CHAPTER ONE

INTRODUCTION

1.1 BACKGROUND TO THE STUDY

Cancer is a group of diseases characterized by uncontrolled cell division leading to growth of abnormal tissue (Stephan, 2011). The two main characteristics are uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites (metastasis). If the spread is not controlled, cancer can result in death. Breast Cancer (BC) is a malignant growth that begins from the cells of the breast (Stephan, 2011). It is increasingly considered to be not one disease, but a group of diseases distinguished by different molecular subtypes, risk factors, clinical behaviours and responses to treatment [American Cancer Society (ACS), 2013].

Breast Cancer is the commonest cancer affecting women in Nigeria with a steady increase in prevalence over the years (Adebamowo and Ajayi, 2000; Adetifa, 2009). According to global statistics on cancer, BC is the most frequently diagnosed cancer among women worldwide and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths (Jemal *et al.*, 2011). It is a prevalent disease that requires intense and prolonged treatment (ACS, 2005). Surgery to remove the tumor, especially when diagnosed early is usually the first line of management. Adjuncts to surgery include the use of chemotherapy, radiation therapy, hormone therapy, physiotherapy, and targeted or biological therapy (ACS, 2013).

There has been improvement in survival rate of individuals with BC over the past 25 years in the Western countries resulting in a substantial number of BC survivors (ACS, 2012). In the United States of America, BC survivors are estimated to exceed 12 million and 68% of individuals diagnosed with cancer now live more than 5 years (ACS, 2012). This improvement in survival rate is attributed to early detection of the disease and improvement in cancer care (Berry *et al*., 2005; Jemal *et al*., 2011). In Nigeria, survival rate is still very low due to late detection of the disease and poor treatment compliance (Adesunkanmi *et al*., 2006). Increasingly, cancer care is being directed toward developing interventions to improve overall quality of life (QoL) as well as longevity (Courneya *et al*., 2003; Sternfeld *et al*., 2009). Therapeutic exercise has consistently been identified as a central element of rehabilitation for many chronic diseases and has been successful in improving QoL and reducing all-cause mortality (McNeely *et al*., 2006). Observational evidence suggests that moderate-intensity levels of aerobic exercise may reduce the risk of death from BC and therefore may prove to be a valuable intervention to improve not only QoL but overall survival (Holmes *et al*., 2005).

Marshall *et al*. (2009) reported that it took men between 92 and 102 steps per minute to reach moderate-intensity aerobic exercise while the range was between 91 and 115 steps per minute for women. These data support a general recommendation of walking at more than 100 steps per minute on level terrain to meet the minimum of the moderate-intensity aerobic exercise guideline. Because health benefits can be achieved with bouts of exercise lasting at least 10 minutes, a useful starting point for an individual is to accumulate 1,000 steps in 10 minutes, before building up to 3,000 steps in 30 minutes (American College of Sports Medicine, 2006). Stretching

exercise is a form of therapeutic exercise in which a specific skeletal muscle (or muscle group) is deliberately elongated, often by abduction from the torso, in order to improve the muscle's felt elasticity and reaffirm comfortable muscle tone (Weerapong *et al*., 2004). It results in increased muscle control and flexibility as well as increased range of motion of the joints of the body (Weerapong *et al*., 2004). It is common for athletes to stretch before and after exercise in order to reduce injury and increase performance (Yessis, 2006). Stretching can also strengthen muscles (Weerapong *et al*., 2004).

Cardiopulmonary capacity may be compromised in BC survivors because of the pathology of the disease, therapeutic regimens, weight gain and inactivity secondary to treatment (Brockstein *et al*., 2000; Gianni *et al*., 2001; Courneya *et al*., 2003; Jones *et al*., 2010). In some studies, it was observed that cardiopulmonary fitness was approximately 30% below that of age-matched sedentary healthy women up to three years following the completion of adjuvant therapy (Jones *et al*., 2007; Mackey *et al*., 2009). The precise causes of poor cardiopulmonary fitness are not known but are likely to be a consequence of direct cytotoxic therapy-associated injury to the cardiovascular system together with lifestyle perturbations (e.g., deconditioning and weight gain) (Jones *et al*., 2010). This reduction in cardiopulmonary capacity may lead to reductions in QoL and premature death (Courneya *et al*., 2003). Emerging research evidence indicates that poor cardiopulmonary fitness may be of central importance for certain adverse late effects of the disease including impaired left ventricular ejection fraction, elevated cardiovascular disease (CVD) risk profile, poor QoL, and fatigue following the completion of adjuvant therapy for operable BC (Herroro *et al*., 2006; Jones *et al*.,

2007). Again, weight gain and obesity are common occurrences in women diagnosed with BC (Demark-Wahnefried *et al*., 2001; McInnes and Knobf, 2001) and increasing body mass index (BMI) is a risk factor for the development of new cases of BC and also affects survival in women who have already been diagnosed with BC (McTiernan, 2006; Protani *et al*., 2010). Gain in weight usually ranges from 2.0 to 6.0 kg during the first year of diagnosis (Irwin *et al*., 2003). Multiple reasons for this post-diagnosis weight gain in BC survivors have been suggested and they include receiving chemotherapy, infertility following treatment after diagnosis, decreased physical activity, and increased total caloric intake (Irwin *et al*., 2003; McTiernan, 2006). Both weight gain and obesity adversely increase the risk for cardiovascular disease, hypertension, and diabetes (Calle *et al*., 1999; Kopelman, 2000), conditions for which women who have been diagnosed with BC are at increased risk (Aziz, 2002).

Studies evaluating the effects of different types of therapeutic exercises on cardiopulmonary, anthropometric and QoL parameters in BC survivors are few and most of them have been carried out in the western countries. This study was therefore designed to determine the effects of aerobic and/or stretching exercises on cardiopulmonary, anthropometric and QoL parameters in BC survivors in a Nigerian population.

1.2 STATEMENT OF THE PROBLEM

The global burden of BC continues to increase especially in economically developing countries and this is associated with increased mortality and morbidity due to various complications associated with it (Jemal *et al*, 2011). Cardiopulmonary capacity compromise in BC survivors due to the pathology of the

disease, therapeutic regimens, weight gain and inactivity secondary to treatment has been reported (Brockstein *et al*., 2000; Gianni *et al*., 2001; Courneya *et al*., 2003; Jones *et al*., 2010). This reduction in cardiopulmonary capacity may lead to reductions in QoL and premature death (Courneya *et al*., 2003). Poor cardiopulmonary fitness may be of central importance for certain adverse late effects of the disease including impaired left ventricular ejection fraction, elevated CVD risk profile, poor QoL, and fatigue following the completion of adjuvant therapy for operable BC (Herroro *et al*., 2006; Jones *et al*., 2007). Again, weight gain and obesity are common occurrences in women diagnosed with BC (Demark-Wahnefried *et al*., 2001; McInnes and Knobf, 2001) and BMI is a risk factor for the development of new cases of BC and also affects survival in women who have already been diagnosed with BC (McTiernan, 2006; Protani *et al*., 2010). Both weight gain and obesity adversely affect risk for cardiovascular disease, hypertension, and diabetes (Calle *et al*., 1999; Kopelman, 2000), conditions for which women who have been diagnosed with BC are at increased risk (Aziz, 2002).

Identifying therapeutic interventions which will reduce risk of BC recurrence, improve cardiopulmonary functions, anthropometric and QoL parameters and overall survival of BC survivors is a pressing concern. Therapeutic exercise has been identified as an intervention that reduces the risk of recurrence and morbidity associated with the disease and improves QoL as well as overall survival of BC survivors (Holmes *et al*., 2005; McNeely *et al*., 2006). However, although a number of research groups have investigated the efficacy of supervised exercise training interventions (aerobic, resistance, or aerobic and resistance combination training) to counteract therapy-induced poor cardiopulmonary fitness both during and following the completion of adjuvant therapy (McNeely *et al*., 2006), the importance of

cardiopulmonary fitness for women following a BC diagnosis has received limited attention (Jones *et al*., 2007). Also, as research in this area is still at the preliminary stage, an ideal dosage of therapeutic exercise/s (in terms of frequency, intensity, time and type/s) that will improve the cardiopulmonary, anthropometric and QoL parameters in BC survivors has not been established. At present, no study has compared the effects of aerobic exercise on cardiopulmonary, anthropometric and QoL parameters with those of stretching exercises on the same parameters in BC survivors. There is no research on the combined effects of aerobic and stretching exercises on cardiopulmonary, anthropometric and QoL parameters in BC survivors. No study has observed the effects of these therapeutic exercises on cardiopulmonary, anthropometric and QoL parameters in premenopausal and postmenopausal BC survivors simultaneously for the purpose of comparison between the two groups of subjects.

Again, most of the findings on the effects of exercise on selected outcome parameters in BC survivors are mainly from studies carried out among Caucasian women. Little is known about the effects of therapeutic exercises on cardiopulmonary functions, anthropometric and QoL outcomes in BC survivors among Nigerian women despite the low survival rate among these women (Adesunkanmi *et al*., 2006). This may be particularly important because of some differences between the demographic characteristics of BC survivors in Nigeria and those of their Caucasian counterpart. For example, 70% of BC survivors in Nigeria are premenopausal women with peak age of affectation ranging between 36 years and 45 years (Ihekwaba, 1993; Adesunkanmi *et al.*, 2006; Adetifa, 2009) but BC is diagnosed among Caucasian women who are over 65 years old 50% of the time (ACS, 2005). This study was therefore designed to determine the effects of aerobic

and/or stretching exercises on cardiopulmonary functions, anthropometric, and QoL parameters in BC survivors in a Nigerian population.

1.3 AIM AND OBJECTIVES

1. The overall aim of this study was to determine the effects of therapeutic exercises on cardiopulmonary, anthropometric and QoL parameters in premenopausal and postmenopausal BC survivors.

1.4 SPECIFIC OBJECTIVES

The specific objectives of this study were to determine:

1. The effects of aerobic exercise using treadmill on selected cardiopulmonary, anthropometric, and QoL parameters in premenopausal and postmenopausal BC survivors.
2. The effects of stretching exercise on selected cardiopulmonary, anthropometric, and QoL parameters in premenopausal and postmenopausal BC survivors.
3. The effects of combined aerobic exercise using treadmill and stretching exercise on selected cardiopulmonary, anthropometric, and QoL parameters in premenopausal and postmenopausal BC survivors.
4. An ideal dosage of therapeutic exercise that improves the cardiopulmonary, anthropometric and QoL parameters in premenopausal and postmenopausal BC survivors.

1.5 SIGNIFICANCE OF THE STUDY

The result of this study may help to determine the appropriate type (mode) of therapeutic exercise/s at the right frequency, intensity and duration that can be safe

and effective in improving the cardiopulmonary, anthropometric and QoL parameters in both premenopausal and postmenopausal BC survivors. Hence, it may serve as a guide for physiotherapists in exercise prescription for this group of patients. This in turn may help diminish the morbidity and mortality associated with BC in Nigeria.

The findings from this study may answer the questions surrounding one of the mechanisms by which therapeutic exercises improve the health status of BC survivors. This is by determining the efficacy of moderate intensity aerobic exercises and/or stretching exercises in reducing obesity among BC survivors as there are inconsistent results over the fact that exercise improves the health status of BC survivors through weight loss (McTiernan, 2007). Obesity and weight gain post BC diagnosis has been described as a risk factor for both primary and secondary BC and it affects survival in BC survivors (McTiernan, 2007).

The findings of this study can be added to the database of research studies on the management of BC. It may also stimulate interest for further research in this area.

1.6 LIMITATIONS OF THE STUDY

Many BC survivors were unwilling to participate in the study due to the side effects of chemotherapy and/or radiotherapy such as Cancer related fatigue (CRF) that they were experiencing at the time of the study. Another limitation was the sensitivity of the area of the body involved. Some of those who were willing to participate in the study were referred to LUTH for treatment from hospitals in other states of the country; therefore, they were unable to stay for the total duration of the study. These factors accounted for the delay in completion of the study.

1.7 SCOPE OF THE STUDY

This study was a randomized controlled trial which was conducted at the Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria. The subjects recruited for this study were female premenopausal and postmenopausal BC survivors with Stage 1, II and III BC. Their ages ranged from 30 to 74 years.

1.8 DEFINITION OF TERMS

1. **Breast Cancer:** This is a malignant tumor that starts from the cells of the breast (Stephan, 2011).
2. **Therapeutic Exercise** is the physical activity performed in a systematically dosed manner (e.g. a specific frequency, intensity, duration and mode) with the intention of improving health-related outcomes, such as cardiovascular fitness, muscular strength, body composition, depression, anxiety, sleep, cognition, and fatigue (American College of Sports Medicine, 2006).
3. **Aerobic Exercise** consists of rhythmic, repeated and continuous movements of some large muscle groups that result in increased activity of the heart and lungs in order to meet the body's increased oxygen demand (Ronald *et al*., 2007).
4. **Stretching Exercise** is a form of physical exercise in which a specific skeletal muscle (or muscle group) is deliberately elongated, often by abduction from the torso, in order to improve the muscle's felt elasticity and reaffirm comfortable muscle tone (Weerapong *et al*., 2004).
5. **Quality of Life** is a multifactorial, functional effect of an illness and its consequent therapy upon a patient. QoL must be measured from the patient's perspective, to reflect the importance and effect of the patient's beliefs,

values, and judgments on the results of the interventions (Spilker, 1990; Patrick and Erickson, 1993).

6. **Premenopause** is a word used to describe the years that lead up to the last menstrual flow (period) of a woman's life from menarche (Schmitz *et al*., 2008).

7. **Postmenopause** is a term that applies to women who have not experienced a menstrual bleed for a minimum of 12 months, assuming that they do still have uterus, and are not pregnant or lactating. Thus postmenopause is all of the time that follows the point when a woman's ovaries become inactive (Courneya *et al*., 2003).

1.9 LIST OF ABBREVIATIONS

BC - Breast cancer

QoL - Quality of life

BMI - Body mass index

FACT B - Functional Assessment of Cancer Therapy – Breast

FACT G - Functional Assessment of Cancer Therapy – General

TOI - Trial Outcome Index

RSBP - Resting systolic blood pressure

RDBP - Resting diastolic blood pressure

RRPP - Resting rate pressure product

SaO_2 - Arteriooxyhaemoglobin saturation

FVC - Forced vital capacity

VO_2max - Maximal oxygen uptake

WHR - Waist hip ratio

THR - Target heart rate

MHR - Maximal heart rate

HR@rest - Heart rate at rest

HRR - Heart rate reserve

MVO_2 - Myocardial oxygen consumption

%Fat - Percentage body fat composition

AET - Aerobic exercise using treadmill

SE - Stretching exercises

CAETSE - Combined aerobic exercise using treadmill and Stretching exercises

CHAPTER TWO

LITERATURE REVIEW

2.1 DEFINITION OF CANCER

Cancer is not just one disease, but a large group of almost 100 diseases characterized by uncontrolled cell division leading to growth of abnormal tissue (Stephan, 2011). Such abnormal cells can grow out of control and form a mass or 'tumour'. Its two main characteristics are uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites. If the spread is not controlled, cancer can result in death. A tumour is considered benign if it is limited to a few cell layers and does not invade surrounding tissues or organs. It is considered malignant or cancerous if it spreads to surrounding tissues or organs. Carcinoma is the term used to describe most common cancers that originate from epithelial tissues. Sarcoma is the term used to define tumours that arise from bone, muscle, fat, or connective tissue (ACS, 2013).

2.1.1 Definition of Breast cancer

Breast Cancer is a malignant growth that begins from the cells of the breast (Stephan, 2011). Carcinoma of the breast develops when malignant changes occur in the epithelial cells that line the lobules (lobular carcinoma) or more commonly, the ducts (ductal carcinoma) (ACS, 2013). It is increasingly considered to be not one disease, but a group of diseases distinguished by different molecular subtypes, risk factors, clinical behaviours and responses to treatment (ACS, 2013). Distinguished molecular subtypes of BC have been identified using gene expression profiles, a process that is both complex and costly (Perou *et al*., 2000).

2.2 EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is the most frequently diagnosed cancer among women in Nigeria, and in many other parts of the world (Adebamowo and Ajayi, 2000; ACS, 2005). According to global statistics on cancer, BC is now the most frequently diagnosed cancer among women worldwide and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths (Jemal *et al.*, 2011). Excluding cancers of the skin, BC is the most common cancer among US women, accounting for 29% of newly diagnosed cancers (ACS, 2013). It represents 16% of all female cancers (World Health Organization (WHO), 2006). It is the second most common cause of cancer death among women after lung cancer in the United States of America (ACS, 2013). In 2004, BC caused 519,000 deaths worldwide, which is about 7% of cancer death and almost 1% of all deaths (WHO, 2006). The incidence of BC varies greatly around the world, being lower in less-developed countries and greatest in the more-developed countries. In the twelve world regions, the annual age-standardized incidence rates per 100,000 women are as follows: in Eastern Asia, 18; South Central Asia, 22; sub-Saharan Africa, 22; South-Eastern Asia, 26; North Africa and Western Asia, 28; South and Central America, 42; Eastern Europe, 49; Southern Europe, 56; Northern Europe, 73; Oceania, 74; Western Europe, 78; and in North America, 90 (Stewart and Kleihues, 2003).

The United States has the highest annual incidence rates of BC in the world; 128.6 per 100,000 in whites and 112.6 per 100,000 among African Americans (ACS, 2007). In 2007, BC was expected to cause 40,910 deaths in the US (7% of cancer deaths; almost 2% of all deaths) (ACS, 2007). In 2013, approximately 39,620 women are expected to die from BC only after lung cancer (ACS, 2013). In 2000, an

estimated 182,800 women were diagnosed with BC in the United States of America. In 2001, about 200,000 women were diagnosed with the disease and the number rose to 217,000 in 2005 (ACS, 2005). The incidence rates continue to rise. More than 2.9 million United State women with history of BC were alive on January 1, 2012 (ACS, 2013). Approximately 80% of women with BC are expected to survive at least 5 years following diagnosis (ACS, 2005). The 5 year relative survival rate is lower is lower among women diagnosed with BC before age 40 (85%) compared to women diagnosed at 40 years of age or older (90 %) (ACS, 2013). This may be due to tumours diagnosed at younger ages being more aggressive and / or less responsive to treatment (Anders *et al*., 2009).

The incidence of BC among the Caucasians varies with age being very low in the twenties gradually increasing and reaching a plateau at the age of 45 and then increasing dramatically after 50 (ACS, 2013). It is diagnosed in women over 65years old 50% of the time (ACS, 2013). In Nigeria, about 70% of BC patients are premenopausal women ranging between 26 and 50 years old. The peak age range is 36 to 45 years old (Ihekwaba, 1993; Adesunkanmi *et al.*, 2006; Adetifa, 2009).

The longer a woman lives, the higher her risk becomes. For example, a 40 year-old woman has only 1 in 1,200 chance of developing BC during the next year and about 1 in 120 chance of developing it during the next decade (ACS, 2013). 1 of every 7 women who lives to age 95 or older will develop BC. Data from the surveillance, Epidemiology and End Results (SEER) programme at the National Cancer Institute, a population based data system consisting of 9 separate states and local cancer registries that cover about 10% of the United States population, clearly demonstrate the relationship between age and incidence of BC (ACS, 2013).

Although rare, BC also occurs in men. It can occur at any age, but it is most common between the ages of 60 and 70 years. For every 100 cases of BC in the United States, less than 1 are found in men and approximately 1.08 per 100,000 men per year are diagnosed with BC (Giordano *et al.*, 2004). There may be an increased incidence of BC in men with prostrate cancer. The prognosis, even in stage 1 cases, is worse in men than in women (Armando and Giuliano, 2006).

2.3 AETIOLOGY OF BREAST CANCER / RISK FACTORS

Today, BC, like other forms of cancer, is considered to result from multiple environmental and hereditary factors.

1. Lesions to DNA such as genetic mutation. For example, exposure to oestrogen has been experimentally linked to the mutations that cause BC (Cavalieri *et al*., 2006). Aside from oestrogen, viral oncogenesis and the contribution of ionizing radiation also cause lesions to DNA.
2. Failure of immune surveillance, which usually removed malignancies at early phases of their natural history (Fairey *et al*., 2005).
3. Abnormal growth factor that triggers the interaction between stromal cells and epithelial cells (Reis-Filho and Pusztai, 2011). For example, in the angiogenesis necessary to promote new blood vessels that feed new cancer cells.

The definite cause/s of BC is still unknown in about 95% of BC cases but certain risk factors have been linked to it (Madigan *et al.*, 1995). These are

i. **Age**: About 60% of BCs occur in women older than 60. Risk is greatest after age 75 (ACS, 2013).

ii. **Sex**: Men are generally at lower risk for developing BC than women (ACS, 2013).

iii. **Previous Breast Cancer**: At highest risk are women who have had BC in one breast. After the removal of the diseased breast, the risk of developing cancer in the remaining breast is about 0.5 to 1.0% each year. Women diagnosed with early onset BC (Age < 40 years) have almost a 4.5-fold increased risk of subsequent BC (ACS, 2009).

iv. **Family History of Breast Cancer**: Breast cancer in a first-degree relative (mother, sister, or daughter) increases a woman's risk by 2 or 3 times; but BC in more distant relatives (grandmother, aunty, or cousin) increases the risk only slightly. Breast cancer in two or more first-degree relatives increases a woman's risk by 5 to 6 times (Collaborative Group on Hormonal Factors in Breast Cancer, 2001).

v. **Breast Cancer Genes**: Two separate autosomal genes for BC (BRCA 1 and BRCA 2) have been identified in two separate small groups of women. These genes are present in less than 1% and accounts for 5% to 10 % BC cases (Malone *et al*., 1998; Chen and Parmigiani, 2007). If a woman has one of these genes, her chances of developing BC are very high, possibly as high as 50 to 85% by age 80 (Malone *et al*., 1998; Chen and Parmigiani, 2007). However, if such a woman develops BC, her chances of dying of it are not necessarily greater than those of any other woman with BC. Women likely to have one of these genes are those who have a strong family history of BC. The incidence of BC in men is increased in families with the BRCA 2 gene.

The incidence of ovarian cancer and pancreatic cancer is increased in families with both BC genes. The presence of NBR 2 near BRCA 1 has been

identified and research into its contribution to BC pathogenesis is ongoing (Auriol *et al*., 2005).

vi. **Other Genes:** Other inherited conditions associated with smaller increased BC risk include Li-Fraumeni and Cowden syndromes and a number of more common genetic mutations (Turnbull and Rahman, 2008). TP53, PTEN and RS 4973768 are also associated with increased risk of BC.

vii. **Ovary Removal:** Ovary removal can reduce 51% risk of BC in women who have mutation in BRCA 1 or BRCA 2 genes (Rebbek *et al*., 2009).

viii. **Fibrocystic Breast Disease:** Having fibrocystic breast disease seems to increase risk only in women who have an increased number of cells in the milk ducts (Kabat *et al*., 2010).

ix. **Age at puberty, first pregnancy, menopause and child bearing**

The earlier menstruation begins, the greater the risk of developing BC. The risk is 1.2 to 1.4 times greater for women who first menstruated before age 12 than those who first menstruated after age 14 (Kelsey *et al*., 1993). The later menopause occurs and the later the first pregnancy, the greater the risk (Kelsey *et al*., 1993). There appears to be a transient increase in BC risk following a full-term pregnancy, particularly among women who are older at first birth (Kelsey *et al*., 1993). Having more children (about 7% lowered risk per child) and breastfeeding lowers the risk of BC (Byers *et al*., 1985; Faupel-Badger *et al*., 2013). Never having a baby also doubles the risk of developing BC. These factors probably increase risk because they involve longer exposure to oestrogen, which stimulates the growth of certain cancers.

x. **Prolonged use of Oral Contraceptives or Oestrogen Therapy**

Most studies do not show any relationship between the use of Oral contraceptives and the later development of BC, except possibly for women who took them for many years (National Cancer Institute (NCI), 2006; Chlebowski *et al*., 2010). After menopause, taking oestrogen therapy for 5-9 years may slightly increase risk. Taking hormone therapy that combines oestrogen and progesterone increases the risk (Chlebowski *et al*., 2003) but it reduces the risk of cancer of the Uterus (NCI, 2006). It also increases mammographic density (Lundstrom *et al*., 1999; Rutter *et al*., 2001; Greendale *et al*., 2005).

xi. **Mammographic Density:** There is now extensive evidence that mammographic density is an independent risk factor for BC that is associated with large but relative and attributable risks for the disease (McCormack and Dos Santos Silva, 2006; Boyd *et al*., 2007). Women with high levels of mammographic density have a fourfold to six fold greater risk of developing BC than women with lower levels of mammographic density; thus, mammographic density is a stronger predictor of BC risk than most traditional risk factors. Mammographic density reflects proliferation of the breast epithelium and stroma, in response to growth factors induced by current and past circulating sex hormone levels. Mammographic density reflects variations in the tissue composition of the breast. It is the proportion of the breast area in the mammogram that is occupied by dense breast tissue (Wolfe, 1976). The epidemiology of mammographic density, including the influences of age, parity and menopause, is consistent with it being a marker of susceptibility to BC, in a manner similar to the concept of 'breast tissue

age' described by the Pike model (Pike *et al*., 1983). It is associated positively with collagen and epithelial and non-epithelial cells, and negatively with fat. Mammographic density is influenced by some hormones and growth factors as well as by several hormonal interventions. Extensive mammographic density is associated with an increased risk for atypical hyperplasia and in situ BC (Boyd *et al*., 1992), which are associated with an increased risk for subsequent invasive BC (Dupont and Page, 1985; Hartmann *et al*., 2005). It is also associated with urinary levels of a mutagen. Twin studies have shown that most of the variation in mammographic density is accounted for by genetic factors.

xii. **Obesity after Menopause:** Risk is somewhat higher for obese postmenopausal women. The risk of postmenopausal BC is about 1.5% higher in over-weight women and about 2% higher in obese women than in lean women (La Vecchia *et al*., 2011). In contrast, a large meta-analysis found that overweight and obese women who were ages 40-49 had 14% and 26% lower risk for developing BC respectively than normal weight women (Nelson *et al*., 2012).

xiii. **Radiation Exposure:** Exposure to radiation such as that given for cancer or significant exposure to x-rays before age 30 increases risk (Preston *et al.*, 2002).

xiv. **Tobacco and Alcohol:** A recent meta-analysis by ACS researchers found that current smokers have a 12% higher risk of BC than women who never smoked (Gaudet *et al*., 2013). Alcohol consumption increases the risk of BC by 7% - 12% for each 10g (roughly one drink) of alcohol consumed per day

(Chen *et al*., 2011). Women who have 3 or more drinks a day increase their risk by 30%.

xv. **Physical Inactivity:** Women who exercise regularly have been shown to have reduced risk of BC (McTiernan, 2006). Regular exercises reduce risk by 10% to 20% in postmenopausal women more than premenopausal women (World Cancer Research Fund (WCRF) / American Institute for Cancer Research (AICR), 2007). The International Agency for Research on Cancer (IARC) review panel in 2002 also examined this issue and stated that in industrialized countries the value would be expected to be at least 11%.

2.4 PATHOGENESIS

Cancerous cells develop from healthy cells in a complex process called **transformation**. Excess production of free radicals in the body has been implicated as one of the major cause of BC (McTiernan, 2006; Schmitz *et al*., 2008). Free radicals are atoms or groups of atoms with odd (unpaired) number of electrons that can be formed when oxygen interacts with certain molecules. Once formed these highly reactive radicals can start a chain reaction, like dominoes. There are three important steps in free radical reaction (Hart, 1991). The initial step is chain initiation, in which a free radical is formed. The second step, chain propagation occurs when a free radical is consumed but a new free radical is produced to continue the chain. As the reaction proceeds, many free radicals are produced at once. The final step is when a chain termination reaction occurs, in which 2 free radicals combine, thus pairing off each other's lone electrons.

These unpaired electrons readily react with cellular components such as proteins (structural, contractile, enzymatic), membrane lipids, and even nucleotides within

DNA and RNA, changing the structures of these molecules. The chief danger of free radicals comes from the damage they can do when they react with DNA or the cell membrane. If enough damage occurs to the DNA segments of a cell that controls cell division and growth, cancer can develop from a single cell (McTiernan, 2006).

The first step in the process of cancer development is **initiation**, in which a change in the cell's DNA and sometimes in the chromosome structure primes the cell to become cancerous (Cavalieri *et al*., 2006). This change may occur spontaneously or be brought about by carcinogens. Carcinogens include many chemicals, tobacco, viruses, radiation and sunlight. A genetic flaw in a cell and chronic physical irritation may make a cell more susceptible to carcinogen. The second and final step in the development of cancer is called **promotion.** Promoters are agents that promote the growth of cancer cells and they may be substances in the environment or even drugs such as Barbiturate. Promoters have no effect on non-initiated cells. Some carcinogens are sufficiently powerful to cause initiation and promotion. For example, ionizing radiation used in X-rays, produced in nuclear power plant and atomic bomb explosions.

Breast cancer may spread to other surrounding tissues through the lymphatic system (Figure 1) or bloodstream.

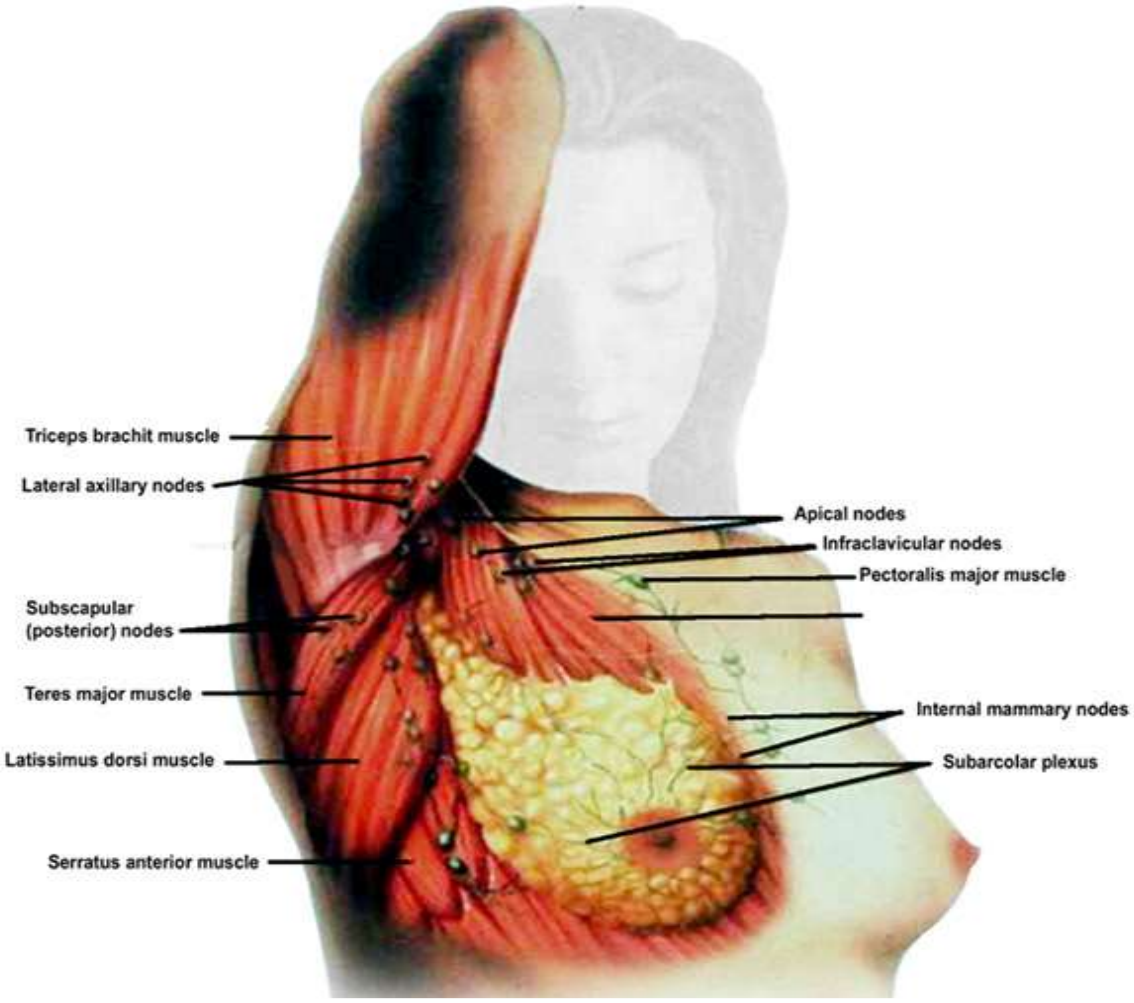

Figure 1: Lymphatic drainage and other structures around the breast (ACS, 2007).

2.4.1 How Free Radicals are formed in the Body

1. Free radicals can be formed during normal metabolic activity in the body. At the mitochondria of cells, specifically the cytochrome of electron chain, enzymes are present to assist in processing oxygen. While these enzymes have evolved to efficiently process oxygen during the generation of energy, about 2-5% of all the oxygen flowing through this transport chain goes bad, forming reactive oxygen species (ROS) and free radicals (Cheeseman and Slater, 1993). Under normal resting conditions, the human body consumes about 3.5ml of oxygen per kilogram of body mass per minute. This means that an average 80kg individual would consume about 403 litres of oxygen in a day.
2. Free radicals can be formed during inflammation. Not all free radical formation in biological systems is accidental. Some enzymes cause catalysis at the active site in response to inflammation using free radicals (Hart, 1991; Pathak *et al*., 2005).
3. Free radicals are also formed when cells are exposed to radiation such as from the atmosphere, x-rays and ultra-violet rays etc.

2.4.2 Biomarkers for Measurement of Oxidative Stress

Because it is not possible to directly measure free radicals in the body, scientists have approached this question by measuring the by-products that result from free radical reactions. If the generation of free radicals exceeds the antioxidant defenses then one would expect to see more of these by-products. These measurements have been performed in athletes under a variety of conditions. A variety of biomarkers for measurement of oxidative stress in vivo have been proposed, including markers of oxidative damage to DNA, protein and lipids (Kohen and Nyasa, 2002), but a validation study in rats indicated that blood or urinary isopros-tanes and urinary malondialdehyde (MDA) are the best indicators of in vivo oxidative stress (Kadiiska

et al., 2005). These compounds are products of lipid peroxidation produced from the free radical mediated oxidation of arachidonic acid. Isoprostane is a prostaglandin-like compound (Milne *et al*., 2005) and MDA is a known mutagen (Mukai and Goldstein, 1976; Basu and Mamett, 1983).

2.4.3 Relationship of Mitogenesis (cell Proliferation) and Mutagenesis (Free Radical Production)

Increased cell proliferation can cause an increase in production of ROS and lipid peroxidation, and the products of lipid peroxidation themselves can promote cell proliferation via cell signaling (Davis, 1999). Interestingly, MDA and isoprostanes (products of lipid peroxidation) have been reported to be mediators of the increased cell proliferation and collagen production seen in hepatic fibrosis (Comporti *et al*., 2005). Fibrosis, a response to tissue injury and inflammation (which increase oxidative stress), involves the proliferation and activation of fibroblasts and results in accumulation of extracellular matrix and collagen (Hinz, 2007). It is unknown whether the process of fibrosis is related to mammographic density and increased risk for BC. However, chronic inflammation and/or the wound healing response may be involved in the initiation or promotion of cancer (Bhowmick *et al*., 2004; Mark *et al*., 2007), and the presence of BC is associated with reactive stroma, a process that resembles fibrosis (Kalluri and Zeisberg, 2006) that is thought to promote tumour progression and invasion. Thus, the association of increased MDA with higher mammographic density may be either a cause or an effect of increased cell proliferation and collagen production, and the risk for BC may be increased by these processes as well as by mutagenesis. Both stromal and epithelial cells are potential

sites of mutagenesis, either of which might initiate processes that ultimately give rise to BC cancer.

2.4.4 Race and Oxidative Stress

Several lines of evidence suggest that there is an association between oxidative stress and some factors that are known or suspected to influence risk for BC. Chinese women living in China have lower levels of urinary MDA excretion (Yeung *et al*., 1991) and lower BC risk than do Chinese women living in the USA, and Chinese American women have lower urinary isoprostane excretion than Caucasian American women (Tomey *et al*., 2007). The lower risk and oxidative stress observed in Asian women may be related to their lower body weight and dietary fat intake compared with Caucasian women. Lower body weight is associated with lower BC risk (Key *et al*., 2001) and lower levels of isoprostane (Block *et al*., 2002; Keaney *et al*., 2003). Lower dietary fat intake may be associated with reduced BC risk (Prentice *et al*., 2006) and with reduced oxidative stress (Djuric *et al*., 1991; Tomey *et al*., 2007). Markers of oxidative stress are higher in postmenopausal than in premenopausal women (Trevisan *et al*., 2001; Hong *et al*., 2004) and may be reduced by menopausal hormone therapy (Wakatsuki *et al*., 1998) and tamoxifen (Thangaraju *et al*., 1994). However, oestrogen and its metabolites have both anti-oxidant and pro-oxidant effects (Gago-Dominguez *et al*., 2005), and urinary isoprostane excretion was not associated with blood oestrogen levels (Ide *et al*., 2002).

2.4.5 Exercise and Oxidative Damage

It has been well documented that moderate intensity exercise increases pro-oxidant (free radical) production (Alessio, 1993; Sen, 1995). However, it is known that

exercise is good for the body and in fact, protects against many of the diseases associated with free radical induced damage. The body responds to moderate intensity exercise training with an upregulation of the natural anti-oxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPX) (Dekkers *et al*., 1996; Peters *et al*., 2001; McTiernan, 2006). Therefore, although exercise causes an increase in radical formation, the physiological response to this actually improves the pro-oxidant to anti-oxidant ratio (Sen, 1995; McTiernan, 2006). This means that short term exercise increases free radical production while long term exercise reduces it. Endurance exercise can increase oxygen utilization from 10 to 20 times over the resting state (Milnor, 1980). This greatly increases the generation of free radicals, prompting concern about enhanced damage to muscles and other tissues.

2.4.6 Antioxidants and Free Radicals

Antioxidants are molecules which can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged (Aruoma, 1994; kanter, 1998). They form a defense against cell damage caused by free radicals, which are involved in aging process, cancer formation, muscle, joint, and tendon damage, and even in inflammation and degenerative arthritis. The principal micronutrient (vitamin) antioxidants are vitamin E, beta-carotene, and vitamin C (Ghosh *et al*., 1996; Evans, 2000; Tauler *et al*., 2002). Additionally, selenium, a trace metal that is required for proper function of one of the body's antioxidant enzyme systems, is sometimes included in this category. The body cannot manufacture these micronutrients so they must be supplied in the diet.

Vitamin E (d-alpha tocopherol) is a fat soluble vitamin present in nuts, seeds, vegetable and fish oils, whole grains (esp. wheat germ), fortified cereals, and

apricots. Current recommended daily allowance (RDA) is 15 IU per day for men and 12 IU per day for women (Diplock, 1987; Colgan, 1993).

Vitamin C (Ascorbic acid) is a water soluble vitamin present in citrus fruits and juices, green peppers, cabbage, spinach, broccoli, kale, cantaloupe, kiwi, and strawberries. The RDA is 60 mg per day. Intake above 2000 mg may be associated with adverse side effects in some individuals (Colgan, 1993; Bucci, 1995).

Beta-carotene is a precursor to vitamin A (retinol) and is present in liver, egg yolk, milk, butter, spinach, carrots, squash, broccoli, yams, tomato, cantaloupe, peaches, and grains. Because beta-carotene is converted to vitamin A by the body there is no set requirement. Instead the RDA is expressed as retinol equivalents (RE), to clarify the relationship (Colgan, 1993; Goldfarb, 1993). (Vitamin A has no antioxidant properties and can be quite toxic when taken in excess).

2.5 TYPES OF BREAST CANCER

Breast cancer is usually classified by the kind of tissue in which the cancer starts and by the extent of its spread. Breast cancer that starts in the milk ducts (Figure 2) is called **Ductal carcinoma** which accounts for 90% of all BCs (ACS, 2013). The one that starts in the milk-producing glands (Lobules) (Figure 2) is called **Lobular Carcinoma**. Breast cancer that starts in fatty or connective tissue, a rare type, is called **Sarcoma**.

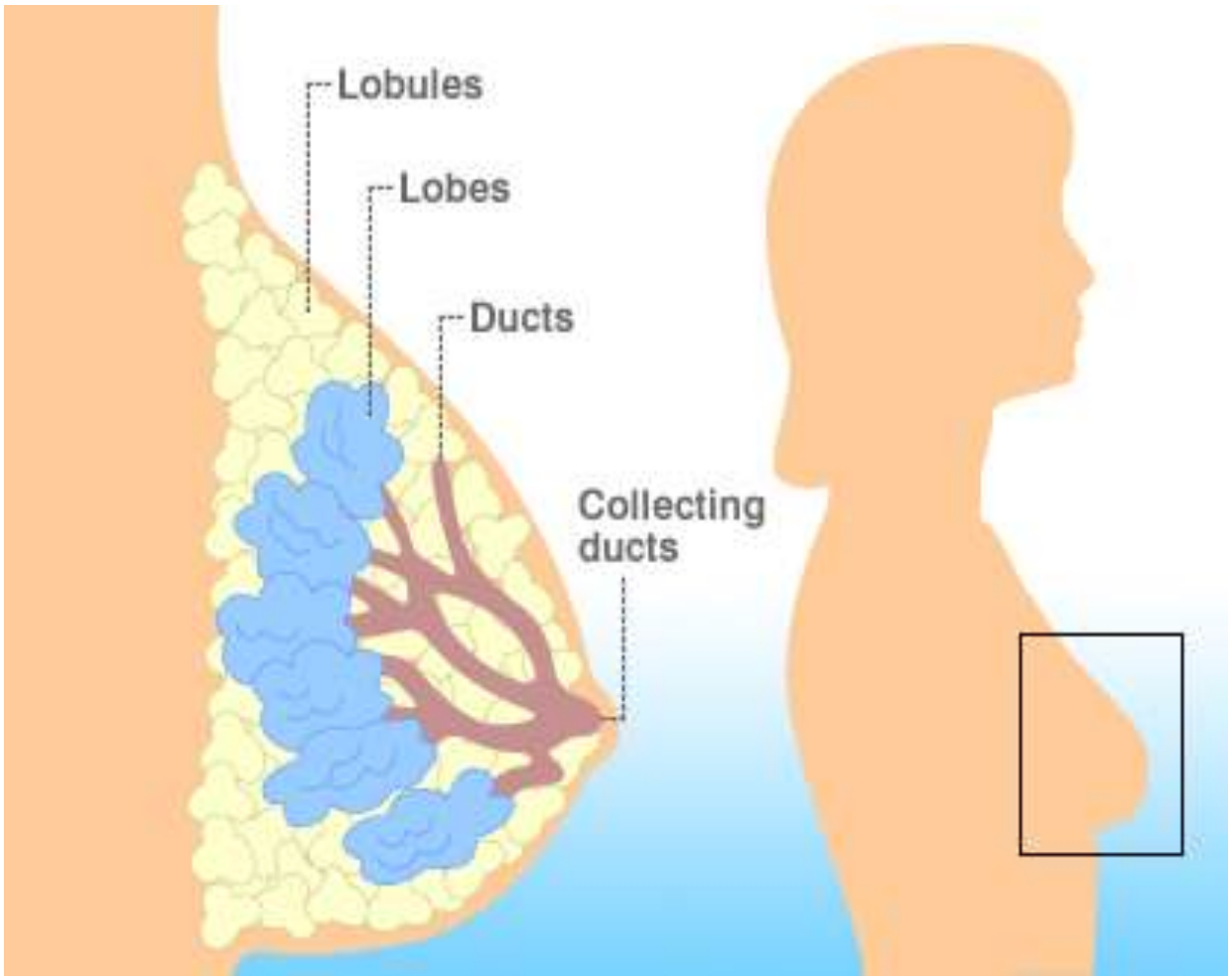

Figure 2: The breast showing the milk glands (ACS, 2007).

The various types of breast cancers are;

a. **Ductal Carcinoma in Situ:** This is confined to the milk ducts of the breast. It does not invade surrounding breast tissue, but it can spread along the ducts and gradually affect a substantial area of the breast. It accounts for 20 to 30% of BCs (ACS, 2013). About one- third of ductal carcinoma in situ progresses to invasive cancer (Allred, 2010).

b. **Lobular Carcinoma in Situ**: The cancer grows within the milk producing glands of the breast. It often occurs in several areas of both breasts. Women with Lobular carcinoma in situ have a 30% chance of developing invasive BC in the same or other breast during the next 24 years. It accounts for 1 to 2% of BCs (ACS, 2013).

c. **Invasive Ducal Carcinoma:** This begins in the milk ducts of the breasts but spreads through the wall of the ducts, invading the surrounding breast tissue. It can also spread to other parts of the body. It accounts for 65 to 80% of BCs (ACS, 2013).

d. **Invasive Lobular Carcinoma:** This begins in the milk-producing glands of the breast but invades surrounding breast tissue and spreads to other parts of the body. It is more likely than other types of breast cancer to occur in both breasts it accounts for 10 to 15% of BCs (ACS, 2013).

e. **Inflammatory Breast Cancer**: This is aggressive and often fatal. It occurs disproportionately in younger people. Cancer cells block the lymphatic vessels in the skin of the breast, causing the breast to appear inflamed (swollen, red and warm). It is initially staged as stage IIIb or stage IV. It is unique because it often does not present with a lump, so it is often undetected by Mammography or Ultrasound. It present with signs and

symptoms of a breast infection like mastitis. Usually cancer spreads to the lymph nodes in the armpit. It accounts for about 1% of BCs (ACS, 2013).

Other rare forms of BC which are types of Invasive ductal carcinoma (IDC) are:

i. **Medullary Carcinoma**: It makes up 15% of BCs. Lesions are well Circumscribed and usually oestrogen and progesterone negative 90% of time (ACS, 2013).

ii. **Tubular Carcinoma:** Tubular carcinoma makes up about 2% of BCs. Lesion is on orderly or well differentiated carcinoma of the breast.

iii. **Mucinous (Colloid) Carcinoma**: This represents 1 to 2% of BC and has well rounded lesions (ACS, 2013).

iv. **Paget disease of the nipple:** This is also a type of Ductal BC but may be insitu or invasive. These rare forms of BC have better prognosis than the common types.

Some other types are:

v. **Cystosarcoma phylloids**

vi. **Adenocystic carcinoma**

vii. **Micropapillary carcinoma**.

2.6 SYMPTOMS OF BREAST CANCER

At first there are no symptoms. About 80% of women with BC discover a lump themselves in the affected breast which usually feels distinctly different from the surrounding tissue (ACS, 2013). There may be skin dimpling or an abnormality in the shape of a breast that is diseased with cancer compared with the unaffected one. In advanced cancer, swollen bumps or festering sores may develop on the skin

(Figure 3). The lump maybe painful or it may not be but pain is an unrealistic sign. Lymph nodes particularly those in the armpit may feel like hard small lumps.

In inflammatory BC, the breast is warm, red, and swollen as if infected but it is not (Figure 4).

- The nipple may become inverted.
- A discharge from the nipple is common.
- Often, no lump can be felt in the breast (ACS, 2013).

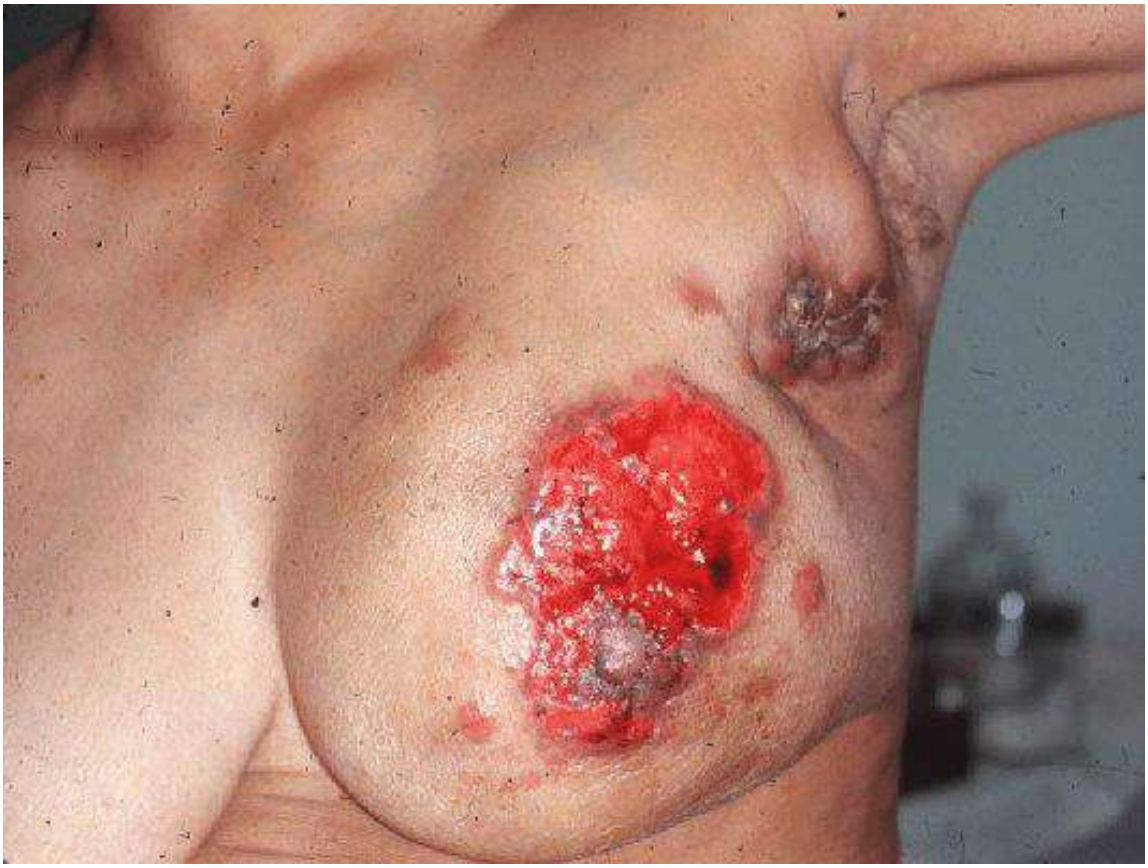

Figure 3: Festering sores on a breast with cancer (ACS, 2008).

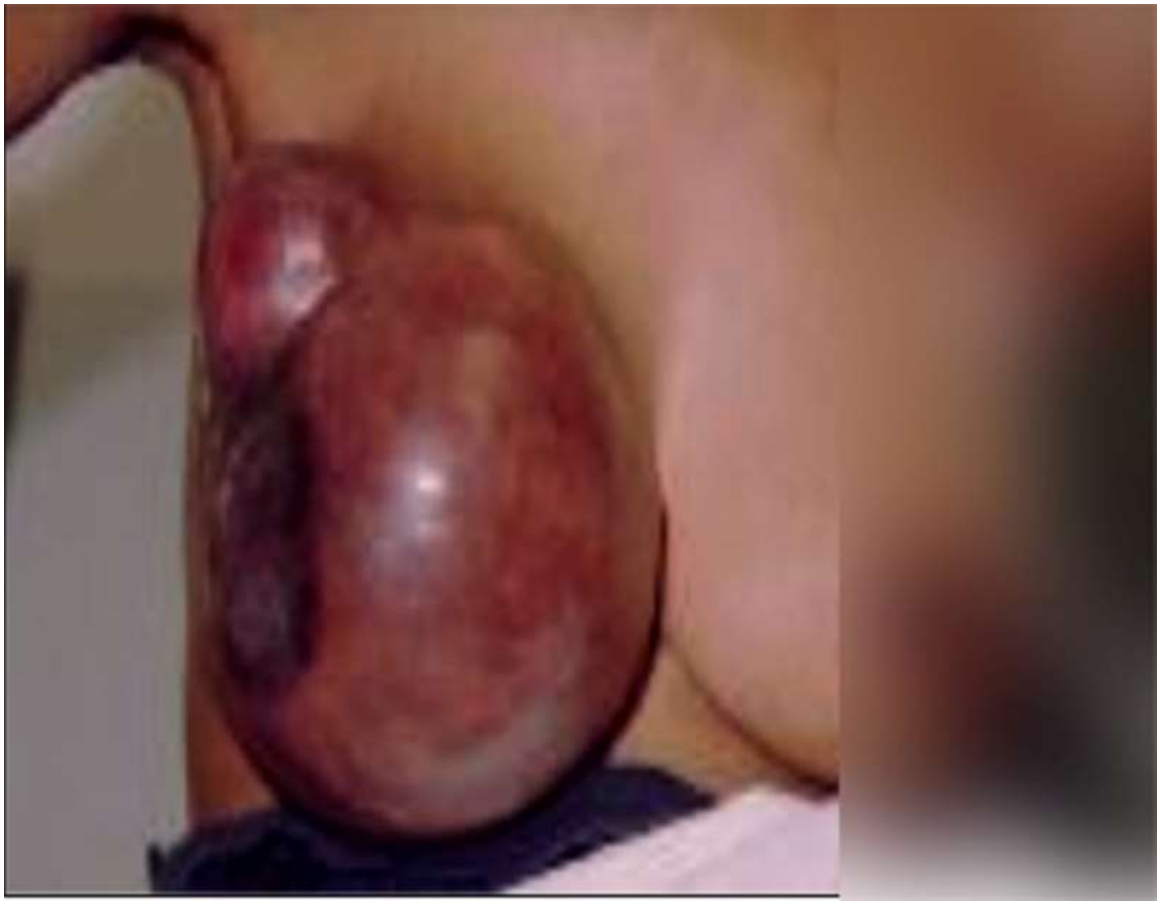

Figure 4: An advanced inflammatory breast cancer (ACS, 2007).

2.7 SCREENING

Early detection and treatment of BC is extremely important in achieving good outcomes. Self-examination and physician's exam will detect cancer at a rate between 70 and 80% (ACS, 2013). Adding screening Mammography (Mammograms) (Figure 5) will increase detection to 96 to 98% (ACS, 2013). However, Mammograms which is today's gold standard for screening will still miss between 10 and 15% of these tumors.

Other screening tools apart from Self-examination, Physicians examination and Mammogram are

a. Breast ultrasound which is often used in conjunction with or after a Mammogram to further evaluate an abnormality.
b. Ductograms/galactograms.
c. Computer-aided scans.
d. Scintimammograph: This uses radio-active tracers.
e. Magnetic Resonance Imaging (MRI): This is a very sensitive screening test which may become the gold standard replacing Mammograms. It can detect smaller tumors than plain Mammography (ACS, 2013).
f. Positrons Emission Tomography (PET) Scans: This is used especially if metastasis is suspected.
g. Biopsies (ACS, 2013).

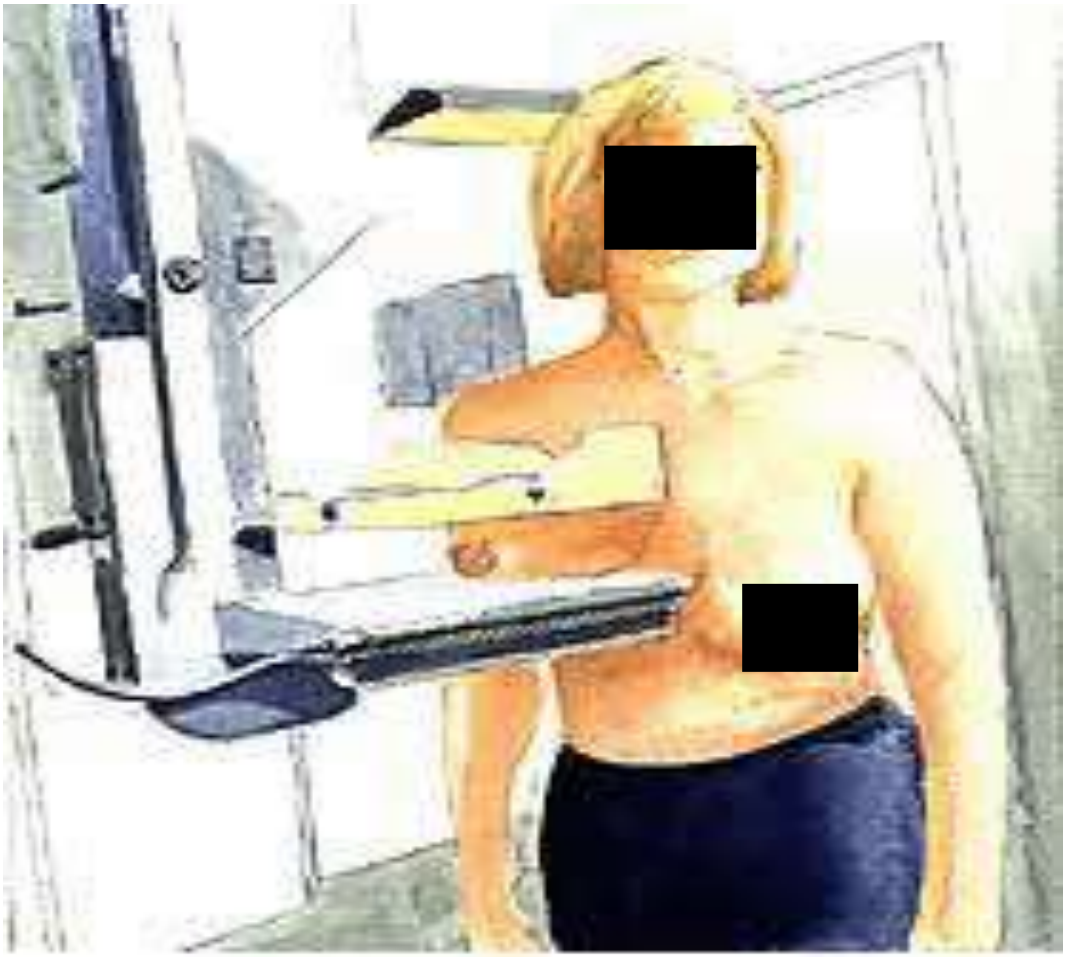

Figure 5: An illustration of a woman having a mammogram (ACS, 2007).

Screening should start with baseline Mammogram at age 35, or younger if there is a strong family history. Annual examinations should be performed once a woman gets to 40 years. Self-examination should be encouraged monthly starting from the age of 20 (ACS, 2013). If a clinically noted mass is followed by a negative Mammogram, the work up should then include a breast Ultrasound, the use of MRI and/or fine-needle aspiration cystology and close internal examination (ACS, 2013). A biopsy is usually carried out to confirm the diagnosis.

2.8 STAGING AND OTHER PROGNOSTIC DETERMINERS

If cancer cells are detected in the biopsy, the sample is further analyzed for important prognostic determiners such as

1. Stages of the disease,
2. Histology and nuclear grade,
3. Oestrogen and progesterone receptor status (Reis-Filho and Pusztai, 2011),
4. The number of HER2 (Human epidermal growth factor receptor 2) present on the cancer cells (Reis-Filho and Pusztai, 2011).

Staging: Staging determines the type of treatment to be given and the prognosis of the disease.

Staging is designated by a number (0 to IV) and is based on the T, N, and M nomenclature where,

T designates tumor size.

N represents node involvement and

M denotes any metastasis (Edge *et al*., 2010).

For example, T1 N0 M0 is a tumor less than 2cm in size and has not spread to lymph nodes or distant sites. With this the Pathologist can appropriately stage the cancer.

1. **Stage 0:** Cancer is very small and still in situ or non-invasive.
2. **Stage 1:** Cancer is less than 2cm.
3. **Stage II:** Cancer is between 2 to 5cm and may be divided into

i. **Stage IIa:** Cancer has not spread to the lymph nodes in the arm pit.

ii. **Stage IIb:** Cancer has spread to the lymph nodes in the arm pit.

4. **Stage III:** Cancer is larger than 5cm and may be divided into

i. **Stage IIIa:** Cancer has spread extensively to the lymph nodes under the arm.

ii. **Stage IIIb:** Cancer has spread to lymph nodes near the breast bone, muscles, and other tissues near the breast.

iii. **Stage IIIc:** Cancer has spread to lymph nodes beneath the collarbone, lymph nodes near the neck, those within the breast or under the arm and tissues near the breast.

5. **Stage IV:** This is metastatic cancer in which cancer has spread beyond the breast and underarm lymph nodes to other parts of the body.

Stage 0, 1 and II (without lymph node involvement) are **early stages**. **Stage II** with lymph node involvement **and III** are **later stages** while **stage IV** is considered as advanced (ACS, 2013).

2.9 TREATMENT OF BREAST CANCER

There are several treatment options for BC. The treatment options are surgery, radiotherapy, chemotherapy, hormone therapy, biologic response modifier etc (ACS, 2013). The choice and pattern of treatment adopted by the Physician depends on the stage of the disease and other prognostic determiners such as the oestrogen/

progesterone receptor status. Therapeutic exercise in the management of cancer is not an option but a must for all patients with BC. It is beneficial to all patients irrespective of the stage of the disease and other prognostic determiners.

2.9.1 Surgery

Surgery is usually the first treatment given in the early stage of BC. The purpose is to remove all or as much cancer cells as possible from the affected breast. The various types of surgery carried out for BC patients are

a. Lumpectomy: This is also called breast conserving surgery and it involves only the removal of the breast lump and some normal tissue around it.

b. Partial (Segmental) Mastectomy: This involves the removal of more of the breast tissue than a lump. It is usually followed by radiotherapy.

c. Simple or Total mastectomy: This involves the removal of the entire breast without the lymph nodes under the arm.

d. Modified radical mastectomy: This is the removal of the entire breast, and some of the lymph nodes under the arm.

e. Radical Mastectomy: This is extensive removal of the entire breast, lymph nodes and the chest wall muscles under the breast.

2.9.2 Radiation Therapy

This is treatment with high-energy rays such as x-rays to kill or shrink cancer cells. The radiation may come from outside the body (external radiation) or from radioactive materials placed directly in the tumor (brachytherapy).

2.9.3 Chemotherapy

This is the use of cancer-killing drugs (usually a combination of several drugs) injected into a vein or taken as pill (ACS, 2013). It may be given before surgery to shrink the tumor or after surgery to kill any remaining cancer cells and reduce the chance of a recurrence. 'Chemo' can also be used as the main treatment for BC that has spread.

2.9.4 Hormone Therapy

These are hormonal drugs given to patients whose BCs are oestrogen and/or progesterone receptor positive (ACS, 2013). Tamoxifen is an example of drugs that block the effect of oestrogen. Aromatase inhibitors are a type of drug that inhibits the production of oestrogen especially given to postmenopausal BC patients. Some drugs target a particular tumor which has certain genetic markers like HER2/neu receptors e.g. Herceptin while Avastin is an example of drug that target new blood vessels that feed cancer cells.

2.9.5 Biologic Response Modifier

Recombinant technology has resulted in the development of biologic response modifiers, which includes the interferons, interleukins, and tumor necrosis factor (ACS, 2013).

2.9.6 Therapeutic Exercise

Exercise therapy is critical for BC survivors both during and after treatment (Courneya and Mackey, 2001). Therapeutic exercise in BC management focuses on relieving the side effects of treatment, ameliorating the complications of the disease and improving long-term recovery (Holmes *et al*., 2005). The secondary

complications associated with BC and its standard treatments continue to be significant. These complications include decreased QoL, decreased shoulder mobility, loss of arm strength, weight gain, sleep disturbances, cancer related fatigue (CRF), poor body image, increased risk of osteoporosis, CVD, premature menopause, loss of libido and lymphedema (Harris *et al*., 2003). In 2006, the first meta-analysis that focused solely on the effectiveness of exercise interventions in BC patients and survivors led by a Physiotherapist, Margaret McNeely concluded that exercise was an effective intervention to improve QoL, cardio-respiratory fitness, physical functioning, muscle strength and symptoms of fatigue.

During and immediately after treatment, the Physician needs to give his approval before a patient begins an exercise programme. This is because the cancer status such as blood cell counts (red and white blood cell counts) and weight loss need to be considered before beginning an exercise programme (ACS, 2013). For example, those who suffer severe anaemia should delay any aggressive exercise until their cell counts normalize (Hutnik *et al*., 2005; ACS, 2013).

Proper assessment for the cardiopulmonary, musculoskeletal and physical functions of a BC patient by the Physiotherapist is necessary before commencing an exercise therapy. Depending on the type/s of treatment a BC patient is receiving, the types and intensity of the exercise is important. During chemotherapy and radiation therapy, it is important to reduce the intensity of exercise because of the increased risk of fracture due to loss of bone mineral density (Courneya and Mackey, 2001).

Benefits of Therapeutic Exercises in Breast Cancer Management

1. Aerobic exercises, such as walking, jogging, cycling and swimming improve cardio-respiratory function, reduce CRF, assist in weight management and decrease the nausea associated with chemotherapy (Harris *et al*., 2003).
2. Aerobic exercises can diminish the possibility of lymphedema and reduce the likelihood of a recurrence (Harris *et al*., 2001).
3. Weight bearing exercises assist in maintaining bone density that may be lost during treatment. Aerobic exercise has been thought to reduce the effects of 'chemo brain' or the forgetfulness that is often associated with chemotherapy (Burnham and Wilcox, 2002).
4. Stretching/flexibility exercises (Figures 6 and 7) especially for the upper body increases the range of motion around the affected area such as the shoulder girdle (Harris *et al*., 2003).
5. Resistance training with light weights maintains strength of the muscles around the shoulder and the affected arm (Harris *et al*., 2003; Winter-Stone *et al*., 2012).
    - Relative high repetition resistance exercises help to manage existing lymphedema and improve endurance of the BC patient.
    - It is generally believed that light to moderate weight lifting can cause lymphedema but this is not so as movement improves drainage of the lymphatic fluid (Harris and Niesen-vertommen, 2000).
6. Exercise-related fatigue which is distinct from CRF may reduce sleeplessness of the cancer experience (Burnham and Wilcox, 2002).
7. Exercise therapy has been shown to reduce the depression and anxiety common to BC patients (Burnham and Wilcox, 2002).

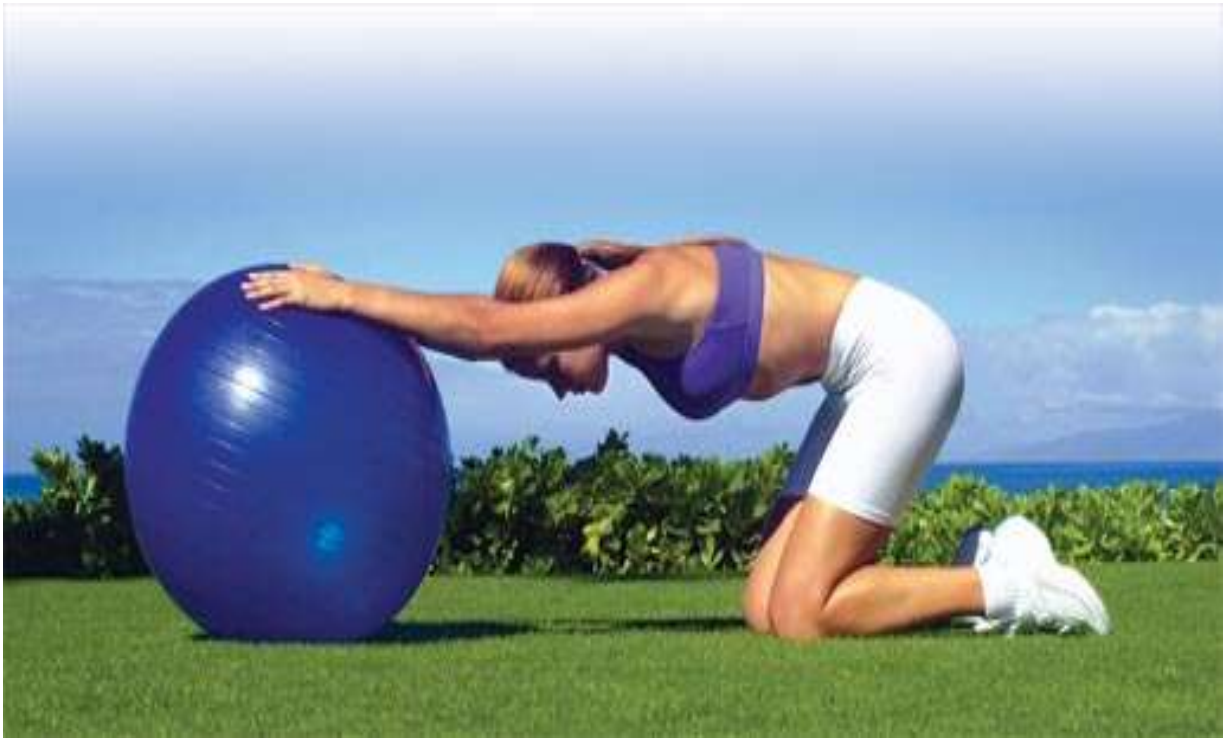

Figure 6: Flexibility/Stretching exercise for the upper body in a kneeling position using a medicine ball (ACS, 2005).

Figure 7: Breast cancer survivors performing therapeutic exercises (ACS, 2005).

8. The ability to perform daily tasks without undue fatigue and restriction leads to an increased sense of control and improved state of mind which are often lost during the cancer experience (Burnham and Wilcox, 2002).
9. Exercise has been shown to maintain blood cell counts during chemotherapy (Hutnik *et al*., 2005).

2.10 COMPLICATIONS OF BREAST CANCER AND ITS STANDARD TREATMENTS

The complications associated with BC and it's standard treatment include decreased QoL, decreased shoulder mobility, loss of arm strength, weight gain, sleep disturbances, cancer related fatigue (CRF), poor body image, increased risk of osteoporosis, CVD, premature menopause, loss of libido and lymphedema (Harris *et al*., 2003). Other complications are chest pain, back pain, bone and joint pain, abdominal pain, phantom breast pain, dry mouth, dry skin, dizziness/fainting, depression, fever, hair changes, headaches, heart problems, high/low blood pressure, haematoma, high cholesterol, hot flashes, infections, itching, kidney problems, liver problems, lung problems, low white blood cell count, memory loss, menopause and menopausal symptoms, mood swings, mouth and throat sores, nail changes, nausea, neuropathy, nosebleeds, numbness, osteonecrosis of the jaw, post-traumatic stress disorder, rash, runny nose, scar tissue formation, seroma (fluid build-up), skin discolouration, skin sensitivity, swallowing problems, sweating, swelling, taste and smell changes, urinary tract infection, urine discolouration, vaginal discharge, vaginal dryness, vision problems, vomiting, weakness, weight changes, addiction, allergic reactions, anemia, anxiety, appetite changes, and armpit discomfort.

2.10.1 Cardiopulmonary Toxicity of Cancer Treatment

The development of aggressive treatment for a number of cancers has yielded increasing survival rates but has also been associated with increasing frequency of cardiac and pulmonary toxicity (Brosius *et al*., 1981; Lingos *et al*., 1991; Wesselius, 1992; Hochster *et al*., 1995; Stover and Kaner, 1997). There is often a synergistic effect of irradiation and some of the therapeutic agents. Some of the drugs when used in combination also have a synergistic effect, which increases their degree of cardiac or pulmonary toxicity (Allen, 1992; Albert, 1997; Ewer and Benjamin, 1997; Jones, 1997). Therapeutic radiation to the chest for the treatment of BC and some other cancers necessarily exposes the heart and lungs to varying degrees of radiation, depending on the extent of the disease. The pericardium is the most commonly affected structure resulting in pericarditis, which is usually mild to moderate, but can occasionally be severe. Other cardiac manifestations of radiation toxicity include acute myocardial ischaemia and infarction due to radiation-induced vascular injury and accelerated atherosclerosis; restrictive cardiomyopathy and ECG changes, including varying degrees of heart block, due to endocardial fibrosis; mitral regurgitation resulting from papillary muscle dysfunction; and vavular regurgitation as a consequence of endocardial vavular thickening (Brosius *et al*., 1981; Gustavsson *et al*., 1990). Radiation effects on cardiac tissue may occur early, even before the completion of radiotherapy, or they can appear years later. Fortunately, more refined treatment techniques have resulted in dramatic decreases in the incidence of these sequelae to less than 2.5% (Carmel and Kaplan, 1976).

Chest irradiation can also produce lung injury (Gross, 1977; Lingos *et al*., 1991; Wesselius, 1992; Monson *et al*., 1998). Acute radiation pneumonitis occurs in approximately 3 to 15% of patients who receive irradiation to the chest. Factors that

increase the risk of developing radiation pneumonitis include concomitant chemotherapy, previous irradiation, and withdrawal of steroids. It usually develops 2 to 3 months following completion of treatment. It requires no treatment and resolves within days to months, however less than 5% of the patients develop severe pneumonitis which requires hospitalization and aggressive supportive care (Tarbell *et al*., 1990). Although frequently asymptomatic, patients often complain of dyspnoea, cough, and fever. Over the next 6 to 24 months, most patients then develop gradual progressive fibrosis, which commonly stabilizes after 2 years and is usually asymptomatic. Some patients with no history suggestive of radiation pneumonitis go on to develop late pulmonary fibrosis. It is characterized primarily as a restricted lung disease, with varying degrees of dyspnoea, depending on the amount of fibrotic lung tissue. In cases of persistent fibrosis of a large volume of lung tissue, late radiation fibrosis can be severe, with Cor pulmonale and respiratory failure. Current research trials are examining agents that might modulate the fibrotic process, such as pentoxifyline, ACE inhibitors, and transforming growth factor beta antagonists (ACS, 2013).

Likewise the treatment of cancer using chemotherapeutic agents and biologic response modifiers is associated with both cardiac and pulmonary toxicity. Cardiotoxicity most frequently results from the use of the anthracycline antibiotics, doxorubicin, and daunorubicin (Allen, 1992; Hochster *et al*., 1995; Shan *et al*., 1996). Antracycline cardiotoxicity can develop as an acute or subacute injury, as a chronic cardiomyopathy, or as late-onset ventricular dysfunction years to decades after completing treatment. Arrhythmias and conduction disturbances are the most common manifestations of acute toxicity; more rarely, subacute left ventricular dysfunction and acute congestive heart failure can develop, as well as myocarditis,

sudden death and myocardial ischaemia and infarction. Chronic cardiomyopathy presents within a year of treatment and is the most common form of damage. Late cardiotoxicity appears as a chronic cardiomyopathy appearing after a prolonged asymptomatic period in 38 to 60% of patients treated with doxorubicin, though it is clinically apparent in less than 15% of patients (Praga *et al*., 1979; Steinherz *et al*., 1991; Mott, 1997). Young females may be at particular increased risk for late cardiac dysfunction, which is a major concern because doxorubicin is frequently used to treat BC (Lipshultz *et al*., 1995). The prognosis with clinically apparent doxorubicin cardiomyopathy (both early and late onset) is generally poor, with the mortality rate as high as 48% in patients who present in the first month following therapy, although most patients respond to treatment and appear to stabilize (Schwartz *et al*., 1987). Fortunately, modification of treatment schedules to 48 to 96 hour infusion has greatly reduced the incidence of early cardiomyopathy (Ewer and Benjamin, 1997). Research has led to the development of dexrazoxane, a specific cardioprotectant agent, which dramatically reduces the cardiotoxic effects of the anthracycline (Speyer *et al*., 1992; Mott, 1997). Recombinant technology has resulted in the development of biologic response modifiers, including the interferons, interleukins, and tumor necrosis factor, which also have some adverse cardiovascular effects. Hypotension and tachycardia are the most common problems, though there have also been reports of myocardial ischaemia and infarction. These adverse effects appear to be caused by significant alterations in fluid balance rather than any native dysrhythmic or cardiotoxic properties of the drugs. Fortunately, many of the cardiac complications associated with chemotherapeutic agents and biologic response modifiers are transient and reversible.

The lungs are also a common site of chemotherapy-related toxicity, and are associated with an increasing number of drugs (Lehne and Lote, 1990; Kriesman and Wolkove, 1992; MacDonald *et al*., 1995; Stover and Kaner, 1997). Interstitial pneumonitis is the most frequently encountered manifestation of pulmonary toxicity, which presents clinically as dyspnoea with or without a nonproductive cough and fever. The most common abnormalities seen on pulmonary function testing are a decreased diffusion capacity for carbondioxide and decreased lung volumes indicative of restrictive lung disease. There may also be arterial hypoxemia, especially with exercise. Some drugs cause unexplained pulmonary oedema in up to 38% of patients (Haupt *et al*., 1981). Biologic response modifiers and a few drugs are less commonly associated with pulmonary toxicity.

2.11 CARDIOPULMONARY CAPACITY OF BREAST CANCER SURVIVORS

Cardiopulmonary capacity may be compromised in BC survivors because of the pathology of the disease, therapeutic regimens, weight gain and inactivity secondary to treatment (Courneya *et al*., 2003). This reduction in cardiopulmonary capacity may lead to reductions in QoL and premature death.

2.12 PHYSICAL ACTIVITY AND BREAST CANCER RISK

There are epidemiological data which show that women who exercise regularly have a lower incidence of BC than women who do not exercise (McTiernan, 2006). A panel of expert scientists assembled by the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) in 2007 reviewed existing studies on the association of physical activity and BC risk. The WCRF/AICR panel concluded that physical activity probably has a preventive effect on postmenopausal BC. However, panel members found less evidence for a relationship between

physical activity and premenopausal BC, and they rated this association as being limited but suggestive. An earlier review was in agreement with this conclusion. In 2002, an expert panel of the International Agency for Research on Cancer (IARC) issued a report stating that there was sufficient evidence that greater physical activity has a preventive effect on BC in humans. However, they did not differentiate pre- from post-menopausal BC.

Studies examining physical activity and BC risk have, on average, reported a 20 to 40 percent lower risk of BC among women who are most physically active (McTiernan, 2006; WCRF / AICR, 2007). The studies examining premenopausal women separately have found an average 40 percent decrease in risk. The studies examining postmenopausal women reported an average 33 percent decrease in BC risk (McTiernan, 2006; WCRF / AICR, 2007). These values are considered to represent a weak to moderate decrease in BC risk. This finding is important because physical activity (exercise) levels, unlike most BC risk factors, can be modified.

Decreased BC risk has been associated with increased physical activity in women of all but extremely large body sizes (McTiernan, 2006). This finding suggests that physical activity has benefits for BC risk reduction beyond those associated with weight loss. There is also evidence that physical activity holds considerable promise for improving survival after a diagnosis of BC. Observational evidence suggests that moderate levels of exercise may reduce the risk of death from BC and therefore may prove to be valuable intervention to improve not only QoL but overall survival (Holmes *et al*., 2005). In a study by Holmes *et al*., (2005), the survival of 2,167 nurses who had been diagnosed with stage I, II, or III BC was assessed using a questionnaire that measured levels of physical activity every 2 to 4 years. The results

showed that those women who exercised for 3 to 5 hours per week had half the risk of death from BC than of women who exercised for less than 1 hour per week.

A dose-response relationship between physical activity and BC risk reduction was confirmed by most of the studies that investigated this connection. A dose-response relationship means that the more active women were, the greater the reduction in BC risk. In other words, the more frequently women were physically active, the greater was the decrease in their BC risk (WCRF / AICR, 2007). Using the results from seventeen case-control studies, the expert panel assembled by WCRF / AICR in 2007 found a statistically reliable six percent decrease in BC risk for each additional hour of physical activity per week. The analysis assumed that the activity was continued throughout a woman's life. Like the frequency of physical activity, the duration of physical activity is systematically related to decrease BC risk and plays an important role in this effect (McTiernan, 2006; WCRF / AICR, 2007). The intensity of physical activity is also important for reduced BC risk. In the studies conducted to date, a decreased BC risk has been found with both moderate and vigorous intensity activity. A slightly stronger risk reduction exists for women who do vigorous activity; however there is a benefit with even moderate activity (McTiernan, 2006; WCRF / AICR, 2007).

2.12.1 Recommended Frequency, Length of Time or Intensity of Exercise that will best reduce Breast Cancer Risk?

The WCRF/AICR panel that reviewed physical activity and BC risk in 2007, recommended that women should aim for 60 or more minutes of moderate intensity or 30 minutes of vigorous activity every day. The IARC panel recommendation was

similar 30 to 60 minutes a day of moderate to vigorous physical activity. These recommendations are comparable to that made by the U.S. Centers for Disease Control and Prevention and the American College of Sports Medicine as beneficial to health in general.

Marshall *et al*. (2009) measured how many steps per minute that were needed to achieve moderate-intensity aerobic exercise by monitoring oxygen uptake in 58 women and 39 men while they completed four different 6-minute sessions on the treadmill. The results showed that for men, it took between 92 and 102 steps per minute to reach moderate-intensity aerobic exercise while the range was between 91 and 115 steps per minute for women. These data support a general recommendation of walking at more than 100 steps per minute on level terrain to meet the minimum of the moderate-intensity aerobic exercise guideline. Because health benefits can be achieved with bouts of exercise lasting at least 10 minutes, a useful starting point for an individual is to accumulate 1,000 steps in 10 minutes, before building up to 3,000 steps in 30 minutes (American College of Sports Medicine, 2006).

2.12.2 Physical Activity and Body Mass Index (BMI)

Women with both high and low BMI (a measure of body fat) benefit from increased physical activity (McTiernan, 2006). Several lines of evidence support this concept. There have been 11 cohort studies and 5 case control studies that have studied the effect of physical activity on BC risk based on women grouped by their BMI's (WCRF / AICR, 2007). In a number of studies, a different and more detailed analysis looking for an interaction between BMI and physical activity on BC risk was conducted. None of these studies found such an interaction supporting the concept that women's body sizes have no effect on the benefits of physical activity.

Also in support of these results, one study has directly examined the effect of physical activity on oestrogens in postmenopausal women with high and low BMI values. This study found that the women with higher physical activity levels generally had lower levels of oestrogens than women with similar BMIs and low levels of physical activity. Thus physical activity was linked to a decrease in a well-established BC risk factor in women of all BMI values. However it should be also kept in mind that some analyses have found that women with extremely high BMI values did not display a BC risk benefit from physical activity. Nonetheless, these findings are encouraging as they indicate that women of almost all body sizes can benefit from physical activity. They also support the idea that physical activity affects BC risk by doing more than just changing body fat content.

2.13 BIOLOGICAL MECHANISMS BY WHICH EXERCISE REDUCES RISK OF BREAST CANCER RECURRENCE

A number of physiologic responses to exercise training have been postulated to be intermediate markers in the reduction of the development and progression of BC (McTiernan, 2006). These biologic mechanisms are

1. **Immune Function:** Changes in the immune function may mediate the relationship between exercise training and BC recurrence risk (McTiernan, 2006). The immune system is thought to play a role in protecting against BC (both primary and secondary) by recognizing and eliminating abnormal cells. These abnormal cells include those whose DNA have been damaged by free radicals. Exercise training improves the immune system of BC survivors both functionally and numerically (Fairey *et al*., 2005; McTiernan, 2006). Previous data suggests that cancer and its treatments are associated with

pronounced immune deficiency and that blood immune function is positively associated with progress-free and over all survival (Fairey *et al*., 2005).

2. **Free Radical Scavenger Enzymes**

Short term exercises promote free radical (pro-oxidant) production whereas long term exercises improve the body's free radical defense mechanisms (McTiernan, 2006). A healthy body is well equipped to destroy free radicals and prevent cells with damaged DNA from becoming cancerous (McTiernan, 2006). The body is capable of quickly recognizing and destroying free radicals. For example, the body has an enzyme called Superoxide dismutase (SOD) that regularly cleans up free radicals and prevents them from damaging cells and proteins. Other enzymes in the body that scavenge on free radicals are Glutathione peroxidase (GPX) and Catalase. They act as antioxidants. These defense mechanisms step up as soon as the cell is challenged by excessive pro-oxidant activity and attempt to maintain a favourable pro-oxidant to anti-oxidant balance. Exercise training provides a good example of this principle in action. It has been well documented that moderate/vigorous intensity exercise increases pro-oxidant production, and it is also a well-known fact that exercise training protects against many diseases associated with radical induced damage (Kanter, 1998; Schmitz *et al*., 2008). The body responds to the increase in free radical production caused by short term moderate/vigorous intensity exercise by up-grading the natural anti-oxidant enzymes. Therefore, although short term exercise causes an increase in radical formation, the physiological response to this actually improves the pro-oxidant to anti-oxidant ratio. Exercise training may therefore reduce risk of BC recurrence through this pathway.

3. **Sex Hormones**

Exercise training is significantly associated with decreased concentrations of sex hormones (oestrogen and progesterone) in healthy postmenopausal women (De Souza, 2003; McTiernan *et al*., 2004). It decreases the production of these sex hormones and increases the metabolism of oestrogen in premenopausal women (Pasagian- Macaulay *et al*., 1996; De Cree *et al*., 1997; De Cree, 1998) and postmenopausal women (Friedenreich, 2004). Sex steroid hormones such as oestrogen derivatives have powerful mitogenic and proliferative influences on the breast tissues and are strongly associated with the development of BC (Endogenous Hormones and Breast Cancer Collaborative Group, 2002; McTiernan, 2006). A pooled analysis of nine cohort study showed that the risk of BC in postmenopausal women increased significantly with increasing concentrations of estradiol, and estrone (Endogenous Hormones and Breast Cancer Collaborative Group, 2002). Women who were in the highest quintile for these sex hormones had a twofold increased risk for BC compared with women in the lowest quintile. Other findings from epidemiological studies further support the etiologic role of oestrogen in BC, showing that BC risk is associated with early menarche, late menopause, low parity, and use of exogenous oestrogens, all of which are linked to prolong or extensive exposure of breast tissue to oestrogen stimulation (Endogenous Hormones and Breast Cancer Collaborative Group, 2002; McTiernan, 2006). Finally, a number of clinical trials show that oestrogen ablation increases survival after diagnosis of BC.

However, studies of sex hormones and exercise in premenopausal women have been inconsistent. Several studies of young women athletes,

participating in sports involving high levels of moderate to vigorous activity, reported that these athletes had symptoms of decreased hormone production. These included delayed menarche (beginning of menstrual cycling), irregular menstrual periods and menstrual periods without ovulation (De Souza, 2003). While these observations likely reflect changes in hormone levels, direct examination of hormone level yielded different results (Campbell *et al.*, 2007; Schmitz *et al.*, 2008). A 15-week-long randomized controlled trial directly examined rate of lipid peroxidation and endogenous oestrogen levels in 15 sedentary premenopausal women undergoing aerobic exercise training (Schmitz *et al*., 2008). This study saw no effect on the levels of active and inactive oestrogen metabolites but a significant decrease in F_2-isoprostane in urine was observed. The findings of this study supported the mechanism that exercise reduces BC risk, both primary and secondary via a reduction in free radical level rather than a reduction in oestrogen level in premenopausal women. Some other studies found significant changes in oestrogen levels of premenopausal women after some weeks of exercise training (Pasagian-Macaulay *et al.*, 1996; De Cree *et al.*, 1997). The reason for this inconsistency may be that levels of ovarian hormones vary in the blood throughout the menstrual cycle in premenopausal women. Also exercise training has been associated with shortened luteal phase, increased frequency of anovulation, and an increased incidence of oligomenorrhea and amenorrhea in adult premenopausal women (McTiernan, 2006). More studies will be required to resolve this issue.

4. **Obesity/Fat Metabolism**

Postmenopausal women, whose ovaries are no longer producing oestrogen and progesterone, can produce oestrogens from the conversion of other hormones in fat tissue. Fats are used as substrate for oestrogen production through aromatization (Figure 8) (Judd *et al*., 1982).

The primary mechanism by which exercise training influences sex hormones in postmenopausal women is via decreased body fat which is a substrate for oestrogen, and testosterone production. Exercise training results in having fewer tissues that are capable of aromatization of the adrenal androgens to oestrogens. A randomized controlled exercise trial by McTiernan *et al*., (2004), observed that a decreased sex hormone concentrations in healthy postmenopausal women following a period of exercise training, was higher among women who lost body fat with exercise than those who did not lose body fat with exercise. During exercise training, fat is utilized to produce Adenosine-triphosphate (ATP) needed by the working muscles instead of being used in the production of oestrogen which is associated with BC recurrence risks.

Again, obese women have 30% increased circulatory levels of insulin, and IGF (Goodwin *et al*., 2002; Key *et al*., 2003). Exercise training which brings about a reduction in weight leads to a reduction in these hormones, thereby reducing the risk of a recurrence in survivors (Friedenreich, 2001).

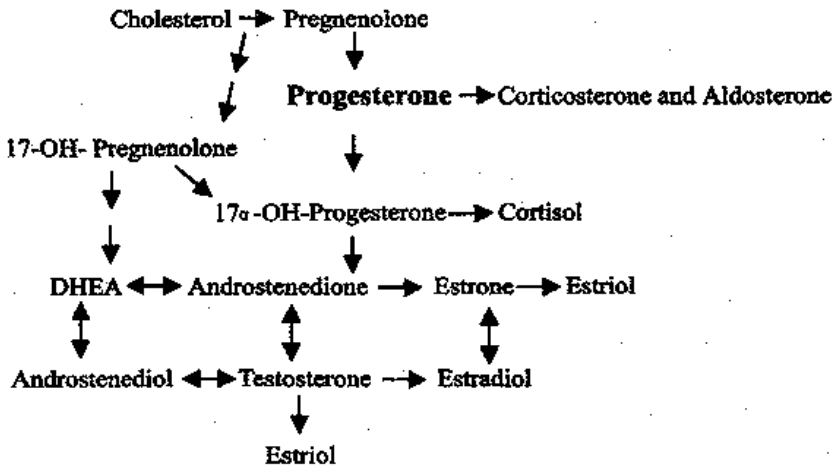

Figure 8: A chart that describes how the body converts cholesterol to oestrogen.

5. **Oestrogen-Binding Globulins**

Exercise may also lower risk of primary and secondary BC in postmenopausal women by lowering the availability of free oestrogens. This effect may occur through an exercise-associated increase in the levels of a protein that binds strongly to and carries oestrogen in the blood (McTiernan *et al*., 2004; McTiernan, 2006). The strong binding of oestrogen to this protein makes oestrogen less available and decreases its effect on the breast of women who are physically active.

6. **Insulin and Insulin-like Growth Factors (IGF) 1 and 11**

Circulating concentration of Insulin and Insulin-like growth factors I and II reduce with exercise training (Roberts *et al*., 2002; Fairey *et al*., 2003) and this may affect BC risk and prognosis (Goodwin *et al*., 2002; McTiernan, 2006). In a study of women with early-stage BC, higher insulin levels were associated with a two and three times higher risk of recurrence or BC death, respectively (Goodwin *et al*., 2002), and in preclinical studies, insulin has a mitogenic effect on normal breast tissue and can stimulate growth of BC cell lines. Exercise allows for better blood sugar control and less secretion of insulin. Insulin secretion has been linked to secretion of IGF I. That means that, when there is less secretion of insulin, there will also be less secretion of IGF I and an increase in IGF-binding proteins (decreasing the availability of IGF present) (McTiernan, 2006). IGF has been associated with premenopausal, but not postmenopausal BC risk (McTiernan, 2006). Both hormones have mitogenic effect on normal breast tissue. However, the few trials that have assessed the effect of exercise on IGFs have had variable results (McTiernan, 2006). Randomized controlled trials testing the effect of

exercise on insulin and IGFs are needed to elucidate the biological mechanisms by which exercise training protects against the development of primary or secondary BC.

7. **Mammographic Density**

Factors that change mammographic density may also change BC risk. Exercise training may influence mammographic density by favorably changing certain hormones associated with mammographic density and BC risk. Both mammographic dense area and percent density have been found to be inversely related to physical activity in obese postmenopausal women (Pierce *et al*., 2002; McTiernan, 2006). Women with high levels of mammographic density have a fourfold to six fold greater risk of developing BC than women with lower levels of mammographic density; thus, mammographic density is a stronger predictor of BC risk than most traditional risk factors. Mammographic density reflects proliferation of the breast epithelium and stroma, in response to growth factors, current and past circulating sex hormone levels. Extensive mammographic density is associated with an increased risk for atypical hyperplasia and in situ BC (Boyd *et al*., 1992), which are associated with an increased risk for subsequent invasive BC (Dupont and Page, 1985; Hartmann *et al*., 2005). Five out of seven studies of blood oestrogen levels and percentage mammographic density have found either no association or an inverse association with estrone levels (Aiello *et al*., 2005; Tamimi *et al*., 2005; Noh *et al*., 2006; Warren *et al*., 2006; Verheus *et al*., 2007) or with total or free estradiol (seven out of eight studies) (Boyd *et al*., 2002; Aiello *et al*., 2005; Tamimi *et al*., 2005; Noh *et al*., 2006; Warren *et al*., 2006; Bremnes *et al*.,

2007; Verheus *et al*., 2007) in premenopausal or postmenopausal women. An exception is the study carried out by Greendale *et al*., (2005) in the Postmenopausal Oestrogen/Progestin Intervention Trial, which identified a positive association between percentage density and estrone, estradiol and free estradiol levels in postmenopausal women. Bremnes *et al*., (2007) found a positive association of mammographic density with estrone levels (which was statistically significant only in women with insulin-like growth factor [IGF]-I levels below the median) but not with estradiol or free estradiol levels. Progesterone levels have not been shown to be associated with mammographic density in premenopausal or postmenopausal women. Sex hormone binding globulin has been found to have a significant positive association with mammographic density in two studies after adjustment for other variables (Boyd *et al*., 2002; Bremnes *et al*., 2007), and in four other studies before adjustment (Greendale *et al*., 2005; Tamimi *et al*., 2005; Noh *et al*., 2006; Verheus *et al*., 2007). Testosterone and androstenedione have not been shown to be associated with mammographic density in postmenopausal women and have not yet been studied in premenopausal women. Blood levels of growth hormone have been found to be positively associated with mammographic density in premenopausal women, but this association became non-significant after adjustment for body size (Boyd *et al*., 2002). Because growth hormone is one of the factors that influence body size, this may be over-adjustment. Prolactin levels were found to be positively associated with the area of dense tissue in premenopausal women in one study (Boyd *et al*., 2002), with percentage mammographic density in postmenopausal women in two studies (Boyd *et al*., 2002; Greendale *et al*.,

2007), and in a further study statistical significance was lost after adjustment for other variables (Tamimi *et al*., 2005). Mammographic density was found to be positively associated with serum IGF-I levels in premenopausal women in three (Byrne *et al*., 2000; Boyd *et al*., 2002; Diorio *et al*., 2005) out of five studies (Maskarinec *et al*., 2003; dos Santos Silva *et al*., 2006), and one study found an association in postmenopausal women (Bremnes *et al*., 2007). Results with IGF-binding protein (IGFBP)-3 and the ratio of IGF-I to IGFBP-3 have been inconsistent. In a longitudinal study, women with higher levels of serum IGF-I during the premenopausal period experienced a smaller increase nondense area and a slightly smaller decrease in dense area during menopause (Verheus *et al*., 2007).

CHAPTER THREE

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Subject Selection

Ninety-six (96) female breast cancer (BC) survivors completed the study. They were recruited through referrals by physicians from the Radiotherapy and Oncology Department of the Lagos University Teaching Hospital (LUTH), Idi-Araba, Lagos.

Inclusion Criteria

The subjects that participated in the study were:

1. Women with stage I, II and III BC (Courneya *et al*., 2003, Ohira *et al*., 2006; Ligibel *et al*., 2008). This was ascertained through the histo-pathological reports of the subjects.

Stage 1: Cancer size is less than 2cm,

Stage II: Cancer size is between 2cm to 5cm and may be divided into:

Stage IIa: Cancer has not spread to the lymph nodes in the arm pit.

Stage IIb: Cancer has spread to the lymph nodes in the arm pit,

Stage III: Cancer size is larger than 5cm and may be divided into:

Stage IIIa: Cancer has spread extensively to the lymph nodes under the arm.

Stage IIIb: Cancer has spread to lymph nodes near the breast bone, muscles, and other tissues near the breast.

Stage IIIc: Cancer has spread to lymph nodes beneath the collar bone, lymph nodes near the neck, those within the breast or under the arm and tissues near the breast (Courneya *et al*., 2003; Ohira *et al*., 2006; Ligibel *et al*., 2008).

2. Premenopausal women (those who are still experiencing their menstrual periods) and postmenopausal women (not experiencing menstrual periods for the previous 12 months).
3. Those who had undergone lumpectomy or mastectomy and had started or completed radiation and / or chemotherapy.
4. Those that had not smoked for the previous one year.

Exclusion Criteria

Individuals excluded from the study were:

1. Breast cancer survivors who had been involved in structured exercises such as aerobic exercises during the previous six months.
2. Breast cancer survivors with severe cardiopulmonary pathologies and severe complications of cancer therapy such as uncontrolled hypertension, known cardiac diseases, severe pneumonitis, and severe pericarditis.
3. Breast cancer survivors with musculoskeletal impairments in the lower limbs such as severe osteoarthritis and rheumatoid arthritis.
4. Breast cancer survivors with contraindications to exercise such as a feeling of breathlessness, severe fatigue, fainting/dizziness on the basis of an exercise stress test.

3.2 ETHICAL CONSIDERATION

Ethical approval was obtained from the Health Research and Ethics Committee of the Lagos University Teaching Hospital (LUTH) (Appendix 1). Written informed consent was also obtained from all the subjects who participated in the study (Appendix 2).

3.3 INSTRUMENTATION

The following instruments were used;

1. Treadmill machine; model Hp 7,000, 3.5 horsepower (Health Park, England): This was used by the subjects in Groups A and C to carry out moderate intensity aerobic exercise.
2. Mercury Sphygmomanometer (Accoson, England): This was used to measure the resting arterial blood pressure of subjects.
3. Stethoscope (Hannary Quality Brand, USA): This was also used to measure the resting arterial blood pressure as well as the resting heart rate of subjects.
4. Pulse Oxymeter; model C16828IL (Check-mate, Israel): This was used to measure the resting arterial oxyhaemoglobin saturation of subjects.
5. Hand-held Medical Spirometer (Kent ME_1 2Az, England): This was used to measure the forced vital capacity of subjects.
6. Fat Loss Monitor; model HBF-306C (Omron, Illinois, USA): This was used to measure the percentage body fat of subjects.
7. Combined Weighing scale and height meter model RGZ-160 (Leaidal Medical LTD, UK): This was used to measure the body weights and heights of subjects.
8. Stop watch and timer (Moron, England): This was used for time keeping.
9. A non-elastic tape rule calibrated in centimeter and inches (Butterfly, China): This was used to measure the waist-hip circumference ratio of subjects.
10. Harvard step bench: This was a step bench of 33 cm height which was used to perform exercise stress test by subjects.

11. Digital Metronome; model DM-50 (Seiko, China): This was used to provide rhythm and timing for stepping up and down the step bench at the rate of 22.5 steps per minute.
12. Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire: This was used to assess the QoL of subjects.

3.4 RESEARCH DESIGN

The study design was a randomized controlled trial.

3.5 SAMPLE SIZE DETERMINATION

The sample size for comparative research studies was derived from the formular;

$$N = \frac{4\delta^2(Z_{crit} + Zpwr)^2}{D^2}$$

Where N = Total sample size,

Z_{crit} = is the desired significance criterion at 0.05 = 1.960,

Zpwr = is the desired statistical power at 80% = 0.842

δ = is the assumed SD of each group based on preliminary study

= 5.34kg/ml/min

D = is the minimum expected difference between the means of the changes in VO_2max of preliminary and present study (Eng, 2003). These means are 5.14 kg/ml/min and 2.00 kg/ml/min = 3.14 kg/ml/min.

$$N = \frac{4\,(5.34)^2\,(1.960 + 0.842)^2}{(5.14\text{-}2.00)^2}$$

= 90.83

Therefore the minimum expected population for this study is 91 subjects.

3.6 SAMPLING TECHNIQUE

One hundred and twelve (112) consecutively referred BC survivors were screened for eligibility based on the inclusion and exclusion criteria of the study using the assessment form (Appendix 3). Four (4) were not eligible and therefore were excluded. The remaining 108 eligible subjects were randomly assigned to four groups (A, B, C and D). Each of the groups was further subdivided into subgroup 1 and 2 based on the subjects' menopausal status. The randomization was done using the fish bowl method. This method consisted of numbered papers that represented different groups of subjects placed in 2 bowls which were picked by subjects. One of the 2 bowls was for premenopausal BC survivors while the other was for postmenopausal BC survivors. Ninety six (96) subjects completed the study. Twelve (12) subjects withdrew from the study for reasons such as transportation problems, inability to stay in the town of study (Lagos) for the 12 weeks duration of study as well as exacerbation of side effects of radiotherapy / chemotherapy (Figure 9).

Study Groups

Group A: Subjects in this group underwent moderate intensity aerobic exercise using treadmill and also had educational and counseling sessions.

Subgroup A_1 consisted of premenopausal BC survivors while

Subgroup A_2 consisted of postmenopausal BC survivors.

Group B: Subjects in this group underwent stretching exercises and also educational and counseling sessions.

Subgroup B_1 consisted of premenopausal BC survivors while

Subgroup B_2 consisted of postmenopausal BC survivors.

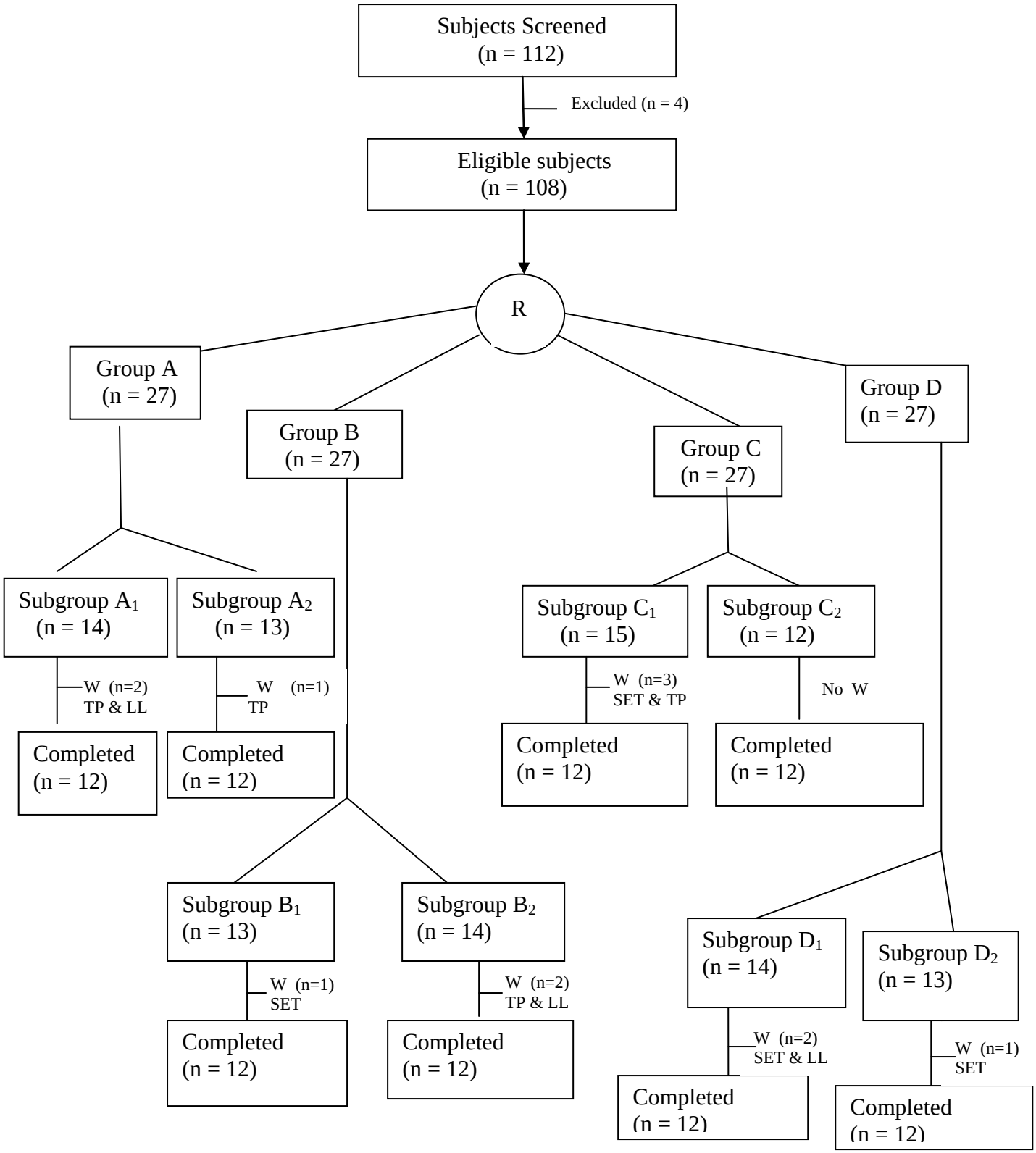

Figure 9: Recruitment and randomization of subjects into groups. R= Randomization. Group A= Aerobic exercise group, Group B= Stretching exercise group, Group C= Combined aerobic & stretching exercise group, Group D= Control group, Subgroup 1= Premenopausal BC survivors, Subgroup 2= Postmenopausal BC survivors, W=Withdrawal, TP= Transport Problems, SET=Side Effects of Treatment exacerbated, LL=Left Lagos during the 12 weeks of study.

Group C: Subjects in this group underwent combined moderate intensity aerobic exercise using treadmill and stretching exercises as well educational and counseling sessions.

Subgroup C_1 consisted of premenopausal BC survivors while

Subgroup C_2 consisted of postmenopausal BC survivors.

Group D: Subjects in this control group had no therapeutic exercise intervention but participated in group educational and counseling sessions.

Subgroup D_1 consisted of premenopausal BC survivors while

Subgroup D_2 consisted of postmenopausal BC survivors.

Harvard Stress Test

Exercise stress test was performed for all subjects using the Harvard step test (Alison and Pettersen, 2007). It was used to measure the endurance and fitness of the cardiovascular systems of subjects that performed moderate intensity aerobic exercises. It is a simple 6-minute test that involves stepping up and down a step bench (33cm height) at the rate of 22.5 steps per minute. A digital metronome was used to provide the timing for stepping up and down the step bench. Those who did not have contraindications to exercise proceeded with the study. Some of the contraindications to exercise are a feeling of breathlessness, severe fatigue, fainting/dizziness, nausea and symptoms of heart problems.

3.7 PRE-INTERVENTION ASSESSMENT

The baseline measurements of all the selected outcome parameters were taken for the participants after a rest period of 15 minutes (Andersen *et al*., 2010). Overall

QoL of all the subjects were assessed at baseline using the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale (Appendix 4). It was administered by self-report or by interview. Administration time for any one assessment of QoL was usually less than 15 minutes. The other selected outcome measures that were assessed at baseline were Resting arterial blood pressure (RSBP and RDBP), Resting Rate pressure product (RRPP), Arterial oxyhaemoglobin saturation (SaO_2), Forced vital capacity (FVC), VO_2 max, Weight, Height, Body mass index (BMI), Waist-hip circumference ratio (WHR) and Percentage body fat.

3.8 RESEARCH PROCEDURES

Study Group A

Therapeutic Exercise mode

The therapeutic exercise mode for this study group was aerobic exercise using treadmill adopted from the protocols of Courneya *et al*. (2007) and Schmitz *et al*. (2008).

Vital Signs Measurements/Calculations on Appointment Days

1) **Arterial blood pressure at rest:** The resting systolic blood pressure (RSBP) and resting diastolic blood pressure (RDBP) of all the subjects in this group were measured in mm Hg on the appointment days using a sphygmomanometer and a stethoscope. This was measured after they had rested for 15 minutes (Andersen *et al.*, 2010).
2) **Heart rate at rest (HR @ rest):** The HR at rest of all the subjects in this group was measured in beats per minute after a rest period of 15 minutes using a stethoscope (Andersen *et al*., 2010). The stethoscope was placed at the 5^{th} intercostal space at the left side of the mid clavicular line.

3) **Arterial Oxyhaemoglobin Saturation (SaO_2) at rest** was measured in percentage for all the subjects in the group using a pulse oxymeter. This was also done on the appointment days after a rest period of 15 minutes.
4) **Maximal Heart Rate (MHR)** of all the subjects in this group was calculated in beats per minute with the formular stated below.
5) **Target Heart Rate (THR)** was calculated in beats per minute for each subject in this group using the Karvonen's formular as described below.

Intensity

The intensity of aerobic exercise was moderate intensity which was equivalent to the subjects' target heart rate (THR). THR was determined using the Karvonen's formular;

THR = 0.6 (MHR - HR @ rest) + HR @ rest (Tanaka *et al*., 2001). Where MHR is Maximal heart rate and HR @ rest is Heart rate at rest. The formular for MHR for females is; (226 – age in years) (Bumgardner, 2008). Since MHR – HR @ rest = Heart rate reserve (HRR), another formular for THR is; **THR = (HRR x 0.6) + HR @ rest** (Tanaka *et al.*, 2001).

Warm up Exercise

The subjects in this group performed 5 minutes warm exercise by walking round the gymnasium at each subject's normal walking speed.

Intervention

After the warm-up exercise, subjects in this group started walking on the treadmill at a speed of 3 km per hour and gradually increased until they reached their THR (Figure 10). This was displayed on the screen of the treadmill. Subjects that could not perform their exercise session at once were allowed to walk on the treadmill for short periods of 5 minutes with a rest period of 2 minutes in between exercise periods until they completed the total duration for the session. This enabled them to regain their strength to complete the total exercise duration for the session.

Cool Down Exercise

After they had carried out their aerobic exercise, they performed 5 minutes cool down exercise by walking round the gymnasium at each subject's normal walking speed.

Intervention Duration and Progression

The exercise duration began at 15 minutes for weeks 1 – 3 and systematically increased by 5 minutes every 3 weeks. This means that exercise duration for weeks 4 – 6 was 20 minutes, weeks 7 – 9 was 25 minutes and weeks 10 – 12 was 30 minutes (Courneya *et al*., 2003).

Exercise Frequency

Exercise frequency for this study group was 3 days a week for 12 weeks. The exercise training days were at least every other day (Courneya *et al*., 2003).

They also had educational and counseling sessions for 30 minutes, once every week for 12 weeks.

Figure 10: A subject performing aerobic exercises on treadmill.

Outcome Measures

The outcome measures that were assessed for subjects in this group included the following;

Cardiovascular parameters (Arterial blood pressure at rest (Systolic and Diastolic) and Rate pressure product); Pulmonary parameters (Arterial oxyhaemoglobin saturation (SaO_2), Forced vital capacity (FVC) and VO_2max); Anthropometric parameters (Body mass index (BMI), Waist-hip circumference ratio (WHR) and percentage body fat (%Fat)) and QoL. They were measured at baseline, at the end of the 3^{rd} week, 6^{th} week, 9^{th} week and 12^{th} week.

Study Group B

Therapeutic Exercise Mode

The therapeutic exercise mode for this study group was stretching exercise.

Vital Signs Measurements/Calculations on Appointment Days

This was as described above for subjects in Group A except for **THR** which was not calculated for subjects in this group.

Intervention

All the subjects in this group carried out stretching exercises in standing and sitting positions.

A) Stretching exercises that were done in standing position were;

1. **Pectorialis Stretch**: In standing position, the subjects faced the wall and raised the 2 hands on the wall over their head until they felt the stretch around the shoulders and upper trunks. They maintained this position for 15 to 20 seconds and then started again (Figure 11).

Figure 11: A Subject performing pectoralis stretch exercise.

2. **Triceps Stretch**: In standing position, the subjects placed one hand between their shoulder blades. This hand pointed downwards while the elbow pointed upwards. The opposite hand was used to gently press down the elbow until they felt a stretch in the triceps. They maintained this position for 15 to 20 seconds before repeating the exercise on the other side (Figure 12).
3. **Standing Calf Stretch (Wall Pushing Posture)**: From a standing position, the subjects took one exaggerated step forwards. The rear legs were kept in full extension while their extended upper limbs held on to the wall for support and their front knees kept at 90° position over their feet. They leaned forwards slightly so that their rear legs and their bodies made a continuous line. They maintained this position for 15 to 20 seconds before repeating the exercise on the other side (Figure 13).
4. **Chest / Biceps Stretch**: From a standing position, the subjects with full extended arms held on to the wall for support at the shoulder level. They gently turned their bodies away from their arms and then pressed their shoulders forwards. They maintained this position for 15 to 20 seconds before repeating the exercise on the other side (Figure 14).

Figure 12: A Subject performing right triceps stretch exercise.

Figure 13: A Subject performing standing calf stretch exercise.

Figure 14: A subject performing chest / biceps stretch exercise.

B) Stretching Exercises that were done in Sitting Position were

1. **Neck (Upper trapezius) Stretch**: In sitting position, the subjects gently pulled their heads towards their shoulders with one of their hands – i.e. their ears towards their shoulders. They then applied gentle pressure with their arms over their heads and held for 15 to 20 seconds before repeating the exercise on the other side (Figure 15).
2. **Shoulder stretch**: The subjects sat upright, then with the opposite hand grabbed one of their elbows and gently pulled across their bodies to one side and held for 15 to 20 seconds. They repeated this exercise on the other side (Figure 16).

Intervention Duration and Progression

The duration for each of the 6 different stretching exercises that were performed during a treatment session depended on the exercise duration for that treatment session. For example, for weeks 1-3 when the treatment duration was 15 minutes, each of the 6 stretching exercises was performed for 2 minutes 30 seconds by subjects in this group. This duration was derived by equally dividing 15 minutes among 6 stretching exercise types i.e. 15/6 = 2.5minutes. For weeks 4-6 when the treatment duration was 20 minutes, each of the 6 stretching exercises was performed for 3 minutes 20 seconds. For weeks 7-9 when the treatment duration was 25 minutes, each of the 6 stretching exercises was performed for 4 minutes 10 seconds. Lastly, for weeks 10-12 when the treatment duration was 30 minutes, each of the 6 stretching exercises was performed for 5 minutes. The subjects were allowed to rest for 2 minutes when they became tired and then continued the stretching exercises until they completed the exercise duration for each treatment session.

Figure 15: A subject performing neck (upper trapezius) stretch exercise.

Figure 16: A subject performing shoulder stretch exercise.

Exercise Frequency

Exercise frequency for this study group was also 3 days a week for 12 weeks. The exercise training days were at least every other day.

They also had educational and counseling sessions for 30 minutes, once every week for 12 weeks.

Outcome Measures were as described above for study group A.

Study Group C

Therapeutic Exercise Mode

The therapeutic exercise mode for this study group was a combination of aerobic exercise on treadmill and stretching exercise.

Vital Signs Measurements/Calculations on Appointment Days

This was as described above for subjects in Group A.

Warm up Exercise

The subjects in this group performed 5 minutes warm exercise by walking round the gymnasium at each subject's normal walking speed.

Intervention

Each treatment session was divided into 2 parts for subjects in this group. One part was aerobic exercise training at moderate intensity using the treadmill and the second part was stretching exercise training. The duration for the 2 parts of treatment was equal. After the warm up exercise, they started walking on the treadmill at a speed of 3 km per hour and gradually increased until they reached their THR. Subjects were allowed to walk on the treadmill for short periods of 5

minutes with a rest period of 2 minutes in between exercise periods until they completed the total duration for the session.

Cool Down Exercise

After they had carried out their aerobic exercise, they performed 5 minutes cool down exercise by walking round the gymnasium at each subject's normal walking speed.

During the second part of treatment, the subjects carried out stretching exercises as described for those in Group B but the duration reduced by half.

Intervention Duration and Progression

For weeks 1 - 3, aerobic exercise on treadmill was done for 7 minutes 30 seconds while stretching exercises was done for the same 7 minutes 30 seconds. For weeks 4 - 6, aerobic exercise on treadmill was done for 10 minutes while stretching exercises was done for the same 10 minutes. For weeks 7 - 9, aerobic exercise was done for 12 minutes 30 seconds while stretching exercises was also done for 12 minutes 30 seconds. For weeks 10 - 12, aerobic exercise on treadmill was done for 15 minutes while stretching exercises was done for the 15 minutes.

Exercise Frequency

Exercise frequency for this study group was 3 days a week for 12 weeks. The exercise training days were at least every other day (Courneya *et al*., 2003).

They also had educational and counseling sessions for 30 minutes, once every week for 12 weeks.

Study Group D

Intervention

There was no therapeutic exercise intervention during the 12 weeks of study for this control group; rather they had group educational and counseling sessions. They were offered the therapeutic exercise interventions after the 12 weeks of study. Topics discussed during the group educational and counseling sessions included;

1. The problems BC survivors are faced with as a result of the disease and its treatment.
2. The means they could use to deal with these problems. These included;

i. The Cognitive-behavioural psychotherapy model: The subjects were taught how to manage their thinking by being aware of their thoughts (Spiegel, 1989).

ii. Relaxation Methods: Subjects were advised to practice relaxation (Spiegel, 1989).

iii. Self-help Tips: Subjects were advised on 10 things they could do to reduce stress.

iv. Diet and Nutrition: Participants were advised to eat fruits, vegetables and low fat diets which have been proven to reduce the incidence of cancer (Quillan, 2008).

v. A Sense of Community: They were advised on the importance of being part of BC support groups and be consistent at attendance to meetings (Spiegel, 1989) (Appendix 5).

Duration/Frequency

The duration and frequency for the educational and counseling sessions was 30 minutes once every week for 12 weeks.

Outcome measures are already described above under Group A.

3.9 OUTCOME MEASURES

The primary outcome variables for this study included selected cardiovascular parameters, pulmonary parameters, anthropometric parameters and QoL measures.

Cardiovascular Parameters

The cardiovascular parameters that were measured included arterial blood pressure at rest (systolic and diastolic) and resting rate pressure product.

1. **Resting Arterial Blood Pressure (systolic and diastolic)**: These were measured in mm Hg using a sphygmomanometer and a stethoscope after a rest period of 15 minutes (Andersen *et al*., 2010). This was the auscultatory method and was carried out in sitting position.
2. **Resting Rate Pressure Product (RRPP) or Resting Double Product** is the product of systolic blood pressure and heart rate at rest. It is a useful index of the cardiac stress and is known to be a valid predictor of the myocardial oxygen consumption (MVO_2) at rest and during exercise (Kispert, 1987). Conditions such as exercise, increased systemic vascular resistance, and high output states that increase heart rate and/or blood pressure will increase RPP. However, as exercise training improves these parameters, RRPP will improve with exercise training.

Pulmonary Parameters

The pulmonary parameters that were measured included Arterial oxyhaemoglobin saturation (SaO_2), Forced vital capacity (FVC) and VO_2max.

1. **Arterial Oxyhaemoglobin Saturation**: The procedure for the measurement of arterial oxyhaemoglobin saturation using a pulse oximeter (unit) was as

follows; a finger of the subject that fitted easily into the thimble of the unit was selected. The pulse oximeter (unit) was fitted into the subject's finger in sitting position before starting. The display of the unit faced up as the subject placed the hand relaxed on a table (a flat surface). Dashes first appeared on the display while the unit acquired data but the reading appeared within 20 seconds. Pulse oximetry provides estimates of arterial oxyhaemoglobin saturation (SaO_2) by utilizing selected wavelengths of light to noninvasively determine the saturation of oxyhaemoglobin (AARC, 1991). Pulse oximetry is one of the noninvasive means of monitoring the respiratory function that is convenient, accurate in showing trends, involves minimal complications and causes little discomfort to the person (AARC, 1991). When oxygen saturation is monitored during exercise, saturation is kept at or above 90%. At 90%, the partial pressure of oxygen (Po_2) in the blood is approximately 60 mm Hg, so pulse oximetry below 90% signifies that the cellular demand of oxygen cannot be met. This may lead to anaerobic metabolism and ultimately to lactic acidosis (Guyton, 1986). Therefore, caution should be exercised if pulse oximetry is below 90% and exercise should be stopped if it falls to 86%.

2. **Forced Vital Capacity (FVC)**: This is the largest volume of gas that can be forcefully exhaled from the lungs after a maximal inspiratory effort. This was measured in litres using a hand held medical spirometer. The subjects in sitting position were asked to take the deepest breath they could, and then exhale into the sensor as hard as possible, for as long as possible. A nose clip was used just before each subject exhaled into the mouth piece. That guaranteed that breath flowed only through the mouth. Each subject

performed this procedure 3 times and the mean value taken and recorded. It was necessary to coach the subjects to achieve their maximal expiratory efforts before taking the actual measurements because FVC is highly dependent upon the amount of force used by the subjects in early expiration. The normal value is about 4.0 L. Lower values may indicate restrictive problems.

3. **VO_2 max**: This is the maximum volume of oxygen consumed by the body in one minute during exercise. It is the product of cardiac output and arterio-venous oxygen difference. In this study, an estimate of the VO_2 max for the subjects in the 4 groups was obtained using the formular;

$$\mathrm{VO_2\ max} = 15\frac{HR_{max}}{HR_{rest}}$$

Where HR_{max} = Maximal heart rate

HR_{rest} = Heart rate at rest (Uth *et al*., 2005).

Anthropometric Parameters

The anthropometric parameters that were measured in this study included body mass index (BMI), waist circumference and waist-hip circumference ratio.

1. **Body Mass Index**: BMI of all the subjects in the 4 groups was calculated using the formular; BMI = weight (kg) divided by height^2 (m^2).
2. **Waist-hip Circumference Ratio**: The ratio was calculated for all the subjects in the 4 groups using the measurements for the narrowest part of the torso (waist circumference) and the maximal part of the buttocks (hip circumference). These were measured in standing using a non-elastic tape.

3. **Percentage Body Fat**: Percentage body fat of all the subjects in the 4 groups was measured using Omron Fat Loss Monitor. Before taking each subject's measurement, her personal data such as the height, weight, age and gender were entered into the Monitor using the set, down and up buttons. The subject stood with both feet slightly apart and placed both hands on the grip electrodes of the monitor in such a way that the middle fingers wrapped around the grooves of the handle and the thumbs pointed up. The subject then held the arms straight (extended elbows) with the shoulders at 90^{o} angle to the body. The start button was then pressed for the monitor to automatically start measurement, after which the reading was displayed on the screen.

Quality of Life (QoL)

Overall QoL of all the subjects in the 4 groups was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale. This questionnaire contains subscales for physical well-being (7 items), functional well-being (7 items), emotional well- being (6 items), and social or family well-being (7 items). A BC subscale contains 9 additional items. It has been used for previous study and is validated and reliable (Brady *et al*., 1997; Courneya *et al*., 2003).

3.10 DATA ANALYSIS

Data was analysed using descriptive statistics of mean and standard deviation. Results were illustrated in tables and charts. Statistical Package for Social Sciences (SPSS) version 20.0 was used to analyse data. The following statistics were done;

1. Analysis of variance (ANOVA) was used to compare the physical characteristic variables of subjects across groups.

2. Repetitive ANOVA was also used to determine the statistical significance of the cardiovascular, pulmonary and anthropometric variables across the baseline, end of 3^{rd}, 6^{th}, 9^{th} and 12^{th} weeks of each group.
3. Paired *t* test was used to compare the baseline and end of 12^{th} week mean values of cardiovascular, pulmonary and anthropometric variables within groups.
4. Paired *t* test was used to compare the changes in the selected variables of premenopausal BC survivors with those of postmenopausal BC survivors at the end of 12^{th} weeks.
5. Paired *t* test was also used to compare the changes in the various exercise groups with those of the control group.
6. Friedman test was used for analysis of QoL values within groups and Kruskal-Wallis H test across groups.
7. A least significant difference post hoc test was used to determine the exact points (weeks) that the significant variables became significant and the exclusively significant group. Level of significance was set at $p \leq 0.05$.

CHAPTER FOUR

RESULTS

4.1 Physical Characteristics of Premenopausal and Postmenopausal Breast Cancer Subjects

Table 1 shows the physical characteristics of premenopausal and postmenopausal BC subjects. The mean age of premenopausal BC subjects of different groups ranged from 39.43 $\pm$ 5.41 years to 41.71 $\pm$ 5.28 years. The mean BMI of premenopausal BC subjects of different groups ranged from 27.44 $\pm$ 3.22 kg/m^2 to 29.98 $\pm$ 9.50 kg/m^2. There were no significant differences in mean age and mean BMI across the groups.

The mean age of postmenopausal BC subjects of different groups ranged from 51.00 $\pm$ 1.63 years to 55.00 $\pm$ 6.29 years. The mean BMI of postmenopausal BC subjects of different groups ranged from 26.29 $\pm$ 6.10 kg/m^2 to 33.28 $\pm$ 2.56 kg/m^2. There were no significant differences in mean age and mean BMI across the groups.

Table 1: Physical Characteristics of Premenopausal and Postmenopausal BC Subjects

GROUP	AGE (YRS) $\bar{X}$+SD	WEIGHT (KG) $\bar{X}$+SD	HEIGHT (CM) $\bar{X}$+SD	BMI (KG/M^2) $\bar{X}$+SD
Premenopausal				
A_1	40.88 ± 5.38	74.21 ± 10.58	164.38 ± 6.48	27.44 ± 3.22
B_1	41.71 ± 5.28	76.86 ± 13.06	159.16 ± 3.15	27.93 ± 5.52
C_1	39.43 ± 5.41	76.39 ± 18.53	160.03 ± 4.63	29.66 ± 6.52
D_1	39.75 ± 2.87	81.50 ± 31.67	163.75 ± 8.58	29.98 ± 9.50
F	0.28	0.15	1.45	0.22
p-value	0.84	0.93	0.26	0.88
Postmenopausal				
A_2	54.29 ± 8.75	80.60 ± 10.99	165.60 ± 6.70	29.80 ± 4.81
B_2	52.43 ± 3.82	70.09 ± 9.25	159.91 ± 5.95	28.50 ± 5.36
C_2	55.00 ± 6.29	71.70 ± 12.52	166.65 ± 10.74	26.29 ± 6.10
D_2	51.00 ± 1.63	83.33 ± 12.55	158.00 ± 9.30	33.28 ± 2.56
F	0.45	1.92	1.49	1.85
p-value	0.72	0.16	0.25	0.17

Key:

$\bar{X}$+SD = Mean ± Standard Deviation,

BMI = Body Mass Index

A_1 = Premenopausal aerobic exercise group

B_1 = Premenopausal stretching exercise group

C_1 = Premenopausal combined aerobic and stretching exercise group

D_1 = Premenopausal control group

A_2 = Postmenopausal aerobic exercise group

B_2 = Postmenopausal stretching exercise group

C_2 = Postmenopausal combined aerobic and stretching exercise group

D_2 = Postmenopausal control group

4.2 Cardiopulmonary and Anthropometric Variables of Subjects in Group A_1

Table 2 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group A_1 at 3^{rd}, 6^{th}, 9^{th} and 12^{th} week. Repetitive ANOVA shows that there were significant differences in the RSBP and RRPP. There were no significant differences in the RDBP, SaO_2, FVC, VO_2max, BMI, WHR and %Fat. Post hoc analysis shows that the significant change in RSBP occurred between baseline and 6^{th} week, baseline and 9^{th} week and baseline and 12^{th} week. Significant change in RRPP occurred between baseline and 12^{th} week.

4.3 Cardiopulmonary and Anthropometric Variables of Subjects in Group A_2

Table 3 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group A_2 at 3^{rd}, 6^{th}, 9^{th} and 12^{th} weeks. Repetitive ANOVA shows that there were significant differences in the RSBP, RDBP and RRPP. No significant differences were observed in the SaO_2, FVC, VO_2max, BMI, WHR and %Fat. Post hoc analysis shows that the significant changes in RSBP and RRPP occurred between baseline and 12^{th} week while significant changes in RDBP occurred between baseline and 9^{th} week and between baseline and 12^{th} week.

Table 2: Cardiopulmonary and Anthropometric Variables of Subjects in Group A_1

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value	Post hoc
GROUP A_1								
CVS								
RSBP (mmHg)	123.00 ± 9.07	114.00±9.91	110.25 ± 8.51	106.75 ± 6.04	103.75±6.27	6.77	0.00*	a&c, a&d, a&e
RDBP (mmHg)	79.50 ± 10.68	75.00±10.80	71.75 ± 9.04	70.50 ± 5.93	67.75 ± 7.89	1.99	0.12	
RRPP (beats/min/mmHg)	9835.00 ± 1862.32	8911.00± 1579.69	8563.00 ± 1623.22	8091.00 ± 1614.36	7398.00 ± 1284.78	2.58	0.05*	a&e
Pulmonary								
SaO_2 (%)	98.25 ± 0.71	98.13±0.83	98.00 ± 0.53	98.13 ± 1.13	98.50 ± 0.53	0.47	0.75	
FVC (Litres)	1.79 ± 0.50	1.95±0.55	2.04 ± 0.58	2.09 ± 0.63	2.25 ± 0.54	0.73	0.58	
VO_2max(kg/ml/min)	33.89 ± 4.34	34.93±4.53	35.34 ± 5.34	36.38 ± 6.09	38.42 ± 4.83	0.92	0.46	
Anthropometric								
BMI (kg/m^2)	27.44 ± 3.22	27.35±3.39	27.13 ± 3.20	26.88 ± 3.37	26.69 ± 3.29	0.07	0.99	
WHR	0.86 ± 0.08	0.86±0.08	0.86 ± 0.08	0.86 ± 0.07	0.84 ± 0.07	0.08	0.99	
%Fat	33.71 ± 2.81	33.30±3.48	32.86 ± 3.25	32.70 ± 3.30	32.15 ± 3.49	0.26	0.90	

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition. *= significant at $p \leq 0.05$

T**able 3: Cardiopulmonary and Anthropometric Variables of Subjects in Group A_2**

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value	Post hoc
GROUP A_2								
CVS								
RSBP (mmHg)	125.43±14.50	114.86±5.76	113.14±8.71	112.5 ±8.77	108.00±5.54	3.42	0.02*	a&e
RDBP (mmHg)	84.57 ± 10.63	79.43±5.38	76.29 ± 4.23	72.29 ± 6.26	70.57 ± 3.78	5.19	0.00*	a&d, a&e
RRPP (beats/min/mmHg)	9192.00 ± 587.24	8761.14± 734.08	8381.71 ± 726.62	8408.00 ± 1044.89	7834.29 ± 787.97	2.83	0.04*	a&e
Pulmonary								
SaO_2 (%)	97.43 ± 0.53	97.86±0.38	98.14 ± 0.69	98.00 ± 0.00	98.14 ± 0.69	2.22	0.09	
FVC (Litres)	1.70 ± 0.43	1.90±0.47	1.93 ± 0.47	2.01 ± 0.46	2.17 ± 0.49	0.93	0.46	
VO_2max(kg/ml/min)	33.35 ± 2.67	32.21±3.66	32.76 ± 2.53	32.20 ± 1.97	33.35 ± 2.93	0.25	0.91	
Anthropometric								
BMI (kg/m^2)	29.80 ± 4.81	29.86±4.86	29.77 ± 4.84	29.71 ± 4.76	29.53 ± 4.75	0.00	1.00	
WHR	0.82 ± 0.05	0.84 ± 0.06	0.84 ± 0.04	0.83 ± 0.05	0.83 ± 0.06	0.06	0.99	
%Fat	38.33 ± 6.39	38.50±6.06	37.48 ± 6.95	37.30 ± 6.71	37.25 ± 6.82	0.05	0.99	

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition. *= significant at $p \leq 0.05$

4.4 Cardiopulmonary and Anthropometric Variables of Subjects in Group B_1

Table 4 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group B_1 at 3^{rd}, 6^{th}, 9^{th} and 12^{th} week. Repetitive ANOVA shows that there was significant difference in the FVC. No significant differences were observed in the RSBP, RDBP, RRPP, SaO_2, VO_2max, BMI, WHR and %Fat. Post hoc analysis shows that the significant change in FVC occurred between baseline and 12^{th} week.

4.5 Cardiopulmonary and Anthropometric Variables of Subjects in Group B_2

Table 5 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group B_2 at 3^{rd}, 6^{th}, 9^{th} and 12^{th} week. Repetitive ANOVA shows that there were significant differences in the RSBP and RDBP but no significant differences was observed in the RRPP, SaO_2, FVC, VO_2max, BMI, WHR and %Fat. Post hoc analysis shows that the significant changes in RSBP and RDBP occurred between baseline and 12^{th} week.

Table 4: Cardiopulmonary and Anthropometric Variables of Subjects in Group B_1

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value	Posthoc
GROUP B_1								
CVS								
RSBP (mmHg)	119.14 ±14.83	114.86±15.44	113.43 ±13.35	109.43 ±10.81	107.43±11.30	0.84	0.51	
RDBP (mmHg)	80.29 ± 12.13	77.71±14.63	74.00 ± 12.06	70.00 ± 10.83	68.86 ± 11.19	1.12	0.37	
RRPP (beats/min/mmHg)	9361.14 ± 1737.81	8973.43± 1412.96	8518.86 ± 1488.66	8021.71 ± 1285.68	7973.71 ± 1296.16	1.20	0.33	
Pulmonary								
SaO_2 (%)	97.71 ± 0.49	97.71±0.95	97.57 ± 0.53	97.71 ± 0.76	98.00 ± 0.00	0.43	0.79	
FVC (Litres)	1.69 ± 0.33	1.88 ± 0.28	1.99 ± 0.30	2.09 ± 0.33	2.19 ± 0.34	2.64	0.05*	a&e
VO_2max(kg/ml/min)	34.51 ± 4.08	34.41 ± 3.26	36.02 ± 3.80	36.92 ± 4.27	36.60 ± 5.28	0.55	0.70	
Anthropometric								
BMI (kg/m^2)	28.94 ± 5.89	29.92 ± 5.35	29.85 ± 4.90	29.93 ± 5.14	30.11 ± 4.93	0.05	0.99	
WHR	0.89 ± 0.05	0.88 ± 0.07	0.88 ± 0.06	0.88 ± 0.07	0.87 ± 0.08	0.05	1.00	
%Fat	39.77 ± 11.97	39.50 ± 12.25	39.51 ± 12.01	38.79 ± 10.95	38.96 ± 10.50	0.01	1.00	

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition. *= significant at $p \leq 0.05$

T**able 5: Cardiopulmonary and Anthropometric Variables of Subjects in Group B_2**

VARIABLES	**BASELINE (a)**	**3RD WEEK (b)**	**6TH WEEK (c)**	**9TH WEEK (d)**	**12TH WEEK (e)**	**F**	**p-value**	**Post hoc**
GROUP B_2								
CVS								
RSBP (mmHg)	117.14±17.58	103.43±9.22	105.43±13.75	99.71 ±7.43	98.86±6.82	2.76	0.05*	a&e
RDBP (mmHg)	78.28 ± 12.41	68.57±7.09	70.00 ± 10.33	66.57 ± 5.38	64.00 ± 5.89	2.74	0.05*	a&e
RRPP (beats/min/mmHg)	9584.00 ± 2312.41	7900.00 ± 1349.93	7862.86 ± 1410.64	7442.29 ± 1140.40	7296.00 ± 1082.90	2.52	0.06	
Pulmonary								
SaO_2 (%)	98.29 ± 0.49	97.57±0.79	97.71 ± 0.76	97.43 ± 0.53	97.71 ± 0.49	1.90	0.14	
FVC (Litres)	1.82 ± 0.38	1.89 ± 0.35	1.88 ± 0.39	1.90 ± 0.44	1.94 ± 0.47	0.09	0.98	
VO_2max(kg/ml/min)	31.37 ± 3.35	33.30±2.57	33.23 ± 2.06	33.75 ± 2.39	34.03 ± 2.41	1.13	0.36	
Anthropometric								
BMI (kg/m^2)	27.57 ± 4.83	27.58±5.03	27.54 ± 5.20	27.70 ± 4.94	27.85 ± 4.84	0.01	1.00	
WHR	0.86 ± 0.05	0.85±0.04	0.85 ± 0.04	0.85 ± 0.04	0.85 ± 0.04	0.13	0.97	
%Fat	36.34 ± 5.26	36.27±5.31	35.81 ± 5.28	36.26 ± 5.25	36.37 ± 5.18	0.01	1.00	

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition. *= significant at $p \leq 0.05$

4.6 Cardiopulmonary and Anthropometric Variables of Subjects in Group C_1

Table 6 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group C_1 at 3rd, 6th, 9th and 12th week. Repetitive ANOVA shows that there were significant differences in the RSBP, RDBP, RRPP and SaO_2. There were no significant differences in the FVC, VO_2max, BMI, WHR and %Fat. Post hoc analysis shows that the significant changes in RSBP, RDBP and SaO_2 occurred between baseline and 12th week while significant changes in RRPP occurred between baseline and 9th week and between baseline and 12th week.

4.7 Cardiopulmonary and Anthropometric Variables of Subjects in Group C_2

Table 7 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group C_2 at 3rd, 6th, 9th and 12th week. Repetitive ANOVA shows that there were significant differences in the RSBP, RDBP and RRPP. No significant differences were observed in the SaO_2, FVC, VO_2max, BMI, WHR and %Fat. Post hoc analysis shows that the significant changes in RDBP and RRPP occurred between baseline and 12th week while significant differences in RSBP occurred between baseline and 6th week, baseline and 9th week and between baseline and 12th week.

Table 6: Cardiopulmonary and Anthropometric Variables of Subjects in Group C_1

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value	Post hoc
GROUP C_1								
CVS								
RSBP (mmHg)	115.71±11.69	109.00±12.19	103.71 ±7.95	103.71 ± 7.70	100.57±5.50	2.91	0.04*	a&e
RDBP (mmHg)	74.57 ± 7.63	69.14 ± 8.63	70.29 ± 6.47	65.71 ± 6.47	62.86 ± 5.76	2.81	0.04*	a&e
RRPP (beats/min/mmHg)	8835.43 ± 985.80	8275.43 ± 1153.93	7562.29 ± 852.76	7405.71 ± 537.88	6748.57 ± 555.79	6.29	0.00*	a&d, a&e
Pulmonary								
SaO_2 (%)	98.14 ± 0.38	98.57 ± 0.53	98.43 ± 0.53	98.43 ± 0.53	99.00 ± 0.00	3.43	0.02*	a&e
FVC (Litres)	1.84 ± 0.53	2.05 ± 0.48	2.07 ± 0.50	2.16 ± 0.46	2.28 ± 0.48	0.77	0.55	
VO_2max(kg/ml/min)	35.70 ± 4.19	36.18 ± 3.80	37.41 ± 2.25	37.94 ± 1.59	40.26 ± 2.74	2.38	0.07	
Anthropometric								
BMI (kg/m^2)	29.66 ± 6.52	29.55 ± 6.65	29.52 ± 6.79	29.35 ± 6.76	29.15 ± 6.87	0.01	1.00	
WHR	0.85 ± 0.06	0.85 ± 0.05	0.84 ± 0.06	0.83 ± 0.05	0.83 ± 0.06	0.16	0.96	
%Fat	32.66 ± 11.59	32.33±11.52	32.90 ± 11.54	32.20 ± 11.60	31.83±11.73	0.01	1.00	

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition. *= significant at $p \leq 0.05$

T**able 7: Cardiopulmonary and Anthropometric Variables of Subjects in Group C_2**

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value	Post hoc
GROUP C_2								
CVS								
RSBP (mmHg)	124.33±13.65	114.00±11.10	107.67±7.94	107.33±2.42	102.67±3.93	5.34	0.00*	a&c, a&d, a&e
RDBP (mmHg)	77.00 ± 5.76	72.00±4.38	69.00 ± 6.78	71.00 ± 5.02	65.00 ± 5.18	3.83	0.02*	a&e
RRPP (beats/min/mmHg)	10510.00 ± 1966.32	9220.00 ± 1373.88	8514.67 ± 1665.52	8713.33 ± 1489.77	7722.67 ± 1102.24	2.67	0.05*	a&e
Pulmonary								
SaO_2 (%)	97.33 ± 1.03	98.00 ± 1.26	98.50 ± 0.84	98.00 ± 0.63	98.67±0.52	2.02	0.12	
FVC (Litres)	1.60 ± 0.37	1.81 ± 0.42	1.90 ± 0.41	1.96 ± 0.41	2.10 ± 0.44	1.25	0.32	
VO_2max(kg/ml/min)	28.98 ± 6.72	31.03±4.66	32.23 ± 6.31	31.30±5.76	33.43 ±4.77	0.50	0.74	
Anthropometric								
BMI (kg/m^2)	26.29 ± 6.10	25.96 ± 5.89	26.06 ± 5.88	25.70 ± 5.77	25.70 ± 5.83	0.01	1.00	
WHR	0.91 ± 0.05	0.90 ± 0.06	0.90 ± 0.06	0.89 ± 0.05	0.89 ± 0.06	0.24	0.91	
%Fat	32.68 ± 12.53	32.40 ± 12.01	32.28±12.24	30.98±12.25	30.83±13.03	0.03	1.00	

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition. *= significant at $p \leq 0.05$

4.8 Cardiopulmonary and Anthropometric Variables of subjects in Group D_1

Table 8 shows the changes in cardiopulmonary and anthropometric variables of subjects in group D_1 at 3^{rd}, 6^{th}, 9^{th} and 12^{th} week. Repetitive ANOVA shows that there were no significant differences in all the variables (RSBP, RDBP, RRPP, SaO_2, FVC, VO_2max, BMI, WHR and %Fat).

4.9 Cardiopulmonary and Anthropometric Variables of Subjects in Group D_2

Table 9 shows the changes in cardiopulmonary and anthropometric variables of subjects in Group D_2 at 3^{rd}, 6^{th}, 9^{th} and 12^{th} week. Repetitive ANOVA shows that there were no significant differences were observed in all the variables (RSBP, RDBP, RRPP, SaO_2, FVC, VO_2max, BMI, WHR and %Fat).

Table 8: Cardiopulmonary and Anthropometric Variables of Subjects in Group D_1

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value
GROUP D_1							
CVS							
RSBP (mmHg)	117.00±15.87	117.00±22.24	115.50±17.23	112.50±16.36	117.00±18.07	0.05	1.00
RDBP (mmHg)	77.50 ± 17.08	76.50±16.52	76.00 ± 19.93	73.00 ± 16.37	75.50 ± 17.31	0.04	1.00
RRPP (beats/min/mmHg)	9848.00 ± 2862.41	10201.00 ± 2930.07	9448.00 ± 1180.59	10244.00 ± 1707.45	10021.00 ± 2407.39	0.08	0.99
Pulmonary							
SaO_2 (%)	98.75 ± 0.50	98.00 ± 0.00	98.00 ± 0.00	98.25 ± 0.50	98.00 ± 0.00	0.25	0.89
FVC (Litres)	1.88 ± 0.49	1.98 ± 0.46	1.99 ± 0.54	2.05 ± 0.48	2.04 ± 0.45	0.08	0.99
VO_2max(kg/ml/min)	33.09 ± 4.57	31.69 ± 4.21	30.73 ± 3.78	29.85 ± 2.51	32.25 ± 5.73	0.35	0.84
Anthropometric							
BMI (kg/m^2)	29.98 ± 10.27	29.60 ± 10.39	29.58 ± 10.19	29.10 ± 10.45	29.62 ± 10.55	0.00	1.00
WHR	0.86 ± 0.05	0.84 ± 0.04	0.84 ± 0.03	0.84 ± 0.03	0.83 ± 0.05	0.32	0.86
%Fat	30.10 ± 13.70	28.93 ± 15.18	29.00 ± 14.73	28.43 ± 14.93	28.35 ± 15.86	0.01	1.00

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition.

T**able 9: Cardiopulmonary and Anthropometric Variables of Subjects in Group D_2**

VARIABLES	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	F	p-value
GROUP D_2							
CVS							
RSBP (mmHg)	133.00±12.06	127.50±7.00	125.00±7.02	125.75±11.50	125.00±15.19	0.38	0.82
RDBP (mmHg)	89.00 ± 6.63	83.00±12.49	82.00 ± 5.42	83.00 ± 6.22	82.00 ± 2.83	0.63	0.65
RRPP (beats/min/mmHg)	11515.00 ± 1356.72	10696.00± 880.10	10724.00 ± 582.24	11029.00 ± 509.17	11058.00 ± 660.87	0.60	0.67
Pulmonary							
SaO_2 (%)	97.50 ± 1.73	97.75 ± 0.50	97.00 ± 0.82	97.75 ± 0.50	97.25 ± 0.96	0.42	0.79
FVC (Litres)	1.62 ± 0.67	1.73 ± 0.49	1.75 ± 0.54	1.78 ± 0.49	1.77 ± 0.53	0.06	0.99
VO_2max(kg/ml/min)	29.37 ± 1.60	30.37 ± 2.91	29.63 ± 2.44	28.87 ± 1.54	28.24 ± 1.57	0.59	0.68
Anthropometric							
BMI (kg/m^2)	32.28 ± 2.76	32.93 ± 3.00	33.47 ± 2.99	33.49 ± 3.29	32.91 ± 3.88	0.03	1.00
WHR	0.89 ± 0.05	0.88 ± 0.05	0.87 ± 0.03	0.88 ± 0.03	0.87 ± 0.03	0.16	0.96
%Fat	42.48 ± 1.39	42.10 ± 2.23	42.50 ± 2.29	42.18 ± 2.27	40.88 ± 2.66	0.37	0.83

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, SaO_2=Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition.

4.10 Comparison of Changes in Cardiovascular Variables between Pre-treatment (Baseline) and Post-Treatment (12^{th} week) of the Premenopausal Study Groups

Table 10 shows the comparison of changes in cardiovascular variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the premenopausal study groups. Paired *t* test was used for analysis of data. There were significant differences in RSBP, RDBP and RRPP for Groups A_1 and C_1 while Groups B_1 and D_1 had no significant difference in any of the cardiovascular variables.

4.11 Comparison of changes in cardiovascular variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the postmenopausal study groups

Table 11 shows the comparison of changes in cardiovascular variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the postmenopausal study groups. Paired *t* test was used for analysis of data. There were significant differences in RSBP, RDBP and RRPP for Groups A_2, B_2 and C_2 while Group D_2 had no significant difference in any of the cardiovascular variables.

Table 10: Comparison of Changes in Cardiovascular Variables between Pre-Treatment (baseline) and Post-Treatment (12th week) of the Premenopausal Study Groups

Premenopausal Study groups	CARDIOVASCULAR VARIABLES	PRE-Rx (BASELINE)	POST-Rx (12TH WEEK)	t-value	p-value
GROUP A_1	RSBP(mmHg)	123.00±9.07	103.75±6.27	4.94	0.00*
	RDBP(mmHg)	79.50±10.68	67.75±7.89	2.50	0.03*
	RRPP(beat/min/ mmHg)	9835.00±1862.32	7398.00±1284.78	3.05	0.01*
GROUP B_1	RSBP(mmHg)	119.14 ±14.83	107.43±11.30	1.66	0.12
	RDBP(mmHg)	80.29 ± 12.13	68.86 ± 11.19	1.83	0.09
	RRPP(beat/min/mmHg)	9361.14 ± 1737.81	7973.71 ± 1296.16	1.69	0.12
GROUP C_1	RSBP(mmHg)	115.71±11.69	100.57±5.50	3.10	0.01*
	RDBP(mmHg)	74.57±7.64	62.86±5.76	3.24	0.01*
	RRPP(beat/min/mmHg)	8835.43±985.80	6748.57±555.79	4.88	0.00*
GROUP D_1	RSBP(mmHg)	117.00±14.70	117.00±16.73	0.00	1.00
	RDBP(mmHg)	77.50±17.08	75.50±17.31	0.16	0.81
	RRPP(beat/min/mmHg)	9848.00±2862.41	10021.00±2407.39	-0.09	0.93

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, *= significant at $p \leq 0.05$

Table 11: Comparison of Changes in Cardiovascular Variables between Pre-Treatment (Baseline) and Post-Treatment (12th week) of the Postmenopausal Study Groups

Postmenopausal Study groups	CVS VARIABLES	PRE-Rx (BASELINE)	POST-Rx (12TH WEEK)	t-value	p-value
GROUP A_2	RSBP(mmHg)	125.43±14.50	108.00±5.54	2.97	0.01*
	RDBP(mmHg)	84.57±10.63	70.57±3.78	3.28	0.01*
	RRPP(beat/min/mmHg)	9192.00±587.24	7834.29±787.97	3.66	0.00*
GROUP B_2	RSBP(mmHg)	117.14±17.58	98.86±6.82	2.57	0.03*
	RDBP(mmHg)	78.28 ± 12.41	64.00 ± 5.89	2.75	0.02*
	RRPP(beat/min/mmHg)	9584.00 ± 2312.41	7296.00 ± 1082.90	2.37	0.04*
GROUP C_2	RSBP(mmHg)	124.33±13.65	102.67±3.93	3.74	0.01*
	RDBP(mmHg)	77.00±5.76	65.00±5.18	3.80	0.00*
	RRPP(beat/min/mmHg)	10510.00±1966.32	7722.67±1102.24	3.03	0.02*
GROUP D_2	RSBP(mmHg)	133.00±12.06	125.00±15.19	0.83	0.44
	RDBP(mmHg)	89.00±6.63	82.00±2.83	1.94	0.10
	RRPP(beat/min/mmHg)	11515.00±1356.72	11058.00±660.87	0.61	0.57

Key: RSBP=Resting Systolic Blood Pressure, RDBP= Resting Diastolic Blood Pressure, RRPP=Resting Rate Pressure Product, *= significant at $p \leq 0.05$

4.12 Comparison of Changes in Pulmonary Variables between Pre-Treatment (baseline) and Post-Treatment (12^{th} week) of the Premenopausal Study Groups

Table 12 shows the comparison of changes in pulmonary variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the premenopausal study groups. Paired *t* test was used for analysis of data. There was significant difference in FVC for study group B_1 while study group C_1 had significant differences in SaO_2 and VO_2max. Groups A_1 and D_1 had no significant difference in any of the pulmonary variables of Groups A_1 and B_1.

4.13 Comparison of Changes in Pulmonary Variables between Pre-Treatment (baseline) and Post-Treatment (12^{th} week) of the Postmenopausal Study Groups

Table 13 shows the comparison of changes in pulmonary variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the postmenopausal study groups. Paired *t* test was used for analysis of data. There was significant difference in SaO_2 for study group A_2 while study group C_2 had significant differences in SaO_2 and FVC. No significant difference was observed in any of the pulmonary variables of study groups B_2 and D_2.

Table 12: Comparison of Changes in Pulmonary Variables between Pre-Treatment (Baseline) and Post-Treatment (12th week) of the Premenopausal Study Groups

Premenopausal Study groups	PULMONARY VARIABLES	PRE-Rx (BASELINE)	POST-Rx (12TH WEEK)	t-value	p-value
GROUP A_1	SaO_2(%)	98.25±0.71	98.50±0.54	-0.80	0.44
	FVC(Litre)	1.79± 0.50	2.25±0.54	-1.78	0.10
	VO_2max(kg/ml/min)	33.89±4.34	38.42±4.83	-1.98	0.07
GROUP B_1	SaO_2(%)	97.71 ± 0.49	98.00 ± 0.00	-1.55	0.15
	FVC(Litre)	1.69 ± 0.33	2.19 ± 0.34	-2.80	0.02*
	VO_2max(kg/ml/min)	34.51 ± 4.08	36.60 ± 5.28	-0.83	0.42
GROUP C_1	SaO_2(%)	98.14±0.38	99.00±0.00	-6.00	0.00*
	FVC(Litre)	1.84±0.53	2.28±0.48	-1.64	0.13
	VO_2max(kg/ml/min)	35.70±4.19	40.26±2.74	-2.41	0.03*
GROUP D_1	SaO_2(%)	98.75±0.50	98.00±0.00	1.87	0.09
	FVC(Litre)	1.88±0.49	2.04±0.45	0.48	0.65
	VO_2max(kg/ml/min)	33.09±4.57	32.25±5.73	0.23	0.83

Key: SaO_2 = Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, *= significant at $p \leq 0.05$

Table 13: Comparison of Changes in Pulmonary Variables between Pre-Treatment (baseline) and Post-Treatment (12^{th} week) of the Postmenopausal Study Groups

Postmenopausal Study groups	PULMONARY VARIABLES	PRE-Rx (BASELINE)	POST-Rx (12^{TH} WEEK)	t-value	p-value
GROUP A_2	SaO_2(%)	97.43±0.54	98.14±0.69	-2.17	0.05*
	FVC(Litre)	1.70±0.43	2.17±0.49	-1.90	0.08
	VO_2max(kg/ml/min)	33.35±2.67	33.35±2.93	-0.00	1.00
GROUP B_2	SaO_2(%)	98.29 ± 0.49	97.71 ± 0.49	2.19	0.06
	FVC(Litre)	1.82 ± 0.38	1.94 ± 0.47	-0.56	0.59
	VO_2max(kg/ml/min)	31.37 ± 3.35	34.03 ± 2.41	-1.70	0.11
GROUP C_2	SaO_2(%)	97.33±1.03	98.67±0.52	2.83	0.02*
	FVC(Litre)	1.60±0.37	2.10±0.44	-2.15	0.05*
	VO_2max(kg/ml/min)	28.98±6.72	33.43 ± 4.77	-1.56	0.15
GROUP D_2	SaO_2(%)	97.50±1.73	97.25±0.96	0.25	0.81
	FVC(Litre)	1.62±0.67	1.77±0.53	-0.35	0.74
	VO_2max(kg/ml/min)	29.37±1.60	28.24±1.57	1.01	0.35

Key: SaO_2 = Arterial Oxyhaemoglobin Saturation, FVC= Forced Vital Capacity, VO_2max=Maximal Oxygen Uptake, *= significant at $p \leq 0.05$

4.14 Comparison of Changes in Anthropometric Variables between Pre-Treatment (Baseline) and Post-Treatment (12^{th} week) of the Premenopausal Study Groups

Table 14 shows the comparison of changes in anthropometric variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the premenopausal study groups. Paired *t* test was used for analysis of data. There were no significant differences in BMI, WHR and %Fat of all the premenopausal study groups (A_1, B_1, C_1 and D_1).

4.15 Comparison of Changes in Anthropometric Variables between Pre-Treatment (Baseline) and Post-Treatment (12^{th} week) of the Postmenopausal Study Groups

Table 15 shows the comparison of changes in anthropometric variables between pre-treatment (baseline) and post-treatment (12^{th} week) of the postmenopausal study groups. Paired *t* test was used for analysis of data. There were no significant differences in BMI, WHR and %Fat of all the postmenopausal study groups (A_2, B_2, C_2 and D_2).

Table 14: Comparison of Changes in Anthropometric Variables between Pre-Treatment (Baseline) and Post-Treatment (12th week) of the Premenopausal Study Groups

Premenopausal Study groups	ANTHROPOMETRIC VARIABLES	PRE-Rx (BASELINE)	POST-Rx (12TH WEEK)	t-value	p-value
GROUP A_1	BMI (kg/m^2)	27.44±3.22	26.69±3.29	0.46	0.65
	WHR	0.86±0.08	0.84±0.07	0.47	0.65
	%Fat	33.71±2.81	32.15±3.49	0.99	0.34
GROUP B_1	BMI (kg/m^2)	28.94 ± 5.89	30.11 ± 4.93	-0.40	0.69
	WHR	0.89 ± 0.05	0.87 ± 0.08	0.40	0.69
	%Fat	39.77 ± 11.97	38.96 ± 10.50	0.14	0.90
GROUP C_1	BMI (kg/m^2)	29.66±6.52	29.15±6.87	0.14	0.89
	WHR	0.85±0.06	0.83±0.06	0.49	0.63
	%Fat	32.66±11.59	31.83±11.73	0.13	0.90
GROUP D_1	BMI (kg/m^2)	29.98±10.27	29.62±10.55	0.05	0.96
	WHR	0.86±0.05	0.83±0.05	1.82	0.45
	%Fat	30.10±13.70	28.35±15.86	0.17	0.87

Key: BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition

Table 15: Comparison of Changes in Anthropometric Variables between Pre-Treatment (Baseline) and Post-Treatment (12th week) of the Postmenopausal Study Groups

Postmenopausal Study groups	ANTHROPOMETRIC VARIABLES	PRE-Rx (BASELINE)	POST-Rx (12TH WEEK)	t-value	p-value
GROUP A_2	BMI (kg/m^2)	29.80±4.81	29.53 ± 4.75	0.11	0.92
	WHR	0.82±.05	0.83 ± 0.06	-1.00	0.36
	%Fat	38.33±6.39	37.25 ± 6.82	0.29	0.77
GROUP B_2	BMI (kg/m^2)	27.57 ± 4.83	27.85 ± 4.84	-0.11	0.92
	WHR	0.86 ± 0.05	0.85 ± 0.04	0.38	0.71
	%Fat	36.34 ± 5.26	36.37 ± 5.18	-0.01	0.99
GROUP C_2	BMI (kg/m^2)	26.29±6.10	25.70±5.83	0.17	0.87
	WHR	0.91±0.05	0.89±0.06	0.85	0.41
	%Fat	32.68±12.53	30.83±13.03	0.25	0.81
GROUP D_2	BMI (kg/m^2)	33.28±2.76	32.91±3.88	0.16	0.88
	WHR	0.89±0.05	0.87±0.03	0.57	0.59
	%Fat	42.48±1.39	40.88±2.66	1.07	0.33

Key: BMI=Body Mass Index, WHR=Waist Hip Ratio, %Fat=Percentage Body Fat Composition

4.16 Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group A_1 with those of Subjects in Group D_1 (Control group) at the 12^{th} week.

Table 16 shows the comparison of changes in cardiopulmonary and anthropometric variables of subjects in Group A_1 with those of subjects in Group D_1 at the 12^{th} week. Paired *t* test was used for analysis of data. There were significant differences in RSBP, RDBP, RRPP, SaO_2, FVC and VO_2max.

4.17 Comparison of Changes in Cardiopulmonary and Anthropometric variables of Subjects in Group A_2 with those of Subjects in Group D_2 (Control group) at the 12^{th} week.

Table 17 shows the comparison of changes in cardiopulmonary and anthropometric variables of subjects in Group A_2 with those of subjects in Group D_2 at the 12^{th} week. Paired *t* test was used for analysis of data. There were significant differences in FVC and WHR.

Table 16: Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group A_1 with those of Subjects in Group D_1 (Control Group) at the 12^{th} week.

VARIABLES	A_1 Mean changes	D_1 Mean changes	t-value	p-value
CVS				
RSBP (mmHg)	19.25	0.00	3.71	0.00*
RDBP (mmHg)	11.75	2.00	3.85	0.00*
RRPP (beats/min/mmHg)	2437.00	-173.00	4.28	0.00*
PULMONARY				
SaO_2 (%)	-0.25	0.75	-3.44	0.01*
FVC (Litres)	-0.46	-0.16	-2.83	0.02*
VO_2max(kg/ml/min)	-4.54	0.84	-2.89	0.02*
ANTHROPOMETRIC				
BMI (kg/m^2)	0.75	0.36	1.51	0.16
WHR	0.02	0.03	-1.01	0.34
%Fat	1.56	1.75	-0.21	0.84

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product,

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake,

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition.

Table 17: Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group A_2 with those of Subjects in Group D_2 (Control Group) at the 12^{th} week.

VARIABLES	A_2 Mean changes	D_2 Mean changes	t-value	p-value
CVS				
RSBP (mmHg)	17.43	8.00	1.54	0.16
RDBP (mmHg)	14.00	7.00	1.28	0.23
RRPP (beats/min/mmHg)	1357.71	457.00	1.37	0.21
PULMONARY				
SaO_2 (%)	-0.71	0.25	-1.15	0.28
FVC (Litres)	-0.46	-0.15	-2.86	0.02*
VO_2max(kg/ml/min)	-0.01	1.14	-0.69	0.51
ANTHROPOMETRIC				
BMI (kg/m^2)	0.27	0.37	-0.16	0.88
WHR	-0.01	0.02	-2.89	0.02*
%Fat	1.08	1.60	0.59	0.57

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product,

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake,

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition.

4.18 Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group B_1 with those of Subjects in Group D_1 (Control Group) at the 12^{th} week.

Table 18 shows the comparison of changes in cardiopulmonary and anthropometric variables of subjects in Group B_1 with those of subjects in Group D_1 at the 12^{th} week. Paired *t* test was used for analysis of data. There were significant differences in RDBP, RRPP, SaO_2 and FVC.

4.19 Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group B_2 with those of Subjects in Group D_2 (Control Group) at the 12^{th} week.

Table 19 shows the comparison of changes in cardiopulmonary and anthropometric variables of subjects in Group B_2 with those of subjects in Group D_2 at the 12^{th} week. Paired *t* test was used for analysis of data. There were significant differences in RRPP, VO_2max and %Fat.

Table 18: Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group B_1 with those of Subjects in Group D_1 (Control Group) at the 12th week.

VARIABLES	B_1 Mean changes	D_1 Mean changes	t-value	p-value
CVS				
RSBP (mmHg)	11.71	0.00	2.09	0.07
RDBP (mmHg)	11.43	2.00	4.47	0.00*
RRPP (beats/min/mmHg)	1387.43	-173.00	2.23	0.05*
PULMONARY				
SaO_2 (%)	-0.29	0.75	-3.29	0.01*
FVC (Litres)	-0.51	-0.16	-2.51	0.04*
VO_2max(kg/ml/min)	-2.09	0.84	-1.16	0.28
ANTHROPOMETRIC				
BMI (kg/m^2)	-1.17	0.36	-0.73	0.49
WHR	0.01	0.03	-0.51	0.62
%Fat	0.81	1.75	-0.60	0.57

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product,

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake,

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition.

Table 19: Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group B_2 with those of Subjects in Group D_2 (Control Group) at the 12th week.

VARIABLES	B_2 Mean changes	D_2 Mean changes	t-value	p-value
CVS				
RSBP (mmHg)	18.29	8.00	1.39	0.19
RDBP (mmHg)	14.29	7.00	1.58	0.14
RRPP(beats/min/mmHg)	2288.00	457.00	2.35	0.04*
PULMONARY				
SaO_2 (%)	0.57	0.25	0.32	0.76
FVC (Litres)	-0.13	-0.15	-0.03	0.98
VO_2max(kg/ml/min	-2.66	1.14	-2.55	0.03*
ANTHROPOMETRIC				
BMI (kg/m^2)	-0.28	0.37	-1.06	0.32
WHR	0.01	0.02	-0.91	0.38
%Fat	-0.03	1.60	-2.53	0.03*

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product,

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake,

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition.

4.20 Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group C_1 with those of Subjects in Group D_1 (Control Group) at the 12th week.

Table 20 shows the comparison of changes in cardiopulmonary and anthropometric variables of subjects in Group C_1 with those of subjects in Group D_1 at the 12th week. Paired *t* test was used for analysis of data. There were significant differences in RSBP. RDBP, RRPP, SaO_2 and VO_2max.

4.21 Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group C_2 with those of Subjects in Group D_2 (Control Group) at the 12th week.

Table 21 shows the comparison of changes in cardiopulmonary and anthropometric variables of subjects in Group C_2 with those of subjects in Group D_2 at the 12th week. Paired *t* test was used for analysis of data. There were significant differences in RSBP, RRPP, FVC and VO_2max.

Table 20: Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group C_1 with those of Subjects in Group D_1 (Control Group) at the 12^{th} week.

VARIABLES	C_1 Mean changes	D_1 Mean changes	t-value	p-value
CVS				
RSBP (mmHg)	15.14	0.00	2.78	0.02*
RDBP (mmHg)	11.71	2.00	2.93	0.02*
RRPP (beats/min/mmHg)	2086.86	-173.00	3.93	0.00*
PULMONARY				
SaO_2 (%)	-0.86	0.75	-6.07	0.00*
FVC (Litres)	-0.44	-0.16	-1.77	0.11
VO_2max(kg/ml/min)	-4.57	0.84	-2.68	0.03*
ANTHROPOMETRIC				
BMI (kg/m^2)	0.51	0.36	0.45	0.66
WHR	0.02	0.03	-0.83	0.43
%Fat	0.83	1.75	-1.02	0.34

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product,

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake,

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition.

Table 21: Comparison of Changes in Cardiopulmonary and Anthropometric Variables of Subjects in Group C_2 with those of Subjects in Group D_2 (Control Group) at the 12th week.

VARIABLES	C_2 Mean changes	D_2 Mean changes	t-value	p-value
CVS				
RSBP (mmHg)	21.67	8.00	2.30	0.05*
RDBP (mmHg)	12.00	7.00	1.12	0.29
RRPP (beats/min/mmHg)	2787.33	457.00	3.42	0.01*
PULMONARY				
SaO_2 (%)	-1.33	0.25	-1.63	0.14
FVC (Litres)	-0.50	-0.15	-2.78	0.02*
VO_2max(kg/ml/min	-4.45	1.14	-3.06	0.02*
ANTHROPOMETRIC				
BMI (kg/m^2)	0.59	0.37	0.28	0.79
WHR	0.03	0.02	0.69	0.51
%Fat	1.85	1.60	0.31	0.77

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product,

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake,

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition.

4.22 Comparison of Changes in Cardiovascular Variables of Premenopausal BCS with that of Postmenopausal BCS and the Cumulative Mean Changes in the Variables of Different Groups at the 12th week

Table 22 shows the comparison of changes in cardiovascular variables of premenopausal BCS with that of postmenopausal BCS. Paired *t* test was used for analysis of data. Significant difference in mean changes was observed only in RRPP of study group A. Mean changes in RSBP and RRPP were highest in the postmenopausal BCS of study group C while mean change in RDBP was highest in the postmenopausal BCS of study group B. The cumulative mean changes in RSBP and RRPP were highest in group C while that of RDBP was highest in group A.

Table 22: Comparison of Changes in Cardiovascular Variables of Premenopausal Breast cancer survivors (BCS) with that of Postmenopausal BCS and the Cumulative Mean Changes in the Variables of Different Groups at the 12th week

GROUP	CVS Variables	Premenopausal mean changes	Postmenopausal mean changes	t-value	p-value	Cumulative mean changes
A	RSBP(mmHg)	19.25	17.43	0.39	0.71	36.68
	RDBP(mmHg)	11.75	14.00	-0.61	0.55	25.75
	RRPP(beat/min/mmHg)	2437.00	1357.71	2.19	0.05*	3794.71
B	RSBP(mmHg)	11.71	18.29	-1.54	0.15	30.00
	RDBP(mmHg)	11.43	14.29	-1.27	0.23	25.72
	RRPP(beat/min/mmHg)	1387.43	2288.00	-1.85	0.09	3667.43
C	RSBP(mmHg)	15.14	21.67	-0.97	0.35	36.81
	RDBP(mmHg)	11.71	12.00	-0.01	0.99	23.71
	RRPP(beat/min/mmHg)	2086.86	2787.33	-1.49	0.17	4874.19
D	RSBP(mmHg)	0.00	8.00	-0.26	0.81	8.00
	RDBP(mmHg)	2.00	7.00	-1.73	0.13	9.00
	RRPP(beat/min/mmHg)	-173.00	457.00	0.22	0.84	284.00

*= significant at $p \leq 0.05$

Key:

RSBP = Resting Systolic Blood Pressure,

RDBP = Resting Diastolic Blood Pressure,

RRPP = Resting Rate Pressure Product

4.23 Comparison of Changes in Pulmonary Variables of Premenopausal BCS with that of Postmenopausal BCS and the Cumulative Mean Changes in the Variables of Different Groups at 12th week

Table 23 shows the comparison of changes in pulmonary variables of premenopausal BCS with that of postmenopausal BCS. Paired *t* test was used for analysis of data. Significant difference in mean changes was observed only in VO_2max of study group A. Mean change in SaO_2 was highest in the postmenopausal BCS of study group C. Mean change in FVC was highest in the premenopausal BCS of study group B while mean change in VO_2max was highest in the premenopausal BCS of study group C. The cumulative mean changes in all the 3 pulmonary parameters (SaO_2, FVC and VO_2max) were highest in group C.

Table 23: Comparison of changes in Pulmonary Variables of Premenopausal BCS with that of Postmenopausal BCS and the Cumulative Mean Changes in the Variables of Different Groups at the 12th week

GROUP	Pulmonary Variables	Premenopausal mean changes	Postmenopausal mean changes	t-value	p-value	Cumulative mean changes
A	SaO_2(%)	-0.25	-0.71	-1.89	0.08	-0.96
	FVC(Litre)	-0.46	-0.46	-0.04	0.97	-0.92
	VO_2max(kg/ml/min)	-4.54	-0.01	2.52	0.03*	-4.55
B	SaO_2(%)	-0.29	0.57	-1.25	0.23	0.28
	FVC(Litre)	-0.51	-0.13	1.74	0.11	-0.64
	VO_2max(kg/ml/min)	-2.09	-2.66	0.21	0.84	-4.75
C	SaO_2 (%)	-0.86	-1.33	-1.31	0.23	-2.19
	FVC(Litre)	-0.44	-0.50	-0.44	0.67	-0.94
	VO_2max(kg/ml/min)	-4.57	-4.45	-0.98	0.37	-9.02
D	SaO_2(%)	0.75	0.25	-1.85	0.11	1.00
	FVC(Litre)	-0.16	-0.15	0.15	0.88	-0.31
	VO_2max(kg/ml/min)	0.84	1.14	0.77	0.47	1.98

*= significant at $p \leq 0.05$

Key:

SaO_2 = Arterial Oxyhaemoglobin Saturation,

FVC = Forced Vital Capacity,

VO_2max = Maximal Oxygen Uptake

4.24 Comparison of Changes in Anthropometric Variables of Premenopausal BCS with that of Postmenopausal BCS and the Cumulative Mean Changes in the Variables of Different Groups at 12th week

Table 24 shows the comparison of changes in anthropometric variables of premenopausal BCS with that of postmenopausal BCS. Paired *t* test was used for analysis of data. Significant differences in mean changes were observed in BMI of study group A and %Fat of study group C. Mean change in BMI was highest in the premenopausal BCS of study group A. Mean changes in WHR and %Fat was highest in the postmenopausal BCS of study group C. Mean change in WHR was also highest in the premenopausal BCS of study group D. The cumulative mean changes in BMI and WHR were highest in group C while that of %Fat was highest in group D. The cumulative mean change in WHR was also highest in group D.

Table 24: Comparison of Changes in Anthropometric Variables of Premenopausal BCS with that of Postmenopausal BCS and the Cumulative Mean Changes in the Variables of Different Groups at the 12th week

GROUP	Anthropometric Variables	Premenopausal mean changes	Postmenopausal mean changes	t-value	p-value	Cumulative mean change
A	BMI (kg/m^2)	0.75	0.27	3.22	0.01*	1.02
	WHR	0.02	-0.01	-1.00	0.36	0.01
	%Fat	1.56	1.08	-0.85	0.43	2.64
B	BMI (kg/m^2)	-1.17	-0.28	1.06	0.31	-1.45
	WHR	0.01	0.01	0.55	0.59	0.02
	%Fat	0.81	-0.03	0.76	0.46	0.78
C	BMI (kg/m^2)	0.51	0.59	-0.37	0.72	1.10
	WHR	0.02	0.03	-0.30	0.77	0.05
	%Fat	0.83	1.85	-0.67	0.02*	2.68
D	BMI (kg/m^2)	0.36	0.37	-1.61	0.16	0.73
	WHR	0.03	0.02	0.34	0.74	0.05
	%Fat	1.75	1.60	-0.19	0.86	3.35

Key:

BMI = Body Mass Index,

WHR = Waist Hip Ratio,

%Fat = Percentage Body Fat Composition

4.25 Changes in the Mean RSBP of Premenopausal and Postmenopausal BC Study Groups

Figures 17 and 18 show schematic representations of changes in the mean RSBP of premenopausal and postmenopausal BC study groups from baseline through the 3^{rd}, 6^{th}, 9^{th} to the 12^{th} week. There were progressive reductions in the mean RSBP of the premenopausal and postmenopausal therapeutic exercise groups (Groups A, B and C) from baseline through the 3^{rd}, 6^{th}, 9^{th} to the 12^{th} week.

4.26 Changes in the Mean VO_2max of Premenopausal and Postmenopausal BC Study Groups

Figures 19 and 20 show schematic representations of changes in the mean VO_2max of premenopausal and postmenopausal BC study groups from baseline through the 3^{rd}, 6^{th}, 9^{th} to the 12^{th} week. There were progressive increases in the mean VO_2max of the premenopausal and postmenopausal therapeutic exercise groups (Groups A, B and C) from baseline through the 3^{rd}, 6^{th}, 9^{th} to the 12^{th} week.

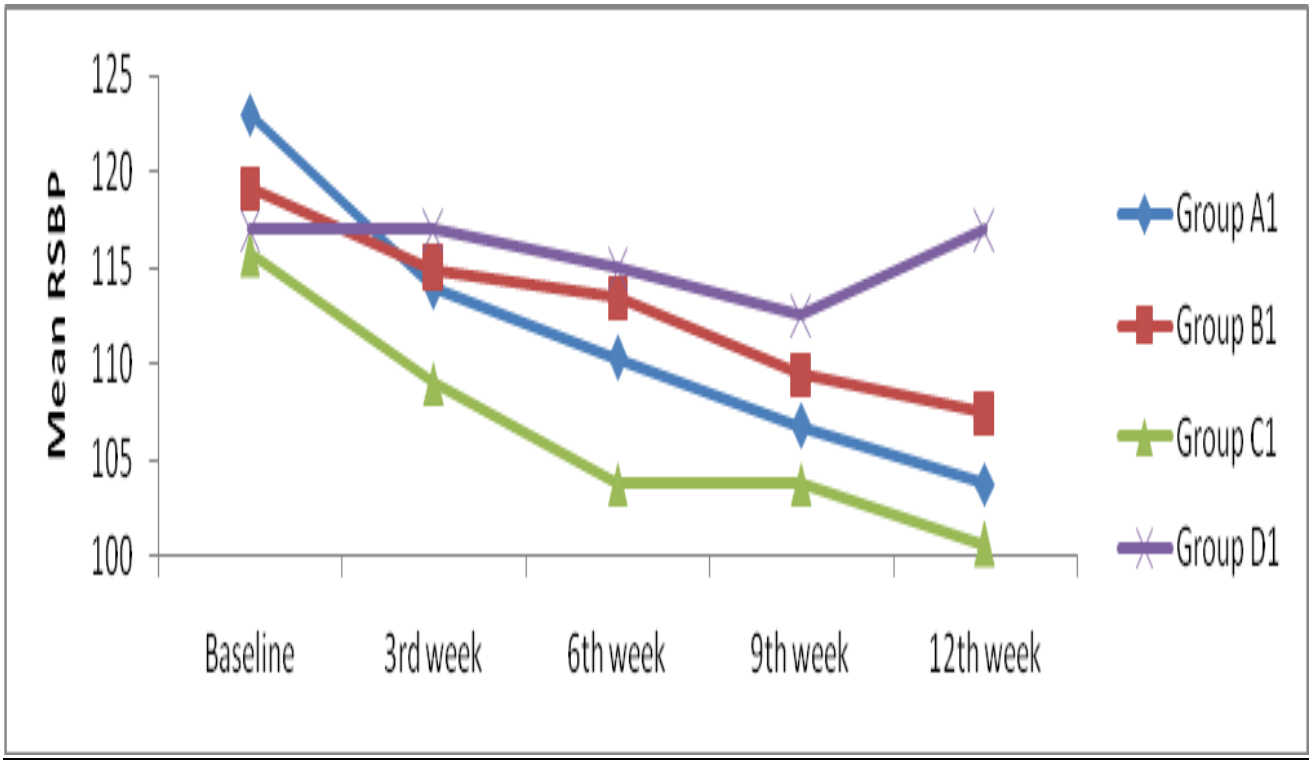

Figure 17: Schematic representation of changes in the mean RSBP of premenopausal BC study groups

Key:

RSBP = Resting Systolic Blood Pressure,

Group A_1 = Premenopausal Aerobic exercise group

Group B_1 = Premenopausal Stretching exercise group

Group C_1 = Premenopausal Aerobic with Stretching exercise group

Group D_1 = Premenopausal Control group

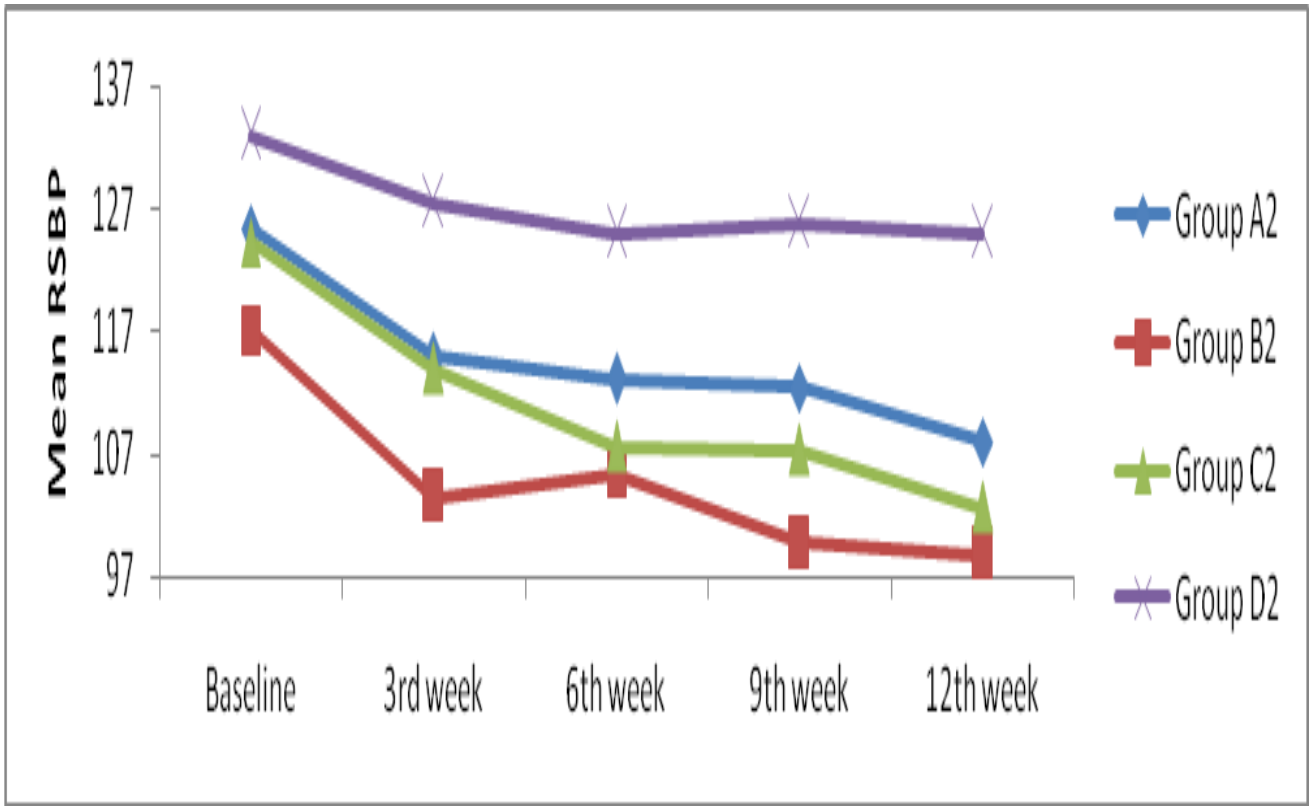

Figure 18: Schematic representation of changes in the mean RSBP of postmenopausal BC study groups

Key:

RSBP = Resting Systolic Blood Pressure,

Group A_2 = Postmenopausal Aerobic exercise group

Group B_2 = Postmenopausal Stretching exercise group

Group C_2 = Postmenopausal Aerobic with Stretching exercise group

Group D_2 = Postmenopausal Control group

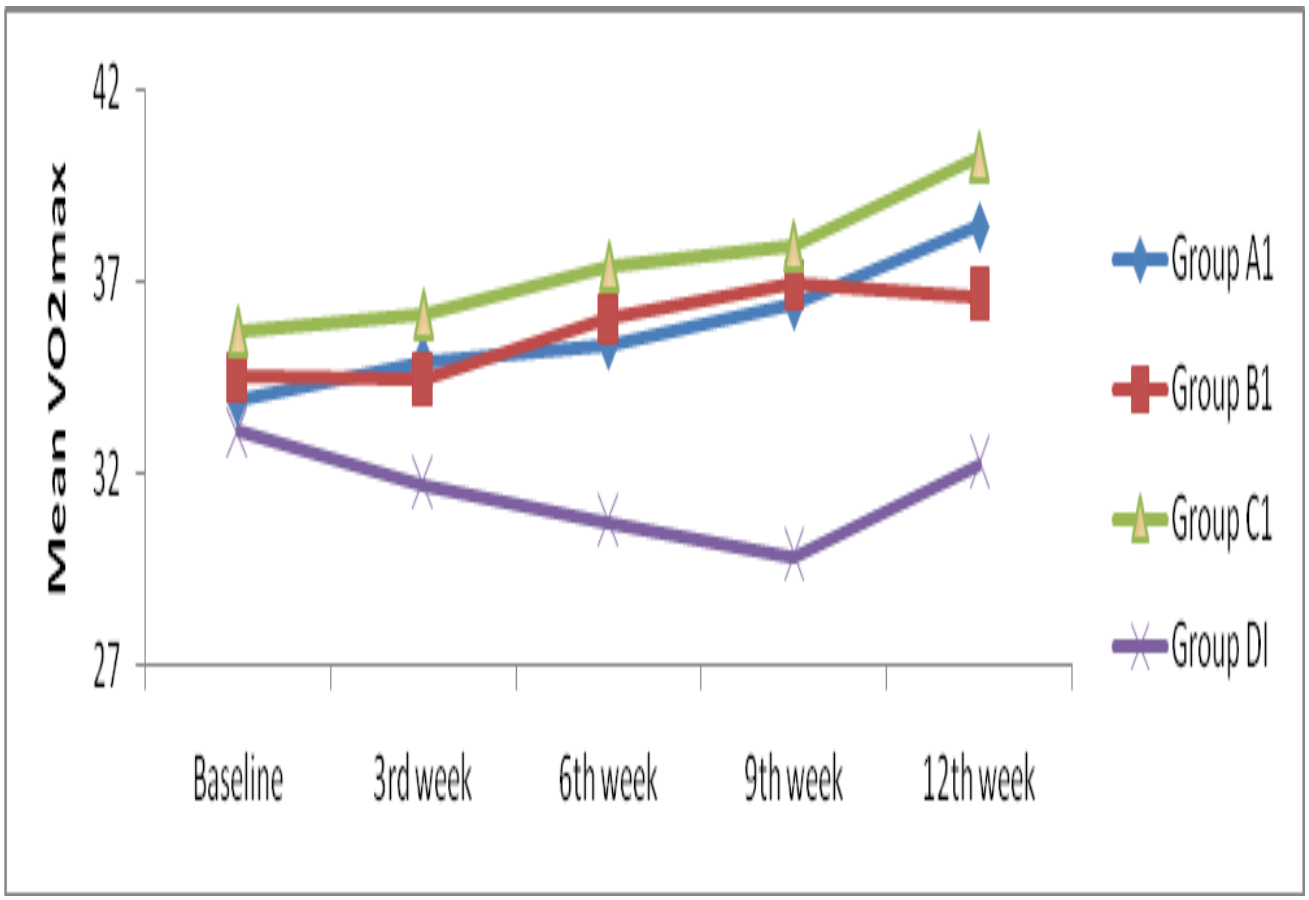

Figure 19: Schematic representation of changes in the mean VO_2max of premenopausal BC study groups

Key:

VO_2max = Maximal Oxygen Uptake

Group A_1 = Premenopausal Aerobic exercise group

Group B_1 = Premenopausal Stretching exercise group

Group C_1 = Premenopausal Aerobic with Stretching exercise group

Group D_1 = Premenopausal Control group

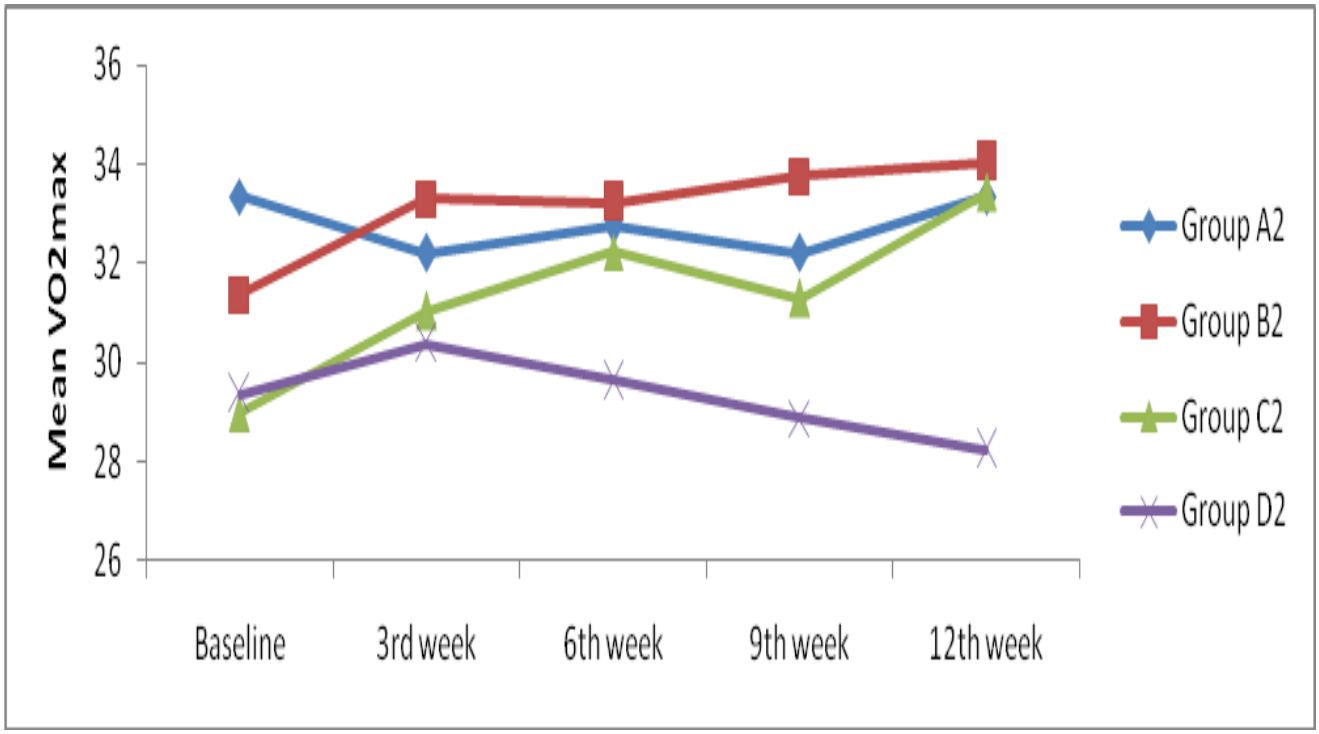

Figure 20: Schematic representation of changes in the mean VO_2max of postmenopausal BC study groups

Key:

VO_2max = Maximal Oxygen Uptake

Group A_2 = Postmenopausal Aerobic exercise group

Group B_2 = Postmenopausal Stretching exercise group

Group C_2 = Postmenopausal Aerobic with Stretching exercise group

Group D_2 = Postmenopausal Control group

4.27 Comparison of Changes in Quality of Life Subscales of Premenopausal BC Subjects

Table 25 shows the comparison of changes in QoL subscales of premenopausal study groups. Friedman test and Kruskal-Wallis H were used for data processing. The values of the 3 subscales of the QoL (TOI, FACT G and FACT B) increased progressively in Group A_1 from baseline to the 12^{th} week. Friedman test showed that there were significant differences in all the 3 subscales at the end of 12^{th} week. Kruskal-Wallis H analysis of data across the premenopausal groups showed significant difference for the 3 subscales only at the end of 12^{th} week.

For Group B_1, the values of the 3 subscales of the QoL (TOI, FACT G and FACT B) did not increase progressively but went below baseline values at the 3^{rd} week and exceeded the baseline values at the 12^{th} week. Friedman test showed significant differences in TOI and FACT B subscales at the end of 12^{th} week but not in FACT G subscale.

For Group $C_{1,}$ the values of the 3 subscales of the QoL (TOI, FACT G and FACT B) increased progressively from baseline to the 12^{th} week. Friedman test showed that there were significant differences in all the 3 subscales at the end of 9^{th} and 12^{th} weeks.

For Group $D_{1,}$ the values of the 3 subscales of the QoL (TOI, FACT G and FACT B) did not increase progressively and Friedman test showed that there were no significant differences in the 3 subscales.

Table 25: Comparison of Changes in QoL Subscales of Premenopausal BC Subjects

	SUBSCALE	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	Z	p-value	Posthoc
GROUP A_1	TOI	55.50 ± 13.65	58.13±12.90	60.75 ± 12.15	64.50 ± 11.44	69.38 ±10.56	23.73	0.00*	a&e
GROUP B_1	TOI	71.43 ± 6.83	69.00±7.67	66.57 ± 8.52	69.57 ± 5.38	75.00 ± 4.47	10.74	0.01*	a&e
GROUP C_1	TOI	65.86 ± 12.55	68.79±10.96	71.71 ± 9.38	77.14 ± 8.88	82.86 ± 8.59	21.00	0.00*	a&d,a&e
GROUP D_1	TOI	60.00 ± 19.87	60.25±19.70	60.50 ± 19.54	60.75 ± 21.13	56.75 ± 17.65	0.95	0.81	
	Z	66.00	66.25	66.50	69.00	73.00			
	p-value	0.44	0.19	0.33	0.13	0.04*			
GROUP A_1	FACT G	72.00 ± 18.02	74.00±16.72	76.00 ± 15.41	80.75 ± 13.90	86.13 ± 11.74	23.54	0.00*	a&e
GROUP B_1	FACT G	84.71 ± 8.44	82.07± 9.89	79.43 ± 11.34	82.57 ± 6.35	86.29 ± 5.99	3.87	0.28	
GROUP C_1	FACT G	77.29 ± 17.76	81.86±13.89	86.43 ± 10.01	93.29 ± 7.30	101.00 ± 3.65	21.00	0.00*	a&d, a&e
GROUP D_1	FACT G	73.50 ± 18.79	73.00±18.58	72.50 ± 18.38	68.00 + 18.00	67.25 ± 17.35	3.30	0.35	
	Z	80.00	80.50	81.00	82.00	87.50			
	p-value.	0.33	0.23	0.13	0.09	0.01*			
GROUP A_1	FACT B	95.25 ± 21.18	97.63±19.89	100.00±18.59	103.88±17.21	109.63 ± 15.08	24.00	0.00*	a&e
GROUP B_1	FACT B	112.86 ± 9.35	107.93±11.77	103.00±14.18	108.00 ±10.04	116.14 ± 9.69	9.34	0.03*	a&e
GROUP C_1	FACT B	102.57±22.10	108.14±16.34	113.71±10.58	120.71 ± 7.61	129.00 ± 5.83	21.00	0.00*	a&d, a&e
GROUP D_1	FACT B	97.25 ± 20.76	97.75±21.48	98.25 ± 22.20	93.75 ± 22.52	92.00 ± 22.08	1.18	0.76	
	Z	105.50	106.75	108.00	110.50	118.50			
	p-value.	0.13	0.24	0.35	0.08	0.00*			

Key: QoL= Quality of Life, TOI= Trial outcome index, FACT G= Functional Assessment of Cancer Therapy- General, FACT B= Functional Assessment of Cancer Therapy- Breast, Z represents Friedman and Kruskall Wallis test value, *= significant at $p \leq 0.05$

4.28 Comparison of Changes in Quality of Life Subscales of Postmenopausal BC Subjects

Table 26 shows the comparison of changes in QoL subscales of postmenopausal study Groups. Friedman test and Kruskal-Wallis H were used for data processing. The values of the 3 subscales of the QoL (TOI, FACT G and FACT B) increased progressively in Group A_2 from baseline to the 12^{th} week. Friedman test showed that there were significant differences in all the 3 subscales at the end of 9^{th} and 12^{th} week. Kruskal-Wallis H analysis of data across postmenopausal study groups showed that only FACT G was significantly different at the end of 12^{th} week.

For Group B_2, the values of the 3 subscales of the QoL (TOI, FACT G and FACT B) increased progressively from baseline to the 12^{th} week. Friedman test showed that there were significant differences in all the 3 subscales at the end of 9^{th} and 12^{th} week.

For Group C_2, the values of the 3 subscales of the QoL (TOI, FACT G and FACT B) increased progressively at the end of 3^{rd}, 6^{th}, 9^{th} and 12^{th} weeks. Friedman test showed that there were significant differences in all the 3 subscales at the end of 9^{th} and 12^{th} week.

For Group B_2, the values of the 3 subscales of the QoL (TOI, FACT G and FACT B) did not increase progressively. Friedman test showed that there were no significant differences in all the 3 subscales.

Table 26: Comparison of Changes in QoL Subscales of Postmenopausal BC Subjects

	SUBSCALE	BASELINE (a)	3RD WEEK (b)	6TH WEEK (c)	9TH WEEK (d)	12TH WEEK (e)	Z	p-value	Posthoc
GROUP A_2	TOI	67.43 ± 13.08	71.57±11.65	75.71 ± 10.23	78.86 ± 8.76	83.29 ± 7.48	20.74	0.00*	a&d, a&e
GROUP B_2	TOI	61.00 ± 13.15	64.36±12.52	67.71 ± 11.88	72.00 ± 12.22	75.43 ± 10.92	16.22	0.00*	a&d, a&e
GROUP C_2	TOI	54.83 ± 12.45	59.75±11.52	64.67 ± 10.60	73.33 ± 9.77	82.00 ± 7.01	18.00	0.00*	a&d, a&e
GROUP D_2	TOI	68.00 ± 7.87	64.88±10.47	61.75 ± 13.07	67.00 ± 7.39	63.00 ± 10.23	5.40	0.15	
	Z	62.50	67.00	71.50	71.00	77.00			
	p-value	0.24	0.40	0.55	0.40	0.11			
GROUP A_2	FACT G	76.14 ± 14.29	81.21±12.04	86.29 ± 9.79	90.86 ± 7.31	97.71 ± 7.46	21.00	0.00*	a&d, a&e
GROUP B_2	FACT G	79.57 ± 14.75	82.21±14.22	84.86 ± 13.69	88.43 ± 13.02	89.43 ± 12.70	10.40	0.02*	a&d, a&e
GROUP C_2	FACT G	72.17 ± 13.69	76.08±12.26	80.00 ± 10.83	88.67 ± 7.97	97.33 ± 6.44	18.00	0.00*	a&d, a&e
GROUP D_2	FACT G	80.75 ± 9.29	79.13±11.08	77.50 ± 12.87	81.50 ± 6.56	81.00 ± 5.77	1.54	0.67	
	Z	77.00	79.78	82.50	88.50	92.50			
	p-value.	0.62	0.58	0.55	0.73	0.03*			
GROUP A_2	FACT B	102.00±19.26	107.14±17.47	112.29±15.68	119.00±12.14	124.71 ± 11.66	19.97	0.00*	a&d, a&e
GROUP B_2	FACT B	105.00±17.22	108.71±16.65	112.43±16.08	116.71±14.59	119.43 ± 15.48	9.73	0.02*	a&d, a&e
GROUP C_2	FACT B	94.00 ± 17.52	98.75±16.77	94.00 ± 17.52	103.50±16.02	125.33 ± 9.69	18.00	0.00*	a&d, a&e
GROUP D_2	FACT B	106.25±15.50	104.13±17.17	106.25±15.50	102.00±18.83	105.25 ± 16.09	4.54	0.21	
	Z	101.50	105.50	109.50	117.50	119.50			
	p-value.	0.81	0.81	0.81	0.96	0.58			

*= significant at $p \leq 0.05$

Key:

QoL= Quality of Life,

TOI=Trial outcome index, FACT G= Functional Assessment of Cancer Therapy- General,

FACT B= Functional Assessment of Cancer Therapy- Breast,

Z represents Friedman and Kruskall Wallis test value,

CHAPTER FIVE

DISCUSSION

5.1 DISCUSSION

5.1.1 Physical Characteristics

The mean age of premenopausal BC subjects groups ranged from 39.43 years to 41.71 years while that of postmenopausal BC subjects ranged from 51.00 years to 55.00 years. This implies that the BC survivors that participated in this study were younger women. Fifty percent of the time, BC is diagnosed among Caucasian women who are over 65 years old (ACS, 2005). Ihekwaba (1993) reported that 70 percent of patients with BC in Nigeria were between 26 years and 50 years old while Adesunkanmi *et al*. (2006) observed that the mean age of patients with BC in Nigeria was 48 years. The observation that the mean BMI values of premenopausal BC subjects at baseline ranged from 27.44 kg/m^2 to 29.98 kg/m^2 while that of postmenopausal BC subjects ranged from 26.29 kg/m^2 to 33.28 kg/m^2 implies that the subjects were generally overweight and obese. This observation corroborates previous studies that weight gain and obesity are common occurrences in women diagnosed with BC (Demark-Wahnefried *et al*., 2001; McInnes and Knobf, 2001).

5.1.2 Cardiopulmonary Parameters

The significant differences observed in two of the cardiovascular parameters (RSBP and RRPP) of Group A_1 and in all the three cardiovascular parameters (RSBP, RDBP and RRPP) of Group A_2 imply that aerobic exercise using treadmill had significant therapeutic effects on the cardiovascular parameters of the premenopausal and

postmenopausal BC survivors. These significant therapeutic effects in RSBP occurred earlier in premenopausal BC survivors (end of 6^{th} week) than postmenopausal BC survivors (end of 12^{th} week) while that of RRPP occurred at the same time (end of 12^{th} week) in the 2 groups of BC survivors. Significant therapeutic effect in RDBP occurred only in the postmenopausal BC survivors at the end of the 9^{th} week and continued to the end of the 12^{th} week. These significant therapeutic effects on the cardiovascular parameters of the premenopausal and postmenopausal BC survivors by aerobic exercise using treadmill were further buttressed by the changes in cardiovascular variables between pre-treatment and post-treatment where all the cardiovascular parameters (RSBP, RDBP and RRPP) showed significant improvements in the 2 groups of BC survivors. These findings may be due to the fact that aerobic exercise improves myocardial circulation and metabolism which in turn protects the heart from hypoxic stress, and also enhances glycolytic capacity as reported by Pollock *et al*. (2000). This improvement of the myocardial circulation and metabolism improves the heart oxygen supply and its contractility during a specific challenge, thus the heart rate and blood pressure are favourably reduced so that the work of myocardium is significantly reduced at rest and during exercise. Aerobic exercise using treadmill brought about more significant therapeutic improvements in RSBP and RRPP of the studied premenopausal BC survivors than the studied postmenopausal BC survivors but in RDBP, the reverse was the case.

Although there were improvements in the 3 pulmonary parameters (SaO_2, FVC and VO_2max) of Groups A_1 and A_2, they were not statistically significant except in SaO_2 of Group A_2 between pre-treatment and post-treatment. This implies that aerobic exercise

using treadmill had therapeutic effects in the pulmonary parameters of the premenopausal and postmenopausal BC survivors. The reason for this may be that the long-term effect of aerobic exercise leads to an expansion of the oxygen transport system, which is reflected by the augmented capacity for maximal work (Wilmore and Costil, 2005; Osho *et al*., 2012). There is larger lung size and vital capacity, higher blood volume and total haemoglobin, larger stroke volume, maximal oxygen uptake and arterio-venous oxygen difference. Aerobic exercise using treadmill brought about more beneficial effect on the VO_2max of the premenopausal BC survivors than that of the postmenopausal BC survivors. The reverse was the case for SaO_2 while it had equal effects on the FVC of the 2 groups of BC survivors. These findings are partly consistent with the results of the study by Schneider *et al* (2007) who reported that moderate intensity, individualized, prescriptive exercise maintains or improves cardiovascular and pulmonary function during and after cancer treatment. Their findings on significant improvement in the pulmonary functions of the subjects differ slightly with that of the present study and this may be due to the differences in the duration of exercise intervention of both studies. The duration of exercise intervention in this study was 12 weeks while that by Schneider *et al* (2007) was 6 months. Burnham and Wilcox (2002), Drouin (2002), Courneya *et al* (2003) and Crowley (2003) reported that moderate intensity aerobic training had significant improvement in the cardiopulmonary parameters of their study participants. Segal *et al* (2001) reported no effects of a lower intensity aerobic exercise programme on aerobic fitness (VO_2peak) of BC patients receiving chemotherapy.

Although there were changes in all the 3 cardiovascular parameters of subjects in Group B_1 and B_2, comparison of the cardiovascular parameters across baseline, end of 3^{rd}, 6^{th}, 9^{th}

and 12th weeks showed no significant difference in any of the cardiovascular parameters of study group B_1 but in RSBP and RDBP of study group B_2. This implies that stretching exercises brought about therapeutic improvements in the cardiovascular parameters of the studied premenopausal and postmenopausal BC survivors. The significant change in RSBP and RDBP of the postmenopausal BC survivors occurred at the end of the 12th week. The analysis of changes in cardiovascular variables between pre-treatment and post-treatment mean values also showed no significant difference in all the 3 cardiovascular parameters of the premenopausal BC survivors but showed significant differences in all the 3 cardiovascular parameters of the postmenopausal BC survivors. Stretching exercise brought about more significant therapeutic improvements in all the 3 cardiovascular parameters (RSBP, RDBP and RRPP) of the postmenopausal BC survivors than the premenopausal BC survivors. Conventionally, stretching exercise is not used to improve cardiovascular function but to increase flexibility of muscles that will promote injury prevention, enhance performance during exercise training and reduce soreness after exercise (Anderson, 2005). Extensive research has been done in sports medicine to examine the role of stretching exercise in injury prevention, post exercise soreness reduction and performance enhancement but systematic reviews of these studies revealed that it had insignificant effects on injury prevention and post exercise soreness (Herbert and Gabriel, 2002; Anderson, 2005).

There were improvements in all pulmonary parameters of subjects in Groups B_1 and B_2 except in SaO_2 of Group B_2 where there was a reduction. These improvements did not attain statistically significant levels when analysed using ANOVA and paired *t* test except in FVC of Groups B_1. The significant change in FVC of the premenopausal BC survivors

occurred at the end of the 12th week. These findings imply that stretching exercise had therapeutic effects on the pulmonary parameters of the premenopausal and postmenopausal BC survivors. Stretching exercise brought about more therapeutic improvements in SaO_2 and FVC of the premenopausal BC survivors than the postmenopausal BC survivors but in VO_2max, the reverse was the case. The reason for the insignificant improvements in the pulmonary parameters of the studied BC survivors following stretching exercise training may be because stretching exercise involves just elongation of specific skeletal muscle or muscle group and not continuous movements of some large muscle groups that result in increased activity of the heart and lungs in order to meet the body's increased oxygen demand as aerobic exercise (Weerapong *et al*., 2004; Ronald *et al*., 2007).

The effects of resistance exercise on cardiopulmonary and anthropometric parameters in BC survivors have been studied (Ohira *et al*., 2006; Courneya *et al*., 2007; Winters-Stone *et al*., 2012). The present study differed from previous studies because it examined the effects of an isolated stretching exercise programme on cardiopulmonary and anthropometric parameters in BC survivors. A recent study that determined the effects of resistance training on muscle strength and physical function in older, postmenopausal BC survivors used stretching exercises as placebo programme for the control group (Winters-Stone *et al*., 2012). They concluded that resistance and impact exercise is superior to stretching at improving maximal muscle strength. Some previous studies examined the effects of supervised exercise training on various parameters in BC survivors having different treatments (Schneider *et al*., 2003; Schneider *et al*., 2007; Hsieh *et al*., 2008). In these studies aerobic, resistance and stretching exercises were all combined for each

participant to achieve an individualized, prescriptive exercise which were carried out for 6 months. They reported that supervised exercise training improved cardiopulmonary function with concomitant reductions in fatigue regardless of treatment type. It is common practice to include stretching exercises as part of warm up and cool down regimen in exercise training as observed in previous studies (Ohira *et al*., 2006; Milne *et al*., 2008).

The significant differences observed in all the cardiovascular parameters (RSBP, RDBP and RRPP) of Groups C_1 and C_2 imply that combined aerobic exercise using treadmill and stretching exercise brought about significant therapeutic improvements in all the cardiovascular parameters of the premenopausal and postmenopausal BC survivors. Although significant changes in some cardiovascular parameters occurred as early as the end of the 6^{th} and 9^{th} weeks, improvements in most of the cardiovascular parameters attained statistical significant level at the end of the 12^{th} week. Combined aerobic exercise using treadmill and stretching exercise brought about more significant therapeutic improvements in all the 3 cardiovascular parameters (RSBP, RDBP and RRPP) of the postmenopausal BC survivors than the premenopausal BC survivors. This combined exercise therapy brought about the overall best improvements in RSBP and RRPP in the postmenopausal BC survivors. These findings may be as a result of a combination of the therapeutic benefits of aerobic exercise and that of stretching exercise.

There were improvements in all pulmonary parameters of subjects in Groups C_1 and C_2. In Groups $C_{1,}$ statistical significant level of improvement was attained in SaO_2 at the end of the 12^{th} week of study and analysis of changes between pre-treatment and post-

treatment showed statistical significant levels of improvements in SaO_2 and VO_2max. In Groups C_2, statistical significant levels of improvements were attained in SaO_2 and FVC only when paired *t* test was used to analyse changes between pre-treatment and post-treatment mean values. These imply that combined aerobic exercise using treadmill and stretching exercise had significant therapeutic effects on the pulmonary parameters of the studied premenopausal and postmenopausal BC survivors. This combined exercise therapy brought about more therapeutic changes in SaO_2 and FVC of postmenopausal BC survivors than premenopausal BC survivors but the reverse was the case in VO_2max. These improvements in the pulmonary parameters of BC survivors who performed the combined exercise therapy may also be as a result of a combination of the therapeutic benefits of aerobic exercise and that of stretching exercise on their respiratory system.

Few randomized controlled trials have examined the effects of combined aerobic and resistance training in breast cancer survivors (Nieman *et al*., 1995; Harris and Niesen-Vertommen, 2000; Ligibel *et al*., 2008; Milne *et al*., 2008). In this study, the effects of combined aerobic and stretching exercise training were examined in BC survivors. Nieman *et al*. (1995) observed that an 8 week combined aerobic and resistance exercise intervention on 12 BC survivors brought about improvement in the cardiovascular parameters and lower limb muscular strength but had no effect on the immune function of the participants. Harris and Niesen-Vertommen (2000) found no change in lymphedema following a programme of 20-30 minutes of moderate intensity aerobic and resistance exercises performed 3 times weekly for 8 months. Ligibel *et al* (2008) reported that 16 weeks combined aerobic and resistance exercise intervention was associated with a significant decrease in insulin levels and hip circumference in BC survivors. Milne *et al*

(2008) concluded that combined aerobic and resistance exercise soon after the completion of BC therapy produces large and rapid improvements in health-related outcomes.

There were no significant changes in the cardiovascular and pulmonary parameters of study Groups D_1 and D_2. This implies that since subjects in this group had no therapeutic exercise intervention, the significant improvements observed in the other study groups that performed therapeutic exercise interventions were due to the therapeutic exercise interventions that they performed.

5.1.3 Anthropometric Parameters

With the exception of WHR in Group A_2, aerobic exercise using treadmill brought about very minimal reductions in all the anthropometric parameters of Groups A_1 and A_2 but they were not statistically significant. Aerobic exercise has been known to improve the body compositions of healthy individuals (McTiernan *et al*., 2007) through breakdown of fats and other micronutrients for energy (Adenosine tri-phosphate (ATP)) production for large muscle groups during repeated and continuous movements. On the other hand, some of the suggested reasons for post-diagnosis weight gain in BC survivors such as chemotherapy, infertility following treatment after diagnosis and increased total caloric intake remained unchanged during the study (Irwin *et al*., 2003). A combination of these factors might have brought about the very minimal reductions in the anthropometric parameters of study group A. The reductions in the anthropometric parameters due to aerobic exercise on treadmill were more in the studied premenopausal BC survivors than the studied postmenopausal BC survivors. This finding is consistent with the findings of

previous studies that reported no significant reductions in body weight and BMI of BC survivors following aerobic exercise training (Drouin, 2002; Courneya *et al*., 2003; Pinto *et al*., 2005). On the other hand, McTiernan *et al* (2007) reported that there were significant reductions in body weight, BMI, waist circumference and body fat of men and women who performed moderate to vigorous aerobic exercises for 12 months. The difference in the duration of exercise, intensity of exercise and type of subjects (Healthy vs Breast cancer) may account for the difference in the results of the two studies. Irwin *et al* (2009) reported that moderate-intensity aerobic exercise performed for 6 months produced favorable changes in body composition (body weight, BMI, body fat and bone mineral composition) of postmenopausal BC survivors. Again, the duration of exercise may account for the difference in the results of the two studies.

There were no improvements in BMI of study groups B_1 and B_2 and also in %Fat of Group B_2. Very minimal reductions were observed in WHR of study groups B_1 and B_2 and also in %Fat of Group B_1. This implies that stretching exercises had no significant therapeutic effects on the anthropometric parameters of the premenopausal and postmenopausal BC survivors. The reason for this may be because stretching exercise involves just elongation of specific skeletal muscle or muscle group and does not cause appreciable muscle contraction/work that breaks down fat molecules and other micronutrients for ATP production used in energy generation (Weerapong *et al*., 2004).

Combined aerobic exercise using treadmill and stretching exercise brought about positive changes in all the anthropometric parameters (BMI, WHR and %Fat) of study groups C_1 and C_2 although none was statistically significant. It brought about more therapeutic

improvements in all the 3 anthropometric parameters of the studied postmenopausal BC survivors than the premenopausal BC survivors. This combined exercise therapy brought about the overall best improvements in %Fat and WHR in the postmenopausal BC survivors. These findings may be as a result of a combination of the therapeutic benefits of aerobic exercise and that of stretching exercise.

5.1.4 Quality of Life Parameters

The finding that all the QoL subscales (TOI, FACT G and FACT B) showed significant differences in study Groups A_1 and A_2 implies that aerobic exercises using treadmill caused significant improvement in the QoL of the premenopausal and postmenopausal BC survivors. Previous studies also reported that moderate intensity aerobic exercise significantly improved the QoL of postmenopausal BC survivors (Courneya *et al*., 2003; Campbell *et al*., 2005). Significant changes in TOI, FACT G and FACT B QoL subscales occurred at the end of 12^{th} week in premenopausal BC group while they occurred in postmenopausal BC group at the end of 9^{th} week through to the end of 12^{th} week.

The finding that two of the QoL subscales (TOI and FACT B) had significant differences in study Group B_1 and all the 3 subscales (TOI, FACT G and FACT B) had significant differences in study Group B_2 implies that stretching exercises brought about significant improvements in the QoL of the studied premenopausal and postmenopausal BC survivors. Significant changes in TOI and FACT B QoL subscales of premenopausal BC group occurred at the end of 12^{th} week while significant changes in the QoL subscales of postmenopausal BC group occurred at the end of 9^{th} week and continued to the end of 12^{th} week.

The significant differences in all the QoL subscales of study Groups C_1 and C_2 implies that combined aerobic exercise using treadmill and stretching exercise caused significant improvement in the QoL of the studied premenopausal and postmenopausal BC survivors. Significant changes in TOI, FACT G and FACT B QoL subscales of premenopausal and postmenopausal BC subjects occurred at the end of 9^{th} and 12^{th} week. A combination of the therapeutic benefits of aerobic exercise and stretching exercise may be the reason why the significant changes in all the QoL subscales of premenopausal BC subjects occurred earlier at the end of 9^{th} week and continued to the end of 12^{th} week.

Since there were no significant differences in the QoL subscales of study groups D_1 and D_2 who had no therapeutic exercise intervention, it implies that the changes observed in the other premenopausal and postmenopausal study groups that had exercise interventions were due to the therapeutic exercise interventions.

CHAPTER SIX

SUMMARY OF FINDINGS, CONCLUSION AND CONTRIBUTIONS TO KNOWLEDGE

6.1 Summary of Findings

Specific Objectives	Summary of Findings
1. To determine the effects of aerobic exercise using treadmill on selected cardiopulmonary, anthropometric and QoL parameters in premenopausal and postmenopausal BC survivors.	1. Aerobic exercise using treadmill (AET) brought about significant improvements in selected cardiovascular parameters of premenopausal and postmenopausal BC survivors. These improvements in two (RSBP and RRPP) out of three cardiovascular parameters were more in the premenopausal BC survivors than the postmenopausal BC survivors. 2. AET brought about changes in selected pulmonary parameters but were not significant in both premenopausal and postmenopausal BC survivors except in SaO_2 of the postmenopausal group. 3. AET also brought about changes in selected anthropometric parameters which were not significant. These improvements in all the 3 anthropometric parameters were more in the premenopausal BC survivors than the postmenopausal BC survivors. 4. AET brought about significant improvements in the QoL of premenopausal and postmenopausal BC survivors.
2. To determine the effects of stretching exercises on selected cardiopulmonary, anthropometric and QoL parameters in premenopausal and postmenopausal BC survivors.	1. Stretching exercise (SE) had significant therapeutic benefits on selected cardiovascular parameters of postmenopausal BC survivors. These benefits in all the 3 cardiovascular parameters were more in the postmenopausal BC survivors than the premenopausal BC survivors. 2. SE brought about changes in the selected pulmonary parameters but only FVC of premenopausal BC survivors was significant. 3. SE had no significant effects on selected anthropometric parameters of premenopausal and postmenopausal BC survivors. 4. SE brought about significant improvements in the QoL of premenopausal and postmenopausal BC survivors.

3. To determine the effects of combined aerobic exercise using treadmill and stretching exercise on selected cardiopulmonary, anthropometric and QoL parameters in premenopausal and postmenopausal BC survivors.	1. Combined aerobic exercise using treadmill and stretching exercise (CAETSE) had significant therapeutic effects on all selected cardiovascular parameters of premenopausal and postmenopausal BC survivors. These effects were more in the postmenopausal BC survivors than the premenopausal BC survivors. 2. CAETSE had significant therapeutic effects on selected pulmonary parameters of premenopausal and postmenopausal BC survivors. These effects were more in the postmenopausal BC survivors than the premenopausal BC survivors. 3. CAETSE brought about changes that were not significant in selected anthropometric parameters of premenopausal and postmenopausal BC survivors. These effects were more in the postmenopausal BC survivors than the premenopausal BC survivors. 4. CAETSE brought about significant improvements in the QoL of premenopausal and postmenopausal BC survivors. 5. CAETSE brought about the best improvements in selected cardiovascular (RSBP, RRPP) and pulmonary (SaO_2, FVC, VO_2max) parameters.
4. To determine an ideal dosage of therapeutic exercise that improves the cardiopulmonary and QoL parameters in premenopausal and postmenopausal BCS.	1. CAETSE performed at a moderate intensity for duration of 30 minutes, 3 times a week for 12 weeks (frequency) is an ideal dosage of therapeutic exercise that improves the cardiopulmonary and QoL parameters in premenopausal and postmenopausal BC survivors.

6.2 CONCLUSION

The global burden of BC continues to increase especially in economically developing countries and this is associated with increased mortality and morbidity due to various complications associated with the disease (Jemal *et al*, 2011). Cardiopulmonary capacity compromise in BC survivors due to the pathology of the disease, therapeutic regimens such as chemotherapy and radiotherapy, weight gain and inactivity secondary to treatment may lead to reductions in QoL and premature death (Brockstein *et al*., 2000; Gianni *et al*., 2001; Courneya *et al*., 2003; Jones *et al*., 2010). Therapeutic exercises are safe and effective in improving the cardiopulmonary capacity and QoL of BC survivors and this in turn will improve overall survival of BC survivors.

The three modes of therapeutic exercise interventions (aerobic, stretching and combination of aerobic and stretching) studied brought about different degrees of significant therapeutic effects on cardiovascular and pulmonary parameters in both premenopausal and postmenopausal BC survivors. Combination of aerobic exercise using treadmill and stretching exercise brought about the most significant therapeutic improvements in cardiovascular and pulmonary parameters in BC survivors. This was followed by aerobic exercise using treadmill alone and then stretching exercise alone. The overall therapeutic effects of SE and CAETSE interventions on the selected parameters especially cardiovascular were more in postmenopausal BC survivors than premenopausal BC survivors but the reverse was the case for AET. Also the 3 modes of exercise interventions all brought about significant improvements in the QoL of premenopausal and postmenopausal BC survivors. These therapeutic exercise modes had

no significant therapeutic effects on selected anthropometric parameters of premenopausal and postmenopausal BC survivors.

6.3 RECOMMENDATIONS

1. Physiotherapists should be more involved as members of the medical team that take care of BC survivors, not only for the treatment of lymphedema but also for the rehabilitation of cardiopulmonary and QoL variables. Physicians who have first contact with these patients should promptly refer them to physiotherapists for proper therapeutic exercise interventions that will improve cardiopulmonary complications associated with the disease and its treatments as well as improve QoL.

2. A combination of moderate intensity aerobic exercise using treadmill and stretching exercise which should be performed for 30 minutes, three times a week for at least 12 weeks should be prescribed by physiotherapists to BC survivors for optimal therapeutic benefits in cardiopulmonary and QoL variables.

6.4 IMPLICATIONS FOR FURTHER STUDIES

1. Further studies may be needed to evaluate the effects of other modes of exercise such as resistance exercise, combined aerobic (non-weight bearing or weight bearing) and resistance exercises on cardiopulmonary, anthropometric and QoL parameters in BC survivors of a Nigerian population.

2. Further studies may be needed to determine the long term effects of these therapeutic exercise modes (aerobic, stretching and combined aerobic and stretching) on BC recurrence and overall survival of BC survivors.
3. Further studies may be needed to determine the effects of these therapeutic exercise modes (aerobic, stretching and combined aerobic and stretching) on pulmonary and anthropometric parameters in BC survivors when performed longer than 12 weeks.
4. Further studies may be needed to determine the effects of these therapeutic exercise modes (aerobic, stretching and combined aerobic and stretching) on cardiopulmonary, anthropometric and QoL parameters in stage IV BC survivors.

6.5 CONTRIBUTIONS TO KNOWLEDGE

1. This study established a therapeutic and effective short duration exercise protocol of 12 weeks for the improvement of the cardiopulmonary functions and QoL of BC survivors.
2. An ideal dosage of therapeutic exercise intervention that improves cardiopulmonary functions and QoL of BC survivors is combined moderate intensity aerobic exercise using treadmill and stretching exercise performed for 30 minutes, 3 times a week for at least 12 weeks.
3. This study established that the overall therapeutic effects of stretching exercise alone and combined aerobic exercise using treadmill and stretching exercise on cardiovascular parameters were more pronounced in the postmenopausal BC survivors compared with premenopausal BC survivors.

4. This study established that combined aerobic exercise using treadmill and stretching exercise is more effective than either aerobic exercise using treadmill alone or stretching exercise alone in improving cardiopulmonary functions of BC survivors.

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