Determinants of Cardiovascular Health in Breast Cancer Survivors Based on Physical Activity Status

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Abstract

While the worldwide incidence of breast cancer is high, the New Zealand 5-year survival rate is encouraging at 86% which can be attributed to improvements in screening programmes and technological advances in chemotherapy (CT) and radiation therapies (RT). However, many anticancer therapies have potentially debilitating side-effects, including the development of cardiac toxicity, reductions in cardiorespiratory fitness and changes in body composition. Although it is well known that these treatments are associated with a relatively high risk of developing both cardiac and endothelial dysfunction, possible determinants of cardiovascular health (CV) in cancer survivors remains unknown. However, across numeral clinical populations such as coronary artery disease and hypertensive individuals, physical activity (PA) has been shown to have a cardio-protective effect on the CV system. Therefore, the purpose of this study was to provide insight into CV health of breast cancer survivors previously treated with CT and/or RT, based on PA status. Specific aims were to investigate whether PA status determines central blood pressures (cBP) and arterial stiffness within this population. A second aim was to investigate whether cardiorespiratory fitness and/or body composition may moderate CV health following these treatments. This study used a cross-sectional design with participants being women previously treated with RT and/or CT for breast cancer who were classified as either physically active (n=44) or inactive (n=21) based on current PA status. The International Physical Activity Questionnaire (IPAQ) Long Form was used to evaluate PA level. A vascular health assessment assessed arterial stiffness and central blood pressures, while a submaximal treadmill walking test was used to estimate VO$_{2\text{max}}$. Body composition was measured by dual energy X-ray absorptiometry. A multiple linear regression was utilised for statistical testing. Active participants had significantly lower central blood pressures (SBP: 111±12 mmHg vs. 120±13 mmHg, p=0.012; DBP: 72±6 mmHg vs. 78±6 mmHg, p=0.026). The body composition was also significantly different with active participants having a lower body fat percentage (23% vs. 29%, p<0.001) and higher lean body mass (56.9 kg vs. 48.9 kg, p<0.001).
vs. 79±7 mmHg, p=0.000) compared to inactive participants; however, arterial stiffness was similar between the two study groups (p=0.659). Linear regression models showed that \( \dot{V}O_{2\text{max}} \) is a predictor of arterial stiffness (AIx \%) and approached significance with myocardial efficiency (indicated by the use of double product, DP); however, the association between \( \dot{V}O_{2\text{max}} \) and AIx becomes non-significant after adjusting for age. Fat mass (\%) (FM \%) was found to be an important moderator of DP not AIx, even after adjusting for both age and \( \dot{V}O_{2\text{max}} \). The novel results from the current study suggest that there is an association between higher levels of recreational PA and lower cBP’s in breast cancer survivors following treatment. Secondly, FM (\%) was identified as an important moderator of myocardial efficiency, with \( \dot{V}O_{2\text{max}} \) a predictor of arterial stiffness. Identifying possible determinants of CV health is imperative for reducing the incidence of cardiovascular disease development and mortality in breast cancer patients following treatment.
Acknowledgements

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Finally, to all of my friends and family that have put up with a busy, tired and often grumpy individual for the last year and a half I owe you the biggest thanks. You all contributed in helping balance my agenda and more importantly bought me back down to earth when things were getting hectic. The continual reminders that ‘there is light at the end of the tunnel’ gave me great reassurance although I probably snapped at you for saying so. Although most of you had no idea what the answer was when I was stuck with a problem your support and ideas were always greatly appreciated. Now for a new Journey to begin!
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<td>Active</td>
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<td>AIx</td>
<td>Augmentation Index</td>
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<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>eNOS</td>
<td>Endothelial Nitric Oxide Synthase</td>
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<td>nNOS</td>
<td>Neuronal Nitric Oxide Synthase</td>
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<td>FM</td>
<td>Body Fat</td>
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<td>CAD</td>
<td>Coronary artery disease</td>
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<td>cBP</td>
<td>Central Blood Pressure</td>
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<td>cDBP</td>
<td>Central Diastolic Blood Pressure</td>
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<td>cPP</td>
<td>Central Pulse Pressure</td>
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<td>cSBP</td>
<td>Central Systolic Blood Pressure</td>
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<tr>
<td>CT</td>
<td>Chemotherapy</td>
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<td>CV</td>
<td>Cardiovascular</td>
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<td>CVD</td>
<td>Cardiovascular Disease</td>
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<td>DP</td>
<td>Double Product</td>
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<td>DXA</td>
<td>Dual-Energy X-ray Absorptiometry</td>
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<td>HR</td>
<td>Heart rate</td>
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<td>IA</td>
<td>Inactive</td>
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<td>IPAQ</td>
<td>International Physical Activity Questionnaire</td>
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<td>LTM</td>
<td>Lean Tissue Mass</td>
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<td>MAP</td>
<td>Mean Arterial Pressure</td>
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<td>MET</td>
<td>Metabolic Equivalent</td>
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<tr>
<td>NO</td>
<td>Nitric Oxide</td>
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<tr>
<td>PA</td>
<td>Physical Activity</td>
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<tr>
<td>pDBP</td>
<td>Peripheral Diastolic Blood Pressure</td>
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<td>pSBP</td>
<td>Peripheral Systolic Blood Pressure</td>
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<td>PP</td>
<td>Pulse Pressure</td>
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<td>PR</td>
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<td>Radiation Therapy</td>
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Chapter 1: Introduction

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer-related death in females in both underdeveloped and developed countries (Jemal, Bray, Center, Ferlay, Ward, & Forman, 2011). In 2008, breast cancer accounted for 23% of all new cancer cases and 14% of all cancer deaths worldwide (Jemal et al., 2011). Similarly, in New Zealand, breast cancer is the most commonly registered cancer in women, accounting for 28% of all new cancer registrations and 15% of cancer-related deaths (Ministry of Health, 2011). The incidence of breast cancer is higher in Western countries due to differences in hormonal (earlier age at menarche and later menopause) and reproductive factors (many women remain nulliparous or have a later age of first birth), and access to technological advances that result in earlier detection (Jemal, Center, DeSantis, & Ward, 2010). Early detection and improved treatments have contributed to worldwide survival rates of almost 90% (SEER, 1975-2007; Stewart, Hoving & Russell, 2010). New Zealand 5-year survival rates have increased and now sit at 86.2% (Ministry of Health, 2012). While survival rates from breast cancer have improved, anticancer therapies have potentially debilitating side-effects, including the development of cardiac toxicity, reductions in cardiorespiratory fitness and adverse changes in body composition, decreased ability to perform activities of daily living, and reduced overall wellbeing (Hewitt, Rowland & Yancik, 2003). Importantly, breast cancer survivors are now more likely to die of heart disease than their cancer (Colzani, Liljegren, Johansson, Adolfsson, Hellborg & Hall, 2011).

Cardiac toxicity is a primary side-effect of both CT and RT and often leads to cardiac dysfunction; particularly myocardial ischemia, congestive heart failure, arrhythmias, left ventricular dysfunction, electrocardiographic changes, pericarditis, coronary artery disease
(CAD), myocardial fibrosis, arterial hypertension and venous and arterial thrombosis
(Giordano, Kuo, Freeman, Buchholz, Hortobagyi & Goodwin, 2005; Adams, Prosnitz,
Constine, Marks & Lipshultz, 2007; Carver, Shapiro, Ng, Jacobs, Schwartz & Virgo, 2007;
Prosnitz, Hubbs, Evans, Zhou, Yu & Blazing, 2007; Bird & Swain, 2008; Stewart, Hoving &
Russell, 2010; Stortecky & Suter, 2010). Numerous randomised control trials and cohort
studies have reported on the toxic effects of RT and various CT agents including
anthracyclines, alkylators, anti-tubulins, anti-metabolites and hormonal targeted therapies in
breast cancer patients. Indeed, evidence shows that CT treatments are associated with a
relatively high risk of developing either acute or long-term cardiac toxicity (Rezkella, Kloner,
Ensley, Al-Sarraf, Revels & Olivenstein, 1989; Swain, Whaley, Gerber, Weisberg, York &
Spicer, 1997; Ryberg, Nielsen, Skovsgaard, Hansen, Jensen & Dombernowsky, 1998; Chan,
Friedrichs, Noel, Pinter, Van Belle & Vorobiof, 1999; Minotti, Menna, Salvatorelli, Cairo &
Gianni, 2004; Bird & Swain, 2008) and the combined or sequential use of RT may increase
the likelihood of breast cancer patients developing some form of cardiac dysfunction. While
the acute and long-term cardiac effects of these treatments are well documented, the effects of
CT and RT on the cardiovascular (CV) system are not as well known. Vascular dysfunction
includes deficits to both functional and structural components of arteries such as; reduced
vasoactive substance synthesis and release, build-up of fatty acid plaques, disarrangement of
elastin, a degeneration of the medial layer of the artery and increased arterial wall thickness
(Vaitkevicius, Fleg, Engel, O’Connor, Wright & Lakatta, 1993) encouraging the development
of atherosclerosis and thromboembolic events, which may contribute to a cardiac event
(Ribeiro, Alves, Duarte & Oliveira, 2010). Previously literature has not examined the effect
CT and/or RT treatments have on central blood pressures (cBP) and arterial stiffness which
are important markers of overall CV health.

Exercise training has become an important secondary prevention measure following
the diagnosis of many chronic diseases. Physical activity (PA) is acknowledged as a key
component in cancer rehabilitation and is an effective strategy to help reduce treatment related side-effects (Visovsky, 2006). While the specific effects of PA on CV health in cancer survivors has not been examined, research has shown that healthy active individuals have superior CV health to age-and gender-matched sedentary individuals (Tinken, Thijssen, Black, Cable & Green, 2008). In addition, PA is highly effective at reducing vascular dysfunction in coronary artery disease (CAD) patients (Hambrecht, Wolff, Gielen, Linke, Hofer & Erbs, 2000). Thus, it could be expected that PA prescription would have positive effects in breast cancer patients.

Additional adverse side-effects of active treatment in breast cancer survivors include unfavourable changes in body composition and cardiorespiratory fitness such as; increases in fat mass (FM), decreases in lean tissue mass (LTM) (Denmark-Wahnefried, Peterson, Winer, Marks, Aziz, & Marcon, 2001) and significant decreases in cardiorespiratory fitness (Jones, Haykowsky, Peddle, Joy, Pituskin, & Tkachuck, 2007a; Jones, Haykowsky, Pituskin, Jendzjowsky, Tomczak & Haennel, 2007b). Although the relationships between CT and/or RT and body composition and cardiorespiratory fitness have been reported, no study has examined whether these relationships may moderate CV health.

Therefore, the purpose of this study was to provide insight into CV health of breast cancer survivors previously treated with CT and/or RT, based on PA status. Specific aims were to investigate whether PA status determines cBP and arterial stiffness within this population. A second aim was to investigate whether cardiorespiratory fitness and/or body composition may moderate CV health following these treatments.
Chapter 2: Review of Literature

With heart disease the leading cause of death in breast cancer patients following survivorship of their cancer, it is essential that rehabilitation programmes are developed to reduce cardiac toxicity associated with treatments, and therefore the risk of CVD development. This review will firstly introduce basic CV physiology and clinical assessment techniques used to assess vascular health. Secondly, it will address the acute and long-term side-effects induced by CT and RT on the CV system, and the effects PA has on attenuating these side-effects. Lastly, it will examine the effects of active treatments on possible moderators of CV health including; PA level, cardiorespiratory fitness and body composition within breast cancer survivors and the effect PA has on these moderators following treatment.

2.1 Cardiovascular Function

The CV system also referred to as the circulatory system is defined as the heart and a closed system of blood vessels within the body (Thibodeau & Patton, 2007). Comparatively, the vascular system is referred to as the vessels that carry and circulate blood and other matter such as lymph waste through the body (Thibodeau & Patton, 2007), thereby indicating the strong inter-connection between the CV and vascular systems. The heart’s primary function is to maintain adequate hemodynamic flow to all regions of the body (Pugsley & Tabrizchi, 2000). The heart has four chambers separated by valves that control the flow of blood from one chamber to another or out into the pulmonary or systemic circulation. These valves open or close in response to pressure differences generated within the heart. Systolic blood pressure (SBP) is the highest arterial pressure of a cardiac cycle and occurs immediately after the contraction of the heart, while diastolic blood pressure (DBP) is the lowest arterial pressure occurring during relaxation of the heart muscle. Blood pressure is typically measured at the brachial artery; however, this does not reflect the blood pressure at the aorta, due to the higher
resistance encountered by the narrowing of the vessels as the arterial tree moves away from the heart.

Due to the large size of the aorta, central systolic and diastolic pressures (cSBP and cDBP, respectively) are lower than that encountered in the peripheral vessels. Blood ejected from the left ventricle moves down the arterial tree in a pulsatile manner via a number of blood vessels that differ in size, shape and compliance (Pugsley & Tabrizchi, 2000) in order to allow; sufficient perfusion of vascular beds to different regions of the body, maintain blood pressure during low and high energy demands and aid blood return to the heart. The difference between SBP and DBP is pulse pressure (PP) (Thibodeau & Patton, 2007) and represents that force that is generated every time the heart beats. With each ejection of blood from the aorta a new pulse starts, which alternately increases and decreases pressure in the vessel, allowing blood to move as a pulsatile load through the body (Thibodeau & Patton, 2007). The intermittent pulse generates a pulse wave that dissipates as it moves down the arterial tree (Thibodeau & Patton, 2007).

A common measure of myocardial workload or efficiency is rate pressure product, also referred to as double product (DP), which is useful for evaluating oxygen demand placed on the myocardium. Double product is calculated by multiplying heart rate (HR) and SBP in order to calculate a numerical value that indicates myocardial oxygen consumption. Double product thereby indicates the response of the coronary circulation to myocardial metabolic demands (Govindaraju & Mital, 1997). There is strong evidence that DP is an accurate calculation of myocardial oxygen consumption in patients with ischemic heart disease (Gobel, Nordstrom, Nelson, Jorgensen & Wang, 1978). During exercise DP significantly increases in comparison to rest as both HR and SBP increase to meet the increased oxygen demand compared to resting state (Forjaz, Matsudaira, Rodrigues, Nunes & Negrao, 1998). Additionally, patients that have CAD or arterial disease have a higher DP at rest and a lower
DP during peak exercise tasks (Saunamaki & Andersen, 1987) due to higher resting HR and SBP and lower maximum HR. Double product is an effective and efficient way of non-invasively assessing myocardial efficiency during both rest and exercise.

2.2 Central vs. Peripheral Blood Pressure

Since, vascular health assessments are not routinely performed, CAD development may not be recognised until changes in blood pressure are seen during clinical routine practice. Because of this, central blood pressure (cBP) assessment may be beneficial for monitoring changes in arterial vasculature in high risk individuals, such as breast cancer patients following active treatment.

Blood pressure in the central arteries is directly related to the pressure on the heart, which becomes amplified at peripheral sites due to the smaller structure of peripheral vessels, increasing total peripheral resistance (Agabiti-Rosei, Mancia, O’Rourke, Roman, Safar & Smulyan, 2007; Wang, Cheng, Chuang, Spurgeon, Ting & Lakatta, 2009). However, it is common practice to measure blood pressure at a peripheral site such as the brachial artery which is non-direct measure of cBP. While pBP measurements have been consistently reported in literature and used in clinical settings, their ability to accurately reflect central pressures, and predict CV outcome and mortality is becoming questionable as new research on central pressures emerges (Avolio, 2013). Previous studies have shown diastolic blood pressure values to be relatively similar between peripheral and central measures with <3 mmHg difference (Sharman, Stowasser, Fassett, Marwick & Franklin, 2008). However, peripheral systolic blood pressure (pSBP) can range between 2 mmHg and >30 mmHg higher than cSBP (Sharman et al., 2008). Pressure amplification to the periphery is also highly variable between subjects, dependent on gender, height and HR, causing analysis issues in relation to validity when comparing between groups or populations (Wilkinson, Franklin,
Current research suggests that cBP indices are superior to pBP at predicting CV events, outcomes, extent of atherosclerosis and all-cause mortality (Roman, Devereux, Kizer, Lee, Galloway & Ali, 2007; Roman, Devereux, Kizer, Okin, Lee & Wang, 2009; Wang et al., 2009; Vlachopoulos et al., 2010; Sharman, Marwick, Gilroy, Otahal, Abhayaratna & Stowasser, 2013). Further to this, Wang et al. (2009) reported cSBP was the best correlate for left ventricular mass, while both cSBP and cPP were the best correlates for intima media thickness. Pulse pressure is becoming an increasingly important index, as persistently elevated PP can cause damage to the microcirculation, leading to increased resistance to blood flow (Wang et al., 2009). This damage was demonstrated in the Framingham Heart Study with increased PP and aortic stiffness associated with reduced microvascular reactivity when ischemic stress presented (Wang et al., 2009). It is clear from emerging literature that the prognostic value of cBP has been recognised by expert consensus (Agabiti-Rosei et al., 2007; Avolio, Van Bortel, Boutouyrie, Cockroft, McEniery & Protagorou, 2009).

Central blood pressures can now be derived non-invasively, using a generalised mathematical transfer function using the peripheral, brachial artery waveform. The transfer function has been shown to have a strong correlation (r=0.9) with actual aortic catheterisation assessments of cBP (Lowe, Harrison, El-Aklouk, Ruygrok & Al-Jumaily, 2009). This finding is promising as it indicates the true accuracy of central pressures and their ability to monitor CV health.
2.3 Arterial Stiffness

All blood vessels within the human body excluding capillaries are made up by three distinct layers; tunica adventitia, tunica media and tunica intima (Pugsley & Tabrizchi, 2000). Over the past 20 years, research has shown that the tunica intima layer comprised of endothelial cells is not merely a structural aspect of the vessel wall (Soultati, Mountzious, Argerinou, Papaxoinis, Pectasides & Dimopoulos, 2012). The endothelial layer of the artery is susceptible to greatest dysfunction due to its exposure to circulating substances within the blood. A healthy endothelial cell’s primary function is to facilitate endovascular function. The endothelium can alter vessel diameter in response to changes in shear stress imposed by increased or decreased blood flow, or by synthesising and releasing vasoactive substances which act on the smooth muscle cells of the artery, helping to maintain vessel tone, vascular permeability, and thromboresistance (Hambrecht et al., 2000).

Nitric oxide is considered the most important vasoactive molecule for endothelial function in vascular tissue. It can be synthesised in response to the activation of endothelial nitric oxide synthase (eNOS) or neuronal nitric oxide synthase (nNOS) production. The most common path for NO synthesis is via eNOS, which is activated in response to increased shear stress (tangential force caused by increased blood flow) on arterial walls. With increased shear stress there is an increase in intracellular calcium, which put simply results in the access to eNOS, leading to increased synthesis of NO in endothelial cells. Nitric oxide then diffuses across the endothelium to the smooth muscle cells causing them to relax and dilation of the artery results (Stoner, Erickson, Young, Fryer, Sabatier & Faulkner, 2012a). Second to this, NO may be produced and released from nNOS found in neurons that line the inside of arteries. Impaired vascular function is thereby characterised by the inability of endothelial cells to produce adequate vasoactive substances such as nitric oxide (Hirase & Node, 2012), as well as prostacyclin and endothelial-derived hyperpolarizing factor which all enable
vasodilation of the artery, reduce platelet aggregation and therefore, reduce the risk of thrombosis and atherosclerotic development (Stoner et al., 2012a).

Atherosclerosis, ‘hardening of arteries’, commonly occurs in individuals who have a number of CV risk factors such as high cholesterol, are overweight, smoke, have hypertension, or are physically inactive. Atherosclerosis occurs when high levels of low-density lipoproteins in the blood, accumulate and embed themselves in the endothelium that lines the artery (Pollard, 2008) causing low level inflammation (Riberio et al., 2010). The consequence of this inflammatory response is formation of a lipid rich plaque that can occlude the vessel, thereby increasing resistance to blood flow and limiting vessel compliance.

Atherosclerosis-induced arterial stiffening, contributes to reductions in vessel compliance, and is a serious health concern. Stiffer vessels influence haemodynamic flow, CV function and heighten morbidity and mortality risk. Increased arterial stiffness results in increased total peripheral resistance and arteries are less able to dilate or constrict accordingly, as each pulsatile load of blood is ejected. This limits the overall amount of blood that is able circulate in one cardiac cycle. Subsequently, work demands on the heart increase, as blood pressure increases to try and maintain adequate blood flow, resulting in an increase heart rate and contractility. Consequently left ventricular ejection fraction decreases due to increased heart rate and reduced filling time and oxygen demand by working muscles is not met, thus potentially restricting an individual’s ability to perform normal activities of daily living.
2.3.1 Assessment of Cardiovascular Health

Given the latency period between active treatment completion in breast cancer patients and potential symptomatic CVD there is a need to detect vascular changes before symptoms appear. Routine CV assessments monitoring vascular changes following CT and/or RT are not performed in breast cancer patients. Recent recommendations have suggested including screening echocardiography 5 years after exposure in high risk individuals and 10 years after exposure in those who remain asymptomatic (Lancellotti, Nkomo, Badano, Bergler-Klein, Bogaert & Davin, 2013). Although this recommendation is welcoming, it is potentially sub-optimal considering long-term, cardiac toxicity related side-effects are known. Assessment of vascular function in clinical settings generally uses non-invasive procedures that are typically reliable, valid, time efficient and relatively inexpensive to perform.

A common technique performed to assess endothelial function is flow-mediation dilation (FMD), which assesses vasodilatory response to certain vasoactive drugs and/or shear stress. Flow-mediated dilation is the gold standard technique for assessing endothelial function (Lekakis, Abraham, Balbarini, Blann, Boulanger, & Cockcroft, 2011). The equipment required for FMD testing is relatively inexpensive and operating expenses are minimal. While FMD has been found to be reliable (Welsch, Allen & Geaghan, 2002) and valid (Inaba, Chen & Bergmann, 2010) expertise is required by a skilled technician (Stoner & Sabatier, 2012).

Arterial stiffness, which represents compliancy and dispensability of the arterial vascular system can be measured locally, regionally, centrally (Jones, Stoner, Brown, Baldi & McLaren, 2013) using ultrasound, pulse wave velocity (PWV) or pulse wave analysis (PWA), (Grotenhuis, Westenberg, Steendijk, Van der Geest, Ottenkamp & Bax, 2009) respectively. Pulse wave velocity using carotid and femoral arteries (aortic PWV) is considered the gold standard method for arterial stiffness assessment (Deanfield, Donald, Ferri, Giannattasio,
Halcox & Halligan, 2005; Laurent, Cockcroft, Van Bortel, Boutouyrie, Hayoz & Pannier, 2006). However, PWV assessment requires expensive equipment, a very high level of expertise and may be impractical in some clinical settings compared to PWA. The same technologies used to measure PWV have been applied to PWA devices. Central arterial stiffness (AIx%) can now be estimated in a more reliable (Climie, Schultz, Nikolic, Ahuja, Fell & Sharman, 2012), economical and operationally friendly assessment, within clinical settings using PWA. Data from PWA devices that use oscillometry closely align with those obtained from the gold standard tonometry methods (Jatoi, Mahmud, Bennett & Feely, 2009; Climie et al., 2012). Commercial PWA oscillometry devices such as SphygmoCor, AtCor Medical or Cardioscope and Puslecor monitor periphery waveform at the brachial artery using oscillometry (Jatoi et al., 2009) or at the radial artery with tonometry (Jatoi et al., 2009), which then use a generalised transfer function to estimate the central aortic waveform (Jatoi et al., 2009; Climie et al., 2012). Augmentation index can then been calculated from this central waveform by calculating the distance between the early and late systolic pressures, expressed as a percentage of pulse pressure (O’Rourke & Hashimoto, 2008; Jatoi et al., 2009; Inaba, Chen & Bergmann, 2010).

Figure 1. Analysis of peripheral blood pressure waveform to predict central arterial stiffness (AIx %), using the PulseCor Cardioscope II.

The central pressure wave is generated by left ventricular ejection fraction which travels down the atrial tree to peripheral sites (forward wave), and the reflected (backward wave) that reflects from peripheral sites (Agabiti-Rosei et al., 2007). A number of studies have examined the relationship of these arterial stiffness measures with age, in normotensive and hypertensive individuals, and in CAD patients. However, as reported by Jones et al. (2013) there has been no literature that has examined AIx in breast cancer patients. Previous research demonstrates that arterial stiffness is further exacerbated in patients with diagnosed CAD, due to atherosclerotic lesions, increasing total peripheral resistance (Weber, Auer, O’Rourke, Kvas, Lassnig & Berent, 2004). Thus, a relatively strong linear relationship between arterial stiffness and AIx, and to some extent the severity of CAD, has been found (Weber et al., 2004). A recent meta-analysis of longitudinal studies also indicated that a 10% increase in AIx%, increased the risk of future CV events by 32% and all-cause mortality by 38% (Vlachopoulos et al., 2010).

With CAD the leading cause of death worldwide, and heart disease the leading cause of death in breast cancer survivors following survivorship of their cancer, it is imperative that primary and secondary preventative programmes are developed for specific clinical populations to reduce disease development and mortality risk. The recent advances in vascular health measuring devices that are portable, relatively inexpensive and non-invasive may allow ease of monitoring in high risk patients such as breast cancer survivors. The following chapter of this review will address the specific acute and long-term side-effects induced by CT and RT on the vascular system and the effects PA has on attenuating these side-effects.
2.4 Effects of Chemotherapy and/or Radiation Therapy on Cardiovascular Health

Chemotherapy is a systemic cytotoxic treatment, which aims to eliminate cells with a high turnover, such as cancer cells at specific phases of the cell cycle, in order to decrease cell proliferation, replication and differentiation (Nygren, 2001). Single or multi-agent CT regimens are administered either prior to other treatments (neoadjuvant) or following other treatments (adjuvant). The timing and types of CT is dependent on the stage and grade of the tumor (Nygren, 2001). Radiation therapy is a loco-regional therapy that involves the administration of gamma rays to a localised area of tissue. Radiation specifically targets cancer cells in the replication phase of the cell cycle aiming to shrink the tumor prior to surgery, or following CT to kill cells in that area and reduce the risk of recurrence. These two active treatments are often used sequentially. Breast cancer patients will receive either or both, CT and RT, which significantly increases the risk of adverse cardiac related side-effects (Valagussa, Zambetti, Biasi, Moliterni, Zucali & Bonadonna, 1994; Shapiro, Hardenbergh, Gelman, Blanks, Hauptman & Recht, 1998).

2.4.1 Chemotherapy

The effects of CT on vascular health, from previous studies have been inconclusive. Anthracyclines, in particular Doxorubicin, are one class of CT drug known to have a significant impact on both the structural and functional components of cardiac vessels, which over time may lead to cardiomyopathy and chronic heart failure (Curigliano, Mayer, Burstein, Winer & Goldhirsch, 2010). Although, the exact mechanisms for these effects have not been identified in humans, animal models demonstrate vascular dysfunction occurs due to the presence of reactive oxygen free radicals, which alter redox cycles and thus cause uncoupling of the electron transport chain, inducing cardiomyocyte and endothelial cell apoptosis in animal models (Shankar, Marina, Hudson, Hodgson, Adams & Meeske, 2008; Wu, Ko, Teng, Ko, Hsu & Hsueh, 2002). Additionally, higher doses of anthracycline involve endothelial cell apoptosis, endothelial DNA damage, reductions in vessel contraction, increased vessel wall
thickness, apoptosis and necrosis of smooth muscle cells and complete loss of vessel contraction (Murata, Yamawaki, Hori, Sato, Ozaki & Karaki, 2001a; Murata, Yamawaki, Yoshimoto, Hori, Sato & Ozaki, 2001b; Eckman, Stacey, Rowe, D’Agostino, Kock & Sane, 2013; Gajalakshmi, Priya, Padeep, Behera, Muthumani & K., & Madhuwanti, 2013). Anthracyclines are not the only class of CT agent to induce myocardial and vessel damage. Anti-tubulins such as the Taxanes, when administered in rodents, cause endothelial damage with a reduction in endothelial cells within the heart, as well as increases in cardiac proteins (cTnI and Caspase-3) that represent vascular damage and apoptosis (Mikaelian, Buness, Vera-Mudry, Kanwal, Coluccio & Rasmussen, 2010).

Although a number of contributory mechanisms responsible for the development of vascular dysfunction following CT have been identified in animals, there is a paucity of data examining vascular health in breast cancer survivors. Some evidence exists, showing chronic impairments to FMD in breast cancer patients following a mixed CT and RT treatment protocol, with impairments localised to arteries receiving RT (Beckman, Thakore, Kalinowski, Harris & Creager, 2001). Furthermore, breast cancer patients with metastatic or early-stage disease treated with the CT agents, cisplatin, paclitaxel and epirubicin, had a decrease in FMD from baseline to post-CT (Vassilakopoulou, Mountzios, Papmichael, Protogerou, Aznaouridis & Katsichti, 2010). Pulse wave velocity has been shown to be higher in CT treated patients compared to healthy age-matched individuals prior to CT treatment with significant increases following treatment, illustrating the contribution of anthracycline treatment to increased vascular stiffness (Chaouwannakit, D’Agostino, Hamilton, Lane, Ntim & Lawrence, 2010).

Thromboembolic events are a further possible vascular complication associated with CT treatment and are the second cause of cancer-related death after the tumour itself (Noble
& Pasi, 2010). Multi-agent CT treatment administered in metastatic disease was responsible for some form of thromboembolic event in 17.6% of a breast cancer survivor cohort (Goodnough, Saito, Manni, Jones & Pearson, 1984). Deep vein thrombosis or myocardial infarction accounted for 28% of the thromboembolic events in these patients (Goodnough et al., 1984). Additionally, breast cancer patients treated with hormonal agents such as Tamoxifen, are at a higher risk of developing thrombosis (Saphner, Tormey & Grey, 1991).

2.2.2 Radiation Therapy

Radiation therapy induces vascular dysfunction via a number of mechanisms. The primary side-effect of radiation-induced vascular dysfunction is increased vascular tone which may lead to unfavourable blood pressure (Bentzen, 2006). The mechanism of action responsible for increased vascular tone is an increase in the production of eicosanoids, endogenous mediators, responsible for changes in lumen diameter, vasculature permeability and thrombus formation (Stewart, Hoving & Russell, 2010; Mulrooney & Duprez, 2012). Although eicosanoids are required for normal vascular function, significant increases in circulating levels (prostaglandins, prostacyclins, thromboxanes and leukotrienes) leads to a pro-thrombotic state causing vascular disruption (Stewart, Hoving & Russell, 2010; Mulrooney & Duprez, 2012). Subsequently, the inflammation induced by the excessive production of eicosanoids may cause endothelial cell detachment, exposing the sub-endothelium, resulting in tissue ischemia and micro-thrombi formation (Stewart, Hoving & Russell, 2010; Mulrooney & Duprez, 2012).

Telangiectasia, small dilated, thin-walled blood vessels on the skin surface, has also been reported to occur in breast cancer patients, one to ten years following RT (Turesson & Notter, 1984; Tanteles, Whitworth, Mills, Peat, Osman & McCann, 2009; Stewart, Hoving & Russell, 2010). Development of telangiectasia in irradiated tissue is the underlying cause of micro-thrombi formation and ischemia of vascular tissue (Stewart, Hoving & Russell, 2010).
Radiation-induced injury to endothelial cells not only cause isolated damage to the endothelial cell, but additionally impairs repair processes, thereby compounding functional loss (Stewart, Hoving & Russell, 2010).

Coronary artery disease (CAD) development following RT with older technology was a likely side-effect in breast cancer patients due to the close proximity of the heart, and is more common in those patients with left-sided disease (Correa, Litt, Hwang, Ferrari, Solin & Harris, 2010). However, due to technological advances in RT, the dose delivered over a specific area has become more targeted, reducing unwanted dose to healthy tissue and therefore minimising the risk of RT induced CV toxicity (Dawson & Jaffray, 2007). Correa et al. (2010) reported stress test abnormalities (chest pain, arrhythmias, abnormal electrocardiogram and/or shortness of breath) in women with stages I-II breast cancer to be more prevalent in those who receive left-sided radiation compared to right-sided, 59% versus 36%, respectively (Correa et al., 2007). Similarly, coronary stenoses in the anterior descending coronary artery was also present in 85% of patients, and in 62% of those patients, the whole vessel was affected (Correa et al., 2007).

Human and rodent trials have demonstrated a range of vascular impairments following CT and RT. Blood vessels are specifically affected with the development of telangiectasia, induction of apoptosis, and/or nuclei damage to endothelial cells leading to ischemia and micro-thrombi formation as well as deficits in vasodilatory molecules (Murata et al., 2001a; Murata et al., 2001b; Tanteles et al., 2009; Stewart, Hoving & Russell, 2010; Gajalakshmi et al., 2013). Smooth muscle cells may also be affected at higher CT doses resulting in apoptosis and reducing the vessel’s ability to vasodilate and/or vasoconstrict (Murata et al., 2001a; Murata et al., 2001b; Eckman et al., 2013). There have been no studies to date that have investigated the effects of active treatments on cBP and arterial stiffness in cancer patients.
2.5 Effects of Physical Activity on Cardiovascular Health

There is a paucity of research on the effects of PA on vascular health in breast cancer patients following CT and/or RT treatment. Three animal studies have examined the cardio-protective effects of exercise training prior to Anthracycline and targeted hormone therapy treatments (Ascensao, Magalhaes, Soares, Ferreira, Neuparth & Marques, 2005; Chicco, Schneider & Hayward, 2006; Wonders, Hydock, Greufe, Schneider & Hayward, 2009). All three exercise aerobic-based endurance interventions were similar in frequency (5 days a week), duration (60 minutes) and consisted of either treadmill running or swimming over several weeks (10-14 weeks). Across all studies there were significant increases in various proteins responsible for cardio-protection, including HSP60, HSP72, plasma cTnI and caspase-2 and -8 (Ascensao et al., 2005; Chicco et al., 2006; Wonders et al., 2009). These three rodent studies have identified that exercise training prior to Anthracycline based CT may provide a cardio-protective effect (Ascensao et al., 2005; Chicco, Schneider & Hayward, 2006; Wonders et al., 2009). There have been no studies that have examined the effect of PA on vascular health in cancer survivors previously treated with CT and/or RT. However, studies examining CAD patients have shown that higher PA energy expenditures are associated with improved endothelial function (Savage, Brochu, Scott & Ades, 2000; Hambrecht, Niebaurer, Marburger, Grunze, Kalberer & Hauer, 1993; Schairer, Keteyian, Ehrman, Brawner & Berkebile, 2003).

Regular PA for those with CVD has been shown to increase exercise capacity (Nieuwland, Berkhuyser, Veldhuisen, Brugemann, Landsman & Sonderen, 2000; Ades, Savage, Cress, Brochu, Lee & Poehlman, 2003; Rognmo, Hetland, Helgerud, Hoff & Slordahl, 2004; Hansen, Eijnde, Roelants, Broekmans, Rummens & Hensen, 2011; Mameletzi, Kouidi, Koutlianos & Deligiannis; 2011) and attenuate endothelial dysfunction (Gokce, Vita, Bader, Sherman, Hunter & Holbrook, 2002; Walsh, Bilsborough, Maiorana, Best, O’ Driscoll & Taylor, 2003; Luk, Dai, Siu, Yiu, Chan & Fong, 2009; Shantsila & Lip,
thereby, improving vascular function (Gokce et al., 2002) and reducing arterial stiffness (Edwards, Schofield, Magyari, Nichols & Braith, 2004). Mechanisms responsible for vascular health improvements in CAD patients include increases in nitric oxide synthesis and availability, which increases circulating levels of endothelial progenitor cells responsible for enhancing endothelium dependent dilation, vasculogenesis, and endothelial repair (Luk et al., 2009; Shantsila & Lip, 2009).

The recommended exercise guidelines for all cancer survivors is similar to those recommended for healthy individuals, comprising at least 150 minutes of moderate-intensity activity or 75 minutes of vigorous aerobic activity a week, with the inclusion of strength training two to three times a week using major muscle groups (Schmitz, Courneya, Matthews, Demark-Wahnefried, Galveo & Pinto, 2010). This amount of PA equates to energy expenditure between 500-1000 MET-minutes a week (Garber, Blissmer, Deschenes, Franklin, Lamonte & Lee, 2011) and has been shown to be sufficient to reduce the risk of developing CVD in healthy, elderly women (Lee, Rexrode, Cook, Manson & Buring, 2001). Improvements in aerobic capacity have also been shown with this level of energy expenditure in older, sedentary, overweight, postmenopausal women (Church, Earnest, Skinner, & Blair, 2007).

While energy expenditure of 500-1000 MET minutes a week has been shown to reduce the risk of developing CVD in various sectors of the population, much higher levels of PA are needed to reduce CAD and improve functional and structural components of the arteries. Specific levels of energy expenditure are required to inhibit progression and stimulate regression of atherosclerosis. Evidence suggests that CAD patients need to have an exercise-related energy expenditure of ≥2,200 kcal/week or 5-6 hours of regular PA to regress atherosclerosis, with expenditure of <1,000 kcal/week insufficient to convey health benefits (Hambrecht et al., 1993). To date, there is no evidence of the energy expenditure requirements to improve vascular health in breast cancer survivors.
In addition to vascular changes induced by CT and RT, other common side-effects of these treatments in breast cancer patients include unfavourable changes in cardiorespiratory fitness and body composition which both have the ability to affect CV health. The following section will examine the effects of active treatments on these possible moderators of CV health within breast cancer survivors, and report if or how PA may be beneficial at improving these moderators following treatment.

2.6 Effects of chemotherapy and/or radiation therapy on possible moderators of cardiovascular health: PA levels, cardiorespiratory fitness and body composition in breast cancer patients.

2.6.1 Physical Activity Levels

Physical activity levels have been shown to significantly decrease following cancer diagnosis, especially during treatment since patients often face debilitating symptoms including nausea, vomiting, fatigue and low mood states (Berglund, Bolund, Fornander, Rutqvist & Sjoden, 1991), which causes fear as to the amount of exertion that can be performed (Winningham, 1991). Indeed, reports show that breast cancer patients decrease their total PA by around 2 hours per week pre- to post-diagnosis, with a greater decrease noted in patients treated with CT and RT (50%) compared to those treated with surgery (24%) or radiation only (23%) (Irwin, Crumley, McTiernan, Bernstein, Baumgartner & Gilliland, 2003). In a long term follow-up, only 32% of breast cancer survivors were engaging in the recommended minimum 150 minutes of moderate and vigorous PA per week (Irwin, McTiernan, Bernstein, Gilliland, Baumgartner & Ballard-Barbash, 2004). However, the inclusion of household chores and gardening activities increased the number meeting 150 minutes per week to 73% (Irwin et al., 2004). There is also a significant decrease in vigorous
intensity PA with increased age (Irwin et al., 2004). This is important to remember as a large proportion of women are diagnosed with breast cancer aged ≥65 years (Ministry of Health, 2011). Not only does a reduced PA level decrease maximal oxygen consumption, but treatments have also been shown to significantly reduce cardiorespiratory fitness via separate mechanisms.

2.6.2 Cardiorespiratory Fitness

Cardiorespiratory fitness is commonly reported in physiological studies as it is an important predictor of an individual’s overall mortality risk (Erikssen, Liestol, Bjornholt, Thaulor, Sandvik & Erikssen, 1998). The American College of Sports Medicine define cardiorespiratory fitness as, “a reflection of the functional capabilities of the heart, lungs and muscles relative to the demands of specific exercise” (Percia, Davis & Dwyer, 2012). Cancer-based research suggests that peak maximal oxygen uptake (VO$_{2peak}$) is a strong indicator of CT-induced CV risk factor development (Jones et al., 2007a).

As outlined in the previous section, PA commonly decreases during active treatment. This reduction in energy expenditure reduces VO$_{2peak}$, which unknowingly leads to worsening of fatigue and further debilitation (Winningham, 1991). Previous studies have reported that following CT, VO$_{2peak}$ in breast cancer patients is approximately 20-40% below that of age- and sex- matched sedentary individuals without a history of cancer (Jones et al., 2007a; Jones et al., 2007b). The suspected mechanism responsible for a decreased VO$_{2peak}$ in breast cancer patients is reductions in both stroke volume and cardiac output at peak exercise due to impairments in left ventricular pre-load and/or contractility caused by chemotherapy-induced cardiac toxicity (Jones et al., 2007b). A lower VO$_{2peak}$ is not only associated with a higher incidence of all-cause mortality, including CVD morbidity and mortality risk (Blair, Kohl, Barlow, Paffenbarger, Gibbons & Macera, 1995; Lee, Artero, Sui & Blair, 2010) but also an unfavourable body composition due to a reduced ability to expend moderate or high levels of energy. Body composition has also been reported to be negatively impacted by CT treatment.
2.6.3 Body Composition

Weight gain has been reported to be a common issue for women receiving treatment for breast cancer, particularly those who are premenopausal and/or are receiving a multi-agent CT regimen (Heasman, Sutherland, Campbell, Elkham & Boyd, 1985; Demark-Wahnefried, Winer, & Rimer, 1993). Weight gain pathology following breast cancer treatment is multifactorial, with treatment-induced menopause, metabolic dysfunction, increased caloric intake, decreased PA and weight status at the time of diagnosis, all identified contributors (Demark-Wahnefried, Hars, Conaway, Havlin, Rimer & McElveen, 1997; Goodwin, Ennis, Pitchard, McCready, Koo & Sidlofsky, 1999). Gains of 2.5-6.2 kg are commonly seen in 50-96% of women, which can predispose the individual to chronic disease development such as hypertension and CVD (Brown, Brauner & Minnotte, 1993). Weight gain in a healthy individual is commonly characterised by an increase in both lean tissue mass (LTM) and fat mass (FM); however, in CT- induced weight gain, cancer patients often present with a loss of LTM concomitant with a greater increase in FM (Demark-Wahnefried et al., 2001). A number of prospective and longitudinal studies examining the effects of CT and/or RT on body composition have reported a decrease in LTM and increases in FM and percentage body fat (FM%) during treatment and up to 6-12 months following treatment completion (Cheney, Mahlock & Freeny, 1997; Aslani, Smith, Allen, Pavlakis & Levi, 1999; Kutynec, McCargar, Barr & Hislop, 1999; Demark-Wahnefried, Peterson, Winer, Marks, Aziz & Marcon, 2001; Freedman, Aziz, Albanes, Hertman, Danform & Hill, 2004; Harvie, Campbell, Baildam, & Howell, 2004; Campbell, Lane, Martin, Gelmon & McKenzie, 2007).

During CT and RT treatment there is a high chance for a premenopausal woman to be forced into early-onset menopause (Bines, Oleske & Cobleigh, 1996). Early onset menopause in younger women has been shown to be associated with an increased risk of CVD (Barrett-Connor & Bush, 1991; Rossi, Grimaldi, Origianni, Fantini, Coppi & Modena, 2002). Increases in centrally-located adipose tissue are prominent in postmenopausal women which is
associated with metabolic complications, such as insulin resistance, hypertension, diabetes mellitus, which are considered risk factors for CVD (Despres, Moorjani, Lupien, Tremblay, Nadeau & Bouchard, 1990; Rossi et al., 2002). Recently, the link between adipose tissue and CV health has strengthened (Despres et al., 1990; Garrison, Higgins & Kannel, 1996; Williams, Jones, Bell, Davies & Bourne, 1997).

Not only is the amount of FM detrimental to vascular health but also where it is positioned within the body. Central adiposity, particularly the visceral compartment, has been shown to be more detrimental to CV health and overall CV risk than peripheral FM (Fantuzzi & Mazzone, 2007). Studies of middle aged women found higher levels of trunk fat to be inversely and significantly associated with the distensibility and compliance of the carotid and femoral arteries (Ferreira, Snijder, Twisk, Van Mechelen, Kemper & Seidell, 2004) and greater carotid-intima media thickness (De Michele, Panico, Iannuzzi, Celentano, Ciardullo & Galasso, 2002). Increased waist to hip ratio, which is used as index of central adiposity, has been reported as an important risk factor for CVD mortality in postmenopausal women (Prineas, Folsom & Kaye, 1993). Concluding, premenopausal women who are pushed into early-onset menopause are potentially at increased risk of arterial stiffening and CVD especially if the FM is centrally located.

It can be concluded from previous studies, that there is a strong trend toward an increased FM %, and decreased LTM and cardiorespiratory fitness during and following the completion of CT treatment. The mechanisms responsible for inducing these changes are multifactorial and more research is needed to identify specific mediators. A reduction in PA is prominent during treatment, which heightens the negative effect CT already has on cardiorespiratory fitness and body composition. Previous studies investigating the effects of RT on these variables are limited and show contradictory results. No study to date has
examined whether body composition and/or cardiorespiratory fitness predict CV health in cancer survivors.

Since PA has been shown across numerous populations to be an effective rehabilitative measure for vascular health and many other aspects of health, the effect of PA on CV health and possible moderators of vascular health following CT and/or RT will be examined in the following sections.

2.7 Effects of Physical Activity on Body Composition and Cardiorespiratory Fitness following Chemotherapy and/or Radiation Therapy.

Research has shown that CT and RT have the ability to reduce LTM, cardiorespiratory fitness and increase FM mass and FM% in breast cancer survivors. However, the results of exercise intervention studies to improve body composition and cardiorespiratory are equivocal. Resistance-based exercise interventions undertaken for 52 weeks have shown mixed results on their ability to improve body composition, with either improvements in LTM and reductions in FM% reported (Schmitz, Ahmed, Hannan, & Yee 2005), or no significant changes in the same outcome measures (Winters-Stone, Dobek, Nail, Bennett, Leo & Naik 2011). While methods to assess body composition were the same, the likely reason for confounding results is due to participant demographics. Participants were older and had a much higher baseline body mass index in the Winters et al. (2011) study compared with those participating in the study by Schmitz et al. (2005).

Most aerobic-based exercise interventions examining body composition have not found any significant changes in LTM or FM% (Pinto, Frierson, Rabin, Trunzo & Marcus, 2005; Courneya, Segal, Mackey, Gelmon, Reid & Friedenreich, 2007; Matthews, Wilcox, Hanby, Ananian, Heiney & Gebretsadik, 2007). However, these studies were of shorter duration (12 weeks), were home-based interventions, used subjective exercise intensities and
required participants to accumulate their total exercise requirement. It is possible that 10 minute bouts of exercise, accumulating to 30 minutes within this population is not sufficient to induce body composition changes. The types of activities performed by participants also varied between weight bearing, non-weight bearing or included activities of daily living thereby, reducing consistency. Additionally, studies used skinfolds and bioelectrical impedance methods to assess body composition which are associated with higher error percentages compared to the gold standard DXA scan (Erseľcan, Candan, Saruhan & Ayca, 2000). However, one study conducted by Irwin, Alvarez-Reeves, Cadmus, Mierzejewski, Mayne & Yu (2009) found a significant decrease in FM and increase in LTM assessed by DXA scan after a 6 month mixed supervised (3x week) and home based (2x week) walking intervention. Participants started at 50% HR_{max} progressing to 60-80% HR_{max} over the intervention period. Frequency and duration of the sessions started with 3 x 15 minutes sessions, increasing to 5 x 30 minute moderate intensity sessions as advised by ACSM recommendations for healthy individuals. The usual care group had increased FM and decreased LTM over the 6 month period.

Exercise capacity, or the ability to utilise oxygen taken in for energy production, can be affected by aerobic-based training. For cancer survivors, aerobic-based exercise training regimes have shown mixed results in the extent to which peak oxygen uptake can be improved. Improvements in VO_{2peak} of between 8% and 36% have been found, (Courneya, Mackey, Bell, Jones, Field & Fairey, 2003; Hutnick, Williams, Kraemer, Orsega-Smith & Dixon, 2005; Herrero, San Juan, Fleck, Bulmer, Perez & Canete, 2006; Courneya et al., 2007; Jones et al., 2007a; Jones et al., 2007b), with statistically significant improvements seen primarily when exercise is undertaken at between 60-80% of the individual’s VO_{2peak} Notwithstanding, exercise undertaken at a lower intensity, 50-60% VO_{2peak}, may also elicit improvements (Segal, Evans, Johnson, Smith, Colletta & Gayton, 2001).
In general, results on the effects of PA on body composition and cardiorespiratory
fitness in breast cancer survivors, previously treated with CT and/or RT have been equivocal.
Further research is required to ascertain appropriate exercise modalities, frequency, intensity
and duration of PA needed to improve body composition and convey CV benefits in this
sector of the population. The consistent use of gold standard methodologies may go some way
towards identifying optimal exercise prescriptions. A compilation of specific studies used as
evidence for the previous sections are tabulated in Appendix I.
2.8 Summary

Research within the breast cancer rehabilitation field has identified a high incidence of cardiac dysfunction as a result of CT and/or RT treatment. The cardio-toxic effects are well documented, but little evidence is available on the impact of these cancer treatments on the health of the vascular system. What is known is that cancer treatments can initiate significant endothelial dysfunction by decreasing nitric oxide production and inducing endothelial apoptosis and pro-inflammatory cytokines which results in a chronic inflammatory state. This evidence stems from a limited number of human and animal studies showing chronic impairments in endothelium-dependent vasodilation, coronary stenosis, apoptosis and necrosis of smooth muscle cells and complete loss of vessel contraction with CT and/or RT. To date, only one study has examined the effect of CT on arterial stiffness, a measure of compliancy within the vascular system. This singular study showed that breast cancer patients treated with CT had increased PWV at baseline compared to age-matched healthy individuals and PWV increased further following treatment (Chaosuwannakit et al., 2010). Higher pulse wave velocity values are associated with greater arterial stiffness, suggesting that CT increases arterial stiffness in breast cancer patients.

Interventions in rodents have shown exercise to provide cardio-protection against CT-induced cardiac toxicity in rodent models and thus, exercise may also be effective in reducing endothelial dysfunction in breast cancer patients following treatment. Exercising for approximately 150-180 minutes at a moderate intensity has been suggested to reduce the risk of developing a second cancer, breast cancer-related and all-cause mortality in breast cancer survivors (Ibrahim & Al-Homaidh, 2011). However, no study to date has investigated whether a relationship occurs between PA status and CV health, more specifically arterial stiffness.
The additional adverse side-effects of treatments in breast cancer survivors include changes in body composition and cardiorespiratory fitness, specifically adverse changes in body tissue components and VO$_{2\text{max}}$. Exercise can attenuate these deleterious changes; however, there have been no studies to date that have identified whether cardiorespiratory fitness or body composition may moderate CV health in this population.

This proposed study is novel, as no previous studies have investigated whether PA status determines CV health, specifically measures of central blood pressure and arterial stiffness, in women previously treated with CT and/or RT for breast cancer. Further to this, no previous studies have examined whether cardiorespiratory fitness and/or body composition may moderate CV health following treatment. The null hypotheses proposed are:

- $H_0$ (i): There will be no difference in CV and body composition variables between AC and IA survivors.
- $H_0$ (ii): Cardiorespiratory fitness and/or body composition will not moderate CV health of breast cancer survivors.
Chapter 3: Methods

3.1 Study Design

The specific aims of this cross-sectional study were to investigate whether PA status determines CV health in women previously treated with CT and/or RT for breast cancer. A second aim was to investigate whether cardiorespiratory fitness and/or body composition moderate CV health. This type of study is useful when time constraints are present, providing both insight and the ability to make comparisons within a specific population with no follow up testing, less economic strain and greater participatory adherence in comparison to a longitudinal study (Mann, 2003). Further to this, when minimal information is known in a specific area, cross sectional studies are appropriate for providing a ‘snap shot’ to aid further in-depth investigation.

3.2 Participants

Women between the ages of 30 and 75 years and previously treated with CT and/or RT for breast cancer were recruited by advertisement in local newspapers, health centres, presentations made to cancer-related support groups and from the EXPINKT™ programme at the School of Physical Education, Sport and Exercise Sciences, University of Otago. Women undertaking ≥150 minutes of physical activity per-week comprised the active (AC) group; the majority of these participants were involved the EXPINKT™ programme. Inactive women were defined as those undertaking <90 minutes PA per-week. An information pack with a brief background of the study and consent form was then given to women who expressed interest and met the study’s inclusion criteria.

Ethical approval was obtained from the University of Otago Human Ethics Committee (13/023). Before any testing commenced, all women gave written consent and were advised of their right to withdraw from the study at any stage during the study period (Appendix A,
Appendix B). All participants completed an American Heart Association (AHA) medical screening form, an initial questionnaire consisting of basic demographic information, past exercise history and cancer treatment history. Women were excluded from participating if they had recurrent breast cancer, distant metastases, diagnosed unstable cardiovascular or peripheral vascular disease or diabetes mellitus, had surgery only for primary breast cancer or were currently taking medication that altered vascular function.

3.3 Sample size

Sample size calculations were computed using G*Power 3.1.3 (University of Kiel, Germany). To achieve a medium effect size ($F^2=0.25$) using 1 predictor variable (H1), with a power of 80% and alpha of 0.05, 34 participants were required. Forty-two participants were required to determine an $R^2$ increase with an additional predictor variable (H2), and 48 participants were required for two additional predictor variables (H3).

3.4 Outcome Measures

Arterial stiffness was measured using augmentation index (AIx), cardiovascular measures were assessed by both peripheral and central pressures (MAP, SBP, DBP and PP) and cardiovascular fitness estimated from a submaximal treadmill walking test. Body composition, total fat mass (kg), fat mass (%), and lean tissue mass (kg) were measured using dual X-ray absorptiometry (DXA). Physical activity levels were assessed with the IPAQ long form, which was validated in a subset of women using the SenseWear Pro Armband monitor (BodyMedia Body Monitoring System, Pittsburgh, PA). Additionally, participants completed the multidimensional fatigue inventory (MFI-20) questionnaire to assess fatigue levels.
3.4.1 Vascular Health

A pilot study was conducted to ensure the validity of Alx (%) measurements across both the small adult (A10) and adult (11L) cuffs. Due to the variation of arm circumference between participants, two blood pressure cuff sizes were tested on a group (n=11) of healthy women ranging from 20 to 57 years of age (26±10.6 years). Participants were asked to attend the validation assessment under the same standardised conditions specified for the present study. However, an additional two vascular assessments were taken using the adult long 11L cuff in order to calculate a correlation between the two sizes (Appendix H).

Pulse wave analysis was performed using the PulseCor R7 CardioScope (PulseCor, Auckland, New Zealand) to assess Alx (%) and cBP. PulseCor determines aortic Alx using pressure waves from the brachial artery. The oscillometric method is used, using a cuff on the upper arm and incorporates a POEM2 module (Welch Allyn, Skaneateles Falls, NY, USA), which complies with the Association for the Advancement of Medical Instrumentation (AAMI SP10) requirements and receives an A/A rating from the British Hypertension Society evaluation protocol. The PulseCor records brachial blood pressures (40 s each measurement cycle) and then one set of suprasystolic (approximately 30 mmHg > systolic pressure) recordings for 10s. The peripheral waveform generated from the brachial artery is then used to determine Alx. Greater arterial stiffness is associated with an early inflection point, with the pulse pressure (%) between the two points increased, giving a higher Alx (O'Rourke & Hashimoto, 2008). Although Alx is determined by local wave reflections at the brachial level, it is indicative of aortic stiffness. The following formula is used by PulseCor to calculate Alx (%):

\[
\text{Peripheral Alx} = \frac{\text{Late systolic pressure (P2)}}{\text{Early systolic pressure (P1)}}
\]

Standardised conditions (Stoner, Lambrick, Faulkner & Young, 2012b) were applied for this assessment in order to reduce and/or eliminate any factors that may affect blood
pressure and thus, impair Alx assessment (Appendix C). Pre-test requirements included; avoiding exercise 24 hours prior to the test, being in a fasted state, not to drink any other fluid apart from water, drink water liberally, not to take any dietary supplements and to refrain from smoking. The participant was asked to lie in a supine position for 20 minutes in a quiet, temperature controlled room (19.5-20.5°C) before measurements were taken (Stoner et al, 2012b). Breast cancer survivors are advised to have blood pressure taken from the arm on the non-involved side of the body, thus all measures were performed accordingly. Two measurements over a 5-minute interval were taken. If the two Alx measurements varied by >4% or blood pressures by >5 mmHg a third measurement was taken and the two closest recordings were averaged (Stoner et al, 2012b).

### 3.4.2 Cardiorespiratory Fitness

#### 3.4.2.1 Single-Stage Treadmill Walk Test

In order to estimate cardiovascular fitness (measured as VO$_2$max), a single-stage submaximal treadmill walking test (Ebbeling, Ward, Puleo, Widrick & Rippe, 1991) was performed. Age-predicted maximal HR was calculated using (220-age). Each participant’s target heart rate range was calculated between 50% and 70% of age-predicted maximum heart rate. The participant was fitted with a heart rate monitor (Polar FT1; Polar Electroly, Kemplele, Finland) and corresponding watch. The participant began walking at 0% gradient and was encouraged to select a comfortable walking speed between 3.2 and 7.2 km/hr that elicited a HR between 50-70% of their age predicted maximum after four minutes of walking. Speed, HR, gradient and rating of perceived exertion (RPE) using the OMNI scale (Robertson, 2004) was recorded every minute. After four minutes, speed remained constant and the gradient increased to 5%. The participant continued walking for another four minutes. HR and RPE were recorded at the end of the warm-up session and the first stage. The gradient was then reduced to 0% and the participant continued walking slowly to cool down. This test
is used in breast cancer survivors in the EXPINKT™ exercise clinic as it is a familiar mode of exercise and is of low intensity, making it tolerable for a wide range of ages and fitness levels. This submaximal test has been validated against maximal stress tests with gas spirometry reporting a strong correlation (Ebbeling et al., 1991; Waddoups, Wagner, Fallon & Health, 2008). The equation used to predict VO_{2max} for this test is:

\[
\text{Predicted VO}_{2\text{max}} (\text{ml.kg}^{-1}.\text{min}^{-1}) = 15.1 + (21.8*\text{speed (kph)}) – (0.327*\text{final HR (bpm)}) – (0.263*\text{speed*age (years)}) + (0.00504*\text{final HR*age}).
\]

Each participant used the same treadmill (Quinton Q65, Quinton Instrument Co, Seattle, WA) to ensure consistency of the results. A submaximal test was chosen for this specific population for safety reasons due to the strong level of evidence associating CT/RT treatments with high levels of cardiac toxicity. Maximal stress tests are not performed in high risk patients without 12-lead ECG monitoring with a cardiac physiologist present. A maximal stress test was outside the scope of this project.

### 3.4.2.2 OMNI scale

During exercise or physical activity of any form an individual’s perception of exertion is established based on the subjective intensity of effort, strain discomfort and/or fatigue of the task (Robertson & Noble, 1997). In many instances Borg’s modified rating of perceived exertion (RPE) scale is administered to assess how an individual perceives the intensity of the task (Borg, 1998). The effort continua developed by Borg aimed to equalise both the minimum and maximum levels of perceived exertion due to individual variation in physiological, psychological and physical activity history (Robertson, 2004). Although Borg’s RPE scale has been traditionally administered, the development and introduction of the OMNI picture system of perceived exertion has become a popular scale (Robertson, 2004). OMNI is an acronym for the word omnibus and refers to a category scale of perceived exertion applicable to a wide range of people in an exercise setting (Robertson, 2004). In addition to a numerical scale (0-10)
and short cues, pictures are combined to depict a gradual increase in exercise intensity (Robertson, 2004). The adult OMNI scale has been suggested to be more relevant in a clinical setting in order to guide the progression of graded exercise tests (Utter, Roberts, Green, Suminski, McAnulty & Nieman, 2004). The OMNI scale (r=0.91 to 0.95) was found to have greater reliability compared to Borg’s 15 point scale (r=0.64-0.78) in adolescent women performing a VO2max treadmill test (Pfeiffer, Pivarnik, Womack, Reeves & Malina, 2002). The OMNI scale of perceived exertion for walking to running in adults was chosen for this study as it has high reliability and validity in treadmill-based exercise tests due to linear increases between RPE and heart rate as well as RPE and VO2 (Utter et al., 2004). Given that many women recruited for this study were unlikely to be experienced in this type of testing, this scale was more likely to aid a participant’s ability to more accurately state RPE (Appendix E).

3.4.3 Body Composition

At visit one, participant’s height was measured using a stadiometer and body mass (kg) was measured using an electronic scale (InBody 230, Biospace, Inbody 230, Seoul, Korea). Body mass index was calculated using the standard height and weight equation, weight (kg) divided by height in metres squared (m²). At visit two, waist and hip circumference were measured, with waist circumference measured at the narrowest part of the trunk between the last rib and the anterior superior iliac spine, while hip circumference was measured at the widest part between the anterior superior iliac spine and the greater trochanter. Dual energy X-ray (DXA) absorptiometry was undertaken within a week of visit one to determine body composition; specifically total FM, LTM and percent body fat. This gold-standard procedure was undertaken by a trained technician at Dunedin Hospital using a Lunar Prodigy DXA scanner (Lunar Prodigy, Lunar Corporation, Madison, WI). This scanning procedure involved participants remaining still, lying in a supine position on the scanner table for approximately 10-20 minutes (Mazess, Barden, Bisek & Hanson, 1990). This procedure including participant positioning, scan protocols and scan analysis remained constant.
throughout the study. The procedure is safe, with a typical radiation dose 1/33rd that of a chest X-ray (Njeh, Fuerst, Hans, Blake & Genanat, 1999).

3.4.4 Physical Activity Levels

All participants were asked to complete the International Physical Activity Questionnaire (IPAQ) Long Form, recalling PA for the week following visit one (Appendix F). This internationally validated questionnaire was designed to comprehensively evaluate total and activity-specific daily PA (Maddison, Mhurchu, Jiang, Vander Hoorn, Rodgers & Lawes, 2007). Total metabolic equivalents minutes (MET-min) were taken as the sum of all recorded activities.

To validate the PA records, 12 participants (active n=8, inactive n=4) wore SenseWear Pro Armband monitors for a seven day period to equate that of the IPAQ recording. The SenseWear Pro Armband (BodyMedia Body Monitoring System, Pittsburgh, PA) is a portable, light weight device worn over the triceps area. This device records data from a 2-axis micro-electromechanical accelerometer that has been designed to improve energy expenditure (EE) predictions by integrating accelerometry with multiple physiologic sensors, including galvanic skin resistance, heat flux, body temperature and near-body ambient temperature (Sanjay 2007). Previous studies in healthy adults suggest this device has good reproducibility and accuracy in predicting resting and activity-related EE (Jakicic, Marcus, Gallagher, Randall, Thomas & Goss, 2004; St-Onge, Mignault, Allison, & Rabasa-Lhoret, 2007).

3.4.3 Fatigue Levels

All participants were asked to complete the MFI-20 written questionnaire (Appendix G) which contains 20 statements, covering different dimensions of fatigue including; general, physical and mental fatigue and reduced activity and motivation (Smets, Garssen, Cull & De Haes, 1996). Each fatigue dimension has four different indicative statements. Participants are asked to mark how they feel in relation to that question on a 1-5
scale. A higher score is indicative of more fatigue and each aspect of fatigue has a maximum score of 20. This scale was chosen for the present study as it has been documented that fatigue can remain for an extended period of time after the cessation of CT and RT (Berglund et al., 1991). Therefore, due to the cross-sectional study design some participants may be more or less affected by fatigue due to significant variations in the time since active treatment completion. This inventory has been validated in cancer patients receiving cancer therapy (Smets, Garssen, Bonke & De Haes, 1995 & Smets et al., 1996).
3.5 Data Collection Procedure

Visit One: School of Physical Education

- AM: Participant arrived under standardised conditions.
  - Interview:
    - Demographic info
    - Exercise History
    - Cancer/Medical history
    - AHA screening form
- Body composition:
  - Height
  - BIA analysis
- Vascular Health assessment (1)
- Vascular Health assessment (2)
- Vascular Health assessment (3)
- Single-stage submaximal walk test
- Explanation of IPAQ and MFI-20 Forms
- Breakfast, participants finished

Visit Two: Dunedin Hospital (performed within one week of visit one).

- Hip and waist measurements taken by DXA technician
- DXA scan performed
- Participant finished

20 min
20 min rest: lying supine
5 min
5 min
5 min
10 min
5 min
--- If needed ---
10 min
15-20 min
3.6 Statistical Analysis

All results were calculated using Statistical Package for the Social Sciences Software (SPSS Inc., version 21, Chicago, Illinois, USA). Independent samples t-tests with descriptive statistics were run to compare differences in physiological and psychological outcome variables between AC and IA study groups, with statistical significance accepted at p<0.05. Frequency statistics were generated using the cross-tabs command to report frequency [n(%)] of string variables. Additionally, absolute change and Cohen’s d effect size (ES) were calculated in Microsoft Excel (2010) to aid data analysis:

\[ dES = \frac{Mean(1) - Mean(2)}{SD(pooled)} \]

Pearson product moment correlation coefficients were undertaken to configure a coefficient correlation matrix between CV health variables and possible moderators of CV health. Linear regression analyses were conducted to evaluate the associations of FM (%) and cardiorespiratory fitness (\( \dot{VO}_{2\text{max}} \)) (independent variables) with systemic arterial stiffness (AIx) and myocardial efficiency (DP) (dependent variables) with and without adjustment age (covariate). Descriptive statistics were run and a correlation coefficient (r-value) was calculated to observe the correlation between IPAQ-Long Form and SenseWear Pro armband monitor in order to validate the use of the IPAQ Long-Form in breast cancers survivors. Both R\(^2\) and adjusted R\(^2\) values were reported for each linear regression model to show changes in variability as each predictor variable was added to the model.
Chapter 4: Results

4.1 Participant Characteristics

A total of 65 participants took part in this study, 44 who were considered active (≥150 minPA/wk) and 21 considered inactive (<90 minPA/wk). A significant difference in both body mass and BMI was observed between the AC and IA study groups (p<0.05). Most women were post-menopausal, and had been diagnosed with stage I-III cancers. Staging diagnoses were not available for five women in the AC group and for three women in the IA group. As a percentage, more women in the IA group were treated with CT in comparison to the AC group. Time since active treatment completion was similar between groups. Current hormonal therapy use was higher in the IA group, compared to the AC group, with standard hormonal therapies prescribed. Furthermore, a greater percentage of women in the IA group had completed hormonal treatment compared to the AC group.
Table 1. Demographic, diagnostic, and treatment-related data for active (n=44) vs. inactive (n=21) study groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active (n=44)</th>
<th>Inactive (n=21)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 10</td>
<td>58 ± 11</td>
<td>0.843</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.61 ± 0.07</td>
<td>1.61 ± 0.06</td>
<td>0.639</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.6 ± 13.5</td>
<td>75.9 ± 14.4</td>
<td><strong>0.049</strong></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>25.9 ± 4.4</td>
<td>29.3 ± 6.1</td>
<td><strong>0.013</strong></td>
</tr>
<tr>
<td>Weekly PA (min)</td>
<td>352 ± 259</td>
<td>75 ± 57</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Ethnicity [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>38 (86.4)</td>
<td>14 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>1 (2.3)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>European</td>
<td>2 (4.5)</td>
<td>3 (14.3)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (6.8)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Menopausal status [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>7 (15.9)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>37 (84.1)</td>
<td>19 (90.5)</td>
<td></td>
</tr>
<tr>
<td>Cancer stage [n(%)]</td>
<td>n=39</td>
<td>n=18</td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td>4 (10.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (25.6)</td>
<td>3 (16.7)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>15 (38.5)</td>
<td>11 (61.1)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>10 (25.6)</td>
<td>3 (16.7)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0 (0.0)</td>
<td>1 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Treatment type [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>44 (100)</td>
<td>21 (100)</td>
<td></td>
</tr>
<tr>
<td>Radiation Therapy</td>
<td>37 (84.1)</td>
<td>18 (85.7)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>30 (68.2)</td>
<td>19 (90.5)</td>
<td></td>
</tr>
<tr>
<td>Time since active treatment completion (years)</td>
<td>6.21 ± 5.77</td>
<td>4.53 ± 5.32</td>
<td>0.284</td>
</tr>
<tr>
<td>Hormonal Therapy current use [n(%)]</td>
<td>25 (56.8)</td>
<td>15 (75.0)</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>12 (48.0)</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Aromatase Inhibitor</td>
<td>3 (12.0)</td>
<td>6 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Herceptin</td>
<td>2 (8.0)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen + AI</td>
<td>6 (24.0)</td>
<td>2 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Herceptin + AI</td>
<td>1 (4.0)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Herceptin + Tamoxifen</td>
<td>1 (4.0)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Hormonal Therapy finished [n(%)]</td>
<td>2 (8.0)</td>
<td>14 (93.3)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: PA= Physical activity, DCIS= Ductal carcinoma in-situ, AI= Aromatase Inhibitor.
Eight women reported a comorbidity; secondary diagnosis of breast cancer n= 6, other secondary cancer n=2 or angina n=1. These participants were not excluded from the study due to the limited pool of breast cancer survivors within the Dunedin area willing to participate. Twenty five participants were using one or more cardiovascular medications (ACE inhibitor, beta-blocker, statin, Angio-II antagonist) and had been stably medicated (no change in dose or medication for > 6 months). More than half the participants in the IA group were on CV medications. The numbers of participants on other non-cardiovascular medications are also presented in Table 2.

Table 2. Chronic disease, cardiovascular medications and/or other medications in breast cancers survivors (n=65) previously treated with chemotherapy and/or radiation therapy.

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Active (n=44)</th>
<th>Inactive (n=21)</th>
<th>Total (n=65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Chronic disease</td>
<td>5(11.4)</td>
<td>3(14.3)</td>
<td>8(12.9)</td>
</tr>
<tr>
<td>Participants on CV medication</td>
<td>14(31.8)</td>
<td>11(52.4)</td>
<td>25(38.5)</td>
</tr>
<tr>
<td>Drug Class [n(%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>5(50.0)</td>
<td>5(50.0)</td>
<td>10</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>2(100.0)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Statin</td>
<td>7(58.3)</td>
<td>5(41.7)</td>
<td>12</td>
</tr>
<tr>
<td>Angio-II antagonist</td>
<td></td>
<td>1(100.0)</td>
<td>1</td>
</tr>
<tr>
<td>H2- antagonist</td>
<td>2(50.0)</td>
<td>2(50.0)</td>
<td>4</td>
</tr>
<tr>
<td>Ca2+ antagonist</td>
<td></td>
<td>1(100.0)</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4(66.7)</td>
<td>2(33.3)</td>
<td>6</td>
</tr>
<tr>
<td>Bone health</td>
<td>1(50.0)</td>
<td>1(50.0)</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid hormone</td>
<td>4(50.0)</td>
<td>4(50.0)</td>
<td>8</td>
</tr>
<tr>
<td>Anti-Depressant</td>
<td>4(44.4)</td>
<td>5(55.6)</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>4(66.7)</td>
<td>2(33.3)</td>
<td>6</td>
</tr>
</tbody>
</table>

NOTE: CV= Cardiovascular, ACE= Angiotensin-converting-enzyme, Angio-II= Angiotensin-II, H2= Histamine2, Ca2+= Calcium
4.2 Cardiorespiratory Fitness & Vascular Assessment

There was no significant difference in cardiorespiratory fitness, calculated as predicted
\( \dot{V}O_{2\text{max}} \) or end HR between the two study groups (p>0.05) (Table 3). However, end RPE was
significantly lower in AC participants (p<0.05). Due to safety concerns, three participants did
not perform or complete the submaximal treadmill walking test (AC=1, IA =2). In relation to
peripheral vascular assessment variables, a statistical significance was found for MAP, DBP
and PR with a large effect noted between the two groups (p<0.05) (Table 3). Systolic blood
pressure was also found to be significantly different and a medium effect size between the
groups (p<0.05) (Table 3). There was no difference in PP between study groups (p>0.05)
(Table 3). Central vascular assessment variables (Table 3) were significant and showed large
effect sizes between the groups for cSBP and cDBP (p<0.05). No statistical significance
between the AC and IA groups was observed for AIx (%) or cPP (p>0.05) (Table 3).
Table 3. Predicted cardiorespiratory fitness, peripheral and central vascular assessment variables of 65 breast cancer survivors categorised as active (n=44) or inactive (n=21) and previously treated with chemotherapy and/or radiation therapy assessed by PulseCor R7 CardioScope; Mean (SD), Pearson’s correlation and Cohen’s-d effect size.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active (n=44)</th>
<th>Inactive (n=21)</th>
<th>p-value</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiorespiratory Fitness (AC=43,IA=19)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted VO₂max (ml.kg⁻¹.min⁻¹)</td>
<td>30.3 (4.7)</td>
<td>29.3 (5.8)</td>
<td>0.480</td>
<td>0.2</td>
</tr>
<tr>
<td>End HR (bpm)</td>
<td>125 (16)</td>
<td>126 (14)</td>
<td>0.747</td>
<td>0.1</td>
</tr>
<tr>
<td>End RPE</td>
<td>5 (2)</td>
<td>6 (2)</td>
<td><strong>0.049</strong></td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Peripheral Vascular Assessment (n=65)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>86 (7)</td>
<td>93 (9)</td>
<td><strong>0.001</strong></td>
<td>-0.9</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>116 (12)</td>
<td>124 (13)</td>
<td><strong>0.015</strong></td>
<td>-0.6</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>71 (6)</td>
<td>78 (7)</td>
<td><strong>0.000</strong></td>
<td>-1.1</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>45 (8)</td>
<td>47 (8)</td>
<td>0.481</td>
<td>-0.3</td>
</tr>
<tr>
<td>PR (bpm)</td>
<td>60 (8)</td>
<td>66 (8)</td>
<td><strong>0.005</strong></td>
<td>-0.8</td>
</tr>
<tr>
<td><strong>Central Vascular Assessment (n=65)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIx (%)</td>
<td>100 (36)</td>
<td>96 (43)</td>
<td>0.659</td>
<td>0.1</td>
</tr>
<tr>
<td>cSBP (mmHg)</td>
<td>111 (12)</td>
<td>120 (13)</td>
<td><strong>0.012</strong></td>
<td>-0.8</td>
</tr>
<tr>
<td>cDBP (mmHg)</td>
<td>72 (6)</td>
<td>79 (7)</td>
<td><strong>0.000</strong></td>
<td>-1.1</td>
</tr>
<tr>
<td>cPP (mmHg)</td>
<td>39 (7)</td>
<td>41 (7)</td>
<td>0.423</td>
<td>-0.3</td>
</tr>
</tbody>
</table>

**NOTE:** AC= Active, IA= Inactive, HR= Heart rate, RPE= Rating of perceived exertion, MAP= Mean arterial pressure, SBP= Systolic blood pressure, DBP= Diastolic Blood Pressure, PP= Pulse pressure, PR= Pulse rate, AIx= Augmentation index, cSBP= Central systolic blood pressure, cDBP= Central diastolic blood pressure, cPP= Central pulse pressure.
4.3 Body Composition & Physical Activity

Dual-energy X-ray absorptiometry (DXA) results showed statistical significance (p<0.05) between the groups for FM (kg) and FM%, with a Cohen’s $d$ indicating a medium effect however LTM did not differ (p>0.05) between AC and IA study groups (Table 4). Waist circumference was significantly smaller in AC participants (p<0.05) however, WHR did not differ between groups. One IA participant failed to return the IPAQ long-form. Results from the IPAQ showed no significance difference between groups in weekly walking, moderate, or vigorous intensity MET-minutes, or overall weekly MET-minutes, nor was there a noticeable difference in the percent of participants categorised as having either a low, moderate, or high PA levels (p>0.05) (Table 4). However, when recreational PA was assessed independently, there was a statistical difference and a medium or large effect size between the groups for weekly walking, moderate intensity PA, and total weekly recreational MET-minutes (p<0.05) (Table 4). Weekly vigorous intensity, recreationally-focused PA approached significance and had a moderate Cohen’s $d$ (Table 4).
Table 4. Body composition assessed by dual-energy x-ray absorptiometry and physical activity data based on the International Physical Activity Questionnaire Long-Form (IPAQ) in 65 breast cancer survivors categorised as active (n=44) or inactive (n=21) and previously treated with chemotherapy and/or radiation therapy; Mean (SD) and IPAQ category [n(%)].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active (n=44)</th>
<th>Inactive (n=21)</th>
<th>p-value</th>
<th>ES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Composition (DXA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WC (cm) (AC=43, IA=21)</td>
<td>87.4 (12.7)</td>
<td>95.2 (15.0)</td>
<td>0.034</td>
<td>0.5</td>
</tr>
<tr>
<td>WHR (m)</td>
<td>0.86 (0.11)</td>
<td>0.84 (0.01)</td>
<td>0.342</td>
<td>0.3</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>25.66 (9.5)</td>
<td>32.13 (10.68)</td>
<td>0.016</td>
<td>-0.6</td>
</tr>
<tr>
<td>FM (%)</td>
<td>36.40 (8.19)</td>
<td>41.58 (7.33)</td>
<td>0.016</td>
<td>-0.7</td>
</tr>
<tr>
<td>LTM (kg)</td>
<td>40.27 (5.74)</td>
<td>40.65 (4.96)</td>
<td>0.795</td>
<td>-0.1</td>
</tr>
<tr>
<td><strong>IPAQ Total PA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=44</td>
<td>n=20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly walking (MET-min)</td>
<td>1867 (1581)</td>
<td>1207 (1455)</td>
<td>0.188</td>
<td>0.4</td>
</tr>
<tr>
<td>Weekly moderate PA (MET-min)</td>
<td>2560 (2185)</td>
<td>3707 (4064)</td>
<td>0.247</td>
<td>-0.4</td>
</tr>
<tr>
<td>Weekly vigorous PA (MET-min)</td>
<td>1211 (1956)</td>
<td>1220 (2674)</td>
<td>0.988</td>
<td>0.0</td>
</tr>
<tr>
<td>Total Weekly PA (MET-min)</td>
<td>5638 (4205)</td>
<td>6134 (6795)</td>
<td>0.722</td>
<td>-0.1</td>
</tr>
<tr>
<td><strong>IPAQ PA Level Categories [n(%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2 (4.5)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14 (31.8)</td>
<td>7 (35.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>28 (63.6)</td>
<td>13 (65.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IPAQ Rec PA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly walking (MET-min)</td>
<td>697 (682)</td>
<td>247 (200)</td>
<td>0.000</td>
<td>0.9</td>
</tr>
<tr>
<td>Weekly moderate PA (MET-min)</td>
<td>311 (483)</td>
<td>84 (179)</td>
<td>0.008</td>
<td>0.6</td>
</tr>
<tr>
<td>Weekly vigorous PA (MET-min)</td>
<td>692 (1294)</td>
<td>260 (482)</td>
<td>0.057</td>
<td>0.4</td>
</tr>
<tr>
<td>Total Weekly Rec PA (MET-min)</td>
<td>1700 (1601)</td>
<td>592 (576)</td>
<td>0.000</td>
<td>0.9</td>
</tr>
</tbody>
</table>

NOTE: DXA= Dual-energy x-ray absorptiometry, WHR= Waist- to hip- ratio, FM= Fat mass, LTM= Lean tissue mass, IPAQ= International physical activity questionnaire, PA= Physical Activity, MET-min= Metabolic equivalent minutes, Rec= Recreational.
4.4 Correlation and regression analyses of central vascular measures with determinants of vascular health

Pearson’s product-moment correlation coefficient (r-value) matrix indicated a number of correlations between vascular/cardiovascular outcome measures and possible determinants of CV health (Table 5). Maximal oxygen consumption ($\dot{V}O_{2\text{max}}$) was inversely correlated with arterial stiffness (AIx) ($p<0.05$) and age ($p<0.01$) (Table 5). Fat mass was also found to be positively correlated with waist circumference, cSBP and DP ($p<0.01$) however, PA level was not correlated with any cardiovascular/vascular variables (Table 5).
Table 5. Pearson’s product-moment correlation coefficient (r-value) matrix between cardiovascular measures (PR, CSBP, DP, AIx) and possible determinants of cardiovascular health (Age, PA, predicted VO₂max, FM, WC) in 62 breast cancer survivors previously treated with chemotherapy and/or radiation therapy.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>PA</th>
<th>VO₂max</th>
<th>FM</th>
<th>WC</th>
<th>PR</th>
<th>cSBP</th>
<th>DP</th>
<th>AIx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>-0.239</td>
<td>-0.717**</td>
<td>0.135</td>
<td>0.192</td>
<td>0.110</td>
<td>0.382**</td>
<td>0.295*</td>
<td>0.457**</td>
</tr>
<tr>
<td>PA</td>
<td>-0.239</td>
<td></td>
<td>0.063</td>
<td>-0.179</td>
<td>0.019</td>
<td>-0.047</td>
<td>-0.055</td>
<td>-0.068</td>
<td>-0.139</td>
</tr>
<tr>
<td>VO₂max</td>
<td>-0.717**</td>
<td>0.063</td>
<td></td>
<td>-0.038</td>
<td>-0.100</td>
<td>-0.200</td>
<td>-0.217</td>
<td>-0.248</td>
<td>-0.291*</td>
</tr>
<tr>
<td>FM</td>
<td>0.135</td>
<td>-0.179</td>
<td>-0.038</td>
<td></td>
<td>0.757**</td>
<td>0.132</td>
<td>0.337**</td>
<td>0.329**</td>
<td>0.087</td>
</tr>
<tr>
<td>WC</td>
<td>0.192</td>
<td>0.019</td>
<td>-0.100</td>
<td>0.757**</td>
<td></td>
<td>0.133</td>
<td>0.316*</td>
<td>0.301*</td>
<td>0.059</td>
</tr>
<tr>
<td>PR</td>
<td>0.110</td>
<td>-0.047</td>
<td>-0.200</td>
<td>0.132</td>
<td>0.133</td>
<td></td>
<td>0.059</td>
<td>0.791**</td>
<td>-0.267*</td>
</tr>
<tr>
<td>cSBP</td>
<td>0.382**</td>
<td>-0.055</td>
<td>-0.217</td>
<td>0.337**</td>
<td>0.316*</td>
<td>0.059</td>
<td></td>
<td>0.649**</td>
<td>0.506**</td>
</tr>
<tr>
<td>DP</td>
<td>0.295*</td>
<td>-0.068</td>
<td>-0.248</td>
<td>0.329**</td>
<td>0.301*</td>
<td>0.791**</td>
<td>0.649**</td>
<td></td>
<td>0.092</td>
</tr>
<tr>
<td>AIx</td>
<td>0.457**</td>
<td>-0.139</td>
<td>-0.291*</td>
<td>0.087</td>
<td>0.059</td>
<td>-0.267*</td>
<td>0.506**</td>
<td>0.092</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: PA= Physical Activity, VO₂max= Maximal oxygen consumption, FM= Fat mass, WC= Waist circumference, PR= Pulse rate, cSBP= Central systolic blood pressure, DP= Double product, AIx= Augmentation Index.

* Correlation is significant at the **0.05** level (2-tailed).

** Correlation is significant at the **0.01** level (2-tailed).
Linear regression analyses were conducted to evaluate the associations of FM (%) and cardiorespiratory fitness ($\bar{VO}_2\text{max}$) (independent variables) with systemic arterial stiffness (AIx) and myocardial efficiency (DP) (dependent variables) with and without adjustment age (covariate). Cardiorespiratory fitness was found to predict AIx (%) independent of FM (%) ($R^2=0.090$, adjusted $R^2=0.060$), but not after co-varying for age ($R^2=0.212$, adjusted $R^2=0.171$) (Table 6). However, FM (%) did not predict AIx (%) (Table 7). In relation to myocardial efficiency, $\bar{VO}_2\text{max}$ was closely associated with DP independently of FM (%) ($R^2=0.164$, adjusted $R^2=0.052$), however not after adjusting for age ($R^2=0.179$, adjusted $R^2=0.136$) (Table 8). Fat mass (%) does predict DP, even after adjustment for both $\bar{VO}_2\text{max}$ and age ($R^2=0.179$, adjusted $R^2=0.136$) (Table 9).

### Table 6. Linear regression models: associations between $\bar{VO}_2\text{max}$ and AIx.

<table>
<thead>
<tr>
<th>Outcome variable: AIx</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>$p$</th>
<th>$R^2$</th>
<th>Adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: unadjusted</td>
<td>-2.414</td>
<td>1.024</td>
<td>-0.291</td>
<td>0.022</td>
<td>0.085</td>
<td>0.069</td>
</tr>
<tr>
<td>Model 2: adjusted FM</td>
<td>-2.390</td>
<td>1.031</td>
<td>-0.288</td>
<td>0.024</td>
<td>0.090</td>
<td>0.060</td>
</tr>
<tr>
<td>Model 3: adjusted FM + Age</td>
<td>0.600</td>
<td>1.392</td>
<td>0.072</td>
<td>0.668</td>
<td>0.212</td>
<td>0.171</td>
</tr>
</tbody>
</table>

B = unstandardized coefficient; beta = standardized coefficient (i.e., variance = 1)

### Table 7. Linear regression models: associations between FM% and AIx.

<table>
<thead>
<tr>
<th>Outcome variable: AIx</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>$p$</th>
<th>$R^2$</th>
<th>Adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: unadjusted</td>
<td>0.449</td>
<td>0.665</td>
<td>0.087</td>
<td>0.502</td>
<td>0.008</td>
<td>-0.009</td>
</tr>
<tr>
<td>Model 2: adjusted $\bar{VO}_2\text{max}$</td>
<td>0.393</td>
<td>0.642</td>
<td>0.076</td>
<td>0.543</td>
<td>0.090</td>
<td>0.060</td>
</tr>
<tr>
<td>Model 3: adjusted $\bar{VO}_2\text{max}$ + Age</td>
<td>0.112</td>
<td>0.610</td>
<td>0.022</td>
<td>0.855</td>
<td>0.212</td>
<td>0.171</td>
</tr>
</tbody>
</table>

B = unstandardized coefficient; beta = standardized coefficient (i.e., variance = 1)
Table 8. Linear regression models: associations between $\dot{V}O_2\text{max}$ and DP.

<table>
<thead>
<tr>
<th>Outcome variable: DP</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>p</th>
<th>$R^2$</th>
<th>Adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: unadjusted</td>
<td>-63.9</td>
<td>32.2</td>
<td>-0.248</td>
<td>0.052</td>
<td>0.062</td>
<td>0.052</td>
</tr>
<tr>
<td>Model 2: adjusted FM</td>
<td>-60.8</td>
<td>30.7</td>
<td>-0.236</td>
<td>0.052</td>
<td>0.164</td>
<td>0.052</td>
</tr>
<tr>
<td>Model 3: adjusted FM + Age</td>
<td>-28.7</td>
<td>44.1</td>
<td>-0.111</td>
<td>0.518</td>
<td>0.179</td>
<td>0.136</td>
</tr>
</tbody>
</table>

B = unstandardized coefficient; beta = standardized coefficient (i.e., variance = 1)

Table 9. Linear regression models: associations between FM% and DP.

<table>
<thead>
<tr>
<th>Outcome variable: DP</th>
<th>B</th>
<th>SE</th>
<th>Beta</th>
<th>p</th>
<th>$R^2$</th>
<th>Adj. $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: unadjusted</td>
<td>52.9</td>
<td>19.6</td>
<td>0.329</td>
<td>0.009</td>
<td>0.109</td>
<td>0.094</td>
</tr>
<tr>
<td>Model 2: adjusted $\dot{V}O_2\text{max}$</td>
<td>51.4</td>
<td>19.1</td>
<td>0.320</td>
<td>0.009</td>
<td>0.164</td>
<td>0.136</td>
</tr>
<tr>
<td>Model 3: adjusted $\dot{V}O_2\text{max}$ + Age</td>
<td>48.4</td>
<td>19.3</td>
<td>0.302</td>
<td>0.015</td>
<td>0.179</td>
<td>0.136</td>
</tr>
</tbody>
</table>

B = unstandardized coefficient; beta = standardized coefficient (i.e., variance = 1)

4.5 Multidimensional Fatigue Inventory

There was no significant difference found across any of the fatigue dimensions between AC and IA study groups ($p>0.05$) (Table 10). One IA participant’s inventory was not returned.

Table 10. Multidimensional Fatigue Inventory scores (Mean±SD) of 64 breast cancer survivors, categorised as active (n=44) or inactive (n=20) and previously treated with chemotherapy and/or radiation therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active (n=44)</th>
<th>Inactive (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Fatigue (1-20)</td>
<td>11 ± 3</td>
<td>12 ± 4</td>
<td>0.146</td>
</tr>
<tr>
<td>Physical Fatigue (1-20)</td>
<td>10 ± 3</td>
<td>11 ± 4</td>
<td>0.125</td>
</tr>
<tr>
<td>Reduced Activity (1-20)</td>
<td>9 ± 3</td>
<td>10 ± 3</td>
<td>0.235</td>
</tr>
<tr>
<td>Reduced Motivation (1-20)</td>
<td>8 ± 2</td>
<td>9 ± 3</td>
<td>0.505</td>
</tr>
<tr>
<td>Mental Fatigue (1-20)</td>
<td>10 ± 4</td>
<td>10 ± 4</td>
<td>0.923</td>
</tr>
</tbody>
</table>
Breast cancer is the most commonly diagnosed cancer in women; however, improved diagnosis and treatment have led to very favourable 5 year survival rates. While impressive, the biggest cause for concern in recent years has been the appearance of adverse cardiac-related side-effects induced by active treatments (CT/RT). Both CT and RT can significantly affect normal CV functioning, increasing the risk of developing CVD. Prior to CVD, the normal pathological process includes increased arterial stiffness, along with raised blood pressures, particularly cBP. While recent advancements have enabled simple assessments of arterial stiffness and cBP, there is a paucity of data examining associations between CT/RT and these important parameters.

Therefore, the purpose of this study was to provide insight into CV health of breast cancer survivors previously treated with CT and/or RT, based on PA status. Specific aims were to investigate whether PA status determines cBP’s and arterial stiffness within this population. A second aim was to investigate whether cardiorespiratory fitness and/or body composition may moderate CV health following these treatments. It was hypothesised that:

The main finding of this study was that AC breast cancer survivors had significantly lower cBP measures compared to IA survivors; however, arterial stiffness was similar between groups and fell within normal ranges for the device. Additionally, AC breast cancer survivors had lower FM in comparison to their less active counterparts. Linear regression models showed $\dot{V}O_{2\text{max}}$ was a predictor of arterial stiffness (AIx %) and approached significance with myocardial efficiency (DP); however, the association between $\dot{V}O_{2\text{max}}$ and AIx became non-significant after adjusting for age. Fat mass (%) was found to be an important moderator of DP not AIx, even after adjusting for both age and $\dot{V}O_{2\text{max}}$. 

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5.1 Central Blood Pressures

Recent emerging research on cBP has been primarily on the degree of difference between peripheral and cBP values, as well as the validity of cBP in estimating CV health, mortality and risk in healthy individuals, hypertensive and CVD patients (Roman et al., 2007; Wang et al., 2009; Vlachopoulos et al., 2010; Sharman et al., 2013). This is the first study to report not only cBP values in breast cancer survivors, but also the association between recreational PA levels and cBP within this population. On average the AC group had an 8% lower cSBP and 10% lower cDBP than the IA group. These results show that breast cancer survivors who perform >150 minutes per week of recreational PA following CT and/or RT have lower cBP in comparison to IA survivors. This same reduction in blood pressure is shown in healthy individuals that go from a sedentary to active lifestyle (Fagard & Tipton, 1994). Blood pressure decreases with regular PA due to a combination of neurohumoral and structural adaptations as well as alterations to vascular responsiveness (Pescatello, Franklin, Fagard, Farquhar, Kelley & Ray, 2004). Neurohumoral changes include; a decrease in sympathetic nervous system activity which reduces vaso-constrictive substance release (norepinephrine, renin, angiotensin II) and thereby decreases vascular resistance (Pescatello et al., 2004). Structural adaptations include; greater strength of the heart muscle allowing for a greater force of contraction (George, Wolfe & Burggraf, 1991), an increase in artery lumen diameter, distensibility and angiogenesis (Pescatello et al., 2004). Structural adaptations improve pumping efficiency of the heart, by decreasing resting heart rate which allows for an increased filling time during diastole, increased stroke volume and consequently increased cardiac output (Green, Jones & Painter, 1990). Vascular responsiveness improves by an increase in vasoactive substance release such as nitric oxide which causes vasodilation of the artery and therefore lowers blood pressure (Pescatello et al., 2004). Since, breast cancer survivors are deemed as high risk individuals for developing cardiac dysfunction, these results
are of great importance, as they suggest PA may be effective within this population at decreasing or reducing an increase in cBP following CT and/or RT.

With previous studies primarily examining cBP in healthy individuals and individuals with hypertension and CAD (Jankowski, Kawecka-Jaszcz, Bryniarski, Czarnecka, Brzozowska-Kiszka & Posnik-Urbanska, 2004; Weber et al., 2004; Sharman et al., 2013) it is difficult to compare cBP results reported in the current study; however, we are able to gauge where AC breast cancer survivors sit in relation to a healthy individuals or individuals with CAD. In previous research by McEniery, Yasmin, Hall, Qasem, Wilkinson & Cockcroft (2005), differences in aortic SBP between genders and across age were examined, with healthy females aged 50-59 years having an average cSBP of 115±11 mmHg and a cPP of 38±8 mmHg. In comparison, AC women in the current study had a slightly lower average cSBP (111 mmHg) with IA participants having a slightly higher cSBP at 120 mmHg. The mean cPP of 39 mmHg versus 41 mmHg in the AC and IA groups, respectively in the current study was similar to the McEniery et al. (2005) study, suggesting that both AC and IA breast cancer survivors in this current study had ‘healthy or normal’ cBP.

It is possible that central indices may be a particularly beneficial, reliable and a non-invasive method at monitoring changes in CV health in high risk patients, such as cancer survivors. Results from this study suggest that healthy cBP measures can be achieved by breast cancer survivors who meet the recommended physical activity guidelines of ≥150 minutes per week. No previous literature has examined cBP differences within this population, nor investigated the possible effect on CV health of performing higher levels of PA following active treatment.
5.2 Arterial Stiffness

Chemotherapy agents and RT are renowned for causing high levels of cardiac toxicity, specifically arterial vascular damage (Beckman et al., 2001; Murata et al., 2001a; Murata, et al., 2001b; Bentzen, 2006; Curigliano et al., 2010; Vassilakopoulou et al., 2010; Stewart, Hoving & Russell, 2010; Mulrooney & Duprez, 2012; Eckman et al., 2013; Gajalakshmi et al., 2013), resulting in increased vascular stiffening (Chaosuwannakit et al., 2010). Although the ability of PA to attenuate treatment-induced arterial stiffness has not been examined previously in cancer survivors, PA has been identified as an effective secondary preventative measure for improving endothelial dysfunction in CAD patients (Savage et al., 2000; Hambrecht et al., 2003; Schairer et al., 2003). In the present study PA level was not found to be associated with arterial stiffness. There was no difference in AIx (%) between AC and IA breast cancer survivors. However, regression analysis did show cardiorespiratory fitness to predict AIx (%) independent of FM (%), with cardiorespiratory fitness recognised as a more reliable indicator of fitness than self-report PA.

It is impossible to determine why arterial stiffness was similar between study groups due to the limitations of a cross sectional study. Although speculative it is possible that time since active treatment completion, minimum ACSM exercise guidelines and/or PA recall independently or in combination played a role as to why AIx (%) was similar between AC and IA survivors. In brief, the long time frame since active treatment completion potentially confounded arterial stiffness results (AC: 6.21±5.77 vs IA: 4.53±5.32 years) as this cross-sectional study did not allow investigation of PA patterns before, during, or immediately after treatment. Commonly, when sedentary individuals begin performing PA functional changes in the first 6 months precede structural adaptations to arterial vasculature (Gokce et al., 2002; Walsh et al., 2003; Tinken, Thijssen, Black, Cable & Green, 2008; Luk et al., 2009; Shantsila & Lip; 2009). If the level of PA does not continue to increase over time a plateau effect occurs due to familiarity of the same exercise stimulus, with physiological adaptations often
stabilising or decreasing (Tinken et al., 2008). Because of this, it is possible that any exercise-induced improvements in arterial stiffness may have been missed if survivors were previously inactive before diagnosis. Equally, it must be noted that cardiac dysfunction in breast cancer survivor appears predominantly 10-15 years following treatment cessation (Lancellotti et al., 2013). Therefore, it is possible that the considerable amount of time since active treatment completion in both groups may not be an issue, although this cannot be validated as a baseline vascular health assessment was not undertaken before treatment started. Future studies could assess arterial stiffness prior to treatment induction and again immediately following active treatment cessation, with follow up assessments undertaken to determine the true effects of PA on arterial stiffness.

Few studies have used the PulseCor to assess arterial stiffness, with the SphygomoCor device commonly used. The SphygomoCor determines AIx (%) by a different means to PulseCor; however, validation studies show accepted limits for the PulseCor device (Stoner, Lambrick, Westrupp, Young & Faulkner, 2014). PulseCor developers have released a vascular age chart for both men and women, based on AIx (%) values obtained from PulseCor which indicates women in the current study should have an AIx (%) of approximately 80 (PulseCor, 2011). However, average AIx (%) for the AC group was 100 % with IA survivors at 96 %. Based on the average AIx (%) values of survivors in the current study they have a vascular age of between 68 and 72 years, which is much higher than the average biological age of participants; however, AIx (%) values are still within the normal range for their age. Comparatively, studies using SphygomoCor to assess arterial stiffness report much lower AIx (%) (Yasmin & Brown, 1999; McEniery, Wallace, Mackenzie, McDonnell, Newby & Cockcroft, 2006). It is difficult to comment on the degree of arterial stiffness of participants due to the lack of prior studies using PulseCor.
American College of Sports Medicine guidelines were used in the present study to categorise participants as either AC or IA as they are generally used by health professionals to guide exercise prescription for specific populations. ACSM guidelines recommend a minimum 150 minutes of moderate-intensity activity or 75 minutes of vigorous aerobic activity a week (Schmitz et al., 2010) equating to an energy expenditure between 500-1000 MET-minutes a week (Garber et al., 2011). Although this amount of PA has been shown to be sufficient in reducing the risk of developing CVD in healthy, elderly women (Lee et al., 2001) cardiac rehabilitation research is suggestive that much higher energy expenditures are needed (Hambrecht et al., 1993). Physical activity data in the current study, assessed by the IPAQ Long-Form calculated an average weekly recreational MET-min of 1700±1601 for AC participants and 592±576 for IA participants. Although AC participant’s average weekly recreational MET-min were significantly higher than the 500-1000 MET-min suggested, arterial stiffness and cardiorespiratory results did not reflect a benefit. These findings may indicate that exercise guidelines suggested by ACSM for a cancer survivor only provide a minimal exercise stimulus and are not sufficient to attenuate active treatment-induced vascular dysfunction or recover and/or increase a decline in $\dot{V}O_2_{max}$ potentiated by treatment.

Further to this, it is likely that participants both under- and over-estimated PA they performed. Participants were categorised at visit one as AC or IA based on self-reported PA they performed in the previous 7-days to visit one, or a ‘regular’ week if the week prior was unusual. Total minutes were summed to classify as AC ≥150 minutes of PA or IA <90 minutes of PA per week. Although the recreational PA section of the IPAQ Long-Form validates the information given for correct categorisation in visit one it must be noted that there is high variability in PA data. Although, average recreational MET-min were significantly higher in AC survivors, total weekly MET-min were similar between groups.

While an international, validated questionnaire was used in the study, like all questionnaires there is a number of validation issues connected to the self-reporting of PA. Self-reporting PA
questionnaires often lead to the under or over estimation of PA energy expenditure, due primarily to the pressure of participants wanting to give socially desirable answers, poor memory recall and/or as the inability of individuals to accurately classify exact exercise intensity (Shephard, 2003 & Prince, Adamo, Hamel, Hardt, Gorber, & Tremblay, 2008).

Arterial stiffness results in the current study showed that although AC breast cancer survivors reported significantly higher total weekly recreational PA they had similar arterial stiffness to IA participants. There are a number of factors (time since active treatment completion, minimum ACSM exercise guidelines and/or PA recall) that may have confounded the results and it is impossible to identify the exact cause based on study design.

5.3 Cardiovascular Health Moderators

5.3.1 Body Composition

There is strong evidence that FM significantly increases during and following CT and RT treatments in breast cancer survivors (Heasman et al., 1985; Demark-Wahnefried, Winer, & Rimer, 1993; Cheney, Mahlock & Freeny, 1997; Aslani et al., 1999; Kutynec et al., 1999; Demark-Wahnefried et al., 2001; Freedman et al., 2004; Harvie et al., 2004; Campbell et al., 2007). Results from this study suggest that higher levels of recreational PA are important for reducing increases in FM and improving myocardial efficiency, but not arterial stiffness in breast cancer survivors following CT and/or RT. The study found that AC breast cancer survivors on average had 12 % less FM than IA survivors. When FM (%) was then used as a covariate in regression models it was not associated with arterial stiffness, but was associated with DP even after adjustment for age and \( \dot{V}O_{2\text{max}} \).

Undesirable weight gains of 2.5-6.2 kg have been reported to occur in 50-96% of women undergoing or following CT and/or RT, increasing the risk of developing obesity.
related morbidities such as HTN and CAD (Brown, Brauner & Minnotte, 1993). Additionally, the association between postmenopausal women and centrally-located FM, places breast cancer patients at higher risk of developing metabolic complications, such as insulin resistance, diabetes mellitus, which are considered risk factors for CVD, due to the higher incidence of breast cancer in older women (Despres et al., 1990; Rossi et al., 2002). Centrally-located FM, particularly the visceral compartment, has been shown to be more detrimental to CV health and overall CV risk than peripheral located FM (Fantuzzi & Mazzone, 2007). Therefore, the combination of treatment-induced weight gain and FM increases induced by menopause can contribute to cardiac dysfunction, and more specifically unfavourable arterial changes (Ferreira et al., 2004); hence, the importance of maintaining appropriate body composition.

Body composition and anthropometric results suggest PA may be effective at reducing this CV risk and CVD development because AC survivors had significantly lower FM (%) and waist circumferences compared to IA survivors. Although FM (%) did not predict arterial stiffness, its prediction of DP, a strong indicator of myocardial efficiency was significant. Double product is a clinically recognized index of myocardial oxygen consumption, indicating the response of the coronary circulation to myocardial metabolic demands (Govindaraju & Mital, 1997). This same association has been reported previously in obese females, reporting significantly higher DP than characteristically matched non-obese women (Peterson, Herrero, Schechtman, Kenneth, Racette & Waggoner, 2004). It is believed resting DP increases with increasing FM due to an accumulation of fatty acids, resulting in increased oxidative stress, myocardial injury and cardiomyocyte apoptosis (Unger, 2002) therefore, reducing myocardial efficiency and increasing oxygen demands of the heart.

Previous studies examining the ability of breast cancer survivors to reduce FM and increase LTM by performing PA following CT and/or RT have shown mixed results. Higher
levels of both aerobic- and resistance-based recreational PA have only been shown to be effective at reducing FM within this population in two known studies (Schmitz et al., 2005; Irwin et al., 2009). Although FM was lower in AC participants in the current study, LTM was similar between the study groups. This result was somewhat expected due to confounding results in previous literature reporting significantly increased LTM when breast cancer survivors performed higher levels of aerobic (Irwin et al., 2009) or resistance-based recreational PA (Schmitz et al., 2005) or no change in LTM with aerobic- based recreational PA (Pinto et al., 2005; Courneya et al., 2007; Matthew et al., 2007). Generally in healthy individuals, resistance training is used to increase LTM, while aerobic training is used to reduce FM. These opposing adaptations occur due to the activation and use of specific substrates between energy systems (McArdle, Katch & Katch, 2010). A number of participants attended a formal exercise programme that includes resistance exercises, but not of a heavy workload. Therefore, it is possible that the primary aerobic exercise performed by AC survivors is responsible for significantly lower FM.

Results suggest that breast cancer survivors that maintain PA from diagnosis or are active following CT and/or RT may be able to prevent increases in total FM (%), which was identified as a potential moderator of myocardial efficiency, and therefore CV health within this population. The potential ability to lessen a decline in myocardial efficiency potentiated by CT and/or RT is important due to the strong body of literature that reports both acute and chronic cardiac dysfunction during and following CT and RT.

5.3.2 Cardiorespiratory Fitness

Active survivors had a small 1.0 ml.kg$^{-1}$.min$^{-1}$ higher maximal oxygen consumption compared to IA counterparts; however it was not found to be significant. A significant inverse relationship between $\dot{VO}_2\text{max}$ and AIx and age was observed, suggesting higher levels of
cardiorespiratory fitness are important for maintaining vascular health in this population. These results also concur with previous studies in healthy populations (Robinson, 1938; Hayward & Kelly, 1997; Mitchell, Parise, Benjamin, Larson, Keyes & Vita, 2004; McEniery, et al., 2005). When $\dot{V}O_{2\text{max}}$ was then used as an independent variable in regression models, $\dot{V}O_{2\text{max}}$ predicted arterial stiffness, independent of FM (%); however, this association did not remain when adjusted for age. These results suggest that $\dot{V}O_{2\text{max}}$ is an important moderator of arterial stiffness but seems fitness is determined by age. Based on the mean values of predicted cardiorespiratory fitness in the current study, both study groups are classified as having a ‘good’ level of cardiorespiratory fitness, in comparison to healthy women aged 40 years and older (Heyward, 1998).

Reductions in $VO_{2\text{peak}}$ as much as 20-40% below that of age- and sex-matched sedentary individuals with no history of cancer have been reported (Jones et al., 2007a & Jones et al., 2007b). This explains why cancer survivors may find PA strenuous at submaximal intensities due to limitations in heart function, impaired stroke volume and cardiac output (Jones et al., 2007b). The AC study group in the present study had an estimated $\dot{V}O_{2\text{max}}$ of 30.3 ml.kg-1.min-1 ±4.7 ml.kg-1.min-1 with the IA study group having an estimated $\dot{V}O_{2\text{max}}$ of 29.3 ml.kg-1.min-1 ±5.8 ml.kg-1.min-1. Although a separate study reported a similar average estimated $\dot{V}O_{2\text{max}}$ of 30.8± 5.8 ml.kg-1.min-1 across 40 sedentary women treated for breast cancer, using the same single-stage walk test (Kolden, Strauman, Ward, Kuta, Woods & Schneider, 2002) most prior studies have reported $\dot{V}O_{2\text{max}}$ to be much lower (Cheema & Gaul, 2006; Schneider, Hsieh, Sprod, Carter & Hayward, 2007). Since, the cohort was classified as having a ‘good’ level of cardiorespiratory fitness in comparison to healthy females of the same age it is possible that the overall cohort is fitter than previous studies participants.
It is difficult to distinguish why $\dot{V}O_{2\text{max}}$ was similar between AC and IA participants because cardiorespiratory fitness is determined by a number of factors. Physiological limiting factors of $\dot{V}O_{2\text{max}}$ include; pulmonary diffusion capacity, cardiac output, oxygen carrying capacity and LTM (Bassett & Howley, 2000); however, it has been suggested that $\dot{V}O_{2\text{max}}$ may be partly genetically determined, with vast inter-individual differences (Bouchard, Daw, Rice, Perusse & Gagnon, 1998). In the present study these outcome measures were not examined. Additionally, during testing situations an individual’s psychological stability, and fatigue state can influence to what degree they push them self especially, if they have a low exercise tolerance.

Further examination of the Single-Stage submaximal walk test and fatigue inventory results may provide insight as to why $\dot{V}O_{2\text{max}}$ was similar between AC and IA survivors. End RPE was just significantly lower in the AC group compared to IA participants ($p=0.049$), despite no differences in end HR or fatigue across any of the fatigue dimensions, between AC and IA survivors. These results show that AC and IA survivors had similar CV responses to the submaximal test; however, AC survivors perceived the intensity to be much easier than IA counterparts despite reporting similar fatigue levels. Although fatigue levels were similar between study groups the means for each fatigue component were much higher than reported by a healthy, general population even after such a considerable period of time since treatment completion (Lin, Brimmer, Maloney, Nyarko, BeLue & Reeves, 2009).

Higher levels of cardiorespiratory fitness are important in clinical populations as they have been associated with a reduced risk of CVD and an overall reduction in mortality risk (Blair et al., 1995; Lee et al., 2010). The similarity in cardiorespiratory fitness reported between AC and IA study groups was unexpected. As discussed above, there are a number of contributing factors that may have influenced or caused the predicted values for each study group such as; similarities in fatigue level, HR response and the nature of a submaximal test.
5.3.3 Physical Activity Levels

Physical activity level was also indicated as a possible determinant of CV health within this population. Physical activity levels were not found to be correlated with any CV measure. Although self-reported weekly PA during the interview in visit one determined categorisation of participant’s to study groups, once IPAQ- PA forms were analysed there was no significant difference in total weekly MET-min between study groups. When recreational PA was examined independently, there was a statistical difference in weekly walking MET-min, moderate PA and total weekly recreational MET-min (walking, moderate and vigorous PA combined), with AC participants having significantly higher energy expenditures. This PA data implies that although AC survivors perform high levels of recreational PA, transportation and household energy expenditure is much less in comparison to IA survivors. It is possible that IA survivors may feel that performing household based duties on a daily basis is sufficient activity and therefore, do not need to participate in recreational PA throughout the week. The trends in this PA data is similar to trends reported by Irwin et al. (2004) who examined PA levels in 806 breast cancer survivors using a 12 month PA recall questionnaire. Irwin et al. (2004) found that within the large sample 73% of women met the recommended minimum 150 min/week of moderate-to vigorous- PA. However, when yard work and household chores were removed from the analysis only 32% of the sample met the recommendation.

In order to gauge the degree of inaccuracy within this group of breast cancer survivors a small sample of women were asked to wear a SenseWear Armband Pro (BodyMedia Body Monitoring System) for a 7-day period so direct energy expenditure data could be compared to that reported in the IPAQ long-form. IPAQ long-form data was found to be 6% higher than direct measures obtained by the Sense Wear arm band, although not significantly different. When average IPAQ MET-min were correlated against SenseWear MET-min no linear correlation was shown. Although one outlier was clearly present within the data set the
removal of this participant did not make any difference to the correlation. Reasons for the IPAQ reporting a 6% higher energy expenditure could be due to participants inaccurately identifying the actual intensity of activities performed, resulting in a higher MET code used in the calculation. It is possible that activities such as house hold chores which many of the women perform daily for a few hours do not equate to an energy expenditure of 3MET’s although the IPAQ uses this code in its calculations, therefore significantly inflating IPAQ total weekly MET-min.

Although, PA data obtained from the IPAQ Long-form was not associated with any CV variable due to great variance in the data set, it was interesting to note that though weekly MET-min was similar weekly recreational PA MET-min was significantly higher in AC participants. The fact that the IPAQ long-form overestimated total weekly MET-min by a non-significant 6%, indicates it is a suitable non-direct method for measuring PA within this population. If variance within the total weekly MET-min was lower an association may have been shown with CV variables.

5.4 Summary

Results from the current study suggest that there is an association between higher levels of recreational PA and lower cSBP’s in breast cancer survivors following treatment. However, there was no association between higher levels of recreational PA and arterial stiffness between AC and IA breast cancer survivors. Secondly, AC breast cancer survivors had significantly lower FM and waist circumferences, reducing their risk of CVD development. Correlational analysis of possible determinants of CV health identified FM (%) as a possible predictor of myocardial efficiency even after adjustment for \( \dot{V}O_{2\text{max}} \) and age. Further to this, \( \dot{V}O_{2\text{max}} \) predicted arterial stiffness after adjustment for FM (%) but not age. Interestingly, PA data reported similar total weekly MET-min between AC and IA survivors;
however, when types of PA were solely examined, AC breast cancer survivors had significantly higher recreational PA compared to IA counterparts.

This is the first study to provide insight into determinants of CV health in breast cancer survivors following CT and/or RT. These preliminary findings set a strong foundation for future research as they have highlighted an association between PA and cBP’s as well as identifying FM (%) and VO$_{2\text{max}}$ as possible moderators of CV health within this population. Since breast cancer survivors leading cause of death is heart disease following survivorship of their cancer, it is imperative that possible determinants of CV health are examined in order to reduce the long-term side-effects CT and/or RT have on the CV system. Due to limitations associated with a cross sectional study a RCT certainly needs to be undertaken, in order to be able to report causation rather than association.
6.1 Study Strengths

Although this study was of cross-sectional design it has effectively measured a vast range of variables including; CV health, vascular health, cardiorespiratory fitness and body composition, setting a solid platform for future research in a multitude of directions. Additionally, the high recruitment rate from the Otago, Central Otago and Southland regions gave a relatively strong sample size given time constraints of the testing period. Not only were there a strong number of participants, a diverse sample was also successfully recruited, giving a wide range of age, treatment regimens and PA status which provided opportunity for a broad overview of survivors. Vascular health assessment was undertaken using PWA. The gold standard technique for PWA is commonly reported as applanation tonometry (Laurent, Cockcroft, Van Bortel, Boutouyrie, Giannattasio & Hayoz, 2006) however, oscillometric devices such as the PulseCor, have been shown to closely align with tonometry readings (Jatoi et al., 2009; Climie et al., 2012). The main strengths of using the PulseCor include a simple, observer-independent and reliable technique (Climie et al., 2012) that is non-invasive and a familiar experience for most individuals. This is important especially in this specific population as most women are against invasive measures due to prior comprehensive surgical resection. Body composition assessments are often associated with many methodological limitations. Fortunately due to approved funding, body composition was able to be measured with the gold standard technique of DXA scan, providing highly reliable results for analysis and minimising issues surrounding bio-impedance analysis use. Ebbeling’s Single-Stage treadmill walk test was not only very appropriate, familiar and comfortable for older survivors, but is also associated with minimal medical risk. The ability to also use the Sense Wear Armband Pro accelerometers allowed for a deeper analysis of the validity of the IPAQ Long-form within this population, by comparing energy expenditures between direct and
indirect measures. In general this study was well designed at providing initial insight into possible determinants of CV health.

6.2 Study Limitations

Like all studies this one was also not without some limitations. The key limitation of the study design was time since active treatment completion. Survivors within the study had all finished CT and/or RT at least 2 months prior to the study but in most instances were completed treatment several years prior. Cardiovascular health was the primary focus of this study, specifically cBP and arterial stiffness differences between AC and IA survivors. The new PulseCor R7 Cardioscope II developed in New Zealand has been shown to have a strong correlation to direct measures of arterial stiffness. Although multiple assessments were taken if variation did occur, it is possible that a greater sample size would yield more valid results for comparisons between groups. Although standardised pre-test specifications were met by all participants, some women were unable to completely relax in the testing room during rest or testing periods cautioning the validity of some results.

In addition to time since treatment completion, validity of PA recall from participants in the visit one interview must be cautioned. It is common for participants to give favourable answers, especially when the study identified that PA was to be examined. Therefore, it is possible that participants overestimated the frequency and duration of recreational PA they performed in the following 7-days or a regular 7-day period and may have been inaccurately categorised as ‘active’. Lastly, the possible effect of anti-hypertensive drugs on pulse pressure, within this group of survivors must also be noted. Realistically survivors on this class of drugs should have been excluded from the present study. However, due to increased incidence of breast cancer in this older age bracket as well as increased FM during and following treatment it is very difficult to recruit a non-medicated sample without significantly reducing sample size. Although all survivors on anti-hypertensives’ were stably medicated,
and there was a similar number in each group, the drugs do have the ability to alter wave reflection morphology, and therefore AIX(%), by altering the stiffness of the arteries at a muscular level, suppressing heart rate and/or effecting vasodilatory mechanisms (Kelly, Millasseau, Ritter & Chowienczyk, 2001; Nichols & Singh, 2002).

6.3 Recommendations for future research

Based on previous research examining the adverse effects of CT and RT in breast cancer survivors the outcome measures in the present study are certainly the most important moderating variables of CV health that need to be examined within this population. To truly measure the effect of PA on CV health a randomised, exercise intervention trial is essential. Randomly assigning IA breast cancer survivors just prior to active treatment completion to an exercise or control group would allow baseline measures to be taken and cause and effect of PA to be made. An exercise intervention should be developed based on exercise intensities and modes that have been found to be effective at stabilising or regressing CAD in cardiac patients over at least a 6 month exercise period, so functional and possibly structural vascular changes can be monitored. Applanation tonometry such as using the SphygmoCor would aid arterial stiffness examination due to the ability to obtain AIX, PWV and cBP values. Additionally, it would also be useful to monitor the intensity of exercise sessions directly with accelerometers through the exercise sessions.

6.4 Summary and Conclusions

This study is novel, as it is the first to examine differences in CV health, primarily arterial stiffness and central blood pressures between AC and IA breast cancer survivors following CT and/or RT. Further to this, this cross sectional study sets a foundation for future work by identifying a few possible mediators of CV health in this specific clinical population. The primary findings of this study were AC breast cancer survivors had significantly lower cBP and similar arterial stiffness compared to IA survivors. Other important findings included
the identification of FM (%) as an important moderator of myocardial efficiency with \( \dot{V}O_{2\text{max}} \) a predictor of arterial stiffness. There is a large gap in the literature not only in breast cancer survivors, but all cancer survivors, on the effect active treatment has on arterial stiffness and possible mediators of CV health in human subjects. As cBP’s are becoming increasingly emergent as superior predictors of CVD development and CVD mortality risk, their ability in clinical settings to estimate CV health during and following CT and/or RT may be highly beneficial in monitoring high risk patients, such as women with breast cancer. Since CVD is the leading cause of death following breast cancer survivorship, it is imperative that secondary preventative programs are developed to reduce this risk and help maintain a sense of normality in daily living.
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Appendices

Appendix A: Participant Information Sheet

[Reference Number 13/023]
[08/02/13]

Vascular health of active breast cancer survivors
INFORMATION SHEET FOR PARTICIPANTS

Thank you for showing an interest in this project. Please read this information sheet carefully before deciding whether or not to participate. If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

What is the Aim of the Project?

Cancer treatments often leave survivors at increased risk for cardiovascular disease. Regular physical activity is promoted as an effective strategy to reduce the risk of non cancer-related death in cancer survivors and has been shown to improve vascular health in individuals who do not have cancer. The effect of physical activity on vascular health in cancer survivors is not known. The primary aim of this study is to determine whether vascular health is improved in physically active cancer survivors previously treated with chemotherapy and/or radiation therapy compared with less active survivors.

What Type of Participants are being sought?

- Recruitment method
  Participants who are currently exercising in the EXPINKT programme will be invited to participate in this study and control participants will be recruited from the general population.

- Selection criteria
  Women who have had a breast cancer diagnosis and who have completed chemotherapy and/or radiation treatment at least two months prior to study entry, no existing joint injuries and are able to walk on a treadmill for 8-10 minutes will be eligible to participate. The exercising group will be those women who complete ≥ 90
minutes of physical activity per week, while the non-exercising controls will undertake ≤ 60 minutes of physical activity per week.

- **Exclusion criteria**
  You will not be eligible to participate if you have recurrent breast cancer, distant metastases, diagnosed cardiovascular or peripheral vascular disease, or diabetes mellitus, have had surgery only for primary breast cancer, are unable to walk for 8-10 minutes on a treadmill, and any women currently taking medication that may alter vascular function.

- People who meet one or more of the exclusion criteria set out above may not participate in this project, because in the opinion of the researchers and the University of Otago Human Ethics Committee, it involves unacceptable risk to them.

- **Number of participants to be involved**
  We are seeking a maximum of 50 women aged between 30 and 75 years of age for each group.

- **Description of any benefit or access to information which the participant will have access to as a result of participating in the research**
  We will provide you with your results from all the tests and a summary of the group results. The bone density results may be of particular interest to you and your GP.

**What will Participants be Asked to Do?**

Should you agree to take part in this study, you will be asked to complete a general health screening questionnaire. If you meet the criteria required to join the study, you will be invited to participate. You will be asked to attend two appointments; the first will assess vascular function and fitness level and a second for the body composition scan. Time commitment will be approximately 60 minutes for the first appointment and 30 minutes for the second. Total time commitment will be approximately two hours.

- Measures of height, weight, waist and hip will be undertaken at your body composition scan appointment. We would ask that you wear light clothing that does not contain any metal (eg jeans with buttons or studs, belts, underwire bras) for these measurements and a female technician will take all of these measurements. A gown will be available if required.

- Body composition will be analysed using dual energy X-ray absorptiometry (DXA). This painless procedure will measure how much muscle and fat you have and also measure your bone density. These scans take approximately 20 minutes and will be undertaken by an experienced technician and are safe (typical radiation dose being 1/33rd that of a chest X-ray).

- The vascular health measure is similar to taking your blood pressure. After resting in a semi-recumbent position for 10 minutes, a cuff will be wrapped around your upper arm, inflated and then deflated to measure your blood pressure. Measurements will take approximately 40 seconds to complete. This measure will be taken using the arm on the
non-involved side. There may be minimal discomfort with the inflation of the cuff, but you may ask for this test to be stopped at any stage.

- A submaximal walking test will be undertaken on the treadmill at a speed of your choice. The test length will be 8-10 minutes. Your heart rate will be monitored throughout each test using a portable heart rate monitor worn around the chest. Heart rate will be displayed on a watch. This test is not expected to cause any significant discomfort and you may end the test at any time. Research staff with first aid certification will be present at all times throughout the exercise test.

- We will also ask you to complete a seven-day physical activity questionnaire. This questionnaire asks about all aspects of your weekly physical activities, including work-related, household, and leisure-time physical activities and will take approximately 30 minutes to complete. A stamped, self-addressed envelope will be provided for you to return this questionnaire to the researchers.

Please be aware that you may decide not to take part in the project without any disadvantage to yourself of any kind.

What Data or Information will be Collected and What Use will be Made of it?

- We will collect information about your vascular health, body composition, physical activity patterns, and fitness levels in response to submaximum exercise efforts.

- We will also ask your age, and measure your height, weight, waist and hip circumferences. We will also gather information on your cancer diagnosis, confirm the date that you completed treatment, and identify treatments administered for breast cancer.

- All data collected will be used to obtain group responses and no information will be related to any individual. These data will be used to write a thesis for the completion of a Master’s degree in Physical Education and will also be used to write research papers for publication.

- The data collected will be securely stored in such a way that only the researchers involved (Dr Lynnette Jones, Dr Lee Stoner, Dr Chris Baldi and Miss Casey Brown), will be able to gain access to it. Data obtained as a result of the research will be retained for at least 10 years in secure storage. Any personal information held on the participants that does not relate to participation in the EXPINKT™ programme may be destroyed at the completion of the research even though the data derived from the research will, in most cases, be kept for much longer or possibly indefinitely.

- The results of the project may be published and will be available in the University of Otago Library (Dunedin, New Zealand), but every attempt will be made to preserve your anonymity.

- You are most welcome to request a copy of the results of the project should you wish and you will receive a copy of your own results for each test.
Can Participants Change their Mind and Withdraw from the Project?

You may withdraw from participation in the project at any time and without any disadvantage to yourself of any kind.

What if Participants have any Questions?

If you have any questions about our project, either now or in the future, please feel free to contact either:-

Miss Casey Brown and/or Dr Lynnette Jones
School of Physical Education
Mobile Number:- 02102269892
Email: broca739@student.otago.ac.nz

Dr Lynnette Jones
School of Physical Education
University Telephone Number:- 4798962
Email: lynnette.jones@otago.ac.nz

This study has been approved by the University of Otago Human Ethics Committee. If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
Appendix B: Participant Consent Form

[Reference Number 13/023]
[08/02/13]

Vascular health of active breast cancer survivors

CONSENT FORM FOR PARTICIPANTS

I have read the Information Sheet concerning this project and understand what it is about. All my questions have been answered to my satisfaction. I understand that I am free to request further information at any stage.

I know that:-

1. My participation in the project is entirely voluntary;

2. I am free to withdraw from the project at any time without any disadvantage;

3. Personal identifying information, e.g. screening questionnaire, will be destroyed at the conclusion of the project but any raw data on which the results of the project depend will be retained in secure storage for at least five years.

4. I am prepared to undergo a vascular health test and submaximal exercise test and am aware that there may be some minimal discomfort.

5. I am prepared to attend all appointments and complete required records for this study.

6. The results of the project may be published and will be available in the University of Otago Library (Dunedin, New Zealand) but every attempt will be made to preserve my anonymity.

I agree to take part in this project.

........................................................................................................
.................................................................................................
(Signature of participant) ......................................................... (Date)

This study has been approved by the University of Otago Human Ethics Committee. If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (ph 03 479 8256). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.
Appendix C: Pre-visit One Participant Requirements

Vascular health of active breast cancer survivors
VISIT ONE: Pre-visit requirements

To ensure the validity of each test, it is necessary that all participants are in a similar physiological state before their assessments. Please read the information below thoroughly and follow the instructions. If you have any questions relating to any of the requirements below please do not hesitate to call;
Dr Lynnette Jones: 479 8962 or Casey Brown: 0210 226 9892.

Participant Preparation

Before the first visit please;
- Avoid exercise 24 hours prior.
- Fast overnight; do not eat following dinner or on the morning before the visit. All testing will be conducted in the morning to reduce discomfort.
- Drink water as needed before the test just not to excess.
- Do not drink any other beverages such as coffee, tea, juice etc.
- Do not take any dietary supplements.
- Refrain from smoking.

Thank you for taking time to participate in this study, we look forward to seeing you at your first visit
Appendix D: Visit One Screening Questionnaire & Data Collection Sheet

Participant ID___________

Vascular Health of Active Breast Cancer Survivors
SCREENING QUESTIONNAIRE

Demographics:
Name_______________________________________________________
Address _______________________________________________________________________________________
Phone (Home) ____________________________    Phone (Cell) ________________________________
D.O.B_____________      Ethnicity________________________

Basic Anthropometry:
Height ______cm     Weight ______ kg    BMI ______ kg/m^2

Previous Exercise History:
Previous 7 days (typical week Yes / No):

Physically active (≥150 mins week) Yes / No
Physically inactive (<150 mins week) Yes / No
Previous exercise training (aerobic, resistance etc):
Medical History:

**AHA Form**

1. Is this the first time you have been diagnosed with breast cancer? Yes / No
2. Do you have distant metastasis? Yes / No

Further Notes:

Current Medications:

1. ________________________________   ____   4. ________________________________   ____ 
2. ________________________________   ____   5. ________________________________   ____
3. ________________________________   ____   6. ________________________________   ____

Cancer Treatment History:

Cancer Grade___________

Mastectomy: Left / Right

Radiation Therapy: Yes / No

Chemotherapy: Yes / No

Agent 1 ____________________________   ____

Agent 2 ____________________________   ____

Agent 3 ____________________________   ____

Agent 4 ____________________________   ____

Active treatment completion date __________

Hormonal Therapy: Yes / No    Agent ____________________________   ____

If finished HT when ________

Menopausal Status: Pre / Post

How many periods have you had in the last six months? _____ Date of last period ________

Signature _________________________          Date __________
MEDICAL SCREENING FORM

Name_________________________________________

History

You have had (please tick the boxes that are true for you):

<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>A heart attack</td>
<td>Experience chest discomfort with exercise</td>
</tr>
<tr>
<td>Heart surgery</td>
<td>Experience unreasonable breathlessness</td>
</tr>
<tr>
<td>Cardiac catheterisation</td>
<td>Experience dizziness, fainting, blackouts</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>You take heart medications</td>
</tr>
<tr>
<td>Pacemaker</td>
<td></td>
</tr>
<tr>
<td>Heart valve disease</td>
<td></td>
</tr>
<tr>
<td>Heart transplantation</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
</tr>
</tbody>
</table>

Other health issues

You have musculoskeletal problems (please list in detail):

You are pregnant

You have concerns about the safety of exercise

Risk factors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>You are a man older than 45 years</td>
<td>You are diabetic or take medications to control your blood sugar</td>
</tr>
<tr>
<td>You are a women older than 55 years or</td>
<td>You are physically inactive (get &lt;30 minutes of physical activity on at least 3 days per week</td>
</tr>
<tr>
<td>You have had a hysterectomy or are post menopausal</td>
<td>You are &gt;10kg overweight</td>
</tr>
<tr>
<td>Your blood pressure &gt; 140/90</td>
<td>You smoke</td>
</tr>
<tr>
<td>You take blood pressure medication or</td>
<td>Your blood cholesterol &gt;5.2 mmol/L</td>
</tr>
<tr>
<td>don’t know your blood pressure</td>
<td></td>
</tr>
<tr>
<td>You have a close blood relative who had a</td>
<td>You don’t know your cholesterol level</td>
</tr>
<tr>
<td>heart attack &lt;55 years (father/brother) or</td>
<td></td>
</tr>
<tr>
<td>&lt;65 (mother/sister)</td>
<td></td>
</tr>
</tbody>
</table>

Signed_____________________________ Date________
**Vascular Health Assessment**

Standardised Protocol: **Yes / No**  
Room Temp____

PulseCor Assessment

<table>
<thead>
<tr>
<th></th>
<th>Arm</th>
<th>Size</th>
<th>#</th>
<th>SBP mm/Hg</th>
<th>DBP mm/Hg</th>
<th>Alx (%)</th>
<th>Pulse rate bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Average

**Cardiovascular Assessment**

APHR: 220-____ = ______  
50% APHR\textsubscript{max}_______  
70% APHR\textsubscript{max}_______

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speed (km/hr) 3.2-7.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gradient (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>RPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
Appendix E: OMNI Scale

Figure 1. OMNI Scale of Perceived Exertion: Adult, walking to Running Format

Appendix F: International Physical Activity Questionnaire: Long-Form

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE
(October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health-related physical activity.

Background on IPAQ
The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ
Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation
Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipea.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ
International collaboration on IPAQ is on-going and an International Physical Activity Prevalence Study is in progress. For further information see the IPAQ website.

More Information
5. How much time did you usually spend on one of those days doing moderate physical activities as part of your work?

___ hours per day
___ minutes per day

6. During the last 7 days, on how many days did you walk for at least 10 minutes at a time as part of your work? Please do not count any walking you did to travel to or from work.

___ days per week
☐ No job-related walking → Skip to PART 2: TRANSPORTATION

7. How much time did you usually spend on one of those days walking as part of your work?

___ hours per day
___ minutes per day

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the last 7 days, on how many days did you travel in a motor vehicle like a train, bus, car, or tram?

___ days per week
☐ No traveling in a motor vehicle → Skip to question 10

9. How much time did you usually spend on one of those days traveling in a train, bus, car, tram, or other kind of motor vehicle?

___ hours per day
___ minutes per day

Now think only about the bicycling and walking you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the last 7 days, on how many days did you bicycle for at least 10 minutes at a time to go from place to place?

___ days per week
☐ No bicycling from place to place → Skip to question 12
11. How much time did you usually spend on one of those days to bicycle from place to place?

   ____ hours per day
   ____ minutes per day

12. During the last 7 days, on how many days did you walk for at least 10 minutes at a time to go from place to place?

   ____ days per week
   [ ] No walking from place to place → Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

13. How much time did you usually spend on one of those days walking from place to place?

   ____ hours per day
   ____ minutes per day

**PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY**

This section is about some of the physical activities you might have done in the last 7 days in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, chopping wood, shoveling snow, or digging in the garden or yard?

   ____ days per week
   [ ] No vigorous activity in garden or yard → Skip to question 16

15. How much time did you usually spend on one of those days doing vigorous physical activities in the garden or yard?

   ____ hours per day
   ____ minutes per day

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate activities like carrying light loads, sweeping, washing windows, and raking in the garden or yard?

   ____ days per week
   [ ] No moderate activity in garden or yard → Skip to question 18
17. How much time did you usually spend on one of those days doing moderate physical activities in the garden or yard?

_____ hours per day
_____ minutes per day

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do moderate activities like carrying light loads, washing windows, scrubbing floors and sweeping inside your home?

_____ days per week

☐ No moderate activity inside home  ➔ Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY

19. How much time did you usually spend on one of those days doing moderate physical activities inside your home?

_____ hours per day
_____ minutes per day

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the last 7 days solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the last 7 days, on how many days did you walk for at least 10 minutes at a time in your leisure time?

_____ days per week

☐ No walking in leisure time  ➔ Skip to question 22

21. How much time did you usually spend on one of those days walking in your leisure time?

_____ hours per day
_____ minutes per day

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do vigorous physical activities like aerobics, running, fast bicycling, or fast swimming in your leisure time?

_____ days per week

☐ No vigorous activity in leisure time  ➔ Skip to question 24
23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

   _____ hours per day
   _____ minutes per day

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis in **your** leisure time?

   _____ days per week

   □ No moderate activity in leisure time  ➔ Skip to **PART 5: TIME SPENT SITTING**

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

   _____ hours per day
   _____ minutes per day

**PART 5: TIME SPENT SITTING**

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend sitting **on a weekday**?

   _____ hours per day
   _____ minutes per day

27. During the **last 7 days**, how much time did you usually spend sitting **on a weekend day**?

   _____ hours per day
   _____ minutes per day

This is the end of the questionnaire, thank you for participating.
Appendix G: Multidimensional Fatigue Inventory

MULTIDIMENSIONAL FATIGUE INVENTORY  
MFI-20

Instructions:
By means of the following statements we would like to get an idea of how you have been feeling lately. There is, for example, the statement:

"I FEEL RELAXED"

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

Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true  

The more you disagree with the statement, the more you can place an X in the direction of “No, that is not true”. Please do not miss you a statement: place one X next to each statement.

1. I feel fit
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

2. Physically I feel able to do a lot
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

3. I feel very active
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

4. I feel like doing all sorts of nice things
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

5. I do not feel tired
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

6. I think I do a lot in a day
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

7. When I am doing something, I can keep my thoughts on it
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

8. Physically I can take on a lot
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true

9. I do not dread having to do things
   Yes, that is true  [ ] [ ] [ ] [ ] No, that is not true
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Yes, that is true</th>
<th>No, that is not true</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.</td>
<td>I do a lot in a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11.</td>
<td>I can concentrate well</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12.</td>
<td>I am rested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>It takes little effort to concentrate on things</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.</td>
<td>Physically I feel I am in a good condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.</td>
<td>I have a lot of plans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.</td>
<td>I hardly get tired</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.</td>
<td>I get a lot done</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.</td>
<td>I feel like doing something</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.</td>
<td>My thoughts hardly wander</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.</td>
<td>Physically I feel I am in an excellent condition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thank you very much for your cooperation.
Appendix H: Pilot Study - Blood Pressure Cuff Size vs. AIx %

Results from the pilot study validated vascular health assessments between the two different arm cuffs (A10, 11L) and indicate acceptable agreement due to high correlation coefficient values for systolic blood pressures (r=0.86), diastolic blood pressures (r=0.85) and augmentation index (r=0.85). These data suggest that the size of the arm cuff does not affect reliability of the measures.

Table 1. Comparisons between average systolic blood pressure (mm/Hg), diastolic blood pressure (mm/Hg) and augmentation index (%) between size A10 and 11L pressure cuffs in healthy active women (n=11, aged; 21-57 years), using the PulseCor R7 CardioScope.

| Participant | Avg SBP (mm/Hg) | A10 cuff | Avg AIx (%) | 11L cuff | Absolute difference | | | | |
|-------------|----------------|---------|-------------|---------|---------------------| | | | |
| 1           | 115            | 69      | 25          | 112     | 3.0                 | 0.5 | 6.5 |
| 2           | 100            | 59      | 28          | 101     | 0.5                 | 1.5 | 3.0 |
| 3           | 107            | 66      | 69          | 113     | 6.0                 | 2.5 | 2.5 |
| 4           | 102            | 67      | 76          | 107     | 4.5                 | 5.0 | 2.8 |
| 5           | 95             | 56      | 38          | 96      | 0.5                 | 0.5 | 1.0 |
| 6           | 111            | 72      | 52          | 104     | 7.0                 | 6.0 | 8.5 |
| 7           | 106            | 70      | 62          | 100     | 6.5                 | 7.0 | 3.5 |
| 8           | 125            | 80      | 87          | 121     | 3.5                 | 0.0 | 36.5 |
| 9           | 101            | 67      | 28          | 103     | 2.0                 | 1.0 | 7.5 |
| 10          | 101            | 65      | 44          | 100     | 0.5                 | 2.0 | 8.5 |
| 11          | 101            | 63      | 67          | 104     | 3.0                 | 2.5 | 27.5 |
| Mean±SD     | 106±8          | 67±6    | 52±21       | 105±7   | 3±2                 | 3±2 | 10±1 |
| r-value     |                |         |             |         | *0.86*              | *0.85* | *0.85* |

NOTE: Avg = Average, SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure, AIx = Augmentation index
Appendix I: Literature Review Summary Tables
Table 11. Effects of chemotherapy and/or radiation therapy on cardiovascular health.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>N</th>
<th>Treatment Type</th>
<th>Outcome Variables</th>
<th>Vascular Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckman et al. (2001)</td>
<td>Cross sectional</td>
<td>N= 26</td>
<td>16 women with prior RT for unilateral BC, 10 of whom also received CT</td>
<td>Endothelium-independent/depen- dent vaso-d</td>
<td>Chronic impairment of endothelium-dependent vaso-d specific to arteries that received RT. Exposed arteries did not vaso-d, while contralateral arteries did (-0.4±0.4% vs. 3.2±0.8%; p&lt;0.001) within the RT group.</td>
</tr>
<tr>
<td>Correa et al. (2007)</td>
<td>Retrospective</td>
<td>N=961</td>
<td>Tangential beam RT</td>
<td>Coronary artery disease: Yes or no</td>
<td>Left sided RT ↑ risk of late RT associated damage. Stress test abnormalities; (59%) in left vs. (36.8%) in right treated; p=0.001. Coronary stenoses in the left anterior descending coronary artery (85%) and in 62%, the whole vessel was affected.</td>
</tr>
<tr>
<td>Chaosuwanakit et al. (2010)</td>
<td>Prospective, case-control</td>
<td>N=53</td>
<td>Doxorubicin (n=10) Daunorubicin (n=10) Cyclophosphamide (n=35) Trastuzumab (n=2)</td>
<td>Arterial stiffness-PWV/aortic distensibility of thoracic aorta. Baseline testing and 4 months after initiation of treatment</td>
<td>At baseline PWV higher and AoD lower compared to control group. Follow up visit; PWV ↑ (p&lt;0.0001) and AoD↓(p=0.0004) compared to baseline in cancer therapy group. Anthracycline treatment ↑ aortic stiffness within the thoracic aorta.</td>
</tr>
</tbody>
</table>

NOTE: RCT = randomised controlled trial. BC= Breast cancer ,CT= Chemotherapy. RT= Radiation therapy, vaso-d= Vasodilation, PWV= pulse wave velocity, AoD= Aortic distensibility, EC= endothelial cell, TNF-α = Tumour necrosis factor-alpha, IL-6 = interleukin-6.

Table 1. continued
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>N</th>
<th>Treatment Type</th>
<th>Outcome Variables</th>
<th>Vascular Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckman et al. (2013)</td>
<td>RCT</td>
<td>N= 32 rats</td>
<td>Doxorubicin</td>
<td>Thickness of adventitia, media and total thickness of adventitia/media in coronary arterioles &amp; LVEF</td>
<td>In both low and high doses, LVEF declined from baseline (p=0.01). High dose DOX sig ↑ in all thicknesses in comparison to saline treated group.</td>
</tr>
<tr>
<td>Gajalakshmi et al. (2013)</td>
<td>Experimental</td>
<td>Cell cultures</td>
<td>Tamoxifen, Epirubicin, Capecitabine</td>
<td>Cell death, NO production &amp; level, eNOS protein level</td>
<td>Sig. ↓ in NO levels in endothelium following treatment.</td>
</tr>
<tr>
<td>Goodnough et al. (1984)</td>
<td>Observational</td>
<td>N=159</td>
<td>Combination CT</td>
<td>Thrombotic episodes, coagulation tests</td>
<td>17.6% patients had a thromboembolic event. 4/25 suffered deep vein thrombosis and 3/25 myocardial infarction.</td>
</tr>
<tr>
<td>Maney et al. (2011)</td>
<td>Experimental</td>
<td>Cell cultures</td>
<td>Doxorubicin, Camptothecin, Thapsigargin</td>
<td>Mitochondrial membrane potential, % of cell death</td>
<td>Both endocardial EC and human aortic EC are relatively resistant to CT agents used. Endocardial EC maintain mitochondrial membrane potential during toxicity.</td>
</tr>
</tbody>
</table>

Table 1. continued
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>N</th>
<th>Treatment Type</th>
<th>Outcome Variables</th>
<th>Vascular Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikaelian et al.</td>
<td>Experimental</td>
<td>Rats</td>
<td>Vinblastine, vincristine, colchicine</td>
<td>Cardiac stress proteins (cTn1, caspase-3)</td>
<td>Sig. ↑ cTn1 after high dose colchicine and vincristine. No evidence of myocardial necrosis. Gene ontology supported vascular/endothelial damage. Decrease in number of cells, and increase in markers of EC damage. Only heart was affected no other organs primarily due to high cell turnover.</td>
</tr>
<tr>
<td>(2010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murata et al.</td>
<td>Experimental</td>
<td>Male Japanese</td>
<td>Doxorubicin at 0.3 mM, 1.0 mM or 10.0</td>
<td>Morphologic and functional changes in mesenteric artery</td>
<td>In the mesenteric artery, noradrenaline-induced contraction reduced in 0.3 mM dose. Apoptosis of smooth muscle cells and apoptotic changes in 1.0 mM and necrosis and muscle contractility abolished in 10.0 mM doxorubicin dosage.</td>
</tr>
<tr>
<td>(2001a)</td>
<td></td>
<td>white rabbits</td>
<td>mM.</td>
<td>using an organ culture.</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. continued
<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>N</th>
<th>Treatment Type</th>
<th>Outcome Variables</th>
<th>Vascular Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murata et al. (2001b)</td>
<td>Experimental</td>
<td>Male Japanese white rabbits</td>
<td>Doxorubicin at 0.3 and 1.0 mM</td>
<td>Endothelial cell damage and vascular tone</td>
<td>In the mesenteric artery EC apoptotic changes and EC nuclei damage at 0.3 mM dose after 7 days. Severe EC DNA damage after 1.0 mM dose after 3 days. EC stripped followed by ↓ endothelium-dependent relaxation when treated with 1.0 mM for 5-7 days. Apoptosis in smooth muscle only at 1.0 mM dose over 5 days.</td>
</tr>
<tr>
<td>Tanteles et al. (2009)</td>
<td>Cohort</td>
<td>RT in N=149 BC patients</td>
<td>RT at least 4 years prior</td>
<td>CVD symptoms</td>
<td>6% population diagnosed CVD, 3-12 years after RT. 32 developed talangiectasiae with 5/32 developing CVD (15.6%) compared to 3/105 (2.9%) in non-talangiectasiae group. Sig. association between long-term risk CVD and presence of talangiectasiae.</td>
</tr>
<tr>
<td>Vassilakopoulou et al. (2010)</td>
<td>RCT</td>
<td>N=37 Cancer of the breast (Metastatic paclitaxel n = 5, early-stage n = 6), Uterine cervix or ovarian n = 16 Controls n =10</td>
<td>Control Group: cisplatin Experimental: metastatic = paclitaxel CT. Early stage = paclitaxel &amp; anthracycline.</td>
<td>Brachial artery reactivity; endothelium-dependent and endothelium-independent vasod. Serum [TNF-α] and [IL-6].</td>
<td>Metastatic and early stage BC groups had significant ↓ in % flow mediated dilatation from baseline to post-CT; p=0.045 and p=0.005 respectively. Early stage BC group - significant decrease in nitrate-mediated dilatation=0.027.</td>
</tr>
</tbody>
</table>
Table 12. Animal studies of the effects of physical activity on cardiovascular health following chemotherapy and/or radiation therapy.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>Exercise regimen</th>
<th>Treatment Type</th>
<th>Outcome Variables</th>
<th>Vascular Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascensao et al.</td>
<td>RCT</td>
<td>Swimming period 1 h/day, 5 days/wk for 14 weeks.</td>
<td>Placebo= 0.9% NaCl DOX</td>
<td>HSP60 CTnI</td>
<td>ET in both placebo and DOX groups showed a ↓ in HSP60 a cardiac stress marker therefore reducing the rise of cardiac disturbances induced by a single bout of DOX. The trained+DOX group had a lower rise in myocardial cTn1 release into plasma compared to non-trained+DOX suggesting ET reduces the loss of cardiomyocyte integrity.</td>
</tr>
<tr>
<td>(2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chicco et al.</td>
<td>RCT</td>
<td>Treadmill running 5 days/week, 1 hour/day, 27 m/min, 5% grade for 12 weeks.</td>
<td>Saline DOX</td>
<td>HSP72 MnSOD</td>
<td>Ex training and DOX ↑ HSP72 but had no effect on MnSOD. No interaction was detected between DOX + ex training. Ex training did not ↓ coronary flow reduction in DOX treated groups. Ex training prior to DOX treatment has a cardio-protective effect on the myocardium providing resistance against free radicals by ↑ production of HSP72</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Author</td>
<td>Study Design</td>
<td>Exercise regimen</td>
<td>Treatment Type</td>
<td>Outcome Variables</td>
<td>Vascular Effect</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Wonders et al. (2009)</td>
<td>RCT</td>
<td>10 week exercise plan. Rats exercised 5 days/week, 30m/min, 18% grade for 60 min.</td>
<td>GW2974 as the HER-2 inhibitor and doxorubicin. Animals sacrificed 2,5, or 10 days following injections.</td>
<td>Cardiac function (LVDP)</td>
<td>Sig. ↓ in LVDP in sedentary groups. Sed+DOX/GW had a 55% ↓ in LVDP 10 days post injections (p&lt;0.05). LVDP values not sig. different between Ex+DOX/GW and Sed+sal at days 2 and 5. Caspase-3 and-8 (markers of cell apoptosis) were sig. higher in the sed+ DOX/GW group than any other. ET is cardio-protective against DOX induced cardiac dysfunction even with a secondary treatment.</td>
</tr>
</tbody>
</table>

NOTE: RCT = randomised controlled trial, DOX=Doxorubicin, LVDP = Left ventricular diastolic pressure, Ex = Exercise, ET = Exercise training, Sal = Saline, Sed =Sedentary, Sig = significant, NaCl = sodium chloride, HSP = heat shock protein, cTnI = cardiac troponin I MnSOD = manganese superoxide dismutase, HER2 = human epidermal growth factor receptor2
Table 13. Effects of chemotherapy and radiation therapy on body composition (LTM, Body fat %) and cardiorespiratory fitness (VO2peak) in breast cancer survivors.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Study Design</th>
<th>N</th>
<th>Treatment Type</th>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aslani et al. (1999)</td>
<td>Prospective study</td>
<td>25</td>
<td>CT</td>
<td>Significant ↑ FM (p=0.008), NS change in LTM</td>
</tr>
<tr>
<td>Campbell et al. (2007)</td>
<td>Prospective Study</td>
<td>10</td>
<td>CT</td>
<td>Significant ↑ FM (p=0.04), No change in LTM</td>
</tr>
<tr>
<td>Cheney et al. (1997)</td>
<td>Observational study</td>
<td>34</td>
<td>CT and RT</td>
<td>↓LTM over time</td>
</tr>
<tr>
<td>Denmark-Wahnefried et al. (2001)</td>
<td>Prospective Trial</td>
<td>53</td>
<td>CT n = 36 LT (Surgery or RT) n = 17</td>
<td>NS changes over the year period. LT: trend toward stable fat mass, slight ↓ in FM%, slight ↑ in leg LTM CT: trend toward ↑ in fat mass, ↓ LTM</td>
</tr>
<tr>
<td>Freedman et al. (2004)</td>
<td>Prospective trial</td>
<td>77</td>
<td>Healthy-matched control n = 51</td>
<td>DXA showed significant ↑ in body fat % between 2 weeks following CT cessation and 6 months post treatment. NS changes in LTM trend toward ↓ with air displacement plethysmography</td>
</tr>
<tr>
<td>Harvie et al. (2004)</td>
<td>Prospective study</td>
<td>38</td>
<td>CT</td>
<td>BIA and skinfolds. Significant ↑ in FM% during CT and 6 months post CT (p&lt;0.01). Decline in LTM in the 6 months post-treatment (p&lt;0.05)</td>
</tr>
<tr>
<td>Jones et al. (2007b)</td>
<td>Cross-sectional study</td>
<td>58</td>
<td>BC n = 47 Healthy-matched control n = 11</td>
<td>BC group ↓ VO2peak relative compared to control (p=0.004) (36%).</td>
</tr>
<tr>
<td>First Author</td>
<td>Study Design</td>
<td>N</td>
<td>Treatment Type</td>
<td>Physiological Effect</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------</td>
<td>----</td>
<td>----------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kutynec et al.</td>
<td>Non-randomised prospective/comparative study</td>
<td>18</td>
<td>CT n =8</td>
<td>DXA: Significant ↑ in LTM in RT group compared to CT group (p=0.01). Over time a significant ↓ in LTM in the legs of both CT and RT groups (p=0.02). NS change in body fat % trend for ↑ both groups</td>
</tr>
<tr>
<td>(1999)</td>
<td>(12 weeks)</td>
<td></td>
<td>RT n =10</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: BC= Breast cancer , CT= Chemotherapy, RT= Radiation therapy, LT= Longitudinal, LTM= Lean tissue mass, FM%= Body fat percentage, NS= Non significant, DXA= Dual-energy X-ray absorptiometry
<table>
<thead>
<tr>
<th>First Author</th>
<th>Exercise intervention</th>
<th>Study Design (n)</th>
<th>Length</th>
<th>Frequency</th>
<th>Duration</th>
<th>Intensity</th>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courneya et al.</td>
<td>Aerobic training</td>
<td>RCT Exercise group N= 24 Control group N= 26</td>
<td>15 weeks</td>
<td>3</td>
<td>15-35 minutes</td>
<td>70-75% VO&lt;sub&gt;2&lt;/sub&gt;peak</td>
<td>EG: VO&lt;sub&gt;2&lt;/sub&gt;peak ↑ sig compared to control (p&lt;0.001).</td>
</tr>
<tr>
<td>Courneya et al.</td>
<td>Aerobic vs. Resistance training</td>
<td>RCT Usual care N=82 Supervised RT (SRT) N=82 Supervised AT (SAT) N=78</td>
<td>Median: 17 weeks</td>
<td>3</td>
<td>15-45 minutes</td>
<td>RT: 3 x week, 8-12/2, 9 exercises 60-70% 1-RM. AT: 3 x week, starting at 60% VO&lt;sub&gt;2max&lt;/sub&gt; up to &gt;80% beyond week 12.</td>
<td>SRT and SAT no sig change in LTM of FM%. ↑VO&lt;sub&gt;2&lt;/sub&gt;peak (p=0.006)</td>
</tr>
<tr>
<td>Herrero et al.</td>
<td>Combined Aerobic and Resistance training</td>
<td>RCT Exercise group N=8 Control group N=8</td>
<td>8 weeks</td>
<td>3</td>
<td>20-30 minutes</td>
<td>AT: 70-80% HR&lt;sub&gt;max&lt;/sub&gt; RT: 60-70% 1-RM</td>
<td>Sig ↑ in VO&lt;sub&gt;2&lt;/sub&gt;peak in exercise group compared to control (p≤0.05)</td>
</tr>
<tr>
<td>Hutnick et al.</td>
<td>Aerobic + resistance</td>
<td>RCT Exercises N=21 Non-exercises N=15</td>
<td>6 months</td>
<td>3</td>
<td>40-90 minutes</td>
<td>AT: 60-75% functional capacity RT: 8 exercises, 8-12 reps, 3 sets</td>
<td>VO&lt;sub&gt;2max&lt;/sub&gt; significantly ↑ from baseline (p&lt;0.05)</td>
</tr>
<tr>
<td>Irwin et al.</td>
<td>Aerobic</td>
<td>RCT Exercise N=38 Usual care N=37</td>
<td>6 months</td>
<td>5</td>
<td>45-150 minutes</td>
<td>50% HR&lt;sub&gt;max&lt;/sub&gt; progressing 60-80 HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Sig ↓FM (p&lt;0.01) and ↑ LTM (p&lt;0.05) in exercise group.</td>
</tr>
</tbody>
</table>

Table 14. Effects of physical activity on body composition (LTM, Body fat %) and cardiorespiratory fitness (VO<sub>2peak</sub>) in breast cancer survivors following chemotherapy and/or radiation therapy.
<table>
<thead>
<tr>
<th>First Author</th>
<th>Exercise intervention</th>
<th>Study Design (n)</th>
<th>Length</th>
<th>Frequency</th>
<th>Duration</th>
<th>Intensity</th>
<th>Physiological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matthew et al. (2007).</td>
<td>Home-based aerobic</td>
<td>RCT Home-based Walking N=22 Control N=14</td>
<td>12 weeks</td>
<td>5</td>
<td>30-40 minutes</td>
<td>Moderate-I: RPE:11-13</td>
<td>NS change in LTM or body fat %</td>
</tr>
<tr>
<td>Pinto et al. (2005)</td>
<td>Aerobic</td>
<td>RCT PA group N=39 Control group N=43</td>
<td>12 weeks</td>
<td>5</td>
<td>30 minutes accumulated</td>
<td>Moderate-I activites 55-65% HRmax</td>
<td>No change in FM %</td>
</tr>
<tr>
<td>Schmitz et al. (2005)</td>
<td>Resistance training</td>
<td>RCT Immediate or delayed treatment groups N=69 Baseline, 6 month and 12month testing</td>
<td>52 weeks</td>
<td>2</td>
<td>~60 minutes</td>
<td>9 common exercises, upper and lower limbs, 3 sets 10,10,12 reps</td>
<td>↑LTM (p=0.008) ↓FM % (p= 0.03)</td>
</tr>
<tr>
<td>Segal et al. (2001)</td>
<td>Aerobic</td>
<td>RCT Usual care N= 34 Self-directed (SD) N=33 Supervised (SU) N=32</td>
<td>26 weeks</td>
<td>5</td>
<td>~</td>
<td>walking 50-60% predicted VO2max.</td>
<td>NS differences from baseline to follow up in VO2max: SD (3.5%↑) SU (2.4↑)</td>
</tr>
<tr>
<td>Winters-Stone et al. (2011)</td>
<td>Strength and Impact training vs. Flexibility training</td>
<td>RCT Strength+Impact N=36 Flexibility N=31</td>
<td>52 weeks</td>
<td>3</td>
<td>45-60 minutes</td>
<td>Strength + Impact: 60-70% 1-RM, 1-3 sets, 8-12 reps, common exercises + box jumps. Flexibility: non-weight bearing full body stretches</td>
<td>NS change in LTM or FM %</td>
</tr>
</tbody>
</table>

NOTE: RCT = randomised controlled trial, BC= Breast cancer ,AT= Aerobic training, RT= Resistance training, 1-RM= 1 repetition max, LTM= Lean tissue mass, FM%= Body fat percentage, NS= Non significant, Moderate-I = moderate intensity
Appendix J: Validation Study: SenseWear Pro Armband Monitor vs. IPAQ Long-Form

Across 12 breast cancer survivors with varying levels of PA, there was no significant difference (p>0.05) between the calculated IPAQ long-from averaged weekly MET-min and actual MET-min reported by the SenseWear Pro armband monitor (Table 11). Variability within the data set was large and identifies one possible outlier (participant 8). Correlational analysis between the two methods of obtaining energy expenditure reported an r-value of 0.12, indicating no linear relationship between the IPAQ long-form and SenseWear Pro armband monitor. There was no change in this correlation when the outlier was removed from the data set.

Table 15. IPAQ long-form calculation of energy expenditure (MET-min) in breast cancer survivors (n=12; AC=8, IA=4) correlated to measured energy expenditure from the SenseWear Pro armband monitor.

<table>
<thead>
<tr>
<th>Participant</th>
<th>SenseWear Total weekly MET-mins</th>
<th>IPAQ Total Weekly MET-mins</th>
<th>Absolute Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5747</td>
<td>2398</td>
<td>3349</td>
</tr>
<tr>
<td>2</td>
<td>1911</td>
<td>3537</td>
<td>1626</td>
</tr>
<tr>
<td>3</td>
<td>5047</td>
<td>2798</td>
<td>2249</td>
</tr>
<tr>
<td>4</td>
<td>13160</td>
<td>2952</td>
<td>10208</td>
</tr>
<tr>
<td>5</td>
<td>980</td>
<td>6063</td>
<td>5083</td>
</tr>
<tr>
<td>6</td>
<td>2639</td>
<td>2966</td>
<td>326.5</td>
</tr>
<tr>
<td>7</td>
<td>3731</td>
<td>6333</td>
<td>2602</td>
</tr>
<tr>
<td>8</td>
<td>6153</td>
<td>17996</td>
<td>11843</td>
</tr>
<tr>
<td>9</td>
<td>7672</td>
<td>9837</td>
<td>2165</td>
</tr>
<tr>
<td>10</td>
<td>3136</td>
<td>2096</td>
<td>1040.2</td>
</tr>
<tr>
<td>11</td>
<td>7364</td>
<td>6960</td>
<td>404</td>
</tr>
<tr>
<td>12</td>
<td>5320</td>
<td>2932</td>
<td>2388</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>5238 ± 3261</td>
<td>5572 ± 4377</td>
<td>3607 ± 3554</td>
</tr>
<tr>
<td>Absolute difference (%)</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r-value</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>