medical care during the intervention period.

The objectives of this study were threefold. Firstly, the primary objective of this study was to implement a 16-week randomised controlled trial to evaluate the effect of resistance training on markers of natural killer cell function in women recovering from breast cancer treatment. I hypothesised that those individuals randomised to the resistance training intervention will show improvements in markers of natural killer cell function at the end of the
trial. A secondary objective of this study was to determine the effect of resistance training on additional markers of immune function and inflammation, quality of life, fatigue and muscular strength in this population. I hypothesised that resistance training will lead to improvements in the inflammatory profile, QOL, fatigue, and muscular strength. The final objective of this study was to explore the relationships between primary and secondary objective outcomes. I hypothesised that improvements in immune function will be related to improvements in body composition, strength and QOL. I also hypothesised that improvements in strength will be related to improvements in body composition, QOL, and fatigue.

### 3.2 Participants

Participants were recruited from the South West Sydney Area Health Service catchment area between July 2012 and December 2013. Campbelltown Hospital Cancer Therapy Centre served as the first point of referral, with additional participants referred from Liverpool hospital. Two local breast cancer support groups were also approached and helped distribute information about the trial. Interested participants were screened for eligibility via telephone interview, email, or in person, as preferred by the participant. Participants were also pre-screened for participation using the Physical Activity Readiness Questionnaire [261] (Appendix 1), and a standardised health history questionnaire (Appendix 2). Individuals deemed “moderate-risk” [262] required the approval of their physician prior to
participation. “High-risk” [262] individuals were excluded from participation. An initial meeting followed where the informed consent (Appendix 3) and participant information sheet (Appendix 4) were distributed. After reading and signing these forms data collection commenced on the next available testing date. Figure 4 shows participant flow through the trial.

3.3 Eligibility criteria

Eligibility criteria included histologically confirmed stage I to IIIA breast cancer with no evidence of recurrent disease; age 18-70 years; completed surgery, radiotherapy and/or chemotherapy, with or without current use of hormonal therapy (e.g. tamoxifen, aromatase inhibitors); sedentary (<30min of continuous moderate-intensity exercise, 3 times per week), with or without existing upper extremity lymphedema; stable underlying chronic diseases; ability to communicate in English; no acute or chronic medical conditions which would make exercise potentially hazardous or primary outcomes impossible to assess; willingness and ability to provide written informed consent to participate in the trial.

3.4 Sample size and statistical power

There are no published data on the effect of resistance training on the function of natural killer cells in women recovering from breast cancer
treatment. Therefore, the sample size estimates are driven by the hypothesised change in functional markers of natural killer cell activity in the experimental and control groups based on a trial of aerobic exercise training on NKCA, as measured by percent lysis, in breast cancer survivors [28]. The data [28] suggest that the control group is estimated to have little or no change in functional markers of natural killer cell activity, while the experimental group is expected to increase functional markers of natural killer cell activity by 5.0±5.0%. Setting the alpha set at 0.05 and beta at 0.20, approximately 34 participants (17 per group) were required per treatment group to detect a large effect (ES=1.0). Recruitment was inflated to 39 to allow for a 15% attrition rate.

3.5 Randomisation

Participants were randomised using a computer-generated list (www.randomization.com) stratified by age (<50yr; >50yr) and current use of hormonal therapy (Yes; No). An investigator not involved in testing or the delivery of the intervention prepared the randomization assignments. Group assignments were delivered to participants in sealed envelopes upon the completion of baseline testing with the intervention commencing the following Monday.
3.5.1 Experimental Group

Participants randomized to the experimental group completed a 16-week supervised RT program prescribed three times per week for approximately 60 minutes per session. Each session consisted of either one-on-one training or with multiple participants exercising concurrently in a circuit (group) style manner. Participants were given an option of morning or afternoon-evening sessions on Monday, Wednesday, and Friday. Three sets of 8-10 repetitions were performed of each exercise. Loads were prescribed based on individualised 8-10 repetition maximum (RM) and were adjusted accordingly with adaptation. The exercise prescription was split into two 8-week programs progressing from an introductory machine-based prescription to a more advanced free weight style prescription (Appendix 5). Program 1 exercises included leg extension, leg curl or Romanian deadlift, lat pull down, machine bench press, seated row, back extension, prone hold or sit ups. In addition, a structured warm up included skill development of the deadlift and squat ensuring competency in movement patterns for the commencement of Program 2. Program 2 exercises included barbell squat, deadlift, free weight barbell bench press, leg press, barbell bent over row and assisted chin up. Exercises were substituted when deemed necessary due to musculoskeletal limitations. Progressions in training volume and adherence to the exercise program were recorded.
3.5.2 Waitlist Control Group

Participants randomized to the control condition received no specific instructions or access to equipment during the initial 16-week intervention period. Upon completion of week 17 testing, the control group were offered the 16 week intervention. The purpose of the waitlist control was to ensure that all women were given an opportunity to participate in the resistance training. This approach potentially improved attrition rates during the control period.

3.6 Provision of information and consent

The University of Western Sydney Human Research Ethics Committee approved all research procedures (Approval Number: H9427) and the trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR #: 12612000346875). All data were collected at the University of Western Sydney Campbelltown campus and a local Douglas Hanley Moir pathology laboratory.

3.7 Collection of blood samples

All participants attended a local Douglas Hanley Moir (DHM) pathology lab for collection of blood samples at week 0 and at week 17. Participants were
instructed to refrain from exercise for 48 hours prior to each collection session to avoid the immune modulation caused by acute exercise from confounding the resting measure [263]. Repeated blood collection for each participant (week 17) was scheduled on precisely the same day of the week and the same time of day as baseline collection. Venous blood was collected in a fasted state and added to 3 lithium heparin, 2 SST, and 1 EDTA vacutainers (DHM, Sydney, Australia). Samples were kept at 4°C and processed within 24h of collection. Once the samples were collected they were sent to two different laboratories for analysis.

The DHM laboratories conducted analysis of the full blood count (required for NKCA analysis), CRP and cholesterol analysis. The remainder of the blood samples were express couriered to the University of Adelaide for analysis of the primary outcome variables and subsequent exploratory immune analysis.

3.8 Natural killer cell function measurement

Fluorescence-activated cell sorting (FACS) was applied for detection of immune cells and their associated functionality by surface and intracellular marker staining. This method enables epidemiologic studies to efficiently process blood samples while retaining cells during transport in a microenvironment similar to that found in vivo. Furthermore, PBMC purification techniques can lead to increased apoptosis of cells [264].
Absolute cell counts of NK cells were enumerated by staining 500uL of unstimulated peripheral blood with appropriately diluted fluorescently labeled monoclonal antibodies to CD3 PercpCy5.5 (BD Biosciences, Sydney, Australia) (BD), CD56 APC (Beckman Coulter) (BC) and CD45 V450/V500 (BD).

Flow cytometry was carried out by adding 500uL of peripheral blood to 12x75mm FACS tubes (Techno Plas). Red blood cells (RBCs) were lysed by addition of 2mL of FACSlyse solution (BD) and incubated for 10 min at room temperature. Tubes were decanted after centrifugation at 2500rpm for 2 min. Cells were permeabilised by addition of 0.5mL 1x FACSperm (BD) and incubated for 10 min at room temperature. Cells were washed with 2mL FACS wash buffer (0.5% BSA (Sigma, Sydney, Australia) in Isoflow (BD) and tubes centrifuged again at 2500rpm for 2min. After decanting supernatant cells were stained with appropriately diluted anti-human mAbs at room temperature. Cells were analysed within 1 hour of staining on a FACS CantoII using FACS Diva software (BD). Cells were analysed by gating using forward (FSC) versus side scatter (SSC) to exclude platelets and debris. Gated viable cells were analysed with CD45 V450/V500 (BD) to determine that cells are of lymphoid origin. A minimum of 50000 CD56+ low SSC events were acquired in list-mode format for analysis. NK cells were identified as CD56+ CD3- low side scatter events. Functional markers of NKCA on NK were granzyme B PE (BD) and perforin PE (BD). These were analysed from unstimulated peripheral blood.
NK intracellular cytokine production including TNFα V450 (BD) and IFNγ FITC (BD) was measured from PMA/Ionomycin/Brefeldin A (P/I/BA) stimulated NK cells via multiparametric flow cytometry. Briefly 500uL peripheral blood was stimulated overnight with PMA (25ug/mL) (Sigma, Sydney, Australia) Ionomycin (1ug/mL) (Sigma) and Brefeldin A (1ug/mL) (Sigma) before lysing RBCs and preparing for flow cytometry staining as described above.

3.9 Natural killer T-like cell measurement

A complete blood count including a differential white blood cell count via standard procedures was conducted with coefficients of variation (CV) ranging between 0.7% and 8.3% (level 2).

C-Reactive Protein (CRP) was analysed via an immunoturbidimetric assay on an Abbott C16000 analyser at a DHM lab with a combined level 2 CV of 4.0%.

Absolute cell counts of NKT-like cells were enumerated by staining 500uL of unstimulated peripheral blood with appropriately diluted fluorescently labeled monoclonal antibodies to CD3, CD56 and CD45. T cells were identified as CD56-CD3+ while NKT-like cells were identified as CD56+ CD3+ low side scatter events.
Functional immune cell marker expression on NKT-like cells was measured from unstimulated peripheral blood to measure cytotoxic granules including granzyme B and perforin. Intracellular cytokine expression of IFN-γ and TNF-α, (e-Biosciences) was measured from PMA/I/BA stimulated NKT-like cells. All expression markers were analysed via multiparametric flow cytometry as outlined for NKCA measurement.

3.10 Serum cytokine analysis

Serum analysis was carried out using a BD Biosciences ES CBA kit protocol for determining IL-6, IL-10 and TNF-α in serum samples. Participant blood was collected as per previous protocol. Serum was aliquoted on the same day approximately 7 hours later in an external laboratory. Serum aliquots were stored at -20C and then transferred to -80C storage for approximately 12 months until analysis.

Serum cytokines IL-6, IL-10 and TNF-α levels were quantified using the BD Biosciences human enhanced sensitivity (ES) cytokine bead array (CBA) kit. Fresh aliquots of serum samples were used and run in duplicate. The minimum theoretical detection limit of these kits is 0.0684pg/mL for IL-6, 0.0137pg/mL for IL-10 and 0.0673pg/mL for TNF-α.
The ES CBA assay was carried out according to manufacturer’s instructions. Briefly 50uL of serum was incubated with the relevant capture bead prior to incubation with the human detection reagent followed by the enhanced sensitivity detection reagent. The FACS Cantoll (BD Biosciences) was used to acquire 300 events per analyte. Individual cytokine concentrations were identified by their fluorescent intensities (FL-2) and were computed using the individual cytokine standard reference curve using the FCAP Array v3 Software (BD Biosciences).

3.11 Body Composition

Anthropometric measurements consisted of a restricted International Standards for Anthropometric Assessment (ISAK) level 1 profile. The ISAK restricted profile consists of 17 measurements (mass, stature, 8 skin fold sites, 5 girths, 2 breadths). Measurements were collected by a qualified ISAK level 3 practitioner who was blinded to the treatment allocation. Please refer to Appendix 6 for anthropometrist ICC and TEM. The same individual collected both pre and post measurements. The 17 measurements were used to calculate outcome measurements including body mass index (BMI), body weight (BW), and percentage body fat(%) [265].

The right side of the body was used for all measurements, except in participants with diagnosed right side lymphedema, in these individuals all
measures were completed on the left side. Consistent with ISAK level 3 requirements, measurements were taken in a rotational order ensuring one full collection of each skinfold site prior to repetition. Two measures were taken for each skinfold, girth and breadth site. A third measurement was taken when the first two differed by more than 5% for skinfolds and 1% for girths and breadths. If two measurements were taken, then the mean was recorded as the value. If three measurements were taken, then the median was the recorded value.

Body weight was measured on a digital scale (A&D UC-321, A&D Company Ltd, Japan). Stature was assessed using a wall mounted stadiometer (Stadiometer, Holtain Ltd, Dyfed, UK) without shoes. Loose fitting clothing was recommended for the testing sessions to allow the assessor ease of access to measurement sites.

Two variations of Skinfold calliper were used depending on the thickness of the skinfold. Measurements were primarily taken using Harpenden callipers (Harpenden skinfold calliper, Baty International, West Sussex, UK); however, when the fold was greater than 40mm an alternative Slim Guide calliper was utilised (Slim Guide, Creative Health Products, MI, USA). ISAK Skinfold sites are based on marked anatomical landmarks. These landmarks are identifiable skeletal points, of which 7 are utilised to find skin fold sites in the restricted profile. Skinfold sites are detailed in Appendix 7. Once the site was located, a fold was pinched and then the site was measured 2cm away
in a specified (differs between sites) direction. The calliper was then applied to this point and the measurement taken.

Girths were measured using 5mm anthropometric tape (Lufkin W606PM flexible steel tape, Lufkin, Ohio, USA) and consisted of the five sites; arm relaxed, arm flexed and tensed, waist, gluteal and calf [266] (Appendix 8).

Breadths were measured at two locations using a sliding calliper (Bicondylar Caliper, Holtain Ltd, Dyfed, UK). Please refer to Appendix 9 for pictures and descriptions.

### 3.12 Muscular strength testing

Lower body muscular strength was assessed using a one-repetition maximum leg press (Cybex, Leg5643-94/Shoulder, 1994) protocol. The participants were seated with their knee joints at 90 degrees and feet placed hip width apart (Figure 3). The mid-sole of the feet were placed on a line on the leg press plate to ensure reproducible foot placement (Figure 3). Standard 1-RM strength testing procedures were employed consisting of an incremental warm up where load increased as repetitions decreased. Rest periods of 3 minutes were provided between sets and 1RM attempts.
Upper body strength was assessed using an iso-lateral isometric chest press protocol. This protocol allowed accurate inter-limb comparisons to be made. An AST-250kg force transducer (PT global, Australia) was connected to a chain and grip handle, secured to a power rack. The participant was seated on an incline bench with the shoulder joint placed at 45 degrees of abduction with the forearm in 45 degrees of pronation Figure 3. The subject was always tested on the non-surgical side first, followed by the other limb. Each participant had 3 warm up attempts at approximately 25%, 50%, 75% effort, followed by three maximal voluntary isometric contractions (MVIC). Three minutes rest was given between trials. The subjects were encouraged to build in to their maximal contractions rather than ‘jerk’ the transducer. Once full contraction was obtained they were encouraged to hold this tension for two seconds. The highest value obtained from the force trace for the three MVIC’s was recorded as the strength value. This measure had a high degree of internal consistency with a Cronbachs alpha on the non-surgical limb of 0.966, and on the surgical limb of 0.951.
Figure 2: An example of the force trace collected during a maximal isometric voluntary contraction chest press.

Diagram A represents the force trace from the non-surgical arm of a selected participant. Diagram B represents the force trace from the surgical arm of the same participant.
Figure 3: A demonstration of the 1RM leg press and isometric upper body strength test positions utilised in this study
3.13 Quality of life

3.13.1 Short Form-36

Quality of life (QOL) was assessed using the Medical Outcomes Trust Short-Form 36 Health Status Questionnaire (SF36) Version 2.0, a validated and extensively utilized survey that assesses eight domains of QOL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health [267].

3.13.2 Functional Assessment of Cancer Therapy - General

Disease-specific QOL was also assessed by the Functional Assessment of Cancer Therapy-General (FACT-G) Quality of Life Instrument (Appendix 10) [268]. The FACT–G is a 28-item questionnaire with scaled answers ranging from 0-4 encompassing the following five areas of life: physical well-being (PWB), social/family well-being (SWB), relationship with doctor, emotional well-being (EWB), and functional well-being (FWB) [268]. The FACT-G is highly reliable with (test-retest correlations 0.91-0.92) between baseline reliability and follow up [166].
3.13.3 Functional Assessment of Chronic Illness Therapy - Fatigue scale

Perceptions of fatigue were assessed with the FACIT-fatigue scale (Appendix 11) [155]. The FACIT-fatigue scale is a 13-item scale encompassing the same scoring system as the FACT-G. The fatigue subscale has strong internal consistency (coefficient alpha range = 0.93 – 0.95) and is a reliable (test-retest correlations = 0.9) and valid measure of fatigue [155].

3.13.4 Modified fear avoidance beliefs questionnaire

The fear avoidance beliefs questionnaire (FAB-Q) was developed by Waddell et al [269] to measure individuals beliefs about how physical activity and work affected back pain. I adapted the questionnaire, and only included the subscale related to physical activity. I then replaced the word “back pain” with “shoulder”. This approach has been done previously with substitution of the word “neck” [270] and “shoulder” [271]. The phrasing of all the individual questions was not modified in this study. While this scale has not been validated for its use in breast cancer survivors, when used for back pain patients it has high internal consistency (α = 0.77) for the physical activity component. Please refer to Appendix 12 for a copy of the questionnaire used. The questionnaire was comprised of 5 questions that were marked on a 7 point likert scale from completely disagree to completely agree. The scale ranges from a score of 0, to a score of 24, as question 1 is excluded.
from analysis due to low commonality [269]. Higher scores indicating higher levels of fear avoidance behaviour.

3.13.5 A summary of utilised methods

Table 6 provides a summary of the primary and secondary outcomes from this study. The table also details the measurement tool utilised to assess these outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Measurement Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Natural Killer Cell function</td>
<td>Flow cytometry</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>Additional inflammatory and immunological variables</td>
<td>Various assays</td>
</tr>
<tr>
<td>Body composition</td>
<td>ISAK level 1 profile</td>
</tr>
<tr>
<td>Muscular strength</td>
<td>Maximal isometric chest press (N), one repetition max leg press (kg)</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>FACT-G, SF-36, FACIT</td>
</tr>
</tbody>
</table>

Abbreviations used: ISAK; International Society for the Advancement of Kinanthropometry; FACT-G, Functional Assessment of Cancer Therapy General; SF-36, Short Form Thirty Six; FACIT, Functional Assessment of Chronic Illness Therapy Fatigue.
3.14 Health and Demographic Data

Additional factors potentially related to the adaptations under investigation were extracted during the recruitment and medical screening process and baseline testing by means of standard questionnaires. These factors included demographic characteristics (i.e. age, gender, occupation, marital status, living arrangement, income, smoking history, and alcohol intake), medication usage and dose, date of breast cancer diagnosis, surgical procedure and adjuvant therapies received, and number of axillary lymph nodes removed (Appendix 13).

Change of health status in the experimental and control group during the 16-week intervention period was documented by means of a structured questionnaire of open-ended questions that was administered weekly, via email for the control group and in person for the experimental group (Appendix 14). Acute illnesses, injury and changes in medication dose and usage were recorded in both the exercise and control group. The Godin Leisure-Time Exercise Questionnaire was also administered pre and post to monitor exercise behavior in the control and experimental group changers over the intervention period (Appendix 15) [272].
3.15 Adverse events

Adverse events were defined as any injury or exacerbation of underlying disease that was potentially attributable to the resistance training program. Any participant who experienced an adverse event during the course of exercise program was referred to a qualified health care practitioner for appropriate management, regardless of whether the adverse event occurred during training or as a result of external circumstances. All adverse events were documented and reported in both the experimental and control group.

3.16 Statistical analysis

Primary analysis was via intention-to-treat and included all participants regardless of dropout or level of adherence [273]. Missing data at week 17 was imputed using the last observation carry forward method [274]. Data was presented as the mean or median, with ranges, SD, and confidence intervals (CI) to express group differences as appropriate. Baseline characteristics were compared between groups using independent t-tests for normally distributed variables and Mann-Whitney U-tests for non-normally distributed variables. Outcome variable change scores were checked for normality via Kolmogorov-Smirnov tests. Variables that were non-normally distributed were analysed with Mann-Whitney U-tests. Variables that were normally distributed were analysed by Independent T-tests. Paired T-tests were also
utilized to examine change over time within groups. Change over time in response to the resistance training intervention was evaluated using independent T-tests on the change scores using data from the intervention group (week 17 – week 0) and the waitlist control group (week 17 – week 0). Effect sizes and 95% confidence intervals were calculated for normally distributed variables. A \( p \) value of <0.05 was considered indicative of statistical significance; clinical significance was interpreted in light of the observed effect sizes and meaningfulness and magnitude of the adaptations observed. Cohens \( d \) effect sizes of over 0.8 were considered large, 0.5 moderate and 0.2 small [275]. A Bonferonni adjustment or alternative was not applied; however, results were interpreted as appropriate in the discussion. Pearson Correlations were examined between variables that returned a significant \( p \) value (<0.05) in the independent T-tests. Pearson’s \( r \) values of over 0.5 were considered high, over 0.3 moderate and over 0.1 low [275]. Correlations between outcome variables that demonstrated significant change were used to assess potential relationships. Following ITT analysis, per protocol analysis was undertaken. Per protocol analysis [276] excluded all participants who did not complete follow up testing and adhered to less than 75% of the intervention. This level of adherence (75%) was selected to try and isolate the true effect of the treatment.
4 RESULTS

4.1 Participants

Recruitment took place between the 16th of May 2012 and the 25th of June 2013. 39 participants were recruited and randomised for this study. Figure 4 shows the flow of participants through the trial. Five participants dropped out prior to collection of follow up data for a variety of reasons (refer to chart for reasons).

4.1.1 Participant characteristics

Baseline participant characteristics are presented in Table 7. There were no significant differences between groups at baseline in age and time since treatment. There was a significant difference in the amount of women taking Arimidex between groups with more women taking Arimidex in the exercise group. There was also a significant difference in the amount of women who identified as Caucasians, with more Caucasian women in the control group.
Figure 4: CONSORT Flow chart of participant recruitment
4.2 Data completeness

No blood parameters were able to be obtained for one participant due to an inability to collect blood. There was also missing baseline blood data for two participants due to an inability of the collection staff to draw blood, therefore blood analysis was conducted on 37 participants. There is missing data for five participant’s leg strength measures. The initial protocol utilised a different piece of equipment on which the software malfunctioned meaning I was forced to swap leg strength measures after the first 5 participants. There is some missing data with the weekly status checks. The exercise group’s average response rate was 81% (13 out of 16 sheets filled in per participant). The control group’s average rate of response for the weekly questionnaire was 59%. The missing data were either due to participants not responding to the weekly email or if an exercise participant missed the Friday exercise session which was the day that forms were distributed.
Table 7: A comparison between groups of the baseline characteristics of breast cancer survivors (Mean or n)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>All women Mean ± SD</th>
<th>Control (C) Mean ± SD</th>
<th>Exercise (E) Mean ± SD</th>
<th>P (C vs E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>39</td>
<td>51.91 ± 8.84</td>
<td>52.68 ± 9.35</td>
<td>51.20 ± 8.50</td>
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<tr>
<td>Time since treatment(m) (range)</td>
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<td>11.55 ± 13.15</td>
<td>13 ± 14.8 (1-44)</td>
<td>10.25 ±11.70 (1-44)</td>
<td>0.53</td>
</tr>
<tr>
<td>Treatments (n)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>38</td>
<td>34</td>
<td>16</td>
<td>18</td>
<td>0.60</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>38</td>
<td>33</td>
<td>16</td>
<td>17</td>
<td>0.95</td>
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<tr>
<td>Hormone therapy</td>
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<td>32</td>
<td>15</td>
<td>17</td>
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<td>11</td>
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<td>0.28</td>
</tr>
<tr>
<td>Ietrozole</td>
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<tr>
<td>Arimidex</td>
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<tr>
<td>Herceptin</td>
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<td>1</td>
<td>1</td>
<td>0</td>
<td>0.31</td>
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<td>Menopause status (n)</td>
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<td>2</td>
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<td>Premenopausal</td>
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<td>38</td>
<td>17</td>
<td>6</td>
<td>11</td>
<td>0.15</td>
</tr>
<tr>
<td>Tertiary</td>
<td>38</td>
<td>16</td>
<td>9</td>
<td>7</td>
<td>0.45</td>
</tr>
<tr>
<td>postgraduate</td>
<td>38</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0.60</td>
</tr>
<tr>
<td>Marital status (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>38</td>
<td>28</td>
<td>14</td>
<td>14</td>
<td>0.80</td>
</tr>
<tr>
<td>Widowed</td>
<td>38</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0.18</td>
</tr>
<tr>
<td>Divorced</td>
<td>38</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0.53</td>
</tr>
<tr>
<td>Separated</td>
<td>38</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.97</td>
</tr>
<tr>
<td>Income (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$15,000</td>
<td>33</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>0.66</td>
</tr>
<tr>
<td>$15,000-$30,000</td>
<td>33</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0.95</td>
</tr>
<tr>
<td>&gt;$30,000</td>
<td>33</td>
<td>16</td>
<td>7</td>
<td>9</td>
<td>0.44</td>
</tr>
<tr>
<td>Ethnicity (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian</td>
<td>38</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>0.87</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>38</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0.34</td>
</tr>
<tr>
<td>Caucasian</td>
<td>38</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>European</td>
<td>38</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0.25</td>
</tr>
<tr>
<td>Middle East</td>
<td>38</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.17</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2 south American, 2 pacific islands)</td>
<td>38</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0.28</td>
</tr>
</tbody>
</table>
4.3 Adherence

Mean adherence rates were 39.95 sessions out of a possible 47 (85%). The introductory exercise familiarisation session was not included in adherence calculations. Five participants adhered to less than 75% of the training programme (Table 8).

<table>
<thead>
<tr>
<th>Table 8: Exercise group session attendance data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>39.95</td>
</tr>
</tbody>
</table>

Missed sessions (161 in total) varied between the day of the week with 34% and 37% of missed sessions on Monday and Friday respectively. The best day of attendance was Wednesday which only accounted for 27% of all missed sessions. Attendance also varied across the duration of the program. Quarter one (weeks 1-4) had the highest level of attendance with only 16% of the total missed sessions occurring in quarter 1. Attendance over quarter 2, 3 and 4 was relatively consistent.

Compliance to exercise prescription was varied across the differing movements. Compliance to prescription of machine based movements was 100%. Modifications were required in the deadlift for 5 participants. All of
these participants required a reduction in the range of motion which was achieved by modifying the movement to commence from blocks. Modifications to range of motion were also utilised in the squat. Each participant reached varying degrees of squat depth as defined by anatomical limitations.

4.4 Additional exercise leisure time

The Godin Leisure-Time Exercise Questionnaire was collected at baseline and follow up to assess changes in exercise behavior over the course of the trial [272]. The control group and experimental group did not differ at baseline with regards to reported exercise leisure time (12.9 ± 11.9 hours for control versus 14.2 ± 13.5 hours for exercise) (p=0.77). The control group did not differ from pre to post intervention (p=0.62) indicating their exercise level remained constant. The exercise group engaged in a significantly greater amount of leisure time following the intervention increasing their average time to 24.9 ± 11.44 hours (p=0.03).

4.5 Health status, adverse events and lymphedema

Change of health status in the experimental and control group was also tracked during the 16-week intervention period. It was documented by means of a structured questionnaire of open-ended questions that was administered weekly, via email to the control group or in person to the
experimental group. Acute illnesses, injury and changes in medication dose were tracked in both groups.

Acute illness and injury were tracked as part of the weekly health status questionnaire. In the exercise group there were only two reports of illness over the intervention period. Over the same period three participants suffered an acute injury, all muscular pain. The injuries persisted for one, two, and three weeks respectively for each of the three participants. In all cases the program was modified to allow continued participation. In each case the injury was attributed to an activity separate from the exercise intervention. One participant was diagnosed with a trigger point in the shoulder which the therapist attributed to dragon boat racing. Another participant suffered an acute bout of low back pain after lifting her children in an awkward manner. The third participant suffered from an unspecified/undiagnosed pain in the trapezius region.

In comparison the control group had three injuries reported by participants, also lasting one, two, and three weeks respectively. Two participants in the control group reported illnesses. The rates of injury and illness are similar between groups even though the response rate was significantly lower in the control group.
Adverse events are defined as any injury or exacerbation of underlying
disease that was potentially attributable to the RT program. Multiple
participants suffered some form of injury during the intervention; however,
these were attributable to activities outside of the gym environment. There
were no injuries directly attributed to the exercise intervention. There were
no new reports of lymphedema diagnosis during the intervention, nor were
there any exacerbations in women with current lymphedema.

4.6 Comparison of groups at baseline for all outcome variables

There were no significant differences between groups at baseline (Table 10
and Table 9) with the exception of NK expression of perforin. The control
group participants had higher body mass, greater percentage body fat and
greater upper body strength than the exercise group although this did not
reach significance.
Table 9: Comparison of baseline values between groups for immunological and inflammatory variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise</th>
<th>Control</th>
<th>p</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK (%)</td>
<td>8.30 (6.90 to 13.90)</td>
<td>8.75 (4.989 to 10.75)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>NKperf (%)</td>
<td>45.48 ± 20.00</td>
<td>33.28 ± 14.68</td>
<td>0.04†</td>
<td></td>
</tr>
<tr>
<td>NKGB (%)</td>
<td>48.58 ± 14.55</td>
<td>48.84 ± 12.41</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>NKIFNγ (%)</td>
<td>26.71 ± 14.99</td>
<td>22.81 ± 11.83</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>NKTNF-α (%)</td>
<td>13.81 ± 4.67</td>
<td>13.53 ± 3.95</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>NKT (%)</td>
<td>6.87 ± 5.09</td>
<td>5.46 ± 3.64</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>NKTperf (%)</td>
<td>21.02 ± 13.93</td>
<td>23.23 ± 15.81</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>NKTGB (%)</td>
<td>49.04 ± 21.80</td>
<td>38.68 ± 15.71</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>NKTIFNγ (%)</td>
<td>69.59 ± 15.30</td>
<td>61.37 ± 19.43</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>NKTTNF-α (%)</td>
<td>9.94 ± 5.90</td>
<td>13.60 ± 6.98</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.00 (0.80 to 3.75)</td>
<td>1.65 (1.05 to 4.38)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Serum IL-10 (fg/mL)</td>
<td>86.69 (20.30 to 169.26)</td>
<td>103.97 (45.04 to 349.81)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Serum IL-6 (fg/mL)</td>
<td>954.50 (653.71 to 3172.14)</td>
<td>1267.67 (584.41 to 3386.67)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>Serum TNF-α (fg/mL)</td>
<td>0.00 (0.00 to 156.81)</td>
<td>0.00 (0.00 to 255.11)</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

† p < 0.05 between groups

Median and (25 to75%) are presented for non-normally distributed variables. Mann Whitney U tests were also used for non-normally distributed variables.

Abbreviations: NK, Natural Killer cell; NKperf, Natural Killer cell expression of perforin; NKGB, Natural Killer cell expression of Granzyme B; NKIFN-γ, natural killer cell expression of interferon gamma; NKTNF-α, natural killer cell expression of Tumour Necrosis Factor alpha; NKT, Natural Killer T-cell; NKTperf, natural killer T-cell expression of perforin; NKGB, Natural Killer T-cell expression of Granzyme B; NKT IFN-γ, Natural Killer T-cell expression of interferon gamma; NKT TNF-α, Natural Killer T-cell expression of Tumour Necrosis Factor alpha; CRP, C reactive protein
<table>
<thead>
<tr>
<th>Variable (unit)</th>
<th>Exercise</th>
<th>Control</th>
<th>p</th>
<th>Difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>72.44 ± 9.18</td>
<td>80.22 ± 16.77</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.63 ± 4.22</td>
<td>29.91 ± 6.46</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>BF (%)</td>
<td>32.61 ± 7.16</td>
<td>37.4 ± 9.98</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>EWB</td>
<td>19.25 ± 3.70</td>
<td>20.42 ± 1.39</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>PWB</td>
<td>23.1 ± 4.68</td>
<td>23.95 ± 3.26</td>
<td>0.52</td>
<td></td>
</tr>
<tr>
<td>FWB</td>
<td>23.25 ± 3.22</td>
<td>22.63 ± 4.21</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>SWB</td>
<td>23.49 ± 4.25</td>
<td>22.99 ± 4.64</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>FACT-G</td>
<td>89.07 ± 11.66</td>
<td>90.00 ± 9.99</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>FACIT</td>
<td>39.05 ± 10.02</td>
<td>38.26 ± 10.51</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>SF36-PCS</td>
<td>40.42 ± 6.87</td>
<td>40.69 ± 8.26</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>SF36-MCS</td>
<td>46.95 ± 9.43</td>
<td>50.18 ± 8.03</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>FABQ-PA</td>
<td>3.00 ± 4.66</td>
<td>4.11 ± 4.45</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Maximal isometric chest press – surgical arm (N)</td>
<td>143.27 ± 24.08</td>
<td>163.25 ± 39.74</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Maximal isometric chest press – nonsurgical arm (N)</td>
<td>151.56 ± 31.47</td>
<td>169.94 ± 26.11</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Leg press (kg)</td>
<td>117.94 ± 41.63</td>
<td>130.30 ± 45.42</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

No between group differences were observed at baseline for these variables.

Abbreviations: BW, body weight; BMI, body mass index; BF, body fat; EWB, emotional well-being; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; FACT-G, functional assessment of cancer therapy – general; FACIT, functional assessment of chronic illness therapy – fatigue.
4.7 The effect of the intervention

4.7.1 Immune function

Table 14 and Table 15 show the effect of the intervention on biomarkers of immune function. Only one of the nine immune parameters demonstrated a change over time when compared to the control group. NK expression of TNF-α reduced significantly following the intervention in the exercise group (p = 0.037), whereas it increased significantly following the intervention period in the control group (p = 0.009). At the end of the intervention NK expression of TNF-α was also significantly different between groups (p = 0.004). NKT expression of TNF-α was also significantly different following the intervention in the exercise group (p = 0.017); however, when compared to the control group there was no difference. A large effect was observed for NK expression of TNF-α. Moderate effects were observed for NK number and NK expression of perforin. Small effects were observed for the remainder of the variables of immune function.

Figure 6, Figure 7, and Figure 8 demonstrate examples of the flow cytometry results examining the peripheral blood mononuclear cells, their biomarkers of expression and cytokines. Each figure demonstrates an example scatter plot for a healthy control, a breast cancer survivor in the control group and a breast cancer survivor in the resistance training intervention group. Healthy control data were collected in the pilot phase of testing for this trial and is included here to give a visual depiction of the differences between healthy
women and those who have survived cancer. The scatter plots are separated into four quadrants. Three of these quadrants represent a specific cell type or expression of a particular biomarker. Quadrant three (bottom left corner) was not used to calculate any results. The number of cells gated to each particular quadrant was then converted to percentages which are expressed in Table 11, Table 12, and Table 13. This is only a representative data sample; the mean group percentage expressions and the change in percentage expression are presented in this thesis. There is an inclusion of a healthy control participants data to demonstrate what a ‘healthy’ representative dot plot would look like in comparison to someone who may have altered immune functioning.
Figure 5: Box plot demonstrating the differences in change in Natural Killer cell expression of TNF-α between the control and exercise groups

Abbreviations used: TNF-α, Tumour Necrosis Factor Alpha

Figure 5 shows that there is large variability in the NK expression of TNF-α in response to the intervention. The control group demonstrated a larger degree of variability with 75% of individuals demonstrating an increase in this NK expression of TNF-α, in comparison; the exercise group shows that almost 75% of participants experienced a reduction in the NK expression of TNF-α.
Figure 6: Representative dot plots indicating the gating strategy from a healthy control, a breast cancer control participant and a breast cancer exercise participant. These plots show the percentage of peripheral blood cells that are NK cells, NKT cells and T cells. The percentages are presented in Table 11.
Table 11: Tabular representation of the percentages of immune cells in peripheral blood cells (PBC’s) before and after intervention period.  
(These numbers are calculated from Figure 6)

<table>
<thead>
<tr>
<th></th>
<th>NK (%)</th>
<th>NKT (%)</th>
<th>T (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 17</td>
<td>Week 0</td>
</tr>
<tr>
<td>Healthy Control</td>
<td>5</td>
<td>NA</td>
<td>5</td>
</tr>
<tr>
<td>Breast Cancer-control group</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Breast Cancer – exercise group</td>
<td>7</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations used: NK, Natural Killer cell; NKT, Natural Killer T-cell; T, T-cell.
Figure 7: Representative dot plots indicating the gating strategy from a healthy control, a breast cancer control participant and a breast cancer exercise participant. These plots show the percentage of NK cells that express GB and CD158b. NK cells expressing GB cells are identified by Q1-3, NK cells expressing CD158b are identified by Q4-3, NKT Cells expressing both GB and CD158b are identified in Q2-3. The percentages are presented in Table 12.
Table 12: Tabular representation of the percentages of natural killer (NK) cells expressing Granzyme-B, CD158, and a combination of the two biomarkers.

(These numbers are calculated from Figure 7)

<table>
<thead>
<tr>
<th></th>
<th>GB (%)</th>
<th>GB/CD158 (%)</th>
<th>CD158 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 17</td>
<td>Week 0</td>
</tr>
<tr>
<td>Healthy Control</td>
<td>51</td>
<td>NA</td>
<td>35</td>
</tr>
<tr>
<td>Breast Cancer-control group</td>
<td>62</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>Breast Cancer – exercise group</td>
<td>42</td>
<td>46</td>
<td>25</td>
</tr>
</tbody>
</table>

Abbreviations used: NK, Natural Killer cell; GB, Granzyme-B; CD-158, Cluster of differentiation – 158.
Figure 8: Representative dot plots indicating the gating strategy from a healthy control, a breast cancer control participant and a breast cancer exercise participant. These plots show the percentage of NKT cells that express GB and CD158b. NKT cells expressing GB cells are identified by Q1-3, NKT cells expressing CD158b are identified by Q4-3, NKT Cells expressing both GB and CD158b are identified in Q2-3. The percentages are presented in Table 13.
Table 13: Tabular representation of the percentages of Natural killer T-cells (NKT) cells expressing Granzyme-B, CD158, and a combination of the two biomarkers.

(These numbers are calculated from Figure 8)

<table>
<thead>
<tr>
<th></th>
<th>GB (%)</th>
<th>GB/CD158 (%)</th>
<th>CD158 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 17</td>
<td>Week 0</td>
</tr>
<tr>
<td>Healthy Control</td>
<td>60</td>
<td>NA</td>
<td>22</td>
</tr>
<tr>
<td>Breast Cancer-control group</td>
<td>67</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>Breast Cancer – exercise group</td>
<td>37</td>
<td>37</td>
<td>13</td>
</tr>
</tbody>
</table>

Abbreviations used: NKT, Natura Killer T-cell; GB, Granzyme-B; CD-158, Cluster of differentiation – 158.
Figure 9 shows the within group variability for selected biomarkers of immune function. The expression of perforin and granzyme B on NK cells are both important biomarkers of immune function in this cohort and represent the inter-individual variability demonstrated across all blood measures. The red line depicts the mean.
Figure 9: Comparison of within group variability for biomarkers of Natural Killer cell function.

The red line represents group mean. Abbreviations used: NK, Natural Killer; GB, Granzyme-B; perf, Perforin.
Figure 10 depicts the individual differences in expression of TNF-α on NK and NKT cells over the course of the intervention. The group means decrease over time for both biomarkers in the exercise group (NK-TNFα p=0.037, NKT-TNFα p=0.017), and remain stable or increase in the experimental group. There is large individual variability, although trends for each group are apparent.

**Figure 10:** Comparison between groups of change in NK and NKT expression of TNF-α over time. The red line represents the group mean. Abbreviations used: NK, Natural Killer cell; NKT, Natural Killer T-cell; TNF-α, Tumor Necrosis Factor-alpha.
Table 14: A comparison between groups of mean change, 95% CI and effect size for percentage expression of biomarkers of Natural Killer cell function

<table>
<thead>
<tr>
<th></th>
<th>Exercise (Mean, 95% CI)</th>
<th>Control (Mean, 95% CI)</th>
<th>Group Differences (Mean, 95% CI)</th>
<th>Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NK (%)</td>
<td>-1.02 (-2.59 to 0.56)</td>
<td>1.07 (-0.78 to 2.91)</td>
<td>-2.08 (-4.41 to 0.25)</td>
<td>0.60</td>
</tr>
<tr>
<td>NK perf (%)</td>
<td>-6.08 (-13.76 to 1.59)</td>
<td>2.52 (-4.89 to 9.93)</td>
<td>-8.60 (-18.91 to 1.71)</td>
<td>0.56</td>
</tr>
<tr>
<td>NK GB (%)</td>
<td>-6.48 (-15.27 to 2.31)</td>
<td>-3.31 (-7.35 to 0.72)</td>
<td>-3.17 (-12.68 to 6.35)</td>
<td>0.22</td>
</tr>
<tr>
<td>NK IFN-γ (%)</td>
<td>0.37 (-4.77 to 5.52)</td>
<td>3.46 (-5.29 to 12.21)</td>
<td>-3.08 (-12.74 to 6.57)</td>
<td>0.21</td>
</tr>
<tr>
<td>NK TNF-α (%)</td>
<td>-1.41 (-3.85 to 1.04)*</td>
<td>4.33 (1.23 to 7.42)</td>
<td>-5.73 (-9.51 to -1.96) †</td>
<td>1.01</td>
</tr>
</tbody>
</table>

*p <0.05 from baseline, **p <0.001 from baseline, † p <0.05 between groups, ‡ p < 0.001 between groups
Median and (25-75%) are presented for non-normally distributed variables

Abbreviations: NK, Natural Killer cell; NK perf, Natural Killer cell expression of perforin; NK GB, Natural Killer cell expression of Granzyme B; NK IFN-γ, Natural Killer cell expression of interferon gamma; NK TNF-α, Natural Killer cell expression of Tumour Necrosis Factor alpha
Table 15: A comparison between groups of mean change, 95% CI and effect size for percentage expression of biomarkers of Natural killer T-cell function

<table>
<thead>
<tr>
<th></th>
<th>Exercise (Mean, 95% CI)</th>
<th>Control (Mean, 95% CI)</th>
<th>Group Differences (Mean, 95% CI)</th>
<th>Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKT (%)</td>
<td>-1.52 (-2.10 to 0.00)</td>
<td>-0.14 (-0.95 to 0.29)</td>
<td>-1.38 (-4.04 to 1.27)</td>
<td>0.43</td>
</tr>
<tr>
<td>NKT perf (%)</td>
<td>-1.11 (-9.85 to 7.64)</td>
<td>-1.80 (-9.04 to 5.44)</td>
<td>0.69 (-10.32 to 11.71)</td>
<td>0.04</td>
</tr>
<tr>
<td>NKT GB (%)</td>
<td>-4.33 (-11.28 to 2.62)</td>
<td>1.57 (-4.47 to 7.62)</td>
<td>0.13 (-14.83 to 3.02)</td>
<td>0.44</td>
</tr>
<tr>
<td>NKT IFN-γ (%)</td>
<td>0.85 (-5.59 to 7.29)</td>
<td>2.97 (-5.22 to 11.18)</td>
<td>-2.13 (-12.12 to 7.86)</td>
<td>0.14</td>
</tr>
<tr>
<td>NKT TNF-α (%)</td>
<td>-3.01 (-5.41 to -0.60)*</td>
<td>0.05 (-4.17 to 4.27)</td>
<td>-3.06 (-7.67 to 1.56)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*p <0.05 from baseline

Abbreviations: NKT, Natural Killer T-cell; NKTperf, Natural Killer T-cell expression of perforin; NKT GB, Natural Killer T-cell expression of granzyme B; NKT IFN-γ, Natural Killer T-cell expression of interferon gamma; NKT TNF-α, Natural Killer T-cell expression of Tumour Necrosis Factor alpha
Table 16 shows the median and inter-quartile range (IQR) for CRP and the serum cytokines, all of which were non-normally distributed. Mann Whitney-U testing on these variables revealed no significant between group differences for any variable.
Table 16: A comparison between groups of the median change score and Inter-quartile range (IQR) for Serum cytokines and CRP

<table>
<thead>
<tr>
<th></th>
<th>Exercise (Median and IQR)</th>
<th>Control (Median and IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>-0.50 (-0.35 to 0.08)</td>
<td>0.00 (-0.10 to 1.10)</td>
</tr>
<tr>
<td>Serum IL-10 (fg/mL)</td>
<td>11.35 (-24.65 to 37.66)</td>
<td>0.00 (-11.89 to 61.62)</td>
</tr>
<tr>
<td>Serum IL-6 (fg/mL)</td>
<td>-236.26 (-610.94 to 34.15)</td>
<td>0.00 (-390.00 to 413.12)</td>
</tr>
<tr>
<td>Serum TNF-α (fg/mL)</td>
<td>0.00 (0.00 to 60.74)</td>
<td>0.00 (-26.46 to 0.00)</td>
</tr>
</tbody>
</table>

Abbreviations used: CRP, C-reactive protein; IL, interleukin; TNF-α, Tumour Necrosis Factor-alpha; mg, milligram; fg, fentogram
4.7.2 Body Composition

Table 17 shows the effect of the training intervention on markers of body composition. No significant changes between groups or within groups overtime were observed for body weight, percentage body fat or body mass index.

4.7.3 Strength

All measurements of strength significantly improved over the course of the intervention for the exercise group (p < 0.001) and differed when compared to the control group (p < 0.001) (Table 17). Large effect sizes were observed for all measurements of strength ranging between 1.48 and 1.83. Figure 11 shows that improvements in upper body strength are of similar magnitude in both the surgical and non-surgical arms. Paired T-tests revealed significant differences in strength between the surgical (143.27 ± 24.08 N) and non-surgical limbs (151.55 ± 31.47 N) (p = 0.037) at the start and end of training period (surgical limb 170.80 ± 37.26, non-surgical limb 184.33 ± 37.45) (p = 0.002) for the exercise group. The control group did not significantly differ between limbs at either time point.
Figure 11: Mean and SEM for the percentage change of the treated and non-treated arms following the intervention period
Table 17: A comparison between groups for scores of mean change, 95% CI and effect size in anthropometric and strength variables

<table>
<thead>
<tr>
<th></th>
<th>Exercise (Mean, 95% CI)</th>
<th>Control (Mean, 95% CI)</th>
<th>Group Differences (Mean, 95% CI)</th>
<th>Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>0.29 (-0.81 to 1.39)</td>
<td>0.54 (-0.67 to 1.74)</td>
<td>-0.25 (-1.82 to 1.33)</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>0.145 (-0.28 to 0.57)</td>
<td>0.18 (-0.27 to 0.64)</td>
<td>-0.39 (-0.64 to 0.56)</td>
<td>0.04</td>
</tr>
<tr>
<td>BF (%)</td>
<td>-1.20 (-2.7 to 0.29)</td>
<td>0.73 (-1.65 to 1.79)</td>
<td>-1.28 (-3.47 to 0.92)</td>
<td>0.38</td>
</tr>
<tr>
<td>Maximal isometric chest press-surgical (N)</td>
<td>27.53 (16.76 to 38.30)**</td>
<td>-5.20 (-12.91 to 2.51)</td>
<td>32.74 (19.81 to 45.66) ‡</td>
<td>1.65</td>
</tr>
<tr>
<td>Maximal isometric chest press-nonsurgical (N)</td>
<td>32.77 (19.84 to 45.72)**</td>
<td>-0.21 (-7.50 to 7.10)</td>
<td>32.98 (18.42 to 47.55) ‡</td>
<td>1.48</td>
</tr>
<tr>
<td>Leg press (kg)</td>
<td>40.04 (28.82 to 51.27)**</td>
<td>4.08 (-4.78 to 12.95)</td>
<td>35.96 (22.22 to 49.70) ‡</td>
<td>1.83</td>
</tr>
</tbody>
</table>

*p < 0.05 from baseline, **p < 0.001 from baseline, † p < 0.05 between groups, ‡ p < 0.001 between groups

Abbreviations: BW, body weight; BMI, body mass index; BF, body fat.
4.7.4 Quality of life

Table 18 shows the effect of the training intervention on markers of QOL. The control group did not significantly improve over time in any measurement of QOL. Four of the 9 variables differed significantly between groups at the end of the intervention with the exercise group demonstrating significant improvements. The effect sizes of the variables that significantly changed were generally large and ranged from 0.79 to 1.09. There were no between group differences at the end of the intervention for both subscales of the SF-36 (PCS and MCS); however, the exercise group did significantly improve on the MCS subscale following the intervention. The exercise group significantly reduced perceived fatigue, as measured by the FACIT, both over the time course of the intervention and in comparison to the control group.

Figure 12 demonstrates that the exercise group significantly improved in 2 of the 4 separate subscale components of the FACT-G subscale, as well as the overall FACT-G questionnaire. The control group did not significantly change in any component.
Figure 12: Comparison of the mean change of the Functional Assessment of Cancer Therapy – General (FACT-G) and its subscales between the exercise intervention and control group.

Abbreviations used: PWB; Physical wellbeing; SWB, social wellbeing; EWB, emotional wellbeing; FWB, functional wellbeing; FACT-G, functional assessment of cancer therapy general.
<table>
<thead>
<tr>
<th></th>
<th>Exercise (Mean, 95% CI)</th>
<th>Control (Mean, 95% CI)</th>
<th>Group Differences (Mean, 95% CI)</th>
<th>Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWB</td>
<td>2.10 (0.57 to 3.62) *</td>
<td>-0.11 (-1.33 to 1.12)</td>
<td>2.21 (0.30 to 4.11) †</td>
<td>0.75</td>
</tr>
<tr>
<td>PWB</td>
<td>2.45 (1.28 to 3.62)**</td>
<td>0.21 (-0.50 to 0.92)</td>
<td>2.24 (0.90 to 3.58) †</td>
<td>1.09</td>
</tr>
<tr>
<td>SWB</td>
<td>1.12 (-0.40 to 2.64)</td>
<td>0.78 (-0.98 to 1.66)</td>
<td>0.34 (-1.38 to 2.06)</td>
<td>0.13</td>
</tr>
<tr>
<td>FWB</td>
<td>1.45 (-0.21 to 3.11)</td>
<td>0.74 (-0.60 to 2.07)</td>
<td>0.71 (-1.38 to 2.78)</td>
<td>0.22</td>
</tr>
<tr>
<td>FACT-G</td>
<td>6.91 (3.05 to 10.77)**</td>
<td>1.62 (-0.50 to 3.75)</td>
<td>5.29 (0.98 to 9.61) †</td>
<td>0.79</td>
</tr>
<tr>
<td>FACIT</td>
<td>6.65 (3.15 to 10.15)**</td>
<td>1.53 (-0.28 to 3.33)</td>
<td>5.12 (1.25 to 8.99) †</td>
<td>0.86</td>
</tr>
<tr>
<td>SF36-PCS</td>
<td>2.77 (-0.95 to 6.50)</td>
<td>0.69 (-2.09 to 3.47)</td>
<td>2.08 (-2.44 to 6.61)</td>
<td>0.30</td>
</tr>
<tr>
<td>SF36-MCS</td>
<td>5.83 (0.10 to 11.55) *</td>
<td>1.05 (-1.72 to 3.81)</td>
<td>4.78 (-1.47 to 11.03)</td>
<td>0.50</td>
</tr>
<tr>
<td>FABQ-PA</td>
<td>-1.5 (-3.86 to 0.85)</td>
<td>1.00 (-1.63 to 3.63)</td>
<td>-2.50 (-5.90 to 0.90)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

* p < 0.05 from baseline, ** p < 0.001 from baseline, † p < 0.05 between groups, ‡ p < 0.001 between groups

Abbreviations: EWB, emotional well-being; PWB, physical well-being; FWB, functional well-being; SWB, social well-being; FACT-G, functional assessment of cancer therapy – general; FACIT, functional assessment of chronic illness therapy – fatigue; SF36-PCS, short form 36 physical component summary; SF36-MCS, short form 36 mental component summary; FAB-Q-PA, fear avoidance beliefs questionnaire physical activity
4.8 Correlations

Pearson’s correlations were calculated on the change scores of variables that were significantly different between groups at the culmination of the intervention. In addition, the relationships of potential covariates were examined.

Correlations for the control group are shown in Table 19. Five significant correlations were found in the control group. Control group women exhibited a significant correlation between change in leg press strength and time since treatment with those who were closer to completion of treatment showing an improvement over the course of the intervention period, regardless of not receiving a training intervention. Significant correlations were also observed in the control group between the leg press change and time since treatment ($r = -0.52$). Correlations were also observed in the control group between the strength change measurements of both upper limbs ($r = 0.53$).

Correlations between changes in NK-TNFα expression and changes in leg press (representative of leg strength) were found in both the exercise and control group and were of similar magnitude (control $r = -0.56$, exercise $r = -0.60$). This is depicted in Figure 13.
Other significant correlations found in the exercise group were between strength change of both upper limbs ($r = 0.63$), between the fatigue measurement (FACIT) and the quality of life measurement (FACT-G) ($r = 0.61$), and between the change in strength of the surgical arm and change in quality of life ($r = 0.46$). The correlations for the exercise group are shown in Table 20.
Figure 13: A comparison between groups of the relationship between changes in leg strength and changes in TNFα expression on NK cells

Abbreviations used: TNF-α, Tumour Necrosis Factor-alpha; NK, Natural Killer cell.
Table 19: Pearson correlations (r) between significant change scores and potential covariates in the control group

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Time since treatment</th>
<th>NK-TNFα</th>
<th>Leg Press (kg)</th>
<th>Surgical arm (N)</th>
<th>Non-surgical arm (N)</th>
<th>FACIT</th>
<th>FACT-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>-0.06</td>
<td>0.18</td>
<td>0.08</td>
<td>-0.10</td>
<td>0.06</td>
<td>0.17</td>
<td>-0.37</td>
</tr>
<tr>
<td>Time since treatment</td>
<td>-0.06</td>
<td></td>
<td>0.15</td>
<td>-0.52*</td>
<td>-0.18</td>
<td>-0.03</td>
<td>-0.23</td>
<td>-0.10</td>
</tr>
<tr>
<td>NK TNF-α</td>
<td>0.18</td>
<td></td>
<td>0.15</td>
<td>-0.56*</td>
<td>-0.18</td>
<td>0.26</td>
<td>0.30</td>
<td>-0.03</td>
</tr>
<tr>
<td>Leg Press (kg)</td>
<td>0.08</td>
<td>-0.52*</td>
<td>-0.56*</td>
<td>0.26</td>
<td>-0.09</td>
<td>0.15</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Surgical arm (N)</td>
<td>-0.10</td>
<td>-0.18</td>
<td>-0.18</td>
<td>0.26</td>
<td>0.53*</td>
<td>0.27</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Non-surgical arm (N)</td>
<td>0.06</td>
<td>-0.03</td>
<td>0.26</td>
<td>-0.09</td>
<td>0.53*</td>
<td>0.39</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>FACIT</td>
<td>0.17</td>
<td>-0.23</td>
<td>0.30</td>
<td>0.15</td>
<td>0.27</td>
<td>0.39</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>FACT-G</td>
<td>-0.37</td>
<td>-0.10</td>
<td>-0.03</td>
<td>0.01</td>
<td>0.22</td>
<td>0.15</td>
<td>0.41</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: NK TNF-α, the expression of Tumour Necrosis Factor alpha on Natural Killer cells; Treated arm – non treated arm – leg press, all refer to strength measurements; FACT-G, functional assessment of cancer therapy – general; FACIT, functional assessment of chronic illness therapy; N, newtons; kg, kilograms

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level
Table 20: Pearson correlations (r) between significant change scores and potential covariates in the exercise group

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Time since treatment</th>
<th>NK-TNFα</th>
<th>Leg Press (kg)</th>
<th>Surgical arm (N)</th>
<th>Non-surgical arm (N)</th>
<th>FACIT</th>
<th>FACT-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.44</td>
<td>0.20</td>
<td>-0.09</td>
<td>0.02</td>
<td>0.19</td>
<td>-0.09</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Time since treatment</td>
<td>0.44</td>
<td>-0.16</td>
<td>-0.14</td>
<td>-0.44</td>
<td>-0.16</td>
<td>-0.32</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>NK-TNFα</td>
<td>0.20</td>
<td>-0.16</td>
<td>-0.60*</td>
<td>0.04</td>
<td>-0.23</td>
<td>-0.04</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Leg Press (kg)</td>
<td>-0.09</td>
<td>-0.14</td>
<td>-0.60*</td>
<td>-0.03</td>
<td>0.22</td>
<td>-0.001</td>
<td>-0.09</td>
<td></td>
</tr>
<tr>
<td>Surgical arm (N)</td>
<td>0.02</td>
<td>-0.44</td>
<td>0.04</td>
<td>-0.03</td>
<td>0.63**</td>
<td>0.34</td>
<td>0.46*</td>
<td></td>
</tr>
<tr>
<td>Non-surgical arm (N)</td>
<td>0.19</td>
<td>-0.16</td>
<td>-0.23</td>
<td>0.22</td>
<td>0.63**</td>
<td>0.32</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>FACIT</td>
<td>-0.09</td>
<td>-0.32</td>
<td>-0.04</td>
<td>-0.001</td>
<td>0.34</td>
<td>0.32</td>
<td>0.61**</td>
<td></td>
</tr>
<tr>
<td>FACT-G</td>
<td>0.08</td>
<td>0.002</td>
<td>0.07</td>
<td>-0.09</td>
<td>0.46*</td>
<td>0.41</td>
<td>0.61**</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: NK TNF-α, the expression of Tumour Necrosis Factor alpha on Natural Killer cells; Treated arm – non treated arm – leg press, all refer to strength measurements; FACT-G, functional assessment of cancer therapy – general; FACIT, functional assessment of chronic illness therapy; N, newtons; kg, kilograms

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level
4.9 Per protocol analysis

When data were analysed per protocol (please refer to statistical methods section for definition), there were 15 participants in the control group and 15 participants in the experimental group. In the experimental group 1 person failed to complete the intervention and did not receive follow-up testing and 4 were excluded as they failed to meet my attendance requirement. In the control group four participants were lost to follow-up. There was no difference between utilising intention to treat statistical analysis versus per protocol statistical analysis in this case (Table 21). Using both protocols, the same 10 variables change scores were statistically significantly different between groups.
Table 21: Between group mean differences, 95% CI and effect size for normally distributed
variables when run in a per
protocol analysis manner

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Group Differences (Mean, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (kg)</td>
<td>0.15 (-1.66 to 1.96)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-1.09 (-0.60 to 0.77)</td>
</tr>
<tr>
<td>BF (%)</td>
<td>0.09 (-3.85 to 1.68)</td>
</tr>
<tr>
<td>UB-surgical strength (N)</td>
<td>38.52 (23.50 to 53.54) ‡</td>
</tr>
<tr>
<td>UB-nonsurgical strength(N)</td>
<td>39.79 (22.25 to 57.33) ‡</td>
</tr>
<tr>
<td>Leg Press (kg)</td>
<td>37.23 (21.38 to 23.09) ‡</td>
</tr>
<tr>
<td>NK (%)</td>
<td>-2.55 (-5.64 to 0.54)</td>
</tr>
<tr>
<td>NKperf (%)</td>
<td>-6.89 (-19.81 to 6.03)</td>
</tr>
<tr>
<td>NKGB (%)</td>
<td>1.18 (-10.33 to 12.68)</td>
</tr>
<tr>
<td>NKIFN-γ (%)</td>
<td>-2.01 (-14.65 to 10.63)</td>
</tr>
<tr>
<td>NKTNF-α (%)</td>
<td>-7.35 (-11.82 to -2.88) †</td>
</tr>
<tr>
<td>NKTperf (%)</td>
<td>0.46 (-13.69 to 14.56)</td>
</tr>
<tr>
<td>NKTGB (%)</td>
<td>-3.14 (-14.31 to 8.04)</td>
</tr>
<tr>
<td>NKTIFN-γ (%)</td>
<td>-0.66 (-13.60 to 12.27)</td>
</tr>
<tr>
<td>NKTTNF-α (%)</td>
<td>-3.61 (-9.75 to 2.53)</td>
</tr>
<tr>
<td>PWB</td>
<td>2.53 (1.10 to 3.97) †</td>
</tr>
<tr>
<td>SWB</td>
<td>0.41 (-1.59 to 2.41)</td>
</tr>
<tr>
<td>FWB</td>
<td>0.67 (-1.97 to 3.31)</td>
</tr>
<tr>
<td>FACT-G</td>
<td>6.09 (1.37 to 10.81) †</td>
</tr>
<tr>
<td>FACIT</td>
<td>6.27 (1.58 to 10.96) †</td>
</tr>
<tr>
<td>SF36-PCS</td>
<td>14.40 (4.07 to 24.73) †</td>
</tr>
<tr>
<td>SF36-MCS</td>
<td>17.80 (7.95 to 27.65) †</td>
</tr>
</tbody>
</table>

† p < 0.05 between groups, ‡ p < 0.001between groups

Abbreviations: BW, body weight; BMI, body mass index; BF, body fat; UB, upper body; NK, Natural Killer cell; NKperf, Natural Killer cell expression of perforin; NKGB, natural killer cell expression of granzyme B; NKIFN-γ, Natural Killer cell expression of interferon gamma; NKTNF-α, Natural Killer cell expression of Tumour Necrosis Factor-alpha; NKT, Natural Killer T cell; PWB, Physical Well-being; FWB, Functional Well-being; SWB, Social Well-being; FACT-G, Functional Assessment of Cancer Therapy – General; FACIT, Functional Assessment of Chronic Illness Therapy – Fatigue; SF-36, short form 36 physical component summary; SF-36 MCS, short form 36 mental component summary.
5 DISCUSSION

5.1 Overall study findings summary

The primary objective of this study was to determine whether resistance training could elicit improvements in markers of NK cell function. The second objective was to determine whether resistance training could improve additional markers of immune function and inflammation, QOL, body composition and muscular strength in breast cancer survivors. Lastly, the third objective of this study was to explore relationships between the aforementioned variables.

The findings from this study demonstrated the ability of resistance training to alter the NK cell expression of TNF-α, a marker of inflammation, in breast cancer survivors. I also observed significant improvements in QOL, perceived fatigue, and muscular strength in the resistance exercise intervention group. I found that improvements in lower body muscular strength were correlated with improvements in inflammation, as measured by NK cell expression of TNF-α, and that muscular strength improvements in the surgical arm were correlated with improvements in QOL.
5.2 Immune function and inflammation

This study determined the effect of resistance training on markers of inflammation and immune function in a cohort of breast cancer survivors. This is the first study to show that resistance training significantly reduced levels of NK cell expressed TNF-α in the exercise group compared to the control group. Further, the exercise group also significantly reduced their NKT cell expression of TNF-α; however, this was not statistically different when compared to the control group. I also observed a clinically meaningful reduction in CRP levels in the resistance exercise group. Interpreted together, these data indicate a reduction in the inflammatory profile of breast cancer survivors following a resistance training intervention.

5.2.1 Mononuclear cell production of cytokines

Two intracellular cytokines were measured in this study; TNF-α and IFN-γ. The primary finding from this study was the reduction in TNF-α expression on NK cells following the resistance training intervention. No change was observed for IFN-γ. While the clinical significance of the reduction of TNF-α expression on NK cells is currently unknown, it is hypothesised that the alteration in expression of TNF-α is related to the anabolic stimulus of resistance training.
5.2.1.1 Resistance training and TNF-α

To my knowledge there is no available research in any cohort measuring changes in cytokine production from mononuclear cells in response to resistance training; however, multiple studies have examined the change over time in the concentration of serum markers, including TNF-α. In addition, several studies have examined the skeletal muscle expression of TNF-α in response to training. Both of these markers have helped to formulate a theory linking levels of TNF-α to alterations in muscle mass, and these data presented here provide additional support for the proposed relationship between TNF-α and muscle mass.

As covered in the literature review, research in ageing populations has provided much of the evidence surrounding resistance exercise and inflammation. Research in ageing populations by Phillips et al. [34] demonstrated that 10 weeks of high intensity resistance training, three times per week, elicited significant reductions in serum concentrations of TNF-α and reduced stimulated production of IL-6 and TNF-α, whereas they observed no change in serum IL-6. Similarly, Kohut et al. demonstrated that exercise reduces multiple serum inflammatory markers in ageing persons, including serum TNF-α [201]. These authors demonstrated that serum concentrations of CRP, IL-6 and IL-18 decreased only in response to aerobic exercise, not in response to resistance exercise. Conversely, TNF-α concentration reduced in response to both modalities of exercise, highlighting
a potentially different mechanism of change for TNF-α. These authors postulated that a potential explanation for this finding was that TNF-α concentration in the serum may have some association with muscle mass [201]. Their theory was based on the possibility that the greater degree of muscle mass allowed for a greater uptake of TNF-α by the increased TNF-α (R1) receptor [201], based on Heled and colleagues research that demonstrated that exercise increases the expression of TNF-α and its receptor TNF (R1) in rat muscle [202].

Greiwe et al. [32] demonstrated that muscle protein synthesis is inversely related to levels of TNF-α in muscle, leading Phillips et al. to hypothesise that the reduction in circulating TNF-α may have contributed to the observed strength gains in their study [34]. Although I did not measure protein synthesis in this study, I demonstrated a significant large negative correlation between leg press score and NK cell expression of TNF-α (Cohen’s d = -0.6), indicating that as leg strength increased, TNF-α expression decreased, further supporting the link between muscle mass and TNF-α.

Philips et al. further postulated that the decrease in inflammation, as evidenced by significantly reduced serum TNF-α, early in a training study, prior to changes in body composition becoming evident, highlights the early health related changes in response to exercise training [32]. Magnitudes of strength gain observed following Phillips et al. study were an average of a 31% increase across multiple exercises. My study also elicited a similar
degree of strength gains and also a reduction in markers of inflammation without a concurrent reduction in body fat or observable change in muscle mass. Previous research has demonstrated a reduction in inflammatory markers, particularly TNF-α, in response to weight loss in obese persons [277, 278]; however, perhaps adaptation in this marker can be elicited via multiple pathways. Conceivably, the apparent early relationship between the reduction in TNF-α and improved strength in both the current study and that of Philips et al. [34] may relate to the aforementioned hypothesis of increased protein synthesis, even before alterations in muscle cross sectional area become apparent.

To my knowledge, in addition to the one study that examined mononuclear cell production of TNF-α [28], there has been only one combined modality study in breast cancer survivors has measured TNF-α levels [178], which found that exercise did not elicit a change in serum levels of TNF-α. The levels of TNF-α in their study were also very low to begin with, potentially explaining the lack of exercise induced change as they were already within normative levels. There has been no isolated resistance training interventions measuring TNF-α in breast cancer survivors; however, there has been one study utilising resistance training in prostate cancer survivors measuring this marker. These authors did not observe a change in response to the intervention [181]; however, their sample size was small with 10 participants, and the serum levels of inflammatory markers were also low at baseline.
In this study I observed a 15.5% reduction in the expression of TNF-α on NK cells; however, I showed no change in serum TNF-α level. A potential explanation for this lack of change could be due to the methodology I employed. In the current study, over 50% of the cohort had serum TNF-α levels that were undetectable. Komatsu has previously stated that serum TNF-α concentration in healthy populations are often too low to be detected by standard ELISA methods [279]. Further, serum TNF-α has an extremely short half-life in the blood [280, 281], compounding its difficulty to measure. Although the cohort in this study was not classified as a healthy population, it appears for this marker of inflammation they were similar to healthy populations as the average serum level of TNF-α in this study was lower when compared to that observed in the serum of healthy controls [282, 283]. This is a similar finding to research carried out in prostate cancer patients where serum TNF-α could not be detected in 87 out of 110 samples [284].

While the comparison of muscle TNF-α, serum TNF-α and mononuclear cell production of TNF-α is not possible, there does appear to be a commonality in the markers response to resistance exercise. Although the receptor hypothesis in muscle mass appears logical in relation to the reduction of serum TNF-α, it cannot explain a reduced expression from NK cells. As the expression of TNF-α on mononuclear cells is prior to circulation, R1 cannot have increased its uptake to reduce expression on these cells and hence this hypothesis does not fit in this case. An alternative hypothesis may relate to the overall altered immune/inflammatory profile as a result of the anabolic influence of the resistance training intervention.
It has been suggested that the catabolic influence of TNF-α may be overridden by adding an anabolic stimuli [285]. While this idea was founded from research in cell studies, in this case, perhaps resistance exercise was the superimposed anabolic stimuli causing the reduction in TNF-α expression at the protein level. As discussed in the literature review, the M1 phenotype, or classically activated macrophages are observed in conditions such as obesity, and are characterised by increased production of TNF-α [256]. When expression of TNF-α is suppressed, it suggests a shift towards an M2 phenotype [286]. The shift from an M1 to a M2 phenotype appears to be important for changing the environment to one that promotes muscle growth [287]. It has previously been demonstrated that levels of circulating cytokines were negatively related to the levels of protein synthesis in skeletal muscle in aging adults [32, 288]. Therefore, perhaps the addition of the anabolic stimulus, resistance training, may have elicited an alteration in the phenotype to M2, and a subsequent reduction in the inflammatory environment.

A limitation of the current study is the lack of measurement of muscle TNF-α and of muscle protein synthesis; however, due to the invasive measurement technique required (skeletal muscle biopsy), I decided that I would focus solely on minimally invasive measuring techniques in this cohort. It was decided in light of the many recent medical procedures endured by all of the
participants in this group, that I would solely explore mononuclear cell production and serum TNF-α.

Although research measuring TNF-α concentration in its varying forms is still limited in this cohort, the link between resistance training and modulation of various forms of TNF-α appears promising. The findings in this study of reduced expression of TNF-α on NK cells, and the significant large correlation between reduced inflammation and improved lower body strength support the previously identified hypothesis of a direct link between muscle mass and TNF-α.

5.2.2 CRP

In addition to a dysfunctional immune system, breast cancer patients have been reported to have an altered inflammatory profile [78]. CRP, an acute phase protein, is indicative of systemic inflammation [289] which is of paramount importance in this cohort as inflammatory status is an important predictor of survival following breast cancer [73]. The findings of this study demonstrated that resistance training led to a clinically meaningful reduction in the level of CRP in the resistance training group in the absence of a statistically significant reduction.
The low initial value of CRP observed in this study may partially explain the lack of significant findings. The baseline level of CRP in this study was an average of 2.9 mg/L. In comparison, a large scale prospective cohort study (n = 734) reported that breast cancer survivors had average levels of CRP of 4.5 mg/L approximately three years after diagnosis [73]. Although the cohort in my study appears to have a lower level of inflammation, and the findings from the current study did not demonstrate a statistically significant difference in change scores between groups in any serum cytokine or in CRP, they may be interpreted as having had a clinically meaningful change. The median change was a reduction of 0.5 mg/L in the resistance exercise group, down from a median of 1.0 mg/L at baseline, representing a median reduction of 50%, compared to the control group median that did not change. This reduction from an average of 2.88 mg/L to 1.68 mg/L in the exercise group, equates to a 41% reduction in level of CRP, which likely represents a clinically meaningful reduction in the resistance exercise group. Fairey and colleagues conducted an aerobic exercise intervention in breast cancer survivors for 15 weeks, and had findings of a similar magnitude to my study, demonstrating a non-significant reduction of 1.39 mg/L in the exercise group [177]. The exercise group in their study had levels of 5.19 mg/L at baseline, and levels of 3.79 mg/L at the culmination of the study (p = 0.06) [177]. Although these findings only approached significance, they were interpreted to be clinically significant due to the associated reduction in risk of all-cause mortality. The interpretation of what is considered a ‘clinically meaningful’ change is related to the level of cardiovascular risk associated with a given level of CRP. A value of <1 mg/L is considered low risk for cardiovascular
disease, values between 1–3 mg/L moderate risk, and above 3 mg/L high risk [290].

As with the other immunological and inflammatory markers, research studying the response of CRP to resistance exercise in cancer survivors is limited. An 8 week aerobic exercise intervention study in breast cancer survivors found no change in CRP levels [291]. This study did not state actual values so there is a possibility that the baseline levels were too low to respond significantly to an exercise intervention, or that the intervention was not of sufficient duration. Two additional studies were conducted in prostate cancer patients. Galvao et al. elicited no change in resting CRP with resistance training in prostate cancer patients; however, their baseline values were extremely small to begin with (0.91 pg/ml) [181]. These authors conducted a subsequent study utilising combined modality exercise training in prostate cancer patients [182]. The exercise group CRP level at baseline was 2.7 mg/L, and decreased to 1.8mg/L after the intervention. The between group difference was statistically significant as the non-exercising group increased their CRP concentrations [182]. These three studies demonstrate the need for additional trials with larger sample sizes conducted with longer duration interventions.

Previous research measuring the response of CRP to resistance training in other populations has had more promising results. Multiple resistance training studies in various overweight and obese populations have
demonstrated significant reductions in CRP [210, 212, 213, 292]. The average range of CRP levels in these studies varied from 3.2 to 7.8 mg/L [210-213, 292], making the initial values larger than the values in many of the cancer studies.

Another potential reason for the lack of statistically significant findings in my study is that CRP levels have been shown to be responsive to exercise only if baseline levels are classified as high, or over 3mg/L [292, 293]. At baseline in this study, 12 participants had levels of CRP over 3mg/L. In the exercise group there were six participants with CRP levels over 3mg/L and at the end of the intervention there were only 3 people with levels over 3mg/L. Of these three people who did not experience a reduction in CRP, one was the sole participant who dropped out of the intervention. As intention to treat analysis was used this individual’s score was carried forward from baseline, and as such, their results were interpreted to have no change. Another of the participants who did not experience a change had an elective surgery in the middle of the intervention period. Surgery of varying kinds is known to cause a systemic inflammatory response including elevated levels of CRP [294, 295] which may not return to normal levels for up to three weeks [294], hence potentially confounding the analysis and reducing the observed effect of the treatment.
5.2.3 Mononuclear cell markers of cytotoxicity

This is the first study to measure markers of mononuclear cell cytotoxicity in this cohort in response to an exercise intervention. These markers were hypothesised to be an important indicator of immune function in this population. Mononuclear cells express a variety of markers, some of which are indicative of cytotoxicity. The perforin and granzyme induced apoptotic pathways are the main pathways used by cytotoxic cells to eliminate tumour cells [66]. Granzyme B and perforin may play a role in suppressing metastasis to lymph nodes in breast cancer patients [296]. Levels of both granzyme B and perforin have been shown to be higher in the tumours of node negative patients when compared to node positive patients [296] and hence may be a helpful predictor of prognosis in these patients [296]. Perforin is a marker for functionally activated cytotoxic lymphocytes such as natural killer cells and natural killer T-cells [297]. In the current study, I found no change in either granzyme B or perforin expression on NK or NKT cells. This was surprising given that previous research has shown that individuals who engage in higher levels of exercise have an increased expression of granzyme B [298] and perforin [298, 299]; however, as far as I am aware no study has yet examined the effect of resistance exercise on these markers of immune function in any population.

This study found that at baseline only 49% of participants NK cells expressed granzyme B and 40% of the participants NK cells expressed perforin. In comparison the values demonstrated here are markedly different from a
previous study that examined percentage expression of these markers in pancreatic, gastric, and colorectal cancer, in addition to healthy control participants [300]. These authors demonstrated that the expression of NK perforin was significantly decreased in all three cancer types compared to the healthy controls. The percentage of NK cells expressing perforin and granzyme B in each subgroup was found to be much higher than the values found in the current research presented here and ranged from 76-98% [300]. The levels demonstrated in Peng and colleagues study are very similar when compared to additional research in healthy populations where approximately 75% of NK cells express Granzyme B [301, 302] and perforin [299, 303]. The baseline differences in the results when compared to the previous research can possibly be explained by treatment differences. Peng et al.’s study population were current sufferers of cancer who had not been through surgery, chemotherapy or radiotherapy yet. In comparison, the cohort of women presented here had completed treatment an average of 11.5 months prior to enrolment in this study. As stated previously, it is well documented that surgery, chemotherapy and radiotherapy all have negative effects on immune functioning [13, 20, 22, 23]; however, an important point to note from Peng’s study is the reiteration that those diagnosed with cancer have dysfunctional NK cells, even prior to treatment [300].

The lack of additional robust randomised controlled trials makes a definitive conclusion impossible; however, these findings suggest that resistance training does not change expression of granzyme B or perforin on NK or NKT cells. The findings do however reaffirm the notion that cancer treatments
have negative effects on immune system functioning as demonstrated by the markedly lower expression of perforin and granzyme B when compared to previous healthy control data.

5.2.4 Heterogeneity in the markers used to define immune function

There are some differences with my results in comparison to previous research, likely due to multiple methodological differences. In this study, I utilised a multifaceted approach to examine immune function. I analysed the percentage of cells expressing Granzyme B and Perforin, markers indicative of cytotoxic activity, on both NK and NKT cells. I also measured the level of expression of cytokines TNF-α and IFN-γ on both NK and NKT cells. Lastly I measured the serum level of multiple markers of inflammation (TNF-α, IL-6, IL-10 and CRP).

The method of choice utilised in this study, fluorescence-activated cell sorting (FACS), was applied for detection of immune cells and their associated functionality by surface and intracellular marker staining. This method enabled efficient processing of blood samples while retaining cells during transport in a microenvironment similar to that found in vivo. Furthermore, commonly used PBMC purification techniques can lead to increased apoptosis of cells [264]. Only five studies have previously examined the effect of exercise on markers of immune function and inflammation in breast
cancer survivors [28, 29, 176-178]. Of these studies, three studies examined the effect on immune function as measured by NKCA [28, 29, 176]. In all three studies NKCA was assessed via percent lysis at differing effector to target ratios using a chromium release assay [28, 29, 176]. NKCA improved in two of the three studies [28, 29]. Both of these studies utilised aerobic exercise as the modality and were reasonably long term in duration (15 weeks and 7 months respectively). The study by Nieman et al. that did not elicit an improvement was short in duration (8 weeks) and had few subjects (n = 16) [176]. The two remaining studies [177, 178] examined the effect of exercise on a variety of serum cytokines and markers of inflammation. Only one of the aforementioned studies examined the change in cytokine production by mononuclear cells [28]. Although these authors found a significant change in NKCA via percent lysis they found no significant differences between groups for change in mononuclear cell production (data not presented) of IL-4, IL-10, TGF-β1, IL-1α, TNF-α and IL-6 [28] in response to an aerobic exercise intervention.

The paucity of previous cancer and exercise immunology research combined with the heterogeneous methodologies make comparisons of the findings of this study with similar research difficult, further highlighting the need for additional robust trials examining these markers of inflammation, and the exercise induced mechanism of change in this cohort.
5.3 Changes in body composition

This intervention did not elicit significant changes in any body composition marker as measured by the ISAK restricted profile assessment. While there has been a small amount of research demonstrating positive shifts (increases in lean body mass, decreases in body fat, or combinations of the two) in body composition in breast cancer survivors in response to resistance training [40, 45, 238], these studies had multiple differences in methodology.

The positive shifts in body composition have all previously been assessed via Dual energy x-ray absorptiometry (DEXA). DEXA has been demonstrated to be the most sensitive measurement technique for detecting small changes in post-menopausal women [304]. The significant changes observed in these studies were reductions of body fat ranging in magnitude from 1.1–1.3% [40, 238], equating to approximately 0.5–1kg of fat mass. In the present study, skinfold assessment was utilised. Skinfold assessment is common due to its low cost and ease of implementation; however, skinfolds, circumferences, BMI, and waist to hip ratios have been deemed too insensitive to detect changes in soft tissues as a result of resistance training [305] or to detect changes associated with weight loss [306, 307]. The precision of skinfold thickness measurements has been reported to be 5–8% [305] and circumferences 7–8% [305]. The combination of the precision of measurement and the magnitude of the previously observed changes mean that it is possible that there were changes that were too small to be detected via skinfold assessment in this study. While I cannot determine the precision
of measurements in the current study, the tester reported their technical errors of measurement, which is indicative of the accuracy or precision of the tester (appendix 6). These measurements ranged between an average 2.7% TEM for the skinfolds and 0.65% for the girths. It has been previously stated that the technical error of measurement should be about 5% for skinfolds and approximately 1% for girths [308], placing the tester utilised in this study well within acceptable accuracy limits.

Three previous studies have observed gains in muscle mass in breast cancer survivors after a resistance training intervention. These gains ranged from 0.1–1.0kg [40, 45, 238], so while significant, they were still modest in magnitude. Two of these three studies that observed positive gains were relatively long studies each lasting six months in duration [40, 238]. One study was similar in length to the intervention utilised in this study [45], these authors observed an average 1kg gain (95% CI 0.5-1.5) in lean muscle mass following the intervention which was conducted during chemotherapy. Due to the large variability in muscle mass gains, it is possible that the data presented here from the resistance training group sample of 20 may have been too small to detect these changes. While this study did not have a direct measure of muscle mass, a gain of mass in the magnitude of that observed in the previous studies may have been too small to detect based on the above assumptions. In addition, an extended training period may have led to a significant detectable alteration in mass.
5.4 Changes in strength

The resistance training intervention in this study elicited significant strength gains. The average improvement in the upper body on the side of cancer treatment was 19%, and the average improvement on the non-treated side was 22%. Lower body strength improved an average of 34%. These results are comparable to previous randomised controlled trial resistance training interventions in this cohort that have elicited strength gains averaging 23% in the upper body and 28% in the lower body [43, 45, 221, 227, 228, 231]. Of note, one of these interventions was 24 months [43], three were 12 months in duration [221, 227, 231], and one was six months [228]. One intervention lasted the duration of chemotherapy [45], and was approximately similar in length to the intervention undertaken in this study.

While the strength gains observed in this study were of similar magnitude to those reported in previous randomised controlled trials, they were achieved in a significantly lesser time period of 16 weeks compared to an average of just under 12 months. As expected the control group did not significantly differ over time, although there was a tendency for the control group to show a slight reduction in all three strength measurements over the course of the intervention period that would be a concerning trend if continued over a longer time frame.
Comparison of overall levels of strength between these data and previous studies is also difficult due to the differing types of resistance training and testing that has been employed. Strength testing has varied between 1RM and 8RM measurements, using free weights and machine weights, and the use of isokinetic dynamometry. Four of the seven studies examining resistance training as a sole modality in rehabilitation programs for breast cancer survivors used 1RM measurements to assess strength [221, 228, 231, 309]. One study utilised a Biodex™ isokinetic dynamometer [43], and one study each used a 6RM and an 8RM testing method respectively [45].

The lower body strength test predominantly employed in breast cancer survivors has been the leg press, as was utilised in this study. Although the leg press was frequently used, direct comparison is still difficult due to the large variability in machines available, and the subsequent inability to compare absolute loads between different machines.

The upper body strength tests in this cohort have often favoured bench press or chest press. No study has utilised a uni-lateral upper body strength measurement protocol to measure adaptation to resistance training in this population. In comparison this study employed a unilateral isometric protocol to accurately measure inter-limb differences. Strength has frequently been reported to be reduced on the treated side compared to the unaffected limb [136, 137, 310, 311]. The magnitude in reduction is again difficult to compare due to the heterogeneous use of measurements. In this study, the treated limb was on average 5% weaker at baseline than the un-treated limb, this increased to 7% after the intervention. The expanding inter-limb strength
discrepancy provides solid rationale for the examination of the efficacy of unilateral resistance training programs in this population. Further, exploration of the neuromuscular adaption in response to resistance training has not been explored in this population.

While previous recent research has indicated that resistance training does not induce nor exacerbate lymphedema [41, 221-224], breast cancer survivors are still often apprehensive about commencing upper body exercise programs. This research supports the notion that resistance training is safe and efficacious, with no new diagnoses of lymphedema throughout the trial, and no exacerbations of current lymphedema. In this cohort, five out of 39 (13%) survivors suffered from lymphedema which is similar with other incidence statistics [312]. Throughout the duration of the study a small number of ladies visited medical professionals due to changes in their perception of arm swelling; however, on every occasion the lymphedema specialist was satisfied that these alterations in perception were due to muscle growth rather than the onset of lymphedema.

Training interventions have also varied greatly in the previous research. In a number of studies insufficient detail was provided with respect to training intensity and volume. The intervention most similar to the current study was that of Courneya et al. [45], who elicited similar strength gains in a similar time frame to this study.
The range of strength gains in the upper and lower bodies differed greatly in my study. Excluding participants who did not complete the program, and would be interpreted as experiencing no change due to ITT methods, the exercise group percentage change in the lower body ranged from 7.7% to 87.5% improvement. On the surgical arm strength improvements ranged from -8% to 49.4%. The other non-treatment arm percentage change ranged from 0.9% to 72.8%. The large range of strength adaptations was surprising, given some degree of improvement would be anticipated in each participant; however, as expected the smallest improvements came from those with the lowest attendance levels. Further, the only participant to display a negative adaptation, an 8% decrease in strength, had the lowest attendance rate of all participants in the trial.

The large range of adaptations cannot be explained by varying degrees of fear avoidant beliefs. While these results were not statistically significant, the participants at both ends of the adaptation spectrum were also those expressing the greatest gains and reductions on the fear avoidance beliefs questionnaire. At baseline, half of the cohort (19 women), recorded a zero score indicating no fear avoidance beliefs in relation to the use of their treated arm during physical activity, with the overall average a score of 3.5 points out of a possible 24. This is somewhat surprising as previous research has documented that 70% of women actively avoid using their treated arm due to fear of lymphedema [313]. This questionnaire was initially developed for use in chronic low back pain populations [269]. Chronic low back pain patients have considerably higher scores than this cohort, with previous
research demonstrating an average range of 12-19. In response to the resistance training intervention, I did not see a significant difference in change scores between groups. Positive results in response to exercise have been observed previously with reductions in fear avoidance beliefs (as measured by the FAB-Q) demonstrated following an exercise program for chronic low back pain [314]. Although these results were not statistically significant, the effect size was moderate, suggesting a potential benefit for exercise to reduce fear avoidant beliefs. These findings suggest that this particular scale may not be an appropriate measurement tool for this population, or that this cohort did not have an issue with fear avoidance behaviours with regards to use of their treated limb.

The physiological basis of strength adaptation is two-pronged with improvements in muscle cross sectional area [315, 316] and neural adaptations [316, 317] combining to improve muscular strength. Neural adaptations are often thought to occur before muscular hypertrophy [316, 317] and are evidenced by an increase in neural drive measured by an increase in EMG amplitude and motor unit firing rate and pattern [316, 317]. This study did not accurately quantify muscle cross sectional area or neural adaption; however, future research should examine whether the physiological basis of strength adaptation is the same in cancer survivors who have undergone a myriad of treatments, compared to regular patterns of strength adaptation. This information would be extremely useful for inter-limb comparisons and the design of specific training programs.
5.5 Changes in quality of life

This study utilised multiple different measurement tools to assess QOL in breast cancer survivors. The findings of this study indicated that resistance training significantly improved QOL as measured by the FACT-G when compared to the usual care control group. These findings are of paramount importance as it has been suggested that relatively small changes in self-reported health subscales may have significant clinical implications [166].

5.5.1 Functional Assessment of Cancer Therapy - General

The functional assessment of cancer therapy general (FACT-G) was used to assess QOL in this study. The results of this study showed a significant improvement over time in the exercise group (p < 0.001) and in change over time between control and experimental groups at follow up (p = 0.018). The average magnitude of change in the exercise group was 6.9 points on the overall scale. An overall change of 4–7 raw scale points on the FACT-G has been suggested to be clinically meaningful [166, 318].

At baseline this cohort scored an average of 89 points. Previous research across a variety of cancer types has documented the average score to be 81.92 ± 15.87 [166]. In comparison, normative data for healthy females gives an average of 79.6 ± 18.6 on the FACT-G [319]. This is interesting given
that the general population report lower overall QOL than cancer sufferers and survivors. Given this samples baseline score was above normative levels, it is interesting that the intervention still elicited a statistically significant and clinically meaningful change. At the culmination of the intervention, the exercise group score was an average of 96 points, much higher than the general population.

In addition to the total FACT-G score, there are four separate subscales of the FACT-G examining physical (PWB), social (SWB), functional (FWB) and emotional wellbeing (EWB). At baseline the cohort in this study had an average score for the PWB and EWB subscales that were very similar to healthy population data, whereas the SWB and FWB subscales were markedly higher than the healthy population and female cancer patient normative data [319]. Following the intervention only the change scores for the PWB and EWB subscales in this study were statistically significantly different between groups. The PWB domain changes were significant over time in the exercise group and between groups with changes averaging 2.5 points on the subscale in the exercise group. The EWB domain changed an average of 2.1 points in the exercise group. Changes of 2-3 raw scale points in the PWB subscale [166] have been suggested to be clinically meaningful. EWB and SWB clinically meaningful changes have not been researched [166]. Both the SWB and FWB subscales did not significantly differ over time or between groups. The FWB subscale of the exercise group changed an average of 1.45 points, just shy of what could be considered clinically meaningful (2-3 points) [166]. As the SWB subscale was a full 4 points
higher, and the FWB subscale 4.6 points higher than healthy population normative data at baseline, it is not surprising that I did not observe a change.

Similar to the findings presented here, the majority of research utilising FACT-G as a measure of QOL in exercise intervention studies in breast cancer survivors have also had positive findings [174, 320-322]. The successful interventions were either undertaken during chemotherapy [321] or once treatment was completed [174, 322]. The interventions were of mixed modalities, although none were solely resistance training based. Average baseline scores ranged from 72 to 88, and the magnitude of the average change score varied between groups and ranged from 5.7 to 11.9 [174, 321, 322]. As expected, the study with the lowest baseline value exhibited the greatest overall improvement in QOL [321].

Although research on QOL in breast cancer survivors is relatively common, the use of a variety of measurement tools makes comparisons difficult. A recent review (2006) and meta-analysis of exercise trials for breast cancer patients and survivors examined exercise RCT’s in this population and included 14 studies in their analysis [173]. Of these 14 studies only seven measured changes in QOL. Three of these utilised FACT-G [174, 321, 323] and a pooled estimate of change was 4.58 points (95% CI 0.35 to 8.8) favouring the exercise groups [173]. Regardless of the measurement tool utilised, these authors estimated an effect size of 0.84 for exercise induced
improvements in QOL, which is similar to the effect size estimated in this study of 0.79, indicating that resistance training is as beneficial as aerobic exercise for inducing positive changes in perceived QOL.

5.5.2 Short Form-36

The SF-36 was analysed according to its two subscales, the PCS and the MCS. The combined group average in this study at baseline for the PCS subscale was 40.6 ± 7.5 and for the MCS subscale was 48.5 ± 8.8. These values are slightly lower than the population norms which for both subscales are approximately 50 [163, 164]. The majority of previous research indicates that women with breast cancer tend to score relatively close to these norms. Trenthan-Dietz and colleagues examined the differences between women with breast cancer and age matched healthy controls [162]. They found that women with breast cancer scored slightly lower on the PCS subscale (average of 40.4 compared to 44.9); however there were no differences between the two groups on the MCS subscale (average of 54.2 compared to 54.8) [162]. These findings are similar to another study who also examined QOL in breast cancer survivors who were on average 3.5 years post diagnosis and found that the PCS subscale average was 50.8 and the MCS subscale average 49.6 [165]. Speck and colleagues also found similar results at baseline reporting an average of 52.1 ± 9.4 for the MCS subscale and an average of 48.4 ± 8.9 for the PCS component [224]. Interestingly, in comparison the Australian population normative data subgroup of...
aged between 45-54 (most similar demographic to the cohort in this study) (n = 1566), scored an average of 49.7 points on the PCS subscale and an average of 50.3 points on the MCS subscale [324]. This demonstrates that breast cancer survivors are reporting values very similar to women their own age in the general population.

5.5.2.1.1 Short Form-36 change in response to exercise

My results demonstrated that the SF-36 did not change in this cohort in response to resistance training. These findings are similar to multiple studies using a variety of exercise interventions that have failed to elicit an improvement in the SF-36 when compared to control groups [224, 323, 325]. These interventions varied in modality and duration. For example Speck et al. elicited non-significant change scores of 1.2 in the MCS domain and 2.7 in the PCS domain in response to resistance training [224]. The exercise group in this study improved an average of 2.8 ± 8.0 on the PCS and 5.8 ± 12.2 points on the MCS subscales. The exercise group improved significantly over time in the MCS component, but this did not reach significance when compared to the control group.

In other clinical populations undertaking exercise interventions, the use of the SF-36 has had predominantly positive results. Resistance training in heart failure patients has elicited a positive improvement in SF-36 scores [326], as did exercise for arterial claudication [327]. Haemodialysis patients also
demonstrated significant improvements in the SF-36 in response to exercise [328, 329]. Exercise training in type II diabetics has had inconsistent results [330, 331]. Combined, these findings question the appropriateness of the use of the SF-36 to detect changes in exercise induced QOL in breast cancer survivors.

5.5.2.2 Functional Assessment of Cancer Therapy – General versus Short Form-36

I chose to include both a generic and a cancer specific QOL life instrument in this trial due to recommendations outlined in a report by the National Cancer Institute (USA) on QOL assessment in cancer trials [332]. My results demonstrate a statistically significant improvement in QOL as measured by the FACT-G, compared to no change as measured by the SF-36. A possible reason for this discrepancy could be that the FACT-G measurement tools specificity for cancer patients and survivors allowed it to distinguish a difference in QOL where the SF-36 tool failed to find a significant difference. While the SF-36 tool is one of the most commonly used QOL measurement tools in research, it was initially designed for use in the medical outcomes study (MOS), a large scale trial assessing outcomes in patients with hypertension, depression, coronary heart disease, and diabetes [333]. Hence this questionnaire was not tailored to the specific detriments in health that may be unique to cancer survivors. The FACT-G was developed for use in oncology clinical trials and to be responsive to clinical change [268].
A review comparing SF-36 results across a variety of studies examining chronic illness’s including incontinence, prostate cancer; COPD, AIDS, fibromyalgia, and hyperlipidaemia in comparison to normative data demonstrated a reduced QOL across many subscales over most illnesses. The exceptions were prostate cancer and hyperlipidaemia patients who reported values very close to normative, or even above normative levels [334] which is in keeping with the data presented here, which showed that breast cancer survivors reported many values similar to that of the healthy population. Another explanation for the lack of findings in this area could potentially be attributed to the previously suggested notion that cancer patients have a tendency to minimize negative personal evaluations and hence often do not provide accurate self-report data [166].

The relationship between improved strength and improved QOL has also been demonstrated in this study where significant improvements in strength on the treated side were correlated with improvements in QOL as measured by FACT-G. This finding is in keeping with previous research demonstrating that arm morbidity causes a negative impact on QOL [335]. It has also been previously reported that activities of daily living are limited in lifting, carrying and reaching in breast cancer survivors [336], and these impairments in activities of daily living may in fact impact on QOL. Supporting this notion is research showing that greater shoulder muscle strength is significantly associated with increased functional wellbeing in breast cancer survivors [337] and increases in strength have been correlated with improvements in QOL [338]. This research further demonstrated this relationship showing
significant correlations between improved strength of the treated limb and improved QOL in exercise participants.

5.5.3 Functional Assessment of Chronic Illness Therapy - Fatigue

The findings of this study indicate that resistance training can significantly reduce the perception of fatigue in breast cancer survivors. The exercise group significantly reduced perceived fatigue over time increasing their score by 6.65 points (p < 0.001) (out of a possible 52, where a higher score indicates lesser fatigue). This differed from the control group by 5.12 points (p < 0.05). Minimal clinically meaningful differences in this scale have been suggested to be a change of 3 points or more [318]. The post intervention values (45.7 ± 7.57) for the exercise group improved to become similar to that reported by the general population.

The baseline levels of perceived fatigue reported in this study were similar to previous research in cancer survivors, and as expected, this cohort was more fatigued than the general healthy population [150, 318]. Although fatigue is frequently observed in cancer survivors, it has not commonly been included as an outcome variable in many exercise studies in this group. Six out of 14 studies in a recent meta-analysis examined fatigue [173], four of which utilised a different subscale from this intervention, the revised piper fatigue scale. These authors provided a pooled estimated effect size across the six
studies of 0.72, similar to the effect size of 0.86 found in this research. Of these six studies, four utilised aerobic interventions, and two utilised mixed modality interventions. None of the studies utilised an isolated resistance training intervention. The varied use of measurement tools and exercise interventions make direct comparisons difficult; however, this research indicates that resistance training is as beneficial as mixed modality and aerobic exercise in eliciting a reduction in perceptions of fatigue.
6 CONCLUSION

Overall this thesis demonstrated that resistance training has the potential to modulate markers of inflammation in breast cancer survivors. The clinically meaningful reduction in CRP, coupled with the significant reduction in NK expression of TNF-α in the exercise group suggest that resistance exercise is associated with an improvement in the inflammatory profile of breast cancer survivors. As markers of inflammation are only one aspect of immune function, I cannot deduce whether the cohort’s immune function increased as I did not have a specific immunological challenge, rather I simply demonstrated a reduction in important markers of inflammation. The clinical significance and exact mechanism of the modified inflammatory profile remain to be elucidated.

This study also demonstrated that resistance exercise can significantly improve strength, enhance QOL, and reduce fatigue as compared to the control, or usual care group. Further, the lack of adverse events provides further support to the notion that resistance training is safe and efficacious for women who have completed breast cancer treatment.

This study also demonstrated significant relationships between various markers of health and wellbeing. The correlations between improved strength and improved QOL, and improved immune function and increased
leg strength, demonstrate the systemic and wide reaching effect of resistance exercise.

### 6.1.1 Limitations of the study

Limitations surrounding the primary outcome include the lack of an accurate quantification of muscle mass or protein synthesis. The decision not to take muscle biopsies was a compassionate one, as well as a financial one. In addition, if funding had permitted, the inclusion of a DEXA scan would have been very beneficial for detecting small changes in body composition (both muscle mass and fat mass). In addition, the use of a relatively new and sparsely used method made comparisons difficult. While the lack of comparisons in this study is a limitation, I chose this particular method as I felt that it would allow me to approach the research question from a different perspective than if I chose to measure NKCA via percent lysis alone. Again, all measurements in combination would be beneficial, but due to funding constraints it was not possible in this study.

Additional limitations of the study included the location, and subsequent recruitment of a narrow socio-economic group; Inclusion criteria, the criteria were broad regarding time since treatment which may have influenced individual variability in all markers; instrument accuracy, the leg press machine had a minimum incremental load increase of 2.8kg which may have been too large to get a very precise measurement of changes in strength;
Self-report medical history, this form of reporting leaves room for incomplete and inaccurate data;

6.1.2 Recommendations for future research

Future research should aim to further elucidate a potential mechanism for the improved immunological and inflammatory profile achieved following exercise. A concurrent accurate measure of muscle mass and protein synthesis, in a well powered RCT examining both immune and inflammatory markers would be extremely beneficial and could provide further insight into the potential link with skeletal muscle. The long term ramification of this alteration in TNF-α expression on mononuclear cells also remains to be elucidated. A long term follow up study, and a longer term training intervention study would provide additional beneficial information.

Lastly, future research should examine the inter-limb differences between the treated and un-treated arm. Examining neuromuscular adaptation patterns would be beneficial to clarify the effect that surgery, chemotherapy and radiotherapy have on the muscles surrounding the shoulder.
REFERENCES


82. Heikkila K, Ebrahim S, Lawlor DA: **Systematic review of the association between circulating interleukin-6 (IL-6) and cancer.** *Eur J Cancer* 2008, 44(7):937-945.


87. Thorand B, Lowel H, Schneider A, Kolb H, Meisinger C, Frohlich M, Koenig W: **C-reactive protein as a predictor for incident diabetes mellitus among middle-aged...**


8 APPENDICIES

8.1 Appendix 1 – Physical Activity Readiness Questionnaire

**PAR-Q & YOU**

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly. Check YES or NO.

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**YES to one or more questions**

Talk with your doctor by phone or in person BEFORE you start becoming more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

**NO to all questions**

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:
- start becoming much more physically active — begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal — this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/84, talk with your doctor before you start becoming much more physically active.

**DELAY BECOMING MUCH MORE ACTIVE**

- If you are not feeling well because of a temporary illness such as a cold or a fever — wait until you feel better.
- If you are or may be pregnant — talk to your doctor before you start becoming more active.

**PLEASE NOTE:** If your health changes so that you then answer YES to any of the above questions, tell your doctor or health professional. Ask what you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity and if doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person below 18 or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME ____________________________

SIGNATURE OF PARENT OR GUARDIAN (for participants under the age of majority)

DATE __________

WITNESS ____________________________

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.
Physical Activity Readiness Questions (PAR-Q)

Get Active Your Way, Every Day – For Life!

Choose a variety of activities from these three groups:

- Walking
- Cycling
- Swimming

Physical activity improves health.

Every little 15 minutes, but more is even better—everyone can do it!

1. Get active your way—
2. Add physical activity to your daily life:
   - at home
   - at school
   - at work
   - at play
   - on the way to or from active living.

Starting slowly is very safe for most people. That’s why you should consult your health professional.

For tips on choosing activities and getting started, call 1-888-384-9189, or www.parqguide.com

Eating well is also important. Follow Canada’s Food Guide to Healthy Eating to make wise food choices.

Fitness and Health Professionals may be interested in the information below:

The Physical Activity Readiness Medical Examination (PARmed-X) — to be used by doctors with people who answer YES to one or more questions on the PAR-Q.

The Physical Activity Readiness Medical Examination for Pregnancy (PARmed-X for Pregnancy) — to be used by doctors with pregnant patients who wish to become more active.

References:


For more information, please contact the:

Canadian Society for Exercise Physiology
200-185 Somerset Street West
Ottawa, ON K1P 0C2
Tel. 1-877-651-9755 • Fax (613) 234-3583
Online: www.cssep.ca

PAR-Q © Canadian Society for Exercise Physiology

Supported by:

Health Canada
Santé Canada

The original PAR-Q was developed by the British Columbia Ministry of Health. It has been revised by an Expert Advisory Committee of the Canadian Society for Exercise Physiology chaired by Dr. N. Godin (2002).

Disponible en français sous le titre «Questionnaire sur l’aptitude à l’activité physique – Q-AAP (revisé 2002).
8.2 Appendix 2 – Background Health Questionnaire

Background Health Questionnaire

What was your date of diagnosis? _______________________________________

What side was your surgery

- Right □
- Left □

When did you have this surgery(s)? _______________________________________

Did you have lymph nodes removed?

- Yes □
- No □

How many? ____________________________________________________________

Have you had adjuvant chemotherapy

- Yes □
- No □

How long did these treatments last? _______________________________________  

When did they commence and finish? ______________________________________

Have you had adjuvant radiotherapy

- Yes □
- No □

How long did these treatments last? _______________________________________  

When did they commence and finish? ______________________________________

Name: __________________________
DOB: ______________________ Age: ______
Date: __________________________

☐ baseline    ☐ 16 weeks
Are you on adjuvant hormone therapy?  Yes ☐  No ☐

When did this commence?  ________________________________________________

When is it expected to finish?  ________________________________________________

Do you currently have diagnosed lymphedema?  Yes ☐  No ☐

Have you ever had a heart attack?  Yes ☐  No ☐

Are you a diabetic?  Yes ☐  No ☐

Have you ever been diagnosed with hypertension?  Yes ☐  No ☐

Have you ever had any other major surgeries?  Yes ☐  No ☐

Have you had any significant musculoskeletal injuries?  Yes ☐  No ☐

Medications:

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8.3 Appendix 3 – Participant Consent Form

Participant Consent Form

This is a project specific consent form. It restricts the use of the data collected to the named project by the named investigators.

Note: If not all of the text in the row is visible please 'click your cursor' anywhere on the page to expand the row. To view guidance on what is required in each section 'hover your cursor' over the bold text.

Project Title: Effect of resistance training on natural killer cell activity in women recovering from breast cancer treatment: A randomised controlled trial

I, ..........................................., consent to participate in the research project titled: Effect of resistance training on natural killer cell activity in women recovering from breast cancer treatment: A randomised controlled trial.

I acknowledge that:

I have read the participant information sheet [or where appropriate, ‘have had read to me’] and have been given the opportunity to discuss the information and my involvement in the project with the researcher/s.

The procedures required for the project and the time involved have been explained to me, and any questions I have about the project have been answered to my satisfaction.

I consent to participating in a 16 week resistance exercise program if I am randomised to that group. I consent to giving a blood sample, having my body composition measured (via skin folds and girths), and having my strength assessed at two different time points (week 0 and week 17). If I am randomised to the control group, I consent to participating in the 16 week resistance exercise program and undergoing one additional blood, strength and body composition assessment at week 35.

I understand that my involvement is confidential and that the information gained during the study may be published but no information about me will be used in any way that reveals my identity. I understand that I may be asked to provide media (radio, internet and newspaper) with information regarding my experience however I am not obliged to do so.

I understand that I can withdraw from the study at any time, without affecting my relationship with the researcher/s now or in the future.

Signed: 

Name: 

Date: 

Return Address: 

Mandy McKee
Sport & Exercise Science
School of Science and Health
University of Western Sydney
Locked Bag 1797, Penrith South DC, NSW 2751

This study has been approved by the University of Western Sydney Human Research Ethics Committee.
The Approval number is: H9427

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through the Office of Research Services on Tel +61 2 4736 0229 Fax +61 2 4736 0013 or email humanethics@uwns.edu.au. Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.
8.4 Appendix 4 – Participant Information Sheet

Participant Information Sheet (General)

An information sheet, which is tailored in format and language appropriate for the category of participant – adult, child, young adult, should be developed.

Note: if not all of the text in the row is visible please ‘click your cursor’ anywhere on the page to expand the row. To view guidance on what is required in each section ‘hover your cursor’ over the bold text. Further instructions are on the last page of this form.

Project Title: Effect of resistance training on natural killer cell activity in women recovering from breast cancer treatment: A randomised controlled trial

Who is carrying out the study?

PhD candidate Mandy McKee (MSc, BSc); M.Mc Kee@uws.edu.au
Dr Bobby Cheema (PhD, AEP, MSc, BHK, ESSAM); B.Cheema@uws.edu.au

You are invited to participate in a study conducted by Mandy McKee, PhD candidate, School of Biomedical and Health Sciences, University of Western Sydney, Campbelltown Campus. Mandy McKee can be contacted on M.McKee@uws.edu.au, phone 0414890342

What is the study about?

The purpose of this study is to implement a randomised controlled trial to evaluate the effect of a 16-week resistance training intervention on NKCA and associated clinical outcomes in women recovering from breast cancer treatment. It is hypothesised that women treated for breast cancer randomised to a 16-week resistance training intervention will significantly improve NKCA as compared to women randomised to the usual care condition. It is also hypothesised that women treated for breast cancer randomised to a 16-week resistance training intervention will significantly improve additional health-related outcome measures, including additional markers of immune system functioning, inflammatory markers, blood lipid profile, body composition, physical fitness and quality of life, as compared to women randomised to a usual care control condition.

What does the study involve?

A testing session to collect blood samples, evaluate muscular strength and complete questionnaires will be required prior to (at baseline) and following a 16-week resistance training program. Each testing session will be approximately 1 hour. After baseline testing you will be randomly assigned (like the toss of a coin) to a resistance exercise group or a non-experimental (control) group. Participants assigned to the resistance exercise group will exercise three times per week (Monday, Wednesday and Friday) in either morning, or afternoon/evening classes lasting 1 hour in duration. The sessions will be located in the gym laboratory, Building 20, UWS Campbelltown Campus.

How much time will the study take?

The study will take approximately 18 weeks to complete.

Will the study benefit me?

If you are randomly assigned to the resistance training group and adhere to the protocols, it is expected that your health status will improve. Specifically your immune functioning, physical fitness, muscular...
strength and quality of life may improve

**Will the study involve any discomfort for me?**
A mild discomfort may be experienced by some individuals during the collection of blood samples. A mild degree of muscle soreness could be expected following resistance training or muscular strength testing, but this soreness should dissipate within 48 hours of the session.

**How is this study being paid for?**
The study is being sponsored by the University of Western Sydney.

**Will anyone else know the results? How will the results be disseminated?**
All aspects of the study, including results, will be confidential and only the researchers will have access to information on participants.

**Can I withdraw from the study?**
Participation is entirely voluntary. You are not obliged to be involved and - if you do participate - you can withdraw at any time without giving any reason and without any consequences.

**Can I tell other people about the study?**
Yes, you can tell other people about the study by providing them with the chief investigator's contact details. They can contact the chief investigator to discuss their participation in the research project and obtain an information sheet.

**What if I require further information?**
When you have read this information, Mandy McKee or Dr Bobby Cheema will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact Mandy McKee via email or telephone; M.McKee@uws.edu.au, mobile 0414890342

**What if I have a complaint?**
This study has been approved by the University of Western Sydney Human Research Ethics Committee. The Approval number is [enter approval number]

If you have any complaints or reservations about the ethical conduct of this research, you may contact the Ethics Committee through the Office of Research Services on Tel +61 2 4736 0229 Fax +61 2 4736 0013 or email humanethics@uws.edu.au

Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.

If you agree to participate in this study, you may be asked to sign the Participant Consent Form.
8.5 Appendix 5 – Participant Training Program

Participants training program

Resistance Exercise, Breast Cancer and Immune Function Trial
2012/2013
SKILL DEVELOPMENT:
EXERCISE:

Squat progressions:

Points to think about:

- The first step in teaching a barbell squat begins without weight. The best way to learn ‘depth’ in the squat is with a swissball. Place your feet in front of you and the swissball in the small of your back. This can also be a good alternative for a barbell squat if your knees are uncomfortable when squatting.
EXERCISE:

Squat progressions:

Points to think about:

- The next step is to learn to keep the torso upright. This is done with a medicine ball (usually 3-4kg). The ball is rested gently against the forehead, and helps active all the upper back muscles, teaching you good technique through your torso.
- Finally, you are ready to body weight squat. Here, the arms are placed out in front for balance.
- You are now ready to barbell squat
**Part one:**

**EXERCISE:**

**Machine bench press**

Points to think about:

- Pushing through the ground with your feet
- Keep shoulders down (do not hunch upwards)
- At the start of the movement you can usually alter the chair or the hand pieces to be at different distances. The closer you are to the part you push, the more difficult and the more flexible you must be. However, if you go too far out you will only be using a limited range of motion and will not get as strong throughout the entire movement. Best seat placement can be based on comfort.
- When it gets heavy, take care not to through your head forward like an emu.
**EXERCISE:**

**Machine Seated Row**

Points to think about:

- Start the movement with a straight back and straight arms.
- Pull the handles in until you touch your ribcage.
- As you pull think about 'squeezing the pea between your shoulder blades'.
- During the movement try and keep the shoulders level taking care not to shrug the shoulders up towards your ears.
- Try and keep your back as still and straight as possible as all the work should be done by your upper back, shoulders and arms.
- As you release the handles back towards your feet take care not to over reach, i.e. do not pop your shoulders forward, keep them in line with your torso.

| Start: | Finish: |
EXERCISE:

Leg extension

Points to think about:

- Grip the handles at the side of the chair.
- Straighten legs.
- Control the weight on the way back down (resist the temptation to drop fast).
**EXERCISE:**

**Leg Curl**

Points to think about:

- Grip the handles beside or near your head.
- Bend the legs as far upwards as you can.
- Slowly control the weight back down.

---

**EXERCISE:**

**Back extension**

Points to think about:

- Start the movement with a completely flat body.
- Bend forward at the hips taking care to keep the upper back nice and flat.
- Pause at the bottom before bending at the hips again, keeping the back straight.
- Weight can be added to this exercise to increase its difficulty
- Get someone to check your form occasionally to check that you are coming the whole way back to the start position. As you get tired there will be a tendency to cut the movement short.
- Also as you get tired take care to maintain a nice slow tempo, there is also a tendency to speed the movement up and use the bounce from the bottom. This will only take away from the benefit of the exercise.

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**EXERCISE:**

**Lat pull down**

Points to think about:

- Grip the bar with an underhand grip approximately shoulder width apart. (grip can be modified to over hand and wider apart, however weight will have to be decreased for this movement)
- Pull the bar down thinking about pulling the arm pits to the floor
- As with the seated row take care not to hunch your shoulders up towards your ears
- Slowly allow the bar to go back up to the start position. Controlling this movement is as important as the pulling down component.
- Try to keep the torso as steady as possible avoiding using body weight to pull the bar down. If you have to do this, the weight is too heavy.

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**EXERCISE:**

Romanian deadlift (Stiff leg deadlift)  
(introduced to substitute for leg curl at midpoint)

Points to think about:

- First movement is ‘bum out’  
  - Bend at the hips as with the back extension taking care to keep the back nice and straight.
  - Bend your knees slightly; the degree of this will vary between individuals. Too large of a bend will defeat the purpose so keep the knees as straight as you can without locking them out.
  - Bend forward until you feel a nice stretch in your hamstrings (back of your legs).
  - Stand back up, dragging the bar along your thighs as you do
  - This is a small yet highly effective movement so do not be surprised if you feel as if you are not moving very far. The degree of movement in this exercise will vary depending on the individuals' flexibility as well as strength.
  - When you are at the bottom, make sure your back is still flat. A good cue to think of is the 'open your chest', or 'squeezing the pea between your shoulder blades', this will help you to keep a nice and flat upper back at the end of the movement
EXERCISE:

Prone hold/crunches
(prone holds introduced to replace crunches at midpoint)

Points to think about:

- In the prone hold try and keep your back and legs as flat as possible. If the movement feels easier than normal your bum is probably in the air!
- If your back feels slightly uncomfortable during the movement you are probably arching your back.
- Remember that this exercise should be challenging and you should be holding for as long as you can. Set yourself time goals and steadily increase your targets.

- With the crunches think about lifting yourself up towards the ceiling
- This is a very small movement
- You may place your hands across your chest or behind your head, this is up to you. If you choose to place your hands behind your head are careful not to pull on your neck.
**Part two:**

**EXERCISE:**

Deadlift

Points to think about:

- Bend your legs as far as you can
- Grip the bar, but let the arms hang straight. Your arms should not be bent at all during the movement; it is your legs that do all the work.
- Before you lift off the ground, make sure you are ‘tight’.
- As you stand up make sure the bar drags all the way along your legs the whole way. If the lift feels heavier than normal you may be letting the bar drift in front.
- Keep your back nice and straight throughout the lift.
- At the bottom of the movement ‘open your chest’, this helps to take the curve out of the upper back
- Look straight in front of you. Looking to the floor may cause your back to round.
- If you cannot obtain a good position from the floor due to flexibility, or painful knees etc, raise the bar on to blocks (as demonstrated at the end of this document).
- When you finish the lift, stand completely upright before lowering the bar back down the same way you picked it up.

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EXERCISE:

Modified deadlift:

Points to think about:

- If you cannot get a straight back when the weights are on the floor, raise the bar on plates, boxes or some form of platform until you can obtain correct posture. The ‘wrong’ picture below demonstrates incorrect posture when the back is bent. At the top, the correct posture is demonstrated.
**EXERCISE:**

**Squat**

**Points to think about:**

- First movement is ‘bum out’
- Grip the bar nice and tight, pulling it down towards you trying to ‘bend the bar over your back’
- Bend forward and squat down as far as you can whilst keeping your chest in line with your lower shank
- At the bottom, make sure your chest is up, i.e., your back is still straight and not hunched forward
- Make sure you control the speed on the way down
- You can go as fast as you like back to standing

---

**Start:**

**Finish:**
EXERCISE:

Barbell bench press

Points to think about:

- Make sure your shoulder blades are 'locked in place' before starting the movement.
- Lower the bar down slowly to approximately nipple height.
- Ideally lower the bar down until you touch your chest, if you cannot handle this range of motion, go as far as you feel comfortable.
- When you lower the bar, you are tucking your arms in on an approximate 45 degree angle. I know this is hard to see, but we have covered it in the gym (just making sure your elbows are not out wide and placing the shoulder under unnecessary stress).
- Remember that you should push through your legs, especially when you are getting tired!

Start:

Finish:
EXERCISE:

Leg press

Points to think about:

- The first rep is the hardest!!!! 😊
- Keep everything nice and ‘tight’, remembering that you ‘push your stomach out’ rather than hollowing it in.
- Keep your knees slightly bent in the finish position taking care not to lock the knee joint.
### EXERCISE:

**Barbell bent over row**

Points to think about:

- First movement is ‘bum out’, just like in the Romanian deadlift.
- Next bend forward from the hips keeping a straight back (just as you would in the back extension).
- Let your arms hang down with no tension.
- Squeeze your shoulder blades back together to ensure that you ‘open your chest up’, this helps to keep your back straight and ensure that you are not rounding your back.
- Pull the bar up as high as you can towards your ribcage, ideally to just touching.

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**EXERCISE:**

**Assisted Chin up**

Points to think about:

- Try and lift the whole way to the top. The top is when your chin is in line with or close to your knuckles.
- Lower down as far as you can. The less bend in your arms the better.
### Technical error of measurements and intraclass correlation coefficients for the anthropometrist

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</tr>
<tr>
<td>2 Stretch stature (cm)</td>
<td>0.02</td>
<td>0.01</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>4 Triceps sf</td>
<td>0.79</td>
<td>2.82</td>
<td>0.99</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>5 Subscapular sf</td>
<td>0.45</td>
<td>1.86</td>
<td>1</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>6 Biceps sf</td>
<td>0.55</td>
<td>4.49</td>
<td>0.99</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>7 Iliac crest sf</td>
<td>0.71</td>
<td>2.85</td>
<td>0.99</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>8 Supraspinale sf</td>
<td>0.56</td>
<td>2.59</td>
<td>1</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>9 Abdominal sf</td>
<td>0.83</td>
<td>2.54</td>
<td>1</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>10 Front thigh sf</td>
<td>0.78</td>
<td>1.78</td>
<td>1</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>11 Medial calf sf</td>
<td>0.84</td>
<td>2.9</td>
<td>1</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td>14 Arm girth (relaxed)</td>
<td>0.25</td>
<td>0.78</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>15 Arm girth (flexed &amp; tensed)</td>
<td>0.3</td>
<td>0.93</td>
<td>0.99</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>19 Waist girth (min)</td>
<td>0.66</td>
<td>0.78</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>20 Gluteal girth (max)</td>
<td>0.49</td>
<td>0.46</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>23 Calf girth (max)</td>
<td>0.13</td>
<td>0.33</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>38 Humerus breadth (biepicondylar)</td>
<td>0.07</td>
<td>1.04</td>
<td>0.97</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>39 Femur breadth (biepicondylar)</td>
<td>0.05</td>
<td>0.51</td>
<td>1</td>
<td>1.5</td>
<td>1</td>
</tr>
</tbody>
</table>
### ISAK skinfold sites [266]

<table>
<thead>
<tr>
<th>Skinfold site</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skinfold site: Triceps</strong></td>
<td>The tricept Skinfold site was located at the Mid-line of the Triceps at the marked Mid-acromiale-radiale level.</td>
</tr>
<tr>
<td><strong>Skinfold site: Biceps</strong></td>
<td>The biceps Skinfold site was located at the most anterior part of the biceps when viewed from the side at the marked Mid-acromiale-radiale level.</td>
</tr>
<tr>
<td>Skinfold site: Subscapular</td>
<td>The subscapular Skinfold site was located 2cm from the Subscapulare in a line 45° laterally downward.</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td>Skinfold site: Iliac crest</td>
<td>The iliac crest Skinfold was taken immediately above the iliocristale, the fold ran slightly downwards anteriorly as determined by the natural fold of the skin.</td>
</tr>
<tr>
<td>Skinfold site: Supraspinale</td>
<td>The supraspinale skinfold runs slightly downwards and anteriorly as determined by the natural fold of the skin. The site was located at the intersection of the line marked from the iliopinale to the anterior axillary border, and the horizontal line at the level of the marked iliocristale.</td>
</tr>
</tbody>
</table>
**Skinfold Site: Abdominal**

![Image](image1.png)

The abdominal Skinfold was taken 5cm to the subjects right from the omphalion. This was a vertical fold.

**Skinfold site: Medial calf**

![Image](image2.png)

The medial calf Skinfold site was taken at the level of maximum girth at the site most medial.

**Skinfold site: Front thigh**

![Image](image3.png)

The front thigh Skinfold site was located at the midpoint of the distance between the inguinal fold and the anterior surface of the patella on the midline of the thigh.
### 8.8 Appendix 8 – ISAK girth sites

<table>
<thead>
<tr>
<th>Girth site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Waist:</strong></td>
<td>The waist measurement was taken at the narrowest point between the lower boarder of the rib cage and the iliac crest. The measurement was taken at the end of normal expiration with the arms relaxed at the sides.</td>
</tr>
<tr>
<td><strong>Gluteal (Hip):</strong></td>
<td>The Hip measurement was taken at the level of the greatest posterior protrusion of the buttocks. The subject stood with feet together and buttocks relaxed.</td>
</tr>
<tr>
<td><strong>Arm flexed and tensed:</strong></td>
<td>The flexed arm girth was measured at the maximum circumference of the right upper arm when raised horizontal to the floor. The subject clenched their hand and moved their fist closer to their shoulder while holding continued tension in the bicep.</td>
</tr>
<tr>
<td>Arm relaxed:</td>
<td>The relaxed arm measurement was taken at the level of the mid-acromiale-radiale while the subject’s arms rested at their sides.</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><img src="image" alt="Image of arm measurement" /></td>
<td></td>
</tr>
<tr>
<td>Calf:</td>
<td>The calf measurement was taken at the maximal girth of the calf.</td>
</tr>
<tr>
<td><img src="image" alt="Image of calf measurement" /></td>
<td></td>
</tr>
</tbody>
</table>
# Appendix 9 – ISAK breadth sites

<table>
<thead>
<tr>
<th>Breadth site</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biepicondylar femur:</strong></td>
<td>The Biepicondylar femur was defined as the distance measured between the medial and lateral epicondyles of the femur when the participant is seated with the knee flexed at 90°</td>
</tr>
<tr>
<td><img src="image1.jpg" alt="Image of measurement" /></td>
<td></td>
</tr>
<tr>
<td><strong>Biepicondylar humerus:</strong></td>
<td>The Biepicondylar humerus breadth was defined as the distance measured between the medial and the lateral epicondyles of the humerus.</td>
</tr>
<tr>
<td><img src="image2.jpg" alt="Image of measurement" /></td>
<td></td>
</tr>
</tbody>
</table>
FACT-G (Version 4)

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

### PHYSICAL WELL-BEING

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have a lack of energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have nausea</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my physical condition, I have trouble meeting the needs of my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am bothered by side effects of treatment</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel ill</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am forced to spend time in bed</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### SOCIAL/FAMILY WELL-BEING

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel close to my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I get emotional support from my family</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I get support from my friends</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My family has accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with family communication about my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel close to my partner (or the person who is my main support)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am satisfied with my sex life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

### Emotional Well-being

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel sad</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am satisfied with how I am coping with my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am losing hope in the fight against my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel nervous</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry about dying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I worry that my condition will get worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

### Functional Well-being

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am able to work (include work at home)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>My work (include work at home) is fulfilling</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am able to enjoy life</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have accepted my illness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am sleeping well</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am enjoying the things I usually do for fun</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I am content with the quality of my life right now</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
### 8.11 Appendix 11 – Functional Assessment of Chronic Illness Therapy - Fatigue

**FACIT Fatigue Scale (Version 4)**

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

<table>
<thead>
<tr>
<th>Statement</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel fatigued</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel weak all over</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel listless (“washed out”)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel tired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have trouble starting things because I am tired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have trouble finishing things because I am tired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am able to do my usual activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I need to sleep during the day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am too tired to eat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I need help doing my usual activities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am frustrated by being too tired to do the things I want to do</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have to limit my social activity because I am tired</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# 8.12 Appendix 12 – Fear Avoidance Beliefs Questionnaire

**FEAR AVOIDANCE BELIEFS QUESTIONNAIRE (Waddell, 1993)**

Here are some of the things which other patients have told us about their pain. For each statement please circle any number from 0 to 6 to say how much physical activity would affect your pain.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Completely Disagree</th>
<th>Unsure</th>
<th>Completely Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My pain was caused by physical activity.</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2. Physical activity makes my pain worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3. Physical activity might harm my shoulder/chest</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4. I should not do physical activities which (might) make my pain worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5. I cannot do physical activities which (might) make my pain worse</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Name: ___________________________  
DOB: ___________________  Age: _____
Date/Time baseline: ___________________  
Date/Time 16 Week: ___________________
8.13 Appendix 13 – Demographic Information Form

Demographic information

<table>
<thead>
<tr>
<th>Patient details</th>
<th>Person for Notification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Relationship</td>
</tr>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Telephone</td>
<td>H:</td>
</tr>
<tr>
<td></td>
<td>W:</td>
</tr>
</tbody>
</table>

Gender

- □ Male
- □ Female

Are you post menopausal?

- □ Yes
- □ No

If yes, are you on hormone replacement therapy?

- □ Yes
- □ No

Name: ___________________________
DOB: ________________ Age: ______
Date: ___________________________
Hormone replacement therapy?
Race / Ethnic background
What is your ethnic background?
- Caucasian
- Australian
- Asian
- Aboriginal
- European
- Middle East
- Black
- Indian
- other ____________

Marital status
Are you married, widowed, divorced, separated, never married?
- married / defacto
- widowed
- divorced
- single/ never married
- separated

Residence
In what type of accommodation do you live?
- house (own)
- house (rented)
- unit (own)
- unit (rented)
- retirement village
- hostel
- nursing home
How long have you lived at this address?

☐ board/rooming house

Years ______ MONTHS ______

Living Situation

With whom do you live?

☐ alone
☐ spouse / partner
☐ family
☐ paid carer
☐ friend
☐ other residents

___________ people

Total number of persons in the household

Education

What is the highest grade or year of school you completed?

☐ never / kindergarten 0
☐ primary school 1 2 3 4 5 6
☐ high school 7 8 9 10 11 12
☐ tertiary 13 14 15 16
☐ post graduate 17 18 19 20

Work

Do you currently work for pay either for yourself or someone else?

☐ yes
☐ no

How many hours per week do you work for pay?

______________ hours / week

Do you currently work as a volunteer?

☐ yes
☐ no
How many hours volunteer hours / week do you work?

__________ hours / week

**Annual income**

In what range is your annual income?

☐ < $ 15,000

☐ $ 15,000- $30,000

☐ >$30,000

**Pension**

Do you receive a pension?

☐ Nil

☐ DVA

☐ Age pension

☐ Widows pension

☐ Disability Pension

**Hospital admissions**

During the past 12 months, how many different times did you stay in hospital over night?

__________ number of times

__________ number of days in hospital

**Smoking**

Have you ever smoked cigarettes, cigars or a pipe on a daily basis?

☐ yes

☐ no

Do you currently smoke at least 1 cigarette, cigar or pipe per day?

☐ yes
If yes, how many cigarettes, cigars or pipes do you smoke on an average day?

________ per day

**Alcohol**

During the past 30 days, about how many days did you drink any alcoholic beverages (beer, wine, liquor)

- □ almost every day
- □ 3-4 times a week
- □ once or twice a week
- □ 2-3 times a month
- □ once a month
- □ none

Comments:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
8.14 Appendix 14 – Weekly Status Check

Name: ____________________________
DOB: _______________ Age: ______

Weekly Status Check

During the past week have you had any of the following?

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

1. Acute illnesses
   Specify____________________________
   ______________________________________

2. Acute injury
   Specify____________________________
   ______________________________________

3. Change in medication (prescribed, over-the-counter, herbal, nutritional supplement)
   Specify: ______________________________
   ______________________________________

4. Visits to a health care professional
   Kind_____________________________
   Indication_______________________
   Treatment_______________________

5. New physical, mental, or emotional
symptoms of any kind

☐ ☐

Describe:________________________________
_______________________________________
_______________________________________

6. Have you attended all exercise sessions? ☐ ☐

If not, number attended___________________

Reason for missed session(s)_________________
_________________________________________

7. Other Questions or Comments of subject:

___________________________________________________________________
___________________________________________________________________
___________________________________________________________________
_________
8.15 Appendix 15 – Godin Leisure-Time Exercise Questionnaire

Godin Leisure-Time Exercise Questionnaire

INSTRUCTIONS

In this excerpt from the Godin Leisure-Time Exercise Questionnaire, the individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS

For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively. Total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light)

The second question is used to calculate the frequency of weekly leisure-time activities pursued "long enough to work up a sweat" (see questionnaire).

EXAMPLE

Strenuous = 3 times/wk
Moderate = 6 times/wk
Light = 14 times/wk

Total leisure activity score = (9 × 3) + (5 × 6) + (3 × 14) = 27 + 30 + 42 = 99

Godin Leisure-Time Exercise Questionnaire

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

   Times Per

   Week

a) STRENUOUS EXERCISE

   (HEART BEATS RAPIDLY)

   (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)
b) MODERATE EXERCISE  
(NOT EXHAUSTING)  
(e.g., fast walking, baseball, tennis, easy bicycling,  
volleyball, badminton, easy swimming, alpine skiing,  
popular and folk dancing)  


c) MILD EXERCISE  
(MINIMAL EFFORT)  
(e.g., yoga, archery, fishing from river bank, bowling,  
horseshoes, golf, snow-mobiling, easy walking)  

2. During a typical 7-Day period (a week), in your leisure time, how often do you engage in any  
regular activity long enough to work up a sweat (heart beats rapidly)?  

      OFTEN         SOMETIMES         NEVER/RARELY  
      1. □□□□□□□□  2. □□□□□□□□  3. □□□□□□□□